COST-EFFECTIVENESS OF APIXABAN, DABIGATRAN, RIVAROXABAN, AND WARFARIN FOR THE PREVENTION OF STROKE PROPHYLAXIS IN ATRIAL FIBRILLATION

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1 CHAPTER 1: INTRODUCTION

1.1 Abstract

Objective: The primary objective of this study was to estimate the long-term cost-effectiveness of stroke prevention in patients with nonvalvular atrial fibrillation (NVAF) in the United States using new anticoagulant therapies – dabigatran 150 mg, apixaban 5 mg, and rivaroxaban 20 mg – as well as the standard treatment, warfarin.

Methods: A Markov decision-analysis model was constructed using data from clinical trials that evaluated the new oral anticoagulants relative to warfarin (apixaban 5 mg & ARISTOTLE, dabigatran 150 mg & RE-LY, and rivaroxaban 20 mg & ROCKET-AF) to compare the lifetime cost and quality-adjusted life expectancy. The Markov model target population was a hypothetical cohort of 70-year old patients with nonvalvular atrial fibrillation, an increased risk for stroke (CHADS$_2$ ≥ 1, or equivalent), a renal creatinine clearance (CrCl) of 50 or above, and no contraindication to anticoagulant therapy. Using pair-wise comparisons of each therapy, analyses were conducted to evaluate incremental cost-effectiveness ratios (ICERs), net monetary benefits (NMBs), lifetime costs, life-years, and quality-adjusted life-years (QALYs).

Results: In the base case, warfarin had the lowest cost of $71,857 (95% confidence interval [CI]: $68,730, $77,452), followed by rivaroxaban 20 mg ($74,023; 95% CI: $70,943, $77,307), dabigatran 150 mg ($78,584; 95% CI: $75,277, $81,968), and apixaban 5 mg ($81,180; 95% CI: $78,642, $83,756). Apixaban 5 mg also yielded the highest QALY estimate, 8.63 (95% CI: 8.52, 8.72), followed by dabigatran 150 mg (8.55;
95% CI: 8.43, 8.67), rivaroxaban 20 mg (8.42; 95% CI: 8.31, 8.54), and warfarin (8.17; 95% CI: 8.1, 8.24). In a Monte Carlo probabilistic sensitivity analysis, apixaban 5 mg, dabigatran 150 mg, rivaroxaban 20 mg, and warfarin were cost effective in 45%, 37%, 19%, 0%, respectively, of the simulations using a willingness-to-pay threshold of $50,000 per QALY gained. From the one-way sensitivity analyses, new anticoagulant (apixaban 5 mg, dabigatran 150 mg, rivaroxaban 20 mg) costs and probabilities associated with intracranial hemorrhage and stroke for patients receiving rivaroxaban 20 mg were identified as significant influential variables impacting model results.

**Conclusion:** In patients with NVAF and an increased risk of stroke prophylaxis, apixaban 5 mg, dabigatran 150 mg, and rivaroxaban 20 mg may all be cost-effective alternatives to warfarin depending on pricing in the United States and neurologic events for rivaroxaban 20 mg.

### 1.2 Background

Atrial fibrillation is a supraventricular tachycardia characterized by uncoordinated atrial activation with possible subsequent degeneration of the atrial mechanical function (Fuster et al., 2006). Supraventricular refers to the atria located above the ventricles in the heart and tachycardia is a rhythm disorders in which the heart beats faster than normal. Data from a national sample of patients covered by various payers and plan benefit designs indicate an estimated 3 million Americans were diagnosed with atrial fibrillation (AF) in 2005 (Naccarelli, Varker, Lin, & Schulman, 2009). The rate of
ischemic stroke in people with nonvalvular atrial fibrillation (NVAF) averages about five percent per year, which is two to seven times the rate of those people without AF (Flegel, Shipley, & Rose, 1987; A. D. Krahn, Manfreda, Tate, Mathewson, & Cuddy, 1995; Lévy et al., 1999; Wolf, Abbott, & Kannel, 1987; Wolf, Abbott, & Kannel, 1991).

Stroke is a term used to describe a brain injury resulting from an abnormality of the blood supply to a part of the brain. Stroke refers to a various different types of diseases involving an acute occlusion of an intracranial vessel resulting in the interruption of blood supply, subsequently causing reduction to a part of the brain the vessel supplies and depriving the brain tissue of oxygen and essential nutrients. There are two broad categories of strokes: hemorrhage and ischemia. The 2009 American Heart Association (AHA) reported 87 percent of strokes are ischemic (IS) and 13 percent are hemorrhagic (HS) (D. Lloyd-Jones et al., 2009). An IS occurs when there is a sudden loss of blood supply to an area of the brain that controls function. An HS occurs when a weakened blood vessel ruptures, resulting in bleeding inside the skull either into the brain or into the fluid surrounding the brain.

Stroke is associated with high prevalence, hospitalization rates, morbidity and mortality, as well as high incidence of long-term costs associated with post-stroke care and recurrent episodes for survivors. An estimated seven million Americans aged 20 years or older have had a stroke (Roger et al., 2012). Projections estimate that by 2030, an additional four million people in the US will have had a stroke, a 24 percent increase in prevalence from 2010 (Heidenreich et al., 2011). Each year, approximately 795,000
people in the US experience a new or recurrent stroke. An estimated 610,000 of these strokes are first attacks and the remaining 185,000 are recurrent (Roger et al., 2012).

Therapeutic agents commonly used to treat patients with AF for the prevention of stroke prophylaxis are antiplatelets and anticoagulants. Antiplatelets inhibit the production of thromboxane, which reduces the risk of stroke in people with history of stroke incidence or those people who have been identified to have other risk factors for stroke. The most common antiplatelet agents used for stroke prophylaxis include aspirin, clopidogrel, dipyridamole, and cilostazole. In contrast, anticoagulants prevent the coagulation (clotting) of blood. The most common anticoagulant used in patients with AF is warfarin.

Studies have been conducted to evaluate the preventative properties of anticoagulation and antiplatelets in patients diagnosed with AF at risk for stroke prophylaxis. Randomized trials with enrolled high-risk AF patients (stroke rates exceeding 6% each year) demonstrated a greater relative risk reduction (RRR) with the use of adjusted-dose oral anticoagulation relative to the antiplatelet drug aspirin (Fuster et al., 2006). In a meta-analysis conducted by Hart and colleagues, authors found adjusted dose warfarin was substantially more efficacious compared to antiplatelet therapy alone, with a RRR in stroke of 37 percent (95% confidence interval [CI], 22%-52%) (R. G. Hart, Pearce, & Aguilar, 2007). Findings from other studies have demonstrated the cost-effectiveness of warfarin treatment versus no therapy or aspirin in patients with AF at a moderate to high risk of stroke, which served as the basis for the current American College of Chest Physicians (ACCP) clinical guideline recommendations (Szucs &
Bramkamp, 2006; You et al., 2012). However, the management strategies necessary to maintain optimal international normalized ratio (INR) levels with warfarin therapy may render anticoagulation therapy less cost-effective in a real-world practice setting (Szucs & Bramkamp, 2006).

Stroke represents a substantial financial burden on the healthcare system, as well as on patients, family, and society. The lifetime cost of IS is estimated to be greater than $90,000 for an individual in 1990 (Taylor et al., 1996), whereas the AHA estimated that in 2008, total national direct and indirect costs of stroke in the US exceeded $34 billion (Roger et al., 2012). Focusing on an older age group, Lee and colleagues examined the costs of stroke subtype for Medicare beneficiaries (≥ 65 years) (Lee, Christensen, Joshi, & Pashos, 2007). In the US, almost 75 percent of the stroke patients are Medicare beneficiaries, qualifying the national health insurance program as the most common payer of healthcare for stroke patients. The total aggregated costs of a four-year follow-up period were $60,177 for subarachnoid hemorrhage (SAH), $50,015 for intracranial hemorrhage (ICH), and $49,996 for IS.

1.3 Statement of the Problem

Since 2009, results of clinical trials assessing the effectiveness of alternative anticoagulant treatments to warfarin have been published. These anticoagulants include apixaban, dabigatran, and rivaroxaban. To date, published economic studies have only focused on the cost-effectiveness comparison between dabigatran and warfarin for stroke prevention in patients with AF (Freeman et al., 2011; Kamel, Johnston, Easton, & Kim,
Each of these six studies evaluating the cost-effectiveness of dabigatran relative to warfarin found dabigatran was cost-effective in some scenarios, however superior clinical and economic benefit was contingent upon therapy dosage, stroke severity, and INR control with warfarin. Most studies assessing the cost-effectiveness of both dabigatran doses, 110 mg and 150 mg, found 150 mg to be the only dose to yield a cost-effective therapy strategy compared to warfarin (Freeman et al., 2011; Kamel, Johnston, Easton, & Kim, 2012; Langkilde, Bergholdt Asmussen, & Overgaard, 2012; Pink, Lane, Pirmohamed, & Hughes, 2011; S. V. Shah & Gage, 2011). Pink and colleagues concluded dabigatran 110 mg offered no clinical or economic advantage over dabigatran 150 mg (Pink, Lane, Pirmohamed, & Hughes, 2011). With respect to stroke severity, Shah and Gage found the cost-effectiveness of dabigatran was dependent upon the patient’s severity of stroke risk. For patients at a low risk of stroke, aspirin was cost-effective; for patients at an intermediate risk for stroke, warfarin was cost-effective; and for patients at a high risk for stroke, dabigatran 150 mg was cost-effective (S. V. Shah & Gage, 2011).

As the studies above show, dabigatran is not a superior cost-effective agent to warfarin and, therefore, there is a need for an evaluation of other alternative anticoagulant therapies. Clinical trial results for apixaban (Apixaban for Reduction In STroke and Other ThromboemboLic Events in atrial fibrillation [ARISTOTLE]) and rivaroxaban (Rivaroxaban Once daily oral direct Factor Xa inhibition Compared with vitamin K
antagonist for the prevention of stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) are now published and are available to use for further investigation of treatment comparisons for both the cost and quality-of-life (C. B. Granger et al., 2011; Patel et al., 2011). For various reasons, including scarce resources, it is not feasible to conduct a clinical trial with all four therapies. Instead, a Markov model is an ideal method to assess four anticoagulant treatments for their aggregate lifetime costs, aggregate life-years, quality-adjusted life-years (QALYs), incremental cost-effectiveness ratios (ICERs), and net monetary benefit (NMB). Economic modeling is a relatively inexpensive and effective way of synthesizing existing data and evidence available on the costs and efficacy of alternative treatment options (A. Briggs & Sculpher, 1998). A Markov model in particular is well suited to model the lifetime progression of stroke prevention in patients with AF as it was built to simultaneously handle costs and effects (A. Briggs & Sculpher, 1998). The implication of this study’s results are to provide a more inclusive, current evaluation of the cost-effectiveness of available anticoagulation therapies to assist clinicians and other healthcare decision-makers make a more informed choice regarding patient treatment.

1.4 Study Purpose

The primary objective of this study was to estimate the long-term cost-effectiveness of stroke prevention in patients with nonvalvular atrial fibrillation (NVAF) in the US using newer anticoagulant therapies – dabigatran 150 mg, apixaban 5 mg, and rivaroxaban 20 mg – as well as the standard treatment, warfarin.
1.5 Study Objectives

This chapter outlines the methodology used to address a set of research questions concerning the prevention of stroke prophylaxis in patients diagnosed with NVAF, who are at an increased risk of stroke. Each research question included the analysis of four anticoagulant therapies: apixaban, dabigatran, rivaroxaban, and warfarin. Study objectives were:

I. Estimated the incremental cost-effectiveness pair-wise among all treatments and assessed whether a difference in treatment cost-effectiveness existed;

II. Estimated the net monetary benefit (NMB) for all treatments and assessed whether a difference exists; and

III. Determined the total direct and indirect costs for each therapy pathway.

Decision modeling methods were used to estimate the survival of patients with AF and their associated total costs (i.e., direct and indirect) over their lifetime once diagnosed. A decision analysis model was a feasible choice given the alternative is a long-term prospective multi-arm trial that would be very expensive to conduct. Significant capital investment and over 20 years of patient follow up would be required to prospectively assess the survival and cost of the outcomes.

1.6 Hypotheses

The primary areas of interest addressed in the hypothesis analyses were ICERs, NMBs, aggregated total lifetime costs, life-years, and quality-adjusted life-years (QALYs). Listed below are five major hypotheses of interest in this study.
1.6.1 Hypothesis I: Incremental Cost-Effectiveness Ratio

The following six hypotheses were used to test the difference in the incremental cost-effectiveness ratios (ICERs) among pair-wise comparisons of four anticoagulant treatments. Note that the ICER was calculated as a ratio of the difference in costs to the difference in effects ($\Delta C/\Delta E$) between products. A treatment was deemed cost-effective in comparison to an alternative treatment using a $50,000 willingness-to-pay (WTP) threshold (Neumann, Sandberg, Bell, Stone, & Chapman, 2000).

Ho1\textsubscript{1}: It was hypothesized that no difference in the ICER exists between dabigatran 150 mg and warfarin using $50,000 as the WTP threshold.

Ho1\textsubscript{2}: It was hypothesized that no difference in the ICER existed between apixaban 5 mg and warfarin using $50,000 per QALY gained as the WTP threshold.

Ho1\textsubscript{3}: It was hypothesized that no difference in the ICER existed between rivaroxaban 20 mg and warfarin using $50,000 per QALY gained as the WTP threshold.

Ho1\textsubscript{4}: It was hypothesized that no difference in the ICER existed between apixaban 5 mg and dabigatran 150 mg using $50,000 per QALY gained as the WTP threshold.

Ho1\textsubscript{5}: It was hypothesized that no difference in the ICER existed between rivaroxaban 20 mg and dabigatran 150 mg using $50,000 per QALY gained as the WTP threshold.
Ho1₆: It was hypothesized that no difference in the ICER existed between apixaban 5 mg and rivaroxaban 20 mg using $50,000 per QALY gained as the WTP threshold.

1.6.2 Hypothesis II: Net Monetary Benefits

The following six hypotheses were used to test the difference in the incremental net monetary benefit among pair-wise comparisons of four anticoagulant treatments. Note that the net monetary benefit (NMB) was calculated as the effectiveness, multiplied by the amount a decision maker is WTP (denoted λ), less the cost (E*λ – C). For the NMB to be positive, the product of the effectiveness and amount the decision maker is willing to invest in the treatment must exceed the cost. For NMB >0, the comparator therapy was considered cost-effective and should be selected for implementation. For NMB <0, greater health improvement could be attained by foregoing the intervention and investing the resources elsewhere. NMB is zero when the incremental cost-effectiveness ratio for a treatment is equal to the WTP threshold ratio selected. A WTP value of $62,000 per QALY gained was used (Shiroiwa et al., 2010).

Ho2₁: It was hypothesized that no difference in the net monetary benefits (NMBs) exists between dabigatran 150 mg and warfarin using $62,000 per QALY gained as the willingness-to-pay (WTP) threshold.

Ho2₂: It was hypothesized that no difference in the NMBs existed between apixaban 5 mg and warfarin using $62,000 per QALY gained as the WTP threshold.
Ho2₃: It was hypothesized that no difference in the NMBs existed between rivaroxaban 20 mg and warfarin using $62,000 per QALY gained as the WTP threshold.

Ho2₄: It was hypothesized that no difference in the NMBs existed between apixaban 5 mg and dabigatran 150 mg using $62,000 per QALY gained as the WTP threshold.

Ho2₅: It was hypothesized that no difference in the NMBs existed between rivaroxaban 20 mg and dabigatran 150 mg using $62,000 per QALY gained as the WTP threshold.

Ho2₆: It was hypothesized that no difference in the NMBs existed between apixaban 5 mg and rivaroxaban 20 mg using $62,000 per QALY gained as the WTP threshold.

1.6.3 Hypothesis III: Lifetime Costs

The following six hypotheses were used to test the difference in lifetime costs among pair-wise comparisons of four anticoagulant treatments. Lifetime cost of treatment for patients with NVAF with an increased risk of stroke included both direct and indirect costs.

Ho3₁: It was hypothesized that no difference in lifetime costs exists between dabigatran 150 mg and warfarin.

Ho3₂: It was hypothesized that no difference in lifetime costs exists between apixaban 5 mg and warfarin.
Ho3: It was hypothesized that no difference in lifetime costs exists between rivaroxaban 20 mg and warfarin.

Ho4: It was hypothesized that no difference in lifetime costs exists between apixaban 5 mg and dabigatran 150 mg.

Ho5: It was hypothesized that no difference in lifetime costs exists between rivaroxaban 20 mg and dabigatran 150 mg.

Ho6: It was hypothesized that no difference in lifetime costs exists between apixaban 5 mg and rivaroxaban 20 mg.

1.6.4 Hypothesis IV: Life-Years

The following six hypotheses were used to test the difference in life-years gained among pair-wise comparisons of four anticoagulant therapies. Life-years were calculated as the sum of years gained attributable to treatment effects.

Ho4: It was hypothesized that no difference in total life-years exists between dabigatran 150 mg and warfarin.

Ho2: It was hypothesized that no difference in total life-years exists between apixaban 5 mg and warfarin.

Ho3: It was hypothesized that no difference in total life-years exists between rivaroxaban 20 mg and warfarin.

Ho4: It was hypothesized that no difference in total life-years exists between apixaban 5 mg and dabigatran 150 mg.

Ho5: It was hypothesized that no difference in total life-years exists between rivaroxaban 20 mg and dabigatran 150 mg.
Ho4\(_6\): It was hypothesized that no difference in total life-years exists between apixaban 5 mg and rivaroxaban 20 mg.

1.6.5 Hypothesis V: Quality-Adjusted Life-Years

The following six hypotheses were used to test the difference in patient QALYs among pair-wise comparisons of four anticoagulant therapies. QALYs were calculated as the sum of the products of utility values associated with a given health state multiplied by the years spent in the health state.

Ho5\(_1\): It was hypothesized that no difference in total QALYs exists between dabigatran 150 mg and warfarin.

Ho5\(_2\): It was hypothesized that no difference in total QALYs exists between apixaban 5 mg and warfarin.

Ho5\(_3\): It was hypothesized that no difference in total QALYs exists between rivaroxaban 20 mg and warfarin.

Ho5\(_4\): It was hypothesized that no difference in total QALYs exists between apixaban 5 mg and dabigatran 150 mg.

Ho5\(_5\): It was hypothesized that no difference in total QALYs exists between rivaroxaban 20 mg and dabigatran 150 mg.

Ho5\(_6\): It was hypothesized that no difference in total QALYs exists between apixaban 5 mg and rivaroxaban 20 mg.
1.7 Abbreviations

**AA** = African American

**ACC** = American College of Cardiology

**ACCP** = American College of Chest Physicians

**ADOPT** = Apixaban Dosing to Optimize Protection for Thrombosis (apixaban clinical trial)

**ADVANCE** = Apixaban Dosed orally Versus Anticoagulation with iNjeCtable Enoxaprin (apixaban clinical trial)

**AF** = atrial fibrillation

**AFL** = atrial flutter

**AHRQ** = Agency of Healthcare Research and Quality

**AHA** = American Heart Association

**AMI** = acute myocardial infarction

**AMPLIFY** = Apixaban after the initial Management of Pulmonary embolism and deep vein thrombosis In First line therapy (apixaban clinical trial)

**APPROPOS** = Apixaban PROphylaxix in Patients undergoing tOtal knee replacement Surgery (apixaban clinical trial)
**ARIC** = Atherosclerosis Risk in Communities

**ARISTOTLE** = Apixaban for Reduction in Stroke and Other Thromboembolic Events in atrial fibrillation (apixaban clinical trial)

**ARR** = absolute risk reduction

**ATLAS ACS TIMI** = Anti-Xa Therapy to Lower cardiovascular events in addiction to aspirin with/without thienopyridine therapy in subjects with Acute coronary Syndrome (rivaroxaban clinical trial)

**AVERROES** = Apixaban Versus acEtylsalicyclic acid to pRevent strOkses (apixaban clinical trial)

**AVM** = atriovenous malformation

**ATRIA** = AnTioagulation and Risk factors In Atrial fibrillation

**CEA** = cost-effectiveness analysis

**CEAC** = cost-effectiveness acceptability curve

**CHADS\textsuperscript{2}** = A scoring system for patients with atrial fibrillation which attempts to determine their risk of stroke; one point is assigned for each of following FOUR risk factors: Congestive heart failure, Hypertension, Age $\geq$ 75 years and Diabetes mellitus; two points are assigned for a patient having had a Stroke or transient ischemic attack

**CI** = confidence interval
CMS = Centers for Medicare and Medicaid Services

CNS = central nervous system

CNVAF = chronic nonvalvular atrial fibrillation

CPT = Current Procedural Code

CrCl = creatinine clearance

CT = computed tomography

DALY = disability-adjusted life-year

DES = discrete event simulation

ECG = echocardiogram

ECH = extracranial hemorrhage

ED = emergency department

EEG = electroencephalogram

EINSTEIN = Evaluating oral, direct Factor Xa inhibitor rivaroxaban in patients with acute symptomatic deep vein thrombosis or pulmonary embolism (rivaroxaban clinical trial)

EKG = electrocardiogram
HEMORR$_2$HAGES = clinical classification scheme for predicting hemorrhage in patients with AF; two points are assigned for a Prior bleed and one point for each of the other risk factors: Hepatic or renal disease, Ethanol abuse, Malignancy, Older (age $\geq$ 75 years), Reduced platelet count or function, Hypertension (uncontrolled), Anemia, Genetic factors, Excessive fall risk and Stroke

HS = hemorrhagic stroke

ICER = incremental cost-effectiveness ratio

ICH = intracranial hemorrhage

INB = incremental net benefit

INR = international normalized ratio

IS = ischemic stroke

ISH = ischemic hemorrhage

ISTH = International Society on Thrombosis and Hemostasis
LAF = lone atrial fibrillation

LY = life-year

MEPS = Medical Expenditure Panel Survey

mg = milligrams

MI = myocardial infarction

mL/min = milliliters per minute

MRI = magnetic resonance imaging

NHLBI = National Heart, Lung, and Blood Institute

NHS = National Health Services

NHW = non-Hispanic white

NICE = National Institute for Health and Clinical Excellence

NIH = National Institute of Health

NNT = number needed to treat

NOMAS = Northern Manhattan Study

NVAF = nonvalvular atrial fibrillation
**ODIXa-KNEE** = Oral Dlrect FactorXa inhibitor BAY 59-7939 in the prevention of VTE in patients undergoing total KNEE replacement (rivaroxaban clinical trial)

**OPD** = outpatient department

**PETRO** = Prevention of Embolic and Thrombotic Events in Patients with Persistent Atrial Fibrillation (dabigatran clinical trial)

**PSA** = probabilistic sensitivity analysis

**QALY** = quality-adjusted life-year

**RECORD** = REgulation of Coagulation in major Orthopedic surgery reducing the Risk of DVT and PE (rivaroxaban clinical trial)

**RE-LY** = Randomized Evaluation of Long-Term Anticoagulation Therapy (dabigatran clinical trial)

**ROCKET-AF** = Rivaroxaban Once daily oral direct Factor Xa inhibition Compared with vitamin K antagonist for the prevention of stroke and Embolism Trial in Atrial Fibrillation (rivaroxaban clinical trial)

**RRR** = relative risk reduction

**SA** = sensitivity analysis

**SAH** = subarachnoid hemorrhage

**SD** = standard deviation
SPECT = single photon emission computed tomography

TCD = transcranial Doppler (ultrasound)

TIA = transient ischemic attack

UK = United Kingdom

US = United States

VKA = vitamin K antagonist

WTP = willingness-to-pay
1.8 Glossary of Terms

Atrial fibrillation = supraventricular tachycardia characterized by uncoordinated atrial activation with possible subsequent degeneration of the atrial mechanical function

Absolute risk reduction (ARR) = the difference in the rates of adverse events between control group and the treated group

Cost-effectiveness analysis (CEA) = systematic method of comparing two or more alternative programs by measuring the costs and consequences (health outcomes) of each

Cost-effectiveness acceptability curve (CEAC) = plots the probability that one treatment is more cost-effective than another, as a function of the threshold willingness-to-pay for one additional unit of efficacy

Discrete event simulation (DES) = modeling of a system as it evolves over time by a representation in which the state variables change only at countable number of points in time

Decision Analysis = an explicit, quantitative, systematic approach to decision making under conditions of uncertainty in which probabilities and consequences of each possible event are explicitly stated and then assessed

Discounting = a method to account for time preferences and adjust the value of future costs or quality-of-life measures to an equivalent value today (i.e., present value)

Hemorrhagic stroke (HS) = stroke caused by the rupture of a blood vessel with bleeding into the tissue of the brain
**Incremental cost-effectiveness ratio (ICER)** = difference between treatment costs (incremental cost) is compared to the difference in treatment outcomes (incremental effects), calculated by dividing incremental costs by incremental effects

**Incremental net benefit (INB)** = net benefit is an alternative method of displaying cost-effectiveness results; when expressed as monetary units it is formally a net monetary benefit; when expressed as units of efficacy or utility it is a net health benefit; the difference between two treatments is an incremental net benefit

**Ischemic stroke (IS)** = stroke caused by thrombosis or embolism

**Markov model** = a special type of state transition model in that transition probabilities depend upon the current health-state and not upon previous health states or the path by which a state was entered

**Probabilistic Sensitivity Analysis (PSA)** = assigns a distribution to all parameters in the model to evaluate the sensitivity of the model to changes in its inputs; ranges are determined by the average value, standard deviation, and ‘shape’ of the spread of data

**Quality-adjusted life-year (QALY)** = method used to estimate a number between zero and one that is multiplied by the length of time in each health state to represent the combined impact of morbidity and mortality outcomes in a linear fashion

**Relative risk reduction (RRR)** = the extent to which a treatment reduces a risk, in comparison with patients not receiving the treatment of interest

**Sensitivity analysis (SA)** = allows one to determine how the results of an analysis would change when parameter inputs, ‘best guess’ estimates, or assumptions are varied over a relevant range of values (one-way deterministic, multi-way deterministic, probabilistic)
**Transient ischemic attack (TIA)** = a brief episode of cerebral ischemia that is usually characterized by temporary blurring of vision, slurring of speech, numbness, paralysis, or syncope and that is often predictive of a serious stroke (aka mini-stroke)

**Transition probability** = the chance that patients in a particular health state might transfer into another particular health state during the course of a cycle

**Willingness-to-pay (WTP)** = method used to determine how much people are willing to pay to reduce the chance of an adverse health outcome
2 CHAPTER 2: LITERATURE REVIEW

2.1 Atrial Fibrillation

2.1.1 Prevalence and Incidence

Data from a national sample of patients covered by various payers and plan benefit designs indicate an estimated 3 million Americans were diagnosed with atrial fibrillation (AF) in 2005 (Naccarelli, Varker, Lin, & Schulman, 2009). From this same sample, an additional 190,000 people were diagnosed with AF and atrial flutter (AFL). The median age of people with AF is estimated at 75 years, and approximately 70 percent of the people with AF are between the ages of 65 and 85 years (RW.ERROR - Unable to find reference:141; A. S. Go et al., 2001; Psaty et al., 1997; Ruo, Capra, Jensvold, & Go, 2004). The overall number of males and females with AF is about equal, however approximately 60 percent of people with AF over the age of 75 are women (RW.ERROR - Unable to find reference:141; A. S. Go et al., 2001; Psaty et al., 1997; Ruo, Capra, Jensvold, & Go, 2004). Furthermore, AF affects about one in 25 adults over the age of 60 and almost one in ten adults 80 years and older (RW.ERROR - Unable to find reference:141; A. S. Go et al., 2001). Using a cohort of 17,974 adults aged 20 years and older diagnosed with AF, Go and colleagues found that AF was more common in men compared to women, 1.1 percent and 0.8 percent, respectively (p<0.001) (RW.ERROR - Unable to find reference:141; A. S. Go et al., 2001). The authors also found among persons aged 50 years and older, the prevalence of AF was higher in white Americans than in blacks (2.2% and 1.5%, respectively (p<0.001)) (RW.ERROR - Unable to find reference:141; A. S. Go et al., 2001). Go and colleagues used a nationally representative
database from a managed care organization to estimate projections of the future prevalence of AF. Among the study results, authors found the projected increase in the prevalence of AF in the United States (US) will be 5.6 million (95% CI, 5.0-6.3) by the year 2050. This estimate indicates more than 50 percent of the affected individuals will be 80 years and older (A. S. Go et al., 2001). Hart and colleagues found that one in every six strokes occurred in a patient with AF. The rate of ischemic stroke in people with nonvalvular atrial fibrillation (NVAF) averages about five percent per year, which is two to seven times the rate of those people without AF (Flegel, Shipley, & Rose, 1987; A. D. Krahn, Manfreda, Tate, Mathewson, & Cuddy, 1995; Lévy et al., 1999; Wolf, Abbott, & Kannel, 1987; Wolf, Abbott, & Kannel, 1991). Age plays a role in the proportion of patients with AF who experience a stroke. Prospective studies show that the incidence of AF increase from less than 0.1 percent per year in people under the age of 40 to over 1.5 percent per year in women and two percent per in males 80 years and older (A. D. Krahn, Manfreda, Tate, Mathewson, & Cuddy, 1995; Psaty et al., 1997; Wolf, Abbott, & Kannel, 1987). Results from the Framingham Heart Study demonstrate that the annual risk of stroke attributable to AF was 1.5 percent in participants 50 to 59 years old and an estimated 23.5 percent in those patients 80 to 89 years old (Wolf, Abbott, & Kannel, 1991). AF is also associated with an elevated long-term risk of stroke (Fuster et al., 2006), heart failure, and all-cause mortality, particular in females (Stewart, Hart, Hole, & McMurray, 2002).

2.1.2 Pathophysiology
The most common sustained arrhythmia is AF (You et al., 2012). An arrhythmia occurs when the heart beats too fast, too slow, or with an irregular rhythm. Atrial fibrillation is a supraventricular tachycardia characterized by uncoordinated atrial activation with possible subsequent degeneration of the atrial mechanical function (Fuster et al., 2006). Supraventricular refers to the atria located above the ventricles in the heart and tachycardias are rhythm disorders in which the heart beats faster than normal. The atria receive blood from the systemic vessels and contract to push the blood downward to deliver the blood to the ventricles. The ventricles then contract to push the blood into the pulmonary artery of the lung and eventually out to the rest of the body to supply vital nutrients. In AF, there is an irregularly irregular supraventricular rhythm in the heart marked by disorganized, rapid, and irregular atrial activation. Supraventricular impulses penetrate the atrioventricular conduction system in varying degrees, resulting in irregular activation of the ventricles leading to poor pumping of blood to distal locations. The disorganized atrial activity causes a loss of synchronized atrial contraction to forward cardiac output of blood. This results in pooling of the blood in the atria. Sustained AF leads to the loss of atrial contractility and inappropriate quickened ventricular response. AF is also associated with the loss of atrial appendage contractility and emptying leading to an increased risk of clot formations. Elevated clot formation is associated with an increase in subsequent thromboembolic events (Longo et al., 2012).

Episodes of AF may be rare, or it may possibly develop into a chronic heart condition. AF is classified based upon the burden of the abnormal rhythm. Paroxysmal AF refers to arrhythmic heartbeats that cease spontaneously within seven days of onset.
Persistent AF lasts longer than a week and requires either chemical or electrical intervention to terminate. Permanent AF is a chronic form of AF lasting more than one year. The American College of Cardiology (ACC), American Heart Association (AHA), and European Society of Cardiology (ESC) have developed the following categories of AF based upon patient characteristics: lone atrial fibrillation (LAF), NVAF, and secondary AF (Fuster et al., 2006). LAF describes paroxysmal, persistent, and permanent AF in an individual without structural heart disease or another known predisposing factor. Individuals less than 60 years typically experience this category of AF. This form of AF is uncommon, occurring in about 12 percent of the individuals affected with AF (Sanoski, 2009). NVAF is categorized by the absence of rheumatic mitral valve disease, a prosthetic heart valve, or mitral valve repair. Secondary AF occurs in the setting of a primary condition, such as myocardial infarction, cardiac surgery, pericarditis, myocarditis, hyperthyroidism, pulmonary embolism, pneumonia, or other acute pulmonary disease (You et al., 2012). Underlying cardiovascular diseases, such as left ventricular hypertension, coronary heart disease, and left ventricular systolic dysfunction, are the most common risk factors for AF (Sanoski, 2009). Other cardiovascular risk factors associated with the development of AF include left ventricular hypertrophy and valvular heart disease (especially mitral valve disease) (Sanoski, 2009).

There is range of symptoms patients may experience as a result of AF. Some people are asymptomatic and have no apparent hemodynamic consequences to the development of AF. Others experience minor palpitations or sense irregularity in their pulse rate. The most intense symptoms people may experience are severe palpitations.
The severity of the hemodynamic (i.e., blood movement) effect for those patients experiencing intense palpitations depends upon the person’s need for normal atrial contractility and the ventricular response. People experiencing severe palpitations are also susceptible to hypotension, pulmonary congestion, and angina symptoms. Symptom management options are acute rate control, chronic rate control, or catheter and surgical ablative therapy to prevent recurrent AF.

2.1.3 Diagnosis and Treatment

The diagnosis of AF is established with a patient history and clinical examination to determine the pattern of arrhythmia and cause of AF presentation, along with identifying associated cardiac and extracardiac factors related to the etiology, tolerability, and history of previous management strategies (Fuster et al., 2006). The diagnosis of AF depends upon echocardiogram (ECG) affirmation by at least a recording during the arrhythmia, either in the form of beside telemetry or ambulatory Holter readings (Fuster et al., 2006). Once a diagnosis has been confirmed, an effective therapy guideline may be created. There are three objectives clinicians seek to meet in the management of AF: rate control, thromboembolism prevention, and correction of the rhythmic disturbance (Fuster et al., 2006). Drugs and ablation are optional effective methods for rate and rhythm control, however prescribing anticoagulation administration is solely based upon an increased risk of stroke in AF patients and does not depend upon whether the sinus rhythm is corrected (Fuster et al., 2006).
2.2 Stroke

2.2.1 Prevalence and Incidence

An estimated seven million Americans aged 20 years or older have had a stroke (Roger et al., 2012). Projections estimate that by 2030, an additional four million people in the US will have had a stroke, a 24 percent increase in prevalence from 2010 (Heidenreich et al., 2011). Each year, approximately 795,000 people in the US experience a new or recurrent stroke. An estimated 610,000 of these strokes are first attacks and the remaining 185,000 are recurrent (Roger et al., 2012). Within five years following a stroke event, 24 percent of women and 42 percent of men will experience a recurrent stroke (National Stroke Association, a). Recurrent strokes are often associated with a higher rate of death and disability because parts of the brain already affected during the first stroke are less resilient to surviving a stroke recurrence. Of all strokes, 87 percent are ischemic, ten percent are intracerebral hemorrhagic, and three percent are subarachnoid hemorrhage (Roger et al., 2012). On average, every 40 seconds someone in the US experiences a stroke episode (Roger et al., 2012).

Demographic differences exist among age groups, gender, and race for the risk of stroke. Women have been found to have a higher lifetime risk of stroke compared with men. In the Framingham Heart Study, the lifetime risk of stroke in people aged 55 to 75 was an estimated one in five for women (20% to 21%) and one in six for men (14% to 17%) (Seshadri et al., 2006). Gender discrepancies may be modified by age (Roger et al., 2012). On average, women are older at stroke onset compared to men (approximately 75 years versus. 71 years) (Petrea et al., 2009). With respect to differences in stroke risk
among races, data from the Northern Manhattan Study (NOMAS) showed the age-adjusted incidence of first ischemic stroke (IS) per 1000 patients between the years 1993 and 1998 was 0.88 in non-Hispanic whites, 1.91 in blacks, and 1.49 in Hispanics (H. White et al., 2005). Additionally, Native Americans, Japanese, and Chinese have higher incidences of stroke compared to white Americans (Qureshi, Mendelow, & Hanley, 2009). A review of published studies and data from clinical trials over the last ten years found an increase of 18 percent in hospital admissions related to intracerebral hemorrhage (Qureshi, Mendelow, & Hanley, 2009). This increase is most likely due to the growing number of elderly people in the US, many of whom lack adequate blood pressure control, as well as an elevated use of anticoagulants, thrombolytics, and antiplatelet agents. In addition to demographic differences, it has been suggested that the increase in stroke incidence is also attributable to prescribing behavior and patterns of care. A population-based study reported ICH prophylaxis associated with anticoagulant use comprised 5% of all ICH episodes in 1988, 9% in 1993-1994, and 17% in 1999 (Qureshi, Mendelow, & Hanley, 2009). The rate of anticoagulant-associated intracerebral hemorrhages among people 80 years and older increased from 2.5 (95% CI, 0-7.4) in 1988 to 45.9 (95% CI, 25.6-66.2) in 1999 (p<0.001 for trend) (Flaherty et al., 2007). Over this time period, the incidence rates of cardioembolic stroke were similar, whereas warfarin distribution in the US quadrupled on a per capita basis.
2.2.2 Mortality

On average, every four minutes someone dies from a stroke (Roger et al., 2012). In 2008, stroke was the cause of death in an estimated one in every 18 deaths in the US (Roger et al., 2012). When considered separately from other cardiovascular diseases, stroke is the fourth leading cause of death in the US, following diseases of the heart, cancer, and chronic lower respiratory disease (Roger et al., 2012). According to data from the National Heart, Lung, and Blood Institute’s (NHLBI) Atherosclerosis Risk in Communities (ARIC) study (1987-2001), 7.3 percent (95% CI, 4.7-11.1) of ISs and 33.1 percent (95% CI, 18.1-52.6) of ICHs among people 45 to 64 years of age resulted in death within the first 30 days post stroke (Rosamond et al., 1999). In 2008, women accounted for 60.1 percent of the stroke occurrences in the US (Roger et al., 2012).

Substantial geographic disparities exist for stroke mortality. Higher stroke rates in the US occur in the southeastern region, known as the “stroke belt” (Roger et al., 2012). Eight states usually included in the stroke belt region include North Carolina, South Carolina, Georgia, Tennessee, Mississippi, Alabama, Louisiana, and Arkansas. Among the stroke states included in the stroke belt, three states are referred to as the “buckle” and have an even higher stroke mortality rate than the other stroke belt states (G. Howard et al., 1997). States in the buckle region include the coastal plain of North Carolina, South Carolina, and Georgia. In comparison to the rest of the US, the overall stroke mortality in the stroke belt is about 20 percent higher and is about 40 percent higher in the buckle region (G. Howard et al., 1997).
2.2.3 Pathophysiology

Stroke is a term used to describe a brain injury resulting from an abnormality of the blood supply to a part of the brain. Stroke refers to a various different types of diseases involving an acute occlusion of an intracranial vessel resulting in the interruption of blood supply, subsequently causing reduction to a part of the brain the vessel supplies and depriving the brain tissue of oxygen and essential nutrients. There are two broad categories of strokes: hemorrhage and ischemia. The 2009 American Heart Association (AHA) reported 87 percent of strokes are IS and 13 percent are ICH (D. Lloyd-Jones et al., 2009).

A hemorrhagic stroke occurs when a weakened blood vessel ruptures, resulting in bleeding inside the skull either into the brain or into the fluid surrounding the brain. There are two types of weakened blood vessels that cause hemorrhagic stroke: aneurysms and arteriovenous malformations (AVMs). The area of the brain where a hemorrhage occurs defines the type of stroke. The following three membranes enclose the brain: pia mater, arachnoid, and dura mater. Types of hemorrhagic stroke include intracerebral, subarachnoid, subdural, and epidural. Intracerebral hemorrhages occur inside of the pia mater and result from ruptured small vessels, arterioles and capillaries. This type of hemorrhage is most often due to hypertension. Subarachnoid hemorrhages occur between the pia matter and subarachnoid regions of the brain and are usually caused by a ruptured aneurysm, a weakened artery with a wall distended outward. Once the compromised artery breaks, blood instantly leaks into the spinal fluid that circulates around the spinal cord and brain. The abrupt increase in pressure causes a lapse in brain
function, often causing an affected person to stare, drop to his or her knees, or become confused. Hemorrhages occurring between the arachnoid and dura mater membranes are referred to as subdural hemorrhages. Epidural hemorrhages are located outside of the dura mater, but still inside the skull. Head injuries that tear blood vessels are often the cause of subdural and epidural hemorrhages.

An ischemic stroke is a sudden loss of blood supply to an area of the brain that controls function. During an ischemic event, not enough blood is supplied to the brain to allow continued normal functioning of the effected brain tissue. Strokes are commonly caused by a partial or full blockage of an artery that supplies the brain. Arteries provide sugar, oxygen, and other essential nutrients necessary for survival of the regions of the brain. If the ischemic event occurs long enough, death of the tissue (also known as an infarction) results. Thrombosis, embolism, and systemic hypoperfusion are three categories of ischemic stroke. Each category is related to a mechanism of blood vessel injury or reason for decreased blood flow.

Thrombosis is a term used to characterize a local problem with an artery supplying blood to the brain. The most common underlying condition for this type of obstruction is atherosclerosis, a disease that causes the narrowing of a channel transporting blood (known as a lumen) in an artery. Fatty lipid build-up and inflammatory cell progression inside an affected artery, in combination with hypertrophy of arterial smooth muscle, results in plaque formation associated with atherosclerosis. Eventually plaque accumulation causes the lumen to narrow enough to severely reduce
the flow of blood and the formation of a blood clot results, resulting in total occlusion of the artery.

The process of particles, such as a blood clot, breaking loose and blocking a distant artery characterizes an embolism. Common areas for clots to originate are the heart, the aorta, or one of the major arteries in the neck. A clot that breaks off from a distal artery travels through blood vessels until it reaches vessels in the brain, where the vessels are too small for the clot to maneuver through and a cerebral embolism results. Atrial fibrillation has been associated with causing a cerebral embolism. Irregular heartbeats characterizing atrial fibrillation create a condition where a blood clot can form in the heart.

Systemic hypoperfusion is associated with abnormal pumping mechanism of the heart, leading to low pressure in the system. Low pressure in the system may result from abnormally slow heart rhythms, cardiac arrest, and failure of the heart to adequately pump blood and consequently there is diminished blood flow to the brain. An additional cause of low blood pressure is an inadequate amount of blood or fluid in the vascular compartment of the body. Inadequate amounts of blood perfusion to the brain may be attributable to bleeding, dehydration, and loss of fluid in the body tissues (i.e., shock).

2.2.4 Risk Factors

Medical risk factors for stroke include high blood pressure, atrial fibrillation, high cholesterol, diabetes, atherosclerosis, and circulation problems (National Stroke Association, b). Hypertension is a strong predictor for the risk of both IS and ICH. In a
study that assessed the association between blood pressure and the risk of stroke, participants with blood pressure readings below 120/80 mm Hg had approximately half the lifetime risk of stroke compared to patients with hypertension (W. Cushman et al., 2010). Atrial fibrillation has been found to independently increase the risk of stroke five-fold across all age groups (Roger et al., 2012). However, there is a difference in stroke risk attributable to the presence of AF among age groups. For example, the percentage of strokes associated with AF is an estimated 1.5 percent at 50 to 59 years of age and 23.5 percent at 80 to 89 years (Roger et al., 2012).

Controllable lifestyle risk factors include tobacco use, alcohol use, physical inactivity, and obesity (National Stroke Association, b). Cigarette use is one of the well-established modifiable risks for stroke (Roger et al., 2012). Current smokers have a two to four time greater risk of stroke compared to nonsmokers who have not smoked in ten or more years (R. S. Shah & Cole, 2010). Smoking cessation has been shown to reduce stroke risk regardless of gender, age, or race (Bhat et al., 2008). Physical inactivity is a controllable lifestyle factor shown to be associated with stroke risk. In the prospective cohort study NOMAS, white, black, and Hispanic women in an urban setting were assessed for a median follow-up of 9 years. In this study, moderate- to heavy-intensity physical activity was associated with a 35% reduction in the risk of IS (HR: 0.65; 95%CI 0.44-0.98) (Willey et al., 2009). The effects of activity have also been evaluated to determine the intensity level of activity associated with stroke risk reduction. Another study using patients enrolled in NOMAS found only moderate- to vigorous-intensity
exercise was associated with risk reduction, whereas light exercise (i.e., walking) showed no protection benefit (Grau et al., 2009).

Non-modifiable risk factors are age, gender, race, family history, previous stroke or transient ischemic attack (TIA), fibromuscular dysplasia, patent foramen ovale, and sleep apnea (National Stroke Association, c; Roger et al., 2012). The age of a person has been shown to be a consistent independent predictor of stroke (Laupacis et al., 1994). Almost half of the AF-related strokes occur in patients 75 years of age and older (RW.ERROR - Unable to find reference:131; Botto et al., 1997; Moulton, Singer, & Haas, 1991). Studies evaluating the risk of stroke associated with gender are inconclusive; female gender was determined to be an independent predictor of stroke in three cohort studies of people with AF, but not in several others (H. Diener et al., 1996; Laupacis et al., 1994; Stollberger et al., 1998). Sleep apnea has been shown to have a two-fold increase in the risk of stroke or death (Roger et al., 2012). More severe sleep apnea conditions have been shown to have three- to four-fold increased odds of stroke (Roger et al., 2012). A prior stroke event or TIA was found to be the strongest independent predictor of stroke in patients with NVAF (Fuster et al., 2006). Prior stroke or TIA was significantly associated with an incremental relative risk between 1.9 and 3.7 (average 3.0) across six studies evaluating patients with NVAF (Fuster et al., 2006).

### 2.2.5 Diagnosis

When a patient presents with signs of a stroke, the physician will elicit information from the patient to determine whether the stroke is of a hemorrhage or
ischemic nature. A variety of tests is available to determine the location of the stroke, the extent of the damage to brain, and whether heart or blood abnormalities contributed to stroke development. Furthermore, blood vessels may be evaluated to determine the presence, nature, and severity of abnormalities causing an inadequate amount of blood to the brain. A careful review of past events, a medical history, physical and neurological examination, and laboratory tests are resources used to confirm a diagnosis.

Diagnostic laboratory methods include imaging tests, electrical activity tests, and blood tests. Computed tomography (CT) and magnetic resonance imaging (MRI) are two tests used to distinguish between brain hemorrhages and infarctions. Blood flow tests locate problems that may cause fluctuations in blood flow to the brain. Angiograms, transcranial Doppler ultrasounds (TCD), single photon emission computed tomographies (SPECT), and catheter angiograms are tests used to analyze the flow of blood in the body. The first three tests are noninvasive ways to analyze the arteries supplying blood to the injured brain and identify abnormalities in blood flow. If these tests do not supply enough information, a catheter angiogram is a more invasive test capable of taking pictures inside of the arteries to illustrate areas of narrowing, blockage, aneurysms, and vascular malformations. Because the heart is a common origin source for a stroke, tests assessing heart function offer useful information about clot formation. Two common heart tests are electrocardiograms (EKG) and echocardiographies (ECG). An EKG demonstrates the rate of the heartbeat and identifies abnormalities in the pulse rate of the heart. An ECG is an ultrasound of the heart and supplies pictures of the heart and how adequately the heart is functioning.
The electroencephalogram (EEG) and “evoked response” are two tests used to assess the brain’s electrical activity. During an EEG, electrodes are placed on a patient’s scalp and the electrical signals are printed out for a physician to evaluate. An evoked response test measures how the brain responds to various sensory stimuli, including visual, auditory, and touch. Blood tests are used to identify overly high or low red blood cells, white blood cells, or platelets, as abnormal levels may indicate stroke or other medical conditions. For example, blood lipid tests are used to determine levels of triglycerides, cholesterol, and other lipoproteins in the blood. High levels indicate atherosclerosis and plaque formation in the arteries supplying blood to the heart, brain, and body limbs.

2.2.6 Complications

Stroke is the leading cause of serious, long-term disability among adults in the US (D. Lloyd-Jones et al., 2009). There are three general types of complications associated with stroke: neurological, medical, and psychological. One type of complication resulting from stroke prophylaxis is a neurological complication, including worsening of brain ischemia, brain edema, and seizures. Brain ischemia may continue after the onset of a stroke or bleeding in the brain may persist with hemorrhages. Continued insufficient supply to a portion of the brain may lead to gradual or stepwise loss of brain function. The extent of damage from a stroke depends upon the location of the obstruction in the brain and the magnitude of damage to the brain tissue. Right brain damage may cause paralysis on the left side of the body, vision problems, memory loss, and quick,
inquisitive behavioral style. In contrast, damage to the left side of the brain may cause paralysis on the right side of the body; speech and language impediments; slow, cautious behavior; and memory loss. Brain damage may also affect the brain stem. Depending upon the severity of the injury, a stroke affecting the brain stem may affect both sides of the body and may incur more damage than the right and left brain damages previously discussed. Extended damage may affect a stroke victim’s ability to speak or may prevent movement below the neck.

Another neurologic complication associated with stroke is brain edema and swelling in the brain. Injured tissue in the brain stimulates tissue fluid to pour out, compressing nearby structures and possibly causing headaches, worsening of neurologic defect, or decreased alertness. Brain hemorrhages and infarcts are often surrounding by the accumulation of this tissue fluid, referred to as brain edema. Seizures are not a common result of stroke; however, there are instances in which they do occur. Brain ischemia or hemorrhage damages nerve cells in the brain. Excessive discharge of damaged nerve cells may spread throughout the nervous system, causing an induced seizure.

Medical complications that may arise following a stroke episode include pneumonia, urinary tract infection, thrombophlebitis and pulmonary embolism, myocardial infarction, bedsores, and contractures and shoulder pain (Caplan, ). Stroke often causes structures in the mouth and throat to weaken. Aspiration resulting from weakened swallowing mechanisms allows infected material to reach the lungs, which causes pneumonia. Stroke often affects the mechanics of urination, such as retention of
urine and difficulty voluntarily bladder emptying. Often urinary infections develop when urine remains pooled in the bladder. Stroke patients are prone to developing clots in weakened limbs, such as their legs. These clots are capable of breaking off and traveling to the lungs causing a pulmonary embolism, which is a life-threatening condition. Heart and brain vascular disease are often comorbidities. An abnormally functioning heart may be the cause of a stroke, may be a coexisting problem with a stroke, or may be the result of a stroke.

Psychological issues following a stroke event are a third type of general complication associated with stroke prophylaxis. The reactions of a patient to a stroke event vary substantially. New personality traits may emerge following a stroke, or old traits may become accentuated. Some patients view a stroke as a wake-up call to change their lifestyle and engage in healthier habits to reduce complications and prevent future prophylaxis. Other patients become depressed and feel hopeless about the future.

Results from the NHLBI’s Framingham Heart Study show that among ischemic stroke survivors aged 65 years and older, the following disabilities were observed six months following stroke prophylaxis: some hemiparesis (50%), inability to walk without some assistance (30%), dependent in activities of daily living (26%), aphasia (19%), depressive symptoms (35%), and institutionalized in a nursing home (26%) (Kelly-Hayes et al., 2003). Differences in functional status after a stroke differ between gender and among races. After stroke, women experience greater disability compared to males (Roger et al., 2012). In a cross-sectional study of 5,888 community-living people over the age of 65 who were classified as ambulatory at baseline, women were found to be
half as likely to be independent in activities of daily living after stroke compared to men, after adjustment for age, race, education, and marital status (Whitson et al., 2010). Another prospective study conducted with a Michigan study registry found that women had a 63 percent lower probability of achieving independence in activities of daily living three months after discharge (Gargano & Reeves, 2007). With respect to differences in functioning abilities following stroke among races, Ottenbacher and colleagues found that blacks and Hispanics had a worse functional status at discharge compared to non-Hispanic whites after adjusting for age and stroke subtype (Ottenbacher et al., 2008).

2.3 Antithrombotic Therapies

2.3.1 Clotting Cascade

Hemostasis is the process of blood clot formation at the site of vessel injury. When a blood vessel wall is ruptured, the hemostatic response is quick, localized, and carefully regulated. When a person’s hemostatic response is in proper working condition, thrombin-stimulated fibrin clot formation starts the process to create a clot and stop the bleeding. Once the clot is formed, plasmin-induced clot lysis breaks down the clot and begins the process of tissue remodeling. Abnormal bleeding may be caused by diminished thrombin production or elevated clot lysis.

The clotting cascade is characterized by a sequential activation of a series of either proenzymes or inactive precursor proteins to activate enzymes, resulting in a stepwise response (See Figure 3.1). The clotting cascade consists of two separate pathways; one is intrinsic while the other is extrinsic. The intrinsic pathway is activated
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The clotting cascade is characterized by a sequential activation of a series of either proenzymes or inactive precursor proteins to activate enzymes, resulting in a stepwise response (See Figure 3.1). The clotting cascade consists of two separate pathways; one is intrinsic while the other is extrinsic. The intrinsic pathway is activated through exposure of blood, whereas the extrinsic pathway is activated when tissue factor is exposed at the site of an injury or tissue-like material.
Figure 2.1. Mechanism of action of anticoagulants apixaban, dabigatran, rivaroxaban, and warfarin in the clotting cascade.

a = activated; AT = antithrombin III; FV - FXIII = factor V – factor XIII; LMWH = low-molecular-weight heparin; TF = tissue factor


2.3.2 Antiplatelets

2.3.2.1 Mechanism of Action

Antiplatelet agents act primarily to alter the function of blood platelets, which are fragments of cells. When the skin is broken, for example by a cut or a scrape, platelets release the chemical thromboxane. Thromboxane signals other platelets to release thromboxane to form a clot and eventually stop the bleeding. Without the release of thromboxane, other platelets near the injured area will not receive information about the injury and no clot will form, causing the injured skin to continue bleeding. In a healthy individual, thromboxane is a self-healing material. In an individual
susceptible to stroke prophylaxis, thromboxane’s role in signaling other platelets to form a blood clot is potentially life threatening.

The most common antiplatelet agents most often used for stroke prophylaxis include aspirin, clopidogrel, dipyridamole, and cilostazole. Antiplatelets inhibit the production of thromboxane, which reduces the risk of stroke in people with history of stroke incidence or those people who have been identified to have other risk factors for stroke. Antiplatelet therapy is not recommended for people with a history of liver disease, kidney disease, gastrointestinal disease, peptic ulcers, high blood pressure, bleeding disorders, and asthma.

2.3.2.2 Stroke Prevention

Aspirin has been shown to moderately reduce the risk of stroke in individuals with AF (Fuster et al., 2006). Trials have shown the efficacy of aspirin in stroke prevention is less consistent than that of oral anticoagulation, however differences in patient characteristics may have affected the efficacy of aspirin (Fuster et al., 2006). Aspirin has been more successfully demonstrating prevention in non-disabling strokes compared with disabling strokes (Fuster et al., 2006). Moreover, aspirin has less protective properties in preventing cardioembolic stroke in high-risk individuals with AF (Fuster et al., 2006).

Hart and colleagues performed a meta-analysis to evaluate the efficacy and safety of antithrombotic therapies used for stroke prevention in patients with AF (R. G. Hart, Pearce, & Aguilar, 2007). In total, the meta-analysis included 29 published studies of
29,044 patients. These studies consisted of un-confounded, randomized trials that examined the long-term efficacy (≥ 12 weeks) of antithrombotic therapies in patients with NVAF. Authors identified eight randomized antiplatelet agent trials with a total of 4,876 patients. Compared to a control, antiplatelet agents showed a 22 percent (95% CI, 6%-35%) reduction in stroke (R. G. Hart, Pearce, & Aguilar, 2007).

2.3.3 Anticoagulants

2.3.3.1 Mechanism of Action

The mechanism of action for anticoagulants differs from antiplatelets in that they target clotting factors essential to the blood-clotting process. Clotting factors are proteins made in the liver and rely on vitamin K for production. Vitamin K is commonly found in cabbage, cauliflower, spinach, and other leafy green vegetables. A class of anticoagulant regularly used for stroke prevention in patients with AF is the vitamin K antagonist (VKA). Warfarin is commonly used VKA anticoagulant. Anticoagulants tend to have a more expansive pathophysiology and a higher risk of side effects. Side effects include bruising and skin rash, as well as bleeding in the brain, stomach, and intestines. In addition to potential side effects, anticoagulants tend to have adverse interactions other drugs, vitamins, and certain foods. In comparison to antiplatelet agents, anticoagulants are more potent drugs compared to antiplatelets and are recommended primarily for people with atrial fibrillation or people at high risk for stroke. Properties of an ideal anticoagulant include: orally active agent providing ease of administration; rapid onset of action, obviating the need for
overlap with a parenteral anticoagulant; no food or drug interactions; predictable anticoagulant effect, eliminating the need for routine coagulation monitoring; safe antidote available in case of a major bleed; favorable net clinical benefit; wide therapeutic window; and good bioavailability (K. A. Bauer, 2006).

Clinicians will monitor patients receiving warfarin-type anticoagulants to gauge the susceptibility of clotting. Blood tests are standard monitoring methods where the tendency of blood clotting in a warfarin-treated patient is compared to a normal standard. These blood tests are known as prothrombin time determinations. Prothrombin time determinant results are reported in the following ways: in time (14 seconds); in a ratio of the patient’s prothrombin time to local controls in the lab; or as a ratio determined in relation to the international standardized ratio (INR). An INR of 2.5 (target range between 2.0 and 3.0) is recommended for primary stroke prevention in patients with AF under 75 years old as well as for secondary prevention (Fuster et al., 2006). An acceptable target range of 2.0 (target range between 1.6 and 2.5) is a plausible for primary prevention of stroke in patients older than 75 years at a high risk for bleeding events (Fuster et al., 2006).

2.3.3.2 Stroke Prevention

Studies have been conducted to evaluate the preventative properties of anticoagulation and antiplatelets in patients diagnosed with AF at risk for stroke prophylaxis. Studies performed have focused on individual therapies compared to
placebo, as well as comparative effects of antiplatelets in relation to anticoagulants. In a meta-analysis conducted by Hart and colleagues previously described, the authors identified six trials with a total of 2,900 patients that compared adjusted-dose warfarin with a control and found the anticoagulant therapy had a relative risk reduction (RRR) for stroke prophylaxis of 64 percent (95% CI, 49%-74%) (R. G. Hart, Pearce, & Aguilar, 2007). In the randomized trials, 29 percent of the patients were female, 20 percent had a history of previous stroke or TIA, and the patients enrolled experienced 186 strokes during a mean follow-up time of 1.6 years per patient. When only risk reduction for IS was examined, adjusted-dose warfarin was associated with a 67 percent (95% CI, 54%-77%) RRR. The absolute risk reduction (ARR) for primary prevention of all strokes was 2.7 percent per year (number needed to treat [NNT], 37 patients) and 8.4 percent per year (NNT, 12) for secondary stroke prevention. Compared to no antithrombotic therapy, adjusted-dose warfarin reduced stroke by an estimated 60 percent and reduced mortality by approximately 25 percent in patients with AF.

2.3.3.3 Warfarin

Warfarin is the standard of care for stroke prevention in patients with AF. Warfarin therapy requires ongoing monitoring and dose adjustment; regular INR tests are conducted to ensure the patient is receiving the correct dosage. An insufficient dosage places the patient at a higher risk for stroke or heart attack, whereas an overdose of warfarin may cause excessive bleeding. Multiple food and drug interactions, along with warfarin’s narrow therapeutic index necessitate frequent
coagulation monitoring. Although VKAs are the standard of care of anticoagulation in patients with NVAF, their use is limited due to their narrow therapeutic window, inter-individual differences/variability in dose response, and numerous drug-drug interactions. Titration of warfarin is essential to its efficacy; however, evidence suggests patients spend about a third of the time outside of the ideal therapeutic window (Jones et al., 2005). Therefore, there is a perception that new anticoagulants are needed because current anticoagulant treatment is suboptimal.

Because of the previously described issues with warfarin, the goal of antithrombotic research has been to identify a selective anticoagulant with a safety/risk profile superior to other similar or improved efficacy therapies (Lopes, Piccini, Hylek, Granger, & Alexander, 2008). The search for an ideal anticoagulant has focused on developing an anticoagulant agent that requires no routine therapeutic monitoring, has a broad therapeutic window with low inter- and intra-patient variability, can be used simultaneously with a parenteral anticoagulant for both acute and chronic thromboembolism in the hospital, has minimal risk of adverse events, and is easily reversible with or without an antidote (Wittkowsky, 2010).

2.3.4 Direct Thrombin Inhibitors

Development efforts to create a warfarin alternative have focused on direct thrombin inhibitors and factor Xa inhibitors. Thrombin plays a central role in procoagulant and antifibrinolytic pathways as well as stimulation of negative systems to maintain hemostasis, qualifying it as a logical target for anticoagulation therapies (J.
The first developed direct thrombin inhibitor to move into clinical trials was ximelagatran. It was found to be efficacious in reducing stroke prophylaxis, however it had significant hepatotoxicity side effects and was not approved by the U.S. Food and Drug Administration (FDA) (Boos & Lip, 2006).

2.3.4.1 Dabigatran Clinical Trials

Randomized clinical trials for the thrombin inhibitor dabigatran have been conducted for patients with deep vein thrombosis, AF, venous thrombosis, post myocardial infarction, and post acute coronary syndrome. The study acronyms and meanings are the following: RE-NOVATE; RE-MODEL; RE-MOBILIZE; Randomized Evaluation of Long-term anticoagulation Therapy (RE-LY); Prevention of Embolic and Thrombotic events in patients with persistent atrial fibrillation (PETRO); RE-SONATE; RE-COVER; and RandomizEd Dabigatran Etexilate Dose Finding Study in Patients With Acute Coronary Syndromes Post Index Event With Additional Risk Factors for Cardiovascular Complications Also Receiving Aspirin and Clopidogrel (REDEEM) (ClinicalTrials.gov, 2012b; B. I. Eriksson et al., 2007; B. Eriksson et al., 2007; M. D. Ezekowitz et al., 2009; Oldgren, Budaj, & Granger, 2009; RE-MOBILIZE Writing Committee et al., 2009; S. Schulman et al., 2009). RE-LY was a randomized trial designed to compare two doses of dabigatran with an open-label use of warfarin in patients with NVAF and at least one additional risk factor for stroke (RW.ERROR - Unable to find reference:199; S. J. Connolly et al., 2009). In total 18,113 patients were enrolled in the study between December 22, 2005 and December 15, 2007. Patients were
eligible for study inclusion if they had atrial fibrillation documented on electrocardiography performed during the screening or 6 months prior and had at least one of the following characteristics: previous stroke or transient ischemic attack; left ventricular ejection fraction of less than 40 percent; New York Heart Association class II or higher heart-failure symptoms within six months of the screening; aged 75 years or greater; or an age between 65 and 74 years plus diabetes mellitus, hypertension, or coronary artery disease. Patients were randomized to receive one of two doses of dabigatran (N = 12,091) or warfarin (N = 6022). Dabigatran was administered in a blinded fashion using capsules containing either 110 mg or 150 mg (N = 6015 & N = 6076, respectively) twice daily. Warfarin was administered in an un-blinded fashion in tablets of 1, 3, or 5 mg. Doses were adjusted locally to an INR (target range between 2.0 to 3.0, with measurements taken at least once a month. Characteristics of RE-LY patients receiving dabigatran (150 mg, twice daily) or dose-adjusted warfarin are listed in Table 3.1.

The primary efficacy outcome in the study was stroke or systemic embolism. Rates of stroke or systemic embolism each year was 1.69 percent in patients receiving warfarin, 1.53 percent in patients receiving 110 mg of dabigatran, and 1.11 percent in patients receiving 150 mg of dabigatran. With respect to stroke or systemic embolism, both doses of dabigatran were found to be noninferior to warfarin (p < 0.001 for noninferiority). Furthermore, the 150 mg dose of dabigatran was found to be superior to warfarin (RR: 0.66; 95% CI: 0.53, 0.82; p < 0.001), whereas dabigatran 110 mg was not (RR: 0.91; 95% CI: 0.74, 1.11; p=0.34). The primary safety outcome measured was
major bleeding. Rates of hemorrhagic stroke for patients receiving warfarin was 0.38% per year, compared to the 0.12 percent (RR: 0.31; 95% CI: 0.17, 0.56; p < 0.001) yearly rate in the dabigatran 110 mg patient group and 0.10 percent (RR: 0.26; 95% CI: 0.14, 0.49; p < 0.001) yearly rate in the dabigatran 150 mg group. The rate of major bleeding was 3.36 percent per year in the warfarin patient group. In comparison to the warfarin group, patients receiving dabigatran 110 mg had a rate of major bleeding 2.71 percent (RR: 0.80; 95% CI: 0.69, 0.93; p = 0.003) per year and patients receiving 150 mg had a rate of 3.11% (RR: 0.93; 95% CI: 0.81, 1.07; p = 0.31) per year.

In conclusion, the RE-LY trial compared two doses of dabigatran, 110 mg and 150 mg, with warfarin in patients with atrial fibrillation. As compared to warfarin, the 110 mg dose of dabigatran was associated with similar rates of stroke and systemic embolism and lower rates of major hemorrhage. In contrast, the 150 mg dose of dabigatran was associated with lower rates of stroke and systemic embolism and similar rates of major hemorrhage when compared to warfarin.

PETRO was a second clinical trial evaluating the effects of dabigatran in patients with atrial fibrillation (M. D. Ezekowitz et al., 2007). The study’s primary objective was to identify a safe dose of dabigatran in patients with atrial fibrillation as determined by the occurrence of bleeding and clinical events. A total of 502 patients from 53 centers in Denmark, the Netherlands, Sweden, and the US were randomized to receive dabigatran does of 50, 150, or 300 mg or warfarin alone (N = 105, 166, 161, & 70, respectively). Patients receiving dabigatran were also randomized to receive either no aspirin, or to concomitantly receive aspirin doses of 85 or 325 mg. The trial was double blind with
respect to dabigatran dose, but open-label for concomitant aspirin and randomization between warfarin and dabigatran groups. Warfarin was adjusted to meet achieve a target INR between two and three.

The frequency of all bleeding events was significantly lower in the patient group receiving 50 mg of dabigatran (N = 7) in comparison to patients receiving warfarin (N = 12) (p = 0.044). When patient groups receiving dabigatran were compared to one another, irrespective of aspirin allocation, patients receiving 50 mg of dabigatran had a significantly lower number of total bleeding events (N = 7) compared to the number of bleeding events observed in patients receiving either 150 or 300 mg of dabigatran (N = 37 & 30, respectively) (p = 0.0002 & p = 0.01, respectively). Only two patients in the study presented systemic thromboembolic events; both patients received a combination of dabigatran 50 mg and aspirin (one patient received 85 mg aspirin and the other received 325 mg).

In conclusion, the frequency of thromboembolic events was too low for the authors to draw a conclusion regarding efficacy of dabigatran, however it is noted that both events occurred in the dabigatran patient group administered a dose of 50 mg. The majority of clinical bleeding events were observed in higher dabigatran doses, 150 and 300 mg (N = 37 and 30, respectively); thromboembolic events were seen in the patients receiving the lowest dose of dabigatran, 50 mg (N = 2, 2%).
Table 2.1. Baseline patient characteristics of clinical trials RE-LY for dabigatran, ROCKET-AF for rivaroxaban, and ARISTOTLE for apixaban.

<table>
<thead>
<tr>
<th></th>
<th>RE-LY</th>
<th>ROCKET-AF</th>
<th>ARISTOTLE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dabigatran (150 mg, twice daily)</td>
<td>Warfarin (N = 6022)</td>
<td>Rivaroxaban (20 mg, once daily)</td>
</tr>
<tr>
<td>Age</td>
<td>71.5 (8.8) 1</td>
<td>71.6 (8.6) 1</td>
<td>73 (65-78) 2</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>3840 (63.2)</td>
<td>4300 (60.3)</td>
<td>4301 (60.3)</td>
</tr>
<tr>
<td>Prior stroke, TIA, or systemic embolism, n (%)</td>
<td>1233 (20.3) 3</td>
<td>3916 (54.9) 3</td>
<td>3895 (54.6)</td>
</tr>
<tr>
<td>Prior MI, n (%)</td>
<td>1029 (16.9)</td>
<td>1182 (16.6)</td>
<td>1286 (18.0)</td>
</tr>
<tr>
<td>HF, n (%)</td>
<td>1934 (31.8)</td>
<td>1922 (31.9)</td>
<td>4467 (62.6)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>1402 (23.1)</td>
<td>1410 (23.4)</td>
<td>2878 (40.4)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>4795 (78.9)</td>
<td>4750 (78.9)</td>
<td>6436 (90.3)</td>
</tr>
<tr>
<td>CHADS2 score, n (%)</td>
<td>≤ 1</td>
<td>1958 (32.2)</td>
<td>1859 (30.9)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2137 (35.2)</td>
<td>2230 (37.0)</td>
</tr>
<tr>
<td></td>
<td>≥ 3</td>
<td>1981 (32.6)</td>
<td>1933 (32.1)</td>
</tr>
<tr>
<td>Vitamin K antagonist, n (%)</td>
<td>3049 (50.2)</td>
<td>2929 (48.6)</td>
<td>4443 (62.3)</td>
</tr>
</tbody>
</table>
Table 2.1 (Continued). Baseline patient characteristics of clinical trials RE-LY for dabigatran, ROCKET-AF for rivaroxaban, and ARISTOTLE for apixaban.

<table>
<thead>
<tr>
<th></th>
<th>RE-LY</th>
<th>ROCKET-AF</th>
<th>ARISTOTLE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dabigatran (150 mg, twice daily) (N = 6076)</td>
<td>Warfarin (N = 6022)</td>
<td>Rivaroxaban (20 mg, once daily) (N = 7131)</td>
</tr>
<tr>
<td>Renal function, CrCl, n (%)</td>
<td>NR</td>
<td>NR</td>
<td>67 (52-88)</td>
</tr>
<tr>
<td>CrCl, median (IQR)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Normal, &gt;80 mL/min</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Mild impairment, &gt;50 to 80 mL/min</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Moderate impairment, &gt;30 to 50 mL/min</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Severe impairment, ≤30 mL/min</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

TIA = transient ischemic attack; MI = myocardial infarction; HF = heart failure; CrCl = creatinine clearance; IQR = interquartile range; NR = not reported.

$^1$ Mean (standard deviation); $^2$ Median (IQR); $^3$ Prior TIA or stroke only; $^4$ HF or reduced left ventricular ejection fraction; $^5$ Hypertension requiring treatment.
2.3.5 Factor Xa Inhibitors

In addition to direct thrombin inhibitors, there has been a considerable amount of effort directed towards factor Xa inhibitor development. Factor Xa is an attractive target because it is a common branch node for extrinsic and intrinsic coagulation pathways. Factor Xa’s location higher upstream in the clotting cascade may result in a greater antithrombotic effect downstream and may also reserve parts of un-neutralized thrombin to facilitate other aspects of coagulation as well as inflammation (Ansell, 2007). Idraparinux was one of the first factor Xa inhibitors to be tested for indication in patients with nonvalvular AF, however the clinical trial, Amadeus, was stopped early due to excessive bleeding in the cohort of patients randomly assigned to idraparinux (Bousser et al., ). Other factor Xa inhibitors that have undergone evaluation in clinical trials are apixaban and rivaroxaban.

2.3.5.1 Apixaban Clinical Trials

The clinical trials of apixaban have been conducted for the following clinical conditions: deep vein thrombosis prophylaxis, acute coronary syndrome, atrial fibrillation, and venous thrombosis. The trial acronyms and meanings are the following: Apixaban Dosed orally Versus Anticoagulation with iNjeCtable Enoxaparin (ADVANCE); Apixaban Dosing to Optimize Protection for Thrombosis (ADOPT); Apixaban PROphylaxis in Patients undergoing tOtal knee replacement Surgery (APROPOS); Apixaban for Prevention of Acute Ischemic Safety Events (APPRAISE); Apixaban Versus acEtysalicyclic acid to pRevent strOkES (AVERROES); Apixaban for
Reduction In STroke and Other ThromboemboLic Events in atrial fibrillation (ARISTOTLE); Apixaban after the initial Management of Pulmonary embolism and deep vein thrombosis In First line therapY (AMPLIFY) (Alexander et al., 2009; ClinicalTrials.gov, 2012a; J. W. Eikelboom et al., 2010; Goldhaber et al., 2011; C. B. Granger et al., 2011; M. R. Lassen et al., 2009; M. Lassen et al., 2007). The two trials addressing the effects of apixaban in patients with atrial fibrillation were AVERROES and ARISTOTLE (J. W. Eikelboom et al., 2010; C. B. Granger et al., 2011). The purpose of the AVERROES trial was to evaluate the efficacy and safety of apixaban in patients with atrial fibrillation for whom vitamin K antagonist therapy is considered unsuitable (J. W. Eikelboom et al., 2010). The study was conducted in 522 centers in 36 countries and included a total of 5,599 patients. Patient enrollment started on September 10, 2007 and was completed on December 23, 2009. Patients were eligible for inclusion if they were aged 50 years or older and had documentation of atrial fibrillation 6 months prior to study enrollment or a 12-lead electrocardiography diagnosed atrial fibrillation on the day of screening. In addition to confirmed atrial fibrillation, patients were required to have at least one of the following risk factors for stroke: prior stroke or transient ischemic attack, an age of 75 years or older, arterial hypertension (receiving treatment), diabetes mellitus (receiving treatment), heart failure, a left ventricular ejection fraction of 35 percent or less, or documented peripheral artery disease. At time of the screening, patients were required to not be taking vitamin K antagonist (VKA) therapy either because it was previously determined VKA therapy was unsuitable for them or it was predicted VKA therapy was unsuitable. Patients were randomly assigned to receive
apixaban at a dose of 5 mg twice daily (N = 2,808) or aspirin at a dose of 81 to 324 mg per day (N = 2,791). This study provided no comparison between apixaban and warfarin. The primary composite endpoint of stroke and systemic embolism occurred in 3.9 percent per year in aspirin-treated patients compared to 1.7 percent per year in patients receiving apixaban. In patients who fail or refuse VKA therapy aspirin was shown to be an inferior therapy (p<0.001) for stroke prevention and was not safer in terms of hemorrhage or ICH (Ahrens, Lip, & Peter, 2011). This study provided information on the efficacy of apixaban versus aspirin, however this study was excluded as the aim of this study is to compare new anticoagulant therapies with warfarin.

The objective of the ARISTOTLE trial was to compare apixaban with warfarin for the prevention of stroke or systemic embolism in patients with atrial fibrillation and at least one risk factor for stroke (C. B. Granger et al., 2011). The study included 18,201 patients from 1034 clinical sites in 39 countries. Patients were recruited from December 19, 2006 through April 2, 2010. Patients were eligible for inclusion if they had atrial fibrillation or atrial flutter at enrollment or two or more episodes of atrial fibrillation or flutter documented with electrocardiography two weeks apart at least 12 months before enrollment. In addition to atrial fibrillation or atrial flutter, patients were required to have at least one of the following risk factors for stroke: age of at least 75 years; previous stroke, transient ischemic attack, or systemic embolism; systematic heart failure within the previous two months or left ventricular fraction of no more than 40 percent; diabetes mellitus; or hypertension requiring pharmacologic treatment. Randomization was stratified based upon clinical site and whether the patient had previously received
warfarin. Patients were randomized to receive either 2.5 or 5 mg of apixaban (N = 9088) or 2 mg tablets of warfarin (N = 9052). Patients were randomized to a lower dosage of apixaban (2.5 mg) if their age was at least 80 years, a body weight of no more than 60 kg, or serum creatinine level of 1.5 mg/dl or more. Warfarin doses were adjusted to achieve a target INR between 2.0 and 3.0. Characteristics of ARISTOTLE patients receiving either apixaban (5 mg, once daily) or dose-adjusted warfarin are listed in Table 4.1.

For the primary efficacy outcome, stroke or systemic embolism, the rate of occurrence was 1.27 percent per year (N = 212) in the apixaban group as compared to 1.60% per year (N = 265) in the warfarin group (HR: 0.79; 95% CI: 0.66, 0.95; p < 0.001 for noninferiority and p = 0.01 for superiority). The rate of hemorrhagic stroke was 49% lower in the apixaban group compared to the warfarin group. Patients receiving apixaban also experienced an eight percent lower rate of ischemic or uncertain type of stroke than patients in the warfarin group. The rates of ischemic or uncertain stroke were similar in the apixaban and warfarin groups (p = 0.42). With respect to the primary safety outcome major bleeding, patients in the apixaban group had a bleeding rate of 2.13% per year (N = 327) and the warfarin group had a rate of 3.09 percent per year (N = 462) (HR: 0.69; 95% CI: 0.60, 0.80; p < 0.001).

In conclusion, apixaban was superior to warfarin in preventing stroke or systemic embolism in patients with atrial fibrillation. Apixaban significantly reduced the risk of stroke or systemic embolism by 21 percent and lowered major bleeding by 31 percent (p = 0.01 & p < 0.001, respectively). Apixaban also significantly reduced the all-cause mortality rate by 11 percent (p = 0.047).
2.3.5.2 Rivaroxaban Clinical Trials

The clinical trials assessing the effects of rivaroxaban have been conducted for deep vein thrombosis prophylaxis and in patients with acute coronary syndrome, venous thrombosis, atrial fibrillation, and pulmonary embolism. The clinical trial acronyms and meanings are the following: REgulation of Coagulation in major Orthopedic surgery reducing the Risk of DVT and PE (RECORD); Oral DIrect FactorXa inhibitor BAY 59-7939 in the prevention of VTE in patients undergoing total HIP replacement (ODIXa-HIP); Oral DIrect FactorXa inhibitor BAY 59-7939 in the prevention of VTE in patients undergoing total KNEE replacement (ODIXa-KNEE); Anti-Xa Therapy to Lower cardiovascular events in addiction to aspirin with/without thienopyridine therapy in subjects with Acute coronary Syndrome (ATLAS ACS TIMI); Evaluating oral, direct Factor Xa inhibitor rivaroxaban in patients with acute symptomatic deep vein thrombosis or pulmonary embolism (EINSTEIN); Rivaroxaban Once daily oral direct Factor Xa inhibition Compared with vitamin K antagonist for the prevention of stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) (H. R. Buller et al., 2008; B. I. Eriksson, Borris et al., 2006; B. I. Eriksson et al., 2006; Mega et al., 2009; Patel et al., 2011; Turpie et al., 2005). ROCKET-AF was a randomized trial designed to compare the efficacy of rivaroxaban with dose-adjusted warfarin for the prevention of thromboembolic events in patients with atrial fibrillation (Patel et al., 2011). Patient enrollment started in December 2006 and randomization was completed in June 2009. Patients were eligible for enrollment if they electrographically documented NVAF and were at moderate to high risk for stroke. Indicators of increased stroke risk included
history of stroke, TIA, or systemic embolism. Patients were also considered to have an elevated risk of stroke if they had at least two of the following risk factors: heart failure or left ventricular ejection fraction of 35 percent or less; hypertension; aged 75 years or older; or diabetes mellitus. Characteristics of ROCKET-AF patients receiving either rivaroxaban (20 mg, once daily) or dose-adjusted warfarin are listed in Table 3.1.

Following enrollment, patients were classified into subgroups based upon renal impairment. Patients with moderate renal insufficiency were defined as those with a creatinine clearance (CrCl) values between 30 and 49 mL per minute. Patients with a CrCl of 50 or more were considered to have normal renal functionality. Of the 14,264 total patients enrolled in the ROCKET-AF study, 11,277 had a CrCl of 50 mL per minute or greater. Patients were randomly assigned to receive a fixed dose of rivaroxaban (20 mg) (N = 5637) or adjusted-dose warfarin with a target INR range of 2.0 to 3.0 (N = 5640).

The primary efficacy endpoint was the composite of all strokes, both hemorrhagic and ischemic, and systemic embolism. The primary safety outcome assessed was major and non-major clinically relevant bleeding events. An efficacy analysis conducted to assess all patients, regardless of renal function, for the combined outcome of stroke and systemic embolism showed lower event rates in patients receiving rivaroxaban, 15 or 20 mg, (N = 188, 1.71% per year) than in patients with warfarin (N = 241, 2.16% per year) (HR: 0.79; 95% CI: 0.66, 0.96; p < 0.001 for non-inferiority). Event rates for the primary efficacy outcome observed in patients receiving rivaroxaban and warfarin were reported for each stroke type separately (ischemic, hemorrhagic, and undetermined). There were
1.44 per 100 patient-years of follow-up with ischemic stroke in the 20 mg rivaroxaban group and 1.46 per 100 patient-years of follow-up in the warfarin group (HR: 0.99; 95% CI: 0.78, 1.24; p = 0.89); there were 0.25 per 100 patient-years of follow-up with hemorrhagic stroke in the rivaroxaban group and 0.44 per 100 patient-years of follow-up in patients receiving warfarin (HR: 0.58; 95% CI: 0.36, 0.94); and there were 0.14 per 100 patient-years of follow-up with undetermined stroke in patients receiving rivaroxaban compared to 0.13 per 100 patient-years of follow-up in the warfarin patient group (HR: 1.08; 95% CI: 0.51, 2.29; p = 0.92). An efficacy analysis conducted to assess all patients, regardless of renal function, for the combined outcome of stroke and systemic embolism showed lower event rates in patients receiving rivaroxaban, 15 or 20 mg, (N = 188, 1.71% per year) than in patients with warfarin (N = 241, 2.16% per year) (HR: 0.79; 95% CI: 0.66, 0.96; p < 0.001 for non-inferiority). Rates of stroke and systemic embolism for patients with CrCl > 50 mL/min were lower, regardless of treatment than for patients with moderate renal dysfunction (CrCl 39 tp49 mL/min). Subsequent analyses to assess the efficacy outcomes for subgroups of renal patients were not reported.

In regards to major bleeding, patients receiving 20 mg of rivaroxaban had an event rate of 3.39 per 100 patient-years of follow-up, and similarly warfarin patients had an event rate of 3.17 per 100 patient-years of follow-up. In conclusion, patients randomized to receive 20 mg of rivaroxaban had similar stroke (p > 0.05 for stroke – ischemic, hemorrhagic, or undefined) and bleeding events (HR: 1.07; 95% CI: 0.91, 1.26; p = 0.48) compared to patients receiving warfarin.
2.3.6 Risk Factors and Therapy Recommendations

There are low, moderate, and high risk factors for risk of stroke. Risk factors associated with a high risk of stroke (stroke rate > 5% per year) include previous stroke, TIA, systemic embolism, mitral stenosis, and presence of prosthetic heart valve. Moderate risk factors (stroke rate 3-5% per year) are age >=75, hypertension, heart failure (HF), and diabetes. Less validated, weaker risk factors include female sex, aged 65-74 years, coronary artery disease, and thyrotoxicosis.

Risk factors are elements that form the CHADS<sub>2</sub> score. The CHADS<sub>2</sub> scoring mechanism is a simplified algorithm of high and moderate risk factors for stroke. Scores range from 0 to 6, are relatively easy to use in clinical practice, and are a reasonable estimation of stroke risk in patients with AF (Lopes, Piccini, Hylek, Granger, & Alexander, 2008). A description of risk factors and associated recommended antithrombotic therapy according to risk factors and CHADS<sub>2</sub> scores are listed in Table 3.2.

The CHADS<sub>2</sub> score is the most validated risk assessment for stroke, tested in at least ten separate cohorts after its initial development (You et al., 2012). In spite of the wide use and acceptance of the CHADS<sub>2</sub> risk score, there are a few limitations to its applicability (You et al., 2012). First, although congestive heart failure is listed as an indicator of stroke risk in the CHADS<sub>2</sub> scoring mechanism, studies have not consistently found condition to be associated with stroke risk (Arima et al., 2005; Healey et al., 2008; G. Y. H. Lip, Frison, & Grind, 2007). Second, the relative history of hypertension in relation to stroke risk may contrast depending upon the
treatment management (i.e., poorly treated versus well treated hypertension) (Arima et al., 2005; Healey et al., 2008; G. Y. H. Lip, Frison, & Grind, 2007). Third, most studies assessing the applicability of the CHADS\(_2\) score found that the scoring mechanism only had modest predictability of stroke in patients with AF (C statistic, 0.56-0.70) (You et al., 2012). Last, the threshold of stroke risk may decrease with the emergence of new anticoagulants that do not require stringent monitoring of INR values and that also show greater reductions in stroke prophylaxis and a decrease in bleeding events compared to dose-adjusted VKA therapy (Eckman, Singer, Rosand, & Greenberg, 2011).
The American College of Chest Physicians (ACCP) used estimates of absolute non-fatal stroke rates (both ischemic and hemorrhagic) for patients according to their underlying risk of stroke (i.e., CHADS<sub>2</sub> risk scheme) as well as pooled data from clinical trials of antithrombotic therapy for stroke prevention in AF to develop their therapy guideline recommendations (Gage et al., 2004; You et al., 2012). The ACC guideline

<table>
<thead>
<tr>
<th>Stroke Risk Category</th>
<th>CHADS&lt;sub&gt;2&lt;/sub&gt; Score</th>
<th>ACCP Guideline, 8th Edition&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Recommended First-line Therapy</th>
<th>Recommended Alternative Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0</td>
<td>No risk factors</td>
<td>No antithrombotic therapy</td>
<td>Aspirin (75 mg to 325 mg once daily) if therapy is desired</td>
</tr>
<tr>
<td>Intermediate</td>
<td>1-2</td>
<td>Age &gt;75 years, or hypertension, or moderately or severely impaired LVEF and/or heart failure, or diabetes</td>
<td>No therapy or aspirin and clopidogrel combination therapy</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>3-6</td>
<td>Previous stroke, TIA or embolism, or ≥2 moderate risk factors (age ≥75 years, or hypertension, or moderately or severely impaired LVEF and/or heart failure, or diabetes)</td>
<td>Dabigatran 150 mg twice daily</td>
<td>Aspirin and clopidogrel combination if anticoagulation is inappropriate for reasons other than major bleeding,</td>
</tr>
</tbody>
</table>

CHADS<sub>2</sub> = congestive heart failure, hypertension, age > 75 years, diabetes, prior stroke or transient ischemic attack; ACCP = American College of Chest Physicians; LVEF = left ventricular ejection fraction; TIA = transient ischemic attack

recommendations for antithrombotic therapy in patients with AF are stratified based upon the patient’s risk for stroke prophylaxis: low-risk, intermediate-risk, or high-risk (You et al., 2012). Antithrombotic therapy, including both antiplatelets and anticoagulants, should be given to all patients with AF, with the exception of those patients with lone AF (<60 years without heart disease or risk factors for stroke) or known contraindications (i.e. bleeding). Therapy selection should use the same risk factor criteria regardless of the type of AF (paroxysmal, persistent, or permanent).

For patients with a low risk of stroke (e.g., CHADS₂ score = 0: congestive HF, hypertension, age ≥75, diabetes mellitus, prior stroke or TIA), ACC suggests no therapy rather than antithrombotic therapy. For patients who do choose antithrombotic therapy, it is suggested that aspirin (75 to 325 mg once daily), the ACCP recommends no therapy rather than antithrombotic treatment. For patients electing to receive antithrombotic therapy, the ACCP suggests aspirin (75 to 325 mg once daily) should be prescribed in preference to oral anticoagulation or aspirin and clopidogrel combination therapy.

For patients with an intermediate risk for stroke (e.g., CHADS₂ score = 1), the ACCP advises oral anticoagulation should aspirin and clopidogrel combination therapy. It is estimated that compared to no therapy, one year of VKA therapy will result in 15 fewer deaths and 15 fewer non-fatal strokes for every 1,000 patients with a tradeoff of eight additional non-fatal extracranial bleeding events. Furthermore, in comparison to aspirin, one year of VKA therapy is expected to prevent nine non-fatal strokes for every 1,000 patients treated at a cost of three additional bleeds and no reduction in all-cause mortality. Noteworthy are other determinants that may influence the clinician’s decision
of a particular antithrombotic therapy, including the consideration of bleeding risk and
the presence of additional stroke risk factors (i.e., patients aged 65 to 74 years and
female gender). In addition to these factors, patients who place high value on stroke
reduction and low value on avoiding bleeding events and other burdens related to
receiving anticoagulation therapy are likely candidates for anticoagulation rather than
antiplatelet treatment.

For patients with a high risk for stroke prophylaxis (e.g., CHADS$_2$ score = 2), the
ACCP recommends oral anticoagulation therapy in preference to no therapy, aspirin, and
combination therapy with aspirin and clopidogrel. Moreover, for those patients with AF
who have met the stroke risk requirement for oral anticoagulation the ACCP recommends
dabigatran 150 mg twice daily in preference to adjusted-dose VKA therapy (target INR
range between 2.0 and 3.0). Those patients for whom anticoagulant therapy is
inappropriate, for reasons other than concern for risk of major bleeding, aspirin and
clopidogrel combination therapy is suggested rather than aspirin alone. Patients at a high
risk for stroke may anticipate large gain from one year of VKA therapy in comparison to
no therapy. Studies estimate 15 fewer deaths and 30 fewer non-fatal strokes at the
expense of 3 additional non-fatal major extracranial bleeds. Furthermore, one year of
VKA therapy is expected to prevent 11 strokes and have a range of risk for non-fatal
major extracranial bleeding events (between three fewer and four more) relative to
combination therapy of aspirin and clopidogrel.
2.3.7 Clinical Data: Anticoagulants versus Antiplatelets

Randomized trials with enrolled high-risk AF patients (stroke rates exceeding 6% each year) demonstrated a greater relative risk reduction with the use of adjusted-dose oral anticoagulation relative to aspirin. Furthermore, relative risk reductions were consistently lower in trials of patients with AF at a lower risk of stroke (Fuster et al., 2006). Hart and colleagues identified 12 randomized trials (12,963 participants) comparing anticoagulants and antiplatelet agents to include in their meta-analysis (R. G. Hart, Pearce, & Aguilar, 2007). Of the 12 trials, nine randomized trials (N = 3,647) compared anticoagulants (warfarin or other oral vitamin K antagonist) with various dosages of aspirin; three trials (N = 8,101) compared the anticoagulants with other antiplatelets; and two trials (N = 1,385) compared anticoagulants with aspirin combined with low, fixed (ineffective) dosages of warfarin.

The authors of the meta-analysis found adjusted dose warfarin was substantially more efficacious compared to antiplatelet therapy alone, with a relative risk reduction in stroke of 37 percent (95% CI, 22%-52%). When the authors added the two trials with aspirin combined with low-dose warfarin, they found antiplatelet agent yielded a 39 percent (95% CI, 22%-52%) relative risk reduction (RRR), whereas adjusted-dose warfarin yielded a 52 percent (95% CI, 41%-62%) RRR in IS prophylaxis among 12,963 participants. The study’s authors concluded that the results of the meta-analysis confirmed therapy recommendations of using adjusted-dose warfarin in patients with AF at a high risk for stroke and antiplatelet therapy for patients at a low-risk for stroke and those who are unable to safely receive warfarin (R. G. Hart, Pearce, & Aguilar, 2007).
2.4 Economic Burden

2.4.1 Stroke

Stroke represents a substantial financial burden on the healthcare system, as well as on patients, family, and society. The lifetime cost of ischemic stroke is estimated to be greater than $90,000 for an individual in 1990 (Taylor et al., 1996), whereas the American Heart Association estimated that in 2008, total national direct and indirect costs of stroke in the US exceeded $34 billion (Taylor et al., 1996). The mean expense per year for a patient with a stroke in 2007 in the US was estimated at $7,657. In a 15-year incidence based study conducted by Caro and colleagues, cost of illness for an individual with stroke was an estimated $104,629 (1996 USD extrapolated to 2003). Long-term costs of stroke were estimated to be $159,004 for stroke resulting in a major impairment, and $58,582 for a minor stroke (Caro & Huybrechts, 1999).

The estimated direct medical cost of stroke in 2008 was $18.8 billion. Direct costs included hospital outpatient or office-based provider visits, hospital inpatient stays, prescription medications, emergency department (ER) visits, and home healthcare (Taylor et al., 1996). The percentage of direct costs contributing to stroke burden has increased over the past two decades, from a reported 42 percent in 1990 to 67 percent of total costs in 2008 (Taylor et al., 1996).

A number of studies have assessed the cost of stroke stratified by a few different characteristics, including race and ethnicity, stroke subtype, and disease severity. The total cost of stroke from 2005 to 2050 is projected to be $1.52 trillion, $313 billion, and $379 billion for non-Hispanic whites (NHWs), Hispanics, and African Americans (AAs), respectively.
respectively (D. Brown et al., 2006). In this study the total per person cost of ischemic stroke was $15,597, $17,201, and $25,782 for NHWs, Hispanics, and AAs, respectively. The study also projected the aggregate cost of direct and indirect costs of ischemic strokes in NHWs, Hispanics, and AAs from 2005 through 2050 to exceed $2.2 trillion dollars, with the highest per capita contributors to be Hispanics and AAs.

To address the difference in cost of stroke subtype, Taylor and colleagues evaluated the cost separately for subarachnoid hemorrhage (SAH), ischemic hemorrhage (ISH), and IS (Taylor et al., 1996). The 1990 mean lifetime cost of stroke per patient was $228,030 for SAH, $123,565 for ICH, and $90,981 for IS. Averaged across all three stroke subtypes and all individuals included in the study, the estimated lifetime cost of stroke per person was $103,576. It was reported that the higher SAH cost was attributable to higher direct cost as well as an earlier mean age of stroke onset, resulting in the patient requiring a longer time needed for care and a greater lifetime accumulation of indirect costs. The aggregate economic burden associated with approximately 390,000 first strokes in 1990 was estimated at $40.6 billion. Classified by disease severity, SAH accounted for 13.7 percent ($5.6 billion), ICH for 14.8 percent ($6 billion), and IS for 71.5 percent ($29 billion).

Focusing on an older age group, Lee and colleagues examined the costs of stroke subtype for Medicare beneficiaries (≥ 65 years) (Lee, Christensen, Joshi, & Pashos, 2007). In the US, almost 75 percent of the stroke patients are Medicare beneficiaries, qualifying the national health insurance program as the most common payer of healthcare for stroke patients. The average (standard deviation [SD]) reimbursement rate for the
index hospital stay for patients with SAH was $18,612 ($25,554), $10,552 ($16,258) for patients with ICH, and $6,190 ($6,189) for patients with IS. The total aggregated costs were $60,177 for SAH, $50,015 for ICH, and $49,996 for IS. The direct medical costs included in their assessment were inpatient hospital stays, outpatient care, rehabilitation, physician consultations, skilled nursing facility care, and home health care. As Medicare was not responsible for outpatient prescription costs at the time of the study, these were not included in the analysis.

Medicare coverage is available to patients who meet one of the following requirements: 1) aged 65 years or older, 2) aged under 65 with certain disabilities, or 3) people of any age with end-stage renal disease. Medicare offers multiple coverage options to patients based on financial necessity and the ability of the patient to privately finance additional services. Coverage options include the Original Medicare, Medicare Advantage Plans, Medicare Supplement Insurance (Medigap) policy, or a combination of Medicare and Medicaid for those patients who are dual eligible (Centers for Medicare and Medicaid Services, 2012).

Medicare is separated into multiple parts for different areas of healthcare coverage. Medicare Part A services include blood, home health services (i.e., medically-necessary services), hospice care, inpatient hospital care, and skilled nursing facility care. Services covered under Medicare Part B coverage include medically necessary services, such as doctors’ services, outpatient care, home health services, durable medical equipment, other medical services, and many preventative services. Services covered under these two coverage plans require the patient to pay a percentage of the Medicare-
approved amount (i.e., the amount a doctor or supplier that accepts assignment may be
paid and may be less than the actual amount the doctor or supplier charges; Medicare
pays a percentage of this amount and the patient pays the remaining copay) and a
deductible amount that may apply. An important service not covered by Part A or Part B
relevant is long-term care. Long-term care is defined as services that help people with
their medical and non-medical needs over a period of time, otherwise known as custodial
care. Medicare Part D offers extra help paying for prescription drug coverage; however,
patients are still responsible for paying a portion. Patients must meet a monthly income
quota (single or married/living together) in order to qualify for additional assistance.

When assessing the economic burden of disease, some studies considered the
short-term and long-term costs when estimating the lifetime cost of stroke. In an
evaluation of the cost burden in the US associated with IS, Demaerschalk and colleagues
conducted a literature review and found that the majority of the literature addressing
stroke-related costs focused on short-term, in-hospital (Demaerschalk, Hwang, & Leung,
2010). The short-term, in-hospitalization expenditures resulted in costs ranging from
$8,000 to $23,000, dependent upon the length of the hospital stay (Demaerschalk,
Hwang, & Leung, 2010). In the literature review, major short-term expenses were
distributed as follows: 19 percent for medical-surgical short-term care services, 19
percent for radiology, eight percent for rehabilitation therapies, seven percent for
pharmacy, and seven percent for laboratory work. These results were similar to those
reported by Diringer and colleagues, wherein 50 percent of the hospital costs for acute
ischemic stroke were attributed to room charges (34 percent for ward beds & 16 percent
Stroke is associated with high prevalence, hospitalization rates, morbidity and mortality, as well as high incidence of long-term costs associated with post-stroke care and recurrent episodes for survivors. Due to the socioeconomic burden stroke imposes, it is of interest to determine the component(s) of care contributing the most to the cost of stroke. In a study evaluating the overview of costs from incidence-based studies in 16 industrialized countries, Palmer and colleagues concluded there was no clear pattern of major cost drivers identified from cost studies set in Western Europe, North America, and Australia (A. J. Palmer et al., 2005). Variations in cost estimates may be due to healthcare differences in the country, time of the study, cost components included in the analysis, and variations in the distributions of stroke type and patient characteristics, such as age and gender (Payne, Huybrechts, Caro, Craig Green, & Klittich, 2002). Published data suggests that suggest that age (costs were greater in younger stroke patients), stroke severity (more severe strokes were associated with higher costs due to prolonged hospital stays and ongoing disability), and gender (only using direct costs resulted in women having higher stroke costs, whereas the addition on indirect costs resulted in males having higher costs) may influence the cost of stroke (D. Brown et al., 2006; A. J. Palmer et al., 2009).
et al., 2005). In the US study, estimates ranged from $27,000 to $475,000 (1990 values) for patients aged 85 and 25, respectively (Taylor et al., 1996). Patients with severe strokes, classified with a National Institutes of Health (NIH) Stroke Scale score greater than 20, cost twice as much as mild stroke, despite similar diagnostic testing (Diringer et al., 1999). Mean per-person lifetime stroke costs were found to vary substantially by age and gender, such as patients with the greatest costs associated with men who had a stroke in their mid-twenties (Taylor et al., 1996).

2.4.2 Atrial Fibrillation

AF and its associated risk for stroke development contribute a substantial economic burden due to high hospitalization rates and significant utilization of other health care resources (Sanoski, 2009). The economic burden of illness associated with AF is attributable to various direct and indirect costs, including hospitalizations (52%), pharmaceuticals (23%), consultations (9%), further investigations (8%), lost productivity (6%), and paramedical procedures (2%) (Le Heuzey et al., 2004; Stewart, 2004). In 2001, AF in the US was attributable for approximately 350,000 hospitalizations, five million office visits, 276,000 emergency department (ED) visits, and 234,000 outpatient department visits (OPD) (Coyne et al., 2006). An analysis of 2001 data from three federal databases (the Healthcare Cost and Utilization Project database, the National Ambulatory Medical Care Survey database, and the National Hospital Ambulatory Medical Care Survey database) revealed the total annual direct medical costs for the treatment of AF in the inpatient, ED, and hospital outpatient settings in the US were
estimated at $6.65 billion (2005 USD). This estimate includes costs for all hospitalizations where AF was the principal discharge diagnosis ($2.93 billion), the incremental inpatient costs due to AF as a comorbid diagnosis (conservatively estimated at $1.95 billion), and costs for all ambulatory/outpatient treatment of AF ($1.76 billion) (Coyne et al., 2006). This estimation is an underestimate, as the authors did not account for the cost of stroke prevention treatments, inpatient drug costs, remaining encounters with AF as a comorbidity, and outpatient physician fees. Mean direct costs per patient have been found to be significantly higher for those patients with an AF-related stroke event (Brüggenjürgen et al., 2007). Moreover, when adjusted for confounders, direct costs were comparable between AF-related and non-AF-related strokes, however acute hospitalizations remained significantly higher (p < 0.001) in the group of patients with AF-related strokes.

Boccuzzi and colleagues conducted a retrospective, observational study with pharmacy and medical claims of a managed care organization (N = 18.5 million) to characterize the direct costs associated with the onset of chronic NVAF (CNVAF) (Boccuzzi et al., 2009). Costs were estimated relative to warfarin exposure. A 200 percent increase was observed for the total direct healthcare costs pre- and post-AF onset in patients with CNVAF ($412 and $1,235, respectively). Total cohort costs increased 24 percent from $3,446.91 to $4,262.12 per member per month. For those patients who experienced a TIA, IS, or major bleeding event post-AF onset, total healthcare costs increased on average 4.5 times relative to pre-AF costs (Boccuzzi et al., 2009).
2.5 Models

2.5.1 Decision Models

A clinical decision ‘model’ aims to represent the reality of a clinical situation in a simplified manner and, in the process, captures the clinical reality with respect to the fundamental properties and relationships (Stahl, 2008). A model produces an estimate for each possible course of action. The ‘optimal’ course of action is one that optimizes the objective of the model (ISPOR Task Force Working Group, 2012). When considering an optimal course of action, it is important to assess the robustness of the model inputs using evaluation methods, especially in situations where the model parameters vary. Evaluation of model parameters is essential, even when estimates are considered to be well known. Furthermore, if the model’s pathway(s) allows, the results of a model may be generalized to other settings or to another target population of interest.

There are a number of reasons why models and simulations may be suitable analyses for a particular system (Stahl, 2008). One reason to use a model or a simulation is when direct experimentation is not financially or realistically feasible. Direct experimentation requires substantial time and financial commitments that may not be available for the system of interest. Secondly, a simulation model provides an experimental environment in which analysts and policy makers have the flexibility to make mistakes and modify design error in the model rather than making a mistake in the actual system. The opportunity to modify within the model structure allows a developer to identify and eliminate problems that may have otherwise gone unnoticed until the time of system implementation. Identification of errors in a model contributes to the
development of solutions for operational inefficiencies in the system before implementation. Third, rare events may be an inherent characteristic of the system and may require a substantial amount of time to gather information. A simulation may be an alternative option to capture these events. Lastly, a model or simulation may also be used to aid in decision-making as it facilitates a more thorough understanding of the consequences of actions made under conditions of uncertainty. In addition to uncertainty, the outcomes and consequences of different strategies in the system may also be evaluated.

A decision analysis is an analytical technique used to incorporate information in a systematic fashion to compare different treatment or intervention options to select the optimal and/or most cost-effective option (Rascati, 2009). The primary purpose of a decision analysis is to provide information to decision-makers about treatment comparisons at a particular point in time (Sculpher, Fenwick, & Claxton, 2000). There are limited resources available in healthcare and it is, therefore, important to have comparison methods to choose the most appropriate treatment or intervention strategy for resource allocation. Furthermore, it is important to select the most cost-effective treatment or intervention to attain the greatest benefit for the resources invested (S. R. Earnshaw, Wilson, Mauskopf, & Joshi, 2009). Decision-makers should critically evaluate the model structure, probability and cost estimates, and assumptions made to determine if the model results are credible and useful for their intended purpose (Rascati, 2009).
During the model development stage, the analyst selects the structure of a decision model to best reflect the needs of the particular decision problem (RW.ERROR - Unable to find reference:235). The analyst must consider how the model should be specified to determine the appropriate level of complexity to capture the key issues necessary to fully delineate the risk-benefit tradeoff (Detsky, Naglie, Krahn, Naimark, & Redelmeier, 1997). The model structure is typically defined by the relationship between the input (i.e., natural history of disease, clinical pathways, evidence of interventions’ effectiveness, utilities associated with health states, intervention and other costs, etc.) and output measures relevant to the problem of the decision maker (RW.ERROR - Unable to find reference:235). Brennan and colleagues recommend selecting the most parsimonious model that addresses the study’s objectives, the structure of the disease, and the disease’s treatment process (RW.ERROR - Unable to find reference:235). The authors also recommend conceptualizing creative techniques to address interactions and uncertainty regarding the decision problem, as different modeling approaches will produce different results (RW.ERROR - Unable to find reference:235).

2.5.2 Model Outcome Considerations for Stroke

In the process of modeling stroke incidence, there are two types of considerations with respect to the outcome of treatment (S. R. Earnshaw, Wilson, Mauskopf, & Joshi, 2009). The first consideration involves the treatment and immediate recovery from the index stroke event. The second consideration is the long-term management post-stroke event. Treatment benefits and side effects for acute stroke prophylaxis may apply to the
remainder of a patient’s lifetime. Therefore, a model with a lifetime horizon timeline is most appropriate to evaluate the impact of acute stroke treatments on costs and outcomes (S. R. Earnshaw, Wilson, Mauskopf, & Joshi, 2009). It may, however, be beneficial to the decision-maker if the analyst presents both short-term and long-term outcomes to examine the short-term benefits of a treatment as well as the treatment’s long-term impact on the cost of care and a patient’s health status.

2.5.3 Uncertainty Sources and Analytic Methods

Multiple sources of uncertainty exist within the context of decision-analytic models, including parameter uncertainty, modeling/structural uncertainty, and methodological uncertainty (Jain, Grabner, & Onukwugha, 2011). Each model study should include an evaluation of uncertainty as it pertains to the decision problem of interest (ISPOR Task Force Working Group, 2012). Parameter uncertainty deals with the uncertainty surrounding the parameter input values included in the model (i.e., probability of disease progression or effectiveness of a treatment or intervention) (Jain, Grabner, & Onukwugha, 2011). Modeling/structural uncertainty is associated with the uncertainty about the correct functional form in which parameters modeling disease progression are combined (i.e., the number of health states included in the model) (Jain, Grabner, & Onukwugha, 2011). Methodological uncertainty involves the appropriate analytic models to use when evaluating treatments with a model structure (i.e., which discount rate is the most appropriate to use with costs and utilities) (Jain, Grabner, & Onukwugha, 2011). Methodological uncertainty also incorporates the following issues:
1) whether to include values of resources used due to unrelated illness encountered throughout a lifetime; 2) whether to include the value of income conceded due to illness; 3) whether to include the value of non-wage activities that may have intrinsic value for the patient but no market value; and 4) selection of suitable sources for health utilities and/or resource unit prices (Jain, Grabner, & Onukwugha, 2011).

There are multiple ways to address and report for the different types of uncertainty. The primary aim of uncertainty analyses is to assess the confidence in choosing a course of action and establish the value of collecting additional information to better inform the decision-maker (ISPOR Task Force Working Group, 2012). To address parameter uncertainty, the analyst may use deterministic and/or probabilistic sensitivity analyses (PSA). It is preferable for the analyst to include justification for the parameter values, ranges, and/or distributions selected when performing sensitivity analyses (Jain, Grabner, & Onukwugha, 2011). A deterministic sensitivity analysis (SA) involves varying one or multiple parameters over predetermined ranges. Results from a deterministic sensitivity analysis may be presented in a tornado diagram. A tornado diagram is a set of one-way SAs combined into a single graph, where the variable with the most impact on the analysis’ results is listed at the top and the rest of the variables ranked according to their impact below thereafter (creating a visual similar to the look of a tornado) (Koerkamp, Weinstein, Stijnen, Heijenbrok-Kal, & Hunink, 2010). Other techniques used for deterministic SAs include threshold analysis and best/worse-case analysis. In a threshold analysis, a value of a parameter (or in the case of a multi-way analysis, several parameters) that would be needed to change the decision from that based
on expected values is specified (ISPOR Task Force Working Group, 2012). A threshold analysis is used to determine whether the results of an analysis are consistent with a clinical or policy-relevant value (Jain, Grabner, & Onukwugha, 2011). Furthermore, a threshold analysis helps to determine the level within a specified range at which the decision changes (Rascati, 2009). One-way and multi-way SAs are useful as they illustrate the impact of a single or a few parameter(s) (probability, utility, or cost estimate) on the outcomes of the model. A limitation of the deterministic SA is that it does not permit the analyst to make a summary statement about the certainty that the strategy selected by the decision-maker is in fact optimal (Doubilet, Begg, Weinstein, Braun, & McNeil, 1985). Healthcare providers, such as physicians, often request this type of summary statement.

PSA techniques account for uncertainty associated with the parameters of the probability distribution of the outcomes (i.e., second order uncertainty) by varying multiple parameters simultaneously (Jain, Grabner, & Onukwugha, 2011). PSA provides a mechanism to quantify variation in a parameter with a specific probability distribution and evaluate the implication of joint variation in parameters through specified joint distributions (Ades, Claxton, & Sculpher, 2006). Therefore, when performing a PSA it is essential to consider dependency between parameters (Doubilet, Begg, Weinstein, Braun, & McNeil, 1985). The results of PSAs may be presented in the form of cloud diagrams or cost-effectiveness acceptability curves (CEACs) (A. H. Briggs, O'Brien, & Blackhouse, 2002).
Methods such as model averaging and parameterization may be used to address modeling or structural uncertainty in the decision model (Bojke, Claxton, Sculpher, & Palmer, 2009). Parameterizing uncertainty directly in the decision model provides information as to whether further research should be conducted in order to resolve the source of uncertainty. Model averaging consists of building alternative models with different structural assumptions corresponding to alternative sets of judgments and averaging the results from the models, which are weighted by some measure of their adequacy (Bojke, Claxton, Sculpher, & Palmer, 2009). Other methods used to assess structural uncertainty include assessment of health states, functional form of transition probabilities, repeat analyses with different assumptions, subgroup analysis, and stratification or multiple function forms (Bojke, Claxton, Sculpher, & Palmer, 2009).

Methodological uncertainty is concerned with the analytic methods applied in the decision model. Analytic methods include discount rates, definition of cost length of time horizon, and sources of utilities and unit costs (Jain, Grabner, & Onukwugha, 2011). It is possible to repeat an analysis with different analytic assumptions and compare the results. According to Jain and colleagues, “methodological uncertainty can be addressed in part by providing results for a ‘reference case’ in order to simplify the comparison between different evaluation methods and across studies” (Jain, Grabner, & Onukwugha, 2011).

An essential part of any decision analysis and economic evaluation is the validation of the defined model structure, assumptions made, data inputs, calculations, and results (S. R. Earnshaw, Wilson, Mauskopf, & Joshi, 2009). Mandelblatt and
colleagues have stated, “models are only as good as their ability to represent reality at the level needed to draw useful conclusions; this, in turn, depends on their structure and the assumptions that go into the model” (J. S. Mandelblatt, Fryback, Weinstein, Russell, & Gold, 1997). One way to validate a model is through expert review, which provides acceptance from an expert in the field who confirms the model does, in fact, represent the problem in question. A second way to validate a model is to check the consistency between the model’s results and those results that would be expected when treating the condition in the real world (S. R. Earnshaw, Wilson, Mauskopf, & Joshi, 2009). Results may be validated through comparison to clinical or database studies. In the absence of real data, researchers may consider comparisons to other similar models published in the literature.

2.5.4 Markov Model

For many diseases and conditions, more complex model outcomes and longer follow-up periods are required to be modeled. For these complex analyses, patients may transition between different states of health over a period of time. A Markov model is a more complex method for estimating life expectancy and it allows for a more accurate representation of complex disease scenarios that occur over a number of cycles or intervals (Rascati, 2009; Sonnenberg & Beck, 1993). In addition, a Markov analysis provides a method of adding a time component to the conventional decision analysis. Therefore, Markov models are useful when a decision problem involves risk that is
continuous over time, when the time of the events is relevant, and when modeled events may occur more than once (Sonnenberg & Beck, 1993).

There are multiple steps in specifying a Markov model. First, the health states that represent the possible outcomes for each intervention must be specified. As an assumption of the Markov model, it is assumed that a patient is always in one of a finite number of states of health, referred to as Markov states (Sonnenberg & Beck, 1993). Second, the potential transitions between the health states must be determined. All events of interest are modeled as transitions from one health state to the next (Sonnenberg & Beck, 1993). Third, the analyst must specify the time horizon of the model, including how long each Markov cycle will last and how many cycles will be included in the analysis. The time horizon of the Markov model analysis is divided into equal increments of time, which are referred to as Markov cycles. The length of each cycle depends upon the time frame of the model as well as the rate of risk for patients with the disease of interest (Sonnenberg & Beck, 1993). Fourth, the probabilities associated with transitioning between states must be specified. The transitions from each health state may be held at a constant transition probability over time, as specified in a Markov chain analysis, or the transition probabilities may fluctuate depending upon the cycle, which is known as a Markov process analysis (A. Briggs & Sculpher, 1998). Last, the costs and outcomes (i.e., utilities) associated with each health state, and in some cases with the transitions between states of health, must be estimated. Utility and cost estimates accrue for the entire time horizon of the Markov process and the total number of cycles a person spends in each health state are summed (Sonnenberg & Beck, 1993). The contribution of
the cost and utility parameter estimates assigned to each health state and accrued in the overall prognosis will depend upon the length of time each patient spends in the state (Sonnenberg & Beck, 1993).

There are a couple of noteworthy advantages of Markov models for handling ongoing risk of events (Sonnenberg & Beck, 1993). First, Markov models are capable of handling events with uncertain timing. This has important significance because the utility of an outcome is often dependent upon the timing of the event. Furthermore, in an economic analysis both costs and utilities are discounted to reflect the greater impact of events happening earlier in a person’s life compared to those events occurring later. A second advantage of using a Markov model is the possibility for a single event to occur more than once. The ability for a Markov model to handle repetitive events is advantageous compared to a simple decision tree model, where it is difficult to portray uncertain timing of events.

An important limitation of the Markov model is known as the Markovian assumption or Markov property, where it is assumed that the probability of moving between states or within a single state is not dependent upon previous health states a patient may have experienced (Sonnenberg & Beck, 1993). More specifically, the Markov model has no memory for previous health states, referred to as a ‘memoryless’ property. This assumption is essential to allow for modeling a particular prognosis with a finite amount of health states.
2.5.5 Monte Carlo Simulation

According to Stahl, a simulation model provides a method to describe, evaluate, explore, predict, and persuade with respect to a system (Stahl, 2008). The simulation process describes the system under study and allows the analyst to evaluate the consequences of a given strategy or a set of strategies. Furthermore, the model allows flexibility for the suggestion of new theories as well as the identification of gaps in knowledge. Once fully constructed, the model’s predictive characteristic provides information about the system’s future as well as a forecast of the behavior of the system. Last, a model is capable of persuading decision-makers through consensus building and evidence.

One type of simulation approach is the Monte Carlo method, which may be used in tandem with the Markov model to determine the estimated outcomes for a large number of individual patients (Sonnenberg & Beck, 1993). A Monte Carlo simulation uses stochastic analytic methods to allow for uncertainty or variability at the patient level; this is also referred to as first-order uncertainty (A. H. Briggs, 2000). For each Monte Carlo simulation process, patients propagate through the model individually and at the end of each cycle, a random number generator is used to determine which state the patient will transition to next (Sonnenberg & Beck, 1993). The Monte Carlo simulation process is repeated a large number of times (on the order of $10^4$ or greater) and the mean and standard deviation over all runs of the expected utility values for each strategy are recorded (Doubilet, Begg, Weinstein, Braun, & McNeil, 1985; Sonnenberg & Beck, 1993). In addition, the results of a Monte Carlo simulation yield the distribution of
survival values and the frequency with which each treatment or intervention strategy is optimal (Doubilet, Begg, Weinstein, Braun, & McNeil, 1985).

2.5.6 Cost-Effectiveness Analysis

A cost-effectiveness analysis (CEA) approach may be conducted as an extension of a Monte Carlo simulation Markov model. CEAs are an approach to measure relative value for money in health care as well as aid in making decisions about allocation of limited health care resources (M. Gold, Siegel, Russell, & Weinstein, 1996). The primary purpose of a CEA is to describe and compare the effectiveness and costs of the course of events for a treatment or intervention as compared to the expected costs and outcomes of an accepted comparator treatment for a specified treatment or intervention (M. Gold, Siegel, Russell, & Weinstein, 1996). The incremental CEA ratio compares the net costs and net effectiveness of two discrete interventions to demonstrate the cost of achieving an additional unit of health effect (M. Gold, Siegel, Russell, & Weinstein, 1996; L. B. Russell et al., 1996). From this ratio, an incremental cost-effectiveness comparison may be made between the alternative intervention strategy and the standard comparator. CEA is a useful method for a decision-maker with limited financial resources who is considering a limited range of treatment options within a given field (Drummond MF, Sculpher MJ, Torrance GW, 2005).

The methodology of a CEA serves to identify interventions that provide the most health and beneficial outcomes for the health care resources available (L. B. Russell et al., 1996). Methodological considerations for model design include: viewpoint, cost
categories (which are dependent upon the viewpoint), effectiveness measure, medical
evidence source, and parameters requiring a sensitivity analysis (Drummond MF,
Sculpher MJ, Torrance GW, 2005). The viewpoint of the study may include one or more
of the following parties: individual patient, specific institution, target group for the
specific services, third-party payer (i.e., an insurance company), and/or societal
perspective (i.e., community) (Drummond MF, Sculpher MJ, Torrance GW, 2005). The
perspective of the analysis impacts the numerator of the cost-effectiveness ratio and,
ultimately, defines the final ratio value. The societal perspective is the most
representative of public interest. This perspective is compatible with the notion that
decisions affecting people with different interests are more likely to be fair if made by
those individuals who do not stand to lose or gain from the decision (L. B. Russell et al.,
1996). Gold and colleagues recommend the framework of a CEA analysis to include a
range of individuals affected by the intervention as well as all types of costs and health
outcomes (M. Gold, Siegel, Russell, & Weinstein, 1996).

In the US, CEA are used to determine the effectiveness of treatments, as this is a
federal requirement for pharmaceutical products. Increased market entry prices and more
costly innovative drugs combined with more stringent healthcare budgets provide a need
for CEAs (M. Gold, Siegel, Russell, & Weinstein, 1996). Insurance companies and
management care organizations regulating patient drug formularies also use CEAs to
value drug effectiveness before purchasing. Outside of the US, CEAs for pharmaceutical
products are driven by the government’s requirements or price regulation (M. Gold,
Siegell, Russell, & Weinstein, 1996). Regardless of which stakeholder party initiates the
requirement for a CEA, a CEA should demonstrate both the cost-effectiveness ratio as well as background information regarding the components that make up costs and effects to allow decision-makers to evaluate trade-offs carefully. Cost and effect components include kinds and magnitudes of costs, individuals who benefit or who are harmed, and to what extent the individual is affected (L. B. Russell et al., 1996).

2.5.7 Cost-Utility Analysis

A cost-utility analysis (CUA) is a form of economic evaluation that uses quality of life gained or lost as an outcome measure to assess the effectiveness of a treatment or intervention in relation to a standard reference comparator (Drummond MF, Sculpher MJ, Torrance GW, 2005). A CUA has many similarities to a CEA with respect to their measurement of cost, however they differ in the way outcomes are elicited and reported. A CEA uses program-specific outcomes with no associated value, such as cases of disease avoided and life-years gained. In contrast, the outcomes used in a CUA incorporate the notion of value and are more generic, such as quality-adjusted life-years (QALYs) and disability-adjusted life-years (DALYs) (Drummond MF, Sculpher MJ, Torrance GW, 2005).

In a CUA, quality of life measures are assigned a preference weight for each health state, time spent in each health state is determined, and subsequent estimates of life expectancy are calculated as the sum of the products of each preference weight and time spent in a given health state (Szucs & Bramkamp, 2006). CUAs are particularly useful and applicable for decision-making processes because generic outcome measures allow
the results of one study to be compared to studies evaluating other health care activities (e.g., screening for hypertension) as well as non-health care programs (e.g., transportation safety) (Szucs & Bramkamp, 2006). The diverse nature of the results from a CUA qualify the evaluation useful to assist society in determining if a particular intervention is worth the cost investment, as well as help in assisting the prioritization of intervention and treatment options.

### 2.6 Cost-Effectiveness Analyses

#### 2.6.1 Anticoagulation versus No Therapy or Aspirin

Studies assessing the cost-effectiveness of anticoagulation therapy are driven by the amount of risk reduction attained rather than possible benefits estimated from the clinical trials (Szucs & Bramkamp, 2006). A number of studies have been performed to evaluate the cost-effectiveness of anticoagulation therapy in patients with AF in relation to no therapy or aspirin (Desbiens, 2002; Eckman, Levine, & Pauker, 1992; Eckman, Levine, Salem, & Pauker, 1998; Gage, Cardinalli, Albers, & Owens, 1995; Gage, Cardinalli, & Owens, 1998). Overall these studies demonstrated that, in most cases, VKA therapy compared to no therapy was associated with either a low-cost-per-QALY gained or was deemed a superior therapy (i.e., reduced cost and increased QALY outcome). These results were especially true in patients with a moderate-to-high risk of stroke (Szucs & Bramkamp, 2006).

A study conducted by Gage and colleagues, for example, found in patients with NVAF, VKA therapy dominated compared to no antithrombotic therapy for patients at
high risk of stroke prophylaxis (saves $2,800 and adds 0.5 QALYs) and patients at moderate risk (saves $500 and adds 0.37 QALYs) (1994 values). A cost-effectiveness ratio of $14,000 per QALY was found for patients at low risk for stroke (Gage, Cardinalli, Albers, & Owens, 1995). Study findings demonstrated the cost-effectiveness of warfarin treatment (vs. no therapy or aspirin) in patients with AF at a moderate to high risk of stroke, which parallels current clinical guideline recommendations (Szucs & Bramkamp, 2006; You et al., 2012). However, the management strategies necessary to maintain optimal INR levels with warfarin therapy (i.e., because of genetic diversity in drug metabolism; drug, food, and alcohol interactions; concomitant disease, changes in lifestyle, and compliance problems) may render anticoagulation therapy less cost-effective in a real-world practice setting (Szucs & Bramkamp, 2006).

2.6.2 Dabigatran versus Warfarin

This section reviews the six Markov models and one discrete event simulation (DES) comparing the cost-effectiveness of dabigatran to warfarin. The primary objective of the RE-LY trial was to compare the use of dabigatran, at doses of 110 mg twice daily and 150 mg twice daily, with warfarin in patients with atrial fibrillation to study the prevention of stroke or systemic embolism (S. J. Connolly et al., 2009). Since the publication of the results in 2009, seven cost-effectiveness models conducted in three different countries have been published (Freeman et al., 2011; Kamel, Johnston, Easton, & Kim, 2012; Kansal et al., 2012; Langkilde, Bergholdt Asmussen, & Overgaard, 2012; Pink, Lane, Pirmohamed, & Hughes, 2011; S. V. Shah & Gage, 2011; Sorensen et al.,
Three studies concentrated on the cost-effectiveness of the new therapy in the US (Freeman et al., 2011; Kamel, Johnston, Easton, & Kim, 2012; S. V. Shah & Gage, 2011), two focused on the impact of therapies in the UK (Kansal et al., 2012; Pink, Lane, Pirmohamed, & Hughes, 2011), one in Denmark (Langkilde, Bergholdt Asmussen, & Overgaard, 2012), and one in Canada (Sorensen et al., 2009). The Markov states, time frame, Markov cycle length, and SA approach for the six Markov models are delineated in Table 3.3. Study details, such as treatment comparisons and baseline ICER values, for all seven cost-effectiveness studies are summarized in Table 3.4 and Table 3.5.
Table 2.3. Summary of decision analysis models with Markov processes for stroke prevention using dabigatran (110 mg and/or 150 mg twice daily) or warfarin in patients with atrial fibrillation.

<table>
<thead>
<tr>
<th>Author (Publication Year)</th>
<th>Markov States</th>
<th>Time Frame</th>
<th>Markov Cycle Length</th>
<th>Sensitivity Analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kamel et al (2012)</td>
<td>1. No disability&lt;br&gt;2. IS&lt;br&gt;3. ICH</td>
<td>4. Recurrent or combined stroke and/or ICH&lt;br&gt;5. Death</td>
<td>20 years or until death</td>
<td>One month&lt;br&gt;1-way SA &amp; PSA</td>
</tr>
</tbody>
</table>
Table 2.3. (Continued). Summary of decision analysis models with Markov processes for stroke prevention using dabigatran (110 mg and/or 150 mg twice daily) or warfarin in patients with atrial fibrillation.

<table>
<thead>
<tr>
<th>Author (Publication Year)</th>
<th>Markov States</th>
<th>Time Frame</th>
<th>Markov Cycle Length</th>
<th>Sensitivity Analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorensen et al* (2011)</td>
<td>1. Unchanged 7. ICH excluding HS</td>
<td>Lifetime</td>
<td>Three months</td>
<td>1-way SA &amp; PSA</td>
</tr>
<tr>
<td></td>
<td>2. Primary IS 8. HS</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>3. Recurrent IS 9. Major ECH</td>
<td></td>
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<tr>
<td></td>
<td>4. TIA 10. Minor bleeding</td>
<td></td>
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<tr>
<td></td>
<td>5. SE 11. Death</td>
<td></td>
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<tr>
<td></td>
<td>6. Acute MI * 4 additional states</td>
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</table>

QALY = quality-adjusted life-year; BID = twice a day; NVAF = nonvalvular atrial fibrillation; RIND = reversible ischemic neurological event; ICH = intracranial hemorrhage; MI = myocardial infarction; NR = not reported; SA = sensitivity analysis; PSA = probabilistic sensitivity analysis; IS = ischemic event; TIA = transient ischemic attack; SE = systemic embolism; HS = hemorrhagic stroke; ECH = extracranial hemorrhage

* Note: This was a semi-Markov model with 11 primary health states and four additional states representing temporary therapy discontinuation.
Table 2.4. Summary of cost-effectiveness analyses conducted in the United States comparing dabigatran (110 mg and/or 150 mg twice daily) with warfarin in patients with atrial fibrillation.

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Perspective</td>
<td>Societal</td>
<td>Societal</td>
<td>Third party payer</td>
</tr>
<tr>
<td>Baseline population</td>
<td>Aged ≥ 65 years; NVAF; stroke risk factors (CHADS$_2$ ≥ 1 or similar); &amp; no anticoagulant contraindications</td>
<td>Aged ≥70 years; NVAF; prior stroke or TIA; &amp; no anticoagulant contraindications</td>
<td>70 years old; AF; moderate stroke risk; &amp; no anticoagulant contraindications</td>
</tr>
<tr>
<td>Treatment comparisons</td>
<td>1. DBG 110 mg</td>
<td>1. DBG 150 mg</td>
<td>1. No therapy</td>
</tr>
<tr>
<td></td>
<td>2. DBG 150 mg</td>
<td>2. Warfarin</td>
<td>2. Aspirin</td>
</tr>
<tr>
<td></td>
<td>3. Warfarin</td>
<td></td>
<td>3. Aspirin &amp; clopidogrel</td>
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<td></td>
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<td></td>
<td>4. DBG 110 mg</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>5. DBG 150 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6. Warfarin</td>
</tr>
<tr>
<td>Year &amp; Currency</td>
<td>2008 USD</td>
<td>2010 USD</td>
<td>2012 USD</td>
</tr>
<tr>
<td>DBG cost per day (range)</td>
<td>DBG 110 mg = $9.50 (6-13)</td>
<td>DBG 150 mg = $6.75 (5-30)</td>
<td>DBG 110 mg &amp; DBG 150 mg = $8.90 (7-11)</td>
</tr>
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<td></td>
<td>DBG 150 mg = $13.00 (8-19)</td>
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<tr>
<td>Base case ICER</td>
<td>DBG 110 mg* = $51,229/QALY; DBG 150 mg* = $45,372/QALY; *vs. Warfarin</td>
<td>DBG 150 mg vs. Warfarin = $25,000/QALY</td>
<td>DBG 110 mg* = $150,000/QALY; DBG 150 mg* = $86,000/QALY; *vs. Warfarin$^a$</td>
</tr>
</tbody>
</table>
Table 2.4 (Continued). Summary of cost-effectiveness analyses conducted in the United States comparing dabigatran (110 mg and/or 150 mg twice daily) with warfarin in patients with atrial fibrillation.

<table>
<thead>
<tr>
<th>Author (Publication Year)</th>
<th>Markov Models</th>
<th>Shah &amp; Gage (2011)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study conclusion</td>
<td>DBG may be a cost-effective alternative for the study population relative to warfarin depending upon pricing in the US.</td>
<td>DBG 150 mg appears to be cost-effective relative to warfarin, however results may not apply with good INR control using warfarin.</td>
</tr>
</tbody>
</table>

AF = atrial fibrillation; CHADS<sub>2</sub> = congestive heart failure, hypertension, age ≥ 75, diabetes mellitus, previous stroke or transient ischemic attack; DBG = dabigatran etexilate (twice daily); ICER = incremental cost-effectiveness ratio; INR = international normalized ratio; NVAF = nonvalvular atrial fibrillation; TIA = transient ischemic attack; USD = United States dollar; WTP = willingness-to-pay; *The focus of this paper is dabigatran versus warfarin and ICER values for other treatments may be found in the original study.*
<table>
<thead>
<tr>
<th>Author (Publication Year)</th>
<th>Markov Models</th>
<th>Discrete Event Simulation</th>
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</thead>
<tbody>
<tr>
<td>Country</td>
<td></td>
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<tr>
<td>United Kingdom</td>
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<td>NR</td>
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<tr>
<td>NR</td>
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<tr>
<td>Matched RE-LY patients</td>
<td></td>
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</tr>
<tr>
<td>Matched RE-LY trial patients (mean age 71 years; AF; CHADS₂ ≥ 1 or LVF &lt; 40%)</td>
<td>Matched RE-LY trial patients (mean age 71 years; AF; CHADS₂ ≥ 1 or LVF &lt; 40%)</td>
<td>Matched RE-LY trial patients (mean age 71 years; AF; CHADS₂ ≥ 1 or LVF &lt; 40%)</td>
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<tr>
<td>Treatment comparisons</td>
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<td>1. DBG 110 mg</td>
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<td>2. DBG 150 mg</td>
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<td>5. Aspirin c</td>
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<td>Year &amp; Currency</td>
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<tr>
<td>2010 GBP</td>
<td>2012 CAD</td>
<td>2011 Euros</td>
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<tr>
<td>DBG cost per day (range)</td>
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<td>2009 GBP</td>
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<tr>
<td>2010 GBP</td>
<td>2012 CAD</td>
<td>2011 Euros</td>
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<tr>
<td>DBG 110 mg &amp; DBG 150 mg = £2.52 (NR)</td>
<td>DBG 110 mg &amp; DBG 150 mg = $3.20 (NR)</td>
<td>Dabigatran = €2.60</td>
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</tbody>
</table>

Table 2.5. Summary of cost-effectiveness analyses conducted in the United Kingdom, Canada, and Denmark comparing dabigatran (110 mg and 150 mg twice daily) with warfarin in patients with atrial fibrillation.
Table 2.5. (Continued). Summary of cost-effectiveness analyses conducted in the United Kingdom, Canada, and Denmark comparing dabigatran (110 mg and 150 mg twice daily) with warfarin in patients with atrial fibrillation.

<table>
<thead>
<tr>
<th>Author (Publication Year)</th>
<th>Markov Models</th>
<th>Discrete Event Simulation</th>
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<tbody>
<tr>
<td><strong>Base case ICER</strong></td>
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<tr>
<td>DBG 110 mg* = 7,090/QALY;</td>
<td>DBG 110 mg* =</td>
<td>DBG vs. Warfarin =</td>
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<tr>
<td>DBG 150 mg* = £4,831/QALY;</td>
<td>$29,994/QALY;</td>
<td>€6,950/QALY</td>
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<tr>
<td>Sequential DBG dosing* =</td>
<td>DBG 150 mg* =</td>
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<td>£3,457/QALY</td>
<td>$9,041/QALY;</td>
<td>*vs. Warfarin</td>
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<td>*vs. Warfarin</td>
<td>$10,440/QALY;</td>
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<td><strong>Study conclusion</strong></td>
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<tr>
<td>DBG is a cost-effective</td>
<td>Dabigatran is</td>
<td>Dabigatran is a cost-</td>
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<td>first-line treatment</td>
<td>highly</td>
<td>effective relative to</td>
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<td>with a WTP threshold of</td>
<td>cost-effective</td>
<td>warfarin from a Danish</td>
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<td>£20,000.</td>
<td>alternative to</td>
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<td>with AF.</td>
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</table>

AF = atrial fibrillation; CAD = Canadian dollar; CHADS$_2$ = congestive heart failure, hypertension, age ≥ 75, diabetes mellitus, previous stroke or transient ischemic attack; DBG = dabigatran etexilate (twice daily); GBP = Great Britain pound; ICER = incremental cost-effectiveness ratio; INR = international normalized ratio; NR = not reported; NVAF = nonvalvular atrial fibrillation; RE-LY = Randomized Evaluation of Long-Term Anticoagulation Therapy; TIA = transient ischemic attack; WTP = willingness-to-pay.

*Sequential DBG (dabigatran etexilate) dosing: Age < 80 yr = Dabigatran 150 mg; age ≥ 80 = Dabigatran 110 mg

*It is not clear which doses of dabigatran were used, however authors constructed their model using Sorensen 2011 study

*Aspirin and no treatment were included as treatment options in the case of anticoagulation discontinuation
2.6.2.1 Freeman and colleagues, 2011

Freeman and colleagues used a Markov model to evaluate the cost-effectiveness of three treatment strategies: dabigatran 110 mg (twice daily), dabigatran 150 mg (twice daily), and adjusted-dose warfarin (target INR between 2.0 and 3.0) (Freeman et al., 2011). The authors used a hypothetical cohort of patients aged 65 years and older with AF who were at an increased risk for stroke and had no previously documented contraindication to anticoagulants. Nine Markov health sites were modeled, with a period of 35 years or until the patient died (see Table 3.3). The model was structured from the perspective of an ideal insurer (i.e., third party payer) that covered inpatient, outpatient, and prescription costs, but did not include payment for direct costs (e.g., wages).

Authors applied utilities and costs to each outcome in two-week increments, the shortest cycle of all the published Markov models. Utility values were estimated in a variety of ways: author estimation; reference to other published CEAs; or selected from previously published studies that assessed quality of life measures in the AF population (Fryback et al., 1993; Gage, Cardinalli, & Owens, 1996; C. L. O’Brien & Gage, 2005; Sullivan & Ghushchyan, 2006; Thomson, Parkin, Eccles, Sudlow, & Robinson, 2000). Warfarin therapy and 14 INR management visit costs were derived from the Center for Medicare and Medicaid Services (CMS) using the associated Current Procedural Code (CPT, 99363). In a sensitivity assessment, authors allowed patients to receive CMS reimbursement for up to eight additional INR tests for anticoagulation initiation for 90 days. As dabigatran was not yet on the U.S. market at the time of the article’s
publication, authors used the price set in the UK National Health Service (NHS) and historical cost ratios for on-patent cardiovascular medications to set a price for dabigatran (see Table 3.5) (Pharmacy Checker, ). Cost of patient care visits scheduled at one and three months, every three months for the first year, and every four months for the remainder of the model duration were included. An annual discount rate of three percent was applied to both utilities and costs (no reference provided). Model creation and analyses were performed using TreeAge Pro Suite 2009 and Microsoft Excel version 2007.

Authors ran multiple sensitivity analyses to assess the impact of each individual variable, combinations of variables, and probabilistic sampling from distributions of event rates or probabilities, utilities, and costs. One-way sensitivity analyses were performed for each variable over plausible ranges. A two-way sensitivity analysis was conducted to evaluate the cost-effectiveness of dabigatran over combinations of stroke and ICH risk. First-order Monte Carlo simulations varying every model parameter simultaneously were run 10,000 times. Two different willingness-to-pay (WTP) thresholds were used to evaluate the result of the PSA ($50,000 per QALY and $100,000 per QALY).

Freeman and colleagues reported the ICER between dabigatran 150 mg and warfarin was $45,372 per QALY, whereas the ICER for dabigatran 110 mg was $51,229 per QALY (see Table 3.4). Using the WTP threshold of $50,000 per QALY, dabigatran 150 mg was favored for the base case as well as for patients with a higher risk for both IS and ICH. Dabigatran 110 mg was the preferred therapy for patients with a low absolute
risk for IS, especially if the individual had a relatively high concurrent risk for ICH. Dabigatran 150 mg twice daily was found to be cost-effective 53 percent of the time using the $50,000 per QALY WTP threshold, and 68 percent of the simulations for a WTP threshold of $100,000 per QALY. Dabigatran 110 mg twice daily was cost-effective in fewer of the simulations for both $50,000 per QALY and $100,000 per QALY WTP thresholds (30% and 26% of the simulations, respectively). Both doses of dabigatran were preferred over warfarin in more than 80 percent of the simulations using a WTP threshold of $50,000 per QALY and in more than 95 percent of the simulations using a WTP threshold of $100,000 per QALY.

Freeman and colleagues found the results of their study were robust over a range of variable values, but was most sensitive to the cost of dabigatran. In their study, the ICER of dabigatran 110 mg compared with warfarin exceeded $50,000 per QALY when dabigatran was priced greater than $9.36 per day. The ICER of dabigatran 150 mg compared with warfarin exceeded the WTP threshold of $50,000 per QALY when the price of dabigatran was greater than $13.70 per day. When the other model variables were varied over plausible ranges, the ICER for dabigatran 150 mg compared with warfarin varied by less than $15,000 per QALY and retained an ICER of less than $85,000 per QALY.

2.6.2.2 Kamel and colleagues, 2012

Kamel and colleagues assess the cost-effectiveness of two treatment strategies, adjusted-dose warfarin (target INR between 2.0 and 3.0) and dabigatran 150 mg (twice
daily), using a Markov model (Kamel, Johnston, Easton, & Kim, 2012). Authors modeled a hypothetical patient cohort of individuals aged 70 years or older with NVAF with a history prior stroke or TIA and no contraindication to anticoagulation. For a time horizon of 20 years or until death, the patient cohort was followed through five Markov health states (see Table 3.3). Additionally, a societal perspective was adopted for this model. All analyses were performed using TreeAge Pro Suite 2011.

Estimates for costs and utilities were obtained from CMS reimbursement data and studies similar to the RE-LY trial. The cost of dabigatran therapy was estimated using CMS CPT codes for 1) the wholesale cost of dabigatran and 2) regular office visits for monitoring (CPT code 99211) (see Table 3.3). The cost of warfarin therapy included CMS reimbursement for 90 days of anticoagulation monitoring (CPT code 99363) and 14 INR visits. The Agency of Healthcare Research and Quality (AHRQ) Health Cost and Utilization Project (HCUP) were used to estimate hospitalization costs for adverse events (Agency for Healthcare Research and Quality, 2009). Median values listed in published studies and Medicare reimbursement rates were used to estimate the cost of ongoing care related to adverse events (Agency for Healthcare Research and Quality, 2009; Holloway, Witter Jr, Lawton, Lipscomb, & Samsa, 1996; Kauf et al., 2006; Leibson et al., 1996; S. V. Shah & Gage, 2011). Authors chose to remain consistent with QALY estimates published in a previous CEA of ximelagatran for dabigatran since there are no quality of life studies currently available for dabigatran (Gage, Cardinalli, & Owens, 1996). All other utility estimates were obtained from the published medical literature (Freeman et al., 2011; Fryback et al., 1993; Sullivan & Ghushchyan, 2006; Young, Benesch, &
Jahromi, 2010). Costs and life-years were discounted at an annual rate of three percent (no reference provided).

Two types of sensitivity analyses were performed in this study, deterministic and probabilistic. One-way sensitivity analyses of all model inputs were varied over plausible ranges (based on CIs reported in RE-LY sub-study or other published studies) to determine influential model variables. First-order Monte Carlo simulations using 10,000 iterations were conducted for the PSA.

Kamel and colleagues found in the base case of the patient cohort 70 years and older with NVAF there was an incremental benefit of 0.36 QALYs for dabigatran 150 mg twice daily with an associated cost of $9,000, yielding an ICER value of $25,000 (see Table 3.3). Variables found to be influential in Kamel and colleagues’ model included monthly cost of combined or recurrent stroke and/or cerebral hemorrhage, starting age of the cohort, relative risk of stroke prophylaxis with dabigatran compared to warfarin, the cost of dabigatran, the average time in a therapeutic INR range for patients receiving warfarin, and the utility of mild ischemic stroke. When influential variables (e.g., monthly cost of combined or recurrent stroke and/or cerebral hemorrhage) were varied across plausible ranges, the ICER associated with dabigatran 150 mg relative to warfarin did not exceed $50,000 per QALY. Therefore, dabigatran was found to be cost-effective when using the chosen model inputs and a threshold value of $50,000/QALY.

Kamel and colleagues applied a threshold value of $50,000/QALY for a series of Monte Carlo simulations to evaluate the cost-effectiveness of dabigatran in a PSA and found dabigatran was a cost-effective therapy in 57 percent of the simulations. When the
WTP threshold value was increased to $100,000/QALY, dabigatran was deemed cost-effective in 78 percent of the Monte Carlo simulations. Although dabigatran 150 mg was cost-effective in a number of the analyses, the authors acknowledged the cost-effectiveness appeared to be dependent upon the adequacy of anticoagulation management clinics to help patients maintain an INR level in the acceptable therapeutic range (between 2.0 and 3.0).

2.6.2.3 Kansal and colleagues, 2012

Kansal and colleagues estimated the cost-effectiveness of dabigatran in relation to warfarin using a Markov model (Kansal et al., 2012). A hypothetical cohort of eligible patients with a mean age of 71, AF, and increased risk of stroke were modeled with a ‘sequential dabigatran dosing’ regime. Sequential dosing with dabigatran entailed patients receiving dabigatran 150 mg (twice daily) until the age of 80 and dabigatran 110 mg (twice daily) thereafter. Sequential dabigatran dosing is in line with the routine therapy practice for the UK (i.e., the study’s setting). Nine Markov states were specified with model duration up to 100 years (i.e., lifetime). Markov states differed from other models in that they were specified as a combination of stroke history and disability resulting from stroke prophylaxis (see Table 3.3). Any subsequent event (no event, IS, HS, ICH, ECH, systemic embolism, AMI, TIA, minor bleed, or death) could occur within each Markov cycle of three months and had the potential impact to alter a patient’s health state. A societal viewpoint was used as the model’s perspective.
Costs were calculated using the UK’s National Institute for Health and Clinical Excellence (NICE) clinical data resources and a UK stroke registry, whereas utilities were estimated using published literature studies. The average annual cost of warfarin INR monitoring was based on NICE-reported values. Acute and long-term management costs were based on NHS reference costs and a published UK stroke registry. NICE clinical guidelines were used to estimate costs for management of minor bleeds. Utility values were taken from published literature (Gage, Cardinalli, & Owens, 1996; Sullivan & Ghushchyan, 2006) and were summarized previously in an online appendix from another published CEA (Sorensen et al., 2011). See Table 3.5 for dabigatran costs. An annual discount rate of 3.5 percent was applied to future costs and outcomes (no reference provided). The model was implemented using Microsoft Excel (version year not provided).

Deterministic and probabilistic sensitivity analyses were performed to compare sequential dabigatran dosing with warfarin. Deterministic sensitivity analyses varying all parameter values individually were used to identify key determinants of cost-effectiveness. PSAs (5,000 simulations ran) performed for each treatment comparison simultaneously varied clinical, cost, and utility parameters using 95 percent confidence intervals (CIs) and means of the parameter value (where 95% CIs were not reported, standard errors were assumed to be 20% of the mean). A WTP threshold of £20,000 was used to assess ICER results.

Compared with warfarin, patients receiving sequential dabigatran dosing over their remaining lifetime experienced similar IS events per 100 patient-years (4.19 versus
4.13) but total ICH and HS events were more than halved in the dabigatran-treated group (0.58 versus 1.32). For those patients who initiated dabigatran therapy before 80 years old, the ICER was £4,831 per QALY gained. Those who initiated at 80 years old had a higher ICER value of £7,090 per QALY gained (see Table 3.5). Key parameters identified to have substantial impact on the cost-effectiveness results were degree of INR control for warfarin patients; relative risk (RR) and overall event rates of IS, ICH, and HS; cost of long-term follow-up care for patients with disability; time horizon analyzed; and significant differences in the cost of warfarin monitoring.

Kansal and colleagues found the PSA results demonstrated patients aged 80 and above initiating treatment had increased QALYs in all simulation runs; patients receiving therapy under the age of 80 years experienced increased QALY values for 82 percent of the simulations. Using the £20,000 WTP threshold, dabigatran had a 98 percent probability of being cost-effective for patients receiving therapy before the age of 80 in relation to warfarin and 63 percent probability in patients who initiated dabigatran therapy at the age of 80 or older.

2.6.2.4 Langkilde and colleagues, 2012

Langkilde and colleagues (Langkilde, Bergholdt Asmussen, & Overgaard, 2012) adopted a semi-Markov economic model of long-term costs and clinical outcomes used for a Canadian population (Sorensen et al., 2011), which is summarized below. Treatment strategies evaluated included warfarin, sequential dosing of dabigatran (dabigatran 150 mg twice daily for patients < 80 years of age and dabigatran 110 mg
twice daily for patients $\geq 80$ years), aspirin, and no treatment. Outcomes and costs were estimated for a cohort of 10,000 patients with a similar stroke risk profile (identified using CHADS$_2$ scoring) to those patients enrolled in the RE-LY trial. Authors modeled long-term health outcomes using estimations of the number of clinical events, life expectancy (life-years), and QALYs. Healthcare resource use and costs were estimated using from the Danish Health Care System. Microsoft 2007 was the software used to construct the model. Boehringer Ingelheim, Denmark provided project funding.

The baseline analysis used in this model was based off the Canadian adaptation previously published (Sorensen et al., 2011). Health states incorporated into the model included represent ischemic stroke history, degree of disability following stroke, current treatment, and death. Transitions between health states could occur every three months. Clinical outcomes modeled were ischemic stroke, TIA, systemic embolism, acute MI, ICH, hemorrhagic stroke, other major hemorrhages, and minor bleeds. Warfarin and dabigatran event rates were estimated from reported values in the RE-LY trial. Aspirin and no therapy event rates were based upon an adaptation of a published meta-analysis analyzing the controlled clinical trials involving warfarin, aspirin, and/or placebo. Utility estimates for Danish patients with AF were not available and, therefore, the authors used values applied in Sorensen and colleagues’ Canadian model. Cost estimates were derived from Danish government agencies (e.g., Danish Medicines Agency, Danish Ministry of Health) and other literature sources when Danish cost estimates were not available. Future costs and outcomes were discounted at an annual rate of two percent (sensitivity analysis: 0% and 4%) in accordance with Danish Ministry of Health standards.
In the base case analysis, the lifetime cost for warfarin and dabigatran was €18,752 and €16,886, respectively. Authors noted the primary reason for a cost difference was attributable to drug cost. Estimated QALYs were 8.32 for patients receiving warfarin and 8.59 for patients receiving dabigatran. Although Denmark does not have an accepted WTP threshold, authors used the value of €30,000 per QALY gained. The calculated ICER between warfarin and dabigatran was €6,950 per QALY gained, which is deemed cost-effective (see Table 3.5). In a sensitivity analysis performed to assess efficacy and safety of warfarin associated with the achieved quality of INR monitoring, the TTR was allowed to deviate from that reported in the RE-LY trial for warfarin treated patients. Two scenarios were evaluated for INR monitoring cost and/or a high quality of INR monitoring. When INR monitoring cost was varied based on different methods of care practiced in Denmark, dabigatran was regarded as cost-effective compared to warfarin using any reasonable INR monitoring method and its associated cost under base case assumptions. Taking into consideration the achieved quality of INR monitoring based on the center average TTR, the ICER between dabigatran and warfarin ranged from €6115/QALY for the lowest level of quality to €29,019/QALY for the highest level of quality. Authors concluded dabigatran would be regarded cost-effective relative to warfarin regardless of the average center TTR achieved for patients receiving warfarin. With respect to influential model variables impacting model results, the risk of ICH had a substantial impact on both incremental cost and incremental QALYs. Langkilde and colleagues concluded dabigatran was a cost-effective oral anticoagulant alternative to warfarin from a Danish healthcare perspective.
2.6.2.5 Pink and colleagues, 2011

Pink and colleagues used a discrete event simulation to develop a health economic evaluation to determine the incremental net health benefits as well as estimate the cost-effectiveness of dabigatran 110 mg twice daily and dabigatran 150 mg twice daily compared to warfarin (Pink, Lane, Pirmohamed, & Hughes, 2011). A discrete event simulation model was developed to consider the individual patient, his or her characteristics, and his or her experience of clinical events and outcomes as he or she aged over a lifetime time horizon. Identical cohorts of 50,000 patients were included in the simulation for each treatment. Every individual was assigned an age and health profile defined by the presence/absence of any of the following baseline characteristics: hypertension, diabetes mellitus, congestive heart failure, previous stroke, previous transient ischemic attack, previous myocardial infarction, and previous intracranial hemorrhage. Patients in the cohorts were diagnosed with NVAF and a moderate to high risk for stroke (mean baseline CHADS$_2$ = 2.1). Authors modeled the net health benefits and expected clinical event rates of both doses of dabigatran and warfarin to quantify the lifetime benefits and adverse effects of competing treatments, while also taking into consideration uncertainties in the parameters. In the economic analysis estimating the cost-effectiveness of the treatments, the model was extended to include resource use and costs. Resource use and costs were estimated from the perspective of the NHS (i.e., third party payer). The modeling software used was not reported.

The authors stratified the study population into multiple subgroups, which included: RE-LY population, CHADS score 2, CHADS score ≥3, Center time within
therapeutic range (TTR) ≥ 65.5 percent, Center TTR < 65.5 percent, patients TTR ≥ 66.8 percent, patients TTR < 66.8 percent, CRCL < 30-50 mL/min, previous stroke or TIA, age ≥ 75 years, vitamin K naïve. The analysis also considered the probability of therapy discontinuation to better reflect the real-world use of oral anticoagulation. At two years, 21 percent of the patients randomized to dabigatran therapy discontinued compared to 17 percent of the warfarin patients. Patients who were discontinued from dabigatran from a bleed, or warfarin patients discontinued for any reason, were switched to aspirin. Patients who were discontinued from dabigatran for reasons other bleeding were switched to warfarin.

Costs and utilities were estimated from published medical literature and NHS references. Costs included in the first and subsequent years following a stroke event or MI were ward costs (staffing, equipment, consumables, and overheads), procedure costs (also included cost of hospital drugs), inpatient and outpatient costs, cost of general practitioners’ and district nurse visits, and the cost of other drugs and estimates were obtained from a previously published study (Hemingway, 2010). NHS reference costs were used for pulmonary emboli, TIAs, and management of major and minor bleeds. Warfarin therapy and associated monitoring costs were calculated from a published study of 165 patients with AF (Jorgensen et al., 2009). Dabigatran cost estimates were derived from drug acquisition costs listed in the British National Formulary (see Table 3.5). Utility estimates for baseline health state, cardiovascular sequelae adverse events, and hemorrhagic adverse events were obtained from a report of EQ-5D scores elicited from several thousand respondents to the US Medical Expenditure Panel Survey (MEPS).
(Meckley, Gudgeon, Anderson, Williams, & Veenstra, 2010; Sullivan & Ghushchyan, 2006). Utility losses for treatment use came from a study of 83 patients with AF (Gage, Cardinalli, & Owens, 1996). An annual discount rate of 3.5 percent was applied to costs, life years, and QALYs but not to discrete clinical events (Torgerson & Raftery, 1999).

Multiple sensitivity and scenario analyses were performed. A univariate SA of each parameter was tested based on plausible value ranges. PSAs were performed using 2,000 sets of Monte Carlo simulations, varying every model parameter simultaneously. In the economic analysis, the PSA was used to analyze the joint uncertainty in costs and utility measures to estimate the cost-effectiveness of dabigatran at varying WTP threshold values and in different clinical scenarios. Scenario analyses included the base case and two additional scenarios. The base case assumed the benefit of treatment persists for the patients’ lifetime. The first alternative scenario assumed the benefit persisted for only two years, while the second assumed the benefit decreased linearly to zero over ten years following the trial. Analyses for the subgroups were performed to calculate the NHB, ICERs, and probability of cost-effectiveness in pre-specified populations discussed above.

Pink and colleagues study results showed the ICER for dabigatran 110 mg versus warfarin was £43,074 per QALY gained and was £23,082 per QALY for dabigatran 150 mg (see Table 3.5). Compared with warfarin, corresponding incremental NHBs for dabigatran 110 mg and 150 mg were 0.094 (95% central range: -0.083, 0.267) and 0.146 (95% central range: -0.029, 0.322), respectively. No discernible differences in lifetime
incidence of MI were found between the two doses of dabigatran (110 mg and 150 mg), however the rates for these therapies were about 19 percent higher than that of warfarin.

Results of the PSA indicated warfarin had the highest probability of being cost effective at thresholds of £24,400 or lower, whereas dabigatran 150 mg was the most probable cost-effective option at thresholds above that value. Considering a pair-wise-comparison between warfarin and dabigatran 150 mg, dabigatran 150 mg was the most cost-effective treatment at a WTP threshold above £22,800. PSA for the NHB found that compared with warfarin, dabigatran 110 mg and dabigatran 150 mg were associated with a positive incremental NHB in 86 percent and 94% of the simulations, respectively. Among the subgroups analyzed, the mean incremental net health benefit consistently favored both doses of dabigatran over warfarin and dabigatran 150 mg twice daily over 110 mg twice daily (results reported in Pink and colleagues’ article). Dabigatran 150 mg was most cost-effective in patients with a high risk for stroke (CHADS_2 ≥ 3), however the probability of being cost-effective was only 68 percent.

2.6.2.6 Shah and Gage, 2011

Shah and Gage used a Markov model to compare the projected quality-adjusted survival and costs of the following alternative treatment strategies for patients with AF: dabigatran 110 mg (twice daily), dabigatran 150 mg (twice daily), warfarin, dual therapy with aspirin and clopidogrel, aspirin alone, or no antithrombotic therapy (S. V. Shah & Gage, 2011). A hypothetical cohort of 70-year-old patients with AF, a moderate risk of stroke, and no contraindication to anticoagulation therapy were modeled. Eight Markov
health states were included in the model and patients were followed for 20 years (or until death) (see Table 3.3). One-month health state transitions were used to model the progression of disease over a time. The model perspective was that of an insurance company, such as Medicare.

Cost estimates focused on relative comparisons between treatments and, therefore, excluded absolute costs, such as medical costs unrelated to antithrombotic therapy, hemorrhage, neurological ischemia, dyspepsia, or myocardial ischemia. Costs for adverse events were estimated using the median value or geometric mean of published studies, HCUP, and Medicare remuneration (Agency for Healthcare Research and Quality, 2009; Holloway, Witter Jr, Lawton, Lipscomb, & Samsa, 1996; Leibson et al., 1996; Matchar & Samsa, 2000; C. L. O'Brien & Gage, 2005). Costs of warfarin therapy were calculated by combining its prescription cost with Medicare reimbursement for 14 INR tests and minimal established patient office visits (CPT code 99211 or 99212). The median cost for dabigatran was estimated from a survey of four pharmacies (see Table 3.4). Utility estimates for IS, HS, and warfarin were obtained from results of a previously published survey of 69 patients with AF (Gage, Cardinalli, & Owens, 1996). Nonfatal ECHs and minor bleeds were estimated from previously studies on anticoagulant therapy guidelines and catalog of health state quality factors (Fryback et al., 1993; Thomson, Parkin, Eccles, Sudlow, & Robinson, 2000). The estimate for MI was only applied for 30 days (Gore et al., 1995). The mean utility estimate was based on the following factors: 1) less than aspirin because it requires twice daily dosing; 2) greater than warfarin because it requires no routine monitoring; and 3) similar to a previous
estimate for an older thrombin inhibitor, ximelagatran (RW.ERROR - Unable to find reference:256). Both costs and QALYs were discounted at an annual rate of three percent (M. C. Weinstein, Siegel, Gold, Kamlet, & Russell, 1996).

Sensitivity analyses were performed for all model variables over plausible ranges. Two prediction rules were used to quantify rates of stroke and hemorrhage, CHADS₂ and HEMORR₂HAGES, respectively. Calculated cost-effectiveness CHADS₂ is a clinical prediction rule in which stroke rate is dependent upon the following risk factors: CHF, hypertension, age greater than 75 years, diabetes mellitus, and a history of stroke or TIA. Each risk factor is assigned one point, with the exception of history of stroke or TIA, which is assigned two points (Gage et al., 2001). CHADS₂ is a clinical prediction rule in which hemorrhage rate is dependent upon the presence of hepatic or renal disease, ethanol abuse, malignancy, age greater than 75 years, reduced platelet count, prior bleed, uncontrolled hypertension, anemia, genetic factors, excessive fall risk, and stroke. Each risk factor is assigned one point, with the exception of prior bleed, which is assigned two points (Gage et al., 2006). SMLTREE was used to calculate cost-effectiveness ratios of dabigatran across combinations of stroke and hemorrhage risk.

Shah and Gage reported that the projected marginal cost per QALY in the base case of dabigatran 150 mg versus warfarin was $86,000 per QALY and was $150,000 per QALY for dabigatran 110 mg (see Table 3.4). Neither dabigatran 110 mg nor dual therapy (aspirin and clopidogrel) was cost-effective at any rate of stroke or hemorrhage risk. The most influential variables were stroke and hemorrhage rates, cost of dabigatran, and time in INR range. Two-way and three-way sensitivity analyses demonstrated the
cost-effectiveness of a given therapy – dabigatran, warfarin, aspirin, dual therapy – depended upon the severity of stroke risk. Two-way sensitivity analyses of stroke and hemorrhage risk confirmed that low stroke rates favored preferred therapy, moderate rates preferred warfarin, and high stroke and/or hemorrhage rates preferred dabigatran 150 mg. Shah and Gage found that in scenarios where dabigatran 150 mg cost less than $1,800 per year, dabigatran was consistently more cost-effective than warfarin (regardless of stroke and hemorrhage rates).

2.6.2.7 Sorensen and colleagues, 2011

Sorensen and colleagues developed a semi-Markov model to quantify comparisons of current anticoagulation therapies to dabigatran for the prevention stroke in Canadian patients with AF (Sorensen et al., 2011). A baseline cohort of 1,000 patients aged 70 years and older was followed for the remainder of their lifetimes to capture the lifelong consequences of stroke and hemorrhage. Approximately 20 percent of the patients had a history of previous stroke and were at an increased risk of recurrent stroke prophylaxis. In accordance with the dosing regimen approved by Health Canada, the model evaluated dabigatran in a sequential dosing approach, where patients under 80 years of age received dabigatran 150 mg (twice daily) and patients 80 years an older received 110 mg (twice daily). The sequential dosing of dabigatran 150 mg (twice daily) or 110 mg (twice daily) was compared to warfarin under ‘trial-like’ INR control conditions (i.e., patients spent the same proportion of time within, above, and below therapeutic INR range as measured in the RE-LY trial), as well as to a ‘real-world’
prescribing scenario that accounts for stroke prophylaxis in warfarin-eligible Canadian patients with AF as observed in actual clinical practice (Parkash et al., 2007; Partington, Abid, Teo, Oczkowski, & O'Donnell, 2007). Therapy dosing in clinical practice may include receiving prophylaxis with warfarin, aspirin, or no treatment. The concept of the model structure was published in a previous article by the authors (RW.ERROR - Unable to find reference:32). The semi-Markov model consisted of eleven health states with four additional states representing discontinuation of therapy (see Table 3.3). Three-month model cycles were selected because authors claimed it was unlikely that a patient would experience more than one major event during this time. The analysis perspective was that of a Canadian payer perspective (i.e., third party payer). The model was implemented using Microsoft Excel version 1997-2003.

Costs and utility measures were applied at the beginning of each Markov cycle. Medication cost for warfarin was obtained from the Ontario Drug Benefit formulary (Roskell, Lip, Noack, Clemens, & Plumb, 2010), whereas the cost of dabigatran was obtained from the corporation, Total Pricing System. Costs for quarterly follow-up of IS clinical events and resulting disability level were obtained from the Economic Burden of Ischemic Stroke in Canada (BURST) study, as well as a few other studies extrapolating the four- to six-month data presented in the BURST study to estimate long-term costs (Cadilhac, Carter, Thrift, & Dewey, 2009; Ghatnekar, Persson, Glader, & Terent, 2004; Mercaldi et al., 2011). Other costs associated with ICH and HS were derived from a study evaluating the one-year cost of stroke among 365 Canadian patients (Goeree, Blackhouse, Petrovic, & Salama, 2005). Utilities were derived from two sources: 1)
nationally representative catalogue of EQ-5D scores from the 2000-2002 MEPS data and 2) a published meta-analysis of quality of life estimates for patients with stroke prophylaxis (Sullivan & Ghushchyan, 2006). All costs and outcomes were discounted at an annual rate of five percent.

The authors included a few model assumptions with respect to treatment efficacy, functional status, and treatment discontinuation. As long as patients remained adherent to treatment, efficacy was assumed to remain constant over time for dabigatran and warfarin. The authors decided to take a conservative approach with regard to functional status following an event and assumed patients could not improve to a better functional status than the one they were in prior to an event like IS, HS, or ICH. Following one of these events, the patient was allowed to remain in the same functional state or their status worsened. The authors projected the discontinuation for warfarin and dabigatran for up to six years using a Weibull survival function; patients were assumed to remain adherent beyond six years.

One-way sensitivity analyses were conducted to identify key determinants of model results. Authors estimated the uncertainty surrounding the cost-effectiveness estimates using PSA to compare dabigatran with ‘trial-like’ warfarin and ‘real-world’ warfarin prescribing. In the PSA, the cumulative effect of varying all the model parameters simultaneously randomly within their statistical distributions (based on 95% CIs) was tested.

The ICER in the Canadian model of dabigatran 150 mg versus ‘trial-like’ warfarin was CAD 9,041 per QALY and CAD 29,994 for the 110 mg group (Sorensen et al.,
2011). Compared to ‘trial-like’ warfarin, patients treated sequentially over a lifetime with dabigatran 150 mg before 80 years and dabigatran 110 mg 80 years and older experienced fewer ICH and IS events per 100 patient years. In comparison to the ‘real-world’ warfarin-prescribing scenario, patients receiving either dose of dabigatran experienced fewer IS, systemic embolism, TIA, and ICH events per 100 patient-years. In both ‘trial-like’ and real-world’ case scenarios, patients receiving dabigatran experienced more ECH and AMI events per 100 patient years. The costs and utilities of adverse events, including major and minor stroke, major and minor hemorrhage, transient ischemic attack, and MI, did not significantly affect the study findings. Key parameters affecting the results of the Canadian study were the degree of INR control attained by warfarin patients as well as the cost of INR monitoring. In addition to the cost of dabigatran, two-way and three-way sensitivity analyses of adverse events and INR control showed the cost-effectiveness of dabigatran was considerably sensitive to INR control. Assuming a WTP threshold of CAD (Canadian dollar) 30,000 per QALY, the results of PSA demonstrated dabigatran dosed sequentially (110 mg for patients ≥ 80 years, 150 mg for patients < 80 years) was cost-effective in 82 percent of the simulations compared to ‘trial-like’ warfarin and 99 percent of the simulations in comparison with ‘real-world’ warfarin prescribing.

2.6.3 Influential Model Variables

To assess the robustness of the model, sensitivity analyses were performed to evaluate a range of values for various variables and determine if a fluctuation in the
values of a particular variable(s) significantly affects the results of the model. In the US, the cost-effectiveness of dabigatran versus warfarin was most sensitive to the cost of dabigatran (Freeman et al., 2011; S. V. Shah & Gage, 2011). These authors also found the results of their study were robust over a range of variable values, but was most sensitive to the cost of dabigatran. The ICER of dabigatran 110 mg compared with warfarin exceeded $50,000 per QALY when dabigatran was priced greater than $9.36 per day. The ICER of dabigatran 150 mg compared with warfarin exceeded the WTP threshold of $50,000 per QALY when the price of dabigatran was greater than $13.70 per day. Shah and Gage found that in scenarios where dabigatran 150 mg cost less than $1,800 per year, dabigatran was consistently more cost-effective than warfarin (regardless of stroke and hemorrhage rates) (S. V. Shah & Gage, 2011).

In addition to the cost of dabigatran, two-way and three-way sensitivity analyses of adverse events and INR control showed the cost-effectiveness of dabigatran was considerably sensitive to INR control (Kansal et al., 2012; Sorensen et al., 2011). The costs and utilities of adverse events, including major and minor stroke, major and minor hemorrhage, TIA, and MI, did not significantly affect the study findings in the Canadian study (Sorensen et al., 2011). Key parameters affecting the results of the Canadian study were the degree of INR control attained by warfarin patients as well as the cost of INR monitoring (Sorensen et al., 2011).

Influential parameters having a substantial impact on the study results of Kansal and colleagues were the degree of INR control for warfarin patients; RR and overall event rates of IS, ICH, and HS; the cost of long-term follow-up care for patients with
disability; the time horizon analyzed; and significant differences in the cost of warfarin monitoring (Kansal et al., 2012). Variables found to be influential in Kamel and colleagues’ model included monthly cost of combined or recurrent stroke and/or cerebral hemorrhage, starting age of the cohort, relative risk of stroke prophylaxis with dabigatran compared to warfarin, the cost of dabigatran, the average time in a therapeutic INR range for patients receiving warfarin, and the utility of mild ischemic stroke (Kamel, Johnston, Easton, & Kim, 2012). Although dabigatran 150 mg was cost-effective in a number of the analyses, the authors acknowledged the cost-effectiveness appeared to be dependent upon the adequacy of anticoagulation management clinics to help patients maintain an INR level in the acceptable therapeutic range (between 2.0 and 3.0).

2.6.4 Study Conclusions

Each of the six studies evaluating the cost-effectiveness of dabigatran relative to warfarin found dabigatran was cost-effective in some scenarios, however superior clinical and economic benefit was contingent upon therapy dosage, stroke severity, and INR control. Most studies assessing the cost-effectiveness of both dabigatran doses, 110 mg and 150 mg, found 150 mg to be the only therapy dose to yield a cost-effective therapy strategy compared to warfarin (Freeman et al., 2011; Kamel, Johnston, Easton, & Kim, 2012; Pink, Lane, Pirmohamed, & Hughes, 2011; S. V. Shah & Gage, 2011). Pink and colleagues concluded dabigatran 110 mg offered no clinical or economic advantage over dabigatran 150 mg. The study conducted in a Canadian setting, however, evaluated dabigatran 110 mg for patients under the age of 80 and dabigatran 150 mg for patients 80
years and older and found in a lifetime analysis dabigatran versus trial-like warfarin resulted in fewer ischemic strokes and life-threatening major bleeds (Sorensen et al., 2011). Kansal and colleagues found dabigatran had a higher probability (98%) of being cost-effective for patients receiving therapy before the age of 80 in relation to warfarin compared to a 63 percent probability in patients who initiated dabigatran therapy at the age of 80 or older (Kansal et al., 2012).

With respect to stroke severity, Shah and Gage found the cost-effectiveness of dabigatran was dependent upon the patient’s severity of stroke risk. For patients at a low risk of stroke, aspirin was cost-effective; for patients at an intermediate risk for stroke, warfarin was cost-effective; and for patients at a high risk for stroke, dabigatran 150 mg was cost-effective (S. V. Shah & Gage, 2011). A few studies addressed the notion of trial-like warfarin control seen in the RE-LY trial results relative to warfarin control seen in the real world (Kamel, Johnston, Easton, & Kim, 2012; Pink, Lane, Pirmohamed, & Hughes, 2011; S. V. Shah & Gage, 2011). Data in the RE-LY trial reported patients treated with warfarin therapy remained in the target INR therapeutic range 64 percent of the time (S. J. Connolly et al., 2009). This percentage of time in therapeutic range affects the reported efficacy of warfarin therapy in the RE-LY trial, which in turn influences the results of the models comparing dabigatran with warfarin-treated patients (Kamel, Johnston, Easton, & Kim, 2012). It is important to emphasize that many anticoagulation clinics have reported patients receiving warfarin have maintained INR control in excess of 80 percent of the time (Baker, Pierce, & Ryals, 2011; Garton & Crosby, 2011). Study conclusions highlighted that the cost-effectiveness of dabigatran appeared to depend upon
the adequacy of warfarin management, with a greater advantage for dabigatran in centers with poor INR control in warfarin-treated patients (Kamel, Johnston, Easton, & Kim, 2012; Pink, Lane, Pirmohamed, & Hughes, 2011). Shah and Gage conclude dabigatran 150 mg (twice daily) was cost-effective in AF populations at a high risk of hemorrhage or stroke unless INR control with warfarin was excellent (time in therapeutic range >72.6%) (S. V. Shah & Gage, 2011).
3  CHAPTER 3: METHODS

3.1  Study Purpose

The primary objective of this study was to estimate the long-term cost-effectiveness of stroke prevention in patients with nonvalvular atrial fibrillation (NVAF) in the US using newer anticoagulant therapies – dabigatran 150 mg, apixaban 5 mg, and rivaroxaban 20 mg – as well as the standard treatment, warfarin.

3.2  Study Objectives

This chapter outlines the methodology used to address a set of research questions concerning the prevention of stroke prophylaxis in patients diagnosed with NVAF, who are at an increased risk of stroke. Each research question includes the analysis of four anticoagulant therapies: apixaban, dabigatran, rivaroxaban, and warfarin. Study objectives include:

I. Estimated the incremental cost-effectiveness pair-wise among all treatments and assessed whether a difference in treatment cost-effectiveness existed;

II. Estimated the net monetary benefit (NMB) for all treatments and assessed whether a difference exists; and

III. Determined the total direct and indirect costs for each therapy pathway.

Decision modeling methods were used to estimate the survival of patients with AF and their associated total costs (i.e., direct and indirect) over their lifetime once diagnosed. A decision analysis model was a feasible choice given that a long-term prospective multi-arm trial would be very expensive to conduct and length of time
necessary to collect data on the outcomes of interest. Significant capital investment and over 20 years of patient follow up would be required to prospectively assess the survival and cost of the outcomes.

### 3.3 Hypotheses

The primary areas of interest addressed in the hypothesis analyses were ICERs, NMBs, aggregated total lifetime costs, life-years, and QALYs. Listed below are five major hypotheses used in this study.

#### 3.3.1 Hypothesis I: Incremental Cost-Effectiveness Ratio

The following six hypotheses were used to test the difference in the incremental cost-effectiveness ratios (ICERs) among pair-wise comparisons of four anticoagulant treatments. Note that the ICER was calculated as a ratio of the difference in costs to the difference in effects (ΔC/ΔE) between products. A treatment was deemed cost-effective in comparison to an alternative treatment using a $50,000 per QALY gained willingness-to-pay threshold (WTP) (Neumann, Sandberg, Bell, Stone, & Chapman, 2000).

**Ho1₁:** It was hypothesized that no difference in the ICER existed between dabigatran 150 mg and warfarin using $50,000 per QALY gained as the WTP threshold.

**Ho1₂:** It was hypothesized that no difference in the ICER existed between apixaban 5 mg and warfarin using $50,000 per QALY gained as the WTP threshold.
H013: It was hypothesized that no difference in the ICER existed between rivaroxaban 20 mg and warfarin using $50,000 per QALY gained as the WTP threshold.

H014: It was hypothesized that no difference in the ICER existed between apixaban 5 mg and dabigatran 150 mg using $50,000 per QALY gained as the WTP threshold.

H015: It was hypothesized that no difference in the ICER existed between rivaroxaban 20 mg and dabigatran 150 mg using $50,000 per QALY gained as the WTP threshold.

H016: It was hypothesized that no difference in the ICER existed between apixaban 5 mg and rivaroxaban 20 mg using $50,000 per QALY gained as the WTP threshold.

3.3.2 Hypothesis II: Net Monetary Benefit

The following six hypotheses were used to test the difference in the incremental net monetary benefit among pair-wise comparisons of four anticoagulant treatments. Note that the net monetary benefit (NMB) was calculated as the effectiveness, multiplied by the amount a decision maker is WTP (denoted λ), less the cost (E*λ – C). For the NMB to be positive, the product of the increase in effectiveness and amount the decision maker is willing to invest in the treatment must exceed the increase in cost. For NMB >0, the comparator therapy is considered cost-effective and should be selected for implementation. For NMB <0, greater health improvement could be attained by
foregoing the intervention and investing the resources elsewhere. NMB is zero when the incremental cost-effectiveness ratio for a treatment was equal to the WTP threshold ratio selected. A WTP value of $62,000 per QALY gained was specified (Shiroiwa et al., 2010).

Ho2₁: It was hypothesized that no difference in the NMBs existed between dabigatran 150 mg and warfarin using $62,000 per QALY gained as the WTP threshold.

Ho2₂: It was hypothesized that no difference in the NMBs existed between apixaban 5 mg and warfarin using $62,000 per QALY as the WTP threshold.

Ho2₃: It was hypothesized that no difference in the INMB existed between rivaroxaban 20 mg and warfarin using $62,000 per QALY as the WTP threshold.

Ho2₄: It was hypothesized that no difference in the INMB existed between apixaban 5 mg and dabigatran 150 mg using $62,000 per QALY as the WTP threshold.

Ho2₅: It was hypothesized that no difference in the INMB existed between rivaroxaban 20 mg and dabigatran 150 mg using $62,000 per QALY as the WTP threshold.

Ho2₆: It was hypothesized that no difference in the INMB existed between apixaban 5 mg and rivaroxaban 20 mg using $62,000 per QALY as the WTP threshold.
3.3.3 Hypothesis III: Lifetime Costs

The following six hypotheses were used to test the difference in lifetime costs among pair-wise comparisons of four anticoagulant treatments. Lifetime cost of treatment for patients with AF with an increased risk of stroke included both direct and indirect costs.

Ho3₁: It was hypothesized that no difference in lifetime costs exists between dabigatran 150 mg and warfarin.

Ho3₂: It was hypothesized that no difference in lifetime costs exists between apixaban 5 mg and warfarin.

Ho3₃: It was hypothesized that no difference in lifetime costs exists between rivaroxaban 20 mg and warfarin.

Ho3₄: It was hypothesized that no difference in lifetime costs exists between apixaban 5 mg and dabigatran 150 mg.

Ho3₅: It was hypothesized that no difference in lifetime costs exists between rivaroxaban 20 mg and dabigatran 150 mg.

Ho3₆: It was hypothesized that no difference in lifetime costs exists between apixaban 5 mg and rivaroxaban 20 mg.
3.3.4 Hypothesis IV: Total Life-Years

The following six hypotheses were used to test the difference in life-years gained among pair-wise comparisons of four anticoagulant therapies. Life-years were calculated as the sum of years gained attributable to treatment effects.

Ho4_1: It was hypothesized that no difference in total life-years exists between dabigatran 150 mg and warfarin.

Ho4_2: It was hypothesized that no difference in total life-years exists between apixaban 5 mg and warfarin.

Ho4_3: It was hypothesized that no difference in total life-years exists between rivaroxaban 20 mg and warfarin.

Ho4_4: It was hypothesized that no difference in total life-years exists between apixaban 5 mg and dabigatran 150 mg.

Ho4_5: It was hypothesized that no difference in total life-years exists between rivaroxaban 20 mg and dabigatran 150 mg.

Ho4_6: It was hypothesized that no difference in total life-years exists between apixaban 5 mg and rivaroxaban 20 mg.
3.3.5 Hypothesis V: Total Quality-Adjusted Life-Years

The following six hypotheses were used to test the difference in patient quality-adjusted life-years (QALYs) among pair-wise comparisons of four anticoagulant therapies. QALYs were calculated as the sum of the products of utility values associated with a given health state multiplied by the years spent in the health state.

Ho5₁: It was hypothesized that no difference in total QALYs exists between dabigatran 150 mg and warfarin.

Ho5₂: It was hypothesized that no difference in total QALYs exists between apixaban 5 mg and warfarin.

Ho5₃: It was hypothesized that no difference in total QALYs exists between rivaroxaban 20 mg and warfarin.

Ho5₄: It was hypothesized that no difference in total QALYs exists between apixaban 5 mg and dabigatran 150 mg.

Ho5₅: It was hypothesized that no difference in total QALYs exists between rivaroxaban 20 mg and dabigatran 150 mg.

Ho5₆: It was hypothesized that no difference in total QALYs exists between apixaban 5 mg and rivaroxaban 20 mg.

3.4 Model Specification

3.4.1 Model Structure

A Markov model was constructed and included the following health states: ischemic or unspecified stroke (minor or major), intracranial hemorrhage (ICH) (minor or
major), myocardial infarction (MI), gastrointestinal hemorrhaging, minor/nonmajor hemorrhaging, and death. At any given time point in the model, a patient inhabited one of these discrete health states. Figure 4.1 shows a depiction of the decision tree with the Markov states and events associated with disease progression. Each event was defined in accordance with clinical definitions from the therapy’s respective trial – ARISTOTLE (apixaban 5 mg, twice daily), RE-LY (dabigatran 150 mg, twice daily), or ROCKET-AF (rivaroxaban 20 mg, once daily) (S. J. Connolly et al., 2009; C. B. Granger et al., 2011; Patel et al., 2011). Table 4.1 delineates the characteristics of the various clinical trials that have evaluated the therapies of interest for this study. The table provides definitions of outcomes and patient inclusion/exclusion criteria for each trial. Previously published models, discussed in Chapter 2, were used as aids to help determine the most appropriate model structure and identify parameter values (Freeman et al., 2011; Kamel, Johnston, Easton, & Kim, 2012; Kansal et al., 2012; Langkilde, Bergholdt Asmussen, & Overgaard, 2012; Pink, Lane, Pirmohamed, & Hughes, 2011; S. V. Shah & Gage, 2011; Sorensen et al., 2011). In addition to literature resources, a pharmacist expert with extensive experience in an anticoagulation clinic was consulted to ensure the model reflected a real-world clinical application for the patient population.

As a part of the Markov approach, time was explicitly modeled over a series of discrete event time periods known as cycles. The 2012 American Chest of College Physicians (ACCP) evidence-based clinical practice guidelines recommend INR testing every four weeks for patients receiving vitamin K antagonist (VKA) therapeutic effect was unstable (Holbrook et al., 2012). Therefore, one-month cycles were used in the base
Sensitivity analyses with INR testing occurring every three months and every 12 weeks were performed to evaluate the variable impact of INR stability consistency. For each one-month discrete time cycle, transitions between health states were used to determine which health state the patient inhabited for the current health state. The ‘memoryless’ assumption of the Markov model was observed in that the probability of transitioning out of a state was independent of the nature or timing of earlier transitions in the model. In other words, the patient’s transition to the next health state was not contingent upon his or her previous health state(s).

A probability was specified for the movement between health states using clinical trial results and published studies which examined the probability of stroke prophylaxis and related adverse events in patients with AF (S. J. Connolly et al., 2009; S. J. Connolly, Ezekowitz, Yusuf, Reilly, & Wallentin, 2010; C. B. Granger et al., 2011; Patel et al., 2011). Event rates were converted into probabilities using the following conversion equation (Fleurence & Hollenbeak, 2007):

$$p = 1 - e^{-rt}$$

where

- $p$ is the probability,
- $r$ is the rate,
- $t$ is the unit of time

Life tables from US vital statistics reports and other literature sources were specified in the model to incorporate fluctuating mortality probabilities as a patient’s age increased as well as increasing risks associated with myocardial infarction (MI), ischemic stroke, and intracranial hemorrhage (ICH) (Arias, 2011; Dennis et al., 1993; Kannel, Sorlie, & McNamara, 1979). A Monte Carlo simulation method was used to promulgate the
process of patients through various health states, which allowed each individual patient to accrue costs and utilities/disutilities for the time spent in each health state they experienced during their simulated lifetime.
Table 3.1. Characteristics of clinical trials for newer anticoagulant agents: dabigatran and Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY); rivaroxaban and Rivaroxaban Once daily oral direct Factor Xa inhibition Compared with vitamin K antagonist for the prevention of stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF), apixaban and Apixaban for Reduction In STroke and Other ThromboemboLic Events in atrial fibrillation (ARISTOTLE).

<table>
<thead>
<tr>
<th></th>
<th>RE-LY</th>
<th>ROCKET-AF</th>
<th>ARISTOTLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Multi-center, prospective, open-label, randomized trial with blinded evaluation of all outcomes</td>
<td>Multi-center, randomized, double-blind, double-dummy, event-driven study</td>
<td>Multi-center, randomized, double-blind, double-dummy</td>
</tr>
<tr>
<td>Study location</td>
<td>Number of sites: 951</td>
<td>Number of sites: 1178</td>
<td>Number of sites: 1,034</td>
</tr>
<tr>
<td></td>
<td>Number of countries: 44</td>
<td>Number of countries: 45</td>
<td>Number of countries: 39</td>
</tr>
<tr>
<td>Study duration</td>
<td>2 years</td>
<td>707 days (~2 years)</td>
<td>2.0 years</td>
</tr>
<tr>
<td>(median follow-up)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study participants</td>
<td>N = 18,113, patients with AF and a risk of stroke</td>
<td>N = 14,264, patients with NVAF who are at an increased risk for stroke</td>
<td>N = 18,201, patients with AF and at least one additional risk factor for stroke</td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>Atrial fibrillation documented on EKG and one additional characteristic: previous stroke or TIA, left ventricular ejection fraction of less than 40%, New York Heart Association class II or higher heart-failure symptoms within 6 months before screening, and an age of at least 75 years or an age of 65 to 74 years plus diabetes mellitus, hypertension, or coronary artery disease</td>
<td>Age ≥ 18 years; persistent or paroxysmal AF documented on ≥2 episodes; risk of future stroke, including history of stroke/TIA or systemic embolism OR ≥2 risk factors (CHF or left ventricular ejection fraction &lt;35%; hypertension; ≥75 years; diabetes mellitus</td>
<td>Age ≥ 18 years; permanent or persistent AF or AFL on ECG; one or more risk factor for stroke: age ≥75 years, prior stroke/TIA/systemic embolus, symptomatic CHF within 3 months or LV dysfunction, diabetes mellitus, hypertension requiring medication, women of childbearing potential must use contraception</td>
</tr>
<tr>
<td></td>
<td>RE-LY</td>
<td>ROCKET-AF</td>
<td>ARISTOTLE</td>
</tr>
<tr>
<td>--------------------------</td>
<td>------------------------------------------------------------------------</td>
<td>-----------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Exclusion criteria</strong></td>
<td>Presence of a severe heart-valve disorder, stroke within 14 days or severe stroke within 6 months of screening, a condition that increased the risk of hemorrhage, CrCl &lt; 30 ml/min, active liver disease, and pregnancy</td>
<td>Cardiovascular-related conditions (prosthetic heart valve; AF secondary to reversible disorders; active endocarditis; hemodynamically significant mitral stenosis); hemorrhage-related conditions (active internal bleeding; history of, or condition associated with increased bleeding risk); or concomitant conditions and therapies (any stroke w/in 14 days before randomization; TIA w/in 3 days before randomization; indication for anticoagulant therapy other than AF; treatment with ASA &gt;100-mg daily, ASA in combination with thienopyridines w/in 5 days before randomization, IV antiplatelets w/in 5 days before randomization); patients with CrCl &lt;30 mL/min</td>
<td>AF or AFL due to reversible cause; moderate/severe mitral stenosis; contraindication to oral anticoagulation; persistent uncontrolled hypertension; active infective endocarditis; planned major surgery; planned AF or AFL ablation; use of unapproved investigational drug or device; required aspirin &gt;165 mg/d; simultaneous tx with aspirin and a thienopyridine; severe comorbid condition with life expectancy &lt;1y; active alcohol/drug abuse/psychological reasons; recent stroke (within 7 days); severe renal insufficiency (CrCl &lt;25 mL/min); platelet count ≤ 100,000/mm³; hemoglobin &lt;9 g/dL; inability to comply with INR monitoring</td>
</tr>
<tr>
<td><strong>Treatment therapy</strong></td>
<td>Dabigatran doses of 110 mg or 150 mg oral twice daily</td>
<td>CrCl &gt; 50 mL/min = rivaroxaban 20-mg once daily</td>
<td>Apixaban 5-mg oral twice daily, or apixaban 2.5-mg if two or more criteria were met (at least 80 years, body weight no more than 60 kg, or serum creatinine level of 1.5 mg per deciliter or more) [Note: apixaban groups are not separated in the results]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CrCl 30 to 49 mL/min = rivaroxaban 15-mg once daily</td>
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<tr>
<td></td>
<td>RE-LY</td>
<td>ROCKET-AF</td>
<td>ARISTOTLE</td>
</tr>
<tr>
<td>----------------</td>
<td>--------------------------------------------</td>
<td>-----------------------------------------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td>Reference therapy</td>
<td>Adjusted-dose warfarin</td>
<td>Adjusted-dose warfarin</td>
<td>2-mg tablets and adjusted to achieve a target INR of 2.0 to 3.0</td>
</tr>
<tr>
<td>Dosing specifications</td>
<td>No rivaroxaban dose adjustments post-baseline for changing CrCl (see treatment therapy); patients with CrCl &lt;30 mL/min were required to discontinue study drug</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary efficacy outcome(s)</td>
<td>Stroke (hemorrhagic and ischemic) or systemic embolism</td>
<td>Stroke (hemorrhagic and ischemic) and systemic embolism</td>
<td>Combined endpoint IS or ICH and systemic embolism; all-cause death</td>
</tr>
<tr>
<td>Definition(s) of primary outcome(s)</td>
<td><strong>Stroke</strong> = acute onset of a focal neurologic deficit of presumed vascular origin lasting for ≥24 hours or resulting in death; categorized as ischemic, hemorrhagic, or unspecified (hemorrhagic transformation of IS was not considered to be a HS); fatal stroke defined as death from any cause within 30 days of the stroke; <strong>ICH</strong> = HS and subdural or SAH; <strong>Systemic embolism</strong> = acute vascular occlusion of an extremity or organ, documented by means of imaging, surgery, or autopsy</td>
<td><strong>Stroke</strong> = sudden, nonfocal neurologic deficit resulting from a presumed cerebrovascular cause that is not reversible within 24 hours and not due to a readily identifiable cause, such as a tumor or seizure; all ICH is included in the primary end point analysis as HS; <strong>TIA</strong> = matches the definition of a stroke but lasts &lt;24 hours; outcome of all strokes classified with the modified Rankin scale; subjects dying from stroke w/in 30 days of stroke onset are regarded as having fatal stroke; <strong>Non-CNS systemic embolism</strong> = abrupt vascular insufficiency associated with clinical or radiologic evidence of arterial occlusion in the absence of other likely mechanisms</td>
<td><strong>Stroke</strong> = nontraumatic abrupt onset of a focal neurological deficit lasting at least 24 hours; a retinal ischemic event (embolism or thrombosis) will be considered a stroke; strokes classified as ischemic, ischemic with hemorrhagic transformation, hemorrhagic, or of uncertain type; HSs subclassified as subdural, subarachnoid, or intraparenchymal; <strong>TIA</strong> = nontraumatic abrupt onset of a focal neurological deficit lasting &lt;24 hours</td>
</tr>
</tbody>
</table>
Table 3.1 (Continued). Characteristics of clinical trials for newer anticoagulant agents: dabigatran and RE-LY; rivaroxaban and ROCKET-AF, apixaban and ARISTOTLE.

<table>
<thead>
<tr>
<th></th>
<th>RE-LY</th>
<th>ROCKET-AF</th>
<th>ARISTOTLE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Secondary efficacy outcome(s)</strong></td>
<td>Stroke, systemic embolism, and death; MI; pulmonary embolism; TIA; and hospitalization</td>
<td>All-cause death, vascular death, or MI</td>
<td>Composite IS, ICH, systemic embolism, and all-cause death; composite (warfarin naïve patients) IS, ICH, systemic embolism, and major bleed; composite of IS, ICH, systemic embolism, and major bleeding; composite of IS, ICH, systemic embolism, major bleeding, and all-cause death; composite of IS, ICH, systemic embolism, MI, and all-cause death; major bleeding</td>
</tr>
<tr>
<td><strong>Definition(s) of secondary outcome(s)</strong></td>
<td>MI = endpoints depend on whether PCI or CABG has been performed; Deaths = vascular (including bleeding) or nonvascular due to other specified causes (i.e., malignancy or of unknown etiology)</td>
<td>MI = adjudication of MI as a clinical end point considers the occurrence relative to PCI or CABG or clinical symptoms consistent with MI and cardiac biomarker elevation; Deaths = having been caused by vascular (e.g., stroke, embolism, or acute MI) or nonvascular due to conditions such as malignancy or hemorrhage</td>
<td></td>
</tr>
<tr>
<td><strong>Primary safety outcome(s)</strong></td>
<td>Major hemorrhage</td>
<td>Major and non-major clinically relevant bleeding events</td>
<td>Major bleeding</td>
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</table>
Table 3.1 (Continued). Characteristics of clinical trials for newer anticoagulant agents: dabigatran and RE-LY; rivaroxaban and ROCKE-T-AF, apixaban and ARISTOTLE.

<table>
<thead>
<tr>
<th></th>
<th>RE-LY</th>
<th>ROCKE-T-AF</th>
<th>ARISTOTLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition(s) of</td>
<td><strong>Major bleeding</strong> = reduction in the hemoglobin level of at least 20 g per liter, transfusion of at least 2 units of blood, or symptomatic bleeding in a critical area or organ; life-threatening bleeding was a subcategory of major bleeding that consisted of fatal bleeding, symptomatic intracranial bleeding, bleeding with a decrease in the hemoglobin level of at least 50 g per liter, or bleeding requiring transfusion of at least 4 units of blood or inotropic agents or necessitating surgery;</td>
<td><strong>Major bleeding</strong> = clinically overt bleeding associated with any of the following: fatal outcome, involving a critical site (i.e., intracranial, intra-spinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, or retroperitoneal), or clinically overt bleeding associated with a fall in hemoglobin concentration of ≥2 g/dL, or leading to transfusion of ≥2 units of packed RBCs or whole blood; Non-major bleeding = overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, unscheduled contact with a physician, temporary cessation of study drug, pain, or impairment of daily activities</td>
<td><strong>Major bleeding</strong> = clinically overt bleeding accompanied by a decrease in the hemoglobin level of at least 2 g per deciliter or transfusion of at least 2 units of packed red blood cells, occurring at a critical site, or resulting in death (defined using ISTH criteria)</td>
</tr>
<tr>
<td>primary safety</td>
<td><strong>Minor bleeding</strong> = all other clinical bleeds that do not fulfill the criteria for major bleeds</td>
<td><strong>Minor bleeding</strong> = all other overt bleeding episodes not meeting the criteria for major or clinically relevant non-major bleeding are classified as minor bleeding</td>
<td><strong>Minor bleeding</strong> = clinically overt bleeding that did not satisfy the criteria for major bleeding and that led to hospital admission, physician-guided medical or surgical treatment, or a change in antithrombotic therapy</td>
</tr>
<tr>
<td>outcome(s)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary safety</td>
<td>Minor bleeding</td>
<td>Minor bleeding</td>
<td>Minor bleeding</td>
</tr>
<tr>
<td>outcome</td>
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<tr>
<td>Definition of</td>
<td></td>
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<td></td>
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<tr>
<td>secondary safety</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>outcome</td>
<td></td>
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</tbody>
</table>
Table 3.1 (Continued). Characteristics of clinical trials for newer anticoagulant agents: dabigatran and RE-LY; rivaroxaban and ROCKET-AF, apixaban and ARISTOTLE.

<table>
<thead>
<tr>
<th></th>
<th>RE-LY</th>
<th>ROCKET-AF</th>
<th>ARISTOTLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary statistical</td>
<td>To test whether either dose of dabigatran was noninferior to</td>
<td>To test whether rivaroxaban was inferior to warfarin on treatment population</td>
<td>Test whether apixaban was noninferior to warfarin in reducing the rate of IS or HS or systemic embolism among patients with AF and at least one other risk factor for stroke</td>
</tr>
<tr>
<td>analysis</td>
<td>warfarin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FDA approval status</td>
<td>Brand name: Pradaxa Approval date: October 19, 2010 Approved doses: 75 &amp; 150 mg [Note: 75 mg was not included in the clinical trial]</td>
<td>Brand name: Xarelto Approval date: November 4, 2011 Approved doses: 10, 15, 20 mg</td>
<td>Brand name: Eliquis Approval date: March 30, 2012 in the UK, not yet approved in the US</td>
</tr>
</tbody>
</table>

AF = atrial fibrillation; NVAF = nonvalvular atrial fibrillation; EKG = electrocardiogram; TIA = transient ischemic attack; CHF = chronic heart failure; AFL = atrial flutter; LV = left ventricular; CrCl = creatinine clearance; ASA = aspirin; IV = intravenous; INR = international normalized ratio; IS = ischemic stroke; HS = hemorrhagic stroke; ICH = intracranial hemorrhage; SAH = subarachnoid hemorrhage; MI = myocardial infarction; CNS = central nervous system; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft; RBC = red blood cell; ISTH = International Society on Thrombosis and Hemostasis; FDA = United States Food and Drug Administration
Figure 3.1. Schematic diagram of the model structure.

Base case: 70 year-old patient with nonvalvular atrial fibrillation, an increased risk for stroke (CHADS$_2$ ≥ 1, or equivalent), a renal creatinine clearance (CrCl) of 50 or above, and no contraindication to anticoagulant therapy
3.4.2 Model Time Frame

Once a patient is diagnosed with AF, the effects and cardiovascular consequences of the disease, such as hemorrhage and stroke, are present for the remainder of a patient’s lifetime. Therefore, the model assumed a lifetime horizon where quality-adjusted survival and net costs accumulated during the lifetime of the base case patient population.

3.4.3 Target Population and Perspective

Baseline characteristics of patients in the model matched those of the clinical trial for their respective anticoagulation treatment (S. J. Connolly et al., 2009; C. B. Granger et al., 2011; Patel et al., 2011). The baseline patient population was a hypothetical cohort of 70-year old patients with nonvalvular atrial fibrillation, an increased risk for stroke (CHADS$_2$ $\geq$ 1, or equivalent), a renal creatinine clearance (CrCl) of 50 or above, and no contraindication to anticoagulant therapy.

The disease progression of AF imposes a significant burden on society with its associated adverse events and succeeding sequelae, as well as treatment management. A number of considerations have been addressed regarding the appropriate perspective to use in a model in a consensus statement issued from the panel on cost-effectiveness in health and medicine (M. C. Weinstein, Siegel, Gold, Kamlet, & Russell, 1996). A healthcare panel recommends the use of a societal perspective in decision analysis theory (M. C. Weinstein, Siegel, Gold, Kamlet, & Russell, 1996). For these reasons, the decision analysis was modeled to reflect the societal perspective.
3.4.4 Treatment Allocation

Four treatment strategies and their associated outcomes were assessed in this model: apixaban 5 mg, twice daily; dabigatran 150 mg, twice daily; rivaroxaban 20 mg, once daily; or adjusted-dose warfarin (target INR between 2.0 and 3.0). Three clinical trials evaluating warfarin treatment with the alternative antithrombotic therapy apixaban, dabigatran, and rivaroxaban were identified through a review of the medical literature (S. J. Connolly et al., 2009; C. B. Granger et al., 2011; Patel et al., 2011). The patient characteristics, study objectives, and trial outcomes for each clinical trial were delineated in Chapter 2.

In the ARISTOTLE study, patients who received apixaban were administered a dose of 5 mg twice daily (2.5 mg twice daily for those aged 80 years or older or those with a serum creatinine level of 1.5 mg/dl or greater) (C. B. Granger et al., 2011). Model inputs for dabigatran 150 mg were based on the most current RE-LY trial results (S. J. Connolly et al., 2009; S. J. Connolly, Ezekowitz, Yusuf, Reilly, & Wallentin, 2010). In the ROCKET-AF study, rivaroxaban was administered once daily in 15 mg or 20 mg fixed doses depending upon the renal function of the patient (Patel et al., 2011). Patients with a creatinine clearance (CrCl) between 30 and 49 mL/min received the former dose and patients with a CrCl equal to or greater than 50 mL/min were administered the latter. Treatment selection was based upon evidence presented in the literature, which illustrated the performance of anticoagulation agents superiority to no therapy, aspirin, or aspirin and clopidogrel combination in patients with AF and at a higher risk for stroke (R. G. Hart, Pearce, & Aguilar, 2007). For patients with an intermediate or high risk for stroke
prophylaxis (e.g., CHADS₂ score ≥ 1), the ACCP recommends oral anticoagulation over aspirin or aspirin and clopidogrel combination therapy (You et al., 2012).

3.4.5 Stroke Severity and Risk

In the base case, stroke risk for apixaban 5 mg twice daily, dabigatran 150 mg twice daily, and rivaroxaban 20 mg once daily were identified in their respective clinical trials, ARISTOTLE, RE-LY, and ROCKET-AF (S. J. Connolly et al., 2009; C. B. Granger et al., 2011; Patel et al., 2011). Stroke probability for adjusted-dose warfarin was calculated from pooled clinical trial results reported in ARISTOTLE, RE-LY, and ROCKET-AF (S. J. Connolly et al., 2009; C. B. Granger et al., 2011; Patel et al., 2011). Initial ischemic stroke was classified into one of four categories: fatal, major, minor, or no residual neurologic sequelae (see Table 4.2). Stroke severity probabilities were based on aggregated values published in a study by Kamel and colleagues (Kamel, Johnston, Easton, & Kim, 2012). Those patients with no residual neurologic sequelae incurred the cost and disutility associated with ischemic stroke for a single cycle and returned to the ‘Well’ Markov health state in the next cycle. Patients who experienced a minor or major stroke event transitioned to ‘Post-minor/post-major ischemic stroke’ Markov health states for the remainder of the model duration (Freeman et al., 2011; S. V. Shah & Gage, 2011). The rate of stroke increased by a factor of 1.4 per decade of life (multiplicative adjustment) (Freeman et al., 2011; Laupacis et al., 1994). Following an ischemic stroke or intracranial hemorrhage, a patient’s risk of mortality increased by a factor of 3.7 (Dennis et al., 1993; Nakamizo & Yamamoto, 2010).
Table 3.2. Model Inputs: Event Rates & Utilities

**Events**

<table>
<thead>
<tr>
<th>Events</th>
<th>Patients (N)</th>
<th>Event (N)</th>
<th>Probability</th>
<th>Range</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annual probability of ischemic stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban, 5 mg</td>
<td>9120</td>
<td>162</td>
<td>0.0088</td>
<td>(0.0075-0.0100)</td>
<td>1</td>
</tr>
<tr>
<td>Dabigatran, 150 mg</td>
<td>6076</td>
<td>111</td>
<td>0.0091</td>
<td>(0.0080-0.0100)</td>
<td>2,3</td>
</tr>
<tr>
<td>Rivaroxaban, 20 mg</td>
<td>7061</td>
<td>156</td>
<td>0.0110</td>
<td>(0.0090-0.0119)</td>
<td>4</td>
</tr>
<tr>
<td>Warfarin(^2)</td>
<td>22185</td>
<td>490</td>
<td>0.0110</td>
<td>(0.0090-0.0120)</td>
<td>1-4</td>
</tr>
<tr>
<td>Ischemic strokes with apixaban, dabigatran, rivaroxaban, or warfarin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-disabling</td>
<td>0.091</td>
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<td></td>
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<td>5</td>
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<tr>
<td>Minor</td>
<td>0.415</td>
<td></td>
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<tr>
<td>Major</td>
<td>0.392</td>
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<td>5</td>
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<tr>
<td>Fatal</td>
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<td></td>
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<table>
<thead>
<tr>
<th>Hemorrhage</th>
<th>Patients (N)</th>
<th>Event (N)</th>
<th>Probability</th>
<th>Range</th>
<th>References</th>
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<tr>
<td>Annual rate of ICH</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Apixaban, 5 mg</td>
<td>9088</td>
<td>52</td>
<td>0.0029</td>
<td>(0.0020-0.0040)</td>
<td>1</td>
</tr>
<tr>
<td>Dabigatran, 150 mg</td>
<td>6076</td>
<td>38</td>
<td>0.0031</td>
<td>(0.0020-0.0040)</td>
<td>3</td>
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<tr>
<td>Rivaroxaban, 20 mg</td>
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<td>55</td>
<td>0.0039</td>
<td>(0.0030-0.0050)</td>
<td>4</td>
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<tr>
<td>Warfarin(^2)</td>
<td>22199</td>
<td>296</td>
<td>0.0066</td>
<td>(0.0055-0.0075)</td>
<td>1-4</td>
</tr>
<tr>
<td>ICHs with apixaban, dabigatran, rivaroxaban, and warfarin</td>
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<tr>
<td>Minor</td>
<td>0.17</td>
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<tr>
<td>Major</td>
<td>0.41</td>
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<td>5</td>
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<tr>
<td>Fatal (within 30 days)</td>
<td>0.42</td>
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<table>
<thead>
<tr>
<th>Annual probability of GI hemorrhage</th>
<th>Patients (N)</th>
<th>Event (N)</th>
<th>Probability</th>
<th>Range</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban, 5 mg</td>
<td>9088</td>
<td>105</td>
<td>0.0058</td>
<td>(0.0045-0.0070)</td>
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<tr>
<td>Dabigatran, 150 mg</td>
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<td>188</td>
<td>0.0154</td>
<td>(0.0050-0.0250)</td>
<td>3</td>
</tr>
<tr>
<td>Rivaroxaban, 20 mg</td>
<td>7111</td>
<td>224</td>
<td>0.0156</td>
<td>(0.0050-0.0250)</td>
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<tr>
<td>Warfarin(^2)</td>
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<td>399</td>
<td>0.0089</td>
<td>(0.0080-0.0100)</td>
<td>1-4</td>
</tr>
<tr>
<td>Annual probability of minor hemorrhage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban, 5 mg</td>
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<td>1743</td>
<td>0.0914</td>
<td>(0.0800-0.1000)</td>
<td>1</td>
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<td>Dabigatran, 150 mg</td>
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<td>1787</td>
<td>0.1368</td>
<td>(0.1200-0.1500)</td>
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<tr>
<td>Rivaroxaban, 20 mg</td>
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<td>1185</td>
<td>0.7994</td>
<td>(0.0700-0.0900)</td>
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<td>Warfarin(^2)</td>
<td>22199</td>
<td>5265</td>
<td>0.1118</td>
<td>(0.1000-0.1200)</td>
<td>1-4</td>
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<tr>
<td>Annual probability of fatal hemorrhage</td>
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<td></td>
<td></td>
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<td>Apixaban, 5 mg</td>
<td>9120</td>
<td>34</td>
<td>0.0018</td>
<td>(0.0010-0.0030)</td>
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<td>Dabigatran, 150 mg(^3)</td>
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<td>23</td>
<td>0.0019</td>
<td>(0.0010-0.0030)</td>
<td>1,4</td>
</tr>
<tr>
<td>Rivaroxaban, 20 mg</td>
<td>7111</td>
<td>27</td>
<td>0.0019</td>
<td>(0.0010-0.0030)</td>
<td>4</td>
</tr>
<tr>
<td>Warfarin(^2)</td>
<td>22228</td>
<td>151</td>
<td>0.0034</td>
<td>(0.0020-0.0045)</td>
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<tr>
<td>Myocardial Infarction</td>
<td>Patients (N)</td>
<td>Event (N)</td>
<td>Probability</td>
<td>Range</td>
<td>References</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-------------</td>
<td>-----------</td>
<td>-------------</td>
<td>-------</td>
<td>------------</td>
</tr>
<tr>
<td>Annual rate of MI</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban, 5 mg</td>
<td>9120</td>
<td>90</td>
<td>0.0049</td>
<td>(0.0040-0.0060)</td>
<td>1</td>
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<tr>
<td>Dabigatran, 150 mg</td>
<td>6076</td>
<td>97</td>
<td>0.0080</td>
<td>(0.0070-0.0090)</td>
<td>3</td>
</tr>
<tr>
<td>Rivaroxaban, 20 mg</td>
<td>7061</td>
<td>101</td>
<td>0.0071</td>
<td>(0.0060-0.0080)</td>
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<tr>
<td>Warfarin²</td>
<td>22185</td>
<td>303</td>
<td>0.0068</td>
<td>(0.0060-0.0080)</td>
<td>1,3-4</td>
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<table>
<thead>
<tr>
<th>Event risk rate</th>
<th>Factor</th>
<th>References</th>
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</thead>
<tbody>
<tr>
<td>Increased risk rate of event per decade of life (multiplicative adjustment)</td>
<td>1.4</td>
<td>6</td>
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<tr>
<td>Ischemic stroke</td>
<td>1.97</td>
<td>7</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>1.3</td>
<td>8</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Utilities</th>
<th>QALY (SE)</th>
<th>Range</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial Fibrillation (ICD-9 427)</td>
<td>0.81 (0.0001)</td>
<td>(0.70-0.90)</td>
<td>9</td>
</tr>
<tr>
<td>Decrement for age</td>
<td>-0.0003</td>
<td>(0.000001)</td>
<td>9</td>
</tr>
<tr>
<td>Decrement for anticoagulation</td>
<td>-0.0105</td>
<td>(-0.0110 - -0.0090)</td>
<td>14</td>
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<tr>
<td>Decrement for ischemic stroke (CCC 109)</td>
<td>-0.1393</td>
<td>(0.0001) (-0.1500 - -0.1200)</td>
<td>10</td>
</tr>
<tr>
<td>Neurological event (stroke and ICH) with residual minor</td>
<td>-0.2916</td>
<td>(-0.30 - -0.28)</td>
<td>11</td>
</tr>
<tr>
<td>Major</td>
<td>-0.4455</td>
<td>(-0.46 - -0.43)</td>
<td>11</td>
</tr>
<tr>
<td>Decrement for MI (ICD-9 410)</td>
<td>-0.1351 (0.0002)</td>
<td>(-0.1450 - -0.1200)</td>
<td>9</td>
</tr>
<tr>
<td>Decrement for GI</td>
<td>-0.0486</td>
<td>(-0.0600 - -0.0300)</td>
<td>12</td>
</tr>
<tr>
<td>Decrement for minor hemorrhage</td>
<td>-0.0031</td>
<td>(-0.0040 - -0.0020)</td>
<td>13</td>
</tr>
<tr>
<td>Decrement for dyspepsia4</td>
<td>-0.0032</td>
<td>(-0.0040 - -0.0020)</td>
<td>12</td>
</tr>
</tbody>
</table>

NR = not reported; NC = not calculated; ICH = intracranial hemorrhage; GI = gastrointestinal; MI = myocardial infarction; QALY = quality-adjusted life-year; SE = standard error

¹ Summed ischemic and unspecified strokes for rivaroxaban 20 mg, once daily
² Warfarin event rates were pooled warfarin events from ARISTOTLE, RE-LY, and ROCKET-AF
³ Fatal hemorrhage was not reported in the apixaban trial (ARISTOTLE). A weighted average was calculated using RE-LY (dabigatran 150 mg) and ROCKET-AF (rivaroxaban 20 mg).
⁴ Dyspepsia event only for patients receiving dabigatran 150 mg, twice daily

3.4.7 Hemorrhage Severity and Risk

Rates of hemorrhage events for each therapy were obtained from published clinical trials (S. J. Connolly et al., 2009; S. J. Connolly, Ezekowitz, Yusuf, Reilly, & Wallentin, 2010; C. B. Granger et al., 2011; Patel et al., 2011). Hemorrhage was classified as one of four categories: fatal, ICH, gastrointestinal, or nonfatal minor extracerebral. Similar to ischemic stroke, pooled hemorrhage events from the clinical trials for the other three therapies were used for warfarin values (S. J. Connolly et al., 2009; C. B. Granger et al., 2011; Patel et al., 2011). Using aggregated probabilities reported in a study by Kamel and colleagues, an ICH event was further subcategorized as fatal, major, or minor (see Table 4.2) (Kamel, Johnston, Easton, & Kim, 2012).

3.4.8 Mortality Rates

Mortality rates for the baseline population were initially adjusted in the model for age (starting at 70 years) (Arias, 2011). A patient’s mortality risk was adjusted for age and post-event mortality risks (MI, ischemic stroke, and ICH) throughout the course of the patient’s lifetime and disease progression (Arias, 2011; Dennis et al., 1993; Kannel, Sorlie, & McNamara, 1979).

3.4.9 Myocardial infarction

Rates of MI were recorded from published clinical trial results (S. J. Connolly et al., 2009; C. B. Granger et al., 2011; Patel et al., 2011). Warfarin MI rates were pooled from the results of the warfarin therapy control arms in the three clinical trials. The
increased risk of MI each decade of the patient’s lifetime was increased by a factor of 1.3 (multiplicative adjustment) (Freeman et al., 2011). Mortality rates following an MI event increased multiplicatively by a factor of 1.051 (Kannel, Sorlie, & McNamara, 1979).

3.4.10 Dyspepsia

A relatively common side effect of using dabigatran 150 mg is dyspepsia. As reported in the RE-LY trial, 11.3 percent of patients receiving dabigatran 150 mg experienced a dyspepsia event. The associated cost and utility decrement with dyspepsia was included for patients with the side effect (Agency for Healthcare Research and Quality, 2009; S. R. Earnshaw, Scheiman, Fendrick, McDade, & Pignone, 2011).

3.4.11 Therapy Adherence and Discontinuation

Therapy adherence rates were assumed to be similar across all treatments and were, therefore, not parameterized in the model. Furthermore, the efficacy was assumed to remain constant over time for apixaban, dabigatran, rivaroxaban, and warfarin.

3.4.12 Discounting

Discounting was used to reflect an individual’s positive rate of time preference (Drummond MF, Sculpher MJ, Torrance GW, 2005). There are a few reasons why people have higher preference for benefits today rather than in the future. First, the individual may have a short-term view of life and may not feel they will not reap the rewards of future benefits. Second, the future is uncertain and individuals tend to want
benefits immediately rather than wait to see what future returns may bring. Third, industrialized countries have seen a positive economic growth since the Second World War and believe they will be wealthier in the future. Therefore, monetary earnings today will be worth more than in the future when an individual expects to have a higher income. Lastly, as the trend of individuals leans toward positive rate of time preference, one will usually make a positive return when engaging in a riskless investment (Drummond MF, Sculpher MJ, Torrance GW, 2005). For these reasons, discounting was used to reflect a patient’s time preference for both treatment benefits and costs. An annual discount rate of three percent was applied in the primary model, with a subsequent sensitivity analysis (SA) of zero and five percent (M. C. Weinstein, Siegel, Gold, Kamlet, & Russell, 1996).

3.4.13 Costs

Costs incurred at the societal level include all the direct costs associated with the third party payer perspective as well as indirect costs the patient and his or her care giver(s) incurred. Direct costs included costs of hospitalization for an event, costs of patient visits, cost of INR testing (only for warfarin), and treatment costs. Costs of hospitalization for ischemic stroke with no neurologic sequelae (ICD-9 434.91), intracranial hemorrhage (ICD-9 430-432), myocardial infarction (410.71), and gastrointestinal hemorrhage (ICD-9578.9) were estimated from 2009 mean costs published online by the Agency for Healthcare Research and Quality (AHRQ) from Healthcare Cost and Utilization Project (HCUP) data under relevant primary ICD-9 codes.
and diagnosis-related group (DRG) codes for Medicare remuneration (Agency for Healthcare Research and Quality, 2009). Costs for minor ischemic stroke (ICD-9 434.91 & DRG 64) and major ischemic stroke (ICD-9 434.91 & DRG 65) were estimated using the average mean cost values reported from 2009 AHRQ HCUP online (Agency for Healthcare Research and Quality, 2009). Cost of a minor hemorrhage was based on remuneration for an expended problem-focused physician visit for an established patient (Current Procedural Terminology [CPT] code 99213) (American Medical Association, 2009). Costs of INR testing (CPT code 85610) and physician visits (CPT codes 99211 & 99212) were estimated using Medicare remuneration values published in Roche’s 2009 Medicare Reimbursement Handbook (American Medical Association, 2009). Mean prescription drug costs for dabigatran 150 mg, rivaroxaban 20 mg, and warfarin were estimated using wholesale acquisition costs (WAC) listed in the Medi-Span drug database. Apixaban has not yet been approved for the US market and, therefore, the US price has not been established. The listed price for apixaban 5mg in the United Kingdom reported in the National Institute for Health and Clinical Evidence (NICE) costing statement was used (£3.43 per day) and converted to US dollars (National Health Service, 2012).

Direct costs included long-term costs, whereas indirect costs included the economic cost of physician visits and INR testing. Long-term costs were estimated using Leibson and colleagues study evaluating the utilization of acute care services 12 months following an ischemic stroke or intracranial hemorrhage (Leibson et al., 1996). Jonas and colleagues’ study eliciting patient time requirements for warfarin anticoagulation therapy
was used to estimate the economic cost of patient time (Jonas, Shilliday, Laundon, & Pignone, 2010). The study by Jonas and colleagues was a prospective observation design evaluating adult patients receiving treatment in a university-based anticoagulation program. Authors used patient questionnaires and record diaries to calculate the time required for one visit to the anticoagulation clinic, which included travel time, waiting time, and the length of the clinic visit. The human capital approach, a method which estimates the foregone earnings of a patient attributable to a health condition in the absence of market prices, was used to estimate the value of the patients’ time. An equivalent study has not been conducted for new anticoagulant therapies and, therefore, the estimate of clinic visits alone (excluding anticoagulation-related activities) was used for patients modeled to receive apixaban, dabigatran, or rivaroxaban. Indirect costs typically include costs associated decreased productivity. Annual market earnings, however, peak in the 45 to 54 year range and diminish considerably after the age of 65. The baseline population age in the model was 70-years old and, therefore, indirect costs associated with earnings did not apply in this model (Taylor et al., 1996). All model costs are listed in Table 4.3 (Agency for Healthcare Research and Quality, 2009; Coyne et al., 2006). Costs were implemented in each cycle according to the health state the patient occupied. The cost for each Markov state was weighted according to the amount of time a person spent in the health state. After completing the model simulations, a summed amount was calculated for each treatment. When necessary, costs were inflated to 2012 US dollars (USD) using the medical care component of the US Bureau of Labor Statistics’ Consumer Price Index (CPI). All costs were expressed in 2012 USD.
<table>
<thead>
<tr>
<th>One-time event costs</th>
<th>Mean (SE)</th>
<th>Range</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic stroke, no residua</td>
<td>$9,503.39 ($163.02)</td>
<td>($4,000-$16,000)</td>
<td>1</td>
</tr>
<tr>
<td>(ICD-9 434.91, DRG 66)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor ischemic stroke</td>
<td>$10,669.51 ($163.02)</td>
<td>($4,000-$16,000)</td>
<td>1</td>
</tr>
<tr>
<td>(ICD-9 434.91, DRG 65)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major ischemic stroke</td>
<td>$13,337.50 ($259.13)</td>
<td>($10,000-$25,000)</td>
<td>1</td>
</tr>
<tr>
<td>(ICD-9 434.91, DRG 64)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>$20,790.34 ($520.70)</td>
<td>($15,000-$65,000)</td>
<td>1</td>
</tr>
<tr>
<td>(ICD-9 430-432)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>$20,323.17 ($350.38)</td>
<td>($10,000-$45,000)</td>
<td>1</td>
</tr>
<tr>
<td>(ICD-9 410.71)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal hemorrhage</td>
<td>$10,201.12 ($159.37)</td>
<td>($5,000-$15,000)</td>
<td>1</td>
</tr>
<tr>
<td>(ICD-9 578.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>$6,648.00 ($447.00)</td>
<td>($3,500-$9,000)</td>
<td>1</td>
</tr>
<tr>
<td>(ICD-9 536.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor hemorrhage</td>
<td>$83.94 ($0 - $200)</td>
<td>2, 3</td>
<td></td>
</tr>
<tr>
<td>(CPT 99213)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>$10,000.00 ($0 - $20,000)</td>
<td>3, 4</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Long-term event costs, yearly</th>
<th>Estimate</th>
<th>Range</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor ischemic stroke</td>
<td>$20,880.24</td>
<td>($12,000 - $48,000)</td>
<td>5</td>
</tr>
<tr>
<td>Major ischemic stroke</td>
<td>$64,629.36</td>
<td>($24,000 - $102,000)</td>
<td>5</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>$96,926.04</td>
<td>($24,000 - $120,000)</td>
<td>5</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>$3,638.40</td>
<td>($1,568.28 - $7,267.68)</td>
<td>6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Therapy costs, yearly</th>
<th>Estimate</th>
<th>Range</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban 5 mg</td>
<td>$3,920.10</td>
<td>($1,825 - $5,475)</td>
<td>7</td>
</tr>
<tr>
<td>Dabigatran 150 mg</td>
<td>$2,664.50</td>
<td>($1,460 - $3,650)</td>
<td>8</td>
</tr>
<tr>
<td>Rivaroxaban 20 mg</td>
<td>$2,660.85</td>
<td>($1,460 - $3,650)</td>
<td>8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Warfarin</th>
<th>Mean (SE)</th>
<th>Range</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$164.25 ($181.56)</td>
<td>($109.90-$730)</td>
<td>8</td>
</tr>
</tbody>
</table>
A utility value ranging from zero to one corresponding to the quality of life for that health state was used. Quality-adjusted life-years (QALYs) were estimated using utility values calculated for each health state. The QALY is a summary measure of health assigned to each health state over time. QALYs were calculated as the product of the utility for the health state multiplied by the amount of time spent in the health state. Aggregate lifetime QALY measures were the sum of every calculated QALY in the treatment pathway. The number of QALYs represented the number of healthy years of life that were valued equivalently to the actual health outcome.

The baseline patient utility value was adjusted for age, AF, and anticoagulation treatment to reflect the disutility associated with the comorbidity AF and aging, as well as the disutility affiliated with receiving anticoagulation therapy (Gage, Cardinalli, & Owens, 1996; Sullivan & Ghushchyan, 2006). Subsequent disutilities associated with

<table>
<thead>
<tr>
<th>Table 3.3 (Continued). Model Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Warfarin associated costs, yearly</strong></td>
</tr>
<tr>
<td>INR testing (monthly)* (CPT 85610)</td>
</tr>
<tr>
<td>Minimal established visits (monthly)* (CPT 99211, 99212)</td>
</tr>
<tr>
<td>Economic value of patient time for INR test*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Non-warfarin associated costs</strong></th>
<th>Estimate</th>
<th>Range</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal established visit (every 3 months)** (CPT 99211, 99212)</td>
<td>$136.00</td>
<td>($68 - $408)</td>
<td>2</td>
</tr>
<tr>
<td>Economic value of patient time for office visit**</td>
<td>$229.36</td>
<td>($114.68 - $688)</td>
<td>9</td>
</tr>
</tbody>
</table>

DRG = Diagnostic Related Group; SE = standard error; CPT = Current Procedural Terminology; INR = International Normalized Ratio
1 Dyspepsia costs for patients receiving dabigatran 150 mg, twice daily.
* Low range value = every 3 months; high range value = every 2 weeks
** Low range value = every 6 months; high range value = every month

disease progression were estimated using pooled nationally representative Medical Expenditure Panel Survey (MEPS) data, as well as published population-specific articles (see Table 4.2) (Gage, Cardinalli, & Owens, 1996; Pignone, Earnshaw, Pletcher, & Tice, 2007; Sullivan, Lawrence, & Ghushchyan, 2005; Sullivan & Ghushchyan, 2006; Tengs & Lin, 2003). When necessary, utilities reported in the literature were transformed into utility decrements relative to AF using the following equation:

\[ \text{Utility decrement} = u_{AF} - (u_{AF} \times U), \]

where

\( u_{AF} \) represents the utility for AF (i.e., QALY = 0.81) and \( U \) represents the utility, measured as a QALY, for a given event.

An annual discount rate of three percent was applied, with a subsequent utility sensitivity analysis (SA) of zero and five percent (M. C. Weinstein, Siegel, Gold, Kamlet, & Russell, 1996).

### 3.5 Statistical Analyses

#### 3.5.1 Model Outcomes

For each treatment pathway, model outcomes included the number of clinical events (normalized to 100 patient-years), aggregated QALYs, total and disaggregated costs (prescription, clinical event, and follow-up care), aggregated life-years (LYs) and ICERs per QALY gained.
3.5.2 Sensitivity Analyses

The base analysis compared costs and effects of apixaban, dabigatran, rivaroxaban, and warfarin. A univariate SA was used to estimate to vary specified parameters one at a time in order to evaluate the impact on study results. A tornado diagram was constructed to assess the relative impact of 1) each parameter based on the results of the sensitivity analyses conducted and 2) key model assumptions. The results of the tornado diagram were used to identify key determinants of cost-effectiveness for therapy-aided stroke prevention in patients with AF.

To reflect the full uncertainty of stochastic parameter inputs, first- and second-order Monte Carlo simulations were used to conduct probabilistic sensitivity analyses (PSAs). A first-order simulation was used to investigate the uncertainty in the estimated cost and effects as they relate to the uncertainty inherent in the probabilistic structure of the model (A. H. Briggs, 2000). First-order uncertainty distinguishes the random variation in outcomes for individual patients, contingent upon underlying parameter values such as disease prevalence, case mortality rates, treatment efficacy, mean and variance of resource utilization, and mean and variance of health state utilization. To perform the first-order simulation analysis, 5,000 patients were followed through the model individually. The path followed by patients will differ for each individual, as the paths are directly related to chance. Following each patient individually through the model allowed an overall profile of costs and outcomes generated for each patient’s path. The resulting cost and effect differences were plotted in a cost-effectiveness plane.
Second-order uncertainty characterizes the imprecision of known evidence for the parameter values themselves. Second-order simulation analyses were performed with appropriate distributional assumptions for each variable parameterized, which related to the nature of the variable. A gamma distribution was used for costs to address the skewed nature of data. Transition probabilities and utilities (i.e., QALYs) are bound by the zero to one interval and, therefore, these parameters were assumed to have beta distributions (A. H. Briggs, 2000). Monte Carlo simulations of 100 sets of simulated parameters were used to estimate ICERs for each anticoagulant treatment, along with the associated 95 percent confidence intervals (95% CIs).

3.5.2.1 Incremental Cost-Effectiveness Ratio

The incremental cost-effectiveness ratio (ICER) derived from treatment costs and effects was used to compare a new treatment (T$_1$) (i.e. comparator treatment) with a standard (i.e. reference treatment), accepted therapy (T$_0$). This ratio is defined in the following way:

$$\text{ICER} = (C_1 - C_0)/(E_1 - E_0) = \Delta C/\Delta E$$ \hspace{1cm} (2)

The calculated ICER was constructed from the sample means of cost and effect estimates (C$_1$, C$_0$ and E$_1$, E$_0$, respectively). The numerator of this ratio is the incremental cost, whereas the denominator denotes the incremental benefit of the new treatment relative to the comparator. The ratio was interpreted as the additional investment of
resources necessary for each additional unit of health improvement expected to result from investment in treatments $T_1$ rather than $T_0$ (Stinnett & Mullahy, 1998).

Due to the uncertainty surrounding these estimates, an important component to ICER estimation is calculating the uncertainty surrounding the ratio. A probabilistic sensitivity approach, as previously discussed, was used to incorporate information about the joint probability distribution of cost and benefit estimates. Using this method, the 95 percent confidence interval (CI) depicting the uncertainty around the ICER for each of the four anticoagulants was calculated.

ICERs were plotted on a cost-effectiveness (CE) plane to illustrate the deterministic estimate of the incremental cost and benefit of one treatment compared to another, as well as to depict the stochastic uncertainty surrounding this point estimate. Figure 4.2 is an example of a CE plane and the associated results of treatment comparisons for ICERs plotted in each quadrant. When the ICER is plotted in Quadrant IV (Southeast), the comparator treatment was considered ‘dominant’ in relation to the reference treatment, whereas if the ICER is in Quadrant II (Northwest), the comparator is ‘dominated’ and would be considered an inferior treatment choice compared to the reference treatment. If the ICER is graphed in either Quadrant I (Northeast) or Quadrant III (Southwest), comparator treatment trade-offs exists for either the treatment cost or effect in relation to the reference treatment.
If the ICER is plotted in Quadrant I, then there is an increased benefit from the comparator treatment at the cost of elevated treatment prices. When an ICER is plotted in Quadrant III it signifies a decrease treatment effect with an associated decrease in treatment cost. A comparator treatment located in Quadrant III may be cost-effective if the difference in treatment effect is not clinically significant. Probabilistic ICER values with the corresponding 95 percent CI was depicted as a ‘cloud’ (similar to an elliptical shape) of point estimates and the result often overlapped into two or more quadrants, resulting in a more complicated treatment decision. Figure 4.3 illustrates a cost-effectiveness plane with nine scenarios of the joint distribution of costs and effects, each located on a different part of the plane with varying interpretations. In the figure, scenarios A-D are equivalent to Quadrants I-IV, respectively, described above. Scenarios E-H represent situations where 95 percent of the joint density ($\Delta C$, $\Delta E$) occupies two quadrants and it becomes more difficult to determine treatment dominance. In other cases the joint density will occupy all four quadrants, as depicted with scenario I.
3.5.2.2 Cost-Effectiveness Acceptability Curve

Cost-effectiveness acceptability curve (CEAC) plots were included as a complimentary figure to the stochastic value plotted on the CE plane to aid a decision-maker. The CEAC was originally introduced as an alternative representation of confidence intervals around ICERs to demonstrate the uncertainty regarding the cost-effectiveness of a health care treatment in the context of decisions involving two competing interventions (Fenwick, O'Brien, & Briggs, 2004). The CEAC was derived from the joint density of incremental costs ($\Delta C$) and incremental effects ($\Delta E$) and represented the proportion of density where the comparator treatment was cost-effective for a range of values of $\lambda$, otherwise known as the willingness-to-pay (WTP) threshold. WTP may be thought of as the amount society is willing to pay for a unit of health effectiveness. Alternatively, WTP may also be interpreted as the cost per unit of
effectiveness of some other program from which resources must be diverted in the case of new treatment adoption. Estimation with the Monte Carlo simulation produced a CEAC as the proportion of \((\Delta C, \Delta E)\) points where the intervention was cost-effective (Fenwick, O’Brien, & Briggs, 2004). Figure 4.4 illustrates the CEAC derived from the joint density \((\Delta C, \Delta E)\) scenarios presented above.

**Figure 3.4.** Cost-effectiveness acceptability curve derived from probabilistic ICER values demonstrating the joint density from the four cost-effectiveness plane quadrants.

More specifically, the curves A-D correlate with the A-D scenarios described above. Curve A correlates with an ICER plotted in Quadrant I (i.e., trade-off treatment), curve B in Quadrant IV (i.e., dominant treatment), curve C in Quadrant III (i.e., trade-off treatment), and curve D in Quadrant II (i.e., dominated treatment). When a Monte Carlo
simulation is used, the CEAC is determined as the proportion of \((\Delta C, \Delta E)\) points where the intervention is cost-effective.

3.5.2.3 Incremental Net Benefit

A negative ICER creates a complicated interpretation and is a major criticism of the method. An alternative comparison method that circumvents the issue of the negative ICER is the incremental net benefit (INB) estimation. For each comparator treatment, the INB is the difference in \(\Delta E\) (the expected increase in effectiveness of offering a comparator treatment rather than the standard) and \(\Delta C/\lambda\) (the expected reduction in effectiveness caused by diverting resources from one treatment to fund another). In keeping with similar notation introduced for the ICER equation, the INB may be estimated in the following way:

\[
\text{INB} = (C_1 - C_0) - (E_1 - E_0)/\lambda = \Delta C - \Delta E/\lambda
\]

For INB greater than zero, the comparator treatment is deemed cost-effective at the selected WTP threshold and should be selected for implementation. For INB less than zero, more health benefit could be attained by foregoing the comparator treatment and investing the healthcare resources elsewhere. In the case where INB equals zero, the additional health benefit exactly offsets the cost of the implementing the comparator treatment. However, when using continuously distributed costs and effects to estimate the INB, the probability of the INB being exactly zero is zero.
3.5.3 Software

Model implementation, sensitivity analyses, and outcome calculations were performed using TreeAge Pro 2011 (TreeAge Software, 2012). There were multiple advantages of using this software program for the study: 1) user-friendly interface; 2) created specifically for decision analyses; 3) allowed multiple outputs and graphing options; 4) had the capacity to include variable distributions; 5) allowed Monte Carlo sampling; and 6) had the ability to incorporate dynamic transition probabilities. There were also a few limitations to using TreeAge Pro. First, use of the model in the program was limited to users with a software license. This makes it difficult to share the model and allow other parties to make alterations. Furthermore, the software is expensive (annual license of $575 for the Suite version), which deters other stakeholders from purchasing it. Second, the program did not allow the implementation of a discrete event simulation. This limits the analyst to using population-level data instead of patient-level data.

3.6 Study Limitations

There were several limitations to this study that may be categorized into three main sources: limitations related to available data sources, limitations related to model assumptions applied, and limitations related to modeling capabilities.

Values used to populate model parameters were extrapolated from a variety of different data sources. Treatment efficacy and adverse events for apixaban, dabigatran, and rivaroxaban were based on a single clinical trial for each therapy (ARISTOTLE, RE-
LY, and ROCKET-AF, respectively) (S. J. Connolly et al., 2009; S. J. Connolly, Ezekowitz, Yusuf, Reilly, & Wallentin, 2010; C. B. Granger et al., 2011; Patel et al., 2011). Each trial had a median follow-up of two years and enrolled patients with an average age of 71 years. There were a few limitations using these particular trials. First, reliance on one clinical trial for each therapy is the sole of clinical data is a potential cause for concern. Although ARISTOTLE, RE-LY, and ROCKET-AF are some of the largest trials of AF, this makes assessing the effect of any possible weaknesses in the design of the studies difficult. Second, rates of adverse events may vary over the long term and extrapolation of two-year data to a lifetime model may not accurately represent the lifetime progression of the disease. Third, extrapolating from 70 years to future age decades may lead to inaccurate results as patients may have different treatment responses as they age.

The next two limitations for the use of these clinical trials were related to differences among trial patients, which may have influenced the model results. First, patients enrolled in the rivaroxaban trial (ROCKET-AF) were at a higher risk of stroke according to the CHADS\(_2\) scores. Trials with apixaban and dabigatran (ARISTOTLE and RE-LY, respectively) had a fairly similar distribution for patients CHADS\(_2\) scores less than or equal to one, score of two, or scores greater than or equal to three (32.2%, 35.2%, and 32.6%, respectively for dabigatran; 34%, 35.8% and 30.2%, respectively for apixaban) (Patel et al., 2011). Patients in clinical trial for rivaroxaban (ROCKET-AF) had no patients in the lowest CHADS\(_2\) score group (CHADS\(_2\) ≤ 1), 14 percent of the patients in the middle score group (CHADS\(_2\) = 2), and 86 percent of the patients in the
highest stroke risk group (CHADS$_2$ $\geq$ 3) (Patel et al., 2011). Given the substantial differences in risk for stroke prophylaxis, the results for apixaban and dabigatran relative to rivaroxaban may be skewed. Second, clinical trials like ARISTOTLE, RE-LY, and ROCKET-AF use algorithms for imputing dummy INR of the warfarin placebo in patients who are not receiving warfarin in order to maintain blinding (del Zoppo & Eliasziw, 2011). Trials like these also typically use a method in which the measured INR values and the interval between INR tests are both taken into account (del Zoppo & Eliasziw, 2011). Based on this approach, INR values were within a therapeutic range a mean of 62 percent in the ARISTOTLE trial, 64 percent in the RE-LY trial, and 55 percent in the ROCKET-AF trial (S. J. Connolly et al., 2009; C. B. Granger et al., 2011; Patel et al., 2011). The interpretation on noninferiority in a given trial may be due to not only homogeneity of trial design and patients, but also on the treatment accuracy of the warfarin cohort and on the dummy INR algorithm used (del Zoppo & Eliasziw, 2011).

Because not all the information needed to populate a model was included in the clinical trials, it was necessary to include a variety of other data sources to populate the model. Other sources were used to collect values for costs, utilities, and other adverse events (i.e., stroke severity and disability following stroke). The necessity of bringing together data from a wide variety of sources has the potential to introduce bias into the analysis. It was also necessary to pool the data for warfarin patients from each clinical trial.

There were a number of assumptions specified for the model structure and parameters that limit the accurateness of the model. First, two studies were included in
addition to the clinical trials to estimate the post-stroke severity as well as the death and disability following an ICH (Fang et al., 2007; Hylek et al., 2003). A study by Fang and colleagues was used to derive death and disability following ICH events (Fang et al., 2007). The study included a cohort of 13,559 patients with NVAF enrolled in the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study. The ATRIA study included subjects enlisted as patient members of Kaiser Permanente in Northern California. The mean age of the patients was slightly higher (78 years) than those included in the clinical trials. The time in therapeutic range was not reported, however the patients with an ICH event had a median INR of 2.7 (interquartile range [IQR]: 2.3-4.0). Stroke severity for following an stroke event was derived from a study conducted by Hylek and colleagues, who also used patients enrolled in the ATRIA study (Hylek et al., 2003). Patients included in the study were categorized as having an ischemic stroke in accordance with the antithrombotic status at hospital admission. Patients had a median INR of 1.7 (IQR: 1.3-2.2).

A couple of further assumptions were included in the model. First, it was assumed that treatment efficacy was sustained beyond the trial period, as there was no biological reason to assume that efficacy of anticoagulants would change in adherent patients. Furthermore, therapy adherence rates were assumed similar across all treatments and were not parameterized in the model. Second, patients were assumed to remain adherent to assigned therapies.

Limitations related to model capabilities were associated with the health state specifications and the comparison of treatment ICER results. With regard to health state
specifications, a Markov model has an inherent memoryless property that limits the way the disease progression is modeled. In other words, the progression between health states is not representative of real life in that the patient’s health state is not contingent upon the prior health state. In real life, the patient’s health status depends on their previous health status and the prior health state would influence the subsequent health state. With respect to ICER comparisons, there was no statistical measure to evaluate the difference between the final ICER values of the four anticoagulant therapies. It was possible to assess the deterministic ICER value along with its associated confidence interval in relation the other therapies, however, no statistical test was performed to test the difference between the ICER values.
4 RESULTS

4.1 Introduction

This chapter presents the results of a Markov model used to assess the cost-effectiveness of anticoagulation treatments for the prevention of stroke prophylaxis in patients with atrial fibrillation. Results presented in this chapter include the following:
(1) a comparison of the clinical trials, (2) overall results, (3) incremental cost-effectiveness ratios (ICERs) for pairwise comparisons among treatments, (4) incremental net monetary benefit (INMB) pairwise comparisons among treatments, (5) total lifetime costs for each treatment pathway, (6) total direct costs for each treatment pathway, (7) total indirect costs for each treatment pathway, (8) total life-years yielded for each therapy, (9) total quality-adjusted life-years (QALYs) produced for each treatment, (10) one-way sensitivity analyses for costs, utilities, and probabilities, (11) probabilistic sensitivity analyses (PSAs), and (12) conclusions from hypothesis test proposed for this study.

4.2 Clinical Trial Comparisons

Overall, the Phase III clinical trials (ARISISTOTLE, RE-LY, and ROCKET-AF) assessing new anticoagulants’ efficacy relative to warfarin have suggested that all three therapies are at least as efficacious as dose-adjusted warfarin and have a similar hemorrhaging profile (S. J. Connolly et al., 2009; S. J. Connolly, Ezekowitz, Yusuf, Reilly, & Wallentin, 2010; C. B. Granger et al., 2011). In each trial, the new anticoagulant agents were determined to be at least noninferior to warfarin for the
composite endpoint of stroke (including hemorrhage) and systemic embolism (Miller, Grandi, Shimony, Filion, & Eisenberg, 2012). In addition, ARISTOTLE and RE-LY trials demonstrated superiority of apixaban and dabigatran, respectively, relative to warfarin for the composite outcome of stroke and systemic embolism. All three new therapies were associated with significantly decreased risk for hemorrhagic stroke in comparison to warfarin. Dabigatran and rivaroxaban were found to have comparable risks of major hemorrhaging relative to warfarin, whereas apixaban demonstrated superiority for this safety outcome. Miller and colleagues deemed gastrointestinal (GI) hemorrhage heterogeneous among the trials and, therefore, this outcome was not included in their meta-analysis (Miller, Grandi, Shimony, Filion, & Eisenberg, 2012).

The ARISTOTLE study was a randomized, double-blind, multicenter, noninferiority trial evaluating apixaban 5 mg, twice daily relative to dose-adjusted warfarin (C. B. Granger et al., 2011). The results of the clinical trial showed apixaban was superior to warfarin in preventing stroke or thromboembolism (Hazard Ratio (HR): 0.79; 95% confidence interval [CI]: 0.66, 0.95; p=0.01). Furthermore, apixaban reduced both major hemorrhage (HR: 0.69; 95% CI: 0.6, 0.8; p<0.001) and ICH (HR: 0.42; 95% CI: 0.3, 0.58; p<0.001) relative to warfarin.

The RE-LY clinical trial was a randomized, multicenter study assessing dabigatran 150 mg twice daily with dose-adjusted warfarin, and the only trial out of the three to distribute therapies as open-label (S. J. Connolly et al., 2009). When compared with dose-adjusted warfarin, dabigatran 150 mg was associated with a lower incidence of
stroke and thromboembolism (HR: 0.65; 95% CI: 0.52, 0.81; p<0.001) and similar major hemorrhaging (HR: 0.93; 95% CI: 0.81, 1.07; p=0.32) relative to warfarin.

The ROCKET-AF trial was a randomized, double blind, double-dummy, multicenter study evaluating rivaroxaban 20 mg, once daily with dose-adjusted warfarin (Patel et al., 2011). Compared to dose-adjusted warfarin, rivaroxaban 20 mg did not achieve statistical significance in stroke and thromboembolism reduction (HR: 0.88; 95% CI: 0.75, 1.03; p=0.12). Similarly, rivaroxaban did not reach statistical significance in lowering major or nonmajor hemorrhage (HR: 1.04; 95% CI: 0.9, 1.2; p=0.58) in patients with AF relative to warfarin.

There were a number of similarities and differences in patient characteristics and risk profiles among patients enrolled in these three clinical trials, ARISTOTLE, RE-LY, or ROCKET-AF (see Table 3.1). Trials were similar with regards to age, proportion of females, prior myocardial infarction (MI), and prior aspirin use. The mean/median ages of patients enrolled as well as the proportions of female patients were broadly similar (G. Y. Lip, Larsen, Skjoth, & Rasmussen, 2012). Likewise, the proportion of patients entering the trials with prior MI and prior aspirin use were similar among the trials.

Differences existed between the three clinical trials with respect to the patient risk profiles (i.e., CHADS2 scores), prior comorbidities, secondary prevention, and prior warfarin use. With respect to patient characteristics, there was greater than a 50 percentage point difference in CHADS2 scores for those patients enrolled in ROCKET-AF compared to patients in ARISTOTLE and RE-LY (G. Y. Lip, Larsen, Skjoth, & Rasmussen, 2012). Patients enrolled in the ROCKET-AF trial also had a higher
prevalence of prior heart failure, hypertension, and diabetes relative to patients in the other two clinical studies. Furthermore, there was approximately a 35 percentage point difference in the proportion of patients enrolled in the trial as secondary prophylaxis prevention between ROCKET-AF patients compared to the other trials (G. Y. Lip, Larsen, Skjoth, & Rasmussen, 2012). The high-risk patients recruited for the ROCKET-AF trial may be a contributing factor for rivaroxaban’s non-superiority relative to the trial patients receiving dose-adjusted warfarin (O’Dell, Igawa, & Hsin, 2012). In a subgroup analysis of the RE-LY trial, dabigatran 150 mg did not demonstrate superiority in comparison to warfarin but did maintain noninferiority in high-risk patients with CHADS\textsubscript{2} scores \( \geq 3 \) (H. C. Diener et al., 2010). Management of warfarin’s therapeutic effect in the ROCKET-AF study appeared to be suboptimal relative to warfarin’s therapeutic effect in the other two studies, in which time in therapeutic range (TTR) in the ROCKET-AF trial was 55 percent, whereas RE-LY and ARISTOTLE trials had 64 percent and 62 percent, respectively (S. J. Connolly et al., 2009; C. B. Granger et al., 2011; Patel et al., 2011).

There are important differences among trials with regards to study design and drug administration. Dabigatran and warfarin therapy assignments were not concealed in the RE-LY trial (S. J. Connolly et al., 2009). In contrast, ARISTOTLE and ROCKET-AF trials successfully achieved double blind therapy administration (C. B. Granger et al., 2011; Patel et al., 2011). Dabigatran and apixaban treatments were administered twice daily, whereas rivaroxaban was administered once each day (S. J. Connolly et al., 2009; C. B. Granger et al., 2011; Patel et al., 2011). Prior warfarin use varied slightly among
the patients, with 62.4 percent in the ROCKET-AF trial, 50 percent in RE-LY (by design), and 57 percent in ARISTOTLE (S. J. Connolly et al., 2009; C. B. Granger et al., 2011; Patel et al., 2011).

### 4.3 Overall Results

Mean costs and QALYs derived from the probabilistic sensitivity analysis are presented in table 4.1. The least expensive therapy was warfarin with a mean cost of $71,843 (Standard Deviation (SD): $2,192), whereas the most expensive treatment was apixaban (mean: $81,176; SD: $1,308). Although apixaban was the most expensive therapy among the four treatments, it yielded the highest mean QALY value of 8.63 (SD: 0.05) and warfarin had the lowest mean QALY yield of 8.17 (SD: 0.04).

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Cost (SD)</th>
<th>95% CI</th>
<th>QALYs (SD)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban (5mg, BID)</td>
<td>$81,176 ($1,308)</td>
<td>($78,642, $83,756)</td>
<td>8.63 (0.05)</td>
<td>(8.52, 8.72)</td>
</tr>
<tr>
<td>Dabigatran (150 mg, BID)</td>
<td>$78,558 ($1,714)</td>
<td>($75,277, $81,968)</td>
<td>8.56 (0.06)</td>
<td>(8.43, 8.67)</td>
</tr>
<tr>
<td>Rivaroxaban (20 mg, QD)</td>
<td>$74,028 ($1,619)</td>
<td>($70,943, $77,307)</td>
<td>8.42 (0.06)</td>
<td>(8.31, 8.54)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>$71,843 ($2,192)</td>
<td>($68,730, $77,452)</td>
<td>8.17 (0.04)</td>
<td>(8.1, 8.24)</td>
</tr>
</tbody>
</table>

BID = twice daily; CI = confidence interval; SD = standard deviation; QD = once daily

Figure 4.1 illustrates the baseline costs and effectiveness measures of the four treatment therapies assessed in this analysis. All four therapies were non-dominated treatment options that present a set of possible optimal choices given the threshold value set.
Figure 4.1. Cost-effectiveness plot of apixaban 5 mg, dabigatran 150 mg, rivaroxaban 20 mg, and warfarin.

Figure 4.2 shows a scatterplot of the costs and utilities estimated for each treatment derived from the probabilistic sensitivity analysis. This scatterplot suggests that each treatment offers more utility at a higher cost than the previous treatment. Warfarin is the least costly therapy with the least number of QALYs gained, whereas patients receiving the most costly therapy, apixaban 5mg, experienced the highest number of QALYs gained (see Table 5.1).
4.4 Objective 1: Incremental Cost-Effectiveness Ratios

4.4.1 Hypothesis I: Pair-wise ICER Comparisons

$H_{01}$: It was hypothesized that no difference in the incremental cost-effectiveness ratio (ICER) existed between dabigatran 150 mg and warfarin using $50,000 per QALY as the willingness-to-pay (WTP) threshold. Of the estimated ICER values, 98.9 percent of these demonstrated dabigatran 150 mg was a cost-effective alternative to warfarin (see Figure 5.2). Given the percentage of cost-effective values exceeded 95 percent and is, therefore, significant, the null hypothesis was rejected.

$H_{02}$: It was hypothesized that no difference in the ICER existed between apixaban 5 mg and warfarin using $50,000 per QALY as the WTP threshold. Of the estimated ICER values, 99.8 percent of these
demonstrated apixaban 5 mg was a cost-effective alternative to warfarin (see Figure 5.3). Given the percentage of cost-effective values exceeded 95 percent and is, therefore, significant, the null hypothesis was rejected.

Ho13: It was hypothesized that no difference in the ICER existed between rivaroxaban 20 mg and warfarin using $50,000 per QALY as the WTP threshold. Of the estimated ICER values, 97.4 percent of these demonstrated rivaroxaban 20 mg was a cost-effective alternative to warfarin (see Figure 5.4). Given the percentage of cost-effective values exceeded 95 percent and is, therefore, significant, the null hypothesis was rejected.

Ho14: It was hypothesized that no difference in the ICER existed between apixaban 5 mg and dabigatran 150 mg using $50,000 per QALY as the WTP threshold. Of the estimated ICER values, 55.6 percent of these demonstrated apixaban 5 mg was a cost-effective alternative to dabigatran 150 mg (see Figure 5.4). Given the percentage of cost-effective values did not exceed 95 percent and is, therefore, insignificant, the null hypothesis was not rejected.

Ho15: It was hypothesized that no difference in the ICER existed between rivaroxaban 20 mg and dabigatran 150 mg using $50,000 per QALY as the WTP threshold. Of the estimated ICER values, 65.6 percent of these demonstrated rivaroxaban 20 mg was a cost-effective alternative to dabigatran 150 mg (see Figure 5.5). Given the percentage of cost-
effective values did not exceed 95 percent and is, therefore, insignificant, the null hypothesis was not rejected.

Ho16: It was hypothesized that no difference in the ICER existed between apixaban 5 mg and rivaroxaban 20 mg using $50,000 per QALY as the WTP threshold. Of the estimated ICER values, 69.1 percent of these demonstrated apixaban 5 mg was a cost-effective alternative to rivaroxaban 20 mg (see Figure 5.6). Given the percentage of cost-effective values did not exceed 95 percent and is, therefore, insignificant, the null hypothesis was not rejected.

ICERs relate the costs of a treatment to its clinical effectiveness in terms of a ratio expression, indexed as the amount per clinical effectiveness unit (e.g., dollars per quality-adjusted life-year). When considering two treatment options, a calculated ICER estimates the additional costs that must be invested in order to obtain one additional clinical benefit using the comparator treatment instead of the baseline treatment. Table 5.1 illustrates the baseline total costs, QALYs, and ICER values for each treatment. Therapies in the table are ranked from least costly to most expensive and a treatment’s ICER is calculated relative to the therapy immediately preceding it on the ranking list. Warfarin is ranked the least costly therapy and is, therefore, considered the reference therapy in the ranking list.
Table 4.2. Point estimates of total costs, quality-adjusted life-years, and incremental cost-effectiveness ratios for apixaban 5 mg, dabigatran 150 mg, rivaroxaban 20 mg, and warfarin.

<table>
<thead>
<tr>
<th></th>
<th>Total Costs</th>
<th>QALY</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>$71,857</td>
<td>8.17</td>
<td>--</td>
</tr>
<tr>
<td>Rivaroxaban, 20 mg</td>
<td>$74,023</td>
<td>8.42</td>
<td>$8,664</td>
</tr>
<tr>
<td>Dabigatran, 150 mg</td>
<td>$78,584</td>
<td>8.55</td>
<td>$552</td>
</tr>
<tr>
<td>Apixaban, 5 mg</td>
<td>$81,180</td>
<td>8.63</td>
<td>$32,450</td>
</tr>
</tbody>
</table>

QALY = quality-adjusted life-year; ICER = incremental cost-effectiveness ratio

Monte Carlo simulation methods were used to conduct a PSA in order to estimate costs, utilities, and probabilities. Cost estimations were derived from gamma distributions, whereas utility and probability estimates were generated from beta distributions. Incremental cost-effectiveness (ICE) scatterplot plots demonstrate plotted points for all iterations calculated from the PSA. Points plotted represent pairs of incremental cost and clinical effectiveness values of a comparator therapy in reference to a baseline therapy. A WTP value of $50,000 per QALY gained was selected \textit{a priori} as the cost-effectiveness threshold. The WTP threshold is plotted as a straight line intersecting the plot at the origin. Points intersected by the WTP line represent joint incremental cost and effectiveness points that are exactly equal to the WTP value. The points below the line represent the number of iterations conducted in the PSA for which the comparator is cost-effective relative to the baseline treatment. The ellipse surrounding a group of ICER points in the ICE scatterplot represents the 95 percent CI around the mean ICER value. Alternatively, points above the line denote ICER values for which the comparator treatment is not cost-effective in contrast to the baseline therapy. Figures 5.2 to 5.7 illustrate the ICE scatterplots for each pairwise comparison of
the four therapies specified in the study hypotheses: (1) dabigatran vs. warfarin; (2) apixaban vs. warfarin; (3) rivaroxaban vs. warfarin; (4) apixaban vs. dabigatran; (5) rivaroxaban vs. dabigatran; and (6) apixaban vs. rivaroxaban. Table 5.2 delineates the proportion of ICERs estimated from the probabilistic sensitivity analysis that were cost effective for the comparison treatment relative to the baseline therapy. The ICER value for each pair-wise treatment comparison of the mean cost and effectiveness measures was less than the WTP threshold of $50,000 per QALY gained.

Figure 4.3. Probabilistic incremental cost-effectiveness plot of dabigatran 150 mg relative to warfarin.
Figure 4.4. Probabilistic incremental cost-effectiveness plot of apixaban 5 mg relative to warfarin.

Figure 4.5. Probabilistic incremental cost-effectiveness plot of rivaroxaban 20 mg relative to warfarin.
Figure 4.6. Probabilistic incremental cost-effectiveness plot of apixaban 5 mg relative to dabigatran 150 mg.

![Cost-Effectiveness Plot of Apixaban vs. Dabigatran](image1)

Figure 4.7. Probabilistic incremental cost-effectiveness plot of rivaroxaban 20 mg relative to dabigatran 150 mg.

![Cost-Effectiveness Plot of Rivaroxaban vs. Dabigatran](image2)
Table 4.3. Probabilistic ICER point estimates and percentage of cost-effective iterations for comparisons of four anticoagulation therapies in patients with atrial fibrillation using a $50,000 willingness-to-pay threshold.

<table>
<thead>
<tr>
<th>Treatment Comparison (Comparator vs. Baseline)</th>
<th>Mean ICER</th>
<th>Cost-Effective (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran 150 mg vs. Warfarin</td>
<td>$17,305</td>
<td>98.9%</td>
</tr>
<tr>
<td>Apixaban 5 mg vs. Warfarin</td>
<td>$20,385</td>
<td>99.8%</td>
</tr>
<tr>
<td>Rivaroxaban 20 mg vs. Warfarin</td>
<td>$8,503</td>
<td>97.4%</td>
</tr>
<tr>
<td>Apixaban 5 mg vs. Dabigatran 150 mg</td>
<td>$37,509</td>
<td>55.6%</td>
</tr>
<tr>
<td>Rivaroxaban 20 mg vs. Dabigatran 150 mg</td>
<td>$34,560</td>
<td>65.6%</td>
</tr>
<tr>
<td>Apixaban 5 mg vs. Rivaroxaban 20 mg</td>
<td>$35,585</td>
<td>69.1%</td>
</tr>
</tbody>
</table>

ICER = incremental cost-effectiveness ratio

4.5 Objective 3: Net Monetary Benefits

4.5.1 Hypothesis II: Pair-wise NMB Comparisons

Ho2: It was hypothesized that no difference in the net monetary benefits (NMBs) existed between dabigatran 150 mg and warfarin using $62,000 per QALY as the willingness-to-pay (WTP) threshold. The NMBs of dabigatran 150 mg (NMB: $349,219; 95% CI: $340,164, $357,814) and warfarin (NMB: $349,219;
$336,532; 95% CI: $329,409, $342,655) were not statistically significantly different from one another. Therefore, the null hypothesis was not rejected.

Ho$_{22}$: It was hypothesized that no difference in the NMBs existed between apixaban 5 mg and warfarin using $62,000 per QALY as the WTP threshold. The NMBs of apixaban 5 mg (NMB: $350,091; 95% CI: $342,755, $357,149) and warfarin (NMB: $336,532; 95% CI: $329,409, $342,655) were statistically significantly different from one another. Therefore, the null hypothesis was rejected.

Ho$_{23}$: It was hypothesized that no difference in the NMBs existed between rivaroxaban 20 mg and warfarin using $62,000 per QALY as the WTP threshold. The NMBs of rivaroxaban 20 mg (NMB: $347,196; 95% CI: $338,305, $355,691) and warfarin (NMB: $336,532; 95% CI: $329,409, $342,655) were statistically significantly different from one another. Therefore, the null hypothesis was not rejected.

Ho$_{24}$: It was hypothesized that no difference in the NMBs existed between apixaban 5 mg and dabigatran 150 mg using $62,000 per QALY as the WTP threshold. The NMBs of apixaban 5 mg (NMB: $350,091; 95% CI: $342,755, $357,149) and dabigatran 150 mg (NMB: $349,219; 95% CI: $340,164, $357,814) were not statistically significantly different from one another. Therefore, the null hypothesis was not rejected.
Ho$_{25}$: It was hypothesized that no difference in the NMBs existed between rivaroxaban 20 mg and dabigatran 150 mg using $62,000 per QALY as the WTP threshold. The NMBs of rivaroxaban 20 mg (NMB: $347,196; 95\% \text{ CI}: $338,305, $355,691) and dabigatran 150 mg (NMB: $349,219; 95\% \text{ CI}: $340,164, $357,814) were not statistically significantly different from one another. Therefore, the null hypothesis was not rejected.

Ho$_{26}$: It was hypothesized that no difference in the NMBs existed between apixaban 5 mg and rivaroxaban 20 mg using $62,000 per QALY as the WTP threshold. The NMBs of apixaban 5 mg (NMB: $350,091; 95\% \text{ CI}: $342,755, $357,149) and rivaroxaban 20 mg (NMB: $347,196; 95\% \text{ CI}: $338,305, $355,691) were not statistically significantly different from one another. Therefore, the null hypothesis was not rejected.

Incremental net monetary benefit (INMB) calculations represent the product of the difference in clinical effectiveness between two treatments and a WTP threshold, less the difference in cost between the comparator relative to the baseline therapy selected ($\Delta E^*\text{WTP} – \Delta C$). Figures 5.9 to 5.14 illustrate the INMB as a function of an increasing WTP threshold for each pair-wise comparison of the four therapies specified in the study hypotheses: (1) dabigatran vs. warfarin; (2) apixaban vs. warfarin; (3) rivaroxaban vs. warfarin; (4) apixaban vs. dabigatran; (5) rivaroxaban vs. dabigatran; and (6) apixaban vs. rivaroxaban. The inflection point where comparator therapy becomes a cost-effective strategy in comparison to the baseline treatment is the mean ICER estimated from the
Monte Carlo simulations (see Table 5.2). With the exception of rivaroxaban versus dabigatran, every pair-wise treatment comparison had a positive INMB for WTP thresholds greater than the mean ICER estimation calculated between the two therapies. In comparison to dabigatran, rivaroxaban had a positive INMB for values below the mean ICER (Figure 5.13).
Figure 4.9. Incremental net monetary benefit between the comparator dabigatran 150 mg and the baseline therapy warfarin using a willingness-to-pay threshold of $62,000.

![Dabigatran v. Warfarin](image)

Figure 4.10. Incremental net monetary benefit between the comparator apixaban 5 mg and the baseline therapy warfarin using a willingness-to-pay threshold of $62,000.

![Apixaban v. Warfarin](image)
Figure 4.11. Incremental net monetary benefit between the comparator rivaroxaban 20 mg and the baseline therapy warfarin using a willingness-to-pay threshold of $62,000.

Figure 4.12. Incremental net monetary benefit between the comparator apixaban 5 mg and the baseline therapy dabigatran 150 mg using a willingness-to-pay threshold of $62,000.
4.6 Objective 2: Total Direct and Indirect Costs

4.6.1 Hypothesis III: Total Lifetime Costs

$Ho_3$: It was hypothesized that no difference in lifetime costs existed between dabigatran 150 mg and warfarin. Mean lifetime costs of dabigatran 150
mg (mean: $78,558; 95% CI: $75,277, $81,968) and warfarin (mean: $71,843; 95% CI: $68,730, $77,452) were not statistically significantly different from one another. Therefore, the null hypothesis was not rejected.

**Ho3:** It was hypothesized that no difference in lifetime costs existed between apixaban 5 mg and warfarin. Mean lifetime costs of apixaban 5 mg (mean: $81,176; 95% CI: $78,642, $83,756) and warfarin (mean: $71,843; 95% CI: $68,730, $77,452) were statistically significantly different from one another. Therefore, the null hypothesis was rejected.

**Ho3:** It was hypothesized that no difference in lifetime costs existed between rivaroxaban 20 mg and warfarin. Mean lifetime costs of rivaroxaban 20 mg (mean: $74,028; 95% CI: $70,943, $77,307) and warfarin (mean: $71,843; 95% CI: $68,730, $77,452) were statistically significantly different from one another. Therefore, the null hypothesis was not rejected.

**Ho4:** It was hypothesized that no difference in lifetime costs existed between apixaban 5 mg and dabigatran 150 mg. Mean lifetime costs of apixaban 5 mg (mean: $81,176; 95% CI: $78,642, $83,756) and dabigatran 150 mg (mean: $78,558; 95% CI: $75,277, $81,968) were not statistically significantly different from one another. Therefore, the null hypothesis was not rejected.
Ho3₅: It was hypothesized that no difference in lifetime costs existed between rivaroxaban 20 mg and dabigatran 150 mg. Mean lifetime costs of rivaroxaban 20 mg (mean: $74,028; 95% CI: $70,943, $77,307) and dabigatran 150 mg (mean: $78,558; 95% CI: $75,277, $81,968) were not statistically significantly different from one another. Therefore, the null hypothesis was not rejected.

Ho3₆: It was hypothesized that no difference in lifetime costs existed between apixaban 5 mg and rivaroxaban 20 mg. Mean lifetime costs of apixaban 5 mg (mean: $81,176; 95% CI: $78,642, $83,756) and rivaroxaban 20 mg (mean: $74,028; 95% CI: $70,943, $77,307) were statistically significantly different from one another. Therefore, the null hypothesis was rejected.

Total lifetime costs were estimated as the sum of total direct and indirect costs for each therapy. Direct costs included the following components: therapy cost, one-time cost of an event, long-term cost of an event (if relevant), physician visits, and international normalized ratio (INR) testing (warfarin only). Indirect costs calculated were comprised of the cost of the patient’s time to attend therapy-specific physician visits and INR tests as well as the cost of death. Table 5.3 delineates the total, direct, and indirect costs for each anticoagulant therapy.
Table 4.4. Total, direct, and indirect costs for disease pathways of patients with atrial fibrillation by treatment.

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Total Costs</th>
<th>Direct Costs</th>
<th>Indirect Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin (SD)</td>
<td>$71,843 ($2,192)</td>
<td>$46,066 ($2,166)</td>
<td>$25,746 ($53)</td>
</tr>
<tr>
<td>95% CI</td>
<td>($68,730, $77,452)</td>
<td>($42,960, $51,474)</td>
<td>($25,640, $25,847)</td>
</tr>
<tr>
<td>Rivaroxaban, 20 mg (SD)</td>
<td>$74,028 ($1,619)</td>
<td>$64,531 ($1,622)</td>
<td>$9,484 ($6)</td>
</tr>
<tr>
<td>95% CI</td>
<td>($70,943, $77,307)</td>
<td>($61,456, $67,787)</td>
<td>($9,473, $9,496)</td>
</tr>
<tr>
<td>Dabigatran, 150 mg (SD)</td>
<td>$78,558 ($1,714)</td>
<td>$69,121 ($1,696)</td>
<td>$9,469 ($6)</td>
</tr>
<tr>
<td>95% CI</td>
<td>($75,277, $81,968)</td>
<td>($65,894, $72,558)</td>
<td>($9,456, $9,482)</td>
</tr>
<tr>
<td>Apixaban, 5 mg (SD)</td>
<td>$81,176 ($1,308)</td>
<td>$71,706 ($1,305)</td>
<td>$9,466 ($6)</td>
</tr>
<tr>
<td>95% CI</td>
<td>($78,642, $83,756)</td>
<td>($69,196, $74,308)</td>
<td>($9,456, $9,477)</td>
</tr>
</tbody>
</table>

CI = confidence interval; SD = standard deviation

4.6.2 Hypothesis IV: Life-Years

Estimated life-years for apixaban, dabigatran, rivaroxaban, and warfarin are 14.04, 13.99, 13.77, and 13.33, respectively. Listed below are the results of hypothesis testing for pair-wise comparisons of life-years.

Ho4₁: It was hypothesized that no difference in total life-years exists between dabigatran 150 mg and warfarin. Mean total life-years of dabigatran 150 mg (mean: 13.99; 95% CI: 13.8, 14.21) and warfarin (mean: 13.33; 95% CI: 13.21, 13.43) were statistically significantly different from one another. Therefore, the null hypothesis was rejected.

Ho4₂: It was hypothesized that no difference in total life-years exists between apixaban 5 mg and warfarin. Mean total life-years of apixaban 5 mg (mean: 14.04; 95% CI: 13.88, 14.18) and warfarin (mean: 13.33; 95% CI:
13.21, 13.43) were statistically significantly different from one another. Therefore, the null hypothesis was rejected.

Ho43: It was hypothesized that no difference in total life-years exists between rivaroxaban 20 mg and warfarin. Mean total life-years of rivaroxaban 20 mg (mean: 13.77; 95% CI: 13.59, 13.95) and warfarin (mean: 13.33; 95% CI: 13.21, 13.43) were statistically significantly different from one another. Therefore, the null hypothesis was rejected.

Ho44: It was hypothesized that no difference in total life-years exists between apixaban 5 mg and dabigatran 150 mg. Mean total life-years of apixaban 5 mg (mean: 14.04; 95% CI: 13.88, 14.18) and dabigatran 150 mg (mean: 13.99; 95% CI: 13.8, 14.21) were not statistically significantly different from one another. Therefore, the null hypothesis was not rejected.

Ho45: It was hypothesized that no difference in total life-years exists between rivaroxaban 20 mg and dabigatran 150 mg. Mean total life-years of rivaroxaban 20 mg (mean: 13.77; 95% CI: 13.59, 13.95) and dabigatran 150 mg (mean: 13.99; 95% CI: 13.8, 14.21) were not statistically significantly different from one another. Therefore, the null hypothesis was not rejected.

Ho46: It was hypothesized that no difference in total life-years exists between apixaban 5 mg and rivaroxaban 20 mg. Mean total life-years of apixaban 5 mg (mean: 14.04; 95% CI: 13.88, 14.18) and rivaroxaban 20 mg (mean:
13.77; 95% CI: 13.59, 13.95) were not statistically significantly different from one another. Therefore, the null hypothesis was not rejected.

4.6.3 Hypothesis V: Quality-Adjusted Life-Years

QALYs calculated for apixaban, dabigatran, rivaroxaban, and warfarin are 8.63, 8.56, 8.42, and 8.17, respectively. The ranking order of highest QALY to lowest are identical to the life-years delineated above with apixaban most efficacious and warfarin least. Listed below are the results of hypothesis testing for pair-wise comparisons of QALYs.

Ho5₁: It was hypothesized that no difference in total quality-adjusted life-years (QALYs) existed between dabigatran 150 mg and warfarin. Mean total QALYs of dabigatran 150 mg (mean: 8.56; 95% CI: 8.43, 8.67) and warfarin (mean: 8.17; 95% CI: 8.1, 8.24) were statistically significantly different from one another. Therefore, the null hypothesis was rejected.

Ho5₂: It was hypothesized that no difference in total QALYs existed between apixaban 5 mg and warfarin. Mean total QALYs of apixaban 5 mg (mean: 8.63; 95% CI: 8.52, 8.72) and warfarin (mean: 8.17; 95% CI: 8.1, 8.24) were statistically significantly different from one another. Therefore, the null hypothesis was rejected.
Ho53: It was hypothesized that no difference in total QALYs existed between rivaroxaban 20 mg and warfarin. Mean total QALYs of rivaroxaban 20 mg (mean: 8.42; 95% CI: 8.31, 8.54) and warfarin (mean: 8.17; 95% CI: 8.1, 8.24) were statistically significantly different from one another. Therefore, the null hypothesis was rejected.

Ho54: It was hypothesized that no difference in total QALYs existed between apixaban 5 mg and dabigatran 150 mg. Mean total QALYs of apixaban 5 mg (mean: 8.63; 95% CI: 8.52, 8.72) and dabigatran 150 mg (mean: 8.56; 95% CI: 8.43, 8.67) were not statistically significantly different from one another. Therefore, the null hypothesis was not rejected.

Ho55: It was hypothesized that no difference in total QALYs existed between rivaroxaban 20 mg and dabigatran 150 mg. Mean total QALYs of rivaroxaban 20 mg (mean: 8.42; 95% CI: 8.31, 8.54) and dabigatran 150 mg (mean: 8.56; 95% CI: 8.43, 8.67) were not statistically significantly different from one another. Therefore, the null hypothesis was not rejected.

Ho56: It was hypothesized that no difference in total QALYs existed between apixaban 5 mg and rivaroxaban 20 mg. Mean total QALYs of apixaban 5 mg (mean: 8.63; 95% CI: 8.52, 8.72) and rivaroxaban 20 mg (mean: 8.42; 95% CI: 8.31, 8.54) were not statistically significantly different from one another. Therefore, the null hypothesis was not rejected.
4.7 One-way Sensitivity Analyses

One-way sensitivity analyses were conducted for costs, utilities, probabilities, age, and the discount rate to determine influential variables with the most impact on the model’s results. Ranges used to vary the model parameters in the sensitivity analysis are listed in Tables 4.2 and 4.3. A tornado diagram illustrating the costs variables in descending order of influence are is shown in Figure 5.15. Costs with the most influence on total costs estimated from the model are costs of therapy for new anticoagulants (apixaban, dabigatran, and rivaroxaban) and the long-term costs for a major intracranial hemorrhage.

Figure 4.15. Tornado diagram of one-way sensitivity analyses on cost variables that influenced the incremental cost-effectiveness of comparisons of apixaban 5 mg, dabigatran 150 mg, rivaroxaban 20 mg, and warfarin.

Cost variables tested: cApixaban = yearly apixaban 5 mg cost; cDeath = cost of death; cDabigatran = yearly dabigatran 150 mg cost; cMajor_IS_post = long-term cost of major ischemic stroke; cRivaroxaban = yearly rivaroxaban 20 mg
Figures 5.16 to 5.19 show the one-way sensitivity analyses for each of these four cost variables. Dotted vertical lines on the plot represent the inflection cost where one treatment becomes more/less costly than one or more other treatment(s). Other marginally influential cost variables recognized are cost of dyspepsia, one-time and long-term costs for myocardial infarction, and cost of a gastrointestinal hemorrhage.

Figure 4.16. One-way sensitivity analysis of the yearly cost of apixaban 5 mg, administered twice daily.

![Sensitivity Analysis Graph](image)

cApixaban = yearly cost of apixaban 5 mg
Figure 4.17. One-way sensitivity analysis of the yearly cost of dabigatran 150 mg, administered twice daily.

\[ c_{\text{Dabigatran}} = \text{yearly cost of dabigatran 150 mg} \]

Figure 4.18. One-way sensitivity analysis of the yearly cost rivaroxaban 20 mg, administered once daily.

\[ c_{\text{Rivaroxaban}} = \text{yearly cost of rivaroxaban 20 mg} \]
Influential utility parameters are ranked in the tornado diagram shown in Figure 5.20. Utilities contributing the most impact to model results were atrial fibrillation and myocardial infarction. The utility associated with the condition of atrial fibrillation was used as a baseline adjustment in conjunction with receiving anticoagulation therapy and an adjustment for age. For myocardial infarction, a utility decrement was subtracted from the baseline utility. Figures 5.21 and 5.22 show the one-way sensitivity analyses for these two utility variables.
Figure 4.20. Tornado diagram of one-way sensitivity analyses on quality-adjusted life-year variables that influenced the incremental cost-effectiveness of comparisons of apixaban 5 mg, dabigatran 150 mg, rivaroxaban 20 mg, and warfarin.

Utility variables tested (measured in QALYs): uAF = atrial fibrillation; uAnticoagulation = anticoagulation; uMI = myocardial infarction; uIS_ICh_major = major stroke or intracranial hemorrhage; uIS_ICh_minor = minor stroke or intracranial hemorrhage; uMinorHem = minor hemorrhage; uGI = gastrointestinal; uIS_NoDisability = stroke with no neurologic residua; uMajorHem = major hemorrhage; uDyspepsia = dyspepsia.
Figure 4.21. One-way sensitivity analysis of the utility specified for atrial fibrillation.

Sensitivity Analysis

![Graph](image)

\[ u_{AF} = \text{QALY associated with atrial fibrillation} \]

Figure 4.22. One-way sensitivity analysis of the utility specified for myocardial infarction.

Sensitivity Analysis

![Graph](image)

\[ u_{MI} = \text{QALY decrement associated with a myocardial infarction} \]

Figure 5.23 portrays the tornado diagram for influential probability parameters in descending order. Probabilities contributing the most leverage to model results were intracranial hemorrhage for dabigatran, apixaban, and rivaroxaban as well as ischemic or unspecified stroke for rivaroxaban and dabigatran. Figures 5.24 to 5.29 show the one-
way sensitivity analyses of these parameter variables. Other slightly influential probability variables identified in the tornado diagram included fatal hemorrhage for apixaban and dabigatran, myocardial infarction for apixaban and dabigatran, and gastrointestinal hemorrhage for dabigatran and rivaroxaban.

Figure 4.23. Tornado diagram of one-way sensitivity analyses on event probability variables that influenced the incremental cost-effectiveness of comparisons of apixaban 5 mg, dabigatran 150 mg, rivaroxaban 20 mg, and warfarin.
Figure 4.24. One-way sensitivity analysis of the event probability for intracranial hemorrhages associated with dabigatran 150 mg.

\[ p\text{ICH}_\text{Dabigatran} = \text{probability of an intracranial hemorrhage with dabigatran 150 mg} \]

Figure 4.25. One-way sensitivity analysis of the event probability for ischemic or unspecified strokes associated with apixaban 5 mg.

\[ p\text{IS}_\text{Apixaban} = \text{probability of an ischemic stroke associated with apixaban 5 mg} \]
Figure 4.26. One-way sensitivity analysis of the event probability for ischemic or unspecified strokes associated with rivaroxaban 20 mg.

\( p_{IS\_Rivaroxaban} \) = probability of an ischemic stroke associated with rivaroxaban 20 mg

Figure 4.27. One-way sensitivity analysis of the event probability for intracranial hemorrhages associated with apixaban 5 mg.

\( p_{ICH\_Apixaban} \) = probability of an intracranial hemorrhage associated with apixaban 5 mg
Figure 4.28. One-way sensitivity analysis of the event probability for ischemic or unspecified strokes associated with dabigatran 150 mg, twice daily.

\[ p_{IS\_Dabigatran} = \text{probability of an ischemic stroke associated with dabigatran 150 mg} \]

Figure 4.29. One-way sensitivity analysis of the event probability for intracranial hemorrhages associated with rivaroxaban 20 mg, twice daily.

\[ p_{ICH\_Rivaroxaban} = \text{probability of an intracranial hemorrhage associated with rivaroxaban 20 mg} \]
### Table 4.5. Influential model variables identified in one-way sensitivity analyses.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Range</th>
<th>Inflection Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Costs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban 5 mg (yearly)</td>
<td>$3,920.10</td>
<td>($1,825, $5,475)</td>
<td>$3,935.29</td>
</tr>
<tr>
<td>Dabigatran 150 mg (yearly)</td>
<td>$2,664.50</td>
<td>($1,460, $3,650)</td>
<td>$2,649.27</td>
</tr>
<tr>
<td>Rivaroxaban 20 mg (yearly)</td>
<td>$2,660.85</td>
<td>($1,460, $3,650)</td>
<td>$2,403.97</td>
</tr>
<tr>
<td>Long-term major ICH</td>
<td>$96,926.04</td>
<td>($24,000, $120,000)</td>
<td>$48,710.36</td>
</tr>
<tr>
<td><strong>Utilities (QALYs)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>0.81</td>
<td>(0.70, 0.90)</td>
<td>0.735</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>-0.1351</td>
<td>(-0.1450, -0.1200)</td>
<td>-0.122</td>
</tr>
<tr>
<td><strong>Probabilities</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICH with therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban 5 mg</td>
<td>0.0029</td>
<td>(0.0020, 0.0040)</td>
<td>0.010</td>
</tr>
<tr>
<td>Dabigatran 150 mg</td>
<td>0.0031</td>
<td>(0.0020, 0.0040)</td>
<td>0.004</td>
</tr>
<tr>
<td>Rivaroxaban 20 mg</td>
<td>0.0039</td>
<td>(0.0030, 0.0050)</td>
<td>0.004</td>
</tr>
<tr>
<td>IS with therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban 150 mg</td>
<td>0.0088</td>
<td>(0.0075, 0.0100)</td>
<td>0.010</td>
</tr>
<tr>
<td>Dabigatran 150 mg</td>
<td>0.0091</td>
<td>(0.0080, 0.0100)</td>
<td>0.010</td>
</tr>
<tr>
<td>Rivaroxaban 20 mg</td>
<td>0.0110</td>
<td>(0.0090, 0.0019)</td>
<td>0.011</td>
</tr>
</tbody>
</table>

ICH = intracranial hemorrhage; IS = ischemic or unspecified stroke

### 4.8 Probabilistic Sensitivity Analyses

Figure 5.30 illustrates the cost-effectiveness acceptability curve (CEAC). The CEAC graph illustrates the most cost-effective therapy at each WTP threshold. If the WTP value was set at $0 per QALY gained, warfarin would have been the accepted cost-effective strategy 82 percent of the PSA iterations, whereas rivaroxaban 20 mg would be cost-effective 18 percent of the iterations and both apixaban 5 mg and dabigatran 150 mg would not be cost effective (0%). At an increased WTP threshold of $25,000 per QALY gained, warfarin is the least cost-effective strategy (4%), whereas rivaroxaban is deemed...
to be cost-effective for 50 percent of the PSA iterations followed by dabigatran 150 mg (30%) and apixaban 5 mg (16%). Using the WTP threshold selected \textit{a priori} for this analysis, $50,000 per QALY gained, apixaban 5 mg is the most cost-effective anticoagulation treatment in 45 percent of the PSA iterations followed by dabigatran 150 mg (37%) and rivaroxaban 20 mg (19%). At a threshold value of $50,000 per QALY gained, warfarin was not a cost-effective strategy in any of the PSA iterations. When the WTP value was increased to $100,000 per QALY gained, the difference in cost-effectiveness between the treatments became even more pronounced as apixaban was 64 percent cost-effective, whereas dabigatran 150 mg, rivaroxaban 20 mg, and warfarin were cost-effectiveness 31 percent, 5 percent, and 0 percent, respectively, of the time.

\textbf{Figure 4.30. Cost-effectiveness acceptability curve derived from the probabilistic sensitivity analysis.}

![Cost-Effectiveness Acceptability Curve](image)
4.9 Conclusions from hypothesis tests

Conclusions from the five hypotheses along with results are listed in Table 5.6.
<table>
<thead>
<tr>
<th>Hypothesis Statement</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Incremental Cost-Effectiveness Ratio</strong></td>
<td></td>
</tr>
<tr>
<td>Ho1&lt;sub&gt;1&lt;/sub&gt; There is no difference in cost-effectiveness between dabigatran 150 mg and warfarin using $50,000 as the WTP ($\lambda$) threshold for the ICER estimate.</td>
<td>Reject</td>
</tr>
<tr>
<td>Ho1&lt;sub&gt;2&lt;/sub&gt; There is no difference in cost-effectiveness between apixaban 5 mg and warfarin using $50,000 as the WTP threshold for the ICER estimate.</td>
<td>Reject</td>
</tr>
<tr>
<td>Ho1&lt;sub&gt;3&lt;/sub&gt; There is no difference in cost-effectiveness between rivaroxaban 20 mg and warfarin using $50,000 as the WTP threshold ($\lambda$) for the ICER estimate.</td>
<td>Reject</td>
</tr>
<tr>
<td>Ho1&lt;sub&gt;4&lt;/sub&gt; There is no difference in cost-effectiveness between apixaban 5 mg and dabigatran 150 mg using $50,000 as the WTP threshold ($\lambda$) for the ICER estimate.</td>
<td>Fail to Reject</td>
</tr>
<tr>
<td>Ho1&lt;sub&gt;5&lt;/sub&gt; There is no difference in cost-effectiveness between rivaroxaban 20 mg and dabigatran 150 mg using $50,000 as the WTP threshold ($\lambda$) for the ICER estimate.</td>
<td>Fail to Reject</td>
</tr>
<tr>
<td>Ho1&lt;sub&gt;6&lt;/sub&gt; There is no difference in cost-effectiveness between apixaban 5 mg and rivaroxaban 20 mg using $50,000 as the WTP threshold ($\lambda$) for the ICER estimate.</td>
<td>Fail to Reject</td>
</tr>
<tr>
<td><strong>Net Monetary Benefit</strong></td>
<td></td>
</tr>
<tr>
<td>Ho2&lt;sub&gt;1&lt;/sub&gt; There is no difference in the NMB calculated for dabigatran 150 mg and warfarin using a WTP threshold ($\lambda$) equal to $62,000.</td>
<td>Fail to Reject</td>
</tr>
<tr>
<td>Ho2&lt;sub&gt;2&lt;/sub&gt; There is no difference in the NMB calculated for apixaban 5 mg and warfarin using a WTP threshold ($\lambda$) equal to $62,000.</td>
<td>Reject</td>
</tr>
<tr>
<td>Ho2&lt;sub&gt;3&lt;/sub&gt; There is no difference in the NMB calculated for rivaroxaban 20 mg and warfarin using a WTP threshold ($\lambda$) equal to $62,000.</td>
<td>Fail to Reject</td>
</tr>
<tr>
<td>Ho2&lt;sub&gt;4&lt;/sub&gt; There is no difference in the NMB calculated for apixaban 5 mg and dabigatran 150 mg using a WTP threshold ($\lambda$) equal to $62,000.</td>
<td>Fail to Reject</td>
</tr>
<tr>
<td>Ho2&lt;sub&gt;5&lt;/sub&gt; There is no difference in the NMB calculated for rivaroxaban 20 mg and dabigatran 150 mg using a WTP threshold ($\lambda$) equal to $62,000.</td>
<td>Fail to Reject</td>
</tr>
<tr>
<td>Ho2&lt;sub&gt;6&lt;/sub&gt; There is no difference in the NMB calculated for apixaban 5 mg and rivaroxaban 20 mg using a WTP threshold ($\lambda$) equal to $62,000.</td>
<td>Fail to Reject</td>
</tr>
<tr>
<td><strong>Total Lifetime Costs</strong></td>
<td></td>
</tr>
<tr>
<td>Ho3&lt;sub&gt;1&lt;/sub&gt; There is no difference in lifetime costs between dabigatran 150 mg and warfarin in the treatment of patients with AF and an increased risk of stroke.</td>
<td>Fail to Reject</td>
</tr>
<tr>
<td>Ho3&lt;sub&gt;2&lt;/sub&gt; There is no difference in lifetime costs between apixaban 5 mg and warfarin in the treatment of patients with AF and an increased risk of stroke.</td>
<td>Reject</td>
</tr>
<tr>
<td>Ho3&lt;sub&gt;3&lt;/sub&gt; There is no difference in lifetime costs between rivaroxaban 20 mg and warfarin in the treatment of patients with AF and an increased risk of stroke.</td>
<td>Fail to Reject</td>
</tr>
<tr>
<td>Ho3&lt;sub&gt;4&lt;/sub&gt; There is no difference in lifetime costs between apixaban 5 mg and dabigatran 150 mg in the treatment of patients with AF and an increased risk of stroke.</td>
<td>Fail to Reject</td>
</tr>
<tr>
<td>Ho3&lt;sub&gt;5&lt;/sub&gt; There is no difference in lifetime costs between rivaroxaban 20 mg and dabigatran 150 mg in the treatment of patients with AF and an increased risk of stroke.</td>
<td>Fail to Reject</td>
</tr>
<tr>
<td>Ho3&lt;sub&gt;6&lt;/sub&gt; There is no difference in lifetime costs between apixaban 5 mg and rivaroxaban 20 mg in the treatment of patients with AF and an increased risk of stroke.</td>
<td>Reject</td>
</tr>
</tbody>
</table>
### Table 4.6 (Cont.). Summary of Hypothesis Statements and Conclusions.

<table>
<thead>
<tr>
<th>Hypothesis Statement</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lifetime Life Years</strong></td>
<td></td>
</tr>
<tr>
<td>Ho4&lt;sub&gt;1&lt;/sub&gt; There is no difference in the number of lifetime life-years gained between dabigatran 150 mg and warfarin in patients with AF at an elevated risk of stroke.</td>
<td>Reject</td>
</tr>
<tr>
<td>Ho4&lt;sub&gt;2&lt;/sub&gt; There is no difference in the number of lifetime life-years gained between apixaban 5 mg and warfarin in patients with AF at an elevated risk of stroke.</td>
<td>Reject</td>
</tr>
<tr>
<td>Ho4&lt;sub&gt;3&lt;/sub&gt; There is no difference in the number of lifetime life-years gained between rivaroxaban 20 mg and warfarin in patients with AF at an elevated risk of stroke.</td>
<td>Reject</td>
</tr>
<tr>
<td>Ho4&lt;sub&gt;4&lt;/sub&gt; There is no difference in the number of lifetime life-years gained between apixaban 5 mg and dabigatran 150 mg in patients with AF at an elevated risk of stroke.</td>
<td>Fail to Reject</td>
</tr>
<tr>
<td>Ho4&lt;sub&gt;5&lt;/sub&gt; There is no difference in the number of lifetime life-years gained between rivaroxaban 20 mg and dabigatran 150 mg in patients with AF at an elevated risk of stroke.</td>
<td>Fail to Reject</td>
</tr>
<tr>
<td>Ho4&lt;sub&gt;6&lt;/sub&gt; There is no difference in the number of lifetime life-years gained between apixaban 5 mg and rivaroxaban 20 mg in patients with AF at an elevated risk of stroke.</td>
<td>Fail to Reject</td>
</tr>
<tr>
<td><strong>Lifetime Quality-Adjusted Life-Years</strong></td>
<td></td>
</tr>
<tr>
<td>Ho5&lt;sub&gt;1&lt;/sub&gt; There is no difference in lifetime QALY values between dabigatran 150 mg and warfarin in patients with AF at a higher risk of stroke.</td>
<td>Reject</td>
</tr>
<tr>
<td>Ho5&lt;sub&gt;2&lt;/sub&gt; There is no difference in lifetime QALY values between apixaban 5 mg and warfarin in patients with AF at a higher risk of stroke.</td>
<td>Reject</td>
</tr>
<tr>
<td>Ho5&lt;sub&gt;3&lt;/sub&gt; There is no difference in lifetime QALY values between rivaroxaban 20 mg and warfarin in patients with AF at a higher risk of stroke.</td>
<td>Reject</td>
</tr>
<tr>
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</tr>
<tr>
<td>Ho5&lt;sub&gt;5&lt;/sub&gt; There is no difference in lifetime QALY values between rivaroxaban 20 mg and dabigatran 150 mg in patients with AF at a higher risk of stroke.</td>
<td>Fail to Reject</td>
</tr>
<tr>
<td>Ho5&lt;sub&gt;6&lt;/sub&gt; There is no difference in lifetime QALY values between apixaban 5 mg and rivaroxaban 20 mg in patients with AF at a higher risk of stroke.</td>
<td>Fail to Reject</td>
</tr>
</tbody>
</table>

ICER = incremental cost-effectiveness ratio; LY = life-year; NMB = net monetary benefit; QALY = quality-adjusted life-year
5 DISCUSSION

5.1 Introduction

The following sections discuss the major study findings as related to the cost-effectiveness of anticoagulation treatments, as well as findings associated with total, direct, and indirect costs; quality-adjusted life-years (QALYs); and life-years. Influential model variables and their impact on model results are also explored in this section. Additionally, the following sections include discussions regarding comparisons of study findings reported in published cost-effectiveness analyses as well as model concerns related to comparability of clinical trials and time spent in therapeutic range (TTR) for patients receiving warfarin.

5.2 Summary of major findings

The purpose of this study was to examine the costs and effectiveness affiliated with standard (warfarin) and three novel oral anticoagulant therapies (apixaban 5 mg, dabigatran 150 mg, and rivaroxaban 20 mg) in the prevention of stroke prophylaxis and other clinical events associated with atrial fibrillation (AF) in patients aged 70 years and older. Pair-wise ICER estimates for apixaban 5mg, dabigatran 150 mg, or rivaroxaban 20 mg compared to warfarin illustrated that each new anticoagulant was more cost-effective than warfarin using the \textit{a priori} selected willingness-to-pay (WTP) threshold of $50,000 per QALY gained. The analysis further demonstrated no difference in cost-effectiveness existed among the new oral anticoagulants (apixaban 5 mg, dabigatran 150 mg, and rivaroxaban 20 mg). Using a cost-effectiveness acceptability (CEAC) curve to determine
the cost-effectiveness of treatments as a function of increasing WTP thresholds, apixaban 5 mg was deemed to be cost-effective in 45 percent of the PSA iterations at a WTP threshold of $50,000 per QALY gained, followed by dabigatran 150 mg (37%) and rivaroxaban 20 mg (19%) (see Figure 5.30). Warfarin was found to have a very low probability of being cost-effective at this threshold value. Apixaban 5 mg also yielded a statistically significantly higher net monetary benefit (NMB) estimate (NMB: $350,091; 95% confidence interval [CI]: $342,755, $357,149) in comparison to warfarin (NMB: $336,532; 95% confidence interval [CI]: $329,409, $342,655), but did not appear to be significantly greater than dabigatran 150 mg (NMB: $349,219; 95% confidence interval [CI]: $340,164, $357,814) or rivaroxaban 20 mg (NMB: $347,196; 95% confidence interval [CI]: $338,305, $355,691). After accounting for the difference in treatment costs, the greater NMB estimations associated with the novel oral anticoagulant treatments indicate these therapies were clinically more effective relative to warfarin (using a WTP threshold of $62,000 per QALY gained).

Treatment-specific lifetime costs were estimated and evaluated to determine if differences existed among the four anticoagulation therapies. Although apixaban 5 mg was the most cost-effective therapy, it was significantly more expensive (mean: $81,176; 95% CI: $78,642, $83,756) than both warfarin (mean: $71,843; 95% CI: $68,730, $77,452) and rivaroxaban 20 mg (mean: $74,028; 95% CI: $70,943, $77,307) (see Table 6.3). In addition to costs, QALYs were estimated for each treatment to assess therapy effectiveness with regards to life expectancy. Apixaban 5 mg also was the most effective therapy in terms of QALYs (mean: 8.63; 95% CI: 8.52, 8.72), which was greater than
dabigatran 150 mg (mean: 8.56; 95% CI: 8.43, 8.67), rivaroxaban 20 mg (mean: 8.42; 95% CI: 8.31, 8.54), and warfarin (mean: 8.17; 95% CI: 8.1, 8.24).

5.3 Primary findings for Objective 1

The hypotheses tested in Objective 1 evaluated the incremental cost-effectiveness ratios among four anticoagulation treatments – apixaban 5 mg, dabigatran 150 mg, rivaroxaban 20 mg, and warfarin - for the prevention of stroke in patients with AF. The ICER estimation approach provides a mechanism for health economical ranking of different treatment options for AF (Krummenauer & Landwehr, 2005). Overall, apixaban 5 mg, dabigatran 150 mg, and rivaroxaban 20 mg were cost-effective relative to warfarin using a WTP value of $50,000 per QALY gained (ICER percentages: dabigatran 150 mg vs. warfarin = 98.9%; apixaban 5 mg vs. warfarin = 99.8%; rivaroxaban 20 mg vs. warfarin = 97.4%) (Table 5.2 & Figures 5.2-5.4). When the three new oral anticoagulant therapies were compared to each other, no strategy was significantly more cost-effective compared to the other treatments (apixaban 5 mg vs. dabigatran 150 mg = 55.6%; rivaroxaban 20 mg vs. dabigatran 150 mg = 65.6%; apixaban 5 mg vs. rivaroxaban = 69.1%). Also noteworthy are the ICER values delineated in Table 5.2 that show the ratio of incremental cost and incremental clinical benefit for each therapy comparison is less than $50,000 per QALY gained. The cost-effectiveness scatter plot illustrates the separation of the anticoagulation treatments with respect to clinical effectiveness and costs associated with the therapy (see Figure 5.8). Warfarin is the least clinically effective treatment, however it is also the least expensive strategy. In contrast, apixaban
offers the most clinical benefit, however it is associated with the highest costs of the four treatment strategies. Plotted ICER values estimated in the PSA demonstrated the ranking of cost-effective treatments as a function of WTP on a CEAC (see Figure 5.30). Warfarin was the most preferred strategy at a WTP value of zero (82%), whereas apixaban was the most preferred therapy using $50,000 per QALY gained as the \textit{a priori} specified WTP threshold (45%).

### 5.4 Primary findings for Objective 2

The hypotheses tested in Objective 2 assessed the net monetary benefits among four anticoagulation therapies – apixaban 5 mg, dabigatran 150 mg, rivaroxaban 20 mg, and warfarin – for the prevention of stroke prophylaxis in elderly patients aged 70 years and older with atrial fibrillation. The only statistically significant difference in NMB values observed using a WTP threshold of $62,000 per QALY gained existed between apixaban 5 mg (NMBs: $346,996; 95% CIs: $342,973, $351,019) and warfarin (NMB: $334,385; 95% CI: $329,976, $338,794).

### 5.5 Primary findings for Objective 3

The hypotheses tested in Objective 3 evaluated the total lifetime costs associated with anticoagulation treatments apixaban 5 mg, dabigatran 150 mg, rivaroxaban 20 mg, and warfarin in the treatment of patients with AF and an increased risk of stroke prophylaxis. Apixaban 5 mg (mean: $81,176; 95% CI: $78,642, $83,756) was the only new anticoagulant therapy to yield statistically significantly higher lifetime costs relative
to lifetime costs estimated for warfarin therapy (mean: $71,843; 95% CI: $68,730, $77,452). In contrast, lifetime costs between warfarin and both dabigatran 150 mg and rivaroxaban 20 mg were not significantly different. In contrast, lifetime costs among new oral anticoagulants – apixaban 5 mg, dabigatran 150 mg, and rivaroxaban 20 mg – were not statistically significantly different from one another. Further investigation of total cost components showed that direct costs contributed about $70,000 to lifetime costs of apixaban 5 mg and dabigatran 150 mg, and about $65,000 for rivaroxaban 20 mg (see table 6.3). Lifetime costs associated with the treatment of AF with warfarin were approximately $46,000. While warfarin therapy had lower direct costs compared to the new anticoagulants, indirect costs associated with warfarin were on average over $26,000 for each patient relative to an approximate average of $9,400 associated with indirect costs of new oral anticoagulant agents.

5.6 Secondary findings

5.6.1 Life years and QALYs

The hypotheses tested in secondary analyses assessed the lifetime LYs and QALYs associated with the anticoagulant therapies apixaban 5 mg, dabigatran 150 mg, rivaroxaban 20 mg, and warfarin. LYs measured for apixaban 5 mg (mean: 14.04; 95% CI: 13.88, 14.18), dabigatran 150 mg (mean: 13.99; 95% CI: 13.8, 14.21), and rivaroxaban 20 mg (mean: 13.77; 95% CI: 13.59, 13.95) were statistically significantly greater than the LY estimated for warfarin (mean: 13.33; 95% CI: 13.21, 13.43). Similarly, QALYs estimated for apixaban 5 mg (mean: 8.63; 95% CI: 8.52, 8.72),
dabigatran 150 mg (mean: 8.56; 95% CI: 8.43, 8.67), and rivaroxaban 20 mg (mean: 8.42; 95% CI: 8.31, 8.54) were also greater than the estimated QALY for warfarin (mean: 8.17; 95% CI: 8.1, 8.24). No difference in estimated QALYs existed between apixaban 5 mg and dabigatran 150 mg, however both therapies had significantly higher QALYs compared to rivaroxaban 20 mg.

5.7 Influential Model Variables

One-way sensitivity analyses were conducted to assess the impact of individual model parameter values and the following variables were found to be the most influential on the model results: cost of apixaban 5 mg, dabigatran 150 mg, and rivaroxaban 20 mg; long-term costs associated with intracranial hemorrhage (ICH); utilities for atrial fibrillation (AF) and myocardial infarction (MI); probability of ICH associated with apixaban 5 mg, dabigatran 150 mg, and rivaroxaban 20 mg; and probability of stroke associated with apixaban 5 mg, dabigatran 150 mg, and rivaroxaban 20 mg. Costs of each new oral anticoagulant – apixaban 5 mg (twice daily), dabigatran 150 mg (twice daily), and rivaroxaban 20 mg (once daily) – significantly impacted the model results. Dabigatran 150 mg (twice daily) and rivaroxaban 20 mg (once daily) costs were an estimated $3.65 per dose and $6.59 per dose, respectively, using wholesale acquisition costs (WAC) listed in the Medi-Span drug database. Inflection values computed in a sensitivity analysis note the estimate where there is a change in cost-effectiveness for a therapy strategy. Inflection values for the cost of dabigatran 150 mg and rivaroxaban 20 mg were $3.65 per dose (range: $4, $10) and $7.59 per dose (range: $4, $10),
respectively, demonstrated these therapies were cost effective at a dose price less than these estimates. Apixaban 5 mg is not currently available in the US and, therefore, the cost was estimated using the listed pricing for apixaban 5 mg in the United Kingdom, $5.37 per dose (range: $3, $10). Similar to dabigatran 150 mg and rivaroxaban 20 mg, the inflection value for the cost of apixaban 5 mg, $5.39 per dose, was very close to the point estimate and illustrated that below this price, the therapy was a cost-effective strategy. Another influential cost variable identified in the tornado analysis was the cost of long-term care for a patient with an ICH, however the effect of this cost on the model results was minimal (point estimate: $96,926 per year; range: $24,000, $120,000; inflection estimate: $48,710.36 per year) and only affected the cost-effectiveness of apixaban 5 mg and dabigatran 150 mg.

Utilities and probabilities were also evaluated to determine if particular variables impacted the model results. With respect to the utilities, the tornado diagram indicated the utility for atrial fibrillation (point estimate: 0.8; range: 0.7, 0.9; inflection estimate: 0.735) and utility decrement for myocardial infarction (point estimate: -0.1351; range: -0.145, -0.12; inflection estimate: -0.122) influenced model results, however these variables had a minimal effect on the cost-effectiveness of all therapies. In regards to probabilities specified in the model, a tornado analysis showed probabilities for ICH and stroke for each of the new anticoagulant agents – apixaban 5 mg, dabigatran 150 mg, and rivaroxaban 20 mg – were influential on model results. Probabilities specified for ICH and stroke for both apixaban 5 mg (ICH: point estimate: 0.0029; range: 0.002, 0.004; inflection estimate: 0.01; Stroke: point estimate: 0.0088; range: 0.0075, 0.01; inflection
estimate: 0.01) and dabigatran 150 mg (ICH: point estimate: 0.0031; range: 0.002, 0.004; inflection estimate: 0.004; Stroke: point estimate: 0.0091; range: 0.008, 0.01; inflection estimate: 0.01) were minimally influential, however the inflection points were the upper end of the range evaluated. ICH and stroke probabilities were more influential on the cost-effectiveness of rivaroxaban 20 mg. The estimated probability of an ICH event with rivaroxaban 20 mg was 0.0039 (range: 0.003, 0.005). The results of the one-way sensitivity analysis showed rivaroxaban 20 mg was cost-effective below a probability of 0.004, which implies this variable significantly impacts the results of the model for this therapy. The probability of stroke with rivaroxaban 20 mg was moderately influential on the cost effectiveness of the therapy (point estimate: 0.011; range: 0.009, 0.0019; inflection estimate: 0.011).

5.8 Clinical Trial Comparisons

The results of the model are partially driven by the respective clinical trials for each of the newer oral anticoagulants. This section will examine how differences among those studies may have affected the results. First, Miller and colleagues performed a quality assessment of ARISTOTLE, RE-LY, and ROCCKET-AF using the Cochrane Collaboration’s tool for assessing risk bias (Miller, Grandi, Shimony, Filion, & Eisenberg, 2012). In the ARISTOTLE inferiority trial, an intention-to-treat (ITT) analysis was used for all efficacy outcomes but not for safety outcomes. Instead, the analyses evaluating safety outcomes considered only patients who received one or more doses of the study drug. Miller and colleagues concluded the study was unclear in the
domain of other sources of bias. With respect to the RE-LY trial, patients were unblinded with regards to treatment assignment (i.e., either dabigatran or warfarin). However, all the investigators, coordinating center members, the steering committee, the event adjudication committee, and the sponsor were blinded during event monitoring and analysis. Therefore, Miller and colleagues concluded the risk for bias in the RE-LY trial was low in the domain of blinding. Although the primary objective of the ROCKET-AF trial was noninferiority, the efficacy and safety analyses were performed on the basis of per protocol and as-treated populations rather than ITT, with the exception of the primary aggregate efficacy outcome of stroke and systemic embolism that was reported as the ITT population. Miller and colleagues concluded that although the per-protocol and as-treated analyses are appropriate for noninferiority designs, the integrity of randomization is compromised and this may lead to potential confounding and selection bias. Consequently, Miller et al. rated the ROCKET-AF trial as unclear in terms of sources of bias.

Miller and colleagues also performed a meta-analysis with the three trials and assessed the relative risk (RR) for the primary composite endpoint (stroke and systemic embolism), ischemic stroke, hemorrhagic stroke, all-cause mortality, myocardial infarction (MI), major hemorrhage, gastrointestinal (GI) hemorrhage, and intracranial hemorrhage (ICH) (Miller, Grandi, Shimony, Filion, & Eisenberg, 2012). Due to the heterogeneity among the trials, a random-effects model was used in the meta-analysis to account for the between-study dissimilarities (Miller, Grandi, Shimony, Filion, & Eisenberg, 2012). When data from all three clinical trials were pooled, patients receiving
new oral anticoagulants had a 22 percent reduction for the composite endpoint of stroke and systemic embolism as compared to those on dose-adjusted warfarin (RR 0.78; 95% CI 0.67 to 0.92). The risk of ischemic and unidentified stroke (RR 0.87; 95% CI 0.77 to 0.99), hemorrhagic stroke (RR 0.45; 95% CI 0.32 to 0.68), and all-cause mortality (RR 0.88; 95% CI 0.82 to 0.95) were also lower in patients receiving new anticoagulant therapies in comparison to those randomized to receive warfarin. The MI risk was similar among the new anticoagulants and the standard therapy, warfarin (RR 0.96; 95% CI 0.73 to 1.26). Furthermore, new oral anticoagulant therapies were associated with a significant reduction in the risk of an ICH (RR 0.49; 95% CI 0.36 to 0.66). Pooled analyses of the risks of major hemorrhaging (RR 0.88; 95% CI 0.71 to 1.09) and GI hemorrhaging (RR 1.25; 95% CI 0.91 to 1.72) were inconclusive due to wide confidence intervals.

Another study has evaluated the three new anticoagulants, with warfarin as the common therapy using an indirect treatment comparison (G. Y. Lip, Larsen, Skjoth, & Rasmussen, 2012). The authors found there was a significantly lower risk of stroke and systemic embolism for dabigatran 150 mg compared with rivaroxaban 20 mg (by 26%). Additionally, dabigatran had a statistically significantly reduced risk of hemorrhagic stroke by 56 percent (p=0.039) and non-disabling stroke by 40 percent (p=0.038). No significant differences were found between apixaban and dabigatran or rivaroxaban in preventing stroke and systemic embolism. Moreover, the authors concluded no significant differences existed for the endpoint ischemic stroke between the new oral anticoagulant agents. Apixaban had significantly lower major hemorrhaging in
comparison to dabigatran (26%, p=0.003) and rivaroxaban (34%, p<0.001). Similarly, GI and extracranial hemorrhaging was also significantly reduced in patients receiving apixaban compared with dabigatran (41%, p=0.003) and rivaroxaban (26%, p=0.007). Relative to rivaroxaban, apixaban had lower major or clinically relevant hemorrhaging (34%, p<0.001). Overall, the authors concluded there were no significant differences in efficacy between apixaban and dabigatran or rivaroxaban (G. Y. Lip, Larsen, Skjoth, & Rasmussen, 2012).

5.9 Comparison of model results to other cost-effectiveness studies

This section will assess the other cost-effectiveness studies and how their results parallel or differ from the results yielded in this analysis. Clinical trial data for apixaban 5 mg and rivaroxaban 20 mg were released later than the RE-LY trial evaluating dabigatran 150 mg. Due to limited data availability, previously published cost-effectiveness studies have only evaluated the cost-effectiveness of dabigatran 150 mg in reference to warfarin (Freeman et al., 2011; Kamel, Johnston, Easton, & Kim, 2012; Kansal et al., 2012; Langkilde, Bergholdt Asmussen, & Overgaard, 2012; Pink, Lane, Pirmohamed, & Hughes, 2011; S. V. Shah & Gage, 2011; Sorensen et al., 2011). Of the seven published studies, three have been conducted from a US perspective using US costs and a WTP threshold of $50,000 per QALY gained (Freeman et al., 2011; Kamel, Johnston, Easton, & Kim, 2012; S. V. Shah & Gage, 2011). In their original study, Freeman and colleagues reported a baseline ICER of $45,372 per QALY gained of dabigatran 150 mg compared with warfarin. In the PSA performed, the author found
dabigatran 150 mg was cost-effective in 53 percent of the simulations using $50,000 per QALY gained as the WTP value; and was cost-effective in 68 percent of the simulations using a WTP value of $100,000 per QALY gained. Following this analysis, newly released information prompted the authors to perform that analyses a second time incorporating the US cost of dabigatran 150 mg (dabigatran 150 mg was only available on the European and Canadian market at the time of the first analysis) and follow-up RE-LY trial results. New RE-LY trial findings caused modest changes to the rates of ischemic stroke, transient ischemic attack, myocardial infarction, and major hemorrhage (S. J. Connolly, Ezekowitz, Yusuf, Reilly, & Wallentin, 2010). After incorporating adjustments for the cost and probability changes, Freeman and colleagues reported the ICER between dabigatran 150 mg and warfarin decreased to $12,386 per QALY gained (Freeman et al., 2011). This value is much lower and is closer to the ICER reported in this study. In a similar study conducted by Kamel and colleagues, the authors found the ICER between dabigatran 150 mg and warfarin was $25,000 per QALY gained (Kamel, Johnston, Easton, & Kim, 2012). Authors varied the inputs across plausible ranges and concluded the ICER value did not increase between dabigatran 150 mg and warfarin. The PSA results showed dabigatran was cost-effective 57 percent of the time using a WTP threshold of $50,000 per QALY gained and in 78 percent of the simulations using a WTP of $100,000 per QALY gained. These results are similar to those reported in Freeman and colleagues’ study.

Shah and Gage also used a decision analysis to assess the cost-effectiveness between dabigatran 150 mg and warfarin (S. V. Shah & Gage, 2011). The ICER
estimated from their model $86,000 per QALY gained, a higher value than those ICERs estimated in this study and previously discussed studies above. The authors concluded the cost-effectiveness dabigatran 150 mg was dependent upon stroke risk and INR control in patients receiving warfarin therapy. Dabigatran 150 mg was cost-effective for patients at a higher risk of stroke (CHADS$_2$ $\geq$ 3) and for patients with a moderate risk of stroke with either a high risk of hemorrhage (> 6% per year) or who would have poor INR control with warfarin. Overall, the Shah and Gage concluded the benefits of dabigatran 150 mg depended upon how well warfarin therapy was managed. The benefits of dabigatran 150 mg outweighed the costs for patients with AF for those with a moderate to high risk of stroke and/or hemorrhage unless their INR control with warfarin would be excellent.

Four additional studies examined the cost-effectiveness of dabigatran 150 mg in the United Kingdom (Kansal et al., 2012; Pink, Lane, Pirmohamed, & Hughes, 2011), Canada (Sorensen et al., 2011), and Denmark (Langkilde, Bergholdt Asmussen, & Overgaard, 2012). These studies differ from the ones previously discussed in that the costs specified are specific to the respective country of analysis, the adaptation of a cost-effectiveness analysis to a specific population is highlighted, and differences in ICER estimates and conclusions drawn may vary based upon the study population under consideration. For example, for the Canadian perspective (Sorensen et al., 2011), costs of therapies paid by the Ontario Drug Benefit Formulary were used in the analysis. Furthermore, Canadian-specific costs of other model inputs, such as INR monitoring, were included in the model. Sorensen and colleagues were also able to access patient-
level data from the RE-LY trial, which enabled them to evaluate the impact of dabigatran dosage amount for two age groups (< 80 years and ≥ 80 years) in accordance with Canadian-approved drug indications. Canadian-specific drug approval delineated dabigatran to be used in a sequential dosing fashion, where patients less than 80 years received dabigatran 150 mg and patients 80 years and older received dabigatran 110 mg. In addition to sequential dosing, the authors also evaluated scenarios where patients exhibited INR control similar to what is scene in ‘trial-like’ cases as well as what is observed in the ‘real-world.’ Dabigatran was found to be cost-effectiveness for all analyses, with ICERs spanning from CAD 3,962 for the sequential dosing of dabigatran to CAD 29,940 with a fixed dabigatran 110 mg dose in comparison to ‘trial-like’ warfarin prescribing and monitoring.

Kansal and colleagues used an extension of a model described above evaluating the cost-effectiveness of dabigatran from a Canadian payer perspective (Sorensen et al., 2011) and applied the modeling methodology to a UK population (Kansal et al., 2012). For those patients who were started on therapy before the age of 80, the ICER between dabigatran and warfarin was £4,831 (USD 7,729) per QALY gained with a WTP threshold of £20,000 (USD 32,000) per QALY gained for 98 percent of the PSA simulations. For those who started therapy at age 80 or older, the ICER was £7,090 (USD 11,343) and was deemed cost-effective in 63 percent of the PSA simulations using the same WTP value. Authors concluded dabigatran was cost-effective first-line treatment using a WTP threshold of £20,000 (USD 32,000) per QALY gained. Pink and colleagues used a different methodological approach to assess the cost-effectiveness of
dabigatran in the UK (Pink, Lane, Pirmohamed, & Hughes, 2011). Using a discrete event simulation, authors concluded dabigatran 150 was cost-effective with an ICER of £23,082 (USD 36,928) per QALY gained. Additionally, as seen in other studies, authors found that dabigatran 150 mg was more cost-effective in patients with a baseline CHADS\textsubscript{2} score of three or higher. A caveat, however, was the level of INR stability achieved for patients receiving warfarin. At centers where patients achieved adequate INR control, dabigatran 150 mg was no longer found to be cost-effective, with an associated ICER of £42,386 (USD 67,813) per QALY gained. Authors concluded dabigatran 150 mg was cost-effective for patients with an increased risk of stroke or for whom INR is less likely controlled.

Langkilde and colleagues (Langkilde, Bergholdt Asmussen, & Overgaard, 2012) also adopted Sorensen and colleagues’ (Sorensen et al., 2011) economic modeling methodology to assess the use of dabigatran for AF patients in the Danish population. The resulting ICER was approximately €7,000 (USD 9,011) per QALY gained, which is considered cost-effective according to Danish standards. Authors concluded this result was robust to variations in model parameters, including INR monitoring cost and high quality of INR monitoring. Overall, analyses conducted with a variety of different model inputs and using populations and cost-effectiveness standards of various countries showed dabigatran 150 mg was a cost-effective therapy option for patients with AF.

Influential variables affecting models results are essential to consider when performing a decision analysis and drawing conclusions. Model parameters found to be influential for model results in the current study and other published analyses included
the following: cost of dabigatran (Freeman et al., 2011; Kamel, Johnston, Easton, & Kim, 2012; S. V. Shah & Gage, 2011), monthly costs of medical care for patients after an ICH (Kamel, Johnston, Easton, & Kim, 2012), monthly cost of long-term follow-up care for patients with disabilities (Kansal et al., 2012; Sorensen et al., 2011), stroke rates (Kamel, Johnston, Easton, & Kim, 2012; Kansal et al., 2012; Pink, Lane, Pirmohamed, & Hughes, 2011; S. V. Shah & Gage, 2011; Sorensen et al., 2011), and ICH rates (Kansal et al., 2012; Langkilde, Bergholdt Asmussen, & Overgaard, 2012; S. V. Shah & Gage, 2011). Additional variables found to affect model results in other studies were starting age (Kamel, Johnston, Easton, & Kim, 2012), utility for mild ischemic stroke (Kamel, Johnston, Easton, & Kim, 2012), time horizon (Kansal et al., 2012; Sorensen et al., 2011), differences in the cost of INR monitoring while on warfarin (Kansal et al., 2012), and average time in therapeutic range (TTR) (Kamel, Johnston, Easton, & Kim, 2012; Kansal et al., 2012; S. V. Shah & Gage, 2011; Sorensen et al., 2011). Starting age, ischemic stroke utility, and cost differences for INR monitoring were examined in a sensitivity analysis in the current study and were not found to influence model results. TTR was not assessed in this study for reasons discussed in the Time in Therapeutic Range for Warfarin Patients section below.

The model structure and inputs in this study are broadly similar to those specified in the cost-effectiveness analyses mentioned above, however there are several differences that may explain the differences in ICER estimations. First, dyspepsia was explicitly modeled (probability, utility, and associated costs) as a side effect for patients receiving dabigatran 150 mg in this analysis, but this approach was not included in every study
(Freeman et al., 2011; Kamel, Johnston, Easton, & Kim, 2012; Kansal et al., 2012; Langkilde, Bergholdt Asmussen, & Overgaard, 2012; Sorensen et al., 2011). Second, mortality rates were not calibrated to those specified in the clinical trial. Instead, they were based on life tables estimated using national vital statistics reports for the US population (Arias, 2011). Third, transient ischemic attack not explicitly included in every clinical trial publication and was, therefore, not included in this study. Other studies estimated the occurrence of TIA as a proportion of the ischemic strokes (Freeman et al., 2011; Kamel, Johnston, Easton, & Kim, 2012; S. V. Shah & Gage, 2011), however after discussing the approach with a clinician it was recommended not to include this parameter. Fourth, mortality adjustments following a myocardial infarction, ischemic stroke, or ICH were integrated as a model parameter in this study. Mortality following an ICH or stroke was addressed in a couple of studies (Langkilde, Bergholdt Asmussen, & Overgaard, 2012; Sorensen et al., 2011), however ICH and stroke in other studies as well as how post-MI mortality was accounted for in all other reports is unclear. Fifth, cost estimates differed from those modeled in other studies using a US perspective. Yearly costs of long-term care following an ICH ranged from about $64,000 to $70,000 in other studies, whereas the cost was estimated as $96,926.04 in this study (Freeman et al., 2011; Kamel, Johnston, Easton, & Kim, 2012; S. V. Shah & Gage, 2011). The daily cost of warfarin in this study was an estimated $0.45, which is similar to the cost reported in Shah and Gage’s study ($0.49) (S. V. Shah & Gage, 2011) but differs from costs reported in other studies reporting the daily cost to be just over one dollar (Freeman et al., 2011; Kamel, Johnston, Easton, & Kim, 2012). Other studies did not explicitly
incorporate the cost of associated with the patient’s time for anticoagulation therapy (any therapy) or INR management visits (warfarin therapy). Although costs specified in other studies were different with respect to those specified in this study, the one-way sensitivity analyses results indicate these discrepancies do not significantly impact the results of this model.

5.10 Comparison of model structure to other cost-effectiveness studies

A potential source of variation between this analysis and other published papers could have been the model structure. However, the model structure for this analysis was similar to the previously published cost-effectiveness analyses. The baseline age of the model cohorts was broadly similar, modeling patients approximately 70 years of age. All of the studies assessed dabigatran 150 mg and most also evaluated the effect of dabigatran 110 mg (Freeman et al., 2011; Kansal et al., 2012; Langkilde, Bergholdt Asmussen, & Overgaard, 2012; Pink, Lane, Pirmohamed, & Hughes, 2011; S. V. Shah & Gage, 2011; Sorensen et al., 2011). Several studies assessed the effect of sequential dosing with both doses of dabigatran, where patients under the age of 80 years received dabigatran 150 mg twice daily and patients 80 years and older received the lower dose of dabigatran 110 mg twice daily (Kansal et al., 2012; Langkilde, Bergholdt Asmussen, & Overgaard, 2012; Sorensen et al., 2011). The US Federal Drug Administration approved doses of dabigatran are 75 mg and 150 mg. Because 110 mg was not included as an approved dose and no clinical data are available for dabigatran 75 mg, this analysis
included only dabigatran 150 mg twice daily. The standard therapy of warfarin was incorporated in every study.

The cost-effectiveness analyses using Markov models had similar Markov states, time frames, and sensitivity analyses relative to the current study. Similar to the current analysis, the majority of the cost-effectiveness analyses included varying degrees of stroke intensity (i.e., minor and major), MI, ICH, minor bleeding and death (Freeman et al., 2011; Kansal et al., 2012; S. V. Shah & Gage, 2011; Sorensen et al., 2011). A few studies included transient ischemic attacks (TIAs) as a potential adverse event, however the number of TIAs were estimated from other studies and were not included in the clinical trial results (Kansal et al., 2012; S. V. Shah & Gage, 2011; Sorensen et al., 2011). After consultation with a clinical expert, it was decided not to estimate the number of strokes that were classified as TIAs and, therefore, this adverse event was not included in the analysis.

The time frame of this model was specified as 30 years or until death, which was broadly similar to time frames specified as lifetime (Kansal et al., 2012; Langkilde, Bergholdt Asmussen, & Overgaard, 2012; Sorensen et al., 2011), 20 years or until death (Kamel, Johnston, Easton, & Kim, 2012; S. V. Shah & Gage, 2011), or as 35 years or until death (Freeman et al., 2011) in other models. Likewise, the time horizon of this study evaluated patients for 30 years or until death. The cycle length for the Markov models varied greatly among the published cost-effectiveness studies, ranging from two weeks to three months. These differences in cycle lengths reflect the variation in INR control among patients receiving warfarin, from inconsistent control requiring testing
every couple of weeks to stable control allowing for a longer testing time period of every three months. For this study, a cycle length of one month was selected based on ACCP anticoagulation guidelines and a sensitivity analysis was conducted with three months as the lower bound and two weeks as the upper bound. Cycle lengths modeled in other studies ranged from two weeks (Freeman et al., 2011) to one month (Kamel, Johnston, Easton, & Kim, 2012; S. V. Shah & Gage, 2011) to three months (Kansal et al., 2012; Langkilde, Bergholdt Asmussen, & Overgaard, 2012; Sorensen et al., 2011). With the exception of one study (S. V. Shah & Gage, 2011), all cost-effectiveness analyses, including this study, conducted deterministic (one-way and/or multi-way) and probabilistic sensitivity analyses (Freeman et al., 2011; Kamel, Johnston, Easton, & Kim, 2012; Kansal et al., 2012; Langkilde, Bergholdt Asmussen, & Overgaard, 2012; Sorensen et al., 2011).
5.11 Time in Therapeutic Range for Warfarin Patients

Although INR control is a determining factor of the cost-effectiveness of dabigatran in studies conducted in the US and the UK, INR management in real-world populations varies and the TTR for patients receiving warfarin is not consistently ideal (Freeman et al., 2011; Kamel, Johnston, Easton, & Kim, 2012; Pink, Lane, Pirmohamed, & Hughes, 2011; S. V. Shah & Gage, 2011). INRs are a measurement used to evaluate therapy control in patients receiving warfarin anticoagulation therapy. Many of the cost-effectiveness studies concluded time in therapeutic INR range was substantially influenced the cost-effectiveness of dabigatran 150 mg relative to warfarin therapy (Kamel, Johnston, Easton, & Kim, 2012; Kansal et al., 2012; S. V. Shah & Gage, 2011).

Due to varying inter-individual dose responses and day-to-day variation in dose response for each patient, warfarin therapy requires ongoing dose adjustment using an evaluation of the biological therapy effect with the international normalized ratio (INR). Stroke prevention studies assessing patients with AF along with cohort studies have established an INR range of 2.0 to 3.0 to be the target values to receive efficacy benefits of anticoagulation therapy (S. J. Connolly et al., 2008). In a study aimed to determine a minimum time in therapeutic range (TTR) threshold a patient with AF should maintain in order to achieve the benefits of anticoagulation therapy, Connolly and colleagues concluded that practices, centers, and regions should set a minimum target TTR of 60 percent to 65 percent (S. J. Connolly et al., 2008).

Results of studies evaluating INR control in a variety of clinical settings have found many patients were not meeting this target TTR threshold. A study examining the
quality of anticoagulation management by primary care physicians found patient INR values were out target range approximately half the time in patients with AF (G. P. Samsa et al., 2000). Moreover, a number of studies have estimated that patients spend from 41 percent to 72 percent of their time in the recommended INR range for warfarin (S. J. Connolly et al., 2008; A. J. Rose et al., 2010; van Walraven, Jennings, Oake, Fergusson, & Forster, 2006). In a study conducted by van Walraven and colleagues, the authors systematically selected studies measuring the adequacy of anticoagulation control using a patient-time analytic approach (van Walraven, Jennings, Oake, Fergusson, & Forster, 2006). The authors found that, on average, patients spend more than a third of their time outside the TTR. Furthermore, patients receiving care in a community practice demonstrated significantly worse clinical control than those from anticoagulation clinics or clinical trials (van Walraven, Jennings, Oake, Fergusson, & Forster, 2006). Stratifying by study setting, the unadjusted mean percentage TTR for randomized control trials, anticoagulation clinics, and community practice were 66.4 percent (95% CI 59.4% to 73.3%), 65.6 percent (95% CI 63.7% to 67.7%), and 56.7 percent (95% CI 51.5% to 62%), respectively. After adjusting for possible confounding factors, the authors found an absolute decrease in percentage of TTR of 12.2 percent (95% CI 4.8% to 19.5%) in studies where community physicians monitored patients relative to randomized trials. Overall, studies set in the community, patients using warfarin, and patients practice self-monitoring had the lowest percentage TTR (van Walraven, Jennings, Oake, Fergusson, & Forster, 2006).
Low TTR as well as highly variable INR are independent predictors of hemorrhaging and thromboembolic complications with anticoagulation therapy (Holbrook et al., 2012). Considering the studies discussed above, variations in the percentage TTR observed in community practices illustrate patients receiving warfarin therapy were not consistently remaining in therapeutic ranges where anticoagulation has beneficial efficacy. Patients enrolled in two of the three clinical trials used in this study’s analysis had a mean percentage TTR within the target range Connolly and colleagues recommend (62% in ARISTOTLE and 64% in RE-LY) (S. J. Connolly et al., 2009; S. J. Connolly, Ezekowitz, Yusuf, Reilly, & Wallentin, 2010; C. B. Granger et al., 2011). Patients evaluated in the ROCKET-AF study had a mean percentage TTR of 55 percent, however this is within the range of anticoagulation management observed in community practice discussed previously (Patel et al., 2011). Given these mean TTR values recorded in the clinical trials and anticoagulation management observed in the community, variations in TTR percentages were not built into this analysis. Future studies may follow more closely patients receiving new anticoagulation agents in community practices to determine whether the results of clinical trials are generalizable to real-world patient care as well as evaluate the efficacy of new anticoagulants relative to warfarin therapy in real-world settings.
5.13 Limitations

There were several limitations to this study that may be categorized into three main sources: limitations related to available data sources; limitations related to model assumptions applied; and limitations related to modeling capabilities.

Values used to populate model parameters were extrapolated from a variety of different data sources. Treatment efficacy and adverse events for apixaban, dabigatran, and rivaroxaban were based on a single clinical trial for each therapy (ARISTOTLE, RE-LY, and ROCKET-AF, respectively) (S. J. Connolly et al., 2009; C. B. Granger et al., 2011; Patel et al., 2011). Each trial had a median follow-up of two years and patients with an average age of 71 years. There were a few limitations using these sources of data. First, reliance on a single trial for each therapy is a potential cause for concern. Although ARISTOTLE, RE-LY, and ROCKET-AF are some of the largest trials of AF, this makes assessing the effect of any possible weaknesses in the design of the studies difficult. Second, rates of adverse events may vary over the long term and extrapolation of two-year data to a lifetime model may not accurately represent the lifetime progression of the disease. Third, extrapolating from 70 years to future age decades may lead to inaccurate results as patients may have different treatment responses as they age.

The next two limitations for the use of these clinical trials were related to differences among trial patients, which may have influenced the model results. First, patients enrolled in the rivaroxaban trial (ROCKET-AF) were at a higher risk of stroke according to the CHADS$_2$ scores. Trials with apixaban and dabigatran (ARISTOTLE and RE-LY, respectively) had a fairly similar distribution for patients CHADS$_2$ scores
less than or equal to one, score of two, or scores greater than or equal to three (32.2%, 35.2%, and 32.6%, respectively for dabigatran; 34%, 35.8% and 30.2%, respectively for apixaban) (S. J. Connolly et al., 2009; C. B. Granger et al., 2011). Patients in clinical trial for rivaroxaban (ROCKET-AF) had no patients in the lowest CHADS\textsubscript{2} score group (CHADS\textsubscript{2} ≤ 1), 14 percent of the patients in the middle score group (CHADS\textsubscript{2} = 2), and 86 percent of the patients in the highest stroke risk group (CHADS\textsubscript{2} ≥ 3) (Patel et al., 2011). Given the substantial differences in risk for stroke prophylaxis, the results for apixaban and dabigatran relative to rivaroxaban may be skewed. Second, clinical trials like ARISTOTLE, RE-LY, and ROCKET-AF use algorithms for imputing dummy INR of the warfarin placebo in patients who are not receiving warfarin in order to maintain blinding (del Zoppo & Eliasziw, 2011). Trials like these also typically use a method in which the measured INR values and the interval between INR tests are both taken into account (del Zoppo & Eliasziw, 2011). Based on this approach, INR values were within a therapeutic range a mean of 62 percent in the ARISTOTLE trial, 64 percent in the RE-LY trial, and 55 percent in the ROCKET-AF trial (S. J. Connolly et al., 2009; C. B. Granger et al., 2011; Patel et al., 2011). The interpretation of noninferiority in a given trial may be due to not only homogeneity of trial design and patients, but is also is affected by the treatment efficacy in the warfarin cohort and the dummy INR algorithm used (del Zoppo & Eliasziw, 2011).

Because not all the information needed to populate a model were included in the clinical trials, it was necessary to include a variety of other data sources to population the model. Other sources were used to collect values for costs, utilities, and other adverse
events (i.e., stroke severity and disability following stroke). The necessity of bringing together data from a wide variety of sources has the potential to introduce bias into the analysis.

There were a number of assumptions specified for the model structure and parameters that limit the accurateness of our model. First, two studies were included in addition to the clinical trials to estimate the post-stroke severity as well as the death and disability following an ICH (Fang et al., 2007; Hylek et al., 2003). A study by Fang and colleagues was used to derive death and disability following ICH events (Fang et al., 2007). The study included a cohort of 13,559 patients with NVAF enrolled in the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study. The ATRIA study included subjects enlisted as patient members of Kaiser Permanente in Northern California. The mean age of the patients was slightly higher (78 years) than those included in the clinical trials. The time in therapeutic range was not reported, however the patients with an ICH event had a median INR of 2.7 (interquartile range [IQR]: 2.3-4.0). Stroke severity for following an stroke event was derived from a study conducted by Hylek and colleagues, who also used patients enrolled in the ATRIA study (Hylek et al., 2003). Patients included in the study were categorized as having an ischemic stroke in accordance with the antithrombotic status at hospital admission. Patients had a median INR of 1.7 (IQR: 1.3-2.2).

A couple of further assumptions were included in the model. First, it was assumed that treatment efficacy was sustained beyond the trial period, as there was no biological reason to assume that efficacy of anticoagulants would change in adherent
patients. Furthermore, therapy adherence rates were assumed similar across all treatments and were not parameterized in the model. Patients were assumed to remain adherent to assigned therapies.

Limitations related to model capabilities were associated with the health state specifications and the comparison of treatment ICER results. With regard to health state specifications, a Markov model has an inherent memoryless property that limits the way the disease progression is modeled. In other words, the progression between health states is not representative of real life in that the patient’s health state is not contingent upon the prior health state. In real life, the patient’s health status depends on their previous health status and the prior health state would influence the subsequent health state. With respect to ICER comparisons, there is no statistical measure to evaluate the difference between the final ICER values of the four anticoagulant therapies. It is possible to assess the deterministic ICER value along with its associated confidence interval in relation the other therapies, however there no statistical test was performed to test the difference between the ICER values.

5.14 Future study considerations

Differences among trial designs, outcome definitions, and patient populations spotlight the challenges with cross-trial comparisons. Future research should evaluate head-to-head comparisons of these novel therapies to allow for direct comparisons among the new anticoagulant agents as well as with warfarin. Conducting head-to-head studies in real-world community practices will also allow for an assessment of the efficacy of
new oral anticoagulants relative to already established warfarin. Further research should be conducted to evaluate differences in the effect of new oral anticoagulation agents in real-world patient care settings. Furthermore, as TTR was an influential parameter for patients receiving warfarin and significantly impacts the significant and cost-effectiveness of warfarin in previously published cost-effectiveness analyses, it is recommended that the effect of the new oral anticoagulants in real-world patient settings relative to warfarin should be evaluated.

### 5.15 Conclusions

This study demonstrated that in patients aged 70 years and older with AF who are at an increased risk of stroke (CHADS2 score ≥ 1 or equivalent), have proper renal function, a renal creatinine clearance of 50 or above, and no contraindication to anticoagulant therapy, apixaban 5 mg, dabigatran 150 mg, and rivaroxaban 20 mg are cost-effective therapies relative to the standard anticoagulation therapy warfarin. The base case analysis yielded estimates of $20,267 per QALY gained (95% CI $13,054, $23,184) with apixaban 5 mg, $17,703 per QALY gained (95% CI $10,467, $19,415) with dabigatran 150 mg, and $8,664 per QALY gained (95% CI -$483, $10,520) with rivaroxaban 20 mg. Warfarin had the lowest total treatment cost, whereas apixaban 5 mg was the most expensive. Conversely, warfarin was the least effective treatment strategy and apixaban 5 mg showed to be the most effective anticoagulant therapy. In conclusion, each new anticoagulant therapy evaluated in this study was significantly more cost-effective in comparison to warfarin treatment for the AF patient population.
Furthermore, this study did not find a significant difference between the cost-effectiveness of apixaban 5 mg, dabigatran 150 mg, and rivaroxaban 20 mg, demonstrating although costs and effectiveness estimations differed, no specific new anticoagulant therapy did not emerge as a dominant treatment over other new therapies. Therefore, all new products should be available on formularies for patients with atrial fibrillation and a high risk of stroke.
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