EVALUATING THE SAFETY AND EFFECTIVENESS OF NON-VITAMIN K ANTAGONIST ORAL ANTICOAGULANTS IN THE MEDICARE POPULATION

by

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ABSTRACT

For decades, warfarin was the only oral anticoagulant available for the prevention of stroke and systemic embolism in atrial fibrillation. Since 2010, four non-vitamin K antagonist oral anticoagulant agents have gained the Food and Drug Administration approval for this indication: dabigatran, rivaroxaban, apixaban and edoxaban.

Chapter 1 provides an introduction to the three research manuscripts that constitute this dissertation. It reviews the use of anticoagulation therapy in atrial fibrillation and especially the evidence on non-vitamin K antagonist oral anticoagulants.

Chapter 2 (Manuscript 1) is a retrospective cohort study that compares the risk of stroke and bleeding with rivaroxaban 20mg/dabigatran 150mg, and rivaroxaban 15mg/dabigatran 75mg. This study found no difference in the risk of stroke between dabigatran and rivaroxaban; however, rivaroxaban 20mg and rivaroxaban 15mg were associated with higher risk of thromboembolic events other than stroke, death, major bleeding, and any bleeding events than dabigatran 150mg and dabigatran 75mg.

Chapter 3 (Manuscript 2) evaluates the patterns of anticoagulation use following a major bleeding on dabigatran or warfarin, and compares the thromboembolic and bleeding risk between post-hemorrhage treatment groups. In this study, post-hemorrhage resumption of anticoagulation with either dabigatran or warfarin was associated with increased survival and stroke-free

survival, as compared to discontinuing anticoagulation. In addition, this paper revealed that the risk of recurrent major hemorrhage was higher with warfarin than dabigatran.

Chapter 4 (Manuscript 3) is a cost-effectiveness study that compares edoxaban 60mg, apixaban 5mg, dabigatran 150mg, dabigatran 110mg, rivaroxaban 20mg and dose-adjusted warfarin in the prevention of stroke in atrial fibrillation patients with high risk of bleeding, as defined by HAS-BLED score ≥3. This study found that, while apixaban 5mg was the most effective strategy, its incremental cost-effectiveness ratio when compared to edoxaban was slightly above the $100,000 per quality-adjusted life-year threshold.

Public Health Significance

The investigations reported in this dissertation will guide clinicians in the prescription of the most appropriate anticoagulation agent according to the clinical characteristics of atrial fibrillation patients. This will ultimately lead to the prevention of strokes, the second leading cause of mortality worldwide, and bleeding events, the most common complication of anticoagulation therapy.

Key Words

Anticoagulation; Atrial fibrillation; Hemorrhage; Non-vitamin K antagonist oral anticoagulants; Stroke; Warfarin.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

PREFACE

"They shall find wisdom here and faith, in steel and stone, in character and thought; they shall find beauty, adventure and moments of high victory". I came across this quote by Chancellor John Bowman in February 2013, when I received the letter of acceptance to this PhD program. Three years later, I have come to realize that, as Chancellor Bowman predicted, Pitt put in my path many treasures other than scientific training:

Faith: in these three years I learned to believe, especially in myself, in science, and in the existence of a society that appreciates science. A wise society where research matters, influences opinions, impacts decisions and models common knowledge. My time in this program also sharpened my mind, instilling in me not only the analytical and critical traits of a scientific brain, but also the ability to become fascinated by research. Isn't it beautiful to work on something that has the power to delight you? An ocean away from home, each day was full of an endless sense of adventure and enjoyment. Each day was also full of warmth, that one you feel when you are greatly welcomed in the heart of a continent that is not yours—I will dare to say though, that after these three years, America is starting to feel a bit like mine too. And what can I say about victory? I do not conceive moments of higher victory than going to school every morning to work on something you care about, with the support of an extraordinary group of people believing in what you do.

As I leave this PhD program, I feel extremely happy and honored to remain in the Pitt family for a few more years. I only hope that through my work, I can help new Pitt students in their own search of wisdom, faith, beauty, adventure and victory.

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From my days in the University of Navarra School of Pharmacy, I am especially grateful to Dr. José Luis Vizmanos, Dr. Ana Ortega, Dr. José Lopez Guzmán and Dr. José Manuel Irache for their help with my application to PhD programs, for training me as an ethical and devoted pharmacist, and for showing me the beauty in our profession.

I would like to thank “La Caixa” Foundation for sponsoring me these last two years of my PhD. Receiving their scholarship was one of the greatest privileges I have ever received. I hope that through my research and future work I can give back to the Spanish society the opportunity that “La Caixa” Foundation gave me with this scholarship.

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This dissertation is dedicated to my family.

To my parents, to their efforts and sacrifices.

To my Uncle Angel, who was like a second father to me, and from whom I learnt the best and the ugliest sides of medicine. His fully devoted life to his patients taught me the beauty in the clinical practice. His sudden death following an intracranial hemorrhage showed me the ugliest face of medicine: when nothing can be done to save a 39 year old life that much deserved to be lived.

This dissertation will be a success if the research produced during my time in this PhD program prevents the occurrence of just one of those strokes that leave nothing to be done.

1.0 INTRODUCTION

1.1 ATRIAL FIBRILLATION AND RISK OF STROKE

1.1.1 Epidemiology of Atrial Fibrillation

Atrial fibrillation (AF) is the most prevalent type of sustained cardiac arrhythmia, and it is characterized by a disorganized atrial electrical activity.[1] It is estimated that between 2 and 3 million people were affected by AF in the US in 2010, and over 30 million worldwide.[2-4] Every year, there are approximately 200,000-400,000 new cases of AF in the US, and 5 million worldwide.[2,5]

The prevalence of AF increases with age, ranging from 0.1% in patients younger than 55 years to around 9% in those older than 90 years.[3] In 2010, over 70% of US patients with AF were at least 65 years old, and 45% were older than 75.[2] As the population ages, the prevalence of AF will increase: it has been estimated that by 2050, around 7.5-12 million Americans and 18 million Europeans will be affected by AF.[4,6]

1.1.2 Thrombogenesis in Atrial Fibrillation

In 1856, the German physician Virchow proposed three factors that contribute to thrombosis: abnormal blood stasis, structural abnormalities, and abnormal blood constituents.[7] All three factors in Virchow's triad for thrombogenesis are present in AF.[8]

1.1.2.1 Abnormal Stasis of Blood

In AF, many impulses originate simultaneously and spread through the atria, competing with each other.[1] The resulting atrial rhythm is disorganized, rapid and irregular, which results in an uncoordinated atrial contraction.[9] The loss of coordinated contraction promotes the stagnation of blood in the left atrium and, especially, in the left atrial appendage.[10] The left atrial appendage is a blind-ended passage with a narrow inlet and variable morphology that predisposes to blood stasis.

1.1.2.2 Structural Abnormalities

AF is associated with a progressive dilatation of the left atrium and the left atrial appendage, which amplifies the potential for blood stasis.[11,12] In addition, the left atrial endocardium of AF patients presents morphological changes characterized by a granular and wrinkled appearance.[13] This so called "rough endocardium" is associated with edema and fibrinous transformation, and presents numerous areas of endocardial denudation and thrombotic aggregation.[10] Finally, the turnover of the atrial extracellular matrix is disrupted in AF, which is evidenced by the altered amounts of products of collagen degradation observed in AF patients.[14] This disrupted extracellular matrix has the potential of inducing fibrosis and infiltration of the endocardium, also promoting the thrombogenesis.[10]

1.1.2.3 Abnormal Blood Constituents

AF patients present increased levels of plasma markers of thrombogenesis, including thrombin-antithrombin complexes and fibrin D-dimers, as well as increased levels of platelet activation markers, such as beta-thromboglubin or platelet factor 4.[15-18] These abnormalities in blood constituents, together with the increased levels of pro-angiogenic markers such as vascular endothelial growth factor (VEGF), angiopoietin-1, or angiopoietin-2, suggest the presence of a hypercoagulable state in AF.[8,19-21]

1.1.3 Thrombosis Embolization in Atrial Fibrillation

The blood stasis in the left atrial appendage, the endothelic dysfunction and the hypercoagulability of the blood interact synergically maintaining a pro-thrombotic state in AF.[10] The left atrial appendage is, in particular, the origin of 90% of the clinically-relevant thrombus formations in AF.[22] Thrombus formations originated in the left atrium appendage can embolize to the circulation, and get carried towards the brain, where they can block small arteries.[23] The occlusion of brain arteries can interrupt the blood flow, triggering an ischemic stroke or a transient ischemic attack, if the blood supply is quickly restored.[23]

This pathogenesis explains the increased risk of stroke and other thromboembolic events associated with AF. Specifically, AF is associated with a 5-fold increase in the risk of stroke, independently of age.[3] The percentage of strokes that can be attributed to AF is 15% all age groups, and 24% in patients older than 80 years.[24,25] In elderly patients, AF is the most important single cause of ischemic stroke.[23]

1.1.4 Clinical and Economic Burden of Stroke

Stroke ranks as the second leading cause of mortality in the world population, and it is responsible for around 10% of deaths worldwide.[26] Every year, there are around 780,000 strokes in the US, 600,000 of which are first time strokes.[27] The 30-day case fatality rate of stroke has been estimated between 16-23%.[27,28] In the US, around 140,000 people die annually from stroke.[29]

Stroke is the third most common cause of disability in high-income countries, accounting for 4 million disability-adjusted life years (DALYs).[26] Stroke survivors present high rates of functional impairment,[30] recurrent strokes,[31] dementia,[32] and depression.[33] In addition to the physical and cognitive impairment associated with stroke, stroke sequelae include sensory, communication and emotional deficits.[34,35] As a result, stroke survivors require an intensive use of medical services. For instance, around 20% of stroke survivors require institutionalization in the first five 5 years following the occurrence of the stroke.[36,37]

The intensity of the acute and post-acute medical care following a stroke explains the high medical expenditures associated with stroke. In the US, the total annual costs of stroke have been estimated at $65.5 billion, with medical costs accounting for 67% or $44billion.[38] With only half of stroke survivors under 65 years old returning to work after experiencing a stroke, loss of productivity from stroke-related morbidity and mortality is responsible for the remaining 33%, or $22billion.[38,39]

1.2 ANTICOAGULATION THERAPY IN THE PREVENTION OF STROKE

Antithrombotic therapy is crucial to the management of AF patients. Antithrombotic therapy may inhibit the platelet function (antiplatelet therapy), the plasmatic coagulation (anticoagulant therapy), or induce the lysis of a thrombus formation (thrombolytic therapy). This dissertation focuses on the study of anticoagulation therapy in the prevention of stroke in AF.

1.2.1 Impact of Anticoagulation

1.2.1.1 Reduction in Stroke Risk

The clinical trials that evaluated the effectiveness of antithrombotic therapy with warfarin in the prevention of stroke, as compared to placebo were conducted in the 1990s.[40-45] In these trials, warfarin therapy was found to reduce the risk of stroke by around 60%, irrespective of the baseline risk.[40-46] More recent studies have confirmed that antithrombotic therapy with warfarin reduces by two-thirds the risk of stroke.[47,48] In addition, warfarin therapy has been associated with less severe stroke events, as well as reduced post-stroke mortality.[46,49]

1.2.1.2 Increase in Bleeding Risk

The most important safety concern associated with the use of anticoagulation is the increased risk of bleeding. Bleeding events that require hospitalization or involve sensitive locations are of special concern. Associated with the highest rates of mortality and disability, intracranial hemorrhages are specifically the most threatening type of bleeding events.[50] The annual risk of intracranial bleeding for AF patients on anticoagulation has been estimated between 0.2 and 0.4

percent.[48] The incidence of major bleeding events involving other anatomical locations has been estimated at around 4 percent.[48]

1.2.2 Assessment of Individual Patient Risk

Because of the increased risk of bleeding events associated with the use of oral anticoagulation, the assessment of the risk of stroke and the risk of bleeding is crucial before the prescription of oral anticoagulation. There is solid evidence supporting the benefit-risk ratio of anticoagulation in patients with moderate to high risk of stroke.[46,51,52] However, the risk of bleeding can outweigh the benefits of stroke risk reduction in low-risk patients.[53] Several risk prediction models are available to estimate the thromboembolic risk and the risk of bleeding in patients with AF.

1.2.2.1 Estimating Thromboembolic Risk

CHADS2 Score

CHADS2 score is a prediction tool that measures the risk of stroke in patients with AF. It was developed in 2001 on the basis of two previous risk scores: AFI and SPAF.[54] Validated in a national sample of Medicare beneficiaries with AF, CHADS2 score is composed of five independent risk factors: congestive heart failure (CHF), hypertension, age of 75 years or older, diabetes, and a history of previous stroke or transient ischemic attack (TIA) (Table 1-1). All risk factors are assigned one point, except for a history of previous stroke or TIA, which is assigned two points.[54]

Before 2014, CHADS2 score was the prediction tool used by the American Heart Association (AHA), American College of Cardiology (ACC) and Heart Rhythm Society (HRS) in their clinical recommendations for anticoagulation in AF.[55,56] Specifically, the AHA, ACC and HRS recommended the use of oral anticoagulation in patients with CHADS2 score equal or greater than two.[56]

Table 1-1: Risk Factors in CHADS2 and CHA2DS2-Vasc Scores.

Risk factor	CHADS2 Points	CHA2DS2-VASC Points
Congestive Heart Failure	1	1
Hypertension	1	1
Age ≥ 75 years	1	2
Diabetes Mellitus	1	1
History of Stroke or TIA or Thromboembolism	2	2
Vascular disease	N/A	1
Age 65-74 years	N/A	1
Sex category (Female gender)	N/A	1

CHA2DS2-Vasc Score

Developed on the basis of the Euro Heart Survey on AF, CHA2DS2-Vasc score is a prediction tool that measures of the risk of stroke in AF patients.[57] To calculate the CHA2DS2-Vasc score for a given patient, female sex, age between 65 and 74, congestive heart failure, hypertension history, vascular disease history and diabetes mellitus are assigned one point, and age of 75 or older and a history of previous stroke, TIA or thromboembolism are assigned two points (Table 1-1).[57]

Because CHA2DS2-Vasc score showed to be superior to CHADS2 score in defining the risk of stroke,[58,59] the AHA, ACC and HRS commenced to use CHA2DS2-VASc score in their recommendations for the prescription of anticoagulation in 2014. Specifically, the AHA, ACC

and HRS currently recommend the use of oral anticoagulation in patients with CHA2DS2-VASc score equal or greater than two.[60]

1.2.2.2 Estimating Bleeding Risk

ATRIA Score

Defined on the basis of the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study, the ATRIA score is a prediction tool of the risk of major bleeding in AF patients on warfarin therapy.[61] In calculating the ATRIA score, severe renal disease and anemia are each assigned three points, age of 75 or greater is assigned two points, and hypertension and a history of bleeding are each assigned one point (Table 1-2).[61]

Patients with ATRIA score greater than five are at high risk of bleeding, patients whose ATRIA score equals four are at intermediate risk of bleeding, and those with ATRIA score lower than 4 are at low risk of presenting with major bleeding events.[62]

Table 1-2: Risk Factors in ATRIA and HAS-BLED Scores.

Risk factor	ATRIA Points	HAS-BLED Points
Hypertension	1	1
Renal disease	3	1
Abnormal liver function	N/A	1
History of Stroke	N/A	1
History of Bleeding or Predisposition to Bleeding	1	1
Labile INR	N/A	1
Age > 65 years	N/A	1
Age > 75 years	2	N/A
Concomitant Use of Aspirin or NSAIDs	N/A	1
History of Alcohol or Drug Abuse	N/A	1
Anemia	3	N/A

HAS-BLED Score

HAS-BLED score is a prediction measure of the risk of major bleeding in AF patients on oral anticoagulation.[61] It was defined on the basis of the Stroke Prevention Using an ORal Thrombin Inhibitor in Atrial Fibrillation (SPORTIF) clinical trial data, and it includes nine risk factors, each of which are assigned one point: hypertension, renal disease, liver disease, a history of stroke, a history of bleeding or predisposition to bleeding, labile international normalized ratio (INR), age of 65 or greater, use of antiplatelet agents or of nonsteroidal anti-inflammatory drugs (NSAIDs), and alcohol or drug use (Table 1-2).[61]

Patients with HAS-BLED equal or greater than three are at elevated risk of bleeding, patients with HAS-BLED score one or two have a moderate risk of bleeding, and those whose HAS-BLED score equals zero have a low risk for bleeding events.[62] Because HAS-BLED score has shown to be superior to ATRIA in the prediction of the risk of bleeding,[62-64] it is the most commonly used score in the assessment of the risk of bleeding in patients with AF.

Contrary to CHADS2, CHA2DS2-Vasc, and other prediction tools of the thromboembolic risk, ATRIA and HAS-BLED scores are not used to assess whether a patient should initiate anticoagulation therapy, but rather to identify those patients who should use anticoagulants with special caution and those with modifiable risk factors for bleeding.[62]

1.2.3 Pharmacotherapy of Oral Anticoagulation

1.2.3.1 Vitamin K Antagonists

Vitamin K antagonists inhibit the vitamin K epoxide reductase, and thus the synthesis of vitamin K-dependent coagulation factors, including Factors II, VII, IX, X, and proteins C and S (Figure

1-1).[65] From a structural perspective, most Vitamin K antagonists are coumarin derivatives; being warfarin the most commonly used vitamin K antagonist in the US.[66]

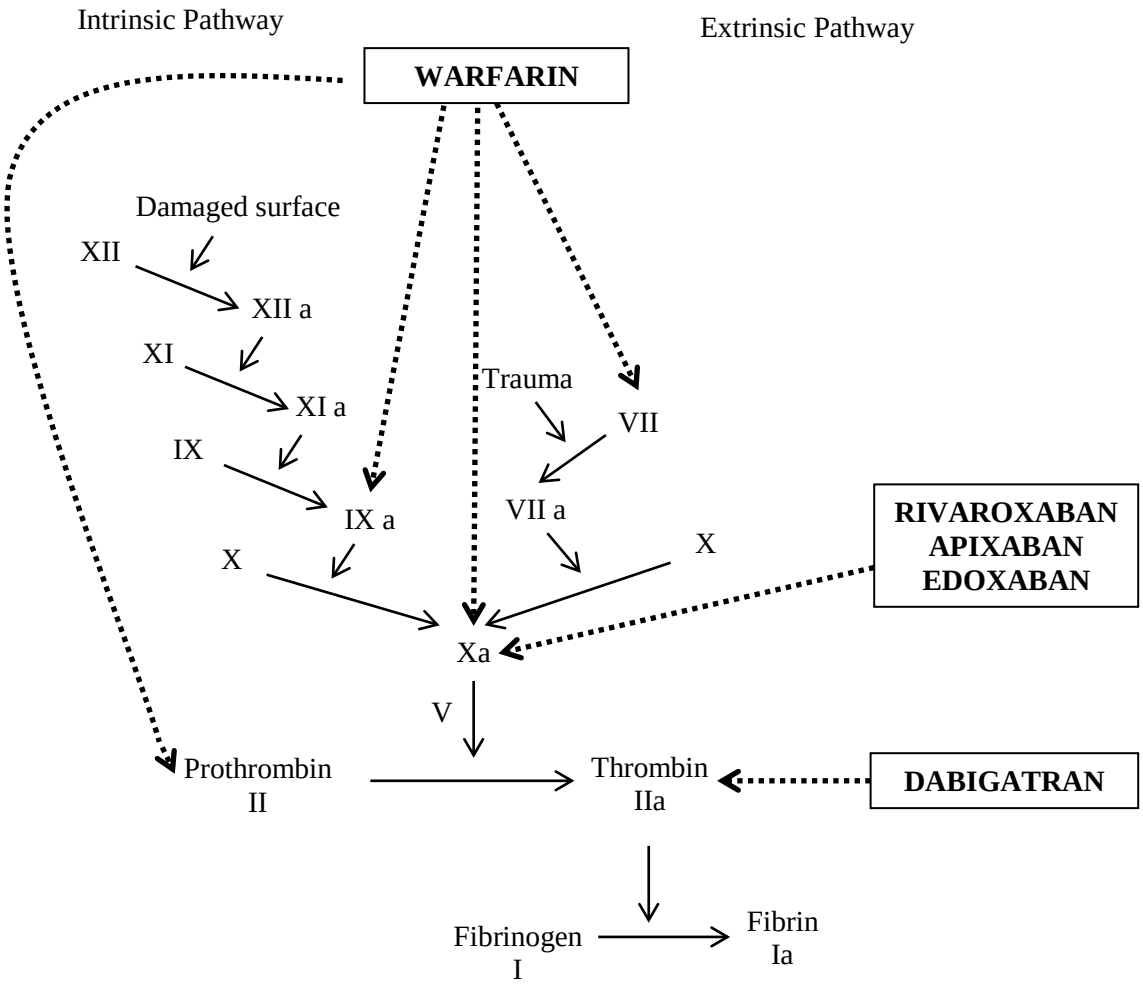

Figure 1-1: Sites of Action of Anticoagulants in the Coagulation Cascade.

Predominantly metabolized by the CYP2C9, warfarin has a highly-variable pharmacokinetic profile, with wide inter-individual variability.[67] As a result, warfarin dosing is personalized for each patient (Table 1-3).[67] Specifically, warfarin dose-adjustment is based on the routine blood monitoring of the prothrombin time or the INR. For patients with AF, the AHA, ACC and HRS recommend a target INR of 2-3.[60] In addition, warfarin presents multiple interactions with other medications and food, which also increases the variability of warfarin

dose-response.[67] In case of emergency, vitamin K can be administered as an antidote to reverse the anticoagulation effects of warfarin.[68]

Warfarin has been consistently shown to reduce the risk of stroke by over 60%;[46] however, warfarin therapy is associated with a high risk of hemorrhagic events and especially of intracranial bleeding, the most threatening bleeding event.[50]

Table 1-3: Summary of the Pharmacokinetic Profile of Oral Anticoagulants.

	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism of Action	Vitamin K epoxide reductase inhibitor	Direct thrombin inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor
Elimination	Predominant hepatic metabolism via CYP2C9	Predominant renal elimination	2/3 metabolic degradation via CYP3A4 and CYP2J2, 1/3 renal excretion	Multiple pathways: Hepatic metabolism via CYP3A4/5, and renal, intestinal and biliary excretion	Renal and intestinal excretion
Half-life	20-60 h	12-17 h	11-13 h	9-14 h	9-11 h
Frequency of Administration	Once a day	Twice a day	Once a day	Twice a day	Once a day
Interactions	Multiple interactions	P-gp inhibitors and inducers	CYP3A4 and P-gp inhibitors and inducers	CYP3A4 and P-gp inhibitors and inducers	P-gp inhibitors and inducers
Antidote	Vitamin K	Idarucizumab	Adaxanet alfa (Phase III)	Adaxanet alfa (Phase III)	Adaxanet alfa (Phase III)
Prodrug	No	Yes	No	No	No
Monitoring	INR monitoring	None	None	None	None

1.2.3.2 Non-vitamin K Antagonist Oral Anticoagulants

For decades, vitamin K antagonists were the only oral anticoagulants available to prevent stroke and systemic embolism in AF patients. Approved by the Food and Drug Administration (FDA) in 2010, the oral direct thrombin inhibitor dabigatran was the non-vitamin K antagonist oral anticoagulants (NOAC) available as an alternative to warfarin.[69] One year later, rivaroxaban, a factor Xa inhibitor, gained approval for the same indication.[70] The market entry of rivaroxaban

was followed by the approval of two new factor Xa inhibitors: apixaban in December 2012 and edoxaban in January 2015.[71,72]

Mechanism of Action and Pharmacokinetics of NOACs

Dabigatran is a competitive and reversible direct inhibitor of thrombin that binds to its active site (Table 1-3).[73] The inhibition of thrombin prevents the conversion of fibrinogen intro fibrin, and the subsequent amplification of the coagulation, cross-linking of fibrin and activation of platelets (Figure 1-1).[73]Dabigatran is administered as dabigatran etexilate, a prodrug that is converted to its active form, dabigatran, by serine esterases (Table 1-3).[74] Because dabigatran absorption is acid-dependent, dabigatran is formulated in capsules with tartaric acid to reduce the variability in its absorption.[75] Dabigatran is predominantly cleared by the kidneys, and it is a P-glycoprotein substrate.[73] As a result, it interacts with strong P-glycoprotein inducers or inhibitors.[76] Dabigatran is administered twice a day, and its half-life has been estimated at 12-17h.[75] In October 2015, five years after dabigatran approval, idarucizumab, a dabigatran-binding monoclonal antibody fragment, was approved by the FDA to reverse the effects of dabigatran in emergency situations.[77]

Rivaroxaban is an reversible direct Factor Xa inhibitor (Figure 1-1).[78] Rivaroxaban inhibits both free Factor Xa and Factor Xa in the prothrombinase complex, thus decreasing the generation of thrombin.[79] Rivaroxaban undergoes hepatic degradation via CYP3A4 and CYP2J2, with one third of rivaroxaban excreted by the kidneys.[78] Substrate of the P-glycoprotein as well, its concurrent administration with CYP3A4 and P-glycoprotein inhibitors and inducers is contraindicated.[70] The half-life of rivaroxaban is 11-13h; however, it follows once a day administration.[80] There are currently no antidotes available to revert the effects of rivaroxaban and other factor Xa inhibitors, but the safety and efficacy of andexanet alfa, a modified Factor

Xa molecule that reverses the effects of the Factor Xa inhibitors, is being tested in phase III clinical trials.[81]

Apixaban is a direct highly-selective inhibitor of Factor Xa (Figure 1-1).[82] Similar to rivaroxaban, it binds both free Factor Xa and the prothrombinase complex.[82] Apixaban is eliminated through multiple pathways, including hepatic metabolism via CYP3A4 and CYP3A5, renal excretion, intestinal and biliary elimination (Table 1-3).[82] Also a substrate of the P-glycoprotein, it interacts with CYP3A4 and P-glycoprotein inhibitors and inducers.[71] Apixaban is administered twice a day, and its half-life has been estimated at 9-14h.[80]

Edoxaban is an oral direct highly-selective inhibitor of the factor Xa (Figure 1-1). [83] Similar to rivaroxaban and apixaban, it inhibits both free and clot-bound factor Xa.[84] Edoxaban has a half-life of 9-11h,[85] it is administered once a day, and it is predominantly excreted unchanged in feces and urine (Table 1-3).[86] Because edoxaban is a substrate of P-glycoprotein and because metabolic degradation is a minor pathway of elimination of edoxaban, the plasmatic levels of edoxaban are highly influenced by the concomitant administration of P-glycoprotein inducers and inhibitors.[87]

Clinical Trials Design and Results

The approval of dabigatran was based on the results of the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) clinical trial.[88] The RE-LY trial was a prospective, non-inferiority, randomized clinical trial that compared dabigatran 150mg and dabigatran 110 mg with warfarin.[88] In this study, dabigatran 150mg was found to be more efficacious in the prevention of stroke than warfarin, but similar in the risk of bleeding (Table 1-4).[88] Dabigatran 110mg, in contrast, was associated with similar rates of stroke, but lower incidence of major bleeding (Table 1-4).[88]

Table 1-4: Summary of the Results of the RE-LY, ROCKET-AF, ARISTOTLE and ENGAGE AF-TIMI Trials

New Oral Anticoagulant	Dose	Stroke prevention	Bleeding risk
Dabigatran	75 mg	Not evaluated in RE-LY trial	Not evaluated in RE-LY trial
	110 mg	Similar	Lower
	150 mg	Superior	Similar
Rivaroxaban	15 mg if CrCl 15-50 mL/min, 20 mg if CrCl> 50mL/min	Similar	Similar
Apixaban	2.5mg if two of the following characteristics: age ≥ 80 yrs, body weight ≤60 kg or serum Cr ≥ 1.5 mg/dL, 5mg otherwise	Superior	Lower
Edoxaban	30 mg	Similar	Lower
	60 mg	Similar	Lower

Rivaroxaban was approved based on the results of the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) trial, a prospective, double-blind, non-inferiority randomized clinical trial that compared rivaroxaban 20 mg/rivaroxaban 15mg in patients with creatinine clearance 30-49mL/min to warfarin.[89] In this clinical trial, rivaroxaban showed to be similar to warfarin in both the prevention of stroke and the risk of bleeding (Table 1-4).[89]

The efficacy and safety of apixaban was compared to that of warfarin in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, a double-blind randomized non-interiority clinical trial.[90] Subjects randomized to the apixaban group received the 2.5mg dose if they presented at least two of the following characteristics: age greater than 80, body weight lower than 60kg or serum creatinine greater than 1.5mg/dL. Otherwise, they were treated with apixaban 5mg. In this trial, apixaban showed to be superior in the prevention of stroke than warfarin, with a lower risk of major bleeding

(Table 1-4).[90] Up to this date, apixaban is the only non-vitamin K antagonist oral anticoagulant to have showed superiority to warfarin in both efficacy and safety, and the only one to show a benefit in terms of survival.[82,90]

The efficacy and safety of edoxaban 30mg and 60mg was compared to that of warfarin in the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction (ENGAGE AF-TIMI) trial.[91] In this clinical trial, both edoxaban 30mg and edoxaban 60mg showed to be similar to warfarin in the prevention of stroke, but with lower rates of major bleeding (Table 1-4).[91]

FDA Approval

Based on the results of the RE-LY trial, the FDA approved dabigatran 150mg for the prevention of stroke and systemic embolism in AF patients with normal renal function (Table 1-5).[69] Based only on pharmacokinetic data, the FDA approved dabigatran 75mg for the same indication, but for patients with creatinine clearance lower than 30 mL/min (Table 1-5).[92] The FDA did not approve dabigatran 110mg, which was however approved by the European Medicines Agency, the Australian Therapeutic Goods Administration, and the Japanese Ministry of Health, Labor and Welfare.[93-95] In the countries where dabigatran 110mg is available, it is indicated in the treatment of patients with AF older than 80 years, with high risk of bleeding or with gastrointestinal irritation.[93-95] In October 2015, the FDA approved dabigatran 110mg for the prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) after hip replacement surgery (Table 1-5).[96] Nevertheless, dabigatran 110mg has not been approved in the US for the prevention of stroke and systemic embolism in AF.

Table 1-5: Dosage Recommendations for Non-Vitamin K Antagonist Oral Anticoagulants.

New Oral Anticoagulant	Dose	FDA-Approved Indications	Subgroup of Patients
Dabigatran	75 mg	AF	CrCl 15-30 mL/min
	110 mg	Prophylaxis of DVT and PE following hip replacement surgery	CrCl > 30 mL/min
	150 mg	AF	CrCl > 30 mL/min
		Reduction of risk of recurrent DVT and PE	CrCl > 30 mL/min
		Treatment of DVT and PE	CrCl > 30 mL/min
Rivaroxaban	10 mg	Prophylaxis of DVT and PE following hip or knee replacement surgery	N/A
	15mg	AF	CrCl 15-49 mL/min
		Treatment of DVT and PE	N/A
	20 mg	AF	CrCl > 50 mL/min
		Reduction of risk of recurrent DVT and PE	N/A
Apixaban	2.5 mg	AF	Patients with two of the following characteristics age ≥ 80 yrs, body weight ≤60 kg or serum Cr ≥ 1.5 mg/dL
		Reduction of risk of recurrent DVT and PE	
		Prophylaxis of DVT following hip or knee replacement surgery	
	5 mg	AF	Patients not included under 2.5 mg recommendations
		Treatment of DVT and PE	After 1 week on 10 mg
	10 mg	Treatment of DVT and PE	Initial week
Edoxaban	30 mg	AF	CrCl 15-50 mL/min
		Treatment of DVT and PE	CrCl 15-50 mL/min, or body weight ≤60 kg, or using P-gp inhibitors
	60 mg	AF	CrCl 50-95 mL/min
		Treatment of DVT and PE	Patients not included under 30 mg recommendations

The FDA approved rivaroxaban 20mg and 15mg for the prevention of stroke and systemic embolism in AF in November 2011.[70] Mirroring the dosing regimens evaluated in the ROCKET-AF trial, the 15mg strength was approved for patients with creatinine clearance lower than 50 ml/min (Table 1-5).[70] In addition, there is another dose of rivaroxaban available, 10 mg, which is indicated in the prophylaxis of venous thromboembolism (VTE) following hip or knee replacement surgery.[70,97]

Following the review of the ARISTOTLE trial data, the FDA approved apixaban 5mg and 2.5mg for the prevention of stroke and systemic embolism in AF patients in December 2012.[71] In addition, apixaban 10mg is indicated in the initial treatment of DVT and PE (Table 1-5).[71] Other approved indications of apixaban 2.5 mg include the reduction of risk of recurrent DVT and PE, and the prophylaxis of DVT in patients undergoing hip or knee replacement surgery.[71]

In January 2015, the FDA approved edoxaban 30mg in the prevention of AF-related stroke in patients with creatinine clearance 15-50 mL/min, and edoxaban 60mg in those with creatinine clearance 50-95 mL/min (Table 1-5).[72] In addition, edoxaban is approved for the treatment of DVT and PE (Table 1-5).[72]

Evidence from Indirect Comparisons of Clinical Trials Data

With the RE-LY, ROCKET-AF, ARISTOTLE and ENGAGE AF-TIMI trials comparing non-vitamin K antagonist oral anticoagulants to warfarin, no clinical trials have directly compared the efficacy and safety of NOACs. In this scenario, some researchers used the results of the RE-LY, ROCKET-AF, ARISTOTLE and ENGAGE AF-TIMI clinical trials to predict how the risk of stroke and the risk of bleeding compare among NOACs. In these indirect comparisons, no differences were predicted in the efficacy of apixaban and dabigatran 150mg.[98,99] However, rivaroxaban was predicted to be less effective in the prevention of stroke than dabigatran 150mg, and similar in the risk of bleeding.[98,100,101] In addition, apixaban was associated with lower rates of major bleeding than dabigatran or rivaroxaban.[99] Because the validity of indirect comparisons is strongly limited by inter-trial population differences, it is important to confirm these results with head-to-head analyses.

Evidence from Observational Studies

Numerous observational studies have compared the incidence of stroke and bleeding with dabigatran or rivaroxaban and warfarin, finding conflicting results on the comparative effectiveness of dabigatran and warfarin.[102-109] Using data from a US nationally representative cohort of Medicare beneficiaries, Graham et al. associated dabigatran with higher effectiveness in stroke prevention than warfarin;[106] however, Larsen and colleagues found no differences in the prevention of stroke between warfarin and dabigatran in a Danish cohort.[102] With regards to safety, dabigatran and rivaroxaban have been associated with similar rates of major bleeding than warfarin, but lower rates of intracranial bleeding.[102,103,110]

To the best of our knowledge, no observational studies have compared head-to-head the real-world effectiveness of dabigatran and rivaroxaban in the prevention of stroke in AF. Furthermore, only one observational study has directly compared the incidence of hemorrhagic events between dabigatran and rivaroxaban.[107] In this study, Sherid et al. used medical records from only two hospitals and did not examine the risk of bleeding by dose of anticoagulant separately.[107] Because the risk of bleeding varies by the strength of anticoagulant, it is necessary to separately examine the risk of bleeding by dose.[105,111,112]

After experiencing a major hemorrhage, clinicians need to assess whether a patient should resume anticoagulation therapy. Patients experiencing a major hemorrhage are at higher risk for presenting recurrent bleeding events;[113] however, the interruption of anticoagulation has been associated with higher risk of thromboembolic events.[114-117] This clinical decision whether a patient should restart anticoagulation after a major bleeding event is especially uncertain because patients at high risk of bleeding are also at high risk of stroke.[118] Furthermore, there are no

specific clinical guidelines to inform the prescription of anticoagulants after a major bleeding event.[60]

Using data from a health system in Michigan, Qureshi et al., estimated that around 51% of AF patients who experienced a major gastrointestinal bleeding on warfarin ceased anticoagulation after the bleeding event.[114] However, no one has evaluated the patterns of NOAC use after a major bleeding event. In addition, some studies have compared the clinical outcomes of patients restarting and interrupting anticoagulation therapy with warfarin after a major bleeding event;[114-117] nevertheless, none of them have done so for the case of NOACs. Because the prescription patterns, therapeutic management and bleeding profile of NOACs differ substantially from those of warfarin,[92,119] it is important to separately compare the risks of stroke and recurrent bleeding events among patients who interrupt anticoagulation after a major bleeding event, and those who resume anticoagulation therapy with warfarin and with NOACs.

Evidence from Cost-Effectiveness Analyses

NOACs present certain advantages over traditional anticoagulant therapy with warfarin, such as fewer interactions and no requirement for routine monitoring of laboratory coagulation markers. However, NOACs are considerably more costly than warfarin: In 2012, the Medicare gross cost for one-month supply of dabigatran and rivaroxaban was $2731 and $2889, compared to $162 for warfarin. As a result, it is important to compare the cost-effectiveness of NOACs and that of warfarin in the prevention of stroke and systemic embolism in AF.

Table 1-6 shows a summary of the studies that have examined the cost-effectiveness of NOACs and warfarin in the prevention of stroke and systemic embolism in AF from the US perspective.[120-129] Specifically, three studies have simultaneously compared the cost-effectiveness of apixaban rivaroxaban, dabigatran and warfarin from the US perspective, finding

conflicting results.[126-128] Whereas Canestaro et al. and Harrington et al. found that apixaban was a cost-effective strategy compared to dabigatran, Coyle and colleagues found that dabigatran was more effective and less costly than apixaban.[126-128]

Table 1-6: Summary of Cost-Effectiveness Analysis for Non-Vitamin K Antagonist Oral Anticoagulants and Warfarin.

Study	Treatments Evaluated	Results
Freeman et al., Ann Intern Med 2011	Dabigatran 150 mg, dabigatran 110mg, and warfarin	ICER of dabigatran 150 mg vs warfarin =$45,372/QALY
		ICER of dabigatran 110 mg vs warfarin =$51,229/QALY
Shah et al., Circulation 2011	Dabigatran 150mg, dabigatran 110mg and warfarin	ICER of dabigatran 150 mg vs warfarin =$86,000/QALY
		ICER of dabigatran 110 mg vs warfarin =$150,000/QALY
Kamel et al., Neurology 2012	Apixaban and warfarin	ICER of apixaban vs warfarin=$11,400/QALY
Kamel et al., Stroke 2012	Dabigatran and warfarin	ICER of dabigatran vs warfarin=$25,000/QALY
Lee et al., Am J Cardiol 2012	Rivaroxaban and warfarin	ICER of rivaroxaban vs warfarin=$27,498/QALY
Lee et al., Plos One 2012	Apixaban and warfarin	Apixaban dominates warfarin
Canestaro et al., Circ Cardiovasc Qual Outcomes 2013	Apixaban 5mg, rivaroxaban 20mg, dabigatran 150 mg and warfarin	ICER of apixaban vs warfarin=$93,063/QALY
Coyle at al., Value Health 2013	Apixaban, rivaroxaban dabigatran and warfarin	ICER of dabigatran vs warfarin=$20,787/QALY
Harrington et al., Stroke 2013	Apixaban, rivaroxaban dabigatran and warfarin	ICER of apixaban vs dabigatran =$64,600/QALY
		ICER of dabigatran vs rivaroxaban=$53,067/QALY
		ICER of rivaroxaban vs warfarin=$3190/QALY
Clemens et al., Am J Cardiol 2014	Dabigatran and warfarin	ICER of dabigatran vs warfarin=$56,131/QALY

Because edoxaban was recently approved, only three cost-effectiveness studies have examined the cost-effectiveness of this agent.[130-132] These studies, all of which were performed from the European perspective, found that edoxaban was cost-effective when compared to warfarin,[132] but it was not favored when compared to apixaban.[131] Because the cost-effectiveness of NOACs is highly sensitive to pricing, and the prices of NOACs are considerably higher in the

US than in Europe, the results of cost-effectiveness analysis performed from the European perspective are not generalizable to the US.[128]

Synthesis of the Evidence on NOACs: What We Know

- On the comparative effectiveness and safety of dabigatran and rivaroxaban:
    - In indirect comparisons of clinical trials data, rivaroxaban was predicted to be less effective in the prevention of stroke than dabigatran 150mg, and similar in the risk of bleeding.
    - Only one observational study has directly compared the safety of rivaroxaban and dabigatran, finding no differences in the risk of bleeding between two NOACs.
- On the use of anticoagulation after a major bleeding event:
    - Around 50% of the patients who have a major bleeding event on warfarin discontinue anticoagulation therapy.
    - The resumption of warfarin therapy after a major bleeding event is associated with increased survival and stroke-free survival, but higher risk of recurrent bleeding.
- On the cost-effectiveness of NOACS:
    - NOACs are a cost-effective strategy when compared to warfarin.
    - From the European perspective, apixaban is cost-effective when compared to edoxaban.

Gaps of Evidence on NOACs: What We Don´t Know

- On the comparative safety and effectiveness of dabigatran and rivaroxaban:
    - It remains unclear whether there are differences in the risk of bleeding events with rivaroxaban and dabigatran.
    - The effectiveness of two doses of rivaroxaban and dabigatran in the prevention of stroke has never been directly compared.
- On the use of anticoagulation after a major bleeding event:
    - The patterns of NOAC use after a major bleeding have never been evaluated.
    - It remains unknown whether the factors that affect post-hemorrhage resumption of anticoagulation are similar for warfarin and NOACS.
    - The effectiveness and safety outcomes associated with post-hemorrhage NOAC resumption, as compared to warfarin resumption or discontinuation of anticoagulation have never been compared.
- On the cost-effectiveness of NOACS:
    - There is conflicting evidence on the comparative cost-effectiveness of dabigatran and apixaban.
    - The cost-effectiveness of edoxaban has never been compared to other NOACs from the US perspective.

1.3 OUTLINE AND RELEVANCE OF THE DISSERTATION

This dissertation is composed of three research manuscripts that target each of the gaps of evidence identified on the effectiveness, safety, and cost-effectiveness of the non-vitamin K antagonist oral anticoagulants dabigatran, rivaroxaban, apixaban and edoxaban, and traditional warfarin therapy:

Manuscript 1 (Chapter 2), entitled "Comparing Stroke and Bleeding with Rivaroxaban and Dabigatran in Atrial Fibrillation", addresses the gap of evidence on the comparative safety and effectiveness of dabigatran and rivaroxaban. Specifically, it compares the risk of ischemic stroke, other thromboembolic events, all-cause mortality, major hemorrhage, intracranial bleeding, gastrointestinal bleeding, and any bleeding event with dabigatran and rivaroxaban, separately for high-dose (dabigatran 150mg and rivaroxaban 20mg) and low-dose initiators (dabigatran 75mg and rivaroxaban 15mg).

Manuscript 2 (Chapter 3), entitled "Anticoagulant Use and Clinical Outcomes Following Major Hemorrhage on Dabigatran or Warfarin in Atrial Fibrillation" identified a cohort of AF patients who experienced a major bleeding event while using warfarin or dabigatran and followed them with two objectives: first, to evaluate the patterns of dabigatran and warfarin use after a first major bleeding event; and second, to compare the risk of ischemic stroke/all-cause mortality and recurrent hemorrhage between patients interrupting anticoagulation after a bleeding event and patients restarting warfarin or dabigatran.

The data source for manuscripts 1 and 2 was pharmacy and medical claims in 2010-2013 for a 5% random sample of Medicare Part D beneficiaries. These two studies have been approved by the Institutional Review Board at the University of Pittsburgh, and the Centers for

Medicare and Medicaid Services (CMS) have authorized the use of this data under Data User Agreement 27815.

Addressing the gap of evidence on the comparative cost-effectiveness of NOACS from the US perspective, manuscript 3 (Chapter 4), entitled “Cost-Effectiveness of Non-Vitamin K Antagonist Oral Anticoagulants for Stroke Prevention in Patients with Atrial Fibrillation at High Risk of Bleeding”, compares the cost-effectiveness of apixaban 5mg, edoxaban 60 mg, rivaroxaban 20mg, dabigatran 150mg, dabigatran 110mg, and dose-adjusted warfarin in the prevention of stroke in a simulated cohort of 65-year old patients with AF and high risk of bleeding, defined by HAS-BLED score equal to or greater than 3.

Chapter 5 summarizes the results from the three research manuscripts, provides an overall perspective for these findings, and elaborates on the public health significance of our research.

2.0 COMPARING STROKE AND BLEEDING WITH RIVAROXABAN AND DABIGATRAN IN ATRIAL FIBRILLATION

2.1 ABSTRACT

The objective of this manuscript was to compare the risk of stroke and bleeding after initiating rivaroxaban 20mg/dabigatran 150mg, or rivaroxaban 15mg/dabigatran 75mg among atrial fibrillation (AF) patients. Using 2010-2013 Medicare Part D data, we selected AF patients initiating dabigatran 150/75mg or rivaroxaban 20/15mg between November 4, 2011 (when rivaroxaban was approved) and December 31, 2013. Our sample included 7,322 dabigatran 150mg users, 5,799 rivaroxaban 20mg users, 1,818 dabigatran 75mg users and 2,568 rivaroxaban 15mg users. We followed them until stroke, other thromboembolic events, bleeding, discontinuation or switch of an anticoagulant, death, or December 31, 2013. We constructed Cox Proportional Hazard Models with propensity score weighting to compare the risk of stroke, other thromboembolic events, death, and bleeding between groups. We further examined the risk of stroke and bleeding in 3 subgroups: those 75 years or older, with chronic kidney disease, and with more than 7 concomitant comorbidities. We found no difference in the risk of stroke between dabigatran 150mg and rivaroxaban 20mg (hazard ratio [HR] 1.05, 95%CI 0.97-1.13) or between dabigatran 75mg and rivaroxaban 15mg (HR1.05, 95%CI 0.94-1.18). Compared to dabigatran 150mg, rivaroxaban 20mg was associated with higher risk of thromboembolic events

other than stroke (HR1.28, 95%CI 1.14-1.44), major bleeding (HR1.32, 95%CI 1.17-1.50), and death (HR1.36, 95% CI 1.19-1.56). The risk of thromboembolic events other than stroke (HR1.37, 95%CI 1.15-1.62), major bleeding (HR1.51, 95%CI 1.25-1.82) and death (HR1.21, 95% CI 1.04-1.41) was also higher for rivaroxaban 15mg than dabigatran 75mg. Results from subgroup analyses were consistent with the overall sample. In conclusion, there was no difference in stroke prevention between rivaroxaban and dabigatran; however, rivaroxaban was associated with a higher risk of thromboembolic events other than stroke, death and bleeding.

2.2 INTRODUCTION

Dabigatran 150mg and 75mg were approved by the US FDA in October 2010 for the prevention of stroke among AF patients, with 75mg indicated for patients with creatinine clearance lower than 30ml/min.[96] Rivaroxaban 20mg and 15mg gained the FDA approval for the same indication in November 2011, with 15mg indicated for patients with creatinine clearance lower than 50ml/min.[70] Both doses of dabigatran are administered twice-a-day, whereas rivaroxaban follows a once-a-day regimen.[70,96] Since the approval of rivaroxaban, two new NOACs have gained FDA approval for the same indication: apixaban in December 2012, and edoxaban in January 2015. [71,72]

The RE-LY clinical trial found that dabigatran 150mg was similar to warfarin in the risk of bleeding, but superior in the prevention of stroke.[88] Dabigatran 75mg was not evaluated in clinical trials, but approved only on the basis of pharmacokinetic studies.[92] The results from the ROCKET-AF trial showed that rivaroxaban 20mg/15mg was similar to warfarin in both the risk of bleeding and the prevention of stroke.[89,133] Because no clinical trials have directly compared

NOACs, previous researchers have used the results of the RE-LY[88] and ROCKET-AF trials [89] to compare the effectiveness and safety of dabigatran and rivaroxaban.[98,100] In these indirect comparisons, rivaroxaban 20mg/15mg was predicted to be less effective in the prevention of stroke and systemic embolism than dabigatran 150mg, but similar in the risk of bleeding.[98,100] Because the validity of indirect comparisons is limited by inter-trial population differences, and the subjects enrolled in the ROCKET-AF trial were considerably sicker than those in the RE-LY trial,[88,89] it is important to perform direct analyses to compare the effectiveness and safety of dabigatran and rivaroxaban using the same population.

Although several observational studies have compared the real-world effectiveness and safety of dabigatran or rivaroxaban with those of warfarin,[102,104,109,134-136] only one study has directly compared the risk of bleeding between dabigatran and rivaroxaban, finding no differences in the risk of bleeding with two oral anticoagulants.[107] However, the authors used medical records from only two hospitals and did not examine the risk of bleeding by dose of anticoagulant separately.[107] Because the risk of bleeding varies by the strength of anticoagulant, it is also necessary to separately examine the risk of bleeding by dose.[105,111,112] To the best of our knowledge, no observational studies have compared head-to-head the effectiveness of dabigatran and rivaroxaban in the prevention of stroke in AF.

In this paper, we used 2010-2013 pharmacy and medical claims data from a 5% random sample of Medicare beneficiaries with AF to compare the risk of stroke, other thromboembolic events, death and bleeding following the initiation of dabigatran and rivaroxaban, separately for high-dose (dabigatran 150mg and rivaroxaban 20mg) and low-dose initiators (dabigatran 75mg and rivaroxaban 15mg).

2.3 METHODS

2.3.1 Data Source and Study Population

We obtained 2010-2013 pharmacy and medical data for a 5% random sample of Medicare beneficiaries from CMS. First, we identified patients who filled a prescription for dabigatran or rivaroxaban between November 4, 2011 (the approval date for rivaroxaban) and December 31, 2013 (n=44,621) (Figure 2-1). The index date was defined as the day of the first prescription filled for dabigatran or rivaroxaban in this time window. Second, we required that patients had a diagnosis of AF any time before the index date according to the CMS Chronic Condition Warehouse definition of AF (n=22,292).[137] Third, we collected the pharmacy claims for oral anticoagulants filled during the three months before the index date and excluded patients who had a claim for dabigatran or rivaroxaban. We excluded them to make sure that we identified patients who initiated dabigatran or rivaroxaban treatment during our study period, when the risk of bleeding is higher.[138] We used a three-month wash-out period because anticoagulants used in AF are usually prescribed as 30-day or 90-day supply prescriptions. Our final sample included 7,322 dabigatran 150mg users, 5,799 rivaroxaban 20mg users, 1,818 dabigatran 75mg users and 2,568 rivaroxaban 15mg users. In our study, we did not include rivaroxaban 10 mg users because this dose has not been approved for the prevention of stroke and systemic embolism in AF.[70] Since apixaban was approved in December 2012, the follow-up period available for this treatment group in our data set was shorter than one year and therefore, we did not include apixaban in our study.

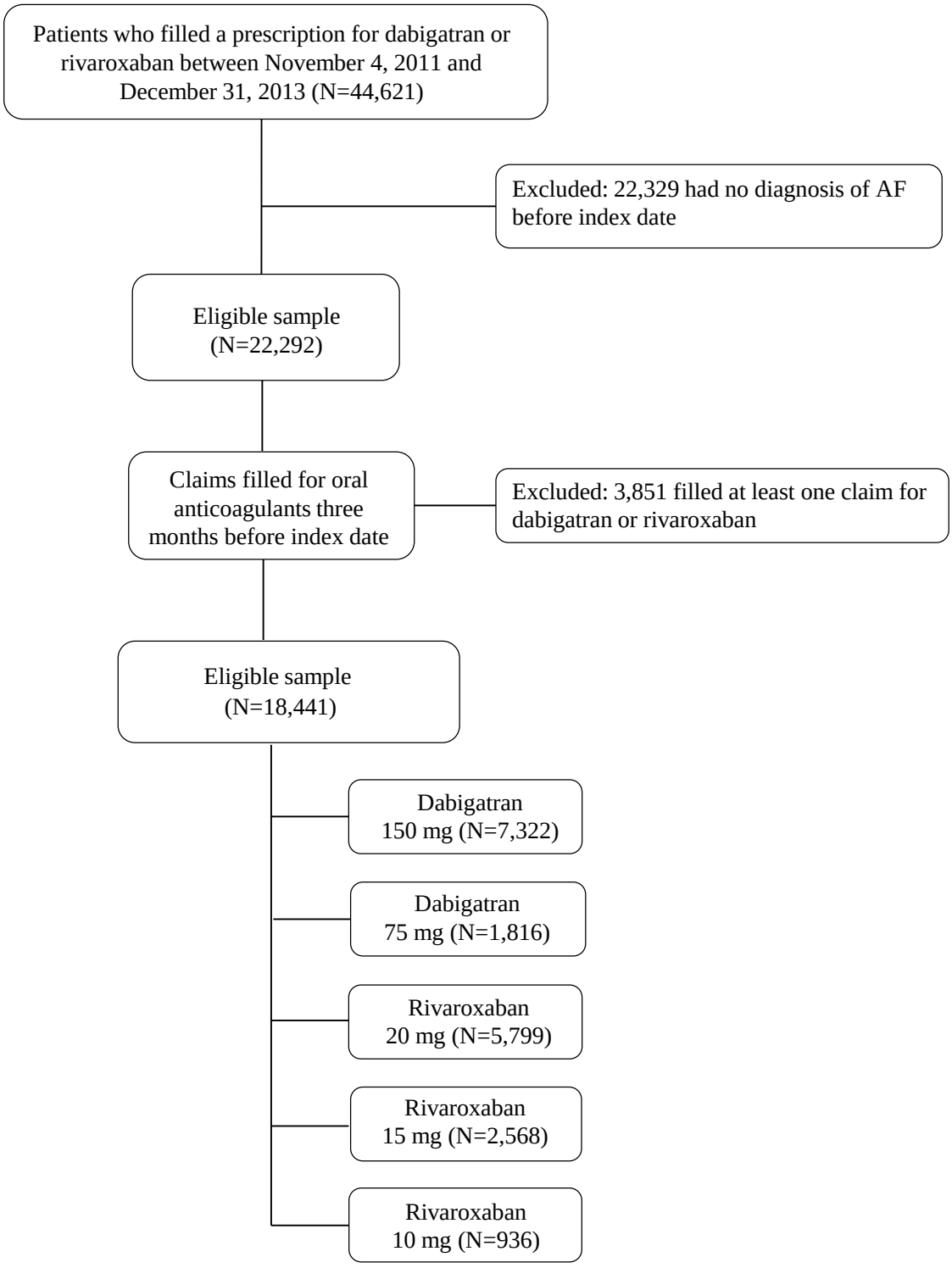

Figure 2-1: Selection of the Study Sample

We followed each individual from the index date until discontinuation of treatment, defined as a gap in anticoagulant treatment for over 60 days, switch of an anticoagulant or dose, death, or December 31, 2013.[104] This study was approved by the Institutional Review Board at the University of Pittsburgh.

2.3.2 Outcomes

Effectiveness outcomes included ischemic stroke, other thromboembolic events and all-cause mortality. Ischemic stroke was defined as having one inpatient, emergency room or outpatient claim with primary or secondary International Classification of Diseases, Ninth Revision (ICD-9) codes 433, 434 or 436.[139,140] Other thromboembolic events included inpatient, emergency room or outpatient claims for systemic embolism (ICD-9=444), transient ischemic attack (ICD-9=435) and pulmonary embolism (ICD-9=415.1). [139,140] Safety outcomes included any bleeding event and major bleeding; we also reported specifically safety outcomes for two anatomical locations: intracranial hemorrhage, and gastrointestinal bleeding. Major bleeding events included intracranial hemorrhage, hemoperitoneum, and inpatient or emergency room stays for gastrointestinal, hematuria, or not otherwise specified hemorrhage. The list of ICD-9 codes used to identify bleeding outcomes is in Table 2-1.

Table 2-1: International Classification of Diseases, Ninth Revision (ICD-9) Codes for Clinical Outcomes

Event	ICD-9 codes
Ischemic Stroke	433, 434 or 436
Systemic Embolism	444
Transient Ischemic Attack	435
Pulmonary Embolism	415.1
Intracranial Bleeding	430, 431, 432
Hemoperitoneum	568.81
Hematuria	599.7
Gastrointestinal Bleeding	530.7, 531.0, 531.2, 531.4, 531.6, 532.0, 532.2, 532.4, 532.6, 533.0, 533.2, 533.4, 533.6, 534.0, 534.2, 534.4, 534.6,569.3, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 535.71, 537.83, 537.84 , 562.02 ,562.03, 562.12, 562.13, 569.85, 578
Epistaxis	784.7
Hemoptysis	786.3
Vaginal Hemorrhage	623.8, 626.2
Hemarthrosis	719.1, 719.2
Not Otherwise Specified Hemorrhage	459

2.3.3 Covariates

We adjusted for demographic variables and clinical characteristics, all of which were measured on the index date. Demographic variables included age, race and Medicaid eligibility. Clinical characteristics included CHADS2 score,[54] chronic kidney disease, hypertension, a history of stroke or TIA, prior acute myocardial infarction, diabetes, congestive heart failure, acquired hypothyroidism, number of other CMS priority comorbidities, a history of bleeding, concomitant use of NSAIDs, and concomitant use of antiplatelet drugs. CHADS2 score is a prediction measure of the risk of stroke in patients with atrial fibrillation. In the calculation of the CHADS2 score, CHF, hypertension, age of 75 years or older and diabetes are assigned one point and a history of previous stroke or TIA is assigned two points; CHADS2 score is calculated as the sum

of all points.[54] The number of other CMS priority comorbidities was calculated as the sum of previous a history of Alzheimer's disease, related disorders or senile dementia, anemia, asthma, benign prostatic hyperplasia, cataract, chronic obstructive pulmonary disease, ischemic heart disease, hip or pelvic fracture, glaucoma, hyperlipidemia, osteoporosis, rheumatoid arthritis or osteoarthritis, breast cancer, colorectal cancer, prostate cancer, lung cancer and endometrial cancer. A history of bleeding was defined as having one claim with ICD-9 codes for any bleeding event in the year before the index date. Concurrent use of NSAIDS was defined as filling a prescription for diclofenac, ibuprofen, naproxen, ketoprofen, fenoprofen, flurbiprofen, piroxicam, meloxicam, mefenamic acid or indomethacin after the index date; and concurrent use of antiplatelet drugs was defined as filling a prescription for aspirin, clopidogrel, prasugrel, dipyridamol, ticlopidine or ticagrelor after the index date.

2.3.4 Statistical Analysis

We compared patient characteristics between dabigatran 150mg initiators and rivaroxaban 20mg initiators (high-dose initiators), and between dabigatran 75mg initiators and rivaroxaban 15mg initiators (low-dose initiators) using chi-square tests. To compare the unadjusted cumulative incidence of effectiveness and safety outcomes at 1 year follow-up, we constructed Kaplan-Meier time-to-event curves.

One of the limitations from using observational data to conduct comparative-effectiveness studies is that individuals in one treatment group may not be comparable to individuals in the other group. To mitigate this problem, we used propensity score weighting, which was conducted in two steps. First, we constructed a logistic regression controlling for all covariates listed in the Covariates Section to calculate the probability of initiating rivaroxaban (propensity score).We

used the Toolkit for Weighting and Analysis of Nonequivalent Groups (TWANG) in statistical software R to find the best logistic regression model to calculate the propensity score. We calculated standardized differences in covariate means between two treatment groups to evaluate whether covariates were balanced between treatment groups after propensity score weighting.[141] Standardized differences with absolute values below 10% indicate a good balance between treatment groups.[142] Second, we constructed Cox Proportional Hazards models to compare effectiveness and safety outcomes between treatment groups, using the inverse of the propensity score for each individual as a weight. Cox models included one indicator variable for rivaroxaban initiation, as well as all pre-defined covariates listed in the Covariates Section. Because one of the limitations of this methodology is the presence of large weights, we checked the distribution of weights and found that none of the subjects had weights larger than 10. For all time-to-event analyses except for the ones that compared the risk of all-cause mortality between treatment groups, the time at risk was censored at the end of the study period (December 31, 2013), or at switch of anticoagulant or dose, discontinuation of anticoagulant therapy, or death. Time-to-event analyses built to compare the risk of all-cause mortality between treatment groups had the same censoring events except death. All analyses were conducted with statistical software SAS 9.4 (Cary, NC).

We further compared the effectiveness and safety of dabigatran and rivaroxaban among three subgroups of patients: those older than 75 years, with chronic kidney disease, or with at least 7 CMS priority conditions other than AF.[143] Specifically, for each subgroup identified, we re-calculated the propensity score, and constructed Cox models to compare effectiveness and safety outcomes following the same methodology as with the overall sample. Cox models

controlled for all the covariates listed in the Covariates Section, except for the one defining the subgroup.

2.3.5 Sensitivity Analyses

One may argue that some of our study participants may have initiated anticoagulation therapy for an indication other than AF. To examine whether this may have affected our results, we collected the medical claims of study participants for venous thromboembolism (ICD-9 codes 452,453), pulmonary embolism (ICD-9=415.5), phlebitis (ICD-9=451), or undergoing hip or knee replacement surgery (ICD-9=V43.64, V43.64 or Healthcare Common Procedure Coding System (HCPCS) codes 27437, 27438, 27440–27443, 27445–27447, 27486, 27487, 27125, 27130, 27132, 27134, 27137, 27138 and 27236) in the three months before the index date.[144,145] Specifically, 171 (2.3%) dabigatran 150mg users, 410 (7.1%) rivaroxaban 20mg users, 62 (3.4%) dabigatran 75mg users and 281 (10.8%) rivaroxaban 15mg users had a medical claim with a diagnosis of these conditions. After excluding these individuals from the sample, we re-calculated the propensity score and constructed Cox models following the same methodology as explained in the Statistical Analysis section. Subjects who used warfarin before the initiation of dabigatran or rivaroxaban may have had remaining warfarin at the time of dabigatran or rivaroxaban initiation. If they experienced a bleeding event soon after the initiation of dabigatran or rivaroxaban, the occurrence of such event may have been affected by the remaining warfarin. To analyze whether our results for the comparative risk of bleeding with two NOACs were affected by this problem, we ran our analyses after excluding subjects who filled a prescription for warfarin six months before index date. Specifically, 1453 (19.8%) dabigatran 150mg users, 1828 (31.5%) rivaroxaban 20mg users, 424 (23.4%) dabigatran 75mg users and 769 (29.9%)

rivaroxaban 15mg users had filled a prescription for warfarin in the 6 months before index date and were therefore excluded from these sensitivity analyses. Because in patients with a history of stroke it is difficult in some occasions to differentiate new events from prior diagnoses of strokes, we conducted sensitivity analyses by including and excluding patients who had a history of stroke or TIA before the index date.

2.4 RESULTS

2.4.1 Patient Characteristics

The mean follow-up period was 385 days for dabigatran 150mg users, 251 days for rivaroxaban 20mg users, 357 days for dabigatran 75mg users, and 239 for rivaroxaban 15mg users (Table 2-2).

Table 2-2. Follow-up Period and Patterns of Anticoagulation Use, by Treatment and Dose.

	Dabigatran 150mg (N=7,322)	Rivaroxaban 20mg (N=5,799)	P-Value
Follow-up period, mean (SD)	385 (247)	251 (177)	<0.001
Discontinuation (%)	13.4	5.1	<0.001
Switch of treatments or dose (%)	14.9	3.4	<0.001
	Dabigatran 75mg (N=1,816)	Rivaroxaban 15mg (N=2,568)	P-Value
Follow-up period, mean (SD)	357 (244)	239 (175)	<0.001
Discontinuation (%)	13.1	4.4	<0.001
Switch of treatments or dose (%)	10.7	0.6	<0.001

Table 2-3 shows the comparison of patient characteristics before and after propensity score weighting for high-dose and low-dose initiators. Before propensity score weighting, rivaroxaban 20mg initiators were more likely to be also eligible for Medicaid benefits, have chronic kidney

disease and acquired hypothyroidism than dabigatran 150mg initiators. The mean age of dabigatran 150mg users was 75.64, and the mean age of rivaroxaban 20mg users was 75.44. Dabigatran 75mg users and rivaroxaban 20mg were 82.0 and 81.71 years old on average, respectively. The use of NSAIDs before propensity score weighting was higher among patients initiating dabigatran 150mg (15.9%) than those initiating rivaroxaban 20mg (11.4%), p-value<0.001. Although low-dose dabigatran and rivaroxaban are only indicated in AF patients with reduced kidney function, only 52.6% of patients on dabigatran 75mg and 51.5% of those on rivaroxaban 15mg had a diagnosis of chronic kidney disease. After propensity score weighting, all patient characteristics were balanced between rivaroxaban and dabigatran groups for both high and low dose initiators.

Table 2-3: Baseline Characteristics of the Study Cohorts, Before and After Propensity Score Weighting, by Treatment and Dose

	Before Propensity Score Weighting						After Propensity Score Weighting					
	High Dose			Low Dose			High Dose			Low Dose		
Variable (%)	Dabigatran (N=7,322)	Rivaroxaban (N=5,799)	P-Value	Dabigatran (N=1,816)	Rivaroxaban (N=2,568)	P-Value	D	R	Standardized Difference in Covariate Means	D	R	Standardized Difference in Covariate Means
Age			0.005			0.565						
<65	5.0	6.3		1.9	1.9		5.5	5.6	-0.7	1.9	1.9	-0.1
65-74	39.3	38.4		14.4	15.5		38.9	38.9	0.1	14.6	14.9	-0.8
≥75	55.7	55.3		83.7	82.5		55.6	55.5	0.2	83.6	83.3	0.8
Male sex	49.5	45.9	<0.001	34.7	32.5	0.132	48.0	47.9	0.0	33.4	33.3	0.2
Race			0.058			0.894						
White	87.5	86.3		86.4	86.5		87.3	87.3	-0.2	87.1	86.8	0.6
Black	5.4	5.5		5.6	5.1		5.4	5.3	0.4	5.2	5.2	0.0
Asian	1.8	1.8		2.7	2.9		1.7	1.7	0.0	2.6	2.6	-0.4
Hispanic	3.9	5.1		4.3	4.7		4.3	4.4	-0.3	4.3	4.5	-0.6
Native American	0.3	0.3		0.3	0.3		0.2	0.2	0.0	0.3	0.3	0.4
Other	1.2	1.1		0.7	0.6		1.1	1.1	0.5	0.5	0.6	-0.5
Medicaid eligibility	20.0	22.7	<0.001	27.3	25.9	0.314	21.0	20.9	0.3	26.2	26.3	-0.2
CHADS2 score--mean (SD)	3.28 (1.30)	3.29 (1.32)	0.961	3.87 (1.29)	3.79 (1.30)	0.039	3.28 (1.75)	3.28 (1.96)	0.0	3.83 (1.99)	3.83 (1.68)	-0.4
CMS priority comorbidities												
CKD	26.3	28.6	0.003	52.6	51.5	0.469	27.2	27.2	-0.1	51.9	51.8	0.1
Hypertension	92.9	92.8	0.976	96.9	96.6	0.577	92.9	92.9	0.0	96.9	96.8	0.3
Previous stroke or TIA	22.7	23.4	0.302	34.7	33.7	0.505	22.9	23.0	-0.2	34.3	34.1	0.3
AMI	6.5	7.4	0.044	11.1	11.1	0.989	6.8	6.8	0.1	10.8	11.0	-0.7
Diabetes mellitus	43.4	44.4	0.258	50.0	50.0	0.992	43.8	43.9	-0.2	50.1	50.0	0.0
CHF	51.8	50.8	0.219	72.5	66.6	<0.001	51.3	51.3	0.0	69.3	69.1	0.5
Acquired hypothyroidism	26.0	29.6	<0.001	38.2	39.5	0.410	27.6	27.7	-0.1	39.3	39.1	0.3
No. of other CMS priority comorbidities			<0.001			0.074						
0-3	22.4	21.5		8.8	7.0		22.0	21.9	0.2	7.8	7.6	1.0
4-6	41.5	38.1		30.1	31.2		40.0	40.0	0.0	30.5	30.7	-0.5
≥7	36.2	40.4		61.1	61.8		38.0	38.0	-0.2	61.7	61.7	-0.1
History of bleeding	19.2	20.2	0.145	25.4	24.7	0.579	19.6	19.5	0.1	24.8	24.9	-0.3
Use of NSAIDs	15.9	11.4	<0.001	13.1	9.9	0.001	13.9	13.7	0.6	11.1	11.0	0.2
Use of antiplatelets	7.1	6.1	0.017	9.5	6.9	0.002	6.6	6.4	0.5	7.7	7.7	0.1

2.4.2 Unadjusted Incidence of Effectiveness and Safety Outcomes

Table 2-4 shows the number of events and the unadjusted cumulative incidence rates of effectiveness and safety outcomes by treatment group. Dabigatran 150mg was associated with lower risk of all-cause mortality, major bleeding, gastrointestinal bleeding and any bleeding events than rivaroxaban 20 mg. However, there was no difference in the unadjusted risk of ischemic stroke, other thromboembolic events, and intracranial bleeding between dabigatran 150mg initiators and rivaroxaban 20mg initiators. The unadjusted incidence of clinical outcomes did not differ between dabigatran 75mg and rivaroxaban 15mg initiators except for any bleeding event, which was higher with rivaroxaban 15mg than dabigatran75mg.

Table 2-4. Number of Events and Cumulative Incidence Rates at 1 Year Follow-up of Clinical Outcomes, by Treatment Group and Dose.

	Number of events (%)		Cumulative Incidence At 1 year (95% CI)	
High Dose	Dabigatran (N=7,322)	Rivaroxaban (N=5,799)	Dabigatran (N=7,322)	Rivaroxaban (N=5,799)
Effectiveness Outcomes				
Ischemic Stroke	1036 (14.2)	580 (10.0)	0.12 (0.11 , 0.13)	0.12 (0.11 , 0.14)
Other Thromboembolic events	386 (5.3)	250 (4.3)	0.041 (0.036 , 0.046)	0.053 (0.046 , 0.061)
All-Cause Mortality	247 (3.4)	229 (3.9)	**0.032 (0.030 , 0.039)**	**0.050 (0.043 , 0.056)**
Safety Outcomes				
Major Bleeding	349 (4.8)	229 (4.0)	**0.034 (0.029 , 0.038)**	**0.050 (0.043 , 0.058)**
Any Bleeding	1658 (22.6)	1008 (17.4)	**0.19 (0.18 , 0.20)**	**0.22 (0.21 , 0.23)**
Intracranial Bleeding	88 (1.2)	33 (0.6)	0.008 (0.006 , 0.010)	0.007 (0.004 , 0.009)
Gastrointestinal Bleeding	722 (9.9)	439 (7.6)	**0.08 (0.07 , 0.08)**	**0.10 (0.09 , 0.11)**
Low Dose	Dabigatran (N=1,816)	Rivaroxaban (N=2,568)	Dabigatran (N=1,816)	Rivaroxaban (N=2,568)
Effectiveness Outcomes				
Ischemic Stroke	316 (17.4)	315 (12.3)	0.16 (0.14 , 0.18)	0.17 (0.15 , 0.19)
Other Thromboembolic events	130 (7.2)	161 (6.3)	0.07 (0.06 , 0.08)	0.08 (0.07 , 0.09)
All-Cause Mortality	146 (8.0)	191 (7.4)	0.087 (0.073 , 0.101)	0.099 (0.085 , 0.114)
Safety Outcomes				
Major Bleeding	107 (5.9)	139 (5.4)	0.053 (0.041 , 0.064)	0.073 (0.060 , 0.087)
Any Bleeding	429 (23.6)	518 (20.2)	**0.21 (0.19 , 0.23)**	**0.27 (0.24 , 0.29)**
Intracranial Bleeding	26 (1.4)	29 (1.1)	0.013 (0.007 , 0.018)	0.018 (0.011 , 0.025)
Gastrointestinal Bleeding	206 (11.3)	229 (8.9)	0.10 (0.08 , 0.11)	0.12 (0.10 , 0.13)

Bold denotes statistical significant results.

2.4.3 Adjusted Hazard Ratio of Effectiveness and Safety Outcomes

Figure 2-2 shows the adjusted hazard ratios for effectiveness and safety outcomes after propensity score weighting. The risk of ischemic stroke did not differ between rivaroxaban 20 mg and dabigatran 150mg (HR 1.05; 95% CI 0.97-1.13); however, rivaroxaban 20mg was associated with higher risk of other thromboembolic events (HR 1.28; 95%CI 1.14-1.44) and all-cause mortality (HR 1.36; 95% CI, 1.19-1.56) than dabigatran 150mg. The risk of major bleeding (HR 1.32; 95% CI, 1.17-1.50), any bleeding event (HR 1.17; 95% CI, 1.10-1.24) and gastrointestinal bleeding (HR 1.19; 95% CI, 1.03-1.30) was also higher among patients initiating rivaroxaban 20mg than those initiating dabigatran 150 mg. The risk of intracranial hemorrhage did not differ between high-dose dabigatran and rivaroxaban.

Our results for the comparative risk of effectiveness and safety outcomes among low-dose initiators are consistent with the findings from high-dose initiators: There was no difference in the risk of ischemic stroke and intracranial bleeding between rivaroxaban 15mg and dabigatran 75mg; however, the risk of other thromboembolic events (HR 1.37; 95%CI, 1.15-1.62), all-cause mortality (HR 1.21; 95% CI, 1.04-1.41), major bleeding (HR 1.51; 95% CI, 1.25-1.82), any bleeding event (HR 1.39; 95% CI, 1.27-1.53) and gastrointestinal bleeding (HR 1.25; 95% CI, 1.09-1.44) was higher with rivaroxaban 15mg than dabigatran 75mg.

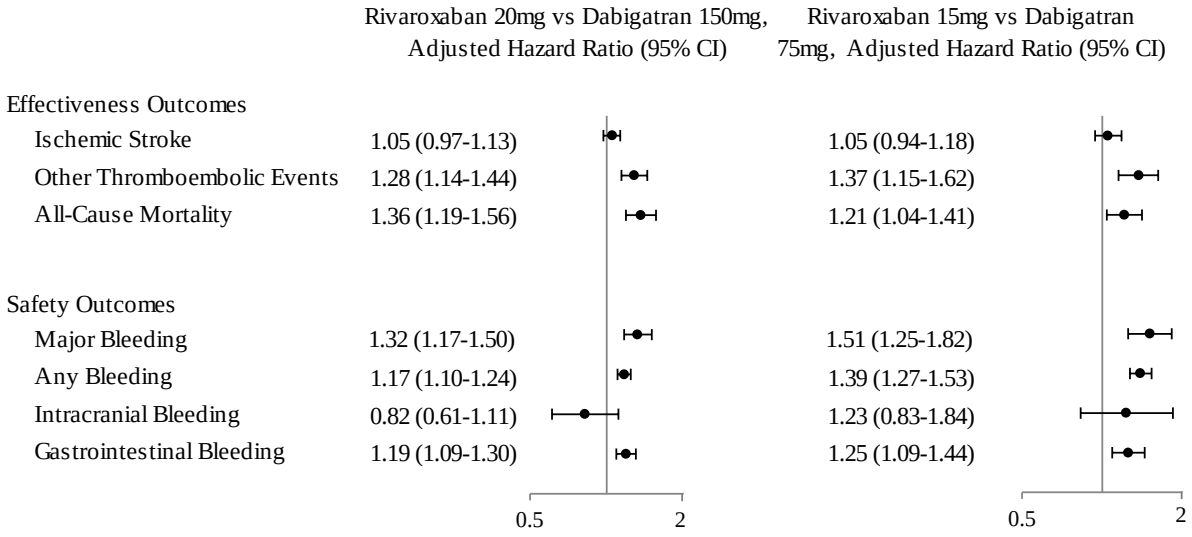

Figure 2-2: Hazard Ratios for Effectiveness and Safety Outcomes, by Treatment and Dose

2.4.4 Subgroup Analyses

Our results for selected effectiveness and safety outcomes in three high-risk subgroups are consistent with the findings from the overall sample (Figure 2-3). Among patients older than 75 years, with chronic kidney disease, or with more than 7 CMS priority conditions other than AF, rivaroxaban was consistently associated with higher risk of thromboembolic events other than stroke, major bleeding and any bleeding events, but similar risk of ischemic stroke than dabigatran.

	Rivaroxaban 20mg vs Dabigatran 150mg, Adjusted Hazard Ratio (95% CI)	Rivaroxaban 15mg vs Dabigatran 75mg, Adjusted Hazard Ratio (95% CI)
	> 75 yrs	
Ischemic Stroke	1.06 (0.96-1.16)	1.06 (0.93-1.20)
Other Thromboembolic Events	1.45 (1.24-1.69)	1.40 (1.16-1.68)
Major Bleeding	1.30 (1.12-1.51)	1.35 (1.11-1.66)
Any Bleeding	1.17 (1.08-1.26)	1.39 (1.25-1.54)
	Chronic Kidney Disease	
Ischemic Stroke	0.98 (0.87-1.12)	1.13 (0.97-1.32)
Other Thromboembolic Events	1.29 (1.05-1.58)	1.17 (0.93-1.48)
Major Bleeding	1.34 (1.10-1.64)	1.48 (1.17-1.88)
Any Bleeding	1.17 (1.06-1.29)	1.34 (1.18-1.52)
	More than 7 Concomitant Comorbidities	
Ischemic Stroke	1.12 (1.01-1.25)	1.05 (0.91-1.20)
Other Thromboembolic Events	1.55 (1.31-1.84)	1.39 (1.14-1.69)
Major Bleeding	1.31 (1.10-1.55)	1.30 (1.03-1.63)
Any Bleeding	1.14 (1.05-1.24)	1.34 (1.19-1.51)

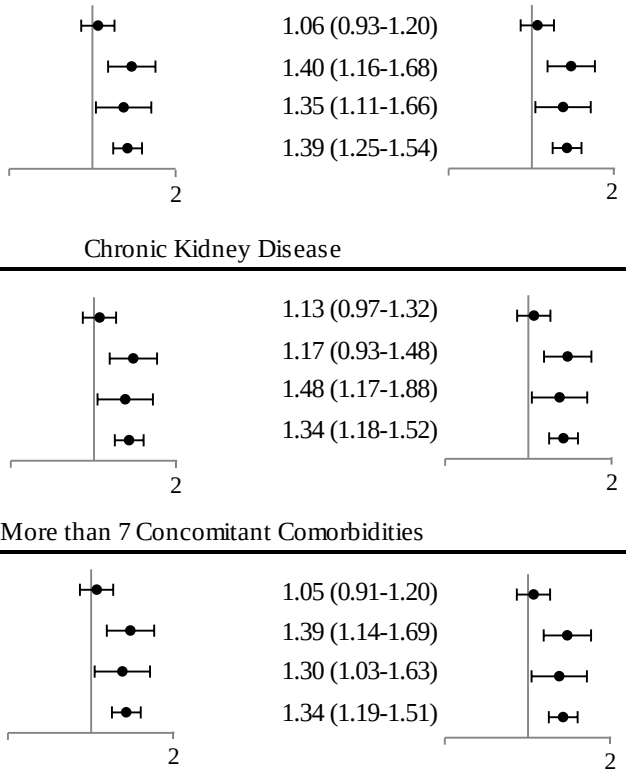

Figure 2-3: Hazard Ratios for Effectiveness and Safety Outcomes, by Subgroup, Treatment and Dose

2.4.5 Sensitivity Analyses

Tables 2-5, 2-6 and 2-7 show the results of the sensitivity analyses. After excluding patients with a diagnosis of an indication for anticoagulation other than AF, there was no difference in the risk of thromboembolic events other than stroke between rivaroxaban and dabigatran, but other outcomes were similar as those from the overall sample. After the exclusion of recent warfarin-experienced subjects from the study sample, the hazard ratios of bleeding events did not vary much (Table 2-6). Finally, the exclusion of patients with a history of stroke or TIA did not

impact our results for the comparative risk of effectiveness outcomes between two oral anticoagulants (Table 2-7).

Table 2-5: Hazard Ratios for Effectiveness and Safety Outcomes after Excluding Patients with a Diagnosis of Thromboembolic Events or Hip or Knee Replacement Surgery.

	Rivaroxaban 20mg vs Dabigatran 150mg, Adjusted Hazard Ratio (95% CI)	Rivaroxaban 15mg vs Dabigatran 75mg, Adjusted Hazard Ratio (95% CI)
Effectiveness Outcomes		
Ischemic Stroke	1.05 (0.97-1.14)	1.04 (0.92-1.17)
Other Thromboembolic Events	1.13 (0.99-1.28)	0.93 (0.76-1.13)
All-Cause Mortality	1.33 (1.15-1.53)	1.19 (1.01-1.41)
Safety Outcomes		
Major Bleeding	1.30 (1.14-1.48)	1.49 (1.22-1.81)
Any Bleeding	1.17 (1.10-1.24)	1.40 (1.26-1.54)
Intracranial Bleeding	0.79 (0.59-1.08)	1.24 (0.81-1.88)
Gastrointestinal Bleeding	1.20 (1.10-1.31)	1.24 (1.07-1.43)

Table 2-6: Hazard Ratios for Bleeding Events after Excluding Recent Warfarin-Experienced Subjects.

	Rivaroxaban 20mg vs Dabigatran 150mg, Adjusted Hazard Ratio (95% CI)	Rivaroxaban 15mg vs Dabigatran 75mg, Adjusted Hazard Ratio (95% CI)
Major Bleeding	1.45 (1.25-1.69)	1.62 (1.29-2.02)
Any Bleeding	1.25 (1.17-1.34)	1.51 (1.35-1.69)
Intracranial Bleeding	0.94 (0.66-1.34)	1.37 (0.88-2.14)
Gastrointestinal Bleeding	1.24 (1.12-1.38)	1.32 (1.12-1.56)

Table 2-7. Hazard Ratios for Effectiveness Outcomes after Excluding Patients with a History of Stroke or Transient Ischemic Attack.

	Rivaroxaban 20mg vs Dabigatran 150mg, Adjusted Hazard Ratio (95% CI)	Rivaroxaban 15mg vs Dabigatran 75mg, Adjusted Hazard Ratio (95% CI)
Ischemic Stroke	1.00 (0.90-1.11)	1.05 (0.88-1.25)
Other Thromboembolic Events	1.23 (1.04-1.45)	1.51 (1.18-1.94)
All-Cause Mortality	1.53 (1.29-1.80)	1.27 (1.04-1.54)

2.5 DISCUSSION

To the best of our knowledge, our study is the first to compare effectiveness and safety outcomes between dabigatran and rivaroxaban, separately by dose, among Medicare patients with AF. Our study yielded two main findings. First, we found no differences in stroke prevention between dabigatran and rivaroxaban; however, rivaroxaban was associated with higher rates of thromboembolic events other than stroke and all-cause mortality than dabigatran. Second, we observed that the risk of major bleeding, gastrointestinal bleeding and any bleeding events was higher with rivaroxaban than dabigatran, but there was no difference in the risk of intracranial bleeding between dabigatran and rivaroxaban.

Previous researchers have conducted indirect comparisons of the results from the RE-LY and ROCKET-AF trials, predicting that dabigatran would be associated with a lower combined risk of stroke and systemic embolism than rivaroxaban (HR 1.35; 95% CI 1.02-1.78), but with a similar risk of ischemic stroke (HR 1.33; 95% CI 0.98-1.78), and a similar risk of bleeding (HR 1.12; 95% CI 0.92-1.37).[98,100] We found no difference in the risk of ischemic stroke with two NOACs (HR 1.05; 95% CI, 0.97-1.13), but we observed that the risk of thromboembolic events other than stroke (HR 1.28; 95% CI, 1.14-1.44) and of bleeding (HR 1.32; 95%CI, 1.17-1.50) was higher with rivaroxaban. The differences between our results for the comparative risk of bleeding with two NOACs and those reported in indirect comparisons may be explained by the difference in patient characteristics of subjects enrolled in two clinical trials.[98,100] For example, 55% and 62% of the subjects enrolled in the ROCKET-AF trial had a prior stroke/TIA and heart failure, compared to 20% and 35% of those enrolled in the RE-LY trial, respectively.[88,89] Using US commercial insurance data, Laliberte et al. compared the effectiveness and safety of rivaroxaban and warfarin, estimating the annual risk of major bleeding on rivaroxaban at

3.3%.[134] Our estimate for the rate of major bleeding on rivaroxaban 20mg (5%) is higher than the estimate reported by Laliberte and colleagues, partially because of the higher prevalence of risk factors for bleeding among our study sample. For instance, 28.6 % of our study participants on rivaroxaban 20mg had a diagnosis of kidney disease, whereas only 7.5% of those included in the study by Laliberte et al. did.[134] To the best of our knowledge, only one study has directly compared the risk of bleeding with dabigatran and rivaroxaban. In doing so, Sherid et al. used medical records from two community hospitals and did not find differences in the risk of bleeding with two NOACs.[107] However, the sample size of this study was very small (227 dabigatran users and 147 rivaroxaban users), which may have prevented the authors from finding significant differences.

Our study is subject to four main limitations. First, propensity score weighting did not adjust for unobserved patient characteristics, such as the result of laboratory tests, because they are not available in Medicare claims data. Thus, some unobserved risk factors for clinical outcomes may have been unbalanced between treatment groups, such as creatinine clearance. However, we balanced the proportion of patients with chronic kidney disease between treatment groups using propensity score weighting, and we also included this as a covariate in our Cox Proportional Hazards models. Second, because of the unavailability of data on INR, we could not calculate the HAS-BLED risk score, which is a prediction tool of the risk of bleeding**.**[113,146] Nevertheless, we balanced all components of HAS-BLED score except for labile INR between treatment groups, and included them as separate covariates in our analytical models as well. Third, in our study, we used 2010-2013 Medicare data, so our study period represents the first two years after rivaroxaban entered the US market. Prescribing patterns of NOACs may change over time as prescribers become more familiar with these agents.[105,112] Fourth, our study did not

include apixaban, which was approved in December 2012, because we would not have enough follow-up period to study effectiveness outcomes. As a result, it will be informative to repeat our analyses as newer Medicare Part D data becomes available, and compare the effectiveness and safety of dabigatran and rivaroxaban to those of apixaban.

Our research has three main implications. First, because there was no difference in stroke prevention with two NOACs but dabigatran was superior in safety to rivaroxaban, the use of dabigatran should be preferred over rivaroxaban. One may argue, however, that the benefit associated with dabigatran might be counterbalanced by lower rates of adherence because of the twice-a-day regimen. In fact, a recent analysis of US commercial insurance claims data found that rivaroxaban users were more adherent than patients on dabigatran.[147] Our study captured the real-world use of two new oral anticoagulants, where adherence to rivaroxaban is likely to be higher, and found no difference in the prevention of stroke with two new oral anticoagulants, yet rivaroxaban was associated with higher risk of bleeding. This implies that despite of the twice-a-day regimen, dabigatran still presents a better benefit/risk ratio in the real-world clinical practice than rivaroxaban. Second, consistent with the results from the overall sample, we found that dabigatran was associated with lower rates of bleeding but similar risk of stroke than rivaroxaban among patients older than 75 years or with kidney disease.[54,113] In these two subgroups of patients with high-risk of bleeding, dabigatran would be especially preferred compared to rivaroxaban because, in case of major hemorrhage, there are two strategies available to revert the effects of dabigatran that are not available for rivaroxaban: a FDA-approved antidote,[77] and hemodialysis.[148] Third, rivaroxaban 15mg and dabigatran 75mg are indicated in the prevention of stroke or systemic embolism in renally impaired patients with AF; however, half of the study participants who initiated rivaroxaban 15mg or dabigatran 75mg did not have a diagnosis of

chronic kidney disease. Our results suggest that low doses of anticoagulants were prescribed off-labelly in 2011-2013 for patients who did not have chronic kidney disease, but who had however other risk factors for bleeding, such as hypertension, a history of stroke or a history of bleeding. These prescribing patterns may have been motivated by the concerns of severe bleeding events with NOACs, the unavailability of dabigatran 110mg in the US, and the lack of an antidote to reverse the anticoagulation effects of rivaroxaban and dabigatran in case of emergency in 2011-2013, the period that our study represents. Idarucizumab, the specific antidote for dabigatran, was approved in October 2015.[77]

In conclusion, we found that dabigatran was superior in safety to rivaroxaban; however, we did not find differences in stroke prevention between two oral anticoagulants. Our findings have important implications to the use of NOACs among AF patients.

3.0 ANTICOAGULATION USE AND CLINICAL OUTCOMES FOLLOWING MAJOR BLEEDING ON DABIGATRAN OR WARFARIN IN ATRIAL FIBRILLATION

3.1 ABSTRACT

Little is known about the patterns of anticoagulation use and clinical outcomes associated with the resumption of anticoagulation after a major hemorrhage. This manuscript had two objectives: first, to evaluate the patterns of anticoagulation use after a first major bleeding event on warfarin or dabigatran; and second, to compare the combined risk of ischemic stroke and all-cause mortality and recurrent hemorrhage between patients interrupting anticoagulation after a bleeding event and patients restarting warfarin or dabigatran. Using 2010-2012 Medicare Part D data, we identified atrial fibrillation patients who experienced a major bleeding while using warfarin (n=1135) or dabigatran (n=404) and categorized them by their post-hemorrhage use of anticoagulation into three groups: those who resumed anticoagulation with warfarin or dabigatran, and those who discontinued anticoagulation. We followed them until a clinical event of ischemic stroke, recurrent hemorrhage, or death through December 31, 2012. We constructed logistic regression models to evaluate factors impacting anticoagulation resumption, and Cox Proportional Hazard models to compare the risk of ischemic stroke, all-cause mortality, and recurrent bleeding between treatment groups. We found that CHA2DS2-Vasc and HAS-BLED scores did not affect the odds of post-hemorrhage anticoagulation resumption. The odds of

resuming anticoagulation decreased however by 11% (95%CI, 4%-18%) and 24% (95%CI, 9%-37%) for every 5 years increase in age for warfarin and dabigatran users, respectively. Resumption of anticoagulation with warfarin (HR0.76; 95%CI, 0.59-0.97) or dabigatran (HR0.66; 95%CI 0.44-0.99) was associated with lower combined risk of ischemic stroke and all-cause mortality than anticoagulation discontinuation. The incidence of recurrent major bleeding was higher for patients who were prescribed warfarin after the bleeding event than for those prescribed dabigatran (HR2.31; 95%CI, 1.19-4.76) or whose anticoagulation ceased (HR1.56; 95%CI, 1.10-2.22), but did not differ between patients restarting dabigatran and those discontinuing anticoagulation. In conclusion, the benefit/risk ratio of dabigatran among atrial fibrillation patients who have survived a major hemorrhage is superior to that of warfarin and of anticoagulation discontinuation.

3.2 INTRODUCTION

Anticoagulation therapy reduces the risk of stroke associated with AF by around 60%.[46] Anticoagulation, however, is not free of risks, being an important determinant of bleeding. Specifically, the annual risk of major bleeding on anticoagulation has been estimated at 8-10%.[104,149,150] The optimal management of AF patients who have experienced a major bleeding complication is uncertain, since there are competing risks from both the resumption and the discontinuation of anticoagulation: while patients experiencing a major bleed are at increased risk of recurrent bleeding events,[63,113] they are also at a high risk of thromboembolic events, if anticoagulation is not reinitiated.[114-117] Furthermore, there are no specific clinical guidelines to inform the prescription of oral anticoagulation agents after a major bleeding event.[60] The

uncertainty surrounding decisions about the post-hemorrhage use of anticoagulation is very relevant from the clinical perspective, particularly because patients who are at highest risk of bleeding are also at highest risk of stroke.[58,59,63,113]

Previous studies that examined the clinical outcomes of patients who resumed versus those who discontinued anticoagulation after a major bleed found that resumption of anticoagulation was associated with lower risk of thromboembolic events, but higher risk of bleeding.[114-117] Nevertheless, in comparing clinical outcomes between these 2 groups of patients, these studies did not account for the type of anticoagulation agent used.[114-117] Moreover, the data used in these publications mostly preceded the market entry of the NOACs.[114-117] Because the prescription patterns of the NOACs differ from those of warfarin,[119] it is important to assess whether the patterns of post-hemorrhage resumption of anticoagulation differ between warfarin and NOAC users. With no requirement for routine INR monitoring, and with a lower risk of intracranial bleeding, the therapeutic management and bleeding profile of the NOACs are also considerably different from those of warfarin.[92] Consequently, the clinical outcomes associated with the resumption of anticoagulation after a major bleeding event may differ between patients reinitiating warfarin therapy and those reinitiating NOACs. Therefore, it is important to separately evaluate the risks of stroke and recurrent bleeding among patients who resume anticoagulation with warfarin, those who reinitiate anticoagulation with the NOACs, and those who discontinue all anticoagulation.

Our present analysis had therefore two objectives: first, to evaluate the patterns of oral anticoagulation use after a major bleeding event on dabigatran or warfarin and to identify predictors for post-hemorrhage resumption of oral anticoagulation; and second, to compare the combined risk of ischemic stroke and all-cause mortality and the risk of recurrent bleeding

events between patients who resume anticoagulation with warfarin or dabigatran versus those whose anticoagulation is ceased.

3.3 METHODS

3.3.1 Data Source and Study Population

We obtained 2010-2012 data for a 5% random sample of Medicare beneficiaries from CMS. First, we identified all patients who had a diagnosis of AF[151] and filled a prescription for dabigatran or warfarin between October 19, 2010 (date of dabigatran approval)[152] and June 30, 2012 (Figure 3-1).

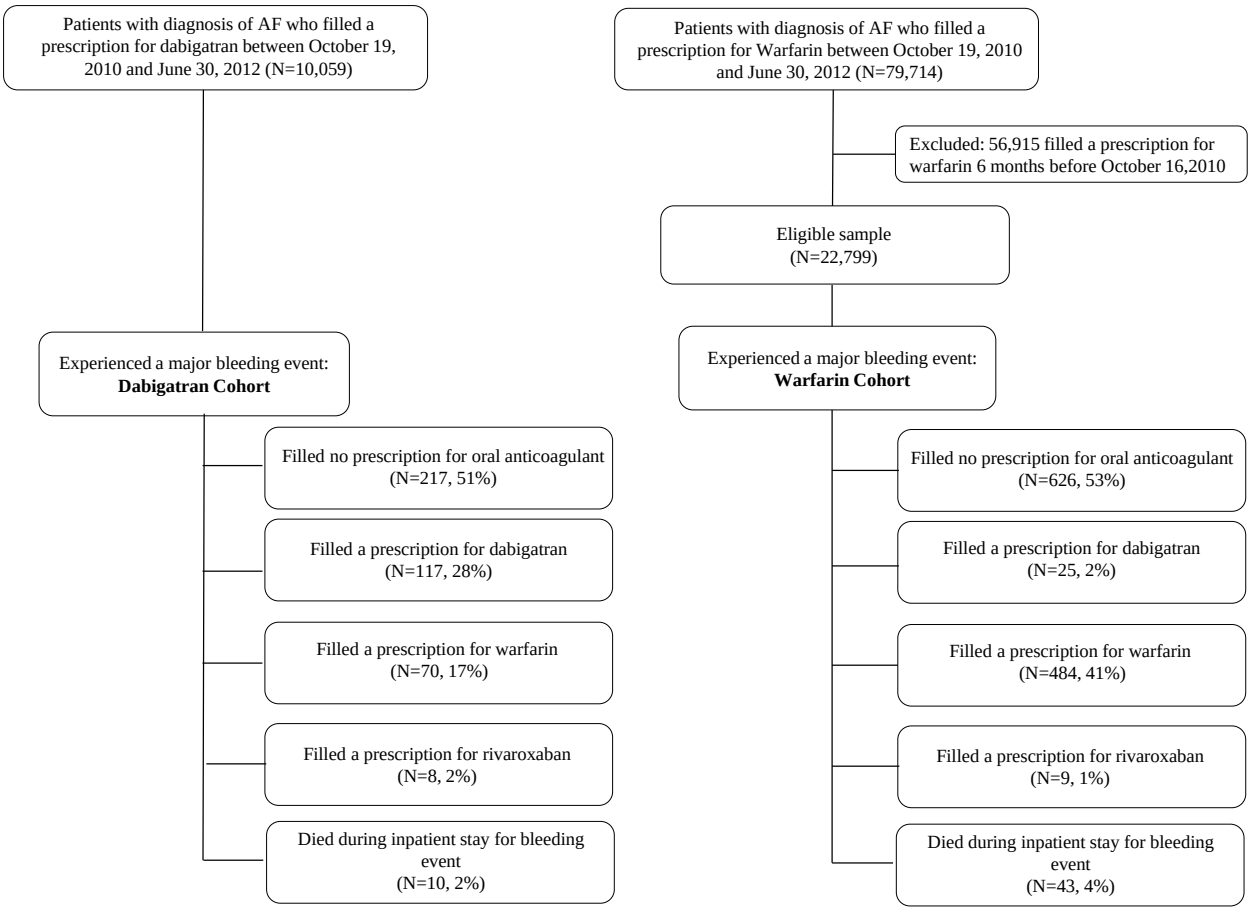

Figure 3-1: Selection of the Study Sample.

To make sure that the warfarin group was representative of patients initiating warfarin and hence, comparable to the dabigatran group, we excluded all individuals who had filled a prescription for warfarin during the six months before October 19, 2010. We followed 10,059 dabigatran users and 79,714 warfarin users from the date of the first prescription of dabigatran or warfarin after October 19, 2010 through December 31, 2012 until the first of the following events: major bleeding, discontinuation of treatment, defined as a gap in treatment for over 60 days, [104] switch of anticoagulant, or death. Second, we selected those who experienced a major bleeding event that required hospitalization (index major hemorrhage) and identified those who were discharged alive. Third, we collected their prescriptions for oral anticoagulant agents filled

after the date of the index major hemorrhage and categorized them according to the oral anticoagulation agent used. Patients who filled a prescription for dabigatran or warfarin after the bleeding event were followed from the date of the first anticoagulant prescription after index major hemorrhage (post-hemorrhage follow-up start date) through December 31, 2012 or until the occurrence of a stroke, a recurrent bleeding event, or death. To set the post-hemorrhage follow-up start date for patients who never filled a prescription for an oral anticoagulant agent after the index major hemorrhage, we performed frequency matching. Frequency matching ensured that the time to start following patients who discontinued anticoagulation had the same distribution as the time to anticoagulant resumption for patients who resumed anticoagulation. Further details on frequency matching can be found in Appendix A. Patients who switched to rivaroxaban were not included in the study because of the small sample size of this treatment group (n=8 in the dabigatran cohort, and n=9 in the warfarin cohort). This study was approved by the Institutional Review Board at the University of Pittsburgh as exempt.

3.3.2 Outcomes

Effectiveness outcomes included ischemic stroke, all-cause mortality, and the composite of ischemic stroke and all-cause mortality. Ischemic stroke was defined as having one inpatient, emergency room or outpatient claim with primary or secondary ICD-9 codes 433, 434 or 436.[139,140] Safety outcomes included recurrent major bleeding and any recurrent bleeding event. A major bleeding event included any inpatient claims with primary or secondary ICD-9 codes for intracranial hemorrhage, hemoperitoneum, genitourinary hemorrhage, gastrointestinal hemorrhage, epistaxis, hemoptysis, vaginal hemorrhage, hemarthrosis, conjunctival hemorrhage or not otherwise specified hemorrhage (the list of ICD-9 codes is displayed in Table 3-1).[104] Any

bleeding event included any inpatient, emergency room or outpatient claim with primary or secondary ICD-9 codes for the same list of bleeding events. In order to avoid double counting, several claims for a bleeding event were considered the same single event if they occurred within 2 weeks of each other.[153]

Table 3-1: International Classification of Diseases, Ninth Revision (ICD-9) Codes for Bleeding Events and for Corrective Surgical Procedures by Anatomical Site

Bleeding Event	ICD-9 Diagnosis Codes to Identify Bleeding Events	ICD-9 Procedure Codes to Identify Corrective Procedures
Intracranial bleeding	430, 431, 432	N/A
Hemoperitoneum	568.81	54.12, 54.4
Hematuria	599.7	57.49, 57.93
GI Hemorrhage	530.7, 531.0, 531.2, 531.4, 531.6, 532.0, 532.2, 532.4, 532.6, 533.0, 533.2, 533.4, 533.6, 534.0, 534.2, 534.4, 534.6,569.3, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 535.71, 537.83, 537.84 , 562.02 ,562.03, 562.12, 562.13, 569.85, 578	42.33, 43.41, 43.89, 44.29, 44.42, 44.43, 44.44, 45.30, 45.34, 45.42, 45.43, 45.73, 45.74, 45.76, 45.82, 45.93, 46.20, 48.35, 48.36
Epistaxis	784.7	21.01, 21.02, 21.03, 21.05, 21.31, 21.61
Hemoptysis	786.3	30.29, 31.1, 31.69, 32.20
Vaginal Hemorrhage	623.8, 626.2	N/A
Hemarthrosis	719.1, 719.2	81.92
Conjunctival hemorrhage	372.72	12.4
NOS Hemorrhage	459	Any of the listed codes

3.3.3 Covariates

We evaluated how different demographic factors, clinical characteristics, anatomical location and severity of the index major hemorrhage affected the post-hemorrhage use of oral anticoagulation. All covariates were measured at the time of the index major hemorrhage. Demographic characteristics included age, gender, race and eligibility for Medicaid coverage.

Clinical covariates included CHA2DS2-Vasc score,[57] HAS-BLED score,[113] and number of other CMS priority comorbidities. Because Medicare claims data does not contain information on INR, we calculated the HAS-BLED score as the sum of all previous factors except labile INR. The number of other CMS priority comorbidities was calculated as the sum of previous a history of acquired hypothyroidism, Alzheimer's disease, related disorders or senile dementia, anemia, asthma, benign prostatic hyperplasia, cataract, chronic obstructive pulmonary disease, ischemic heart disease, hip or pelvic fracture, glaucoma, hyperlipidemia, osteoporosis, rheumatoid arthritis or osteoarthritis, breast cancer, colorectal cancer, prostate cancer, lung cancer and endometrial cancer.

We categorized the anatomical location of the index major hemorrhage into four groups: intracranial bleeding, gastrointestinal hemorrhage, genitourinary hemorrhage, and other bleeding events, which included hemoperitoneum, epistaxis, hemoptysis, hemarthrosis, conjunctival and vaginal hemorrhage and not-otherwise specified hemorrhage. Measures of the severity of the index major hemorrhage included length of inpatient stay, intensive care unit admission, blood transfusion therapy, and whether the patients underwent corrective procedures in the same anatomical area of the bleeding. Length of inpatient stay and indicator variable for use of intensive care unit are variables contained in the Medicare Provider Analysis and Review (MedPAR) data set.[154] Blood transfusion therapy was defined as having at least one procedure with ICD-9 procedure code 990.xx during the inpatient stay for the index major hemorrhage. To identify which patients underwent a corrective surgical procedure, we extracted all ICD-9 procedure codes recorded during the inpatient stay for the index major hemorrhage, and selected the procedures whose objective was to correct the anatomical area where the bleeding event had

happened (the list of qualifying ICD-9 procedure codes for corrective surgical procedures in each anatomical area can be found in Table 3-1).

3.3.4 Statistical Analysis

We compared patient characteristics of three post-hemorrhage treatment groups in each cohort at the time of index major hemorrhage using chi-square tests, Fisher's exact tests and ANOVA, as appropriate. To predict the probability of restarting the same anticoagulation agent used before the index bleeding event or switching to another agent as opposed to discontinuing oral anticoagulation, we constructed a multinomial logistic regression model with generalized logit link function, where the outcome variable was the post-hemorrhage treatment group, and covariates included all variables listed in the Covariates Section.

Kaplan-Meier time-to-event curves were constructed to compare the cumulative incidence rates of effectiveness and safety outcomes at 3 months, 6 months and 1 year post-hemorrhage follow-up among the post-hemorrhage treatment groups. To further control for potential confounders in comparing effectiveness and safety outcomes, we constructed Cox Proportional Hazard models. Cox models built to compare effectiveness outcomes controlled for age, CHA2DS2-Vasc score, HAS-BLED score and an indicator variable for the location of the index major hemorrhage (1 if intracranial, 0 otherwise). Although one of the risk factors included in the calculation of CHA2DS2-Vasc score is age of 75 years or more, Cox models built to compare effectiveness outcomes controlled for continuous age for two reasons: First, age was unbalanced between post-hemorrhage treatment groups (Table 3-3); second; the mortality risk after age 75 changes markedly by every year increase in age.[155] For instance, the mortality risk of a 85 year old patient is almost 3 times that of a 75 year old.[155] Cox models built to compare

safety outcomes controlled for CHA2DS2-Vasc, HAS-BLED score, an indicator variable for the location of the index major hemorrhage (1 if intracranial, 0 otherwise), and the measures of the severity of the index bleeding event, as detailed above. For all time-to-event analyses, time 0 was the post-hemorrhage follow-up start date (defined in the Data Source and Study Population Section). The time at risk was censored at the end of the study period (December 31, 2012) or at the time of death, except for the Kaplan-Meier and Cox models whose outcome included mortality. In those analyses, the time at risk was only censored at the end of the study period. All of these analyses were performed separately for the dabigatran and the warfarin cohorts. In a secondary analysis, we grouped patients from the warfarin and dabigatran cohorts according to the treatment used after the index major hemorrhage, and compared effectiveness and safety outcomes using Cox models in a similar manner, as described above. All analyses were conducted with statistical software SAS 9.4 (Cary, NC).

3.3.4.1 Sensitivity Analysis

Post-hemorrhage clinical outcomes of patients who experienced an intracranial bleeding are likely to differ from those who bled on other anatomical locations. To examine how this may have affected our results for the comparative risk of post-hemorrhage clinical outcomes, we re-run our analysis after excluding patients who experienced an intracranial bleeding. Cox models built to compare effectiveness outcomes controlled for age, CHA2DS2-Vasc score and HAS-BLED score; Cox models built to compare safety outcomes controlled for CHA2DS2-Vasc score and HAS-BLED score.

3.4 RESULTS

3.4.1 Patient Characteristics by Post-Hemorrhage Anticoagulation Use

The proportion of patients who reinitiated anticoagulation after the index major hemorrhage was similar between the warfarin and dabigatran cohorts (49% for dabigatran and 47% for warfarin, p-value=0.497). However, dabigatran users were more likely to switch to warfarin after the bleeding event than warfarin users were to switch to dabigatran (17% versus 2%, p -value<0.001). In addition, resumption of the same oral anticoagulation agent used before the index major hemorrhage was more common in the warfarin cohort than in the dabigatran cohort (41% vs. 28%, with p-value <0.001). The mortality rate during inpatient admission for the index major hemorrhage did not differ between the two cohorts (4% for warfarin and 2% for dabigatran, p-value=0.257). Details on the follow-up of each treatment group can be found in Table 3-2.

Table 3-2. Time to Post-Hemorrhage Anticoagulation Resumption, Follow-up Period, and Patterns of Post-Hemorrhage Anticoagulation Use, by Treatment Group and Study Cohort.

	Treatment Used After First Major Hemorrhage			
Dabigatran Cohort- Mean (SD)	Resumed Dabigatran (n=117)	No Oral Anticoagulation (n=217)	Switched to Warfarin (n=70)	P-Value
Time from first major bleeding to anticoagulation re-start	45 (49)	--	73 (84)	0.005
Follow-up period after first major bleeding	396 (167)	335 (201)	432 (166)	<0.001
Patterns of post-hemorrhage anticoagulation use (%)				
Switched anticoagulation treatment	18.0	--	1.4	<0.001
Discontinued anticoagulation therapy	3.4	--	47.1	<0.001
Warfarin Cohort- Mean (SD)	Resumed Warfarin (n=484)	No Oral Anticoagulation Use (n=626)	Switched to Dabigatran (n=25)	P-Value
Time from first major bleeding to anticoagulation re-start	60 (72)	--	70 (60)	0.501
Follow-up period after first major bleeding	371 (205)	333 (205)	457 (211)	<0.001
Patterns of post-hemorrhage anticoagulation use (%)				
Switched anticoagulation treatment	3.1	--	8.0	0.184
Discontinued anticoagulation therapy	6.4	--	28.0	<0.001

Table 3-3 shows patient characteristics, anatomical location and measures of the severity of the index bleeding for each post-hemorrhage treatment group, by study cohort. Patients who experienced an intracranial bleeding, received a blood transfusion or were admitted to the intensive care unit were less likely to resume the anticoagulation agent used before the index hemorrhage. In both the warfarin and the dabigatran cohorts, older patients had a lower likelihood of resuming oral anticoagulation after the bleeding event. In the dabigatran cohort, there was no difference in CHA2DS2-Vasc and HAS-BLED scores among post-hemorrhage treatment groups. In the warfarin cohort, the CHA2DS2-Vasc score but not the HAS-BLED score was higher in patients who discontinued anticoagulation than those who reinitiated anticoagulation after the index bleeding event.

Table 3-3: Baseline Characteristics of the Cohorts, by Use of Anticoagulation after Index Major Hemorrhage

	Dabigatran Cohort (N=404)				Warfarin Cohort (N=1135)			
Variable - %	Resumed Dabigatran (n=117)	No Oral Anticoagulation (n=217)	Switched to Warfarin (n=70)	P-Value	Resumed Warfarin (n=484)	No Oral Anticoagulation (n=626)	Switched to Dabigatran (n=25)	P-Value
Age, mean (SD)	79.64 (8.67)	81.9 (7.63)	78.73 (8.34)	0.005	77.95 (9.40)	80.20 (8.96)	76.15 (6.79)	<0.001
Male sex	35.0	31.3	32.9	0.788	45.3	39.5	52.0	0.0926
Race				0.745				0.6568
White	90.6	86.6	85.7		82.6	83.2	80.0	
Black	6.8	6.9	7.1		11.2	11.5	8.0	
Hispanic	1.7	2.8	4.3		4.8	4.2	12.0	
Other	0.9	3.7	2.9		1.5	1.1	0.0	
Medicaid eligibility	36.8	27.7	35.7	0.170	34.3	29.4	24.0	0.158
CHA2DS2-Vasc score, mean (SD)	5.96 (1.77)	5.89 (1.58)	5.77 (1.99)	0.773	4.92 (1.57)	5.08 (1.60)	4.28 (1.56)	0.018
HAS-BLED score, mean (SD)	4.16 (0.96)	4.12 (0.95)	3.94 (1.08)	0.306	4.06 (0.90)	4.12 (0.95)	4.00 (0.76)	0.478
No. of other CMS priority comorbidities, mean (SD)	7.21 (2.53)	7.06 (2.32)	6.53 (2.80)	0.178	6.79 (2.48)	7.00 (2.40)	5.92 (2.60)	0.051
Type of bleeding				<0.001				<0.001
IC	0.0	10.6	7.1		4.1	18.5	12.0	
GI Hemorrhage	78.6	84.8	74.7		69.6	68.1	76.0	
Genitourinary hemorrhage	4.3	2.3	2.9		8.7	2.9	4.0	
Other	17.1	2.3	14.3		17.6	10.5	8.0	
Length of stay, median (SD)	4.0 (10.8)	4.0 (19.8)	4.0 (11.5)	0.768	4.0 (7.4)	5.0 (18.5)	4.0 (6.0)	0.253
Use of intensive care unit	33.3	40.6	50.0	0.078	30.6	42.8	56.0	<0.001
Transfusion	33.3	48.4	50.0	0.018	43.4	52.6	52.0	0.010
Surgical procedures in area affected	15.4	17.5	22.9	0.427	20.5	18.4	24.0	0.575

3.4.2 Adjusted Odds Ratio of Post-Hemorrhage Anticoagulation Use

Figure 3-2 shows the odds ratio of restarting dabigatran or switching to warfarin as opposed to discontinuing anticoagulation for patients who experienced a major bleeding event in the dabigatran cohort. Older patients were more likely to discontinue anticoagulation after the index hemorrhage. Specifically, the odds of resuming dabigatran or switching to warfarin compared to discontinuing anticoagulation decreased by 24% (95% CI, 9%-37%) and 28% (95% CI, 10%-42%) for every 5 years increase in age, respectively.

Figure 3-3 shows the odds ratio of resuming warfarin or switching to dabigatran as opposed to discontinuing anticoagulation after a major bleeding event in the warfarin cohort. Older patients, those who experienced an intracranial bleeding, were admitted to the intensive care unit, or received a blood transfusion were more likely to cease anticoagulation. For every 5 years increase in age, the odds of reinitiating warfarin compared to discontinuing anticoagulation decreased by 21% (95% CI, 4%-18%). The odds of resuming warfarin were 79% (95% CI, 66%-88%) lower for patients who experienced an intracranial hemorrhage compared to those who experienced a gastrointestinal bleeding, and 31% (95% CI, 11%-47%) lower for patients receiving a blood transfusion than for those who did not.

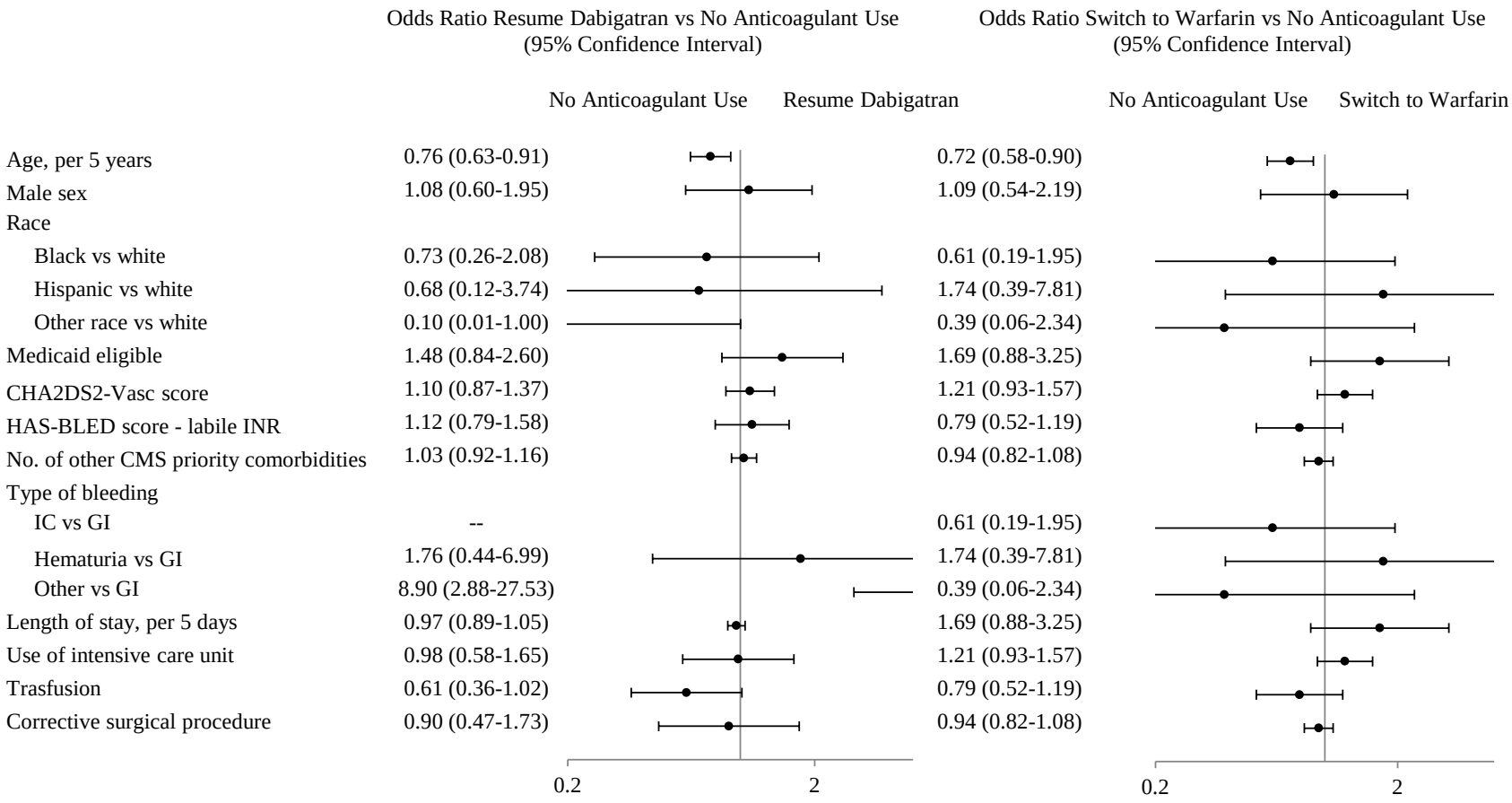

Figure 3-2: Odds Ratio of Post-Hemorrhage Anticoagulation Use for the Dabigatran Cohort

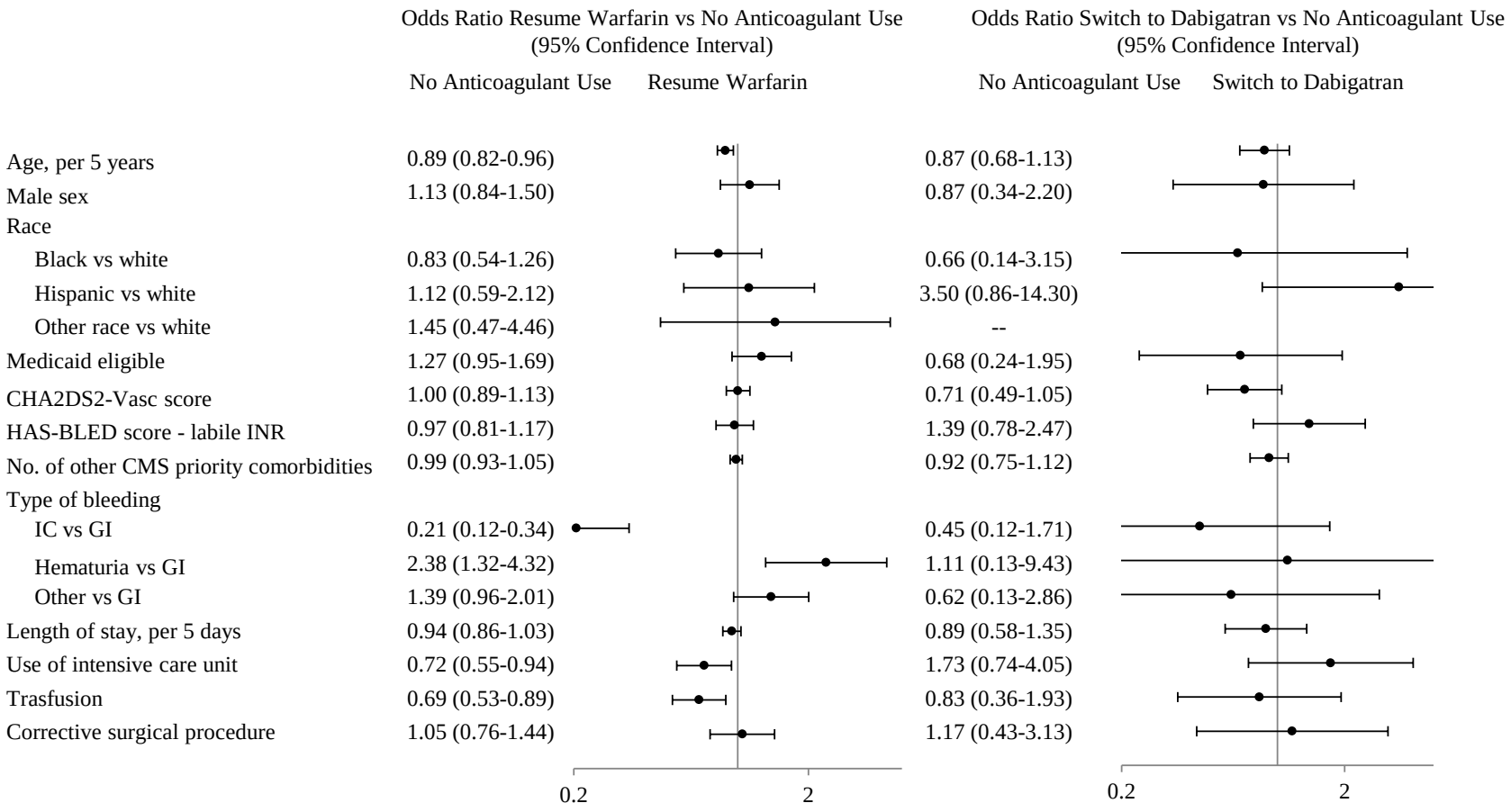

Figure 3-3: Odds Ratio of Post-Hemorrhage Anticoagulation Use for the Warfarin Cohort.

3.4.3 Stroke and All-Cause Mortality

Table 3-4 shows the number of events and the unadjusted cumulative incidence rates of clinical outcomes by post-hemorrhage treatment group. Before adjustment, there was no difference in the composite risk of stroke and all-cause mortality among treatment groups in the dabigatran cohort. However, dabigatran users who resumed dabigatran after the index bleeding had lower mortality risk (cumulative incidence of death at 3 months 0.01; 95% CI, 0.00-0.03) than those who ceased anticoagulation therapy (0.12; 95% CI, 0.07-0.16). In the warfarin cohort, the risk of mortality and the composite risk of stroke and all-cause mortality were lower among patients who restarted warfarin compared to those who did not reinitiate anticoagulation.

Table 3-4: Number of Events and Unadjusted Cumulative Incidence Rates of Post-Hemorrhage Clinical Outcomes, by Cohort and Post-Hemorrhage Treatment Group

Dabigatran Cohort	Resumed Dabigatran (n=117)	No Oral Anticoagulation (n=217)	Switched to Warfarin (n=70)
Effectiveness Outcomes			
Ischemic Stroke and All-Cause Mortality			
Number of events (%)	21 (18.0)	48 (22.1)	13 (18.6)
Cumulative incidence (95% CI)			
At 3 months	0.07 (0.02 , 0.12)	0.18 (0.13 , 0.24)	0.13 (0.05 , 0.21)
At 6 months	0.13 (0.07 , 0.19)	0.21 (0.15 , 0.27)	0.15 (0.06 , 0.23)
At 1 yr	0.21 (0.13 , 0.29)	0.26 (0.19 , 0.33)	0.22 (0.11 , 0.33)
Ischemic Stroke			
Number of events (%)	20 (17.1)	23 (10.6)	12 (17.1)
Cumulative incidence (95% CI)			
At 3 months	0.06 (0.02 , 0.11)	0.07 (0.03 , 0.11)	0.12 (0.04 , 0.20)
At 6 months	0.12 (0.06 , 0.18)	0.08 (0.04 , 0.13)	0.13 (0.05 , 0.22)
At 1 yr	0.20 (0.12 , 0.29)	0.15 (0.08 , 0.21)	0.21 (0.10 , 0.32)
All-Cause Mortality			
Number of events (%)	2 (1.7)	25 (11.5)	2 (2.9)
Cumulative incidence (95% CI)			
At 3 months	0.01 (0.00 , 0.03)	0.12 (0.07 , 0.16)	0.03 (0.00 , 0.07)
At 6 months	0.02 (0.00 , 0.04)	0.13 (0.08 , 0.18)	0.03 (0.00 , 0.07)
At 1 yr	0.02 (0.00 , 0.04)	0.13 (0.08 , 0.18)	0.03 (0.00 , 0.07)
Safety Outcomes			
Major Recurrent Hemorrhage			
Number of events (%)	8 (6.8)	13 (6.0)	6 (8.6)
Cumulative incidence (95% CI)			
At 3 months	0.04 (0.00 , 0.07)	0.05 (0.02 , 0.08)	0.06 (0.00 , 0.11)
At 6 months	0.06 (0.01 , 0.10)	0.05 (0.02 , 0.09)	0.06 (0.00 , 0.11)
At 1 yr	0.07 (0.02 , 0.11)	0.09 (0.04 , 0.14)	0.09 (0.01 , 0.17)
Any Recurrent Hemorrhage			
Number of events (%)	40 (34.2)	60 (27.7)	26 (37.1)
Cumulative incidence (95% CI)			
At 3 months	0.24 (0.16 , 0.32)	0.24 (0.18 , 0.30)	0.26 (0.16 , 0.36)
At 6 months	0.29 (0.21 , 0.37)	0.31 (0.24 , 0.38)	0.29 (0.18 , 0.40)
At 1 yr	0.34 (0.25 , 0.44)	0.40 (0.31 , 0.49)	0.38 (0.25 , 0.51)

Table 3-4 continued

Warfarin Cohort	Resumed Warfarin (n=484)	No Oral Anticoagulation (n=626)	Switched to Dabigatran (n=25)
Effectiveness Outcomes			
Ischemic Stroke and All-Cause Mortality			
Number of events (%)	92 (19.0)	144 (23.0)	6 (24.0)
Cumulative incidence (95% CI)			
At 3 months	0.10 (0.07 , 0.13)	0.20 (0.17 , 0.23)	0.18 (0.02 , 0.33)
At 6 months	0.16 (0.12 , 0.19)	0.23 (0.20 , 0.27)	0.23 (0.05 , 0.40)
At 1 yr	0.23 (0.18 , 0.27)	0.26 (0.23 , 0.30)	0.28 (0.09 , 0.48)
Ischemic Stroke			
Number of events (%)	66 (13.6)	67 (10.7)	5 (20.0)
Cumulative incidence (95% CI)			
At 3 months	0.06 (0.04 , 0.09)	0.09 (0.06 , 0.11)	0.14 (0.00 , 0.28)
At 6 months	0.11 (0.07 , 0.14)	0.11 (0.08 , 0.14)	0.19 (0.02 , 0.36)
At 1 yr	0.17 (0.13 , 0.21)	0.14 (0.11 , 0.18)	0.25 (0.06 , 0.44)
All-Cause Mortality			
Number of events (%)	27 (5.6)	86 (13.7)	1 (4.0)
Cumulative incidence (95% CI)			
At 3 months	0.03 (0.02 , 0.05)	0.14 (0.11 , 0.17)	0.04 (0.00 , 0.13)
At 6 months	0.06 (0.03 , 0.08)	0.15 (0.12 , 0.18)	0.04 (0.00 , 0.13)
At 1 yr	0.07 (0.04 , 0.09)	0.15 (0.12 , 0.18)	0.04 (0.00 , 0.13)
Safety Outcomes			
Major Recurrent Hemorrhage			
Number of events (%)	68 (14.1)	44 (7.0)	1 (4.0)
Cumulative incidence (95% CI)			
At 3 months	0.08 (0.06 , 0.11)	0.06 (0.04 , 0.08)	0.00 (0.00 , 0.00)
At 6 months	0.11 (0.08 , 0.14)	0.08 (0.06 , 0.11)	0.00 (0.00 , 0.00)
At 1 yr	0.17 (0.13 , 0.21)	0.10 (0.07 , 0.13)	0.00 (0.00 , 0.00)
Any Recurrent Hemorrhage			
Number of events (%)	170 (35.1)	188 (30.0)	5 (20.0)
Cumulative incidence (95% CI)			
At 3 months	0.26 (0.22 , 0.30)	0.29 (0.25 , 0.33)	0.17 (0.02 , 0.33)
At 6 months	0.33 (0.29 , 0.38)	0.35 (0.30 , 0.39)	0.17 (0.02 , 0.33)
At 1 yr	0.42 (0.37 , 0.47)	0.39 (0.34 , 0.43)	0.17 (0.02 , 0.33)

Figure 3-4 shows the hazard ratios of effectiveness outcomes after adjustment for potential confounders. Here again, in the dabigatran cohort, the risk of all-cause mortality was lower for patients who resumed dabigatran (HR 0.13; 95% CI, 0.03-0.58) or switched to warfarin (HR 0.21; 95% CI, 0.05-0.91) than for those who did not reinitiate anticoagulation. The composite risk of ischemic stroke and all-cause mortality was however similar among post-hemorrhage treatment groups in the dabigatran cohort. In the warfarin cohort, resumption of warfarin was associated with lower composite risk of ischemic stroke and all-cause mortality (HR 0.75; 95% CI, 0.57-0.98) and lower risk of all-cause mortality (HR 0.37; 95% CI, 0.23-0.58) than discontinuation of anticoagulation. In both the warfarin and the dabigatran cohorts, the risk of ischemic stroke did not significantly differ among post-hemorrhage treatment groups.

When the two cohorts were analyzed simultaneously based on the treatment received after the index hemorrhage, we found that the composite risk of ischemic stroke and all-cause mortality was lower for patients who were prescribed warfarin (HR 0.76; 95% CI, 0.59-0.97) or dabigatran (HR 0.66; 95% CI, 0.44-0.99) than for those whose anticoagulation was discontinued after the major bleeding event. Furthermore, resumption of anticoagulation with warfarin (HR 0.35; 95% CI, 0.23-0.53) or with dabigatran (HR 0.13; 95% CI, 0.04-0.41) was associated with decreased mortality, compared to discontinuation of anticoagulation. Once again, there was no difference in the risk of ischemic stroke among post-hemorrhage treatment groups.

Dabigatran cohort	Adjusted Hazard Ratio (% CI)		
	Resumed Dabigatran vs No Oral Anticoagulant Use	Switched to Warfarin vs No Oral Anticoagulant Use	Switched to Warfarin vs Resumed Dabigatran
Effectiveness Outcomes			
Ischemic Stroke/All-Cause Mortality	0.67 (0.40-1.15)	0.70 (0.38-1.31)	1.04 (0.52-2.09)
All-Cause Mortality	**0.13 (0.03-0.58)**	**0.21 (0.05-0.91)**	1.57 (0.22-11.18)
Ischemic Stroke	1.29 (0.69-2.43)	1.29 (0.63-2.65)	1.00 (0.48-2.09)
Safety Outcomes			
Major Recurrent Hemorrhage	0.68 (0.27-1.72)	1.08 (0.41-2.88)	1.47 (0.58-3.72)
Any Recurrent Hemorrhage	0.87 (0.58-1.32)	1.04 (0.65-1.66)	1.20 (0.70-2.00)

Warfarin cohort	Resumed Warfarin vs No Oral Anticoagulant Use	Swtiched to Dabigatran vs No Oral Anticoagulant Use	Switched to Dabigatran vs Resumed Warfarin
Effectiveness Outcomes			
Ischemic Stroke/All-Cause Mortality	**0.75 (0.57-0.98)**	0.96 (0.42-2.19)	1.28 (0.56-2.94)
All-Cause Mortality	**0.35 (0.23-0.55)**	0.27 (0.04-1.95)	0.77 (0.11-5.69)
Ischemic Stroke	1.26 (0.88-1.80)	1.81 (0.72-4.53)	1.43 (0.57-3.58)
Safety Outcomes			
Major Recurrent Hemorrhage	**1.60 (1.09-2.36)**	0.38 (0.05-2.79)	0.24 (0.03-1.73)
Any Recurrent Hemorrhage	0.95 (0.77-1.18)	0.42 (0.17-1.02)	0.44 (0.18-1.08)

Two cohorts combined	Warfarin vs No Oral Anticoagulant Use	Dabigatran vs No Oral Anticoagulant Use	Dabigatran vs Warfarin
Effectiveness Outcomes			
Ischemic Stroke/All-Cause Mortality	**0.76 (0.59-0.97)**	**0.66 (0.44-0.99)**	0.87 (0.57-1.33)
All-Cause Mortality	**0.35 (0.23-0.53)**	**0.13 (0.04-0.41)**	0.37 (0.11-1.22)
Ischemic Stroke	1.27 (0.93-1.75)	1.37 (0.86-2.17)	1.07 (0.68-1.69)
Safety Outcomes			
Major Recurrent Hemorrhage	**1.56 (1.10-2.22)**	0.65 (0.32-1.33)	**0.42 (0.21-0.84)**
Any Recurrent Hemorrhage	0.97 (0.80-1.17)	0.77 (0.56-1.07)	0.80 (0.58-1.10)

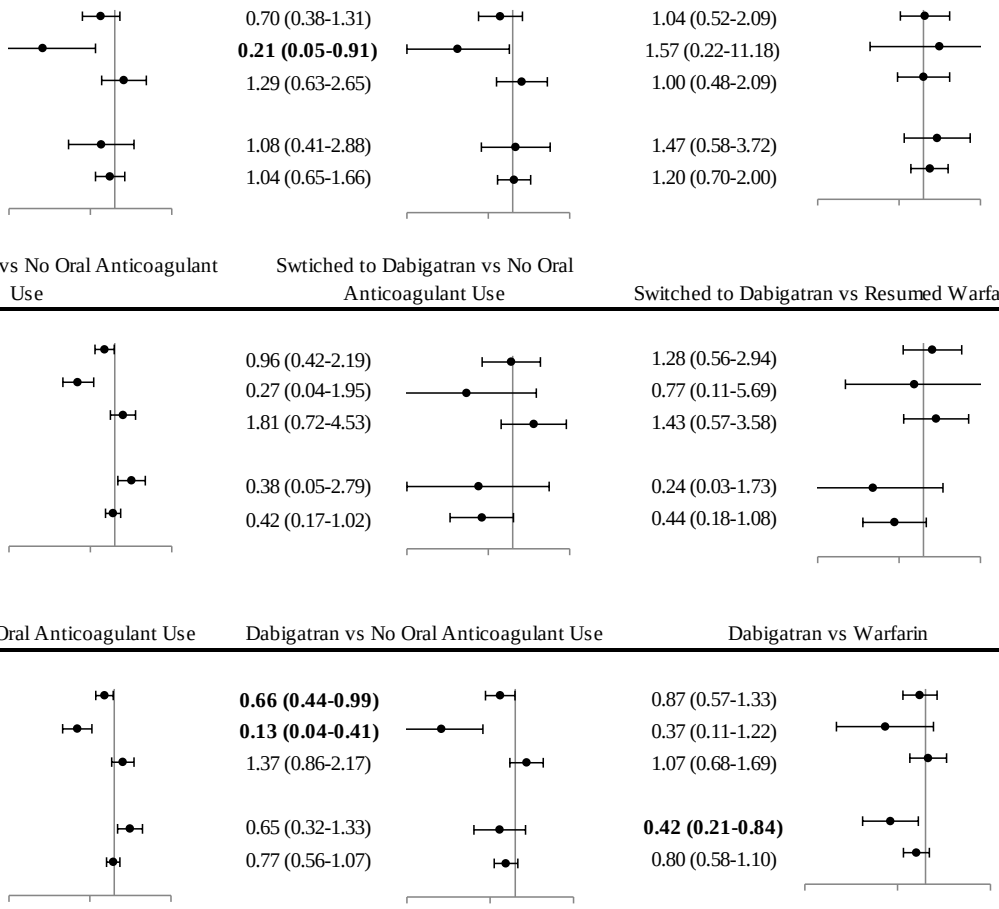

Figure 3-4: Adjusted Hazard Ratios of Post-Hemorrhage Clinical Outcomes

3.4.4 Recurrent Bleeding

There were no differences in the unadjusted risk of bleeding events among post-hemorrhage treatment groups in the dabigatran cohort (Table 3-4). However, in the warfarin cohort, the unadjusted risk of recurrent major bleeding was lower for patients who discontinued anticoagulation (cumulative incidence at 1 year 0.10; 95% CI, 0.07-0.13) than for those who restarted warfarin after the index hemorrhage (0.17; 95% CI, 0.13-0.21).

These unadjusted results were consistent with the findings of the adjusted analysis. The risks of major and any bleeding events were similar for 3 treatment groups in the dabigatran cohort (Figure 3-4). In the warfarin cohort, however, the risk of major bleeding was higher for patients resuming warfarin compared to those discontinuing all anticoagulation (HR 1.60; 95% CI, 1.09-2.36).

When the two cohorts were combined based on the treatment received after the index hemorrhage, we found that the risk of major hemorrhage was higher for patients who were prescribed warfarin than for those who were prescribed dabigatran or who discontinued anticoagulation therapy. Specifically, the hazard ratio of recurrent major bleeding was 0.42 (95% CI, 0.21-0.84) for dabigatran compared to warfarin, and 1.59 (95% CI, 1.10-2.22) for warfarin compared to anticoagulation discontinuation. The risk of bleeding did not differ between patients who were prescribed dabigatran after the index hemorrhage and those whose anticoagulation was discontinued (HR 0.66; 95% CI, 0.32-1.33).

3.4.5 Sensitivity Analyses

Our results for the hazard ratios of post-hemorrhage clinical outcomes were robust to the exclusion of patients who experienced an intracranial bleeding event (Table 3-5).

Table 3-5. Results of Sensitivity Analyses.

Dabigatran cohort	Adjusted Hazard Ratio (% CI)					
	Resumed Dabigatran vs No Oral Anticoagulant Use		Switched to Warfarin vs No Oral Anticoagulant Use		Switched to Warfarin vs Resumed Dabigatran	
Effectiveness Outcomes	Sensitivity Analysis	Base Case	Sensitivity Analysis	Base Case	Sensitivity Analysis	Base Case
Ischemic Stroke/All-Cause Mortality	0.64 (0.38-1.10)	0.67 (0.40-1.15)	0.57 (0.28-1.14)	0.70 (0.38-1.31)	0.88 (0.42-1.88)	1.04 (0.52-2.09)
All-Cause Mortality	**0.13 (0.03-0.56)**	**0.13 (0.03-0.58)**	**0.11 (0.01-0.82)**	**0.21 (0.05-0.91)**	0.83 (0.08-9.20)	1.57 (0.22-11.18)
Ischemic Stroke	1.24 (0.65-2.34)	1.29 (0.69-2.43)	1.17 (0.54-2.54)	1.29 (0.63-2.65)	0.95 (0.44-2.03)	1.00 (0.48-2.09)
Safety Outcomes						
Major Recurrent Hemorrhage	0.71 (0.28-1.83)	0.68 (0.27-1.72)	1.20 (0.44-3.30)	1.08 (0.41-2.88)	1.69 (0.57-5.00)	1.47 (0.58-3.72)
Any Recurrent Hemorrhage	0.91 (0.60-1.39)	0.87 (0.58-1.32)	1.23 (0.76-1.98)	1.04 (0.65-1.66)	1.34 (0.81-2.24)	1.20 (0.70-2.00)

Warfarin cohort	Resumed Warfarin vs No Oral Anticoagulant Use		Swtiched to Dabigatran vs No Oral Anticoagulant Use		Switched to Dabigatran vs Resumed Warfarin	
Effectiveness Outcomes	Sensitivity Analysis	Base Case	Sensitivity Analysis	Base Case	Sensitivity Analysis	Base Case
Ischemic Stroke/All-Cause Mortality	**0.71 (0.54-0.95)**	**0.75 (0.57-0.98)**	0.72 (0.26-1.95)	0.96 (0.42-2.19)	1.00 (0.37-2.74)	1.28 (0.56-2.94)
All-Cause Mortality	**0.35 (0.22-0.55)**	**0.35 (0.23-0.55)**	0.29 (0.04-2.12)	0.27 (0.04-1.95)	0.84 (0.11-6.23)	0.77 (0.11-5.69)
Ischemic Stroke	1.25 (0.84-1.86)	1.26 (0.88-1.80)	1.31 (0.41-4.26)	1.81 (0.72-4.53)	1.05 (0.33-3.37)	1.43 (0.57-3.58)
Safety Outcomes						
Major Recurrent Hemorrhage	**1.63 (1.09-2.44)**	**1.60 (1.09-2.36)**	0.42 (0.06-3.06)	0.38 (0.05-2.79)	0.26 (0.04-1.85)	0.24 (0.03-1.73)
Any Recurrent Hemorrhage	0.94 (0.75-1.18)	0.95 (0.77-1.18)	0.50 (0.20-1.21)	0.42 (0.17-1.02)	0.53 (0.22-1.28)	0.44 (0.18-1.08)

Two cohorts combined	Warfarin vs No Oral Anticoagulant Use		Dabigatran vs No Oral Anticoagulant Use		Dabigatran vs Warfarin	
Effectiveness Outcomes	Sensitivity Analysis	Base Case	Sensitivity Analysis	Base Case	Sensitivity Analysis	Base Case
Ischemic Stroke/All-Cause Mortality	**0.71 (0.55-0.92)**	**0.76 (0.59-0.97)**	**0.60 (0.39-0.93)**	**0.66 (0.44-0.99)**	0.85 (0.55-1.33)	0.87 (0.57-1.33)
All-Cause Mortality	**0.33 (0.22-0.51)**	**0.35 (0.23-0.53)**	**0.13 (0.04-0.41)**	**0.13 (0.04-0.41)**	0.39 (0.12-1.29)	0.37 (0.11-1.22)
Ischemic Stroke	1.24 (0.76-2.02)	1.27 (0.93-1.75)	1.24 (0.88-1.76)	1.37 (0.86-2.17)	1.00 (0.62-1.61)	1.07 (0.68-1.69)
Safety Outcomes						
Major Recurrent Hemorrhage	**1.61 (1.12-2.32)**	**1.56 (1.10-2.22)**	0.68 (0.33-1.39)	0.65 (0.32-1.33)	**0.42 (0.21-0.85)**	**0.42 (0.21-0.84)**
Any Recurrent Hemorrhage	0.99 (0.81-1.21)	0.97 (0.80-1.17)	0.80 (0.58-1.11)	0.77 (0.56-1.07)	0.80 (0.58-1.12)	0.80 (0.58-1.10)

3.5 DISCUSSION

To the best of our knowledge, our study is the first real-world analysis comparing clinical outcomes after a major hemorrhage among patients who reinitiated anticoagulation therapy with dabigatran or warfarin, and those who never resumed anticoagulation. Our study has four main findings: First, we found that post-hemorrhage use of warfarin was more common than that of dabigatran. Second, we observed that the CHA2DS2-Vasc and HAS-BLED scores did not impact the likelihood of reinitiating anticoagulation after a major bleeding event. In contrast, age, anatomical location and severity of the index bleeding event were the most important determinants of resuming anticoagulation. Third, compared to discontinuation of all anticoagulation, resumption of anticoagulation therapy with either dabigatran or warfarin was associated with higher rates of survival and stroke-free survival. Fourth, the risk of recurrent major hemorrhage was higher for patients who were prescribed warfarin after a first major bleeding compared to those who were prescribed dabigatran or those whose anticoagulation was never reinitiated.

Using a US nationally representative sample, we found that 51% of warfarin users and 53% of dabigatran users did not reinitiate anticoagulation after a first major bleeding event. This finding replicates the result from Qureshi et al., who analyzed data from a health system in Michigan and found that 51% of AF patients who experienced a major gastrointestinal bleeding while using warfarin interrupted warfarin therapy after the bleeding event.[114] When assessing the determinants of post-hemorrhage anticoagulation resumption, we observed that CHA2DS2-Vasc and HAS-BLED scores did not impact the likelihood of anticoagulation resumption. This surprising finding is in agreement with a recent study by Staerk and colleagues, who used data from a cohort of Danish patients with AF, finding that CHA2DS2-Vasc and HAS-BLED scores

did not differ between patients who resumed and those who never reinitiated anticoagulation after a major gastrointestinal hemorrhage.[115] In such study, Staerk et al. found that the resumption of anticoagulation was associated with increased risk of recurrent gastrointestinal hemorrhage, which conflicts with the results from Qureshi and colleagues, who found no differences in the risk of recurrent bleeding between those who reinitiated and those who never resumed anticoagulation.[114,115] Our analysis, which included patients experiencing major bleeding events in different anatomical locations, demonstrated that the resumption of warfarin therapy but not of dabigatran was associated with higher risk of major bleeding than the discontinuation of anticoagulation.

When comparing effectiveness outcomes among post-hemorrhage treatment groups, we found that the resumption of anticoagulation after a major hemorrhage was associated with increased survival, as compared to discontinuation of anticoagulation, which is consistent with previous studies.[114,115,117] Our estimate for the hazard ratio of all-cause mortality for patients who reinitiated warfarin compared to those who discontinued anticoagulation (HR 0.35; 95% CI,0.23-0.54) is particularly similar to the one reported by Staerk and collaborators (HR 0.39; 95% CI, 0.34-0.46).[115] Regardless of the consistency of these findings, the association of anticoagulation resumption with increased survival may be subject to residual confounding, because patients who discontinued anticoagulation had higher burden of disease than those who resumed anticoagulation. Our Cox Proportional Hazard models built to compare the risk of all-cause mortality between post-hemorrhage treatment groups controlled for CHA2DS2-vasc and HAS-BLED scores; however, these prediction tools do not distinguish the severity of the risk factors included in their calculation. For instance, the creatinine clearance of patients with chronic kidney disease or the ejection fraction of patients with heart failure may have been lower among

subjects whose anticoagulation was discontinued than those who were prescribed warfarin or dabigatran after the bleeding event. Furthermore, conditions other than the ones included in the calculation of CHA2DS2-Vasc and HAS-BLED scores may have been unbalanced between patients who restarted anticoagulation and those who did not. Consequently, our results for the comparative risk of all-cause mortality between patients who reinitiated and those who discontinued anticoagulation should be interpreted with caution.

Our study contributes significantly to the existing literature because, as opposed to previous work, it stratifies treatment groups into two cohorts according to the type of anticoagulation agent used after the index bleeding event. In doing so, we demonstrate the benefit of the use of anticoagulation therapy after a major bleeding event. More specifically, we show that patients who use dabigatran after a bleeding event have a lower incidence of stroke and all-cause mortality but similar risk of bleeding than those who discontinue anticoagulation. Furthermore, we find that the benefit/risk ratio of post-hemorrhage dabigatran use is superior to that of warfarin because, with comparable effectiveness, dabigatran is associated with lower rates of recurrent bleeding. In contrast, we observe that only half of the patients who experience a major bleeding event restart anticoagulation therapy and that among those who do, the use of dabigatran is substantially less common than the use of warfarin. The lower tendency to prescribe dabigatran as compared to warfarin after a major hemorrhage may be explained by two reasons. First, whereas warfarin therapy requires routine INR monitoring, laboratory coagulation markers are not routinely monitored for patients on dabigatran. In this context, clinicians may be under the impression that they have more control over the coagulation status of patients on warfarin than those on dabigatran, particularly in the early aftermath of a major bleeding event. Second, clinicians may have been especially risk-averse to prescribe dabigatran because of the

warnings on the risk of severe bleeding with dabigatran released by the main international regulatory agencies throughout 2011,[156,157] as well as the lack of antidote to reverse the anticoagulation effects of dabigatran in the time period that this study captures. In this scenario, patients who were prescribed dabigatran after the index hemorrhage were likely to be those at lowest risk of recurrent bleeding. These risk-averse prescription patterns of dabigatran may have introduced residual confounding in our results for the comparative risk of bleeding events with warfarin and dabigatran. With the approval in October 2015 of idarucizumab, a dabigatran-binding monoclonal antibody fragment, prescribers may become more comfortable using dabigatran in patients who have already suffered a major bleeding event on anticoagulation.[77] Therefore, it will be important to repeat analyses similar to ours as newer Medicare Part D data that represents the period after the approval of idarucizumab become available.

In addition to the fact that our results reflect the early experience with dabigatran, our study is subject to three main limitations. First, claims data do not contain laboratory results and therefore, we did not have information about the INR levels of our study subjects, which may have affected the decision to restart anticoagulation therapy in patients who bled on warfarin. Second, we did not stratify our analyses by the anatomical location of the index bleeding event. The post-hemorrhage clinical outcomes of patients experiencing an intracranial bleeding, for example, are likely to be different from those who presented with a gastrointestinal bleeding. We did however control for the anatomical location of the index major hemorrhage when comparing effectiveness and safety outcomes among treatment groups, which should mitigate this problem. Third, in our comparison of clinical outcomes between treatment groups, we did not stratify by the dose of dabigatran used. Nevertheless, the use of dabigatran 75mg was relatively uncommon in the period that our study represents—less than 10% of Medicare beneficiaries with AF on

dabigatran were prescribed dabigatran 75 mg in the first two years after dabigatran approval,[105] and previous cohort studies comparing the risk of bleeding with dabigatran and warfarin have shown that grouping of two doses of dabigatran did not alter the findings.[104-106] With dabigatran 110mg gaining FDA approval in November 2015,[96] it will be informative to reanalyze 2016-2017 Medicare claims data and compare the effectiveness and safety outcomes of patients who discontinue oral anticoagulation, as opposed to those who are started on dabigatran 150mg, dabigatran 110mg, dabigatran 75mg, or warfarin.

In conclusion, we demonstrate that the resumption of anticoagulation with either dabigatran or warfarin after a major bleeding event is associated with increased survival and stroke-free survival, compared to discontinuing anticoagulation. In addition, we show that the risk of recurrent hemorrhage is higher with warfarin than dabigatran. Our findings suggest that the benefit/risk ratio of dabigatran in the prevention of stroke among AF patients who have survived a major hemorrhage is superior to that of warfarin therapy or anticoagulation discontinuation, but will need to be validated in other patient cohorts and with more recent data.

4.0 COST-EFFECTIVENESS OF NON-VITAMIN K ANTAGONIST ORAL ANTICOAGULANTS FOR STROKE PREVENTION IN PATIENTS WITH ATRIAL FIBRILLATION AT HIGH RISK OF BLEEDING

4.1 ABSTRACT

There is conflicting evidence on the comparative cost-effectiveness of apixaban 5mg and dabigatran 150mg, and the cost-effectiveness of edoxaban 60mg has never been evaluated from the US perspective. The objective of this manuscript was to compare the cost-effectiveness of edoxaban 60mg, apixaban 5mg, dabigatran 150mg, dabigatran 110mg, rivaroxaban 20mg and dose-adjusted warfarin in the prevention of stroke and systemic embolism among 65 year old atrial fibrillation patients who are at high-risk of bleeding, which was defined as having a HAS-BLED score greater than or equal to 3.Our baseline cohort simulated patients at high risk of bleeding because first, around 40% of Medicare beneficiaries on oral anticoagulation have HAS-BLED scores equal to or greater than 3, and second, patients at high risk of bleeding are usually at high risk of stroke too, since risk factors for bleeding events also increase the thromboembolic risk. We constructed a Markov state-transition model to evaluate lifetime costs and quality-adjusted life years (QALYs) with each of the six anticoagulation treatments from the perspective of US third-party payers. During each Markov cycle, patients could experience a severe stroke, other thromboembolic event including minor ischemic stroke, transient ischemic attack and

systemic embolism, an intracranial bleeding or an extracranial bleeding event. Probabilities of clinical events were obtained from the RE-LY, ROCKET-AF, ARISTOTLE and ENGAGE AF-TIMI clinical trials; costs were derived from the Healthcare Cost and Utilization Project, and other published studies. To select cost-effective alternatives, we used a $100,000 per QALY gained willingness-to-pay threshold. Because edoxaban is only indicated in patients with creatinine clearance lower than 95ml/min, we re-run our analyses after excluding edoxaban from the compared strategies. We found that treatment with edoxaban 60mg cost $77,565 per QALY gained compared to warfarin, and apixaban 5mg cost $108,631/QALY gained compared to edoxaban 60mg. When edoxaban was not included in the analysis, treatment with apixaban 5mg would cost $84,128 per QALY gained, compared to warfarin. Dabigatran 150mg, dabigatran 110mg and rivaroxaban 20mg were dominated strategies. Results were most sensitive to non-vitamin K antagonist oral anticoagulant costs, and the relative risks of thromboembolic and bleeding events with apixaban 5mg and edoxaban 60mg. In conclusion, for patients with creatinine clearance lower than 95ml/min, edoxaban 60mg was the most cost-effective oral anticoagulation treatment. Apixaban 5mg, however, was the most effective strategy and it would be cost-effective for this population if its price was reduced 1.3%, or if a somewhat higher cost-effectiveness criterion of $150,000/QALY gained or more was used. For patients with creatinine clearance higher than 95ml/min, for whom edoxaban is not indicated, apixaban 5mg was the most cost-effective oral anticoagulation treatment.

4.2 INTRODUCTION

AF is the most prevalent type of arrhythmia and a leading cause of stroke[158,159] – it is associated with a 5-fold increase in the risk of stroke, and around 15% of strokes in all age groups and 24% in elderly patients can be attributed to AF.[160,161] The use of oral anticoagulation therapy has been found to reduce stroke risk by around 60%;[46] however, anticoagulation is associated with an increased risk of bleeding. For this reason, clinical guidelines recommend the assessment of the risk of stroke, as measured by the CHA2DS2-Vasc score, before the prescription of oral anticoagulation.[60,162] In patients with CHA2DS2-Vasc scores lower than 2, the risk of bleeding can outweigh the benefits of stroke risk reduction;[53] however, there is solid evidence supporting the use of anticoagulation in patients with CHA2DS2-Vasc scores equal to or greater than 2, regardless of the risk of bleeding.[46,51,52] The risk of bleeding is measured by the HAS-BLED score; HAS-BLED scores equal to or greater than 3 indicate high risk of bleeding.[113] Representing around 40% of Medicare beneficiaries on oral anticoagulation,[135] patients with HAS-BLED scores equal to or greater than 3 are usually at high risk of stroke too, because risk factors for bleeding events also increase the thromboembolic risk.[58,59,113] For this reason, the appropriate management of anticoagulation therapy in this subgroup of AF patients is especially relevant.

Before 2010, warfarin was the only oral anticoagulant approved for the prevention of stroke and systemic embolism in AF. In October 2010, dabigatran was the first NOAC to reach market entry.[96] The approval of dabigatran was based on the results from the RE-LY trial, which showed that dabigatran 150mg was superior to warfarin in the prevention of stroke and systemic embolism, but similar in the risk of bleeding.[88] The RE-LY trial also evaluated dabigatran 110mg,[88] an intermediate strength that was approved by the main international regulatory

agencies except for the FDA for stroke prevention in patients with high risk of bleeding.[93-95] Since the approval of dabigatran in 2010, three new agents have gained the FDA approval for the prevention of stroke among AF patients with normal kidney function: rivaroxaban 20 mg in November 2011, apixaban 5mg in December 2012 and edoxaban 60mg in January 2015.[88-91]

NOACs present certain advantages over traditional anticoagulation therapy with warfarin, such as fewer interactions and no requirement for routine monitoring of laboratory coagulation markers; however, NOACs are around 15 times more costly than warfarin.[88-91] As a result, NOACs have garnered special attention regarding their cost-effectiveness. Specifically, three studies have simultaneously compared the cost-effectiveness of apixaban 5mg, rivaroxaban 20mg, dabigatran 150mg and warfarin from the US perspective, finding conflicting results.[126-128] Whereas Canestaro et al. and Harrington et al. found that apixaban 5mg was a cost-effective strategy compared to dabigatran 150mg, Coyle and colleagues showed that dabigatran 150mg was more expensive and less effective than apixaban 5mg.[126-128] Because edoxaban was recently approved, only three cost-effectiveness studies have included this agent among the strategies compared, all of which were based on European countries.[130-132] In these studies, edoxaban 60mg was found to be a cost-effective strategy compared to warfarin,[132] however, it was not favored when compared to apixaban 5mg.[131] The results of these studies are not generalizable to the US because the cost-effectiveness of NOACs is highly sensitive to pricing, and the prices of NOACs are considerably higher in the US than in Europe.[128] In summary, there is conflicting evidence on the comparative cost-effectiveness of apixaban 5mg and dabigatran 150mg, and the cost-effectiveness of edoxaban 60mg has never been evaluated from the US perspective.

To address this evidence gap, we adopted a US perspective in comparing the cost-effectiveness of edoxaban 60mg, apixaban 5mg, dabigatran 150mg, dabigatran 110mg,

rivaroxaban 20mg and dose-adjusted warfarin in the prevention of stroke and systemic embolism in AF patients with high risk of bleeding, as defined by HAS-BLED score equal to or greater than 3.[163]

4.3 METHODS

4.3.1 Overview of the Model

We constructed a Markov state-transition model to compare the cost-effectiveness of edoxaban 60mg, apixaban 5mg, dabigatran 150mg, dabigatran 110mg, rivaroxaban 20mg and dose-adjusted warfarin in the prevention of stroke and systemic embolism in AF patients at high risk of bleeding. The base case analysis included a cohort of 65-year old patients with AF, elevated risk of stroke (CHADS2 score≥1), high risk of bleeding (HAS-BLED≥3), normal kidney function (creatinine clearance≥50ml/min), no contraindications for oral anticoagulation use, and who did not use P-glycoprotein inhibitors or CYP3A4 inhibitors. Because edoxaban is only indicated in patients with creatinine clearance lower than 95ml/min, we re-run our analyses after including and excluding edoxaban from the compared strategies. [72]The following states were simulated in the model: AF on an oral anticoagulant agent, AF on aspirin, severe stroke, other thromboembolic events including minor ischemic stroke, transient ischemic attack and systemic embolism, intracranial bleeding, extracranial bleeding and death (Figure 4-1). Transitions between health states were modeled using 1-year cycles, and patients were followed until death or until 90 years of age. Patients reaching the 35th cycle alive were assumed to die at the age of 90. Future costs and benefits were discounted at a 3% annual rate. From the perspective of US-

based third party payers, we quantified costs in 2012 US dollars, effectiveness in QALYs, and calculated incremental cost effectiveness ratios (ICERs). The model was constructed and analyzed using TreeAge Pro Suite 2015 (Williamstown, MA).

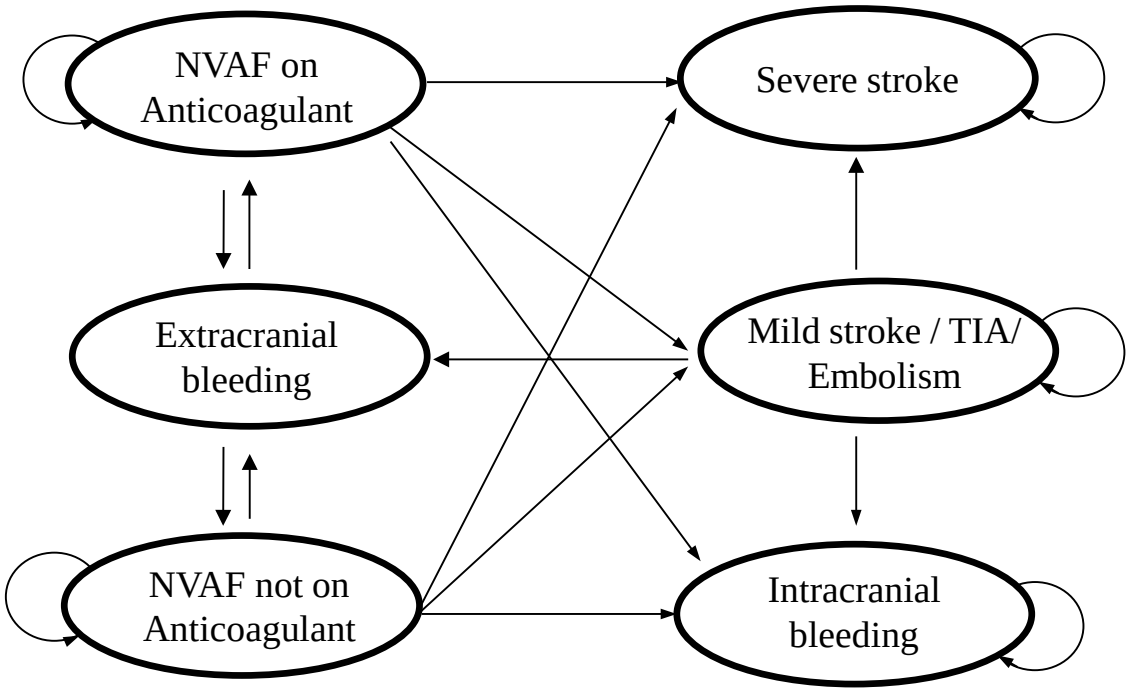

Figure 4-1: Markov Model

4.3.2 Major Model Assumptions

We made the following assumptions: First, patients entering the model are treated with aspirin and one of the following anticoagulant agents: edoxaban 60mg, apixaban 5mg, dabigatran 150mg, dabigatran 110mg, rivaroxaban 20mg or dose-adjusted warfarin (target international normalized ratio [INR] between 2 and 3).[60] Therapy adherence was assumed to be similar across all treatments.[128] Second, during each Markov cycle, patients can experience a severe stroke,

other thromboembolic event including minor ischemic stroke, transient ischemic attack and systemic embolism, an intracranial bleeding or an extracranial bleeding event. After experiencing a severe stroke or other thromboembolic event, patients resume aspirin and anticoagulation with the same agent used before the thromboembolic event. However, we assumed that all patients discontinue anticoagulation therapy after experiencing an intracranial hemorrhage.[164] Based on the FDA summary of the ROCKET-AF trial, 10% of the patients who experienced an extracranial bleeding were assumed to discontinue oral anticoagulation.[165] Patients who discontinue oral anticoagulation after an extracranial bleed proceed to the AF on aspirin state. Third, patients that experience a severe stroke or intracranial bleeding remain in states denoting those events permanently. Fourth, the efficacy and safety of all treatments were assumed to be constant over time. Fifth, patients who do not discontinue anticoagulation use the same anticoagulant agent throughout their lifetime.

4.3.3 Input Parameters

4.3.3.1 Clinical Probabilities

The annual probabilities of severe stroke, other thromboembolic events, and intracranial bleeding with warfarin were obtained from the RE-LY, ROCKET-AF, ARISTOTLE, and ENGAGE AF-TIMI trials (Table 4-1).[88-91] The annual probability of extracranial bleeding represents the annual probability of extracranial bleeding in a cohort of AF patients on warfarin and with HAS-BLED between 3 and 5, weighted by the proportion of patients with HAS-BLED score 3, 4 and 5, respectively.[166] The annual probability of other thromboembolic events was calculated as the sum of the probabilities of minor ischemic stroke, transient ischemic attack or systemic embolism. For all clinical outcomes, event rates for treatments other than warfarin were

estimated using risk ratios relative to warfarin, and were obtained from the RE-LY, ROCKET-AF, ARISTOTLE, and ENGAGE AF-TIMI trials and previously published cost-effectiveness analyses.[88,89,121,167] To adjust the risk of stroke by age, we increased the risk of severe stroke by a factor of 1.4 every ten years of life.[168]

Baseline mortality estimates by age were derived from the US National Vital Statistics Reports.[155] For patients who survive a major stroke, other thromboembolic event or an intracranial hemorrhage, we increased their mortality risk according to post-event mortality risks derived from previous publications, because they are more likely to die compared with those who did not experience such events.[121,169,170] For instance, the baseline annual mortality rate for an average 75-year-old patient was 0.031, but the annual mortality rate for a 75-year-old patient with a history of severe stroke was estimated at 0.074 (0.031+0.043), because the increase in mortality rate associated with experiencing a severe stroke was 0.043.[169]

4.3.3.2 Costs

We obtained the cost for one-year supply of apixaban, edoxaban, dabigatran, rivaroxaban and warfarin from www.goodrx.com, and the cost of aspirin was based on a previous publication.[171] The total cost of warfarin treatment was calculated as the sum of one-year supply of warfarin and the annual costs for INR monitoring.[172] Estimates for the one-time costs, or the costs of acute care provided for clinical events were obtained from the Healthcare and Utilization Project (HCUP).[173] The maintenance costs associated with the follow-up care of patients who experienced clinical events were obtained from two retrospective analyses.[174,175] For both one-time and follow-up costs, the costs of other thromboembolic events were calculated as the average of the costs of minor ischemic stroke, transient ischemic attack and systemic embolism, weighted by their respective annual probability. Costs of healthcare related to diseases other than

AF, thromboembolic or bleeding events were obtained from the Medical Expenditure Panel Survey (MEPS) data.[176] The ranges used for sensitivity analyses were calculated as ±20% of the base case. All costs except for drug costs were inflated to 2012 US dollars using the Consumer Price Index for medical care.[177] Drug costs were not deflated to 2012 US dollars because some of the NOACs were not available in the market at that time (apixaban was approved in December 2012 and edoxaban in January 2015).

4.3.3.3 Quality-of-life Measures

Utilities represent the preference for a health state and range from 0 to 1, with 0 denoting death and 1 perfect health. To adjust life expectancy for quality of life, we multiplied the time spent in each heath state and its respective utility. For example, if a patient spent two years on a state of utility 0.8, the total quality-adjusted life years accrued in such state would be 1.6 (2*0.8). The baseline utility in all cycles was adjusted for age, AF, and anticoagulation use.[178-180] For example, the utility accrued when a 70-year old patient spent one year on the severe stroke state would equal 0.35 [(0.84(utility associated with 70 years of age)*0.989(utility associated with the use of anticoagulation)*0.81(utility associated with AF) *0.514(utility associated with severe stroke)]. The utility estimates for severe stroke, other thromboembolic events, intracranial bleeding and extracranial bleeding were obtained from a catalogue of EQ-5D scores by Sullivan et al. and other relevant publications.[164,181-183] The utility estimate for other thromboembolic events was calculated as the average of the utilities of minor ischemic stroke, transient ischemic attack and systemic embolism, weighted by their respective annual probability.

Table 4-1: Decision Model Inputs: Event Probabilities, Mortality Estimates, Costs and Utilities

Input Variable	Base Case	Range	References
Clinical Parameters			
Annual probability of severe stroke on warfarin	0.0040	0.0020-0.0063	88,89
Percentage of severe strokes that are fatal (%)	16.94	14.00-20.00	121
RR of severe stroke aspirin vs warfarin	2.16	1.57-2.82	121,167
RR of severe stroke dabigatran 150mg vs warfarin	0.76	0.60-0.98	88
RR of severe stroke dabigatran 110mg vs warfarin	1.11	0.89-1.40	88
RR of severe stroke rivaroxaban 20mg vs warfarin	0.89	0.65-1.21	167
RR of severe stroke apixaban 5mg vs warfarin	0.79	0.65-0.95	90
RR of severe stroke edoxaban 60mg vs warfarin	0.97	0.76-1.23	91
Annual probability of other thromboembolic event on warfarin	0.0146	0.0100-0.0200	88,89,167,184
RR of other thromboembolic event aspirin vs warfarin	1.82	1.12-3.02	88,184
RR of other thromboembolic event dabigatran 150mg vs warfarin	0.71	0.47-1.09	88,185
RR of other thromboembolic event dabigatran 110mg vs warfarin	0.68	0.46-1.01	88,185
RR of other thromboembolic event rivaroxaban 20 mg vs warfarin	0.79	0.66-0.96	89
RR of other thromboembolic event apixaban 5mg vs warfarin	0.80	0.64-1.03	90
RR of other thromboembolic event edoxaban 60mg vs warfarin	0.78	0.62-1.02	91
Annual probability of intracranial hemorrhage on warfarin	0.0080	0.0074-0.0094	88,89,128
Percentage of intracranial hemorrhages that are fatal (%)	42.00	35.00-60.00	122
RR of intracranial hemorrhage aspirin vs warfarin	0.51	0.16-1.60	184
RR of intracranial hemorrhage dabigatran 150mg vs warfarin	0.40	0.27-0.60	88
RR of intracranial hemorrhage dabigatran 110mg vs warfarin	0.31	0.20-0.47	88
RR of intracranial hemorrhage rivaroxaban 20mg vs warfarin	0.67	0.47-0.93	165
RR of intracranial hemorrhage apixaban 5mg vs warfarin	0.42	0.30-0.58	90
RR of intracranial hemorrhage edoxaban 60mg vs warfarin	0.47	0.34-0.63	91
Annual probability of extracranial hemorrhage on warfarin	0.0590	0.0410-0.0910	166
Percentage of extracranial hemorrhages that are fatal (%)	5.88	3.00-8.00	186
RR of extracranial hemorrhage aspirin vs warfarin	0.43	0.24-0.75	167
RR of extracranial hemorrhage dabigatran 150mg vs warfarin	1.07	0.92-1.25	88
RR of extracranial hemorrhage dabigatran 110mg vs warfarin	0.94	0.80-1.10	88
RR of extracranial hemorrhage rivaroxaban 20mg vs warfarin	1.15	0.91-1.41	167
RR of extracranial hemorrhage apixaban 5mg vs warfarin	0.79	0.68-0.93	90
RR of extracranial hemorrhage edoxaban 60mg vs warfarin	0.91	0.80-1.05	91
Mortality parameters			
Increase in mortality after severe stroke	0.0427	0.0337-0.0537	169
Increase in mortality after other thromboembolic event	0.0100	0.0030-0.0170	121
Increase in mortality after intracranial hemorrhage	0.0660	0.0500-0.0800	170

Table 4-1 continued

Costs (2012 US Dollars)			
Annual treatment costs			
Aspirin	13.95	11.16-16.74	[171]
Warfarin	162.41	129.93-194.89	[171]
Dabigatran 150mg	4915.15	3932.12-5898.18	[187]
Dabigatran 110mg	4915.15	3932.12-5898.18	[187]
Rivaroxaban 20mg	4092.48	3273.98-4910.98	[187]
Apixaban 5mg	4095.96	3276.77-4915.15	[187]
Edoxaban 60mg	3420.00	2736.00-4104.00	[187]
Annual cost of INR monitoring	1110.38	888.30-1332.46	[172]
One-time costs			
Severe stroke	14843.00	11874.40-17811.60	[173]
Other thromboembolic event	7424.49	5939.60-8909.39	[173]
Intracranial hemorrhage	21256.00	17004.80-25507.20	[173]
Extracranial hemorrhage	7100.00	5680.00-8520.00	[173]
Long-term maintenance costs			
Severe Stroke	30333.82	24267.06-36400.58	[175]
Other thromboembolic event	18735.00	14988.00-22482.00	[174]
Intracranial hemorrhage	23278.51	18622.81-27934.21	[188]
Other costs	9678.00	7742.40-11613.60	[176]
Quality-of-life Estimates			
Anticoagulation	0.989	0.0988-0.991	[178]
Atrial Fibrillation	0.810	0.700-0.900	[180]
Severe stroke	0.514	0.454-0.574	[181]
Other thromboembolic event	0.620	0.560-0.680	[181]
Intracranial hemorrhage	0.600	0.020-1.000	[188]
Extracranial hemorrhage	0.800	0.500-0.990	[189]

4.3.4 Sensitivity Analysis

We performed multiple sensitivity analyses of the input variables over the ranges shown in Table 1. First, we conducted a series of one-way sensitivity analyses to evaluate the relative importance of each parameter, and we identified the threshold of variables at which the anticoagulant strategy favored changed. Second, we performed three-way sensitivity analyses to identify the preferred anticoagulant agent over the plausible ranges of annual probabilities of severe stroke

and of extracranial bleeding, for the base-case value of the annual probability of intracranial bleeding, as well as the upper and lower bound estimates. Third, we simultaneously varied all parameter values 10,000 times in a Monte Carlo probabilistic sensitivity analysis and constructed a cost-effectiveness acceptability curve. We modelled event probabilities and utilities as beta distributions, relative risk of events as log-normal distributions, and costs as gamma distributions. To select cost-effective alternatives, we used $100,000 per QALY gained as willingness-to-pay (WTP) threshold, because this is the most realistic WTP criterion in the US context.[190]

4.4 RESULTS

4.4.1 Base-case Analysis

Table 4-2 shows the costs and effectiveness associated with each treatment, as well as the incremental cost-effectiveness results. In the base case scenario, apixaban 5mg had the highest effectiveness (8.32 QALYs), followed by dabigatran 110mg (8.31), dabigatran 150mg (8.30), edoxaban 60mg (8.25), rivaroxaban 20mg (8.13), and warfarin (7.96). Dabigatran 110mg was the most expensive treatment ($223,922), followed by dabigatran 150mg ($220,927), apixaban 5mg ($214,614), rivaroxaban 20mg ($212,579), edoxaban 60mg ($206,336) and warfarin ($184,525).

When edoxaban was included in the analysis, treatment with edoxaban 60mg cost $77,565 per QALY gained compared to warfarin, and the ICER of apixaban 5mg compared to edoxaban 60mg was $108,631/QALY. When edoxaban was not included in the analysis, treatment with apixaban 5mg would cost $84,128 per QALY gained, compared to anticoagulation therapy with

warfarin. Regardless of the inclusion of edoxaban, rivaroxaban 20mg, dabigatran 150 mg and dabigatran 110mg were dominated strategies, because treatment with apixaban 5mg was more effective and less costly. If apixaban 5mg was also excluded from the analysis, rivaroxaban would be dominated by dabigatran, and the ICER of dabigatran 150mg compared to warfarin would be $107,080/QALY.

Table 4-2: Base-case Analysis Results: Total and Incremental Costs and Quality-Adjusted Life Years per Patient.

Including edoxaban in the analysis	Cost (2012 US Dollars)	Effectiveness (QALYs)	Incremental Costs (2012 US Dollars)	Incremental Effectiveness (QALYs)	ICERs ($/QALY)
Warfarin	184,252	7.9615	--	--	--
Edoxaban 60mg	206,336	8.2462	22,084	0.2847	77,565
Rivaroxaban 20mg	212,579	8.1349	6,243	-0.1113	Dominated
Apixaban 5mg	214,614	8.3224	8,278	0.0762	108,631
Dabigatran 150mg	220,927	8.304	6,313	-0.0184	Dominated
Dabigatran 110mg	223,922	8.3058	9,309	-0.0166	Dominated
Excluding edoxaban from the analysis	**Cost (2012 US Dollars)**	**Effectiveness (QALYs)**	**Incremental Costs (2012 US Dollars)**	**Incremental Effectiveness (QALYs)**	**ICERs ($/QALY)**
Warfarin	184,252	7.9615	--	--	--
Rivaroxaban 20mg	212,579	8.1349	28,327	0.1734	Dominated
Apixaban 5mg	214,614	8.3224	2,035	0.1875	84,129
Dabigatran 150mg	220,927	8.3040	6,313	-0.0184	Dominated
Dabigatran 110mg	223,922	8.3058	9,309	-0.0166	Dominated

Table 4-3 shows the clinical events experienced per 1000 AF patients entering the model and receiving each of the six oral anticoagulation agents. Compared to warfarin, edoxaban 60mg would prevent 37 thromboembolic events other than severe strokes, 57 intracranial hemorrhages and 27 extracranial bleeding events; however, warfarin would prevent 2 severe strokes more than edoxaban 60mg. Compared to warfarin, apixaban 5mg would prevent 12 severe strokes, 190 other thromboembolic events, 45 intracranial hemorrhages and 112 extracranial bleeding events.

Use of apixaban 5mg as compared to edoxaban 60mg would prevent 14 severe strokes, 4 intracranial hemorrhages, and 85 extracranial bleeding events, but edoxaban 60mg would prevent 7 other thromboembolic events more than apixaban 5mg.

Table 4-3: Base-case Analysis Results: Clinical Events per Cohort of 1000 Patients.

Number of lifetime events per cohort of 1000	Warfarin	Rivaroxaban 20mg	Edoxaban 60mg	Dabigatran 150mg	Dabigatran 110mg	Apixaban 5mg
Severe Stroke	84	78	86	70	98	72
Other Thromboembolic Events	220	182	183	170	161	190
Intracranial Hemorrhage	114	79	57	50	39	53
Extracranial Hemorrhage	829	971	802	941	833	717

4.4.2 Sensitivity Analysis

In one-way sensitivity analyses, we identified variables that most influenced the strategy favored at the $100,000 per QALY gained threshold (Table 4-4). The optimal anticoagulation choice was most sensitive to the annual probability of extracranial bleeding and of thromboembolic events other than severe stroke, the proportion of extracranial hemorrhages that are fatal, the relative risk of clinical events with apixaban 5mg, edoxaban 60mg and dabigatran 150mg compared to warfarin, the costs of apixaban 5mg, edoxaban 60mg, and dabigatran, and the quality of life associated with AF and with an extracranial bleeding. When the annual cost of apixaban 5mg was below $4,044 (98.7% of the base-case value), apixaban 5mg was the preferred strategy at the $100,000 per QALY WTP threshold. Apixaban 5mg was also preferred when the annual probability of extracranial bleeding was higher than 8%. We found that under no scenario, warfarin or rivaroxaban 20mg were the preferred strategies at the $100,000 per QALY WTP threshold. When edoxaban was excluded from the analysis, the optimal anticoagulation choice at

the $100,000 per QALY gained threshold was only sensitive to the annual cost of dabigatran 110mg and 150mg, and the relative risk of other thromboembolic events with dabigatran 150mg, compared to warfarin.

Table 4-4: One Way-Sensitivity Analysis: Influential Parameters and Their Thresholds for the Choice of Favored Strategy at $100,000/Quality-Adjusted Life Year Willingness to Pay

Including edoxaban in the analysis				
Parameter	Base-case value	Threshold	Strategy favored below threshold	Strategy favored above threshold
Annual risk of Extracranial Bleeding	0.059	0.080	Edoxaban 60mg	Apixaban 5mg
Annual risk of Other Thromboembolic Events	0.0146	0.012	Apixaban 5mg	Edoxaban 60mg
Proportion of Fatal Extracranial Hemorrhages	5.88	7.95	Edoxaban 60mg	Apixaban 5mg
Relative Risk Severe Stroke				
Apixaban 5mg vs Warfarin	0.79	0.77	Apixaban 5mg	Edoxaban 60mg
Edoxaban 60mg vs Warfarin	0.97	0.99	Edoxaban 60mg	Apixaban 5mg
Relative Risk Other Thromboembolic Events				
Apixaban 5mg vs Warfarin	0.8	0.79	Apixaban 5mg	Edoxaban 60mg
Dabigatran 150mg vs Warfarin	0.71	0.53	Dabigatran 150mg	Edoxaban 60mg
Edoxaban 60mg vs Warfarin	0.78	0.79	Edoxaban 60mg	Apixaban 5mg
Relative Risk Intracranial Hemorrhage				
Apixaban 5mg vs Warfarin	0.42	0.40	Apixaban 5mg	Edoxaban 60mg
Edoxaban 60mg vs Warfarin	0.47	0.49	Edoxaban 60mg	Apixaban 5mg
Relative Risk Extracranial Hemorrhage				
Apixaban 5mg vs Warfarin	0.79	0.74	Apixaban 5mg	Edoxaban 60mg
Edoxaban 60mg vs Warfarin	0.91	0.96	Edoxaban 60mg	Apixaban 5mg
Cost of Apixaban 5mg	4,096	4,044	Apixaban 5mg	Edoxaban 60mg
Cost of Dabigatran 110mg	4,915	3,986	Dabigatran 110mg	Edoxaban 60mg
Cost of Dabigatran 150mg	4,915	4,205	Dabigatran 150mg	Edoxaban 60mg
Cost of Edoxaban 60mg	3,420	3,473	Edoxaban 60mg	Apixaban 5mg
Quality of Life Extracranial Bleeding	0.80	0.64	Apixaban 5mg	Edoxaban 60mg
Quality of Life Non-Valvular Atrial Fibrillation	0.81	0.88	Edoxaban 60mg	Apixaban 5mg
Excluding edoxaban from the analysis				
Parameter	Base-case value	Threshold	Strategy favored below threshold	Strategy favored above threshold
Relative Risk Other Thromboembolic Events				
Dabigatran 150mg vs Warfarin	0.71	0.54	Dabigatran 150mg	Apixaban 5mg
Cost of Dabigatran 110mg	4,915	4,038	Dabigatran 110mg	Apixaban 5mg
Cost of Dabigatran 150mg	4,915	4,258	Dabigatran 150mg	Apixaban 5mg

The results of the three-way sensitivity analyses are shown in Figure 4-2. We found that, regardless of the risk of extracranial bleeding and the risk of intracranial bleeding, edoxaban 60 mg was the strategy preferred when the annual probability of severe stroke at baseline was lower

than 0.42 (the base-case for the annual probability of severe stroke was 0.40). When the annual probability of severe stroke was higher than 0.42, the preferred strategy depended on the probabilities of intracranial and extracranial bleeding. Under no circumstances were rivaroxaban 20mg, dabigatran 150mg, dabigatran 110mg or warfarin the preferred strategies. When edoxaban was excluded from the analysis, apixaban 5 mg was the preferred strategy for all ranges of annual probabilities of severe stroke, intracranial and extracranial bleeding events.

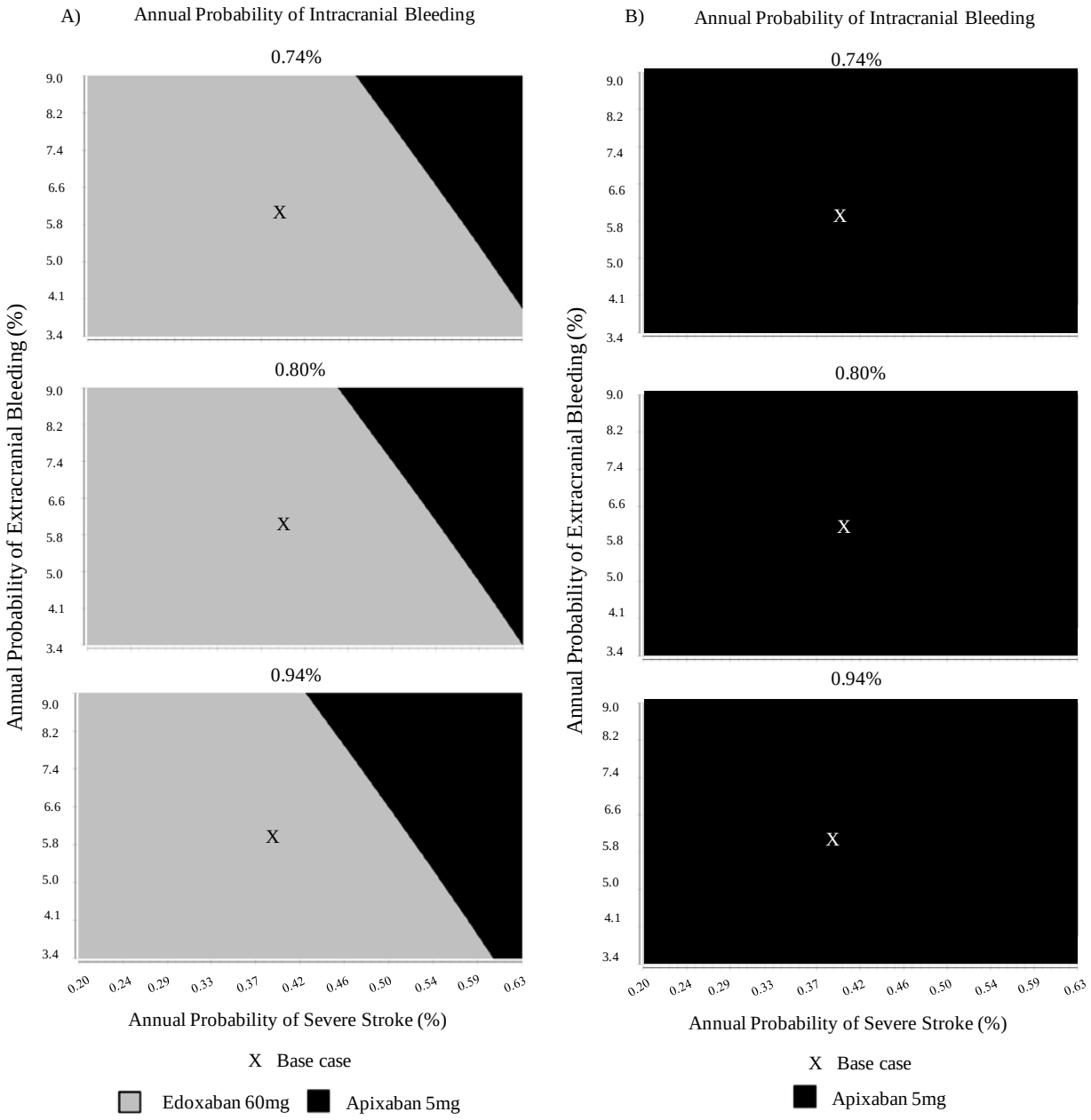

Figure 4-2: Three-Way Sensitivity Analysis.

A) Results when edoxaban was included in the analysis.

B) Results when edoxaban was excluded from the analysis.

Our base-case scenario results are consistent with the findings from probabilistic sensitivity analyses (Figure 4-3). Varying all input parameters simultaneously in a Monte Carlo simulation, we found that at the $100,000 per QALY WTP threshold, edoxaban 60mg had the highest likelihood to be the most cost-effective strategy (40%), followed by apixaban 5mg (36%), dabigatran 150mg (11%) dabigatran 110mg (8%), warfarin (5%) and rivaroxaban 20 mg (1%). Apixaban 5mg had the highest likelihood to be the most cost-effective alternative for WTP thresholds above $115,000/QALY. For WTP thresholds lower than $75,000/QALY, warfarin was likely to be the more cost-effective option. For any WTP threshold, the probability of rivaroxaban 20mg to be the most cost effective strategy was lower than 2%. When edoxaban was excluded from the analysis, apixaban 5mg was likely to be the more cost-effective option for WTP thresholds above $80,000/QALY.

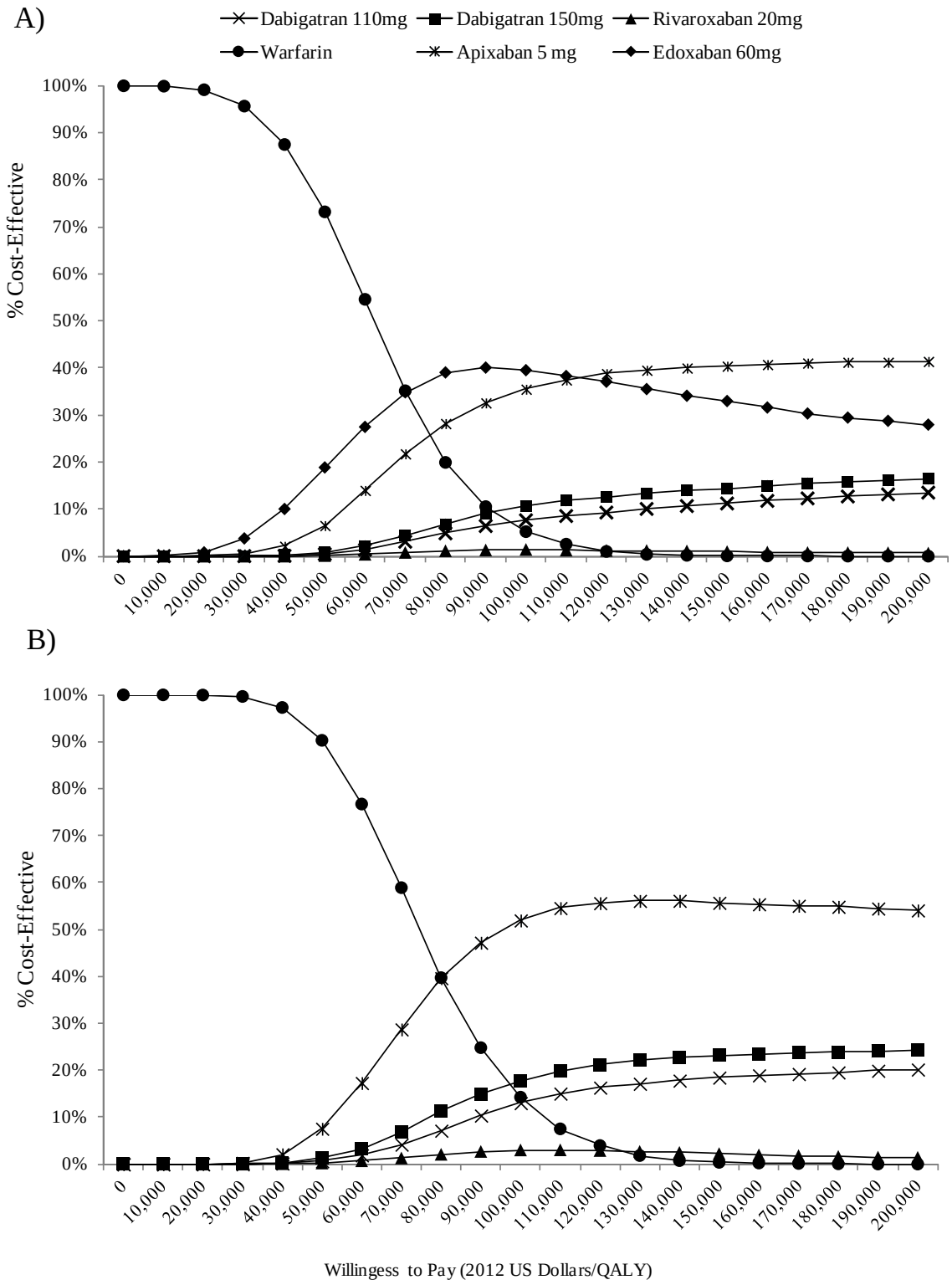

Figure 4-3: Cost-Effectiveness Acceptability Curve.

A) Results when edoxaban was included in the analysis

B) Results when edoxaban was excluded from the analysis.

4.5 DISCUSSION

To the best of our knowledge, our study is the first one to compare the cost-effectiveness of all NOACs approved up to this date in a simulated population of AF patients at high risk of bleeding from the US perspective. Our study has three main findings. First, for patients with creatinine clearance between 50 and 95 ml/min, edoxaban 60 mg was the most cost-effective treatment at the $100,000 per QALY WTP threshold; however, the ICER of apixaban 5mg compared to edoxaban 60mg was slightly above this threshold. The cost-effectiveness of apixaban 5mg and edoxaban 60mg was mostly influenced by the annual probability of extracranial bleeding and of thromboembolic events, the risk of clinical events with apixaban 5mg and edoxaban 60mg, and the costs of apixaban 5mg and edoxaban 60mg. For this population, apixaban 5mg would be a cost-effective strategy if its price was reduced by 1.3%, while the price of edoxaban 60mg was maintained constant, or if a more liberal criterion of WTP was used.[191] Second, for patients with creatinine clearance higher than 95ml/min, for whom edoxaban 60mg is not indicated, apixaban 5mg was the most cost-effective treatment at the $100,000 per QALY WTP threshold. Third, regardless of the levels of creatinine clearance, rivaroxaban 20mg, dabigatran 150 mg and dabigatran 110mg were dominated strategies, because treatment with apixaban 5mg was more effective and less costly.

When we directly compared the cost-effectiveness of apixaban and warfarin, we found that treatment with apixaban cost $84,128 per QALY gained, compared to warfarin; which is consistent with the ICER reported by Canestaro et al. in a recent study ($93,063/QALY).[126] In addition, our estimate for the ICER of edoxaban compared to warfarin ($77,565/QALY) is similar to the Germany-based estimate by Krejczy et al. (€52,000 or $57,000);[130] however, it is considerably higher than the ICER estimated by Rognoni et al. from the perspective of the Italian

National Health System (€7,713 or $8,422).[132] The substantially higher prices of on-patent drugs in the US and Germany as compared to Italy may explain why the ICER of apixaban versus warfarin estimated by Rognoni et al. is considerably lower than our result and the estimate by Krejczy and collaborators.[192] To the best of our knowledge, only one study has directly compared the cost-effectiveness of apixaban 5mg and edoxaban 60mg. In this study, Lip et al. adopted a UK National Health System (NHS) perspective, and estimated the ICER of apixaban 5mg compared to edoxaban 60mg at £6,763 or $9,993 per QALY gained.[131] The difference between this result and our estimate ($108,631/QALY) can be explained by the comparative pricing of edoxaban and apixaban in the UK and the US: In the UK, the cost of apixaban (£804 or $1,187) is identical to that of edoxaban UK (£804 or $1,187), whereas the cost of apixaban in the US ($4,096) is 20% higher than that of edoxaban ($3,420).[131]

Our study is subject to three main limitations. First, we assumed that treatment adherence and discontinuation rates were similar across treatments. This may not be true for two reasons: First, the copayment faced by Medicare Part D beneficiaries towards new oral anticoagulants is considerably higher than the copayment for warfarin. Second, treatment with new oral anticoagulants does not require INR monitoring, whereas warfarin does. Nevertheless, potential differences in the adherence and discontinuation rates between treatments are not likely to affect the ICER of apixaban 5mg compared to edoxaban 60mg, one of the main findings of our study. Second, we assumed that the risk of bleeding with all anticoagulant agents was constant over time. It remains unknown how the risk of bleeding with new oral anticoagulant changes over time; however, the risk of bleeding on warfarin has been shown to decrease 90 days after treatment initiation.[138] Nevertheless, we modeled transitions between health states using 1-year cycles, so this should not affect our results. Third, because patients in clinical trials are closely

monitored, time in the target INR range with warfarin may be higher for patients in clinical trials than in the real-word clinical setting. Therefore, the probabilities of clinical events and the risk ratios of events for new oral anticoagulants compared to warfarin may under-estimate the risk of these events in the real-world setting. However, this should not affect our direct comparisons of NOACs.

Despite these limitations, our study has important implications for the management of anticoagulation in AF patients with high risk of bleeding. In clinical trials, apixaban 5mg was the only new oral anticoagulant agent to show superiority in both efficacy and safety compared to warfarin, and to show a benefit in terms of survival.[82,90] In the current study, we found that, among all oral anticoagulation agents currently available, apixaban is the most effective strategy in the prevention of stroke and systemic embolism among AF patients at high risk of bleeding. For patients with creatinine clearance equal to or lower than 95ml/min, for whom edoxaban 60mg is indicated, apixaban would be cost-effective at the $100,000 per QALY WTP threshold if its price was reduced by 1.3%, while the price of edoxaban was maintained constant. On the other hand, if a more liberal willingness-to-pay criterion was used, for instance, $150,000 or more per QALY gained,[191] apixaban would also be the favored anticoagulation strategy for this population. Because in the US there is no WTP criterion explicitly used, the optimal choice between edoxaban and apixaban will likely depend on the willingness-to-pay of third party payers, as well as on the rebates that health plans negotiate with pharmaceutical manufacturers. For patients with creatinine clearance higher than 95ml/min, for whom edoxaban 60mg is not indicated, apixaban 5mg is likely to be the most cost-effective strategy. In addition, our study found that, in the base case scenario, dabigatran and rivaroxaban were dominated strategies. These findings suggest that, in the formulary making process, health plans should categorize

apixaban or edoxaban as preferred brand names, whereas the dominated NOACs dabigatran and rivaroxaban should be placed in higher tiers. Such categorization of NOACs would incentivize the use of agents whose cost-effectiveness is supported by evidence.

In conclusion, we found that under current pricing, edoxaban 60mg was the most cost-effective oral anticoagulation treatment in the prevention of stroke and systemic embolism in AF patients with high risk of bleeding and creatinine clearance equal to or lower than 95ml/min. Apixaban 5mg, however, was the most effective strategy and it would be cost-effective for this population if its price was reduced 1.3%, or if a somewhat higher cost-effectiveness criterion of $150,000/QALY gained or more was used. For patients with creatinine clearance higher than 95ml/min, for whom edoxaban is not indicated, apixaban 5mg was the most cost-effective oral anticoagulation treatment.

5.0 SYNTHESIS

5.1 OVERVIEW OF RESEARCH FINDINGS

This dissertation evaluated several aspects of the safety, effectiveness and cost-effectiveness of non-vitamin K antagonist oral anticoagulants in the prevention of stroke and systemic embolism among Medicare beneficiaries with atrial fibrillation patients. Our research yielded the following findings:

5.1.1 Comparative Effectiveness and Safety of Rivaroxaban and Dabigatran

When comparing the effectiveness and safety of two doses of dabigatran and two doses of rivaroxaban in a cohort of Medicare beneficiaries with AF, we found no differences in the risk of stroke between dabigatran 150mg and rivaroxaban 20mg (HR 1.05, 95%CI 0.97-1.13) or between dabigatran 75mg and rivaroxaban 15mg (HR1.05, 95%CI 0.94-1.18). Compared to dabigatran 150mg, rivaroxaban 20mg was associated with higher risk of other thromboembolic events (HR1.28, 95%CI 1.14-1.44), major bleeding (HR1.32, 95%CI 1.17-1.50), and death (HR1.36, 95% CI 1.19-1.56). The risk of thromboembolic events other than stroke (HR1.37, 95%CI 1.15-1.62), major bleeding (HR1.51, 95%CI 1.25-1.82) and death (HR1.21, 95% CI 1.04-1.41) was also higher for rivaroxaban 15mg than dabigatran 75mg. Our results for the comparative risk of stroke, death, major bleeding and intracranial bleeding in three high risk

subgroups (patients older than 75 years, with kidney disease or with 7 CMS priority conditions other than AF) were consistent with the findings from the overall sample.

5.1.2 Post-hemorrhage Use of Anticoagulation and Clinical Outcomes

We identified a cohort of AF patients who had a major bleeding event that required hospitalization while using warfarin and dabigatran, and categorized them according to their post-hemorrhage anticoagulation use. We observed that over half of the patients who had a bleeding event on warfarin or dabigatran did not resume anticoagulation therapy. The post-hemorrhage use of warfarin was considerably more common than the use of dabigatran: Only 28% of patients who bled on dabigatran resumed this NOAC after the bleeding event, whereas 41% of warfarin users resumed warfarin (p-value<0.001). In addition, 17% of dabigatran users switched to warfarin after the bleeding event, compared to 2% of warfarin users that switched to dabigatran (p-value<0.001).

We studied which factors affect the resumption of anticoagulation after a major bleeding event, and found that CHA2DS2-VAsc and HAS-BLED scores did not impact the likelihood of anticoagulation resumption. The odds of resuming anticoagulation decreased however by 11% (95%CI, 4%-18%) and 24% (95%CI, 9%-37%) for every 5 years increase in age for warfarin and dabigatran users, respectively. In addition, warfarin users who experienced intracranial bleeding, were admitted to the intensive care unit, or received a blood transfusion were more likely to discontinue anticoagulation than those who did not.

When comparing the clinical outcomes associated with the resumption of warfarin or dabigatran and the discontinuation of anticoagulation after a major bleeding event, we found that post-hemorrhage resumption of anticoagulation with warfarin (HR0.76; 95%CI, 0.59-0.97) or

dabigatran (HR0.66; 95%CI 0.44-0.99) was associated with lower combined risk of ischemic stroke and all-cause mortality than anticoagulation discontinuation. Furthermore, resumption of warfarin (HR0.35; 95%CI, 0.23-0.53) or dabigatran (HR0.13; 95%CI, 0.04-0.41) was associated with decreased mortality, compared to anticoagulation discontinuation. The incidence of recurrent major bleeding was higher for patients who were prescribed warfarin after the bleeding event than for those prescribed dabigatran (HR2.31; 95%CI, 1.19-4.76) or whose anticoagulation ceased (HR1.56; 95%CI, 1.10-2.22).

5.1.3 Comparative Cost-Effectiveness of NOACs

We compared the cost-effectiveness of edoxaban 60mg, apixaban 5mg, dabigatran 150mg, dabigatran 110mg, rivaroxaban 20mg and dose-adjusted warfarin in the prevention of stroke and systemic embolism among 65 year old AF patients with HAS-BLED scores equal to or greater than 3. We found that in the base case scenario, apixaban 5mg had the highest effectiveness, followed by dabigatran 110mg, dabigatran 150mg , edoxaban 60mg, rivaroxaban 20mg, and warfarin. Dabigatran 110mg was the most expensive treatment, followed by dabigatran 150mg, apixaban 5mg, rivaroxaban 20mg, edoxaban 60mg and warfarin. Rivaroxaban 20mg, dabigatran 150 mg and dabigatran 110mg were dominated strategies, because treatment with apixaban 5mg was more effective and less costly. After excluding these three dominated strategies, we found that treatment with edoxaban 60mg cost $77,565 per QALY gained compared to warfarin, and the ICER of apixaban 5mg compared to edoxaban 60mg was $108,631/QALY. Because edoxaban is only indicated in patients with creatinine clearance ≤95ml/min, we re-run our analyses after excluding edoxaban from the compared strategies, finding that the ICER of apixaban 5mg compared to warfarin was $84,128 per QALY gained.

5.2 PUBLIC HEALTH SIGNIFICANCE

The research presented in this dissertation has relevant implications for public health. The second leading cause of mortality in the world, stroke is responsible for around 10% of deaths worldwide.[26] In addition, stroke is the third most common cause of disability in high-income countries.[26] The most important single cause of ischemic stroke,[23] AF is responsible for around 15% of strokes in all age groups, and 24% in patients older than 80 years.[24,25] The use of anticoagulation has consistently been associated with a 60% reduction in the risk of stroke in AF,[40-45] yet, only around half of the AF patients whose use of anticoagulation is recommended by clinical guidelines actually receive anticoagulation therapy.[193,194] Furthermore, a recent US based study found that the proportion of AF patients on anticoagulation did not increase with the risk of stroke, and did not exceed 50% even in patients with CHA2DS2-Vasc scores greater than 4.[195] The reasons behind the lack of concordance between clinical guidelines and real-life prescription of oral anticoagulants remain unknown; however, the reluctance to prescribe anticoagulation for patients at higher risk of stroke has been attributed to bleeding concerns,[195] since patients at highest risk of stroke are also at highest risk of bleeding.[58,59,63,113] The balance of the risk of stroke and risk of bleeding, or in pharmacotherapy terms, the benefit/risk ratio of oral anticoagulant agents is crucial to the management of anticoagulation therapy among all AF patients, but it is especially relevant from the clinical perspective for this subgroup of AF patients at high risk of stroke and high risk of bleeding.

Our research focused precisely on the use of anticoagulation by high-risk patients, and specifically, evaluated several aspects of the safety and effectiveness of NOACs and warfarin in the prevention of stroke in AF. Our research yielded relevant findings on the benefit risk/ratio of oral anticoagulants, which will impact the use and management of anticoagulation therapy in the

following ways: First, our results will orient clinicians in the prescription of the most appropriate NOAC according to the clinical characteristics of AF patients. Second, our findings will encourage the resumption of anticoagulation after a major bleeding event, which has been associated with increased survival and stroke-free survival. Specifically, our findings will incentivize the post-hemorrhage resumption of dabigatran, because with similar effectiveness than warfarin in the prevention of thromboembolic events, it was associated with lower risk of recurrent bleeding. Third, our research results will support the use of cost-effective anticoagulant strategies, incentivizing an optimal allocation of economic resources in healthcare. Fourth, our research will bring attention to the risk-aversion observed in the prescription patterns of NOACs, which prevents the use of the most effective anticoagulation strategy in each type of patient. The evidence arising from this dissertation on the benefit/risk ratio of different oral anticoagulation therapies will allow clinicians to become more familiar with the risks and benefits associated with each of the oral anticoagulation therapies currently available. This information will contribute to mitigate the risk-averse prescription patterns that prevent high-risk patients for whom anticoagulation is recommended from receiving anticoagulation therapy.[195]

In summary, the evidence from this dissertation will guide clinicians in the prescription of the most effective, safe, and cost-effective anticoagulation agent according to the clinical characteristics of AF patients, and will contribute to close the gap between the clinical recommendations and the current use of anticoagulation. This will ultimately lead to the prevention of strokes, the second leading cause of mortality worldwide, and bleeding events, the most common complication of anticoagulation therapy.

5.3 DIRECTIONS FOR FUTURE RESEARCH

Our research identified several gaps of evidence where further research will be needed in the future. First, as clinicians become more familiar with the use of NOACs, and as specific antidotes become available to reverse their anticoagulation effects in case of emergency, prescription patterns of NOACs will likely change. As a result, it will be necessary to compare the effectiveness and safety of NOACs as newer data becomes available. Second, our results for the comparative effectiveness and safety of oral anticoagulants will need to be validated in populations of AF patients other than Medicare beneficiaries. Third, it will be informative to conduct head-to-head analysis of all four NOACs and warfarin in the same population. This will be feasible in 2018, when Medicare Part D data that represents the period after the approval of edoxaban becomes available. Fourth, it will also be important to perform further subgroup analyses in the future for subgroups of AF patients other than the ones specifically evaluated in this dissertation. Fifth, clinical outcomes following a major bleeding event will likely depend on the anatomical location of the index hemorrhage. In future research, it will be informative to perform stratified analysis comparing the effectiveness and safety of anticoagulant resumption with each of the NOACs and warfarin, by anatomical location of the index bleeding event. Sixth, because results from cost-effectiveness analyses for NOACs are highly sensitive to their pricing, it will also be relevant to repeat similar pharmacoeconomic evaluations of NOACS as their prices change in the next few years.[128]

APPENDIX: SUPPLEMENTAL METHODS

Frequency Matching

To select a day to start following patients who interrupted anticoagulation after the index major hemorrhage, we performed frequency matching. To do so, we simulated the distribution of the time to restart of anticoagulation for the groups that filled a prescription for an oral anticoagulation agent after the index major hemorrhage. The time to restart of drug in the dabigatran cohort followed a gamma distribution with α=1.17 and σ=47.5. The time to restart of drug in the warfarin cohort followed a gamma distribution with α=1.12 and σ=54.2. Start date after index major hemorrhage was set up so that the window between the date of the index major hemorrhage and start date followed a similar distribution to that of the time to anticoagulation restart among the subjects that restarted anticoagulation after the index major bleeding event.

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