DABIGATRAN AND WARFARIN FOR STROKE PREVENTION IN ATRIAL FIBRILLATION: USE, SWITCHING, AND CLINICAL EFFECTS FOLLOWING NEW MARKET ENTRY IN REAL-WORLD PATIENTS

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A dissertation submitted to the faculty at the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Division of Pharmaceutical Outcomes and Policy in the UNC Eshelman School of Pharmacy.

Chapel Hill
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ABSTRACT

JULIE C. LAUFFENBURGER: Dabigatran and warfarin for stroke prevention in atrial fibrillation: Use, switching, and clinical effects following new market entry in real-world patients (Under the direction of Gang Fang)

Patients with atrial fibrillation frequently benefit from anticoagulation to prevent stroke and systemic embolism. For decades, warfarin was the primary oral anticoagulant option despite its narrow therapeutic index requiring monitoring and drug-drug interactions. Dabigatran's recent availability provides practical advantages including no monitoring and fewer interactions; however, it lacks a convenient reversal agent for bleeding events. Currently, it is unclear what factors have driven anticoagulant utilization since dabigatran's introduction, and little real-world evidence on the agents' comparative effectiveness and safety is available. The objectives were to describe dabigatran and warfarin's utilization and switching patterns and assess their comparative effectiveness and safety.

A cohort of non-valvular atrial fibrillation patients initiating anticoagulation from a large US database of commercial and Medicare supplement claims from 2009-2012 was extracted. We first examined factors associated with anticoagulant selection using a retrospective cohort design and multivariable regression. We then evaluated the effectiveness and safety of dabigatran compared with warfarin using multivariable Cox proportional hazards regression and propensity score weighting. Finally, we evaluated the clinical effects of switching anticoagulants compared with non-switching using a time-varying exposure design and multivariable Cox proportional hazards regression.

Of the 64,935 patients included in the cohort, 32.5% used dabigatran. Dabigatran users were less likely to have high ischemic stroke or bleeding risk or other clinical comorbidities. Switching anticoagulation was also less frequent among patients with higher ischemic stroke or bleeding risk. Dabigatran was associated with a lower risk of ischemic stroke or venous thromboembolism, and no relation was seen between anticoagulant and harmful outcomes including bleeding events or acute myocardial infarction. However, dabigatran was also associated with a higher risk of gastrointestinal bleeding. Compared with non-switchers, no relation was seen between switching anticoagulants and an increased risk of stroke, systemic embolism, bleeding events, or myocardial infarction.

Despite the rapid uptake of dabigatran, these results highlight that patients initiating dabigatran were generally healthier than those initiating warfarin. Dabigatran may be considered a safe and possibly more effective alternative to warfarin in patients with atrial fibrillation; despite encouraging results from the observed lack of increased adverse outcomes from switching anticoagulants, caution is still recommended.

ACKNOWLEDGEMENTS

This research would not have been possible without first and foremost, the support of my dissertation committee. First, I would like to express my deepest thanks to my dissertation advisor, Gang, for having high expectations for me and for being supportive and understanding. I would also like to sincerely thank Joel, my dissertation chair, for his constant support and help throughout the program. I am also incredibly grateful to the other members of my dissertation committee, Alan, Denise and Anil for their valuable mentoring, guidance, and expertise. In addition, I would like to express gratitude for other formal (or more informal) faculty mentors throughout the program, including but not limited to Mary, Stacie, and Barbara. Additionally, I wish to thank my fellow DPOP graduate students not only for their helpful advice, enthusiasm and help with SAS, but also for making the office much more fun. I also want to express a heartfelt appreciation to other classmates, colleagues, and faculty/staff at UNC for being a great support network. Lastly, I would like to express my deepest appreciation and love for my family and for their support throughout the program and beyond.

Without all of you, this research would not have been possible.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

ACEI/ARB, Angiotensin converting enzyme inhibitor/angiotensin receptor blocker

AF, Atrial fibrillation

AMI, Acute myocardial infarction

ATRIA, Anticoagulation and Risk Factors in Atrial Fibrillation

CCAE, Commercial claims and encounters

CCI, Charlson Comorbidity Index

CDHP, Consumer driven health plan

DVT, Deep Vein Thrombosis

FDA, Food and Drug Administration

HMO, Health Maintenance Organization

INR, International Normalized Ratio

NOAC, Novel oral anticoagulant

PPO, Preferred Provider Organization

POS, Point of Service

PE, Pulmonary Embolism

PVD, Peripheral vascular disease

TTR, Time in Therapeutic Range

VTE, Venous thromboembolism

CHAPTER 1: INTRODUCTION

1.1. OVERVIEW

Atrial fibrillation (AF), a heartbeat irregularity, is typically managed by oral anticoagulants to prevent clot formation in the upper atria chambers of the heart when blood is pumped inefficiently.[1] To prevent ischemic stroke and thromboembolism in atrial fibrillation, current clinical guidelines support the use of warfarin, a Vitamin K antagonist which has been available since the 1950s; however, recently newly-approved oral anticoagulants (known as "novel oral anticoagulants" or "target-specific oral anticoagulants") have been recommended as alternatives and as even first-line options.[2-5] Use of warfarin in atrial fibrillation has been shown to prevent up to 68% of ischemic stroke and lead to a significant reduction in mortality risk.[6,7] Despite its effectiveness, warfarin has a narrow therapeutic index, leading to some safety issues and potential drug-drug interactions, requiring frequent monitoring.[8-10] Initiation of warfarin and subsequent medication adherence, the extent to which patients take their medications as prescribed, to warfarin has also been shown to be low, possibly because of the high perceived risk of bleeding.[11,12] Maintaining patients on chronic warfarin therapy has its challenges, and alternatives to warfarin have been sought for easier monitoring and management.

Since 2010, newer oral anticoagulants have emerged as potential treatment options for atrial fibrillation. Dabigatran etexilate[13,14], a direct thrombin inhibitor that entered the US market in October 2010, has shown superior or similar efficacy in stroke prevention over warfarin in treatment naïve patients with AF in randomized-controlled clinical trials, depending on the dose

studied.[14-16] Moreover, dabigatran requires less frequent monitoring, may have fewer drug-drug interactions, and may be easier for patients to manage.[17,18] However, dabigatran has also been thought lead to higher risk of dyspepsia, bleeding, and myocardial infarction than warfarin.[19] Uncertainty also remains about its relative safety, because, unlike warfarin, dabigatran lacks a direct reversal agent in the event of bleeding complications.[20] Regardless, the utilization and clinical effectiveness of dabigatran in the management of atrial fibrillation compared with warfarin is unclear in real-world clinical practice, despite current clinical guidelines offering dabigatran as a possible anticoagulant alternative to warfarin.

First and foremost, to examine the comparative effectiveness of anticoagulants necessitates the understanding of factors associated with the choice of a particular treatment, especially new pharmaceuticals. If certain characteristics are significantly associated with use of one therapy versus another, the apparent comparative effectiveness could be affected, particularly if these characteristics cannot be fully measured. Secondly, optimal treatment selection may differ in specific patient populations; understanding the risk of clinical outcomes among subgroups can help patients and providers in decision making when managing AF. The factors associated with the uptake of novel pharmaceuticals have been studied in other contexts.[21-23] Certain providers have been shown to be more likely to prescribe therapies with a new mechanism of action or those used for chronic illnesses; both of these situations apply to dabigatran.[24]

Switching to a new medication may also carry an increased risk of therapeutic failure and toxicity[25], especially for a therapy with a narrow therapeutic window, such as warfarin. Early case reports of patients switching from dabigatran to warfarin suggest an overall increased risk of bleeding on dabigatran.[26,27] Yet, the clinical effects of switching between warfarin and an anticoagulant of a different drug class are still somewhat unclear, as most guidelines have

recommended that patients stabilized on warfarin generally should remain on warfarin.[5] Expert opinion suggests that if switching is necessary, additional monitoring is warranted.[28] By comparison, even switching between warfarin product formulations (e.g., brand to generic) has been studied and is thought to be potentially problematic.[28-32] Studies have suggested that switching between warfarin formulations may be possible without avoiding any major adverse consequences while others have found a slight increased risk of bleeding.[31-33] Given this underlying controversy, it is possible that switching between entirely different anticoagulants may lead to an increased risk of adverse events, especially in the absence of validated dosing conversion standards between anticoagulants. Regardless, there is still minimal evidence regarding the factors and consequences associated with switching between warfarin and a different anticoagulant (or vice versa), particularly among patients in the US.[34,35]

1.2. SIGNIFICANCE AND INNOVATION

More than 460,000 individuals in the United States are newly-diagnosed with AF annually. Meanwhile, AF is only increasing in prevalence and incidence as the population ages.[36] An estimated $26 billion dollars is spent by the US health care system annually on the management of AF.[37] As the use and effects of dabigatran in the management of atrial fibrillation are unknown outside of small clinical trials with limited patient diversity, further examination of possible clinical and safety effects is needed. Optimizing anticoagulation in atrial fibrillation is a critical public health need.

Understanding the factors associated with the use of anticoagulants may also help further future patient-centered research by examining areas where treatment effect heterogeneity may exist. Comparative effectiveness research has also been thought to be affected by changing patterns of use in newly-launched therapies.[38,39] While the factors associated with use of

dabigatran versus warfarin for anticoagulation management are still unclear, particularly in the US, some limited evidence is suggesting some channeling away from dabigatran for patients with higher comorbidity burden.[40,41]

Furthermore, the effectiveness and safety of dabigatran compared with warfarin in AF has not been studied extensively outside of randomized-clinical trials (RCTs) or meta-analyses of these RCTs. Concerns have been raised about an increased excess risk of bleeding and myocardial infarction in patients with AF treated with dabigatran, but once adjusted for renal impairment, dabigatran may not carry the same risk.[42,43] Moreover, the Food and Drug Administration (FDA) approved dabigatran at doses of 150mg or 75mg (renally-adjusted) twice daily for AF; however, dabigatran has not been studied at the 75mg dose – either in RCTs or observational studies.[43] Given the potential for many patients being placed on this dose, using secondary data from real-world settings can provide additional evidence for this previously unstudied strength.

Moreover, the introduction of these new anticoagulants may carry increased risks of bleeding or ischemic stroke and have implications for patients and providers in the management of transitioning patients from warfarin to dabigatran. In practice, many patients may not be treatment-naïve to anticoagulants, and the actual effectiveness and safety of transitioning AF patients between drug products should be examined. The clinical effects of switching between warfarin to an entire different drug product in AF patients in the period following the medication transition is still largely unclear, and switching from dabigatran to warfarin is even less studied.

The goal of this study is to investigate the factors associated with new use and switching between anticoagulants, comparative effectiveness of new use of anticoagulants, and the clinical effects of switching anticoagulants following new market entry of dabigatran. The contribution of the proposed research is expected to help inform patients, clinicians, researchers, and third-

party payers of the real-world utilization, comparative effectiveness and safety of dabigatran compared to warfarin, to help improve clinical practice. Because of the increasing prevalence of AF and the rapid introduction of new anticoagulants, understanding their comparative effectiveness and safety is of imperative importance.

1.3. SPECIFIC AIMS AND HYPOTHESES

Specific Aim #1: Assess and investigate patient factors associated with new use of either warfarin or dabigatran and switching between anticoagulants in patients with atrial fibrillation.

Hypothesis 1: Clinical prediction risk scores (e.g., ischemic stroke and bleeding risk) will not differ between new users of warfarin compared with dabigatran.

Hypothesis 2: Clinical prediction risk scores (e.g., ischemic stroke and bleeding risk) will not differ between new users who switch anticoagulants within 12 months compared with those who do not switch.

Proposed contribution to the literature: This aim is designed to describe the clinical and demographic characteristics associated with use of anticoagulants in the setting of dabigatran market introduction while focusing on ischemic stroke and bleeding risk predictions. Because new users are by definition naïve to anticoagulation, individuals using warfarin therapy post-dabigatran approval may be markedly different than those using dabigatran. Previous users of warfarin who switched to dabigatran post-approval may be those more likely to have had adverse events, but these characteristics have not been studied. Examining for potential differences may lend additional insight into real-world drug utilization patterns.

Specific Aim #2: Investigate the comparative clinical outcomes (risk of harm and clinical effectiveness) following new use of either warfarin or dabigatran, adjusting for baseline patient factors.

3.6.3.1 Hypothesis

Hypothesis 3: There are no significant differences in the risk of clinical effectiveness outcomes or harm outcomes or acute myocardial infarction in new users of warfarin compared with users of dabigatran.

Proposed contribution to the literature: The comparative effectiveness and safety of dabigatran versus warfarin have not yet been examined outside of RCTs for newly-initiating patients. By examining clinical effectiveness outcomes (such as ischemic stroke or venous thromboembolism), safety outcomes (such as bleeding events) and acute myocardial infarction, this research is expected to provide insights on real-world outcomes to inform clinical practice.

Specific Aim #3: Explore the comparative clinical outcomes (risk of harm and clinical effectiveness) of switching from warfarin to dabigatran or dabigatran to warfarin compared with non-switchers, adjusting for patient clinical and demographic factors.

Hypothesis 4: Switching from warfarin to dabigatran will not be associated with increased risk of harm or clinical effectiveness outcomes compared with those who remain on warfarin.

Hypothesis 5: Switching from dabigatran to warfarin will not be associated with an increased risk of harm or clinical effectiveness outcomes compared with those who remain on dabigatran.

Proposed Contribution to the Literature: Because many warfarin patients may not be treatment-naïve and may have different clinical risk profiles than new users, examining the clinical effects of switching oral anticoagulants would provide additional insight on

the role of dabigatran post-approval. Said another way, the comparative effectiveness and safety of switching anticoagulants may differ than initiating therapy for the first time.

1.4. SUMMARY

Retrospective, observational examination of the use and outcomes of dabigatran compared with warfarin will allow for understanding the generalizability of findings from RCTs to patients in the US health care system. Previous research has been narrowly focused on specific patient populations due to limitations in randomized-controlled designs, such as small sample sizes, restrictive inclusion and exclusion criteria, and the inability to measure real-world utilization. Understanding the utilization of each drug in patients with atrial fibrillation may allow a better approach to managing such patients.

CHAPTER 2: LITERATURE REVIEW

The following chapter outlines the background of atrial fibrillation (AF) as follows: how AF is diagnosed, risk factors for developing AF and outcomes of atrial fibrillation to explain which types of AF will be examined in this research. The pharmacologic and non-pharmacologic management of AF is also discussed through published randomized-controlled trials (RCTs), observational studies of anticoagulation use to prevent ischemic stroke, and recent guideline recommendations. These findings will be used to outline which dependent variables, covariates and potential confounders will need to be measured as part of this research in Chapter 3. Any published literature about the uptake of dabigatran is also discussed, along with controversies which currently exist in using dabigatran for AF to highlight the types of studies which have already been conducted and underscore what knowledge gaps currently exist which this research will help address.

2.1. ATRIAL FIBRILLATION

2.1.1. Definition and diagnosis

Atrial fibrillation, the most common arrhythmia seen clinically, is characterized by irregular electrical impulses which generate irregular heartbeats.[44] AF may be discovered by measuring a pulse on clinical exam, but clinicians generally confirm AF using an electrocardiogram (ECG).[45] On the ECG, the replacement of consistent P waves with rapid oscillations or fibrillatory waves of irregular, frequently rapid ventricular responses identifies an

AF diagnosis.[3,46] Pathogenically, AF is initiated by a "trigger", an abnormal automaticity arising from non-cardiac sites, including most commonly pulmonary veins, but also other venous sites or autonomic ganglia.[47] While the exact mechanism causing potential "triggers" is unknown, these automaticities may eventually lead to atrial remodeling, causing a permanent change in atrial function or structure.[48] Correspondingly, AF may be considered reversible or irreversible, depending on the atrial "substrate" etiology, other electrophysiological factors, and other clinical conditions. The goal of many treatments for AF is to prevent triggers and control this atrial modeling – to ultimately reduce the likelihood of adverse outcomes.[46]

Major clinical guidelines have generally recognized four different classifications of AF: first detected AF, paroxysmal AF, persistent AF and permanent AF.[3,46,49] *First detected AF* is often characterized by only one diagnosed episode. If the first detected AF terminates spontaneously but a second episode occurs, then the patient is considered to have *paroxysmal AF*, whereby most cases are still short and self-limiting. However, if the paroxysmal AF episode is sustained longer than 7 days, then the patient is classified as having *persistent AF*, which generally requires cardioversion to terminate. If a patient has undergone cardioversion unsuccessfully or is not a candidate for one, then the patient is considered to have *permanent AF*.[49]

In addition to the above definitions, AF has also been classified by clinical guidelines as *lone atrial fibrillation*, indicating the absence of other clinical findings or other cardiovascular disease, *non-valvular AF*, whereby AF occurs in the absence of other mitral valve disease or prosthetic heart valves, and *secondary AF*, in which AF occurs secondarily from another primary condition including acute myocardial infarction, previous surgery, pulmonary embolism, pneumonia, hyperthyroidism or other pulmonary disease.[49] AF etiology may also differ broadly between those with primary AF versus secondary AF. Thus, many studies incorporate baseline

factors prior to AF diagnosis when examining treatment outcomes or study those patients with primary AF or those patients with non-reversible causes of AF.[45,46] For instance, long-term treatment goals of AF may differ when patients develop AF post-operatively versus those without any acute perturbations or illness. When a patient has 2 or more episodes, regardless of classification, the patient is considered to have *recurrent AF*.[46]

While these categories are not considered to be mutually exclusive, the duration of AF seems to be particularly important in determining the management for AF. Pharmacologic or non-pharmacologic management is not considered to clinically change the classification of a patient's AF, though in some cases the AF episodes may terminate permanently.[44,49] Clinicians can often diagnose AF within a single inpatient or outpatient encounter, where thyroid, renal, and hepatic functions are also measured as part of the evaluation.[46,50] As will be discussed in later sections, anticoagulation is typically reserved for cases of persistent, permanent, or recurrent AF, while dabigatran specifically is indicated by the FDA for non-valvular AF only.[3,4] Thus, the proposed research will focus on patients with irreversible persistent or permanent non-valvular AF classifications.

By comparison, *atrial flutter*, may occur via similar mechanisms, but is pathogenically and prognostically different even though the atrial fibrillation and atrial flutter may convert back and forth to each other.[3,4,46] Atrial flutter is usually distinguishable from atrial fibrillation based ECG patterns and is often not treated indefinitely with anticoagulation. For this reason, atrial flutter will not be examined in the context of the proposed research.

2.1.2. Epidemiology, costs, and quality of life

Developing atrial fibrillation is associated with an increased risk of ischemic stroke and thromboembolism through emboli from the atria.[1] AF primarily affects middle aged adults and

older. Thought to impact 3 million Americans, more than 460,000 individuals are newly-diagnosed with AF annually.[36] This number is only expected to grow as the population ages. The lifetime risk is 1 in 4 for persons over the age of 40 years in the United States, and the median age of AF patients is thought to be about 75 years.

Managing atrial fibrillation can also be expensive and burdensome to individuals. The US health care system spends an estimated $26 billion dollars annually on care related to AF.[37] One study found that approximately 350,000 hospitalizations, 5 million office visits, and 276,000 emergency room visits are annually attributable to AF and its complications.[51] Having atrial fibrillation and developing one of its complications can also lead to a decreased quality of life. Measured in quality-adjusted life-years [QALYs], AF can decrease quality of life by up to 20%.[52] Moreover, ischemic stroke, a complication of AF and a main reason for the use of anticoagulation in AF, results in estimated QALYs of 0.87, 0.68, and 0.52 for major ischemic stroke, moderate ischemic stroke, and minor ischemic stroke, respectively, compared with a QALY of 1.0 for those in perfect health.[53]

2.1.3. Risk factors

A number of cardiovascular risk factors have been associated with the development of atrial fibrillation. Commonly-cited cardiovascular risk factors include hypertension, valvular disease, coronary artery disease, cardiomyopathy/heart failure, congenital heart disease, myocardial infarction, post-surgical complications, pulmonary embolism, and use of a pacemaker.[54,55] Of these, congestive heart failure (CHF), hypertension, valvular disease, and previous myocardial infarction appear to be the most studied risk factors. CHF has been associated with odds ratios of 4.5 in men and 5.9 in women compared with patients without CHF, suggesting a vastly increased likelihood of developing AF with CHF.[50] Valvular disease

has been associated with odds ratios of 1.8 in men and 3.4 in women, while previous myocardial infarction has also been shown to increase the risk of developing AF by 40%.[50] Concomitant hypertension increases the AF risk by approximately 50% compared with those without hypertension.[50] Because of its sheer prevalence, hypertension is thought to contribute to a greater AF burden than any other risk factor.[56]

However, some patients with AF have no underlying cardiovascular disease – in fact, as many as 12% of all diagnosed AF patients have no identifiable history of cardiovascular disease.[45,57] Published literature has identified diabetes mellitus, hyperthyroidism, chronic lung disease, chronic kidney disease, alcohol withdrawal, pharmacologic agents (e.g., stimulants, digoxin toxicity, and illicit drugs), smoking, excessive physical exertion, and recent surgery as commonly-cited non-cardiovascular causes contributing to AF.[54,55,58] Though not considered to be independent causal factors, male sex, elevated inflammatory markers, advanced age, sleep apnea, and obesity have also been thought to increase the likelihood of developing AF.[57] The odds ratio of developing AF has been shown to be 2.1 for men and 2.2 for women for each additional decade of life.[50] Having diabetes mellitus doubly increases one's risk, with differences in risks between sexes. Men have a 1.5 times the likelihood of developing AF compared with women.[50,56] In addition, obesity and smoking are associated with a 50%and 40% greater risk of AF, respectively.[59]

While many risk factors for AF have been elucidated, some recent efforts have focused on identifying additional risk factors. Some patients with AF have none of the aforementioned risk factors. Approximately 30-45% of cases of paroxysmal AF and 20-25% of cases of persistent AF occur in patients without underlying disease (e.g., "lone AF").[45] As a result, researchers are continuing to search for other underlying reasons for developing AF.

2.1.4. Outcomes

Having atrial fibrillation is primarily associated with an increased risk of systemic embolism leading to ischemic stroke. While less common due to the physiologic nature of developing acute myocardial infarction (AMI), atrial fibrillation may be associated with an increased risk of AMI. Congestive heart failure (CHF) is also thought to be exacerbated by AF, due to the increased potential for clot formation in general.[60,61] While AF is most often associated with the aforementioned cardiovascular causes, AF may also lead to a significantly increased risk of hyperthyroidism[54] and dementia[62]. Studies have also shown associations with increased risk of mortality through multiple intermediate outcomes, including ischemic stroke, congestive heart failure, and myocardial infarction.[47,63] In particular, the mortality rate of AF patients has been estimated to be twice that of patients with normal sinus rhythm.[60] These outcomes will be discussed further in subsequent sections.

2.1.4.1. Systemic Embolism/Ischemic Stroke

One of the most serious adverse complications of AF is systemic thromboembolism leading to ischemic stroke, which is a distinct consequence from either deep vein thrombosis (DVT) or pulmonary embolism (PE). While treatments for AF are similar for these other embolic conditions, AF itself mechanistically does not lead to an increased risk of either DVT or PE, because these clots form in different locations than the atria.[64] This will be discussed more in the management section below.

Atrial fibrillation increases the risk of developing ischemic stroke, mechanistically occurring through blood vessel obstruction to the brain. The rate of ischemic stroke among patients with non-valvular AF averages approximately 5% per year, which is thought to be 2 to 7 times that of the general US population.[7] In fact, 1 out of every 6 ischemic strokes in the US

occurs in patients with AF.[65] Compared with those with normal sinus rhythm, patients with AF have at least twice the increased risk of developing systemic embolism than those without AF – independent of other cardiac risk factors for AF.[6]

In patients with non-valvular atrial fibrillation, common risk factors for developing ischemic stroke also include: congestive heart failure or ejection fraction ≤35%, hypertension, advanced age, diabetes, stroke, transient ischemic attack (TIA), or systemic emboli.[36,44] In patients with AF, prior stroke or TIA has been shown to be the strongest independent factor in developing ischemic stroke (Relative Risk [RR]: 3.0) in patients with non-valvular AF.[46] Diabetes mellitus significantly increases the risk of ischemic stroke and systemic embolism (RR: 1.7). By comparison, hypertension (RR: 1.6), heart failure (RR: 1.4), and advanced age (RR: 1.4) can also significantly increase the risk of systemic embolism.[46] An AF event lasting greater than 5.5 hours on any given day in the last 30 days has also been associated with a 2-fold increase in the risk of thromboembolism.[66] While the risk of embolic stroke in AF can also be enhanced by other AF risk factors, the risk is higher in patients with AF relative to other causes. Worse, ischemic stroke may spontaneously devolve into conditions leading even to death.[6] The risk of ischemic stroke also increases with age, as demonstrated by the Framingham Heart Study. In this study, the annual risk of stroke attributable to AF increased from 1.5% in those 50-59 years to 23.5% in those aged 80-89 years.[47,60] Age has also been shown to be a modifier of the relationship between hypertension and female gender with ischemic stroke, again increasing the risk of ischemic stroke in these individuals.[47]

2.1.4.2. Congestive heart failure

Another serious complication of AF is the development of or worsening of CHF. Mechanistically, AF can disrupt cardiac contractility, exacerbating congestive heart failure.[60] As

a result, AF can lead to tachycardia-induced heart failure (HF). The co-occurrence of AF and HF has been shown to be increasing in incidence and consequence in the population, especially among older adults.[67] In fact, as many as 39.7% of hospitalized CHF patients had a history of AF.[61] The proportion of heart failure with concomitant AF has been shown to increase over time from 1995 to 2004. The prognosis in AF and CHF together is also thought to be grim.[67] The conditions' co-occurrence also been shown to reduce survival and decrease health-related quality-of-life.[67-69] Patients with HF and AF together are at an increased risk of in-hospital and post-discharge mortality.[61] Consequently, guidelines suggest taking co-occurrence of CHF into consideration when treating AF patients, but anticoagulation management is unlikely to have any major beneficial effect on this condition.[67]

2.1.4.3. Acute myocardial infarction

While less-commonly considered a direct outcome of AF, patients with newly-diagnosed atrial fibrillation are thought to be especially prone to AMI, possibly through excess cardiac demand.[70] New-onset atrial fibrillation may increase oxygen demand over the short term, potentially explaining the increased propensity to develop AMI.[70] The resulting irregular heart rhythms may also further hamper coronary circulation and left ventricular function or lead to severe ventricular tachyarrthymias.[71,72] Concomitant AF diagnoses have been difficult to quantify, but studies have reported that 2.3-21.0% of patients experiencing AMI also had a concomitant AF diagnosis. [72] One study found that AF was newly-diagnosed within 2 weeks prior to 7.1% of index AMI hospitalizations, which was higher than expected. [70]

In addition, patients with AF developing AMI appear to have a different risk profile than general patients experiencing AMI. Patients with atrial fibrillation experiencing AMI are more likely to be of advanced age, produce heart failure symptoms, increased heart rate upon AMI

admission, and have left ventricular dysfunction compared with those without AF.[69,72] Guidelines recommend accounting for risk of AMI during treatment for the prevention of ischemic stroke in atrial fibrillation.[46,73] On the other hand, despite the possible cardiac worsening from AF, anticoagulation treatment for stroke prevention may have beneficial a secondary effects in providing overall emboli prevention advantageous to reducing AMI risk.[74] Thus, risk of AMI should be considered when considering management options for AF.

2.2. MANAGEMENT OF ATRIAL FIBRILLATION

2.2.1. Overview

Management of AF patients usually involves a 3-pronged approach: 1) prevention of thromboembolism; 2) rate control; and 3) consideration of rhythm control.[44,46] The strategy for managing AF primarily includes therapies to prevent thromboembolism and other related complications, such as ischemic stroke or death, as rate and rhythm control alone will not decrease these risks. [44]The rate control strategies often include management of the ventricular rate without regard to efforts to maintain regular sinus rhythm. The goal of rhythm control therapies is to restore or maintain sinus rhythm itself based on severity of symptoms.[45]

Regardless of strategy, pharmacologic therapies usually do not fully correct the underlying rhythm disorder, but are intended to reduce the likelihood of adverse outcomes.[46] Beyond these strategies, in managing AF, electrical cardioversion is often considered to attempt to restore sinus rhythm by "reseting" the heart to a normal rhythm.[44,75] Patient selection for cardioversion depends on several factors including: type, severity and duration of AF, concomitant cardiovascular and non-cardiovascular conditions, patient age, treatment goals, and available treatment options.[44] Ultimately, catheter ablations may be considered when pharmacologic strategies or electrical cardioversion are either ineffective or contraindicated.[76]

These other therapies and strategies used for AF are discussed because they will help guide covariate selection for Chapter 3. These covariates will be used to control potential confounders during the study of anticoagulation effectiveness and safety. Because rate control is generally regarded first as a management option for AF, it is discussed first in this overview, followed by a discussion of rate versus rhythm control and anticoagulation management. All of these approaches in AF will be discussed more thoroughly in subsequent sections.

2.2.2. Rate control strategies

Initial treatment of atrial fibrillation is usually directed at controlling ventricular heart rate. Evidence-based rate control strategies include the use of either digoxin, a beta-blocker, or a calcium channel blocker (particularly a non-dihydropyridine such as diltiazem and verapamil).[44] These therapies are recommended for patients with persistent or permanent AF.[44] Digoxin can be effective but is now considered a second-line agent, especially in patients with concomitant heart failure, left ventricular dysfunction or sedentary individuals.[44,77] Factors favoring rate control strategy alone over rhythm control include patients with less symptomatic AF or concomitant hypertension, while the presence of concomitant systolic dysfunction (heart failure) and potential for adverse effects would hinder a preference for rate control.[55, 44] Rate control strategies are usually continued indefinitely or until cardioversion is successful.

2.2.3. Rate vs. rhythm control

Clinical guidelines recommend rate control as the first-line strategy especially in older adults with concomitant heart conditions.[45,46] However, published studies have found conflicting results.[55] The RACE (Rate Control vs. Electrical cardioversion for persistent atrial fibrillation) study found no differences in rate control versus rhythm control for all adverse outcomes and

mortality.[75] The AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) study also found no differences in the rate of ischemic stroke between patients assigned rate versus rhythm control. However, overall mortality (26.7% vs. 25.9%, p=0.08) and frequency of hospitalizations were higher among those assigned rhythm control.[78] When stratifying on age, older adults were found to have a significantly higher mortality burden in those using rhythm control strategies compared with rate control strategies.[78] However, a recent population-based study found that rhythm control was associated with a lower rate of ischemic stroke compared with rate control (Hazard Ratio [HR]: 0.80, 95% CI: 0.74-0.87).[77] Considering patient quality of life, patients have reported no differences in quality of life in rate versus rhythm control strategies.[75,79]

2.2.4. Rhythm control strategies

Once the ventricular rate is controlled, restoration of an appropriate sinus rhythm is the next AF management goal.[44] In patients with newly-diagnosed atrial fibrillation, restoration of sinus rhythm can be considered immediately in patients experiencing symptoms of AF, such as shortness of breath or fatigue. However, rhythm control strategies have not demonstrated long-term benefits on reducing mortality or ischemic stroke risk. Furthermore, anticoagulation for ischemic stroke prevention and rate control therapies are still generally required.

2.2.4.1 Electrical Cardioversion

Direct-current cardioversion can be considered a treatment choice to restore sinus rhythm, especially if within 48 hours of onset of the AF episode. If the 48-hour window has passed, a transesophageal echocardiography may be ordered to ensure no emboli formation and then cardioversion can be performed. Regardless of specific strategy, anticoagulation is

recommended for at least 4 weeks after cardioversion, depending on whether the causation of AF is considered to be reversible or irreversible. Guidelines also recommend vigilance for thromboemboli immediately following cardioversion. In addition to an increased risk of embolism from the AF, cardioversion itself can also increase embolism risk, but occurrence is almost always within the first 3-10 days following the procedure.[44]

2.2.4.2 Role of Anti-arrhythmic therapies

Pharmacologic rhythmic control therapies can be considered as chemical cardioversion, especially in younger adults, those with paroxysmal lone AF, newly-detected AF and those currently not preferred for electrical cardioversion.[55] However, medication strategies are thought to be less effective than electrical cardioversion. Ibutilide is the most commonly used antiarrythmic drug to emergently restore heart rhythm. Once adequate heart rhythm has been restored, pharmacologic therapies may also be used to maintain normal rhythm.[46] These therapies include flecanide, amiodarone, dronedarone, sotalol, propafenone and dofetilide, and the choice of therapy typically depends on presence of concomitant heart conditions such as CHF and coronary disease. Pharmacologic cardioversion is usually continued indefinitely until clinical need for discontinuation due to adverse effects or clinical need subsides. As a second-line option in the event of antiarrhythmic drug failure, catheter ablation is often considered.

2.2.4.3 Ablation measures

Other ablation strategies are considered as possible curative measures. Radiofrequency catheter ablation (RFCA) or pulmonary vein isolation are recommended as treatment options particularly in patients with recurrent AF or patients not able to tolerate antiarrhythmic therapies. Catheter ablation is thought to better reduce AF recurrence compared with antiarrhythmics with

one meta-analysis finding a 23% recurrence after RFCA versus a 77% recurrence with therapies.[80] Another meta-analysis found that RCFA significantly inhibited recurrence of AF (RR: 0.27; 95% CI: 0.18, 0.41) but with limited effect on reducing mortality (RR: 0.50, 95% CI: 0.04-5.65), complications (e.g., ischemic stroke) (RR: 1.01, 95% CI: 0.18-5.68), or death from thromboembolic events (RR: 3.04, 95% CI: 0.13-73.43).[76]

Ablation of the AV node or accessory pathway to control heart rate appears to be warranted when pharmacological therapy is insufficient or associated with undue adverse effects. However, caution has been suggested in patients of advanced age (≥ 80 years).[81] While discussed more broadly in subsequent sections, anticoagulation may be used to manage patients either post-electrical conversion or post-ablation until successful restoration of sinus rhythm is demonstrated.[48] Two recent studies examined the comparative incidence of bleeding complications in the first week following RFCA in patients using dabigatran and warfarin, finding no differences in bleeding risk, ischemic strokes, TIAs or emboli.[82,83] Future research is warranted in this area.

2.2.5. Overview: Antithrombotic therapies

Regardless of rhythm or rate control strategy, guidelines recommend the use of an oral antithrombotic agent in patients with AF to prevent ischemic stroke, except for patients with lone AF or contraindications.[48] Oral antithrombotic agents consist of two therapy classes: antiplatelets (e.g., aspirin) and oral anticoagulants (OACs) (e.g., warfarin or dabigatran). When prescribing a therapy, clinicians are largely recommended to weigh the benefit of preventing emboli versus the risks of bleeding from the therapies using stroke and bleeding clinical prediction risk scores.[1,45] More detail on these clinical prediction scores will be provided in subsequent sections.

2.2.5.1. Antiplatelet therapy

Antiplatelet therapies examined for the prevention of ischemic stroke in atrial fibrillation have primarily consisted of two medications: aspirin and clopidogrel. Evidence from a widely-disseminated meta-analysis suggested that aspirin reduces the risk of ischemic stroke by 22% (95% CI: 2%-38%).[84] The absolute risk reductions were 1.5% per year for primary prevention and 2.5% per year for secondary prevention of ischemic stroke.[84] Another meta-analysis found a 34% reduced likelihood of ischemic stroke in patients with atrial fibrillation using aspirin compared with no therapy (RR: 0.66, 95% CI: 0.44-0.88).[85] Dual antiplatelet therapy with clopidogrel has seen mixed results.[4,86-88] The ACTIVE W Trial (The Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events) found that anticoagulant therapy was statistically superior to dual antiplatelet therapy with aspirin and clopidogrel in preventing ischemic stroke in patients with AF (RR: 0.56, 95% CI: 0.39-0.82).[87] Among patients deemed inappropriate for anticoagulation, another study found a decreased ischemic stroke risk (RR: 0.72, 95% CI: 0.61-0.85) but increased bleeding risk (RR: 1.50, 95% CI: 1.18-1.89) among dual platelet therapy users compared with aspirin alone. These findings suggest that risk for ischemic stroke should determine use of antiplatelet therapy, if any, but be balanced with bleeding risk.[4]

For patients at low risk of ischemic stroke, clinical guidelines recommend aspirin only or combination therapy with aspirin and clopidogrel rather than anticoagulation to balance risks of bleeding from anticoagulation.[4] More discussion in the choice of antiplatelet versus anticoagulant therapies will be discussed in upcoming sections.

2.2.5.2. Anticoagulation

Prior to late 2010, the only FDA-approved anticoagulant for the prevention of ischemic stroke in atrial fibrillation consisted of an oral vitamin K factor inhibitor (warfarin), which has served as the cornerstone therapy for years.

More recently, oral direct thrombin inhibitors and oral Factor Xa inhibitors have been studied and considered as possible alternatives.[45,89,90] The first seemingly viable alternative to warfarin was considered in the early 2000's but was subsequently revoked: ximelagatran, the first oral direct thrombin inhibitor, was studied into Phase III trials but was removed from consideration for FDA approval in 2006.[91,92] These Phase III RCTs suggested that ximelagatran was similarly efficacious to alternatives in preventing deep vein thrombosis[93,94] and non-inferior to warfarin for ischemic stroke prevention.[91,94] Ultimately, ximelagatran was withdrawn from the FDA approval process in 2006 following reports of hepatotoxicity and elevated liver enzymes in approximately 5-6% of patients.[95] The next viable oral direct thrombin inhibitor alternative to warfarin was FDA-approved in October 2010; dabigatran (Pradaxa™) will be discussed more thoroughly in subsequent sections.

Oral Factor Xa inhibitors have also been developed to prevent ischemic stroke in atrial fibrillation patients. Current FDA-approved therapies include rivaroxaban (approved Nov 2011) and apixaban (approved Dec 2012).[15,19] Edoxaban, a third Factor Xa inhibitor, is currently undergoing FDA-approval, and betrixaban is currently undergoing Phase III clinical trials.[96,97] RCTs and meta-analyses of RCTs have largely shown similar or better efficacy of these agents in preventing ischemic stroke in patients with AF compared with warfarin, but the extent of efficacy appears to differ somewhat across agents.[15,18,89,90,98-102] These agents have also generally been shown to lead to less or equal risk of bleeding compared with warfarin, but concerns have been raised about a potentially increased risk of gastrointestinal bleeding compared with

warfarin.[18,89,90,98-100] It is anticipated that the literature will continue to robustly evolve in this area. The evidence related to these therapies has currently been generally restricted to the randomized-controlled trial setting or meta-analyses of these RCTs; broad observational studies in real-world patients of these Factor Xa inhibitors have not yet been published

More discussion on warfarin and dabigatran will be provided in Section 2.2.6 "Specific Anticoagulants and Atrial Fibrillation". These therapies were the main focus of the dissertation as more longitudinal data were available on them.

2.2.5.3 Bleeding risk from use of antithrombotic therapies

When prescribing antithrombotic therapies for patients with AF, practitioners must weigh the risk of ischemic stroke with the risk of bleeding resulting from the therapies. Hemorrhagic and gastrointestinal bleeding are notable adverse effects from using antithrombotic pharmacotherapy for prevention of ischemic stroke.[84,103] Without using anticoagulants, the baseline risk of hemorrhagic stroke or bleeding in patients with atrial fibrillation has not been shown to be independently elevated compared with those without atrial fibrillation.[4] The risk of hemorrhagic stroke or bleeding while using warfarin and dabigatran will be further discussed in the following section examining pharmacotherapy in atrial fibrillation.

2.2.5.4 Tools to determine antithrombotic therapy

2.2.5.4.1 *Stroke clinical prediction risk scores*

In clinical practice, providers determine the need for anticoagulation for ischemic stroke prevention in atrial fibrillation through the use of clinical risk prediction scores.[4] The two most common ischemic stroke risk scores used in clinical practice are $CHADS_2$[104] and $CHAD_2S_2$-VASc[105] and are described in **Table 1**.[103]

Table 1. Stroke risk scores used in atrial fibrillation

Risk Score	Use	Characteristics	Points	Comment
$CHADS_2$	Stroke	C: Congestive Heart Failure	1	Maximum 6 points
		H: Hypertension above 140/90mmHg	1	
		A: Age ≥ 75 years	1	
		D: Diabetes Mellitus	1	
		S: Prior Stroke/TIA	2	
CHA_2DS_2-VASc	Stroke	C: Congestive Heart Failure	1	Maximum 9 points
		H: Hypertension above 140/90mmHg	1	
		A: Age ≥ 75 years	2	
		D: Diabetes Mellitus	1	
		S: Prior Stroke/TIA	2	
		V: Vascular disease	1	
		A: Age 65-74 years	1	
		Sc: Sex category (Gender)	1	

Of these, clinicians have most frequently used the $CHADS_2$ risk score to help select anticoagulation or antiplatelet therapy.[105,106] While the $CHADS_2$ score has been around for much longer, the CHA_2DS_2-VASc risk score is becoming more commonly used due to better stratification of low-risk patients and better predictive ability for thromboembolism.[105,107] European guidelines have recommended its use for the last few years, and the most recent US clinical guidelines from the American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) recommend the use of the CHA_2DS_2-VASc to estimate ischemic stroke risk.[5]

However, the $CHADS_2$ Score has been most frequently used in observational studies of medical claims, but the CHA_2DS_2-VASc has been increasingly validated in observational data.[108-110] For either score, anticoagulation therapy is recommended in patients with patients with a $CHADS_2$ or CHA_2DS_2-VASc score of 1 or greater and strongly recommended in patients with scores of 2 or greater. Of note, these clinical prediction scores have been validated in warfarin users; however, to our knowledge, neither score to date has been explicitly validated in users of newer anticoagulants.

2.2.5.4.2 *Bleeding clinical prediction risk scores*

When prescribing antithrombotic therapies, providers also need to consider the risk of bleeding in which clinical risk prediction scores are recommended.[4] Three major bleeding risk scores are used in for AF patients in clinical practice (HAS-BLED[111], HEMORR$_2$HAGES[103], and ATRIA[112]). These tools are described in **Table 2** below.[103]

Table 2. Bleeding risk scores used in atrial fibrillation

Risk Score	Use	Characteristics	Points	Comment
ATRIA	Bleeding	Anemia	3	Maximum 10 points
		Severe Renal Disease	3	
		Age ≥ 75 years	2	
		Any prior hemorrhage	1	
		Hypertension	1	
HAS-BLED	Bleeding	H: Hypertension	1	Maximum 9 points
		A: Abnormal Renal and liver function	1 or 2	
		S: Stroke	1	
		B: Bleeding	1	
		L: Labile INRs	1	
		E: Elderly (age > 65 yrs)	1	
		D: Drugs or alcohol	1 or 2	
HEMORR$_2$HAGES	Bleeding	H: Hepatic or renal disease	1	Maximum 11 points
		E: Ethanol abuse	1	
		M: Malignancy	1	
		O: Older age	1	
		R: Reduced platelet count or function	1	
		R: Re-bleeding risk (i.e., prior bleed)	2	
		A: Anemia	1	
		G: Genetic factors (CYP2C9 variant)	1	
		E: Excessive fall risk	1	
		S: Stroke	1	

Of the validated bleeding risk scores, the HAS-BLED score has been the most recommended in clinical guidelines; however, using the ATRIA score for observational studies in medical claims has been thought to be the most accurate, because some of the criteria in the HAS-BLED score cannot be directly or accurately measured in claims, such as labile INRs or drug/alcohol use.[107,113] Of note, these clinical prediction scores have been validated in a strictly warfarin-taking population.

Published literature suggests that combining a bleeding risk score with a stroke clinical prediction rule can help clinicians maximize the risk and benefit tradeoff of prescribing an anticoagulant versus an antiplatelet therapy in patients with atrial fibrillation.[103]

2.2.6. Specific Anticoagulants and Atrial Fibrillation

2.2.6.1. Warfarin: Uses, Efficacy, and Adverse Effects

2.2.6.1.1. *Uses*

Warfarin, an oral Vitamin K antagonist, is FDA-approved for prevention of ischemic stroke and venous thromboembolism.[73] Until very recently, ACC clinical guidelines favored the use of chronic warfarin for patients without mechanical heart valves (non-valvular AF) at moderate to high risk of stroke; however, more recent AHA/ACC/HRS clinical guidelines released in March 2014 have offered no major preference between warfarin and the other novel oral anticoagulants.[1,4,70,73]

To manage warfarin dosing, patients are monitored regularly in provider visits or self-monitoring using international normalized ratio (INR) tests, because warfarin has a narrow therapeutic index.[45,46] In non-valvular AF, patients receive titrated warfarin doses to a target INR of 2.0 to 3.0, monitored and adjusted through these INR tests.[45] When first beginning warfarin, patients generally start on doses of 5.0mg and increase or decrease doses as needed. INRs are generally monitored at least weekly during the initiation of therapy and are recommended to be conducted monthly once anticoagulation is stabilized.[45,46] The use of laboratory tests has historically been a drawback to using warfarin due to the added inconvenience to patients and costs to the health system, but is recommended for chronic therapy.[114]

2.2.6.1.2. *Efficacy and Effectiveness*

A wide body of literature is available on warfarin and its use in prevention of stroke in atrial fibrillation. Warfarin has a strong history of demonstrated effectiveness in ischemic stroke prevention.[115] Long-term anticoagulation therapy with warfarin has been shown to reduce the risk of ischemic stroke in patients with non-valvular AF in RCTs by up to 68%.[6,7,115,116] Meta-

analyses have suggested that the annual incidence of stroke or systemic embolism in AF patients using warfarin is approximately 1.66% (95% CI: 1.41-1.91).[9] However, the risk of ischemic stroke on warfarin can also vary based on underlying risk factors. Ischemic stroke risk has been shown to increase when taken in elderly patients, female patients, patients with a history of stroke, and newly-initiated users (e.g., patients never having taken vitamin K antagonists before).[9] Renal impairment (OR: 1.54, 95% CI: 1.30-1.81), previous aspirin use (OR: 1.19, 95% CI: 1.04-1.37), and higher $CHADS_2$ score (1.64, 95% CI: 1.18-2.27) are also associated with a higher risk of stroke on warfarin, even in more recent RCTs.[117]

Because warfarin has been available for decades, older RCTs were conducted when the quality of care for AF patients was worse. [9,32,117] In addition, the time in therapeutic range (TTR) has been shown to not only vary widely across clinical practice settings but also is strongly related to warfarin's effectiveness.[118,119] More recently, home monitoring for INRs has become available, further mudding the picture.[120] Thus, the debate regarding the effectiveness of warfarin continues and still remains relevant today.

2.2.6.1.3. *Adverse Effects*

Because of its narrow therapeutic index, warfarin has been linked with a number of adverse effects, the most serious being a high risk of bleeding. [45,46] An observational cohort of AF patients beginning warfarin found the rate of major hemorrhage was 7.2 years per 100 person-years (95% CI: 4.9-10.6) and rate of intracranial hemorrhage of 2.5% (95% CI: 1.1-4.7) among those newly initiating warfarin.[121] Anticoagulation therapy has been shown to increase the annual risk for intracranial bleeding by 0.2% to 0.3% in RCTs.[85] In particular, the first 90 days has been associated with a 3-fold increased risk of bleeding.[85] However, the study reporting this finding was conducted at a single site in specifically older adults, and the authors were

concerned that the bleeding risk may even have been underestimated.[121] Warfarin has also been linked to osteoporosis, purple toe syndrome, and warfarin necrosis.[73] Warfarin also has other drug-drug and drug-lab interactions, which lead to many additional adjusted dosing requirements.

2.2.6.2. Dabigatran: Uses, Efficacy, and Adverse Effects

2.2.6.2.1. *Uses*

Dabigatran, a direct thrombin inhibitor, has been FDA-approved since October 2010 for prevention of stroke and embolism in non-valvular atrial fibrillation and for venous thromboembolism prophylaxis.[122] Dabigatran has not been approved for any mechanical valve ischemic stroke prophylaxis. Importantly, patients with mechanical heart valves or significant mitral stenosis were excluded from RCTs used for FDA-approval, and a more recent study indicated dabigatran's increased risk of bleeding compared with warfarin patients with valvular AF.[123] In the US, the FDA approved two doses of dabigatran for the prevention of stroke in atrial fibrillation: 75mg twice daily and 150mg twice daily, while the 110mg dose was studied in RCTs.[19] The 75mg twice daily dose is specifically indicated for patients with renal impairment (CrCl <30mL/min). Notably, no RCTs have been done to study the 75mg dose.

2.2.6.2.2. *Efficacy and Effectiveness*

The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial has provided most of the current evidence surrounding the efficacy of dabigatran for ischemic stroke prevention in patients with AF. This study found a decreased risk of stroke or systemic embolism in patients using dabigatran 110mg or 150mg twice daily versus INR adjusted-dose warfarin.[13] In this study, the rates of stroke or systemic embolism varied from 1.7% in the warfarin group to

1.5% per year in the group receiving dabigatran 110mg (RR: 0.91, 95% CI: 0.74-1.11, p<0.001 for non-inferiority) and 1.1% per year in the group receiving 150mg dabigatran (RR: 0.66, 95% CI: 0.53-0.82, p<0.001 for superiority).[13]

Some sub-analyses of the overall RE-LY trial have also been published. One sub-analysis has found that the risk of ischemic stroke or systemic embolism was significantly higher in patients from Asian countries than from non-Asian countries, though geographic treatment variation is thought to have influenced these differences.[124] Another RE-LY sub-analysis of patients receiving concomitant anti-platelet therapy found that dabigatran was still non-inferior to warfarin in reducing ischemic stroke or systemic embolism, regardless of receipt of anti-platelet therapy.[88] Another third RE-LY sub-analysis following 5,851 patients who had not discontinued dabigatran (with no warfarin comparator) found approximately 1.5% and 1.6%/year rates of ischemic stroke or systemic embolism.[125] These findings were largely similar to the original RCT findings. Whether patients were adequately anticoagulated with warfarin (measured by time in the therapeutic range) in the RE-LY trial was also found to slightly influence the apparent efficacy of dabigatran.[14] Additional post-hoc analyses have been conducted on patients using anticoagulation for secondary prevention versus primary prevention and found similar findings. Overall, these sub-analyses have been useful at elucidating potential areas for further study, but are no substitution for large real-world studies. In addition, a number of meta-analyses summarizing the clinical trials have been published – many of them combining the novel oral anticoagulants together. These meta-analyses have largely found superiority of the novel oral anticoagulants but also caution about possible increased risk of myocardial infarction or gastrointestinal bleeding risk with dabigatran.[18,126,127]

To our knowledge, three observational studies to date have been published to begin to examine the effectiveness of dabigatran in preventing ischemic stroke in AF patients.[128] The

first, a cross-sectional study, followed 103 patients treated with dabigatran for at least 3 months at a single-center anticoagulation clinic without a comparator group. In this study, only 1 ischemic stroke was reported; the authors found no statistically significant difference between treatment-naïve patients and patients previously treated with warfarin. Of the 99 patients they had prescription fill records for, 12% of patients had inadequate adherence over the study period (defined as <80% adherence). The second study, a registry-based study of patients in Denmark, followed 4,978 dabigatran-treated patients against 8,936 propensity-score matched warfarin patients using time-to-event analysis.[129] This study found that while risk of stroke and systemic embolism was not statistically different between the two groups, mortality and risk of AMI was significantly lower in dabigatran patients. However, this study examined dabigatran at a dose of 110mg and 150mg, because the 75mg dose is not used in Europe. This study also exclusively followed new users of anticoagulants. The third study examined the medication adherence and the association between non-adherence to dabigatran and clinical outcomes in a cohort of 5,376 Veterans Affairs patients.[130] They found high medication adherence among this VA population (Mean proportion of days covered [PDC] 94%). Patients with low medication adherence (<80% PDC) were associated with an increased risk for all-cause mortality and stroke (HR: 1.13, 95% CI: 1.07-1.19) per 10% decrease in PDC, but adherence was not associated with increased risk of non-fatal bleeding or myocardial infarction.

In summary, dabigatran has shown relative improved efficacy over warfarin in randomized-controlled clinical trials, though the generalizability of the findings has been questioned, because of the narrow inclusion criteria used in the trials. Specifically, the population included in RE-LY tended to be younger and with fewer comorbidities than has been seen in previous observational studies examining warfarin use.[119,131] In addition, the RE-LY trial excluded patients with renal impairment or hepatic disease, which could be important sub-groups

to analyze in real-world settings. Lastly, patients who were non-adherent were excluded from RE-LY analyses. Using our knowledge about low medication adherence in actual clinical practice suggests that further observational research is continued to be needed.

2.2.6.2.3. *Adverse Effects*

While dabigatran has fewer monitoring requirements and easier dosing arrangements, its use has also been suggested to lead to higher risk of dyspepsia, potentially higher risk of bleeding, and myocardial infarction than warfarin.[19] Uncertainty also remains about its relative safety, because, unlike warfarin, dabigatran lacks a direct reversal agent in the event of bleeding complications, even though some are under development.[20]

Major randomized-controlled trials have shown that dabigatran is associated with decreased intracerebral hemorrhage (ICH) compared with warfarin whether or not patients have prior stroke/TIA and are using anticoagulation for secondary prevention.[13,132,133] The RE-LY trial found that major bleeding was 3.36% per year in the warfarin group compared with 2.71% per year in those receiving dabigatran 110mg ($p=0.003$) and 3.11% per year those receiving dabigatran 150mg ($p=0.31$).[13] In addition, the reported rate of hemorrhagic stroke was 0.38%, 0.12%, and 0.10% per year in the warfarin, dabigatran 110mg ($p<0.001$), and dabigatran 150mg ($p<0.001$) groups, respectively.[13] Mortality did not differ significantly between the groups.[13]

Other RE-LY sub-analyses and case reports have found an increased risk of bleeding in dabigatran, mainly in older adults.[19,42,134] Some RE-LY sub-analyses have found a slightly increased risk of bleeding on dabigatran versus warfarin, while others did not.[14,88,124,125] Case studies suggest that the risk of bleeding in dabigatran may be among those that did not appropriately receive renally-adjusted dosing or among older adults.[27,117,135-137] The FDA has reported a greater proportion of adverse events reported to their MEDWATCH program for

dabigatran than warfarin since dabigatran market entry[138]; however, a Mini-Sentinel analysis found in an unadjusted cohort of patients that the risk of bleeding was not significantly greater than warfarin.[26] Consensus opinion suggests that bleeding complications may be much more difficult to manage, and that those that occur may also be much more severe.[139] Another study examined 2,391 atrial fibrillation patients admitted with intracranial bleeding and their comparative risk of mortality among patients treated with dabigatran compared with warfarin using the TruvenHealth MarketScan® database.[140] They found similar in-hospital mortality and no differences in propensity-score adjusted risk ratios. Overall, much less is known about the comparative efficacy of dabigatran compared with warfarin in real-world use, and even more questions regarding dabigatran's comparative safety remain unanswered.[20]

Dabigatran used for the prevention of stroke in atrial fibrillation has also been thought to lead to increased risk of myocardial infarction, but data examining this outcome have been primarily aggregation of the large randomized, controlled trials.[99,141,142] In addition, the RE-LY trial also found significantly increased risk of dyspepsia-like symptoms compared with warfarin.[13] Sub-analyses have found that gastroesophageal reflux disease (GERD)-related non-bleeding adverse events occurred in 16.9% of those receiving dabigatran and 9.4% of those receiving warfarin (RR: 1.81 [95% CI: 1.66-1.97], $p<0.001$).[143] In this sub-analysis, discontinuation occurred in 4% of patients receiving warfarin due to non-bleeding adverse events.[143]

2.2.7. Guidelines for Anticoagulation in AF

Clinical guidelines recommend tailoring antithrombotic therapy to individual patient's risk of ischemic stroke and other side effects. The following sections discuss the recommended treatment algorithms in patients with AF with regard to antithrombotic therapy. While either

aspirin or warfarin have been shown to reduce stroke risk in patients with atrial fibrillation, warfarin is considered to be significantly more effective than aspirin, but carries increased risk of hemorrhage and other side effects.[3,45]

For either the $CHADS_2$ or the CHA_2DS_2-VASc, a risk score of 0 indicates a low risk of ischemic stroke, whereby no anticoagulation or aspirin use is suggested. A $CHADS_2$ risk score of 1 suggests a moderate risk of ischemic stroke, whereby either aspirin or anticoagulation are indicated based on patient preference.[104,105] A $CHADS_2$ risk score of 2 or greater suggests a moderate or high risk of stroke, whereby anticoagulation is warranted. Anticoagulation with a vitamin K antagonist is recommended for patients with at least 1 moderate risk factor, including age > 75 years, hypertension, heart failure, impaired left ventricular systolic function, and diabetes mellitus (e.g., $CHADS_2$ Score – see previous discussion on this topic).[104] Recently, the guidelines have incorporated equivalencies of the new oral anticoagulant (e.g., dabigatran) or well-controlled warfarin at INR 2.0-3.0 for risk scores of 1 or greater.[3,19,45]

As is discussed in the following sub-sections, the clinical guidelines by the various associations appear to have reached some degree of consensus. Generally, dabigatran is recommended as an alternative to warfarin for clinically-indicated patients, but these guidelines caution against its use in patients with renal impairment and advanced age. As this is a rapidly-growing area, other guidelines are possible, but the major relevant ones have been summarized below.

2.2.7.1. American College of Chest Physicians (ACCP) 2012 Guidelines Update

The American College of Chest Physicians in February 2012 summarized antithrombotic recommendations in a supplement to their 9th edition of clinical practice guidelines.[4] These recommendations for patients with non-valvular irreversible AF are summarized in **Table 3**.

These guidelines use the GRADE approach which classifies recommendations as strong (Grade 1) or weak (Grade 2) based on expert consensus about the overall risks and benefits of therapy.[144,145] The quality of the evidence is also synthesized into high (Grade A), moderate (Grade B), or low (Grade C) according to the overall validity and risk of bias inherent in the available studies.[144]

Notable changes to the ACCP guidelines include an active suggestion towards dabigatran 150mg twice daily rather than adjusted-dose warfarin therapy in patients with $CHADS_2 \geq 2$, but the evidence supporting this recommendation currently is considered to be "weak". In addition, at lower risk levels, other treatment decisions are considered on an individualized basis. All of these include patients with paroxysmal AF.

Table 3. American College of Chest Physicians 2012 Antithrombotic Guidelines Update

Recommendation	Grade
For patients with AF at low risk of stroke ($CHADS_2$: 0), no antithrombotic therapy recommended	2B
- If therapy chosen, aspirin 75mg or 325mg once daily recommended	2B
For patients with AF at intermediate risk of stroke ($CHADS_2$: 1), oral anticoagulation recommended rather than no therapy	1B
- Oral anticoagulation preferred over aspirin or aspirin + clopidogrel	2B
- If precautions against oral anticoagulation, then aspirin + clopidogrel	2B
For patients with AF at high risk of stroke ($CHADS_2$: 2), oral anticoagulation recommended rather than no therapy, or	1A
- Aspirin (75mg or 325mg), or	1B
- Aspirin + clopidogrel	1B
- If precautions against oral anticoagulation, then aspirin + clopidogrel	1B
For patients with AF with oral anticoagulation recommended, dabigatran 150mg twice daily recommended rather than adjusted-dose warfarin	2B
For patients with AF and stable coronary artery disease with oral anticoagulation recommended, adjusted dose warfarin alone rather than adjusted-dose warfarin + aspirin	2C

2.2.7.2. 2012 Focused Update: Recommendations for Prevention of Thromboembolism in Non-valvular AF[3]

The European Society of Cardiology (ESC) convened an update to practice guidelines for atrial fibrillation published in August 2012. Their recommendations related to dabigatran are summarized in **Table 4** below. These guidelines incorporated ratings using the Class and Level of Evidence (LOE) system. Class I indicates that good-quality RCTs are available. Lower levels (up to III) suggest that poor quality evidence is available (such as case series or other studies with no control group). The Level of Evidence ratings suggest how consistent the underlying studies are. Overall, these guidelines provided similar recommendations as the ACCP guidelines, based here on the CHA_2DS_2-VASc score. These guidelines seemed to suggest clinical equipoise between dabigatran and warfarin depending on various risk factors, but that further evidence would be needed to discern differences. These guidelines recommend that selection of therapy be based on risk factors, cost, tolerability, patient preference, drug-drug interactions, TTR, and other clinical risk factors.

Table 4. 2012 European Society of Cardiology (ESC) Focused Update

Recommendation	Class	Level of Evidence
Antithrombotic therapy to prevent thromboembolism is recommended for all patients with AF, except in those patients (both male and female) who are at low risk (aged < 65 years and lone AF) or with contraindications	I	A
In patients with a CHA_2DS_2-VASc score ≥2, OAC therapy with: - Adjusted-dose VKA (INR 2-3); or - A direct thrombin inhibitor (dabigatran); or - An oral factor Xa inhibitor (e.g., rivaroxaban, apixaban) … is recommended, unless contraindicated	I	A
In patients with a CHA_2DS_2-VASc score = 1, OAC therapy with: - Adjusted-dose VKA (INR 2-3); or - A direct thrombin inhibitor (dabigatran); or - An oral factor Xa inhibitor (e.g., rivaroxaban, apixaban) … should be considered, based upon an assessment of the risk of bleeding complications and patient preferences	IIa	A
When patients refuse the use of any OAC, antiplatelet therapy should be considered, using combination therapy with aspirin 75-100mg plus clopidogrel 75mg daily (where there is a low risk of bleeding), or, less effectively, aspirin 75-325mg daily	IIa	B

Abbreviations: AF, Atrial Fibrillation; OAC, Oral anticoagulant; VKA, Vitamin K Antagonist; INR, International Normalized Ratio

2.2.7.3. American Heart Association (AHA)/American Stroke Association (ASA) Science Advisory Committee 2012 recommendations

The AHA/ASA Science Advisory committee published recommendations even more recently than the ACCP guidelines in December 2012 using expert consensus. These guidelines suggested that selection of OACs should be individualized and based on risk factors, cost, tolerability, patient preference, drug interaction potential and INR time in the therapeutic range.[2] Notably, this committee also recommended that dabigatran 150mg twice daily is an efficacious alternative to warfarin (Class I; Level of Evidence (LOE) B). Dabigatran 75mg twice daily may be considered for patients with CrCl 15-30 ml/min but with a caution that safety and efficacy have not been established in renal-insufficient patients (Class IIb; LOE C). The committee did not, however, recommend dabigatran in patients with CrCl < 15ml/min (Class III; LOE C).

Their overall recommendations related to dabigatran are summarized in **Table 5** below. Prior to this update, these guidelines had previously separated out explicit recommendations

based on whether antithrombotic therapy is being used for primary versus secondary prevention of ischemic stroke. However, the committee has generally recommended dabigatran as an efficacious alternative to warfarin for both primary and secondary prevention in patients with at least a moderate risk of ischemic stroke but recommended caution in renal insufficiency.

Table 5. American Heart Association/American Stroke Association 2012 Guidelines Update

Recommendation	Class (LOE)
For prevention of first and recurrent stroke in patients with non-valvular AF, one of the following antithrombotic agents can be considered based on individualized factors:	
- Warfarin	I (A)
- Dabigatran	I (B)
- Rivaroxaban	IIa (B)
- Apixaban	I (B)
Dabigatran 150mg twice daily is an efficacious alternative to warfarin for prevention of first and recurrent stroke in patients with non-valvular AF and ≥1 other risk factor and CrCl >30mL/min	I (B)
Dabigatran 75mg twice daily may be considered for prevention of first and recurrent stroke in patients with non-valvular AF and and ≥1 other risk factor and CrCl 15-30mL/min	IIb (C)
Dabigatran is not recommended in patients with CrCl <15mL/min	III (C)

Abbreviations: LOE, Level of Evidence; AF, Atrial Fibrillation; CrCl, Creatinine clearance

2.2.7.4. American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Rhythm Society 2014 Guidelines

The AHA/ASA/HRS Science Advisory committee released recommendations in late March 2014 regarding the management of atrial fibrillation.[5] Similar to guidelines released in 2012, antithrombotic therapy is still recommended to be individualized based on shared decision-making and recommended for patients with high ischemic stroke risk. In this 2014 version, patients with non-valvular AF are recommended to use warfarin, dabigatran, rivaroxaban or apixaban, with no noted preference among the agents. However, again, patients with end-stage chronic kidney disease or on hemodialysis are not recommended to use one of the novel oral anticoagulants. The largest difference between these guidelines and previous guidelines are that the oral anticoagulants are considered as equal options in newly-initiating patients.

2.2.8. Other adjunctive therapies used in atrial fibrillation

Angiotensin-converting-enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and HMG Co-A-reductase inhibitors (statins) are also under investigation as adjunctive therapies to the 3-pronged approach in managing AF. ACEIs/ARBs have been thought to play a

potential role in decreasing both the incidence of AF and the rate of relapse following cardioversion in patients with AF. These drugs are hypothesized to work by reducing P-wave duration, but their overall primary use in AF is still being evaluated.[146] A recent meta-analysis found that ACEIs and ARBs significantly lowered the risk of incident AF compared with no use (OR: 0.65, 95% CI: 0.55-0.76).[146] Compared with non-users, users of ACEIs and ARBs were also found to have a significantly reduced recurrence of sinus rhythm disturbances (OR: 0.45, 95% CI: 0.31-0.65).[146] However, the included RCTs heavily relied on post-hoc analyses for their conclusions. Statins have also been thought to play a role in maintaining sinus rhythm in patients with persistent lone AF, but their role as a primary agent in AF is still being evaluated and only hypothesized in commentaries.[55] The literature examining the role of adjunctive therapies beyond the 3-pronged approach currently recommended is still evolving, and no strong recommendation for their uses in AF has been given.[55]

2.3. CLINICAL CONTROVERSIES

As previously discussed, dabigatran has shown similar efficacy in stroke prevention over warfarin in treatment naïve patients with AF in randomized-controlled clinical trials.[14-16] While dabigatran requires less frequent monitoring and may lead to decreased intracerebral hemorrhage, it may also lead to higher risk of dyspepsia, other types of bleeding, and myocardial infarction than warfarin.[19] In addition, dabigatran lacks a direct agent in the event of bleeding complications, which may decrease its overall safety.[20] This section explores the clinical controversies surrounding the use of warfarin and dabigatran and identifies the literature available in this area.

2.3.1. Warfarin: Clinical controversies

Despite warfarin's longevity on the market, some clinical controversies remain, especially around patient-centered outcomes and effectiveness. Long-term therapy with warfarin has been shown to decrease quality of life in patients with AF by as much as a mean 1.3% decrease in utility.[52,147] Other studies have also reported that some patients thought their quality of life would be increased with the use of aspirin versus oral anticoagulants.[52,148] In addition, the extent to which warfarin's effectiveness is affected by non-adherence and INR control is still not fully established.[119] INR control is directly related to the TTR for warfarin.[119,149] This issue is particularly important because patients' TTR has been shown to vary widely among warfarin users in not only observational studies but also Phase III RCTs examining the novel oral anticoagulants (NOACs) (including dabigatran).[14,15,118,150] Because TTR has been shown to be related to clinical effectiveness of warfarin, the adequacy of the comparator groups in these settings has been called into question.[14]

Research is also still examining rates and effects of warfarin initiation and discontinuation, despite indications for chronic use, especially given perceived risks of bleeding. Despite knowledge about its effectiveness, patients also have been shown to be fairly non-adherent with using warfarin.[151,152] In addition, research is still assessing long-term outcomes of warfarin use, even years after initiating therapy.[11,153 9]

2.3.2. Dabigatran: Clinical controversies

While the FDA-approved dabigatran at 75mg twice daily, this dose was not studied in Phase III clinical trials.[43] Instead, the RE-LY trial compared dose-adjusted warfarin against dabigatran 110mg (along with the FDA-approved dose of dabigatran 150mg). Other countries did, however, approve dabigatran at 110mg. The fact that dabigatran has not been studied at the

75mg dose has implications for patients, as much further study is warranted to ensure comparative effectiveness of dabigatran at that dose. The lack of current information about the dabigatran110mg dose has raised considerable controversy, underlying the need for observational studies to assess this dose.

There is also interest in the apparent effectiveness of dabigatran in patients with mild-moderate ischemic stroke – with a $CHADS_2$ or CHA_2DS_s-VASc score of 1. Previously, these patients would be treated with antiplatelet therapy. However, some commentaries suggest that dabigatran may be useful in these marginal patients – ones where the decision to anticoagulate had been primarily preference-driven prior to dabigatran's availability.[17,154] Thus, more research will be needed to resolve whether dabigatran can be used in a wider degree of patients than warfarin previously had been.

In addition, providers have raised some concerns regarding the apparent increased risk of bleeding on dabigatran. A recent theheart.org analysis surveyed physicians regarding their concerns of dabigatran use in AF patients.[155] On a scale of 1-6 (6 being very concerned), physicians were asked about intracranial hemorrhage, gastrointestinal (GI) bleeding and left atrial enlargement, renal dysfunction, and recurrent stroke yielding average ratings of 4.11, 4.07, 3.45, 4.04, and 3.85, respectively.[155] By comparison, physician asked about burden of INR monitoring, difficulty maintaining INR, managing multiple medications, side effects, quality of life and compliance in warfarin used yielded average ratings of 4.36, 4.22, 4.13, 4.13, 3.98, and 4.10, respectively.[155]

Management of dabigatran is simultaneously easier and more difficult. Currently, no laboratory monitoring for chronic therapy is recommended; INR testing is neither useful nor determinative.[156] Thrombin time and ecarin clotting time, directly measuring thrombin activity from the plasma, may be used to estimate anticoagulant effect in a concentration-dependent

linear relationship.[135,157] However, no studies have yet been conducted examining the real-world utility of these tests. The fixed-dosing arrangements of dabigatran have also been widely marketed as treatment advancement from INR dose-adjusted warfarin.

Moreover, in the event of over-anticoagulation (e.g., bleeding), no reversal agent exists to stop the bleeding, unlike warfarin whereby phytonadione (vitamin K), among others such as dialysis, factor, and fresh frozen plasma, can be used to reverse warfarin toxicity.[156,157] This lack of antidote for dabigatran has clinical implications, because while the drug is easier to take and easier to dose, adverse outcomes may be more difficult to manage, and costs of managing bleeding outcomes may be much higher than warfarin.[158] Current recommendations for treatment of bleeding include supportive care, activated prothrombin complex concentrate, activated factor VIIs, or dialysis.[19] A recent survey of 221 vascular neurologists found large variations in recommended treatment modalities for bleeding events on dabigatran among these providers.[157] Clearly, much more research is needed in this area as well.

2.3.3. Other controversies in choice of anticoagulation

While not the focus of this research, the use of dabigatran versus warfarin in the setting of catheter ablation is also undergoing strenuous evaluations. Even when undergoing catheter ablation, anticoagulation is still considered a recommended course of therapy as some patients may still experience inconsistent sinus rhythms. Currently, it is still not clear whether dabigatran is as safe and effective compared with warfarin during catheter ablation.[159] One case-control study examining the risk during radiofrequency catheter ablation found no significant difference in perioperative acute risk in terms of major and minor bleeding events.[160] Another study found a decreased risk in rebleeding occurring from dabigatran patients compared with warfarin (20% vs. 44%, p =0.01).[161]

Recent research has also uncovered the challenges of prescribing antithrombotic therapy in patients with new-onset acute myocardial infarction and previous anticoagulation therapy to prevent stroke. While long-term oral anticoagulation is important for the prevention of stroke in atrial fibrillation, the combination of warfarin and antiplatelet medications following AMI creates challenges for such patients. A sub-analysis of the RE-LY trial found that 38.4% of included patients received clopidogrel and aspirin simultaneously along with warfarin or dabigatran in the study.[88] Both doses of dabigatran studied (110mg and 150mg) were found to be non-inferior to warfarin in terms of stroke or systemic embolism risk regardless of platelet use.[88] Major bleeding was also similar to warfarin among those using concomitant antiplatelet therapies (HR: 0.80, 95% CI: 0.70-1.25). Dual antiplatelet therapy (clopidogrel + aspirin) increased the risk of bleeding as well (HR: 1.60, 95% CI: 1.42-1.82). Fewer than 50% of these patients have been shown to use warfarin at discharge, even with $CHADS_2$ greater than 2, and triple therapy (with antiplatelet medications) is used in only 14.6% of patients.[70] Literature has suggested a further research need in this area.

Because of the difficulty in attaining and maintaining an INR in the recommended therapeutic ranges in treatment with warfarin, pharmacogenetic testing for variants in the cytochrome P450 2C9 gene has been developed. Interindividual dose variability has been shown to derive from coding variations and polymorphisms on this gene.[10,162,163] While the uptake of the testing is still limited to some health settings, warfarin dosing can be affected by the results of the test.[164] The cost-effectiveness of the test in determining warfarin dosing has affected its uptake in clinical practice despite recommendations.[163] This potential for better identification of genetic differences in response to warfarin has relevance for comparisons to dabigatran, as researchers better understand idiosyncratic differences in response to warfarin dosing.

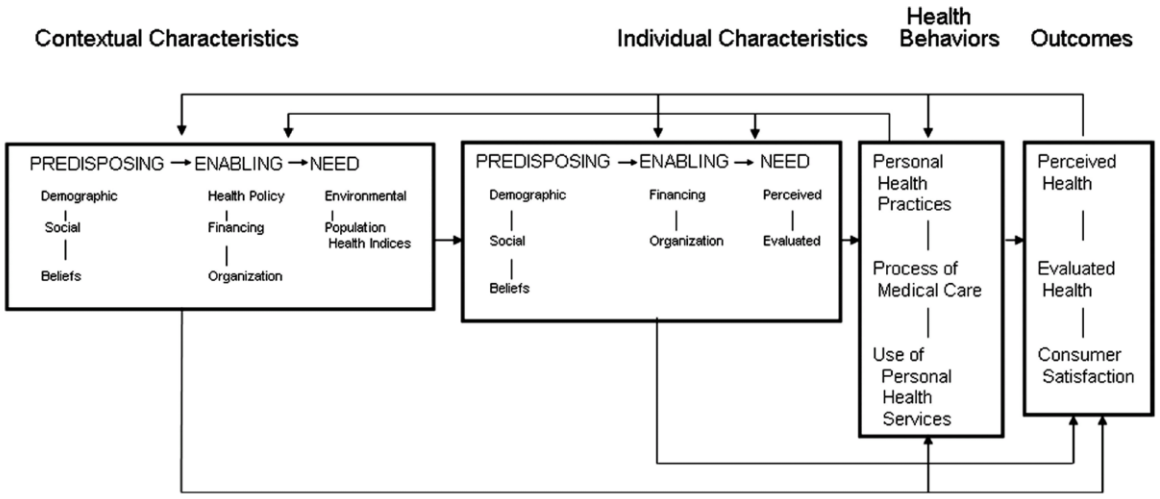
2.4. ISSUES IN USE OF ANTICOAGULATION IN REAL-WORLD PRACTICE

The previous section summarizes the published research examining clinical differences between anticoagulants under optimal clinical conditions. However, selection between available treatment options may also be influenced by additional factors frequently studied in health services research related to health behavior, patient/provider preferences, and willingness and ability to pay. Examining how these factors affect anticoagulant use and outcomes in the real-world is just as important as under optimal clinical conditions and settings to help improve evidence-based clinical practice. This section explores the research related to use of anticoagulants in the management of AF and related contexts.

2.4.1. Andersen's Behavioral Model of Health Services Use

The Andersen's Behavioral Model of Health Services Uses can be used to help illustrate factors associated with the use of anticoagulants in patients with atrial fibrillation. Briefly, the Andersen's Model describes multiple levels of factors that have been historically associated with use of health care services – individual, provider and health-system factors.[165] The first model, created in the 1960s, described that the use of health services is primarily driven by individual predisposition, factors that affect use, and need for the services.[166] More recent models have incorporated system factors that all influence health services, including processes of care and provider interactions as part of health behavior affecting service use.[165-167] More discussion on the Andersen's model and its application to this proposed research will be provided in Chapter 3. The most recent version of the Andersen model is displayed below in Figure 1.

Figure 1. Andersen's Behavioral Model of Health Services Use[166]



In **Figure 1** above, predisposing, enabling and need characteristics are illustrated on multiple levels, including contextual and individual. These factors influence health behaviors and ultimately outcomes, such as perceived health, evaluated (clinical) health, and satisfaction.[165-167] Predisposing demographic characteristics (e.g., age, gender) and social characteristics (e.g., education, race/ethnicity) occur on multiple levels as well. Enabling characteristics (e.g., financial, access to care) may also occur on multiple levels. Need characteristics often encompass both an individual's perceived and evaluated (clinical) need for services. In the setting of this dissertation, evaluated need will serve as the primary measurement for need factors. Because much contextual information is not available in the data source for the study, the dissertation focuses on those variables primarily describing the individual level. The Andersen's Model has also been successfully used in a number of settings examining factors associated with pharmaceutical use.[165] Chapter 3 illustrates the proposed adaption of the model for the dissertation, given the available data and ultimate study questions.

2.4.2. Real-world uptake of anticoagulation in AF

To examine factors associated with the use of anticoagulants, the overall uptake of anticoagulants also needs to be examined. Historically, utilization of anticoagulants in the setting of atrial fibrillation has been shown to be remarkably low, largely because of concerns over perceived risk of bleeding.[121,168,169] Before the introduction of direct thrombin inhibitors and Factor Xa antagonists, the use of warfarin in AF patients has ranged widely in observational studies (9.1%-79.8% across 28 studies; median=49.1%).[168] Other reviews suggest that of eligible patients without contraindications (as indicated by $CHADS_2$ score), only 15-44% are prescribed warfarin.[7] While over time utilization has increased, without alternatives to warfarin in patients with high $CHADS_2$ scores, patients with contraindications to warfarin may have gone undertreated.[95,168] One study found a strong correlation between proportion of patients using warfarin and the year the study was conducted, suggesting some increased initiation of warfarin over time ($r=0.60$; $p=0.002$).[168]

Despite being chronic therapy, discontinuation and medication non-adherence has also been high in patients treated with warfarin. In a population-based cohort of AF patients starting warfarin, 8.9% of patients did not fill a second prescription, 31.8% discontinued therapy within 1 year, and 61.3% discontinued therapy within 5 years with a median time to discontinuation of 2.9 years.[11]

The real-world uptake of dabigatran has been examined in a few, small studies. A study by Kirley et al in 2012 examining the proportion of office visits in the US in IMS Health data from 2007-2011 for AF resulting in anticoagulation prescriptions found that visits attributed to warfarin declined from 2.1 million in 2007 to 1.6 million in 2011.[170] The number of office visits resulting in a dabigatran prescription increased from 0.062 million in quarter 4 of 2010 to 0.363 million visits in quarter 4 of 2011 (3.1% to 18.9% share of visits resulting in oral anticoagulants).

However, the proportion of office visits resulting in warfarin decreased from 60.5% to 44.4% over the same interval. Pharmacy sales for dabigatran also increased from 0.8% to 8.1%. Despite the uptake of dabigatran, the treatment rates of high-risk patients still ranged from 20-80%, depending on the population under study.[170] A very recent study of Medco claims of 41,805 non-valvular patients indicated that patients using dabigatran were less likely to have comorbidities and higher ischemic stroke risk between patients initiating anticoagulation from Feb 2011 to April 2012.[40]

2.4.3. Factors associated with anticoagulant use

Factors associated with real-world use of dabigatran for the prevention of stroke in atrial fibrillation patients are still being elucidated. Characteristics of users of warfarin by comparison have been studied, but primarily in cohorts prior to the introduction of these novel oral anticoagulants though additional research is being released.[171] The Andersen's Behavioral Model of Health Services Use was used to help guide the factors examined for inclusion in the study, as will be described in Chapter 3. Because fewer health-system level factors can be directly measured in the insurance claims data used for the dissertation, the focus of this section is primarily on individual-level factors.

While the use of warfarin is part of the 3-pronged approach for ischemic stroke prevention in atrial fibrillation and overall use has been shown to be less than adequate, some contraindications to therapy do exist.[148,172] The initiation of anticoagulants often depends on precautions or relative contraindications to therapy (e.g., history of bleeding, alcohol use, dementia, falls, cancer or use of nonsteroidal anti-inflammatory medications).[116,172] The need predicted by the stroke prediction scale (e.g., $CHADS_2$ score) can also influence the decision of prescribing anticoagulation.[116,172] Of these factors in the $CHADS_2$ score, advanced age has been

repeatedly cited as one of the largest barriers to anticoagulation.[7,116] History of stroke has also been shown to better predict more aggressive and consistent anticoagulation.[173]

Previous research has also uncovered individual factors associated with the use of warfarin. A widely-cited chart review of 707 patients found that use of warfarin was significantly higher among patients who were younger, had prior stroke or TIA, and concomitantly used beta-blockers, ACEIs, or diuretics.[116] Those with lower activities of daily living or used aspirin were associated with a lower rate of warfarin use.[116] Other studies have corroborated the association of these factors with use of warfarin.[7,116,169,173] Patients with coronary artery disease also trended towards higher use of warfarin.[174] Patient geographic location has also been shown to influence anticoagulation, with patients in the South being shown to be less likely to receive warfarin than other geographic regions, even after adjusting for other measured covariates.[169,173]

Discontinuation after initiation has also been shown to depend on several factors. Younger adult men with lower stroke risk have also been shown to be more likely to discontinue warfarin therapy.[11] However, this study was conducted in Canada with a strictly older adult-based cohort where all patients had comprehensive drug coverage.

The type of physician has also been found to affect initiation of warfarin for anticoagulation.[169,175] Cardiologists or internists were more likely to prescribe anticoagulation compared with antiplatelet therapy (e.g., aspirin) for stroke prevention in atrial fibrillation compared with general and family practitioners.[173]

Only one study using IMS health physician-level data has examined provider-level factors in the use of dabigatran (or any other new anticoagulant since 2010). In the study by Kirley et al examining the proportion of office visits attributable to warfarin versus dabigatran, cardiologists were found to contribute to most of the uptake.[170] Additional literature on the provider-level factors associated with the use of the new anticoagulants is warranted.

2.4.4. Medication switching

2.4.4.1. Switching between generic and brand warfarin products

Because of warfarin's narrow therapeutic index, substitution of generic warfarin for brand warfarin (Coumadin®) clinically has been discouraged in clinical practice guidelines.[4,176] Previous research has largely found minimal effects of switching, but caution that additional monitoring is warranted. In particular, switching between warfarin products has been thought to lead to increased risk of bleeding and other adverse outcomes. Out of 265 patients, Milligan et al saw no statistically significant differences in adverse effects or bleeding between those who switched to generic warfarin from brand over a 1-year period.[177] In a multiple n-of-1 study between generic warfarin and Coumadin and vice versa over 30 weeks, Pereira et al saw no differences in mean INR or number of dosage adjustments required between groups.[33] In an observational study of 2,299 patients, the INR control changed by <10% in 28.0% of patients, where 33.1% experienced a 10% improvement in INR and 38.9% experienced INR control that worsened by greater than 10%. The study authors found these differences to be statistically significant but not clinically significant. A major meta-analysis found strong evidence of clinical equivalence between brand and generic warfarin formulations (5 of 5 RCTs) but did not comment on safety of switching.[25] Overall, switching between warfarin formulations is discouraged but still remains an area of study.

2.4.4.2. Switching between anticoagulants

Compared with switching between warfarin products, the published literature examining switching between warfarin and dabigatran (or any other new anticoagulant) is thin. Most of the literature in non-naïve patients exists solely in the setting of randomized-controlled trials. In the clinical trial RE-LY trial, 50% of the patients enrolled were "warfarin-experienced" resulting in a

0.40 reduction in ICH ($p \leq 0.001$).[13] However, the exact outcomes immediately following the switch to dabigatran were not elucidated.

Some recent literature is emerging via primary data collection methods. A recent study using patient-administered written surveys from Sept to Dec 2010 in one warfarin clinic in 155 chronically warfarin-treated patients studied willingness to switch from warfarin to dabigatran.[178] Of the examined factors, this study found that women were less willing to switch than men (44% vs. 69%, $p=0.003$) and that patients ≥ 70 years versus ≤ 70 years were less willing to switch (71% v. 51%, $p=0.017$).[178] Overall, the actual rate of switching and factors associated with switching have yet to be thoroughly examined empirically.

2.4.5. Concerns associated with newly-approved products

One final issue in examining factors associated with the use of dabigatran versus warfarin lies in the nature of dabigatran being a newly-approved product. Research has suggested that examining the effectiveness of newly-approved products may be difficult for a number of reasons. Some theorize that it may take up to 5-10 years for significant adverse effects to be identified in new drugs until a sufficient number of patients have encountered new medicines.[179] Phase II and III studies often do not have sufficient patients included with comorbidities and complexity of drug regimens that patients in real-world settings typically have; such patients are frequently excluded in clinical trials.[180] It is also difficult to mimic routine clinical care and study every relevant sub-group in head-to-head RCTs.[181] In addition, newly-diagnosed new users of medications may experience different harms and benefits than patients who have been previous users of alternative therapy options.[182]

Related to dabigatran specifically, commentaries examining the generalizability of the RE-LY trial have suggested that dabigatran may be less useful in patients previously stabilized

on warfarin (defined by a high TTR for the INRs).[182,183] Thus, examining the factors associated with patients who are switching from warfarin and the types of outcomes these patients may be experiencing has particular usefulness.

In addition, new pharmaceuticals are usually not adopted equally and universally. Diffusion of innovations theory suggests that a bell-curve distribution of users of a new medication may exist, whereby the innovators/early adopters, using the newer therapies first, may differ innately from those adopting later.[184,185] Moreover, new users of newly-approved products may also not be treatment naïve to other alternative therapies. These users may be those that previously failed these therapies and thus may be different than the ultimate users of medications.[122,186]

Lastly, the apparent comparative effectiveness has also been thought to be influenced by whether a pharmaceutical is newly-approved or not. Some patients with greater need for the new therapy may be treated preferentially upon release of a new pharmaceutical.[21,22] Said another way, sicker patients may be more likely to initiate therapy than healthier patients. Thus, observational studies of factors associated with uptake of dabigatran versus warfarin are needed. Examining the factors associated with the use of new therapies and how these change over time can help to inform future research in this area. This study seeks to advance knowledge in this area by incorporating these concerns about newly-approved products by examining outcomes among new users and switchers alike.

CHAPTER 3: RESEARCH METHODS

3.1. OVERVIEW OF RESEARCH DESIGN AND AIMS

The goal of this research is to investigate the factors associated with use and switching between anticoagulants, the comparative effectiveness and safety of initiating different anticoagulants, and the real-world clinical effects of switching anticoagulants in the setting of new market entry of dabigatran in practice. This chapter provides an overview of the analytic approaches that was used in this dissertation and a rationale for their uses. Details are provided for the conceptual and analytic frameworks used for the study, data sources, study design, measurements of variables, and statistical analyses to support the dissertation aims.

Analytically, Aim 1 consists of two sub-aims (hereafter labeled as Aim 1a and Aim 1b to distinguish the study designs). Aim 1a examined factors associated with new users of either warfarin or dabigatran post-dabigatran market entry (10/19/2010), and Aim 1b examined factors associated with use of dabigatran among new and previous users of warfarin after dabigatran entered the market. Aim 2 examined comparative clinical and safety outcomes among new users of warfarin and dabigatran post-dabigatran market entry. Aim 3 examined effectiveness and safety outcomes of switching therapy classes.

The proposed study employed a retrospective cohort design using health insurance claims. While randomized-controlled trials (RCTs) are considered to provide the highest-level of evidence, robust to many biases, employing an observational approach allows for the study of real-world use patterns and clinical effects. Due to costs associated with RCTs, sample sizes in

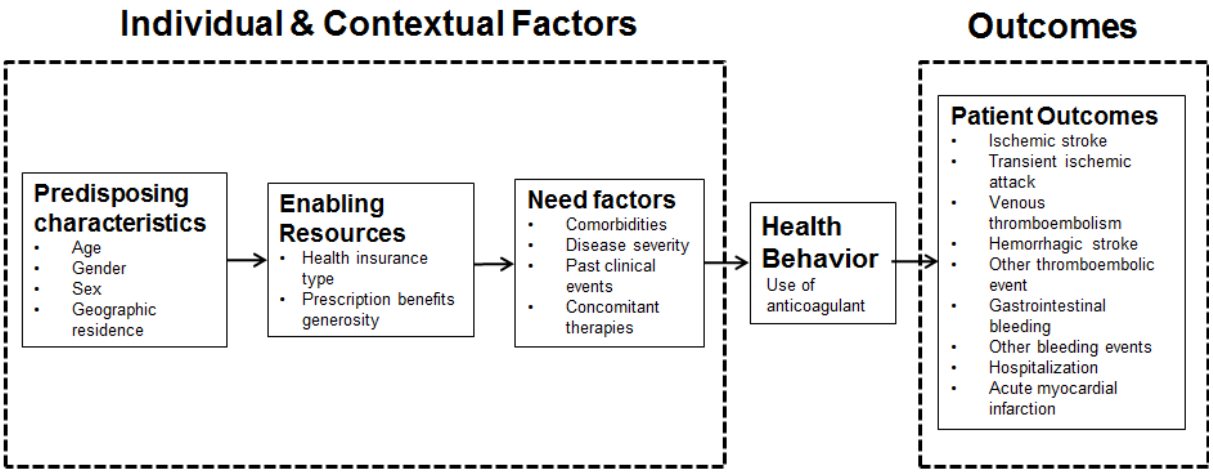
RCTs are often smaller. RCTs are typically more selective with a more homogenous patient population that may not well represent the patient population in clinical practice. Observational studies generally allow for the inclusion of more clinical comorbidities and diverse patient characteristics than RCTs.

3.2. RESEARCH FRAMEWORK

3.2.1. Conceptual Framework

A theoretical framework can be used to explain factors associated with patient outcomes in anticoagulation use for stroke prevention in atrial fibrillation. The Andersen's Behavioral Model of Health Services Use was used as the basis for the conceptual framework.[166] The Andersen's Behavioral Model identifies a 3-stage model where predisposing, enabling, and need characteristics underlie a patient's predisposition and use of health services, including medications.[165,166] The Andersen's Model has been frequently applied in the study of medication use and outcomes in other settings.[167,187,188] Applying the Andersen's Model in this setting helps to identify potential factors associated with anticoagulant use for atrial fibrillation. An application of the Andersen's model can be found in **Figure 2.** In this figure, factors were identified and classified into whether they are predisposing, enabling, or need characteristics affecting the type of medication used and their effects on outcomes. The factors and outcomes pictured in Figure 1 are available within the data source for the study.

Figure 2. Conceptual Framework



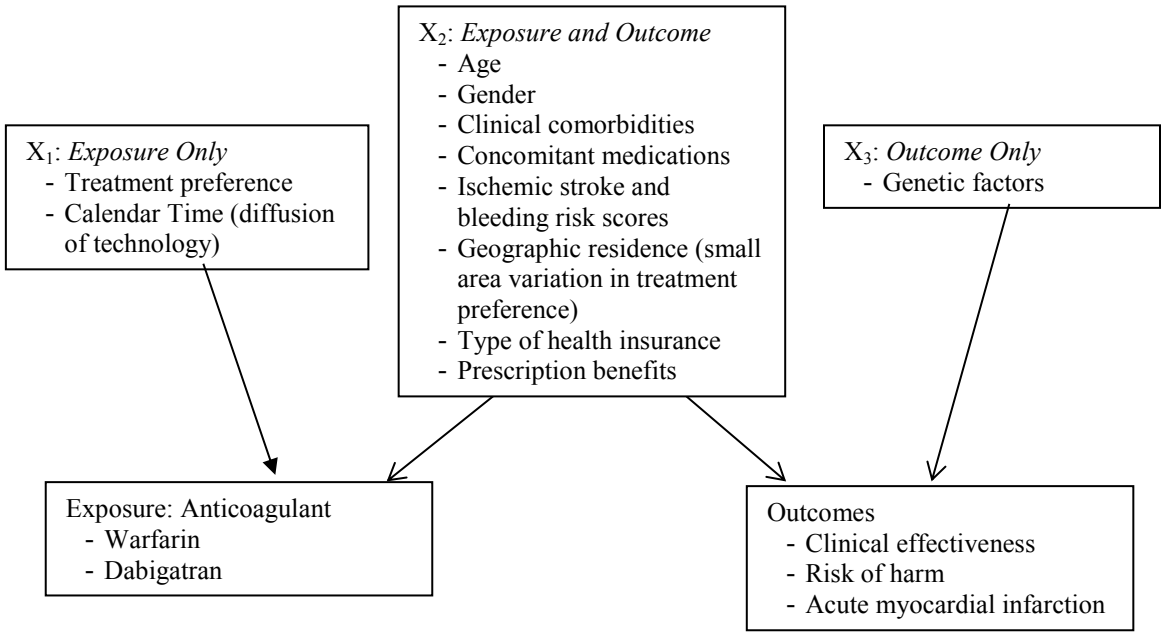
3.2.2. Analytic Diagram

Beyond the conceptual framework, an analytic diagram was used to categorize the factors from the conceptual framework into how they was analyzed as variables in the specific aims. The literature review from Chapter 2 was used to identify these covariates for the analytic diagram. The analytic diagram in **Figure 3** classifies factors identified in the literature review into those associated with: 1) the exposure (anticoagulation therapy), 2) the outcomes (e.g., ischemic stroke), and 3) both the exposure and outcomes (confounders). Some of these factors are measurable using the data source; other factors cannot be measured.

The purpose of the analytic diagram is to help distinguish true confounders from other factors. Confounders by definition are associated with both the exposure and the outcome and are not mediators between exposure and outcome but can lead to biased estimates when not controlled for. The X_1 variables are possible instrumental variables, which could be a potential method to address confounding in the study, but may not be able to be measured within the data[189-191]. In this situation, the X_3 variable would not be adjusted for in regression analyses, as adjustment for these could lead to bias but may influence precision of the estimates, but are not

available within the given data source of the Truven Health MarketScan Research Databases® anyway.[192] The X_2 variables are considered confounders and would be adjusted for in regression analyses.

Figure 3. Analytic Diagram



3.3. DATA SOURCE

The study used the TruvenHealth MarketScan® Commercial Claims and Encounters (CCAE) and Medicare Supplemental Databases from January 1, 2009 through December 31, 2012. These databases include annual information on approximately 30 million commercially-insured individuals and Medicare beneficiaries (with supplement coverage) in the US from over 100 nationwide insurers. These databases are considered to be nationally representative of commercially-insured patients in the United States.[193,194] Those Medicare Supplement enrollees in the database are those who receive employer-sponsored health insurance benefits and may be less generalizable to Medicare Part D beneficiaries on stand-alone plans. These data are also not generalizable to Medicaid patients, as those patients generally differ from those in commercially insured plans.

This proposed dissertation research used inpatient services files, outpatient services files, prescription claims files, laboratory files, and annual enrollment summary files. All files are linked by a unique but encrypted identifier for individual enrollees. The database also includes

the REDBOOK™ supplement, which provides drug name, therapeutic classification, pricing and product strength and dosage forms to identify drugs in the outpatient pharmaceutical claims files by national drug code (NDC). Inpatient services files include dates of admission and discharge, diagnoses and procedures, admission source, length of stay, and discharge destination for each individual. Outpatient services files include dates of service, procedures and diagnoses, and cost information for each individual patient encounter. Pharmaceutical claims files include each prescription filled by the patient, including dates of fill, type of medication, strength, dose, dosage form, quantity copay and coinsurance, and cost to the third-party payer. As with similar databases, no inpatient pharmaceutical claims history is available. Laboratory files are available on approximately 10% of patients in the MarketScan® datafiles. These tests are from the outpatient setting from one large national testing laboratory including dates of the tests, diagnosis, test result, and reference values.

All analyses and cohort selection were performed using SAS 9.3.

3.4. COHORT SELECTION

To address the aims of this project, two cohorts of samples were assembled: a new-user cohort since dabigatran market entry (10/19/2010) and a prevalent user cohort that also includes enrollees using warfarin prior to dabigatran market entry, with some additional restrictions. Published studies[11,30,151,173,195,196] and STrengthening the Reporting of Observational studies in Epidemiology (STROBE) guideline recommendations from an international collaborative of epidemiologists, statisticians, and researchers were used to guide the study design. [197,198] More information on the inclusion and exclusion criteria is provided in the next section.

3.4.1. Aims 1a and 2: Cohort design and identification

This section describes the specifications for the new user cohort that was used for Aims 1a, 2, and 3. By definition, new user designs for medication studies identify patients in the study population who are newly initiating therapy.[199] Generally, a wash-out period in retrospective studies is used to ensure that patients are in fact first beginning therapy after a specific date. Studying new users helps to control for other disease risk factors that may be altered by previous use of the study drugs and fully capture any adverse events that would occur early in therapy use.[199]

3.4.1.1 Inclusion criteria

For all the aims of the project, we selected a cohort of patients meeting the following inclusion criteria: 1) filling ≥ 1 prescription for warfarin or dabigatran after 10/19/2010 (dabigatran FDA approval date), hereafter referred to as the "*index prescription*" with the date of fill as the *index prescription fill date*; 2) ≥ 18 years of age at index prescription fill date; 3) receiving at least 1 inpatient or 2 outpatient International Classification of Diseases, 9th edition (ICD-9) codes for atrial fibrillation (AF) (ICD-9: 427.31) occurring on separate days in the 12 months on or prior to the index prescription fill date; and 4) maintained continuous enrollment for at least 12 months prior to the index prescription fill date. Of note, 1 outpatient ICD-9 AF code could occur after the index prescription fill date. We also required that the 2 ICD-9 codes occur on separate days to eliminate the possibility of using the code as a rule-out condition.

For Aims 1a, 2 and 3, a new user cohort of patients with AF was assembled. By definition of a new user cohort, participants were not included if they have had a warfarin or dabigatran fill in the previous 12 months prior to their index prescription fill date. Patients were also identified as "newly-diagnosed" new users if their first ICD-9 AF code occurred within 30

days prior to the index prescription fill date. For Aim 1b, a prevalent user cohort of AF patients was assembled from this larger cohort meeting the above inclusion criteria, but who are also previous users of warfarin. For Aim 1b, an additional restriction of continuous eligibility was also applied for this prevalent user cohort and for the new user cohort to examine switching the 12-month period following initiation. In addition, Aim 3 utilized the cohort from Aim 1a.

For both cohorts, patients were also required to be enrolled continuously in their insurance plan for at least 12 months prior to their index diagnosis date and up until the index prescription fill date in order to adequately capture baseline clinical characteristics and medication use history. As context, commercial insurance databases have an approximately 25-30% annual turnover in enrollees, with an average enrollment time of approximately 2 years.[200] We have found this statistic to be similar with Truven MarketScan® database.[201] Requiring 12 months of continuous enrollment, while common in these types of studies, may limit the patient sample.[200] However, the internal validity of the study is increased when using an adequate run-in period – both to ascertain that patients are new users and to better capture baseline characteristics.[200] New user study designs and similar inclusion criteria have been used previously when evaluating prescription claims data.[199,202]

3.4.1.2 Exclusion criteria

For the new user cohort used in Aims 1a, 2, and 3, patients were excluded from the study if they received any prior prescription for warfarin or dabigatran within the 12-month baseline period prior to the index date. Excluding these individuals by requiring a 12-month "clean" period of treatment-naïve individuals lowers the potential for including prevalent users.[199] Including a prevalent user population could lead to a potential induction of survivor bias, especially as the likelihood of switching between medications and adverse effects from switching

may vary over time.[199] However, events that occur before the 12-month inclusion period may be missing, because the 12-month look back period is not all-inclusive. For instance, patients with a warfarin prescription fill more than 12 months prior to the index diagnosis date would still be included in the inception cohort. This limitation, however, is common to other observational studies using a new user design.

Because dabigatran is only indicated in non-valvular AF, patients with ICD-9 codes corresponding to valvular and transient AF in the 12-month baseline period were excluded from the analysis to ensure that appropriate comparator groups were maintained.[13,203] These exclusions are similar to those applied in the RE-LY trial and have been applied previously.[13,201] These codes include ICD-9 codes for mitral valve replacement (35, 37, 35.1, 35.2, 35.9, 35.12, 35.23, 35.24, 35.9, 35.96, 35.97, 37.4, 37.35, 37.4, 37.41), heart valve replacement (V42.2, V43.3), mitral valve stenosis (394.0, 394.2, 396.0, 396.1, 396.8), atrial flutter (427.32), hyperthyroidism (242, 242.0, 242.1, 242.2, 242.3, 242.9), hepatic-related diagnosis (571.1, 571.3, 571.5, 571.8, 571.9, 572.8, 573.3, 573.9), vitamin K deficiency (269.0) and coagulation or antiphospholipid deficiencies (286.0-286.8, 286.52, 286.53, 286.59).

3.4.2. Aim 1b: Cohort design and identification

To examine the factors associated with switching between anticoagulants and clinical effects following switching, Aim 1b examined the 12-month period following the index prescription date (or the first prescription post-10/19/2010). As previously discussed, it is possible that the reasons for new users to initiate one therapy versus another may differ from those who have been previously using warfarin therapy, so first, a cohort of newly-initiating patients who were continuously enrolled for 12-months after the index prescription fill date was constructed for Aim 1b. Secondly, a prevalent user cohort was also created, whereby patients

were prevalent users of warfarin, having received at least prescription in the 12-month baseline period. Using this prevalent user design additionally allowed the inclusion of individuals who have previously used warfarin and examine whether certain characteristics over the 12-month baseline are more associated with switching to dabigatran.

Thus, for Aim 1b, with one exception, the same inclusion and exclusion criteria from the new user cohort for Aim 1a applied, including age ≥ 18 years, ≥1 inpatient or 2 outpatient AF diagnoses within the previous 12 months, no reversible AF condition, no warfarin prescription fill, and ≥12 months of continuous eligibility and prescription drug benefits in the previous 12 months. For the new user cohort for Aim 1b, patients were additionally excluded if they did not have continuous eligibility and prescription drug benefits through 12 months after the index anticoagulation date. For the prevalent user cohort, all of the aforementioned inclusion criteria applied, but patients were not excluded if they had a warfarin prescription fill in the 12-month baseline but they were excluded if they were not continuously enrolled through 12 months after their first anticoagulation date after 10/19/10.

3.4.3. Aim 3: Cohort design and identification

For Aim 3, two subcohorts were constructed from non-valvular AF patients using anticoagulation after 10/19/2010. The first primary cohort was constructed from newly-initiating patients who switched anticoagulation following the index prescription fill date using a time-varying method of anticoagulant switching to avoid immortal time bias.[204-206] In this main cohort, patients were selected if they met the Aim 1a cohort criteria (≥18 years of age, newly-initiating anticoagulation after 10/19/2010, having continuous eligibility and ≥1 inpatient or ≥2 outpatient diagnoses within the previous 12 months, at least one of which occurring before the index prescription fill date) and were followed to see if they switched anticoagulation.

In this time-varying analysis, all patients were considered non-switchers from the time of study entry until they lost continuous eligibility, experienced the study outcomes of interest (e.g., clinical effectiveness outcome, as described later), switched anticoagulants, or were censored administratively on 12/31/2012. This time was captured as "non-switcher" time; notably, if patients switched after they experienced a study outcome, they were censored and not included as "switchers". Patients who switched anticoagulants were measured for follow-up time as "switchers" then from the time of the switched until loss of continuous eligibility, administrative censoring, or experiencing the study outcome of interest. This time-varying exposure method (compared with time-fixed methodology) is designed to limit both confounding by indication and immortal time bias by adequately categorizing follow-up time from treatment initiation. As described later, patients who experienced a clinical effectiveness outcome were not censored in the analyses for either the harm outcome composite or acute myocardial infarction outcome, either before or after an anticoagulant switch.

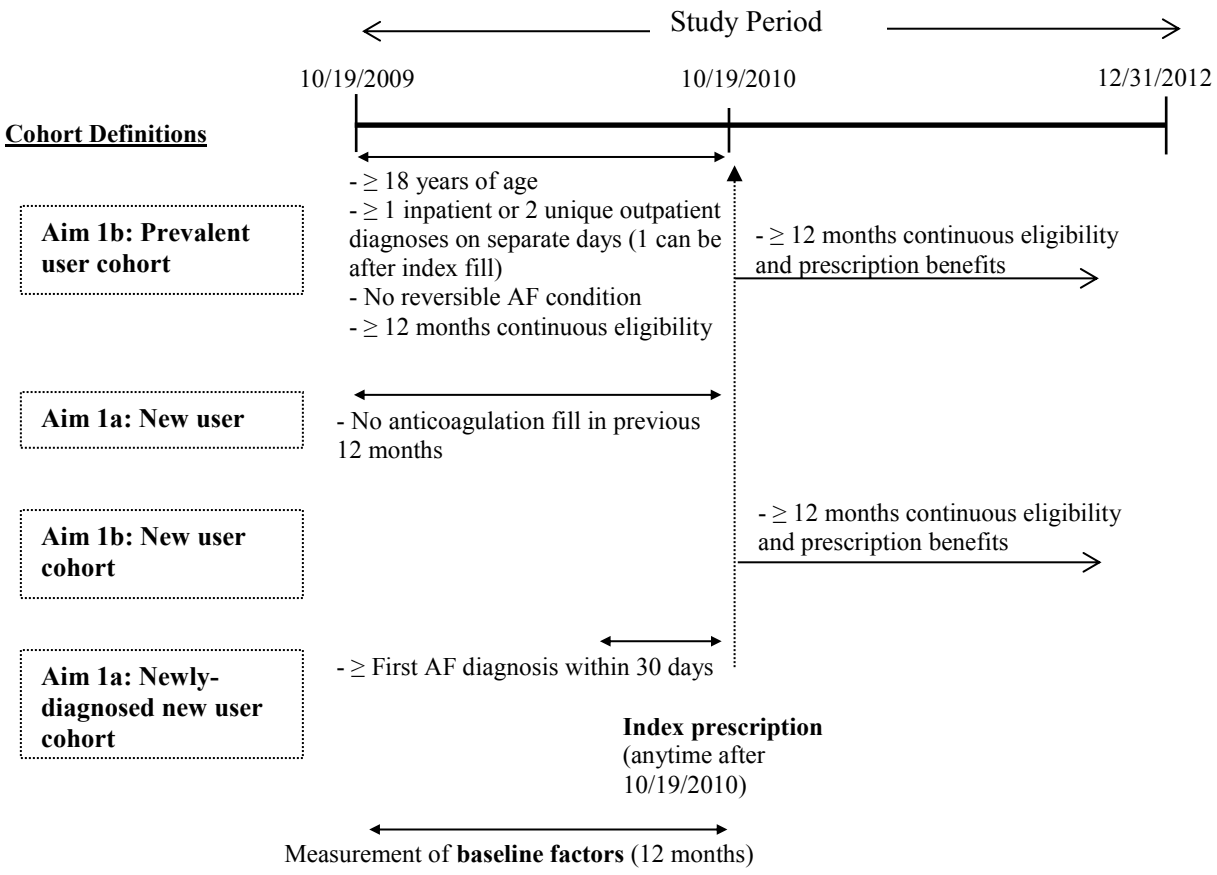
3.4.4. Study Schematic

Figure 4 below illustrates the proposed study schematic for the cohorts. Aims 1a and 1b utilized a retrospective cohort study design to determine factors associated with the anticoagulants' use. Aims 2 and 3 examined comparative clinical and safety outcomes among users of warfarin and dabigatran post-dabigatran market entry using the cohorts assembled for Aim 1a and 1b with the few differences in cohort construction noted above. For Aims 2, patients were followed from the index medication date until either: 1) outcome; 2) loss of continuous eligibility; or 3) end of the administrative period. Aim 3 examined effectiveness and safety outcomes of switching anticoagulants compared with non-switchers using two different methods. For the primary analysis, patients were followed from the index prescription fill date until either:

1) switch; 2) outcome of interest; 3) loss of continuous eligibility; or 4) end of the administrative period. Patients who switched were then followed until one of the following: 1) outcome of interest; 2) loss of continuous eligibility; or 3) end of the administrative period.

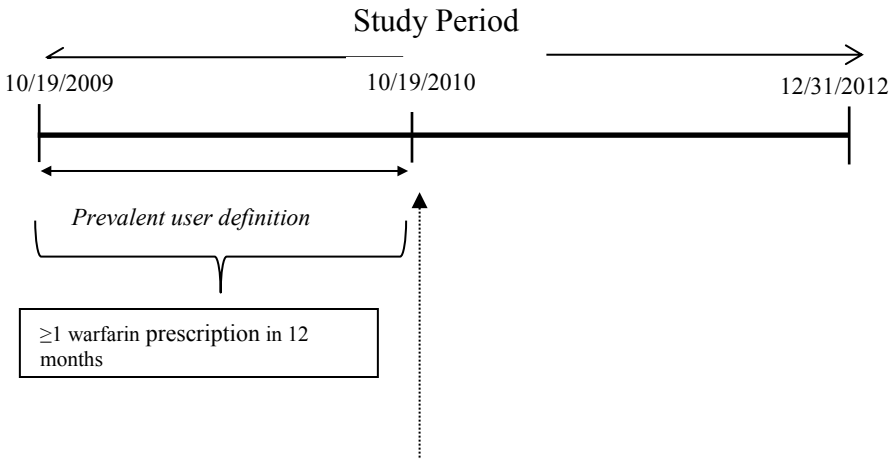
Figure 4. Study Schematic: New User Cohort

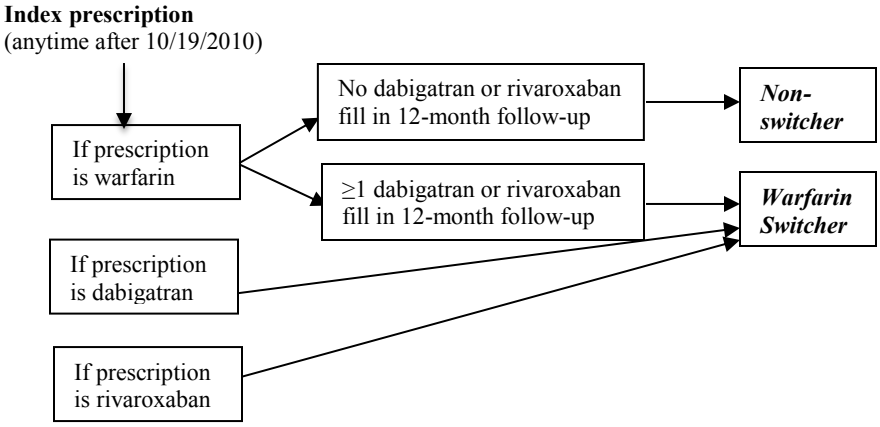
a. <u>Aim 1a and 1b: New User and Switcher Cohorts</u>



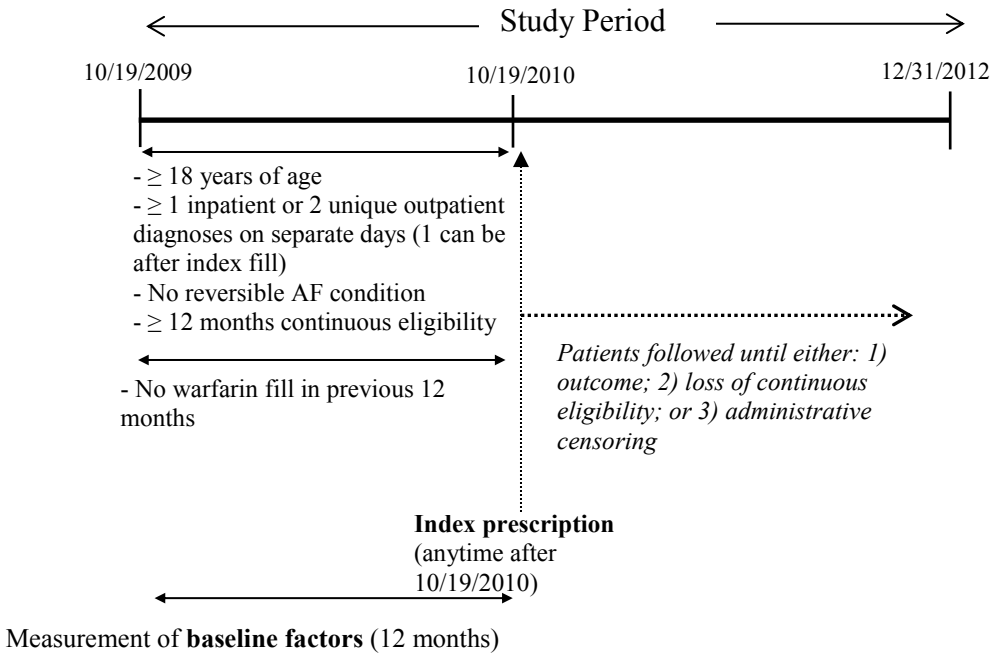
Note: New User and Newly-diagnosed New User Cohorts did not require 12-months of continuous eligibility after index prescription date

b. <u>Aim 1b. Switching definition for prevalent user cohort</u>

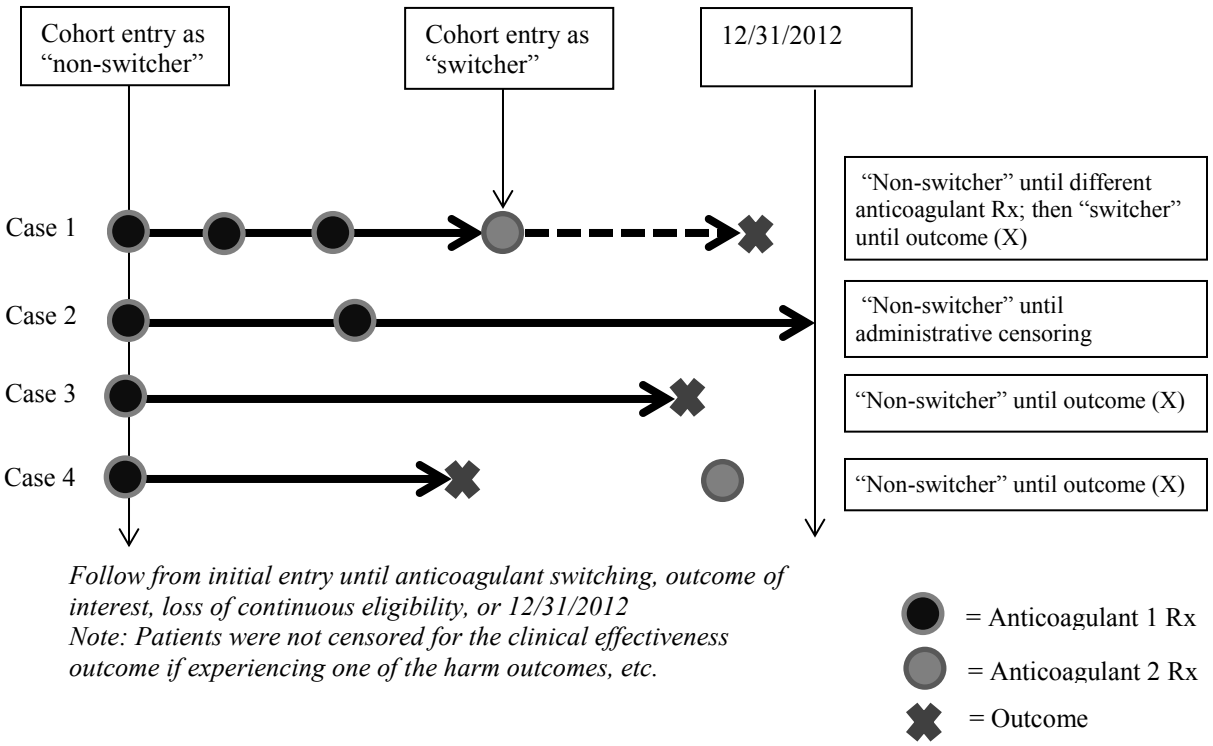




c. <u>Aim 2: New User Cohort: CER</u>



d. <u>Aim 3: Anticoagulant switchers versus non-switchers (primary analysis)</u>



Follow from initial entry until anticoagulant switching, outcome of interest, loss of continuous eligibility, or 12/31/2012
Note: Patients were not censored for the clinical effectiveness outcome if experiencing one of the harm outcomes, etc.

3.4.4. Sample size

The TruvenHealth MarketScan® research database provides information on more than 30 million individuals.[193,194] Sample size calculations were based on the narrowly-defined new user cohort used for Aim 1a and Aim 2. Based on preliminary sample size selection in the 1% sample, the database was anticipated to provide sufficient power for studying the aims. We anticipated the ability to reach this level based on the dataset. From Oct 2010 until Dec 2012, 64,935 new users of warfarin and dabigatran meeting the inclusion criteria were identified in the 100% sample. Given parameters (80% power, 2-tail 0.05 significance level) and event rates from published RCTs, the relationship between the effect size and sample size was estimated using Proc Power in SAS and displayed in **Table 6**.

Table 6. Sample size calculations

Power = 80% and alpha = 0.05 (two-tailed)										
Outcomes	Reference 12-month event-free rate	**Hazard Ratio**								
		Total N needed	1.40	1.35	1.30	1.25	1.20	1.15	1.10	1.05
Stroke (TIA or ischemic)	0.95[7]	N	4,516	5,774	7,688	10,822	16,526	28,694	**63,022**	245,934
VTE	0.93[6]	N	3,234	4,132	5,502	7,744	11,822	20,520	**45,060**	175,792
Effectiveness Composite	0.88[6]	N	1,898	2,424	3,226	4,536	6,922	12,008	**26,350**	102,732
Intracranial hemorrhage	0.99[207]	N	22,480	28,748	38,292	**53,936**	82,392	143,130	314,516	1,227,960
Gastrointestinal hemorrhage	0.95[131]	N	4,516	5,774	7,688	10,822	16,526	28,694	**63,022**	245,934
Other bleeding events	0.96[208]	N	5,640	7,210	9,600	13,518	20,642	**35,846**	78,740	307,310
Harm Composite	0.78[131]	N	1,048	1,338	1,778	2,498	3,806	6,594	14,450	**56,254**
AMI	0.86[72]	N	1,600	2,082	2,770	3,896	5,942	10,306	**22,610**	88,122

Abbreviation: TIA: transient ischemic attack; VTE, venuous thromboembolism; AMI, Acute Myocardial Infarction

The possible hazard ratios comparing warfarin versus dabigatran are displayed in Table 6 with corresponding sample sizes required to note a statistically significant difference. These power calculations also assume approximately equal sample sizes in each of the new user groups. As the table illustrates, this total sample size should have had the power to detect at least a 10% relative risk difference for the clinical effectiveness and harm outcomes composites and the acute myocardial infarction endpoints between warfarin and dabigatran. This relative risk difference is generally considered to be clinically significant.

3.5. MEASUREMENTS

3.5.1. Treatments

Treatment was determined using National Drug Codes (NDC) codes from the outpatient pharmaceutical files. Patients were classified by the type of medication used initially following

the diagnosis date, with either warfarin or Coumadin® use classified as 'warfarin' and fills for dabigatran being classified as dabigatran users. Prescription refill records are often considered the 'gold-standard' for measuring medication use and have demonstrated similar sensitivity and specificity as other observational adherence methods, including pill counts, self-report and electronic records.[209,210] Prescription fill information was also measured, including anticoagulant strength/dose, quantity and days' supply information. Other medications were measured as indicated in the Covariates section, including copay costs.

3.5.2. Outcomes

3.5.2.1 Medication Switching

For Aim 1b, as indicated in Figure 4, a medication switch was defined as the first prescription claim for a different anticoagulant (e.g., warfarin, dabigatran or rivaroxaban) in the outpatient pharmaceutical claims file within the 12 months following the index prescription fill date. This date was referred to as the *medication switch date*. The anticoagulant that the index medication was switched to was also reported. Prescription claims for warfarin and Coumadin® were classified as the same pharmaceutical product for this research. Individuals without a medication switch throughout the entire follow-up period were classified as *non-switchers*.

For Aim 3, as indicated in Figure 4, a medication switch was defined as the first prescription claim for a different anticoagulant (e.g., warfarin or dabigatran) in the outpatient pharmaceutical claims files. If patients were not previously administratively censored, lost continuous eligibility, or experienced a study outcome and then received a prescription for a different anticoagulant, this date is heretofore referred to as the *medication switch date.* Patients switching from warfarin or dabigatran to rivaroxaban were not included in the main analysis.

3.5.2.2 Clinical Effectiveness

Clinical effectiveness was defined as a composite of the occurrence of ischemic stroke, TIA, and other thromboembolic events in the follow-up period. The presence of either a primary or secondary diagnosis using ICD-9 coding in the inpatient or outpatient medical claims was used. Validated ICD-9 coding algorithms were used to measure the outcome events for clinical effectiveness, which are based on published studies found in the literature.[104,211-214] **Table 7** displays the ICD-9 coding schema used to identify clinical effectiveness outcomes; these algorithms are discussed further in the following sections. Patients with previous ischemic stroke were not excluded from the analysis; of note, previous stroke history was adjusted for in the regression analyses.

Table 7. International Classification of Disease, 9th Edition (ICD-9) codes for clinical effectiveness outcome definitions in inpatient and outpatient service claims files

Outcome	ICD-9 Codes	Diagnosis position*
Stroke		
Ischemic stroke Transient ischemic attack	433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434 (excluding 434.x0), 436 435	Primary or Secondary Primary*
Other thromboembolic event (deep vein thrombosis, pulmonary embolism)	415, 451, 453	Primary or Secondary

* Inpatient service claims files only

3.5.2.3 Risk of Harm

The risk of harm is defined as a composite of the occurrence of severe adverse side effects from the use of anticoagulant therapies. The severe adverse side effects was the presence of a primary or secondary diagnosis of intracranial hemorrhage/hemorrhagic stroke, gastrointestinal hemorrhage, other bleeding events, and inpatient hospitalization in the inpatient or outpatient medical files in the follow-up period. Validated ICD-9 coding algorithms from the published literature were used to measure these outcomes. **Table 8** displays the ICD-9 codes used for the risk of harm outcomes; these algorithms are discussed further in the following sections.

Table 8. International Classification of Disease, 9th Edition (ICD-9) codes for risk of harm outcome definitions in outpatient or inpatient service claims files

Outcome	ICD-9 Codes	Diagnosis field position
Intracranial hemorrhage or hemorrhagic stroke	430, 431, 432	Primary or Secondary
Gastrointestinal hemorrhage	455.2, 455.5, 455.8, 456.0, 456.20, 459.0, 578	Any
Other bleeding events	423.0 (hemopericardium), 593.81 (vascular disorders of kidney), 599.7 (hematuria), 719.11 (hemarthrosis), 784.7 (epistaxis), 784.8 (hemorrhage from throat), 786.3 (hemoptysis)	Any
Hospitalization in the follow-up	-	Any encounter in inpatient services files
Measured separately for Aims 2 and 3		
Myocardial infarction[§]	410.x1	Primary or Secondary*

* Inpatient service claims files only
[§] Not included in risk of harm composite outcome

3.5.2.4. Myocardial Infarction

Notably, AMI was measured as an outcome for the study. However, because of how the RE-LY trial collated its outcomes, was not included in either the individual risk of effectiveness or risk of harm composites, but is listed in Table 8. AMI has been thought to be both a "harm" outcome, in that the RE-LY trial showed a slight increase in the risk of AMI compared with warfarin (with an unknown pathophysiology); however, ischemic stroke and AMI frequently co-occur in patients, and warfarin has been used to anticoagulant in patients with AMI.

3.5.2.5. Algorithms to identify outcomes

Tables 7 and 8 illustrate the ICD-9 codes used for the clinical effectiveness outcome and harm outcome definitions in Aims 2 and 3. Each of these clinical effectiveness outcomes was identified using ICD-9 codes in the inpatient or outpatient service claims files unless otherwise

specified; specific diagnosis field position requirements are listed in the table. Outcomes were assessed based on the presence of medical or inpatient claims with either a primary or secondary diagnosis. For Aim 1b, these outcomes were measured as independent variables to be tested for an association with a medication switch. For Aims 2 and 3, these outcomes were considered dependent variables in the comparative effectiveness and safety analyses among new users.

All these ICD-9 codes have been validated and/or used frequently in the published literature (when validation studies not available). Each of these outcomes was identified in inpatient or outpatient service claims files; specific diagnosis field position requirements are listed in Tables 7 and 8.

While a variety of algorithms have been studied to identify these outcomes using ICD-9 codes, some have better reported correlation with clinical records. Usually ICD-9 diagnostic measures are compared using positive predictive value (PPV), which is the proportion of positive tests that are true positives; the higher the PPV, the higher the probability that a positive test indicates the underlying disease condition. Validated algorithms identifying ischemic stroke have generally performed well, resulting in positive predictive values of 85% of higher.[211,215-218] Some algorithms in a recent systematic review recommended also including transient ischemic attack (TIAs) as part of the composite endpoint, shorter ischemic strokes of less severe nature, as long as they were identified in the inpatient file only in the principal position.[211,219] TIA tended to have lower PPV than ischemic stroke algorithms.[211] Studies comparing algorithms using the primary diagnosis code versus the secondary code found slightly higher PPV for algorithms using primary versus secondary, but others have recommended both positions.[211,216] In studying thromboembolic events, the highest PPV has been reported for the combined use of ICD-9 codes 415 (pulmonary embolism), 451, and 453 (deep vein thrombosis) for identifying a VTE event, with a PPV of 65 to 95% in either the primary or secondary diagnostic field.[64,214] Studies have

also recommended studying VTE events in tandem in ICD-9 algorithms compared with either DVT or PE alone.[64,214]

Compared with the clinical effectiveness outcomes, comparably fewer validation studies have been conducted on risk of harm outcomes.[211,215,220] Validation studies examining the identification of intracranial hemorrhage (including intracerebral hemorrhage and subarachnoid hemorrhage) through ICD-9 codes have reported PPVs of 77% or higher compared with abstraction of medical charts, in both the inpatient and outpatient setting.[211,215] The reported PPVs ranged from 80% to 94% for patients with a primary or secondary discharge diagnosis; one study examining codes in any position of the inpatient file still reported a high PPV for intracranial bleeds.[211,215,221] Other bleeding events validation studies are even less frequently studied in the literature.[211] Because these conditions are less likely to present as the primary or secondary diagnoses (and more likely to be less severe), these conditions were identified by diagnosis codes used from previous studies using any diagnosis field position in either the outpatient or inpatient service claims files. In addition, because of limitations with how the coding schemes for intracranial hemorrhage and hemorrhagic stroke overlap in clinical practice, these outcomes were combined together.

Acute myocardial infarction, by comparison, is generally considered to be a relatively well-validated outcome. Previously-validated algorithms for identifying AMI have yielded PPV of 89% to 97% when using 410.x1 in the primary or secondary discharge field.[220,222]

Sensitivity analyses were also conducted on this outcome definition, specifically restricting to only outcomes that occurred in the inpatient setting, which would help examine the comparative effectiveness of the agents on clinically-significant events.

3.5.3. Covariates

Several covariates have been identified from the predisposing characteristics, enabling resources, and need characteristics from the previously-described analytic model. The Truven Health MarketScan® database dictionary and user guide were used to identify the variables which were available. The covariates used in the analysis are frequently used in the published literature in this field of research.[11,13,174,202,223,224] These covariates thought to be predictive of the outcomes in this study were included in the analytic models, described in later sections. These covariates were measured in the 12-month baseline period prior to the medication fill under study for that aim using published algorithms. For Aims 1a, 1b, 2, and the primary analysis for Aim 3, these covariates were measured in the 12 months prior to the index prescription fill date. These definitions are summarized in **Table 9** below.

Table 9. Covariate descriptions and coding strategies for patient characteristics in 12-month baseline period

Patient Characteristics	Covariate Coding	Covariate Definition
Predisposing Characteristics		
Age at Diagnosis	Continuous; Categorical (<55 years, 55-64 years, 65-74 years, >74 years)	Age in years at time of prescription fill
Sex	1=Male, 2=Female	Sex from enrollment file
Geographic Region	Northeast, North central, West, South	Region from enrollment file
Enabling Resources		
Insurance Type	Comprehensive, HMO, POS, PPO, CDHP	Type of insurance from enrollment file
Prescription benefits generosity	None, Poor, Fair, Good	Ratio of patient cost-sharing for prescription payments relative to total payments for prescriptions
Index prescription generosity *(measured descriptively not as covariate)*	None, Poor, Fair, Good	Ratio of patient cost-sharing for index anticoagulation prescription(s), relative to total payments
Need Characteristics		
Comorbidities		
Previous ischemic stroke	0=Absent, 1=Present	Ischemic stroke diagnosis
Renal Impairment	0=Absent, 1=Present	Chronic kidney disease or End Stage Renal Disease diagnosis
Congestive Heart Failure	0=Absent, 1=Present	Congestive heart failure diagnosis
Previous venous thromboembolism (VTE)	0=Absent, 1=Present	VTE diagnosis
Hyperlipidemia	0=Absent, 1=Present	Hyperlipidemia diagnosis
Hypertension	0=Absent, 1=Present	Hypertension diagnosis
Diabetes Mellitus	0=Absent, 1=Present	Diabetes Mellitus diagnosis
Previous myocardial infarction	0=Absent, 1=Present	Myocardial infarction diagnosis
Coronary artery disease	0=Absent, 1=Present	Coronary artery disease diagnosis
Previous major bleeding	0=Absent, 1=Present	Diagnosis of hemorrhagic or gastrointestinal bleeding
Anemia	0=Absent, 1=Present	Diagnosis of anemia
Peptic Ulcer disease	0=Absent, 1=Present	Diagnosis of peptic ulcer disease
Peripheral vascular disease	0=Absent, 1=Present	Diagnosis of peripheral vascular disease
Sleep apnea	0=Absent, 1=Present	Diagnosis of sleep apnea
Cognitive impairment	0=Absent, 1=Present	Diagnosis of dementia, Alzheimer's
Patient Disease Severity		
Charlson Comorbidity Index (CCI)	Continuous, Categorical (0, 1-2, 3-5, 6-8, ≥9)	Patient disease severity
$CHADS_2$	Continuous, Categorical (0, 1, ≥2)	Ischemic Stroke Risk score
CHA_2DS_2-VASc	Continuous, Categorical (0, 1, ≥2)	Ischemic Stroke Risk score
ATRIA	Continuous, Categorical (0-3, 4, ≥5)	Bleeding Risk score
HAS-BLED	Continuous, Categorical (0-2, ≥3)	Bleeding Risk score

Number of hospitalizations	Continuous, Categorical (0, ≥1)	Number of hospitalizations in baseline
Concomitant treatments and therapies		
Antiplatelet therapy	0=Non-use, 1=Use	Prescription fill for clopidogrel, Aggrenox or aspirin
Gastroprotective agents	0=Non-use, 1=Use	Prescription fill for PPIs, H_2RAs, GI protectants (e.g., sucralfate)
Antiarrhythmics	0=Non-use, 1=Use	Prescription fill for flecainide, amiodarone, dronedarone, sotalol, propafenone and dofetilide
Rate control therapy	0=Non-use, 1=Use	Prescription fill for beta-blockers, digoxin, or calcium channel blocker
Catheter ablation	0=No CA, 1=CA	Procedure for catheter ablation
Hormone use	0=Non-use, 1=Use	Prescription fill for oral contraceptive or hormone replacement therapy
ACEI/ARB therapy	0=Non-use, 1=Use	Prescription fill for ACEI/ARB
Statin therapy	0=Non-use, 1=Use	Prescription fill for HMG Co-A-reductase (statin)

Abbreviations: HMO, Health Maintenance Organization, POS, Point-of-service; PPO, Preferred provider organization; CDHP, consumer-driven health plan , PPI, proton pump inhibitor; H_2RA, H_2 receptor antagonist; GI, gastrointestinal; CA, catheter ablation; ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker

3.5.3.1 Patient characteristics

Clinical and demographic characteristics and their coding strategies can be found in Table 9 based on whether they can be classified as predisposing, enabling or need characteristics. Based on the literature, all of these clinical and demographic characteristics were considered to be X_2 covariate variables (identified by the analytic framework) and are displayed by type of characteristic from the conceptual model.

3.5.3.1.1 *Predisposing characteristics*

Available predisposing characteristics, such as age, gender, type of health plan, and geographic location was included as covariates in the 12-month baseline period prior to the index prescription fill date. Sex was coded as “male” or “female”. Geographic region was coded from the “Region” variable in the database, which is based on the employee residence at the time of

the index prescription fill. Previous research in a variety of disease has indicated that patient geographic residence is associated with varying quality of health care received. Controlling for broad geographic regions can help adjust for these variations in care received prior to AF diagnosis to help identify true clinical differences between anticoagulants. Northeast was used as the reference category. Per the TruvenHealth MarketScan® user guide, as of 2011, the 3-digit zip code field throughout the enrollment, inpatient and outpatient files, and pharmaceutical files is no longer supported and has been removed due to data quality issues. Thus, the most granular geographic variable available is the variable indicating the patient's state.

3.5.3.1.2 *Enabling characteristics*

Enabling factors were measured based on information available in the databases. Type of insurance was classified based on the "Plan Indicator" variable in the database, as follows: comprehensive, health maintenance organization (HMO), non-capitated point-of-service (POS), preferred provider organization (PPO), and other (basic/major medical, exclusive provider organization, capitated or partially-capitated point-of-service and consumer-driven health plans). Prescription benefits generosity was calculated from the method described by Artz *et al*[225], which sums the enrollee's cost-sharing contributions for all prescription drugs divided by the total net prescription drug payments (including brand and generic products), because the overall copayment burden may influence medication preferences and a patient's predisposition towards a certain therapy. This prescription benefits generosity measure would not include the study anticoagulant. If a patient has no record of any prescription fill prior to the anticoagulation in the 12-month baseline period, they were coded with a 'missing' value. The ratio was initially categorized into four levels: None (ratio > 0.99), Poor (ratio > 0.80 and ≤ 0.99), Fair (ratio > 0.20 and ≤ 0.80) and Good (ratio ≥ 0 and ≤ 0.20).

The patient's index anticoagulation copay cost and relative cost-sharing proportion compared with the amount paid by the insurer was also measured and categorized using the method by Artz et al described above.[225] Multiple anticoagulation fills may have occurred on the same day (e.g., multiple strengths of warfarin), and these were summed together. These two covariates were examined descriptively and not included in regression analyses.

3.5.3.1.3 *Need characteristics*

Need characteristics included patient baseline comorbidities, patient disease severity, risk of ischemic stroke and bleeding from disease severity measures, and concomitant medications thought to be associated with prognosis in atrial fibrillation. These factors were previously described in Chapter 2. Patient disease severity coding schemes have been published previously, along with diagnosis field code positions.[103,105,111,202]

The Charlson Comorbidity Index (CCI) is a commonly-used composite measure of disease burden which serves as a proxy for patient health status; the higher the score, the greater the comorbidity burden.[226,227] The CCI algorithm using ICD-9 codes has been previously published in a variety of settings and was employed to garner patient baseline disease burden.[28,226,227] The CCI was measured from the 12-month baseline period. In addition, all factors related to adverse outcomes from the medication use were also measured following the index prescription fill date until the medication switch date. These were classified as covariates for Aims 1b and 3 for adjustment in the switcher analysis as previously discussed.

Risk of ischemic stroke was measured using both the $CHADS_2$ and CHA_2DS_2-VASc risk scores while risk of bleeding was measured using the ATRIA and HAS-BLED risk scores. As previously discussed in Chapter 2, ATRIA risk factors are currently considered to be more reliably measured in medical claims compared with other severity indices. As of March 2014,

CHA_2DS_2-VASc score has been recommended for use in the United States over the $CHADS_2$ score.[5] In addition, the HAS-BLED risk score was measured as a sensitivity analysis as it includes additional risk factors beyond the ATRIA and has been more commonly used in observational studies using secondary claims. All of these risk scores were also assessed descriptively.

3.6. ANALYSES

This is a retrospective observational cohort study studying factors associated with use, clinical effectiveness and safety following anticoagulation with either warfarin or dabigatran. For these analyses for all aims, commercially-insured patients were also analyzed separately from the Medicare Supplement patients as a sensitivity analysis, because these patients could have different clinical and demographic backgrounds.[37,193] The following sections detailed the analyses plan for each specific aim.

3.6.2. Aim 1

Specific Aim #1: Assess and investigate patient factors associated with new use of either warfarin or dabigatran and switching between anticoagulants in patients with atrial fibrillation.

Hypothesis 1: Clinical prediction risk scores (e.g., ischemic stroke and bleeding risk) will not differ between new users of warfarin compared with dabigatran.

Hypothesis 2: Clinical prediction risk scores (e.g., ischemic stroke and bleeding risk) will not differ between new users who switch anticoagulants within 12 months compared with those who do not switch.

Analytic model:

Equation 1
Anticoagulant treatment $= \alpha + \beta_1(X_1) + \beta_x(X_l) + \varepsilon$
α = Intercept
β_x = Regression coefficient for X_1
X_l = Independent variable (a risk score)
β_x = Vector of all measured variable coefficients for the X
X_l = Vector of all other measured baseline covariates
ε = Error term

3.6.2.2 Statistical analysis and model diagnostics

As previously described, Aim 1 was analytically structured into two sub-aims: Aim 1a and Aim 1b. Aim 1a assessed factors associated with new use of either warfarin or dabigatran; Aim 1b assessed factors associated with switching from the index anticoagulant following dabigatran market entry. Both sub-aims used the ischemic stroke and bleeding risk scores as primary independent variables for the analysis. Even though these sub-aims involved the separation of cohorts (new user and prevalent user), the statistical analysis of the factors associated with the anticoagulant use is the same.

The number and proportion of patients initiating each medication was described. Descriptive statistics of initiation by medication (Aim 1a) and switches (Aim 1b), including direction (Aim 1b) were presented for each major demographic and clinical characteristic across the entire study period, including the absolute standardized differences between the proportions. The time between the index medication and the medication switch date was measured and reported descriptively

For Aim 1a, the anticoagulation doses and patient cost-sharing (e.g., copayments) at the time of the index prescription were also presented for the doses used in clinical practice and assessed descriptively. Time trends in initiation of the index anticoagulation medication were also examined.

Each covariate was tested separately to determine the bivariate relationship between the predictor and the outcome, without controlling for the other covariates. Multivariable modified Poisson regression models were also applied to investigate the initiation and switch of warfarin and dabigatran for new AF patients with each variable added to the model simultaneously to examine the independent effects of each covariate.

While binary outcomes (e.g., warfarin vs. dabigatran) are often analyzed using logistic regression models to obtain odds ratios for characteristics between two treatment groups, estimating relative risks (RRs) can be more preferable.[228] RRs tend to be more interpretable than odds ratios, especially in commonly-occurring events (such as the anticoagulants each being used frequently in new users, which is suggested by the 100% sample).[229] Relative risk estimation via a modified Poisson approach (using robust error variances) was used to compare characteristics of the comparator groups (using Proc Genmod and a repeated statement in SAS), which lead to direct RRs.[230] By contrast, log-binomial models assume that the probability of an outcome increases linearly on the log scale, while logistic regression models assume that the probability of an outcome increases linearly on the logit scale, which can lead to differences in the predicted probabilities between the two models, especially when the outcome is common.[228] Even compared with the log-binomial model (also yields relative risks using a log scale), the modified Poisson approach avoids the possibility of too narrow confidence intervals and convergence issues and may be a better fit for these data for this aim.

For Aim 1a, the association between new use of each medication and the baseline characteristics was tested using bivariate and multivariate regression to estimate the likelihood of receipt of warfarin versus dabigatran, studying ischemic stroke and bleeding risk clinical prediction scores as the main independent variables. For Aim 1b, the association between switching from the index anticoagulant compared with not switching was assessed using

bivariate and multivariate regression to estimate the likelihood of switching using the clinical prediction scores as the main independent variables. The multivariable regression models included each of the predictors previously described, except for those already included in the risk scores. The general form of the model for Aims 1a and 1b is provided in Equation 1 above. For Aim 1a, sensitivity analyses were conducted on each of the ischemic stroke and bleeding risk clinical prediction scores (e.g., ATRIA versus HAS-BLED).

For Aim 1a, the Quasilikelihood under the Independence model Criterion (QIC) was also used for model comparisons and model selection. Interaction terms were also examined for potential inclusion in the multivariate model to determine any variation in *a priori* determined possible relationships, including age and sex. Upon examining for this effect measure modification, if the interactions are not significant, then they are deemed unnecessary as they would add no additional explanatory power to the model. These tests were conducted to help choose the overall model.

3.6.3. Aim 2

Specific Aim #2: Investigate the comparative clinical outcomes (risk of harm and clinical effectiveness) following new use of either warfarin or dabigatran, adjusting for baseline patient factors.

3.6.3.1 Hypothesis

Hypothesis 3: There are no significant differences in the risk of clinical effectiveness outcomes or harm outcomes in new users of warfarin compared with users of dabigatran.

Statistical model:

Equation 2
$h_i(t_i x_i) = h_0(t) * exp(\beta_T T_i + \beta_x X_i)$,
t = survival time (in days) from the index date to event or censoring
T_i = Treatment (1=dabigatran; 0=warfarin)
X_i = Vector of all measured baseline covariate confounders
β_T= Coefficient of X_1, the change in survival time
β_x = Vector of coefficients of X_i

3.6.3.2 Statistical analysis and model diagnostics

As previously summarized, Aim 2 tests the comparative effectiveness and safety of warfarin versus dabigatran in AF patients initiating anticoagulation in an intention-to-treat analysis. Aim 2 used the same cohort specified in Aim 1a and followed individuals until either one of the composite outcomes was observed or loss of continuous eligibility or the end of the administrative period at 12/31/2012 occurred, using an intention to treat (ITT) perspective.[231] In ITT analysis, every individual beginning warfarin or dabigatran therapy is assigned to that therapy for the analysis, regardless of potential non-adherence, withdrawal or anything else that occurs following the first prescription fill.[231]

Descriptive statistics were generated including the outcome rates per 1,000 person years in each anticoagulant group, the time to the composite outcome events, and the proportion of patients censored. Cox proportional hazard models were also used to estimate the relationship between anticoagulant use and being event-free after controlling for confounders.[232] Cox proportional hazards methods use a semi-parametric model that accounts for multiple predictor variables and provide partial likelihood estimation of experiencing an event by factoring out the baseline hazard of experiencing an event from the covariates. The general form of the model is provided in **Equation 2** above. In this equation, β represents the effect of the exposure on the hazard of experiencing the outcome.[232,233]

Cox models assume that covariates are independent of time and that hazards are proportional across strata of the variable and constant over time, in the event of time-varying covariates. Nested and non-nested models were tested for the AIC to select covariates for the final models. Deviance residuals were used to plot model fit and assess functional form. Ties were assessed using Efron's method, where ties are those instances where two or more patients have the same study time. Additionally, the proportional hazard assumption (in that covariates are multiplicatively related to the baseline hazard and that time does not change this relationship) was assessed using Schoenfeld residuals, supremum tests, Kaplan-Meier plots, and interaction terms with time. Outcomes of anticoagulation were first regressed in the Cox models as the only independent variable (unadjusted model) to examine the effect of the additionally measured covariates added to the multivariable models.

These Cox methods all assume that the patients are independently grouped and that the data do not derive from the same unit or cluster (e.g., are not grouped hierarchically under providers). Other studies using these databases have assumed independence of observations and given the vastness of the database and high prevalence of the condition, we assume that clustering is not common and negligible.

Separate multivariable Cox proportional hazards models were also constructed for a composite of measures of risk (e.g., hemorrhagic bleeding, major bleeding, etc.) and a composite of measures of effectiveness (e.g., ischemic stroke, etc.).[233,234] Cause-specific Cox proportional hazards models were also conducted on each of the clinical effectiveness and risk of harm outcomes, whereby patients were censored at the time one of the other events occurred. Typically, composite measures are used as primary analysis to avoid issues of competing risk.[235] However, as a secondary analysis, cause-specific models were used. As with Aims 1a and 1b, interaction terms were evaluated for inclusion in the final regression models.

3.6.3.3. Propensity Score Risk Adjustment

Risk adjustment methods through multivariate regression, while useful, may not be sufficient when the potential for unmeasured confounding or confounding by indication exists.[236] Because individuals are not randomly selected to receive a specific treatment in this study, endogeneity (selection bias) between treatment and outcomes may exist. In addition, risk adjustment methods assume that all confounders are either measured or that unmeasured confounders are "ignorable" if other measured confounders are controlled.

Propensity score (PS) methods attempt to control for lack of randomization in observational studies by balancing covariate distributions between treatment groups.[237,238] Estimates of the average treatment effect in the treated group can be obtained by PS matching between two comparable groups, such that pairs are formed and these matched individuals have similar values of the PS. Other options involving propensity scores are including the PS as a covariate in multivariable regression models, stratification, or using weighting through inverse-probability treatment weighting (IPTW) or standardized mortality ratios (SMR) weighting from an estimated propensity score in a regression model.

In particular, the PS method proposed in this research employed IPTW as a primary analysis. Specifically, IPTW uses propensity score weights to create a study sample whereby the distribution of measured baseline characteristics does not depend on treatment. In IPTW, each subject's weight is equal to the inverse of the probability of receiving that particular treatment. Regression models can be weighted by the inverse probability of treatment to estimate the average treatment effect of receiving the treatment. Because weights may be unstable for individuals with very low probabilities of receiving treatment, stabilizing weights and 'trimming' subjects are methods often used and were examined here.

For Aim 2, propensity score-adjusted hazard ratios were presented for the Cox proportional hazard models. For this study, IPTW was used as the primary analysis rather than matching on subjects, so as to preserve sample size. These propensity scores were fit by a logistic regression model to predict treatment with the use of the measured covariates. These propensity score models included confounder variables.[237,238] Stabilizing weights and trimming of subjects were used depending on the need when the weights are created.[239] SMR weighting was also used as a secondary analysis, which provides estimates of the treatment effect in the treated group.

These propensity scores were first used to investigate the balance in the treatment groups of patients initiating treatment since market entry. Propensity scores were constructed comparing the baseline characteristics of the new anticoagulant initiators. These propensity scores were used to examine overlap in the distribution of baseline and clinical covariates of users initiating warfarin and dabigatran occurs. The absolute standardized difference was also used to compare the baseline characteristics between warfarin and dabigatran users, whereby significant imbalance of baseline characteristics between groups is usually characterized by an absolute standardized difference > 10.[240] Secondly, the models used IPTW from the propensity scores as a weight in the Cox proportional hazards models to estimate the comparative effect of warfarin versus dabigatran, adjusting for any covariate imbalances. The IPTW propensity score deciles were examined for any underlying heterogeneity of treatment effect in a sensitivity analysis.

3.6.4. Aim 3

Specific Aim #3: Explore the comparative clinical outcomes (risk of harm and clinical effectiveness) of switching from warfarin to dabigatran or dabigatran to warfarin compared with non-switchers, adjusting for patient clinical and demographic factors.

3.6.4.1 Hypotheses

Hypothesis 4: Switching from warfarin to dabigatran will not be associated with increased risk of harm or clinical effectiveness outcomes compared with those who switch remain on warfarin.

Hypothesis 5: Switching from dabigatran to warfarin will not be associated with an increased risk of harm or clinical effectiveness outcomes compared with those who remain on dabigatran.

3.6.4.2 Statistical analysis and model

Statistical model:

Equation 3

$$h_i(t_i x_i) = h_0(t) * exp(\beta_T T_i + \beta_x X_i),$$

t = survival time (in days) from the switch date to event or censoring
T_i = Treatment (1=switcher; 0=non-switcher)
X_i = Vector of all measured baseline covariate confounders
β_T= Coefficient of X_1, the change in survival time
β_x = Vector of coefficients of X_i

Equation 3 illustrates the statistical model for this aim. For the primary analysis, warfarin switchers were compared with non-switchers, and dabigatran switchers were compared with non-switchers. Descriptive statistics were generated including the outcome rates per 1,000 patient years, the proportion of patients censored, and the time to each event. For both analyses, Cox proportional hazards regression was used to assess the association with treatment and outcomes. Equation 3 and Aim 2 describe the general model and the diagnostic approach for assessing Cox proportional hazards models. These models were adjusted using the covariates identified in Table 9 using the previously-described diagnostic steps. The dependent variable for each model was time to outcome event. In the primary analysis, patient days of follow-up were classified as "non-switcher" time until the anticoagulant switch date occurred (or until experiencing the outcome of interest or censoring due to loss-to-follow-up or administratively on 12/31/2012). This time-varying exposure approach has been previously described in settings examining users versus non-users of medications.[206]

3.7. SENSITIVITY AND EXPLORATORY ANALYSES

Certain sensitivity analyses and exploratory analyses were conducted throughout the study. These additional analyses were classified as sensitivity analyses when the analyses were primarily intended to examine the robustness of the study conclusion, such as the lack of mortality data. Other descriptive exploratory analyses were also conducted because of known limitations in the data (such as limited laboratory data), but because of the primary intention-to-treat approach of this dissertation, were descriptive in nature. These approaches included assessments of warfarin patients' monitoring values and medication adherence in the follow-up period.

3.7.1. Mortality

Because the TruvenHealth MarketScan® databases do not measure mortality, censoring/dropout could be attributable to unmeasured death. To test the robustness of the results for Aim 2 and Aim 3, we tested whether significantly more 'censoring' occurs in one anticoagulant group versus another. In addition, the robustness of the results was tested again in the Cox proportional hazards models, whereby all those dropping out were assumed to have experienced the outcome in the anticoagulant group. For patients with a hospitalization in the follow-up period, the discharge variable was examined descriptively to see whether in-hospital mortality had occurred.

3.7.2. Outcomes: Transient Ischemic Attack and Hemorrhagic Stroke

While some algorithms recommended also including transient ischemic attack (TIAs) as part of the composite endpoint, TIAs tend to have lower PPVs than ischemic stroke algorithms and the other clinical effectiveness endpoints.[211,219] To test the robustness of the results for Aim

2, we tested whether removing TIA as part of the composite clinical effectiveness endpoint affects the results. Because TIAs are difficult to identify diagnostically, including TIAs as part of the endpoint could possibly adversely influence the results.

In addition, the parent RE-LY trial measured hemorrhagic stroke both as a clinical effectiveness and a harm outcome, effectively double-counting the outcomes. In this study, the number of hemorrhagic events in the warfarin group far outweighed the number in the dabigatran group, which was a primary driver of the efficacy endpoint in the study. Because the primary results of this study included hemorrhagic stroke as a risk of harm outcome solely (but still included it in the full composite), a sensitivity analysis for Aim 2 was also conducted including the hemorrhagic stroke/intracranial hemorrhagic endpoint in the clinical effectiveness outcomes.

3.7.3. Stratification by dabigatran strengths

Because the RE-LY trial showed different efficacy in prevention of stroke and systemic embolism during separate analyses of dabigatran strengths (110mg and 150mg in the trial), this present study also stratified initiators of dabigatran 75mg and dabigatran 150mg in Aim 2. For this study, the comparative effectiveness and safety of the two dabigatran strengths were also studied in stratified analyses using all doses warfarin as the referent group (as was done in the RE-LY trial). Multivariable and propensity-score adjustment was used for these separate survival analyses and Cox proportional hazards regression in the methods discussed above.

3.7.4. Clinical and demographic subgroups

To explore any underlying heterogeneity in treatment effects, clinical and demographic subgroups were also examined in Aim 2. We stratified patients with certain characteristics that were identified as contributing to non-overlap of the propensity scores and among characteristics

known to affect treatment effects, such as age and clinical prediction risk scores. For these analyses, the composite outcomes of the clinical effectiveness and safety were examined using Cox proportional hazards regression and the application of stratum-specific inverse probability treatment weighted propensity scores.

3.7.5. International Normalized Ratio (INR) laboratory values

As previously described, the TruvenHealth MarketScan® databases contain some laboratory values on approximately 10% of enrollees. INRs, used to measure the effectiveness of warfarin, can be captured through laboratory tests but may also be point of care measurements, done without extensive laboratory examination.[10,135,164] Because the TTR for users of warfarin has been thought to affect clinical outcomes, INRs were captured for those users of warfarin with available laboratory data.[118] These INRs were averaged during the follow-up period descriptively for Aim 2, because the TTR has been seen to drastically affect apparent efficacy in the RCTs examining the new OACs.

3.7.6. Medication adherence

For Aim 2, patient medication adherence in the follow-up period was also measured descriptively comparing between warfarin and dabigatran. We used the proportion of days covered by the prescription supply calculated from the prescription refill records in the outpatient pharmaceutical claims in the follow-up period. Conforming to current literature, a patient was defined as adherent if the patient had ≥80% of days covered with prescription supply. Patient medication refill rates were also measured descriptively, defined as the proportion of patients filling the index medication again in the follow-up period. These analyses were performed descriptively because of the intention-to-treat approach of this dissertation.

3.8. LIMITATIONS

As with other studies using observational data, unmeasured confounding may affect the overall study conclusions. However, the proposed approaches have been shown to limit the effects of unmeasured confounding and heterogeneity in treatment effects. As with other observational designs, causality is often difficult to ascertain, but these approaches may limit this concern. Other limitations due to various study design configurations and assumptions have been previously described in these chapters or are outlined in Chapter 5.

3.9. SUMMARY

The approaches described in Chapter 3 assess the factors associated with new use of anticoagulants, switching between anticoagulants, comparative effectiveness of new use of anticoagulants, and effects following switching between anticoagulants using Poisson and logistic regression, survival analysis, and the application of propensity scores.

CHAPTER 4: RESULTS

AIM 1: ANTICOAGULANT USE AND SWITCHING

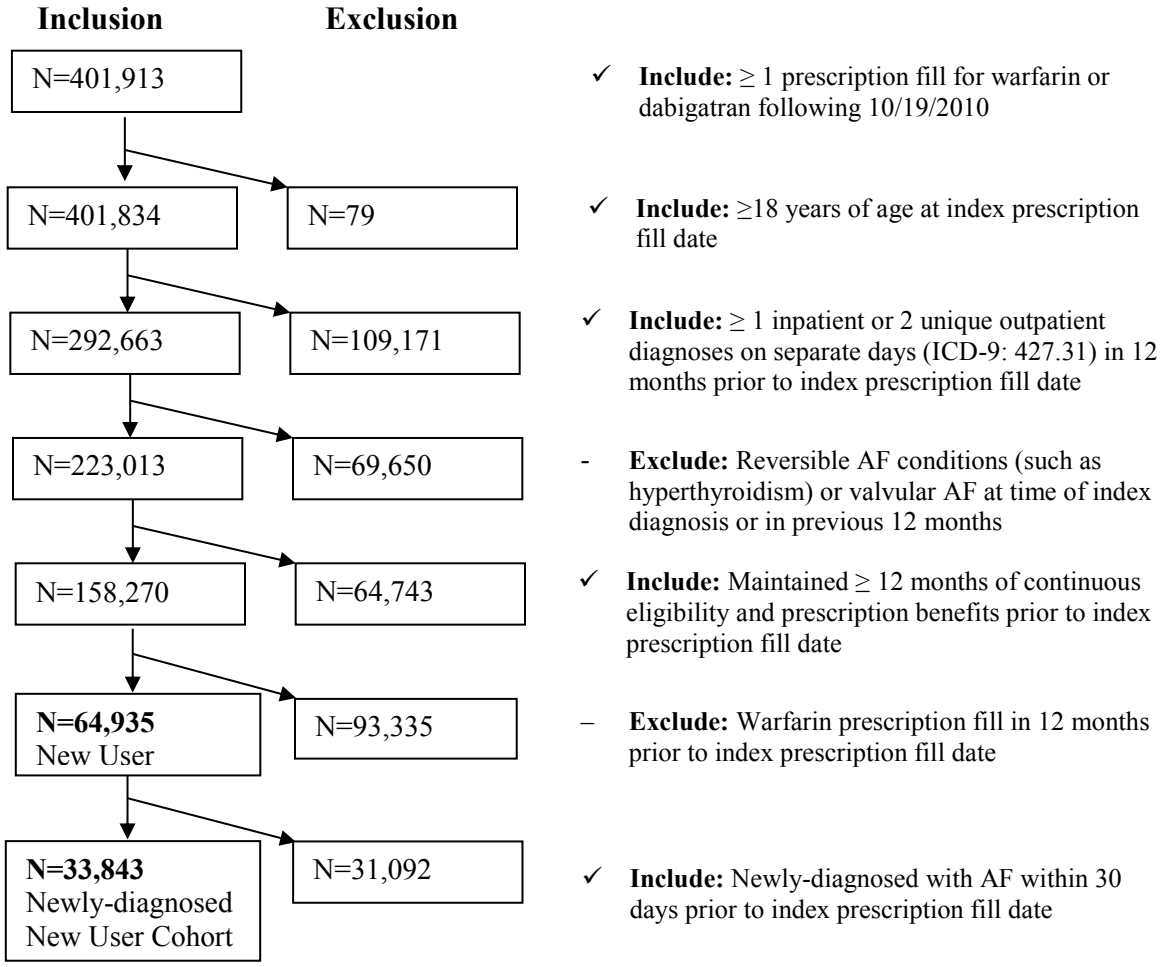
4.1. AIM 1A. RISK SCORES AND ANTICOAGULANT USE

4.1.1. Descriptive statistics

4.1.1.1. Cohort identification

Over 400,000 unique patients were identified as receiving at least one prescription for warfarin or dabigatran after 10/19/2010 until 12/31/2012. Of these, there were 64,935 treatment-naïve AF patients included in the final cohort (**Figure 5**). In total, 33,843 (52.1%) patients were newly-diagnosed with AF, having received their first ICD-9 code for AF within the 30 days prior to the index anticoagulation prescription fill. Of these, 43,865 (67.6%) used warfarin and 21,070 (32.5%) used dabigatran. There were 93,335 patients who were classified as prevalent users of warfarin – i.e., having received warfarin within 12 months prior to the index prescription fill date or the first prescription fill after 10/19/2010.

Figure 5. New User Cohort Flow Diagram



4.1.1.2. Baseline demographic characteristics

Patient sociodemographic characteristics among new users of warfarin and dabigatran are shown in **Table 10**, including the absolute standardized differences for each characteristic category between the two anticoagulants. As previously described in Chapter 3, absolute standardized differences are indexes which measure the effect size between two groups to assess imbalance between groups, with differences greater than 10% in absolute value generally indicating imbalance. New users of dabigatran were more likely to be younger, male, from the South region, use high-deductible health or preferred provider organization insurance health plans, and have good prescription benefits coverage (ratio ≥ 0 and ≤ 0.20) for all of their

medications filled within the previous 12 months. The proportion of newly-diagnosed AF patients with these sociodemographic characteristics was similar across all these baseline demographic categories.

Table 10. Demographic characteristics of new users and newly-diagnosed new users of warfarin and dabigatran

Baseline Characteristic	New users			Newly-diagnosed new users		
	Warfarin, N (%)	Dabigatran, N (%)	Absolute SD	Warfarin, N (%)	Dabigatran, N (%)	Absolute SD
Age						
< 55 years	3,886 (8.9)	2,963 (14.1)	20.2	2,107 (9.5)	1,727 (14.7)	23.5
55-64 years	10,146 (23.1)	6,443 (30.6)	20.5	5,317 (24.1)	3,626 (30.8)	19.6
65-74 years	9,792 (22.3)	4,838 (23.0)	2.1	5,063 (22.9)	2,672 (22.7)	0.6
≥ 75 years	20,041 (45.7)	6,826 (32.4)	34.3	9,591 (43.4)	3,740 (31.8)	28.1
Male Gender	25,562 (58.3)	13,363 (63.4)	11.6	12,867 (58.3)	7,481 (63.6)	12.2
Region						
Northeast	7,589 (17.3)	3,513 (16.7)	2.1	3,777 (17.1)	1,999 (17.0)	0.3
North Central	15,408 (35.1)	6,107 (29.0)	15.7	7,767 (35.2)	3,458 (29.4)	14.9
South	12,181 (27.8)	7,864 (37.3)	26.1	6,131 (27.8)	4,477 (38.1)	28.2
West	7,732 (17.6)	3,259 (15.5)	7.2	4,189 (19.0)	1,659 (14.1)	16.5
Insurance plan						
Comprehensive	15,701 (35.8)	6,812 (32.3)	8.9	7,760 (35.1)	3,893 (33.1)	5.1
HMO	6,368 (14.5)	1,723 (8.2)	24.3	3,475 (15.7)	907 (7.7)	29.9
POS	1,973 (4.5)	1,226 (5.8)	8.6	1,037 (4.7)	693 (5.9)	7.8
PPO	16,889 (38.5)	9,766 (46.4)	19.4	8,510 (38.5)	5,411 (46.0)	18.4
CDHP	707 (1.6)	464 (2.2)	6.7	385 (1.7)	276 (2.4)	7.6
Prescription generosity						
No coverage (> 0.99)	716 (1.6)	35 (0.2)	15.8	296 (1.3)	22 (0.2)	13.7
Poor coverage(> 0.80 and ≤ 0.99)	909 (2.1)	26 (0.1)	9.8	468 (2.1)	18 (0.2)	18.7
Fair coverage (> 0.20 and ≤ 0.80)	21,410 (48.8)	9,769 (46.4)	5.6	10,762 (48.7)	5,458 (46.4)	5.3
Good coverage (≥ 0 and ≤ 0.20)	20,830 (47.5)	11,240 (53.3)	13.5	10,552 (47.8)	6,267 (53.3)	12.8

Abbreviations: SD, Standardized difference; HMO, Health maintenance organization; POS, Point-of-service; PPO, Preferred provider organization; CDHP, consumer-driven health plan

4.1.1.3. Baseline clinical characteristics

Clinical characteristics of the new users of warfarin and dabigatran are shown in **Table 11**. Patients using warfarin for the first time were more likely to have experienced relevant comorbidities, particularly ischemic stroke, congestive heart failure, and venous thromboembolism. Across both new users and newly-diagnosed new users, the proportion of patients receiving warfarin was more likely to have comorbidities, and higher ischemic stroke risk and bleeding risk scores. The absolute standardized differences were somewhat lower among patients who were newly-diagnosed with the exception of hyperlipidemia, peptic ulcer

disease, and cognitive deficiency, although the underlying proportion of patients with those comorbidities altogether influenced these differences. For example, at most, 1.0% of patients were diagnosed with cognitive deficiency, which led to small cell sizes for both new users and newly-diagnosed new users. Patients were also more likely to have had a previous hospitalization if they received warfarin. However, AF patients were more likely to receive dabigatran if they had a catheter ablation in the previous 12 months. Examining the ischemic stroke clinical prediction risk scores, as predicted, the $CHADS_2$ score classified more individuals as low or intermediate risk of ischemic stroke compared with the CHA_2DS_2VASc score.

Table 11. Clinical characteristics of new users and newly-diagnosed new users of warfarin and dabigatran

Baseline Characteristic	New users			Newly-diagnosed new users		
	Warfarin, N (%)	Dabigatran, N (%)	Absolute SD	Warfarin, N (%)	Dabigatran, N (%)	Absolute SD
Ischemic Stroke	4,710 (10.7)	1,495 (7.1)	18.9	1,984 (9.0)	709 (6.0)	14.4
Congestive Heart Failure	12,414 (28.3)	3,851 (18.3)	32.7	5,793 (26.2)	2,022 (17.2)	26.5
VTE	5,385 (12.3)	538 (2.6)	81.8	2,025 (9.2)	232 (2.0)	34.9
Hyperlipidemia	21,710 (49.5)	10,456 (49.6)	0.2	10,730 (48.6)	5,777 (49.1)	1.2
Hypertension	32,043 (73.0)	14,578 (69.2)	9.1	15,900 (72.0)	8,068 (68.6)	8.1
Myocardial infarction	2,001 (4.6)	500 (2.4)	19.9	1,106 (5.0)	312 (2.7)	14.7
Coronary artery disease	15,000 (34.2)	5,942 (28.2)	16.5	6,951 (31.5)	3,076 (26.1)	14.5
Peripheral vascular disease	3,892 (8.9)	1,150 (5.5)	20.2	1,628 (7.4)	571 (4.9)	13.2
Renal impairment	5,517 (12.6)	1,210 (5.7)	39.8	2,481 (11.2)	618 (5.3)	25.7
Diabetes	13,957 (31.8)	5,610 (26.6)	14.6	6,824 (30.9)	3,264 (27.7)	8.6
Major bleeding	5,975 (13.6)	1,983 (9.4)	19.1	2,385 (10.8)	916 (7.8)	13.1
Anemia	8,736 (19.9)	2,241 (10.6)	39.4	3,853 (17.5)	1,102 (9.4)	28.7
Peptic Ulcer disease	320 (0.7)	93 (0.4)	6.7	136 (0.6)	44 (0.4)	45.6
Sleep Apnea	4,546 (10.4)	2,526 (12.0)	6.6	1937 (8.8)	1,187 (10.1)	6.2
Cognitive deficiency	438 (1.0)	126 (0.6)	7.3	157 (0.7)	45 (0.4)	69.0
CCI						
0	10,051 (22.9)	7,091 (33.7)	28.7	5,350 (24.2)	4,008 (34.1)	28.7
1-2	17,657 (40.3)	9,058 (43.0)	6.5	9,345 (42.3)	5,215 (44.3)	4.8
3-5	11,871 (27.1)	4,001 (19.0)	26.2	5,608 (25.4)	2,104 (17.9)	22.3
6-8	3,165 (7.2)	686 (3.3)	29.9	1,322 (6.0)	323 (2.8)	18.8
≥ 9	1,121 (2.6)	234 (1.1)	20.1	453 (2.1)	115 (1.0)	10.8
$CHADS_2$						
0	4,432 (10.1)	3,342 (15.9)	21.3	2,381 (10.8)	1,874 (15.9)	21.7
1	11,319 (25.8)	7,044 (33.4)	20.1	5,937 (26.9)	3,932 (33.4)	18.2
≥2	28,114 (64.1)	10,684 (50.7)	31.3	13,760 (62.3)	5,959 (50.7)	26.2
CHA_2DS_2-VASc						
0	2,935 (6.7)	2,444 (11.6)	20.9	1,531 (6.9)	1,366 (11.6)	24.9
1	6,339 (14.5)	4,665 (22.1)	24.1	3,387 (15.3)	2,626 (22.3)	25.1
≥2	34,591 (78.9)	13,961 (66.3)	30.8	17,160 (77.7)	7,773 (66.1)	27.8
ATRIA						
0-3	30,667 (69.9)	17,602 (83.5)	65.8	16,124 (73.0)	10,018 (85.2)	32.1
4	4,158 (9.5)	1,501 (7.1)	12.6	2,047 (9.3)	808 (6.9)	11.3
≥5	9,040 (20.6)	1,967 (9.3)	50.6	3,907 (17.7)	939 (8.0)	34.4
HAS-BLED						
0-2	38,249 (87.2)	19,608 (93.1)	20.3	19,764 (89.5)	11,128 (94.6)	19.3
≥3	5,616 (12.8)	1,462 (6.9)	31.1	2,314 (10.5)	637 (5.4)	22.9
Hospitalizations						
≥1	25,231 (57.5)	9,431 (44.8)	30.1	13,809 (62.5)	5,726 (48.7)	31.2
Catheter ablation	391 (0.9)	459 (2.2)	12.5	55 (0.3)	44 (0.4)	2.6

Abbreviations: SD, Standardized difference; CCI, Charlson comorbidity index

4.1.1.4. Baseline medication use characteristics

The distributions of patients receiving relevant concomitant medications within the 12 months prior to or including the index prescription fill date are shown in **Table 12**. The absolute standardized differences indicate that the medication use characteristics are relatively balanced between both groups of anticoagulant users. However, patients receiving warfarin were somewhat more likely to receive antiplatelet therapy, a gastroprotective agent (e.g., PPI), rate control therapy with digoxin, beta-blockers or calcium channel blockers, and ACEI/ARBs. Newly diagnosed new user patients were more likely to receive an antiarrhythmic while overall new user warfarin patients were less likely to receive one.

Table 12. Medication use characteristics of new users and newly-diagnosed new users of warfarin and dabigatran

Baseline Characteristic	New users			Newly-diagnosed new users		
	Warfarin, N (%)	Dabigatran, N (%)	Absolute SD	Warfarin, N (%)	Dabigatran, N (%)	Absolute SD
Antiplatelet therapy	5,726 (13.1)	2,684 (12.7)	1.6	2,962 (13.4)	1,360 (11.6)	7.1
Gastroprotective agent	5,558 (12.7)	2,267 (10.8)	8.2	2,740 (12.4)	1,186 (10.1)	9.4
Antiarrhythmic	9,991 (22.8)	5,344 (25.4)	7.6	4,329 (19.6)	2,217 (18.8)	2.6
Digoxin	7,435 (16.9)	2,973 (14.1)	10.5	3,365 (15.2)	1,479 (12.6)	9.6
Beta-blocker	29,513 (67.3)	14,132 (67.1)	0.5	15,753 (71.4)	8,089 (68.8)	6.1
Calcium channel blocker	18,501 (42.2)	8,602 (40.8)	3.4	10,013 (45.4)	4,939 (42.0)	8.0
ACEI/ARB	25,001 (57.0)	11,891 (56.4)	1.4	13,478 (61.0)	6,977 (59.3)	3.9
Statin	23,964 (54.6)	11,205 (53.2)	3.2	12,488 (56.6)	6,308 (53.6)	6.8
Hormone	1,626 (3.7)	959 (4.6)	6.0	894 (4.1)	536 (4.6)	3.5

Abbreviations: SD, Standardized difference; ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker

4.1.1.5. Baseline characteristics: Means and standard deviations

The means and standard deviations for the sociodemographic and clinical characteristics which were also measured continuously are displayed in **Table 13**. The mean age, CCI, stroke risk and bleeding risk prediction scores, and the average number of hospitalizations were all higher in those AF patients filling warfarin as their first anticoagulation prescription. The patient ages in the cohort ranged from 18 to 103 years of age.

Table 13. Means of baseline characteristics of new users and newly-diagnosed new users of warfarin and dabigatran

Baseline Characteristic	New users		Newly-diagnosed new users	
	Warfarin, Mean (SD)	Dabigatran, Mean (SD)	Warfarin, Mean (SD)	Dabigatran, Mean (SD)
Age	71.4 (12.2)	67.5 (12.4)	70.7 (12.0)	67.2 (12.4)
CCI	2.3 (2.3)	1.6 (1.9)	2.1 (2.2)	1.5 (1.8)
$CHADS_2$	2.1 (1.3)	1.7 (1.2)	2.0 (1.2)	1.6 (1.2)
CHA_2DS_2-VASc	2.9 (1.7)	2.3 (1.6)	2.8 (1.6)	2.3 (1.5)
ATRIA	2.9 (2.4)	2.0 (1.9)	2.7 (2.3)	1.9 (1.8)
HAS-BLED	1.4 (1.0)	1.3 (0.9)	1.3 (1.0)	1.1 (0.8)
Number of hospitalizations	0.8 (0.9)	0.5 (0.7)	0.8 (0.8)	0.6 (0.7)

Abbreviations: SD, standard deviation; CCI, Charlson comorbidity index

4.1.1.6. Index anticoagulant prescription characteristics

For the anticoagulation prescriptions filled on each patient's index prescription date, the index prescription benefits generosity and distribution of dosage strengths are shown in **Table 14**. Approximately 90% of dabigatran users received the 150mg dose. Of the 1,448 patients receiving the 75mg dose indicated for patients with renal insufficiency, only 21.7% had diagnosed renal insufficiency. By contrast, 9.7% of patients receiving the 150mg had diagnosed chronic kidney disease, for whom the 150mg dose is neither FDA-approved nor recommended in clinical guidelines. More than half of warfarin patients received 5mg as their index prescription strength, which is generally the guideline-recommended warfarin starting dose. Lastly, of the 43,865 patients newly using warfarin, 1,817 (4.1%) patients filled more than one dosage strength on the same day.

Table 14. Characteristics of the initial warfarin and dabigatran prescriptions

Baseline Characteristic	New users		Newly-diagnosed new users	
	Warfarin, N (%)	Dabigatran, N (%)	Warfarin, N (%)	Dabigatran, N (%)
Prescription generosity				
No coverage	17,321 (39.5)	63 (0.3)	8,732 (39.6)	30 (0.3)
Poor coverage	3,938 (8.98)	20 (0.1)	2,141 (9.7)	9 (0.1)
Fair coverage	10,339 (23.6)	4,760 (22.6)	5,310 (24.1)	2,550 (21.7)
Good coverage	12,267 (28.0)	16,227 (77.0)	5,895 (26.7)	9,176 (78.0)
Dosage strength				
1mg	2,858 (6.5)	N/A	1,149 (5.2)	N/A
2mg	4,953 (11.3)	N/A	2,287 (10.4)	N/A
2.5mg	5,279 (12.0)	N/A	2,555 (11.6)	N/A
3mg	2,977 (6.8)	N/A	1,258 (5.7)	N/A
4mg	2,754 (6.3)	N/A	1,142 (5.2)	N/A
5mg	24,452 (55.7)	N/A	13,315 (60.3)	N/A
6mg	725 (1.7)	N/A	236 (1.1)	N/A
7.5mg	1,108 (2.5)	N/A	542 (2.5)	N/A
10mg	676 (1.5)	N/A	263 (1.2)	N/A
75mg	N/A	1846 (8.8)	N/A	950 (8.1)
150mg	N/A	19,234 (91.3)	N/A	10,818 (92.0)

In addition, the mean warfarin copay ($5.95, 6.54 SD) was lower than the mean dabigatran copay ($37.34, 33.11 SD), as was the proportion of the index prescription paid by the patient relative to insurance benefits. The highest warfarin copay was $233.57 (for brand) while the lowest warfarin copay was $0, with 25th, 50th, and 75th percentiles at $1.54, $5.00, and $8.84, respectively. The highest dabigatran copay was $784.51 while the lowest dabigatran copay was $0, with 25th, 50th, and 75th percentiles at $20.00, $30.00, and $75.00, respectively.

Table 14 also indicates that patients with dabigatran had a lower cost-sharing burden than patients receiving warfarin. Less than 1% of dabigatran patients paid more than 80% of the overall index prescription cost, while more than 75% of dabigatran patients paid less than 20% of the overall index prescription cost. By comparison, almost 50% of warfarin patients paid more than 80% of the overall index prescription cost.

4.1.1.7. Trends in initiation of anticoagulation

Trends in the index date of anticoagulant for each patient initiating therapy were also examined via calendar months and calendar quarters. These calendar months and quarters are displayed in **Figure 6** and were determined in the time interval whereby each new user AF patient's index prescription was filled. New prescriptions for warfarin spiked in January 2011 (and somewhat in January 2012), but generally decreased over time. New prescriptions for newly-diagnosed AF patients receiving warfarin were fairly stable over time but dipped somewhat within the 2011 calendar year and then again in the 2012 calendar year. By contrast, new prescriptions for dabigatran increased from the 4th quarter of 2010 through the 2nd quarter of 2011 but then appeared to decrease beginning in the 1st quarter of 2012 – in line with the FDA-approval of rivaroxaban, another NOAC. Notably, this introduction of rivaroxaban may explain why the proportion of new users initiating anticoagulation in each month appears to decrease overall in 2012.

Figure 6. Trends in initiation of warfarin and dabigatran, 2010-2012

Figure 6a. Initiation of anticoagulation for each patient with atrial fibrillation by calendar month

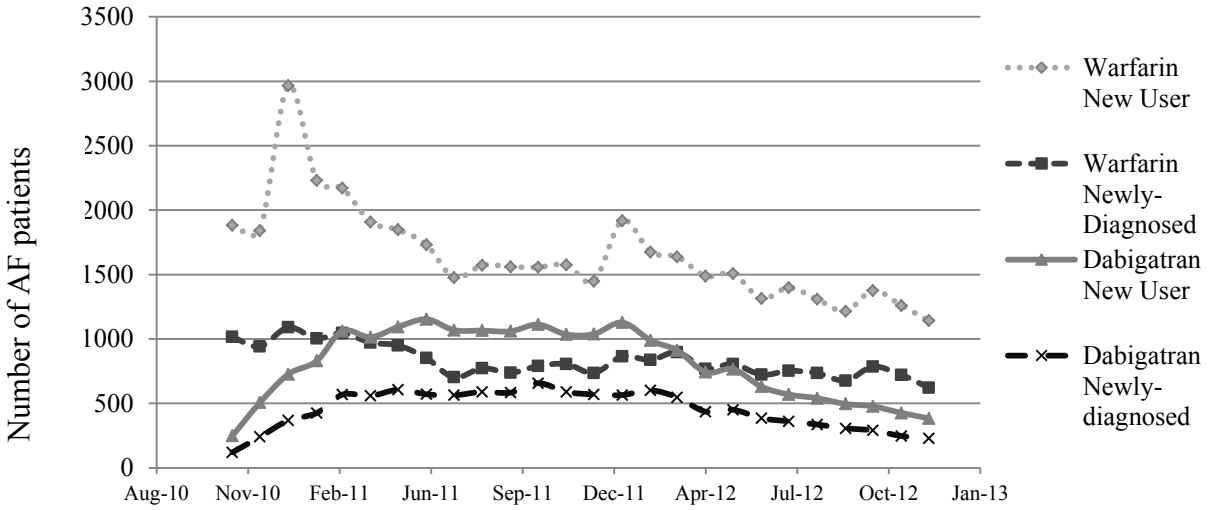
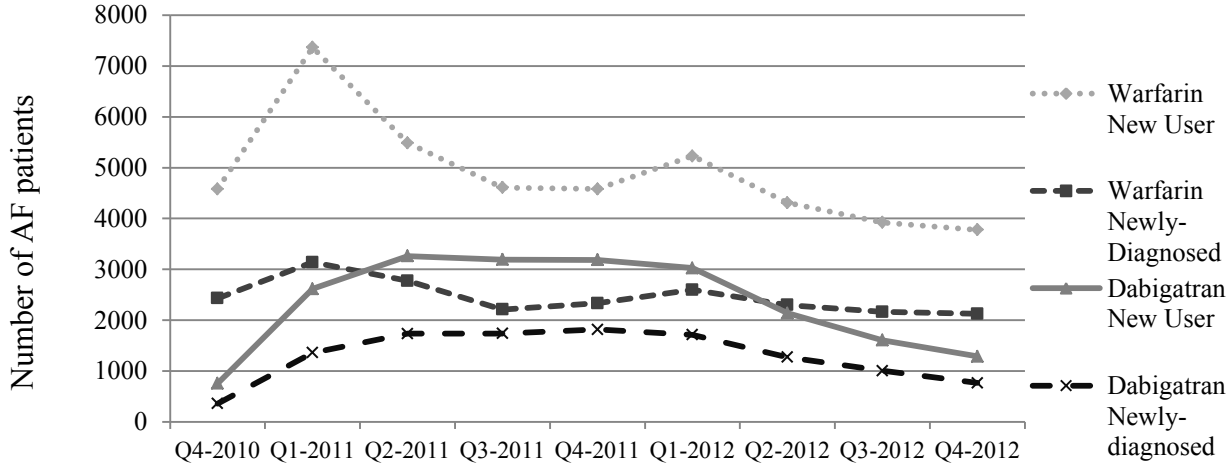


Figure 6b. Initiation of anticoagulation for each patient with atrial fibrillation by calendar quarter



4.1.2. Bivariate analyses of anticoagulant selection

The bivariate association between each clinical and sociodemographic covariate level and anticoagulation use was also assessed, by definition without controlling for the other covariates. These associations were assessed using relative risk estimation by modified Poisson regression with robust error variance. These associations are presented in **Table 15** with warfarin as the referent group. Categories of covariates with fewer than 2% of patients (or n=500, whichever was smaller) with that characteristic were combined with another relevant level (e.g., "No" and "Poor" prescription benefits generosity), when possible. The other identified small cell categories included peptic ulcer disease, cognitive deficiency, and catheter ablation. These associations were conducted on both new users and newly-diagnosed new user cohorts.

In these bivariate associations, because of the large sample size, almost all of the baseline sociodemographic and clinical characteristics were statistically significantly associated with anticoagulant selection, as seen in Table 15. The sole exceptions included: hyperlipidemia, antiplatelet therapy (new user only), antiarrhythmic therapy (newly-diagnosed new user only), beta-blocker therapy (new user only), and ACEI/ARB therapy (new user only). These suggested that the new users and newly-diagnosed new users of dabigatran and warfarin are significantly different from each other at baseline.

Table 15. Bivariate association between warfarin and dabigatran use and baseline sociodemographic and clinical characteristics in the 12-month baseline period

	New Users		Newly-diagnosed new users	
Baseline Characteristic	**RR**	**95% CI**	**RR**	**95% CI**
Demographic				
Age (ref: <55 years)				
55-64 years	0.90	0.87-0.93**	0.90	0.86-0.94**
65-74 years	0.76	0.74-0.79**	0.77	0.73-0.80**
≥ 75 years	0.59	0.57-0.61**	0.62	0.60-0.65**
Gender (ref: Female)	1.16	1.13-1.19**	1.16	1.12-1.19**
Region (ref: Northeast)				
North Central	0.92	0.89-0.95**	0.87	0.84-0.91**
South	1.27	1.23-1.31**	1.20	1.15-1.25**
West	0.96	0.92-0.99*	0.81	0.76-0.85**
Insurance plan (ref: Comprehensive)				
HMO	0.70	0.67-0.73**	0.61	0.57-0.65**
POS	1.25	1.20-1.32**	1.18	1.11-1.25**
PPO	1.20	1.17-1.23**	1.14	1.11-1.18**
CDHP	1.30	1.21-1.39**	1.23	1.12-1.35**
Prescription generosity (ref: None/Poor)				
Fair coverage	8.66	6.77-11.09**	6.76	4.99-9.16**
Good coverage	9.69	7.57-12.40**	7.49	5.53-10.14**
Clinical (ref: 0/None unless specified)				
Ischemic Stroke	0.72	0.69-0.76**	0.74	0.70-0.80**
Congestive Heart Failure	0.67	0.65-0.69**	0.69	0.65-0.69**
VTE	0.26	0.24-0.28**	0.28	0.25-0.32**
Hyperlipidemia	1.00	0.98-1.03	1.01	0.98-1.04
Hypertension	0.88	0.86-0.90**	0.90	0.87-0.93**
Myocardial infarction	0.61	0.56-0.66**	0.62	0.56-0.69**
Coronary artery disease	0.83	0.80-0.85**	0.84	0.81-0.87**
Peripheral vascular disease	0.69	0.58-0.83**	0.73	0.68-0.79**
Renal impairment	0.53	0.50-0.56**	0.55	0.52-0.59**
Diabetes	0.84	0.82-0.86**	0.90	0.87-0.93**
Major bleeding	0.74	0.71-0.77**	0.78	0.74-0.83**
Anemia	0.59	0.56-0.61**	0.60	0.57-0.64**
Peptic Ulcer disease	0.69	0.58-0.83**	0.70	0.54-0.91*
Sleep Apnea	1.11	1.08-1.15**	1.10	1.05-1.16**
Cognitive deficiency	0.69	0.59-0.80**	0.64	0.49-0.83**
CCI (ref: 0)				
1-2	0.82	0.80-0.84**	0.84	0.81-0.86**
3-5	0.61	0.59-0.63**	0.64	0.61-0.67**
6-8	0.43	0.40-0.46**	0.46	0.41-0.51**
≥ 9	0.42	0.37-0.47**	0.47	0.40-0.56**
$CHADS_2$ (ref: 0)				
1	0.89	0.86-0.92**	0.90	0.87-0.94**

≥2	0.64	0.62-0.66**	0.69	0.66-0.71**
CHA_2DS_2-VASc (ref: 0)				
1	0.93	0.90-0.97**	0.93	0.88-0.97**
≥2	0.63	0.61-0.65**	0.66	0.64-0.69**
ATRIA (ref: 0-3)				
4	0.73	0.70-0.76**	0.74	0.70-0.78**
≥5	0.49	0.47-0.51**	0.51	0.48-0.54**
HAS-BLED (ref: 0-2)				
≥3	0.61	0.58-0.64**	0.60	0.56-0.64**
Hospitalizations				
≥1	0.71	0.69-0.72**	0.69	0.67-0.71**
Catheter ablation	1.68	1.58-1.79**	1.28	1.03-1.60*
Medication use				
Antiplatelet therapy	0.98	0.95-1.01	0.89	0.85-0.94**
Gastroprotective agent	0.88	0.85-0.91**	0.85	0.81-0.90**
Antiarrhythmic	1.10	1.07-1.13**	0.97	0.93-1.01
Digoxin	0.86	0.83-0.89**	0.86	0.82-0.90**
Beta-blocker	0.99	0.97-1.02	0.92	0.89-0.95**
Calcium channel blocker	0.96	0.94-0.99*	0.91	0.89-0.94**
ACEI/ARB	0.98	0.96-1.01	0.95	0.93-0.98*
Statin	0.96	0.94-0.98**	0.93	0.90-0.95**
Hormone	1.15	1.09-1.21**	1.08	1.01-1.16*

*p<0.05
**p<0.001
Abbreviations: RR, Relative risk; ref, referent group; CI, confidence interval; HMO, health maintenance organization; POS, point of service; PPO, preferred provider organization; CDHP, consumer driven health plan; VTE, venous thromboembolism; CCI, Charlson comorbidity index; ACEI/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker

Other bivariate analyses were also conducted among characteristics not included in the multivariate analyses (discussed in the next section). Among all new users, AF patients who were newly-diagnosed were 15% more likely to receive dabigatran versus warfarin compared with those who were not newly-diagnosed (RR: 1.15, 95% CI: 1.12-1.18). New user AF patients were much more likely to receive dabigatran if they had also received dronedarone, a newer antiarrhythmic, specifically in the previous 12 months (RR: 1.61, 95% CI: 1.56-1.67). There was a similar likelihood among newly-diagnosed new users with regard to dronedarone receipt (RR: 1.66, 95% CI: 1.66-1.58).

The scores for the ischemic stroke, bleeding risk and overall clinical severity were also compared using those variables as continuous in bivariate analyses for both new users and newly-diagnosed new users as sensitivity analyses. These analyses are shown in the Appendix in

Appendix table 1. For example, for each additional year of age, new users were 1% less likely to receive dabigatran versus warfarin (RR: 0.99, 95% CI: 0.98-0.99). Overall, these bivariate associations were very similar as those assessed categorically in Table 15 for both new users and newly-diagnosed new users.

4.1.3. Multivariate analyses of anticoagulant selection

4.1.3.1 Main analyses

The associations between ischemic stroke and bleeding risk scores and anticoagulant selection were also assessed using multivariable relative risk estimation by modified Poisson regression with robust error variance (**Table 16**). In this model, the independent variables were CHA_2DS_2-VASc and ATRIA risk scores, with the dependent variable being selection for a particular anticoagulant. Warfarin was used as the referent group for all analyses. These models adjusted for all other baseline clinical characteristics which were not already included in the risk scores to avoid collinearity issues to ensure appropriate interpretation of the association of ischemic stroke and bleeding risk scores with anticoagulant selection. The associations with the other baseline characteristics are shown in **Appendix table 2**.

We found that high ischemic stroke risk was significantly associated with anticoagulant selection. Compared with warfarin, new users of dabigatran were significantly less likely to have CHA_2DS_2-VASc ≥ 2 or ATRIA score ≥ 4, even after adjusting for other clinical and demographic characteristics. These results indicate that AF patients using dabigatran were less likely to be at high ischemic stroke or bleeding risk when newly initiating therapy. However, intermediate ischemic stroke risk was not associated with any differential anticoagulant selection. AF patients newly initiating anticoagulation were also less likely to have other clinical comorbidities. These results were also seen consistently in the sensitivity analysis of newly-diagnosed new users.

Table 16. Multivariable association between ischemic stroke and bleeding risk prediction scores and warfarin and dabigatran selection

	New Users		Newly-diagnosed new users	
Baseline Characteristic	**RR**	**95% CI**	**RR**	**95% CI**
Demographic				
CHA_2DS_2-VASc (ref: 0)				
1	0.97	0.94-1.01	0.97	0.92-1.02
≥2	0.91	0.87-0.95**	0.92	0.87-0.98*
ATRIA (ref: 0-3)				
4	0.86	0.82-0.89**	0.85	0.80-0.91**
≥5	0.72	0.69-0.76**	0.71	0.67-0.76**

*p<0.05
**p<0.001
Abbreviations: RR, Relative risk; ref, referent group; CI, confidence interval
NOTE: Adjusted for all other measured baseline covariates, except for those already included in risk scores, as shown in Appendix table 2

4.1.3.2. Model fit diagnostics

The Quasilikelihood under the Independence model Criterion (QIC) was used to compare the insertion of $CHADS_2$ and the HAS-BLED score as possible predictors instead of the CHA_2DS_2-VASc and ATRIA risk scores. The QIC is analogous to the Akaike's Information Criterion (AIC) but is instead used for models fitting generalized estimating equation, such as the regression model used in this case. The QIC can be used for model selection, whereby the optimal model would have the lowest possible QIC. The model possibilities and resultant QICs are shown in **Appendix table 3** and indicate that indeed the CHA_2DS_2-VASc and ATRIA risk scores lead to a better model fit for both new users and newly-diagnosed new users, as that model possibility has the lowest QIC.

Notably, hyperlipidemia and the other medication use characteristics in the bivariate analyses not shown to be significantly significant were still included in the multivariable model as they were specified *a priori*, have been thought to be confounders in other research settings, and may still modify the relationship between predictor and anticoagulant use. The relative risks and 95% confidence intervals for the baseline covariates included in the model are shown in the

Appendix (**Appendix table 2**). Key interactions (e.g., age and gender) were also examined. As discussed in the previous section, age was examined via restriction to the commercially-insured and Medicare supplement patients, and some slight differences were noted. In addition, gender was also examined as an interaction term, and it was not found to have a significant interaction with either the ATRIA score or the CHA_2DS_2-VASc score.

4.1.3.3. Sensitivity analyses

The cohorts were also stratified based on the data sources into commercially-insured and Medicare supplemental claims (**Appendix table 4**). In these analyses, we observed similar associations between bleeding prediction risk scores and anticoagulant selection in the 12-month follow-up period similar to the original results presented in Table 16. The sole difference from the full combined cohort was that neither intermediate nor high ischemic stroke risk was associated with anticoagulation selection among the sub-cohort of Medicare Supplement beneficiaries.

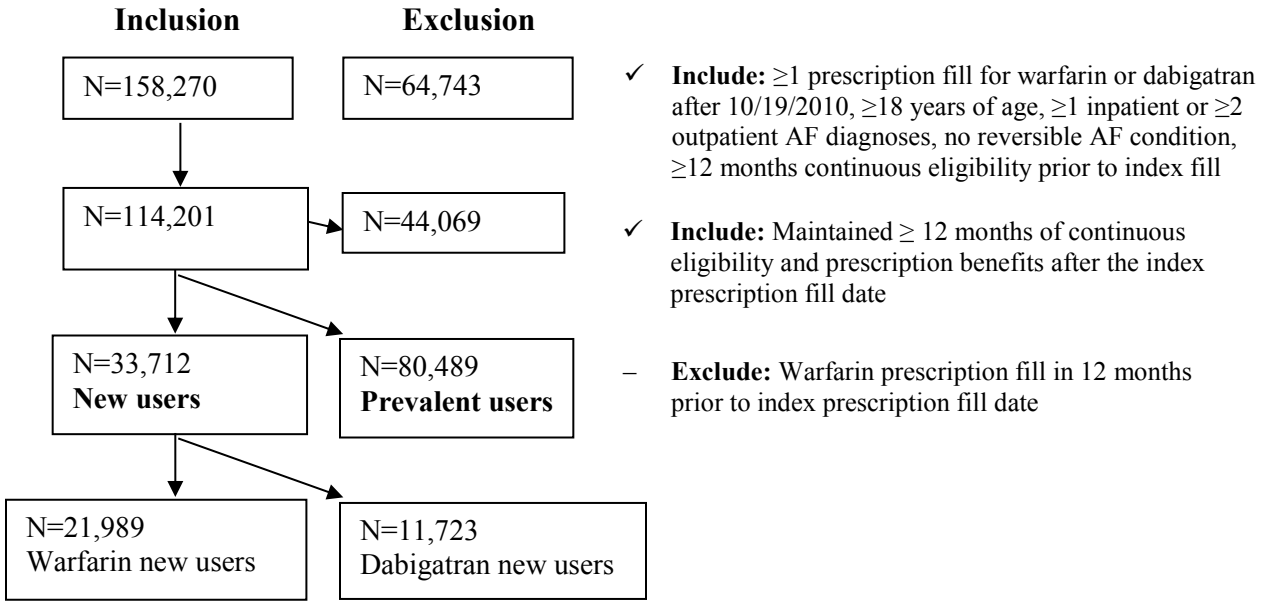
4.2. AIM 1B: RISK SCORES AND ANTICOAGULANT SWITCHING

4.2.1. Descriptive statistics

4.2.1.1. Cohort identification

In total, 64,935 AF patients were treatment-naïve. Of these, 33,712 patients were continuously enrolled for at least 12 months after the index anticoagulant fill date. **Figure 7** shows the switcher cohort selection, as an extension from the new user cohort flow diagram in Figure 5. Of note, these are individuals who are eligible for switching anticoagulants, not that they did within the 12-months post anticoagulation fill. The new users were examined as the primary analysis, with the prevalent users as a secondary analysis. Of the new users, 21,989 (65.2%) and 11,723 (34.8%) filled warfarin and dabigatran as their index prescriptions, respectively. Of note, a similar proportion filled each anticoagulation of the newly-diagnosed new users, with 10,776 (63.0%) and 6,343 (37.1%) filling warfarin and dabigatran, respectively. By contrast, 78,937 (98.1%) of the prevalent users of warfarin had warfarin as their first prescription fill post 10/19/2010. The remaining 1.9% of patients were, in fact, previous users of warfarin who used dabigatran as their first prescription post 10/19/2010.

Figure 7. Switcher Flow Diagram



4.2.1.2. New users: Anticoagulant switching characteristics

In total, 4,216 new user patients switched therapy within 12 months of treatment initiation (12.5%). Of the total new users, 2,800 (12.7%) of warfarin patients and 1,416 (12.1%) of dabigatran patients switched. The demographic, clinical, and medication use characteristics of the AF patients switching from warfarin and dabigatran are provided in **Table 17**. Examining the absolute standardized differences, switchers of warfarin compared with non-switchers were less likely to be aged ≥ 75 years, have an HMO health plan, have CHF, renal impairment, VTE, or anemia, or have high ischemic stroke risk or bleeding risk scores. Switchers from warfarin were, however, more likely to have a PPO health plan and previous hormone use. Switchers of dabigatran compared with non-switchers were more likely to be ≥75 years of age, have higher ischemic stroke risk, and use beta-blockers. However, switchers of dabigatran were less likely to be younger, male, have previously experienced an ischemic stroke, and have a previous catheter ablation. Overall, the characteristics descriptively appear more balanced between dabigatran

switchers and non-switchers compared with warfarin users. Upon further analysis, of the warfarin switchers, 11.7% switched to dabigatran while 1.3% switched to rivaroxaban. By contrast, of the dabigatran switchers, 8.9% switched to warfarin while 3.6% switched to rivaroxaban.

Table 17. Characteristics of switchers and non-switchers of new users of warfarin and dabigatran within 12-months following treatment

	Warfarin New Users (N=21,989)			Dabigatran New Users (N=11,723)		
Baseline Characteristic	**Switcher, N (%)**	**Non-Switcher, N (%)**	**Absolute SD**	**Switcher, N (%)**	**Non-Switcher, N (%)**	**Absolute SD**
Switching, N (%)	2,800 (12.7)	19,189 (87.3)		1,416 (12.1)	10,307 (87.9)	
Demographic						
Age						
< 55 years	246 (8.8)	1,695 (8.8)	0.0	142 (10.0)	1,452 (14.1)	18.1
55-64 years	771 (27.5)	4,195 (21.9)	16.0	361 (25.5)	2,934 (28.5)	8.6
65-74 years	705 (25.2)	4,421 (23.0)	6.4	333 (23.5)	2,428 (23.6)	0.3
≥ 75 years	1,078 (38.5)	8,878 (46.3)	19.1	580 (41.0)	3,493 (33.9)	17.4
Male Gender	1,654 (59.1)	11,232 (58.5)	1.4	826 (58.3)	6,548 (63.5)	12.0
Region						
Northeast	398 (14.2)	3,279 (17.1)	10.9	219 (15.5)	1,685 (16.3)	2.9
North Central	876 (31.3)	6,618 (34.5)	8.5	369 (26.1)	2,872 (27.9)	5.1
South	938 (33.5)	5,379 (28.0)	14.4	571 (40.3)	4,016 (39.0)	3.2
West	493 (17.6)	3,395 (17.7)	0.3	239 (16.9)	1,579 (15.3)	5.6
Insurance plan						
Comprehensive	1,082 (38.6)	7,504 (39.1)	1.2	552 (39.0)	3,669 (35.6)	8.4
HMO	212 (7.6)	2,760 (14.4)	34.1	100 (7.1)	744 (7.2)	0.5
POS	165 (5.9)	911 (4.8)	6.4	72 (5.1)	646 (6.3)	7.5
PPO	1,161 (41.5)	6,729 (35.1)	15.6	611 (43.1)	4,610 (44.7)	3.8
CDHP	54 (1.9)	299 (1.6)	3.1	27 (1.9)	215 (2.1)	2.1
Benefits generosity						
No coverage	40 (1.4)	291 (1.5)	1.2	2 (0.1)	15 (0.2)	4.5
Poor coverage	42 (1.5)	361 (1.9)	4.6	0 (0.0)	11 (0.1)	N/A
Fair coverage	1,267 (45.3)	9,419 (49.1)	8.9	671 (47.4)	4,762 (46.2)	2.8
Good coverage	1,451 (51.8)	9,118 (47.5)	9.9	743 (52.5)	5,519 (53.5)	2.3
Clinical						
Ischemic Stroke	260 (9.3)	1,801 (9.4)	0.5	75 (5.3)	741 (7.2)	11.6
Congestive Heart Failure	611 (21.8)	4,993 (26.0)	12.9	242 (17.1)	1,765 (17.1)	0.0
VTE	159 (5.7)	2,189 (11.4)	33.0	42 (3.0)	267 (2.6)	3.3
Hyperlipidemia	1,253 (44.8)	8,809 (45.9)	2.6	694 (49.0)	4,880 (47.3)	3.9
Hypertension	1,971 (70.4)	13,526 (70.5)	0.2	988 (69.8)	6,943 (67.4)	5.6
Myocardial infarction	86 (3.1)	747 (3.9)	6.4	30 (2.1)	240 (2.3)	2.0
Coronary artery disease	865 (30.9)	6,319 (32.9)	5.3	440 (31.1)	2,905 (28.2)	7.8
Peripheral vascular disease	193 (6.9)	1,510 (7.9)	5.4	91 (6.4)	569 (5.5)	5.1
Renal impairment	184 (6.6)	2,092 (10.9)	23.3	83 (5.9)	527 (5.1)	4.7
Diabetes	845 (30.2)	5,915 (30.8)	1.6	375 (26.5)	2,650 (25.7)	2.3
Major bleeding	318 (11.4)	2,465 (12.8)	5.9	137 (9.7)	997 (9.7)	0.0
Anemia	338 (12.1)	3,424 (17.8)	22.9	151 (10.7)	990 (9.6)	4.8
Peptic Ulcer disease	12 (0.4)	130 (0.7)	6.7	3 (0.2)	44 (0.4)	6.3
Sleep Apnea	343 (12.3)	1,914 (10.0)	9.4	176 (12.4)	1,175 (11.4)	4.1
Cognitive deficiency	15 (0.5)	137 (0.7)	4.0	8 (0.6)	55 (0.5)	1.8
CCI						
0	760 (27.1)	4,810 (25.1)	5.7	447 (31.6)	3,573 (34.7)	8.2
1-2	1,278 (45.6)	7,923 (41.3)	10.2	630 (44.5)	4,488 (43.5)	2.4

3-5	624 (22.3)	4,978 (25.9)	11.0	286 (20.2)	1,856 (18.0)	7.1
6-8	105 (3.8)	1,151 (6.0)	15.8	43 (3.0)	297 (2.9)	0.8
≥ 9	33 (1.2)	327 (1.7)	6.4	10 (0.7)	93 (0.9)	3.4
$CHADS_2$						
0	352 (12.6)	2,075 (10.8)	7.3	190 (13.4)	1,663 (16.1)	10.4
1	820 (29.3)	5,197 (27.1)	6.0	446 (31.5)	3,512 (34.1)	6.9
≥2	1,628 (58.1)	11,917 (62.1)	9.2	780 (55.1)	5,132 (49.8)	12.1
CHA_2DS_2-VASc						
0	224 (8.0)	1,340 (7.0)	5.0	125 (8.8)	1,189 (11.5)	12.8
1	505 (18.0)	2,808 (14.6)	11.7	253 (17.9)	2,239 (21.7)	12.8
≥2	2,071 (74.0)	15,041 (78.4)	11.0	1,038 (73.3)	6,879 (66.7)	15.6
ATRIA						
0-3	2,249 (80.3)	13,963 (72.8)	18.8	1,181 (83.4)	8,734 (84.7)	3.7
4	238 (8.5)	1,683 (8.8)	1.5	91 (6.4)	714 (6.9)	2.8
≥5	313 (11.2)	3,543 (18.5)	30.3	144 (10.2)	859 (8.3)	8.5
HAS-BLED						
0-2	2,122 (75.8)	13,717 (71.5)	10.5	1,117 (78.9)	8,202 (79.6)	1.8
≥3	678 (24.2)	5,472 (28.5)	12.6	299 (21.1)	2,105 (20.4)	2.2
Hospitalizations						
≥1	1,456 (52.0)	10,588 (55.2)	7.4	580 (41.0)	4,512 (43.8)	6.8
Catheter ablation	26 (0.9)	188 (1.0)	1.5	7 (0.5)	230 (2.2)	33.7
Medication Use						
Antiplatelet therapy	363 (13.0)	2,365 (12.3)	2.8	186 (13.1)	1,388 (13.5)	1.6
Gastroprotective agent	330 (11.8)	2,293 (11.9)	0.4	155 (10.9)	1,083 (10.5)	1.7
Antiarrhythmic	707 (25.3)	4,214 (22.0)	9.7	361 (25.5)	2,567 (24.9)	1.7
Digoxin	482 (17.2)	3,282 (17.1)	0.3	205 (14.5)	1,497 (14.5)	0.0
Beta-blocker	1,868 (66.7)	12,714 (66.3)	0.9	1,010 (71.3)	6,853 (66.5)	11.3
Calcium channel blocker	1,201 (42.9)	7,923 (41.3)	3.8	598 (42.2)	4,197 (40.7)	3.6
ACEI/ARB	1,671 (59.7)	10,842 (56.5)	7.3	803 (56.7)	5,835 (56.6)	0.2
Statin	1,551 (55.4)	10,308 (53.7)	3.9	766 (54.1)	5,622 (54.5)	0.9
Hormone	150 (5.4)	704 (3.7)	10.4	75 (5.3)	499 (4.8)	3.1

Abbreviations: SD, Standardized difference; HMO, Health maintenance organization; POS, Point-of-service; PPO, Preferred provider organization; CDHP, consumer-driven health plan; CCI, Charlson Comorbidity Index; ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker

4.2.1.2. Prevalent users of warfarin: Anticoagulant switching characteristics

Of the 80,489 prevalent users of warfarin, 10,561 (13.1%) switched therapies within 12-months. The demographic, clinical and medication use characteristics of these prevalent users are provided in **Table 18**. Prevalent users were less likely to switch (more likely to be classified as "Non-Switchers") if they were >75 years of age, resided in the North Central Region, had HMO health insurance, had poor or fair benefits generosity, VTE, renal impairment, high ischemic stroke risk (CHA_2DS_2-VASc or $CHADS_2 \geq 2$), or high bleeding risk (ATRIA ≥ 5). Prevalent

users were more likely to switch (more likely to be classified as “Switchers”) if they were 55-64 or 65-74 years of age, resided in the South Region, had PPO health insurance, had good benefits generosity, sleep apnea, catheter ablation, intermediate ischemic stroke risk (CHA_2DS_2-VASc = 1), low bleeding risk (ATRIA < 4) or anti-arrhythmic therapies.

Table 18. Characteristics of switchers and non-switchers of prevalent users of warfarin within 12-months following treatment

Baseline Characteristic	Prevalent Users (N=80,489)		
	Switcher, N (%)	Non-Switcher, N (%)	Absolute SD
Switching, N (%)	10,561 (13.1)	69,928 (86.9)	
Demographic			
Age			
< 55 years	588 (5.6)	3,378 (4.8)	4.8
55-64 years	2,169 (20.5)	10,828 (15.5)	16.2
65-74 years	2,847 (27.0)	15,360 (22.0)	14.3
≥ 75 years	4,957 (46.9)	40,362 (57.7)	25.3
Male Gender	6,392 (60.5)	40,640 (58.1)	5.5
Region			
Northeast	1,885 (17.8)	13,468 (19.3)	5.1
North Central	2,579 (24.4)	22,973 (32.9)	24.6
South	4,171 (39.5)	20,856 (29.8)	24.2
West	1,908 (18.1)	12,537 (17.9)	0.7
Insurance plan			
Comprehensive	4,851 (45.9)	32,049 (45.8)	0.2
HMO	626 (5.9)	11,352 (16.2)	57.8
POS	627 (5.9)	3130 (4.5)	8.2
PPO	4,054 (38.4)	20,921 (29.9)	21.3
CDHP	135 (1.3)	782 (1.1)	2.5
Benefits generosity			
No coverage	38 (0.4)	362 (0.5)	2.2
Poor coverage	75 (0.7)	1,040 (1.5)	13.5
Fair coverage	5,016 (47.5)	37,587 (53.8)	14.7
Good coverage	5,432 (51.4)	30,939 (44.2)	16.6
Clinical			
Ischemic Stroke	698 (6.6)	4,644 (6.6)	0.0
Congestive Heart Failure	2,265 (21.4)	16,856 (24.1)	8.4
VTE	473 (4.5)	5352 (7.7)	21.1
Hyperlipidemia	4,691 (44.4)	29,040 (41.5)	6.9
Hypertension	6,984 (66.1)	45,529 (65.1)	2.3
Myocardial infarction	120 (1.1)	879 (1.3)	2.7
Coronary artery disease	3,501 (33.2)	22,296 (31.9)	3.4
Peripheral vascular disease	726 (6.9)	5295 (7.6)	3.8
Renal impairment	714 (6.8)	6302 (9.0)	11.8
Diabetes	3,022 (28.6)	20,511 (29.3)	1.9
Major bleeding	1,544 (14.6)	9,953 (14.2)	1.5
Anemia	1,284 (12.2)	9,937 (14.2)	8.1
Peptic Ulcer disease	51 (0.5)	331 (0.5)	0.0
Sleep Apnea	1,433 (13.6)	6,887 (9.9)	14.5
Cognitive deficiency	69 (0.7)	492 (0.7)	0.0
CCI			
0	3,098 (29.3)	19,416 (27.8)	4.1
1-2	4,692 (44.4)	30,041 (43.0)	3.3
3-5	2,308 (21.9)	16,579 (23.7)	5.5

6-8	373 (3.5)	3,159 (4.5)	7.5
≥ 9	90 (0.9)	733 (1.1)	3.0
$CHADS_2$			
0	1,203 (11.4)	6,804 (9.7)	7.2
1	3,258 (30.8)	19,218 (27.5)	8.9
≥2	6,100 (57.8)	43,906 (62.8)	11.5
CHA_2DS_2-VASc			
0	595 (5.6)	3,593 (5.1)	3.0
1	1,660 (15.7)	8,226 (11.8)	14.3
≥2	8,306 (78.6)	58,109 (83.1)	12.1
ATRIA			
0-3	8,459 (80.1)	53,274 (76.2)	10.0
4	799 (7.6)	5,300 (7.6)	0.0
≥5	1,303 (12.3)	11,354 (16.2)	15.6
HAS-BLED			
0-2	8,208 (77.7)	53,504 (76.5)	3.0
≥3	2,353 (22.3)	16,424 (23.5)	3.7
Hospitalizations			
≥1	3,173 (30.0)	20,538 (29.4)	1.6
Catheter ablation	216 (2.1)	721 (1.0)	10.8
Medication Use			
Antiplatelet therapy	810 (7.7)	4,420 (6.3)	7.2
Gastroprotective agent	1,247 (11.8)	7,752 (11.1)	2.9
Antiarrhythmic	2,845 (26.9)	14,578 (20.8)	17.6
Digoxin	2,878 (27.3)	19,566 (28.0)	2.0
Beta-blocker	7,278 (68.9)	47,226 (67.5)	3.3
Calcium channel blocker	4,614 (43.7)	28,109 (40.2)	8.4
ACEI/ARB	6,676 (63.2)	42,125 (60.2)	6.8
Statin	6,792 (64.3)	42,677 (61.0)	7.5
Hormone	458 (4.3)	2513 (3.6)	4.8

Abbreviations: SD, Standardized difference; HMO, Health maintenance organization; POS, Point-of-service; PPO, Preferred provider organization; CDHP, consumer-driven health plan; CCI, Charlson Comorbidity Index; ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker

4.2.1.3. Anticoagulant switching time periods

The time to switching anticoagulants were also descriptively assessed for both the new user and prevalent user cohorts. Of the 4,216 AF patients newly-initiating an anticoagulant and switching within 12-months, the mean time from initiation until discontinuation was 136.6 days (106.4 SD). Among patients who switched, the switch from warfarin was shorter than the switch to dabigatran. Specifically, the mean switch time from warfarin was 127.4 days (102.1 SD) while the mean switch time from dabigatran was 155.0 days (112.3 SD). Of the prevalent users, the mean switch time was 168.4 days (97.3 SD). Of the patients newly-initiating warfarin and

switching within 12 months, 568 (20.3%) and 1,002 (35.8%) switched therapies within 30 and 60 days since initiation, respectively. These proportions represent 1.7% and 3.0% of the total warfarin new-initiators. The proportion of patients newly-initiating dabigatran and switching within 30 and 60 days was somewhat lower (30 days: 16.7%, N=236; 60 days: 29.0%, N=411). As many as 151 (5.4%) and 51 patients (3.6%) of the warfarin and dabigatran patients who switched to another anticoagulant did so within 7 days of newly-initiating the respective therapies.

4.2.1.4. Anticoagulant switching prescription copayments

The distributions of the proportion of the index prescription copayments paid by the new user and prevalent user AF patients are shown in **Appendix table 5**.

4.2.2. Bivariate analyses

The bivariate association between each clinical and sociodemographic covariate level and anticoagulation switching for each type of anticoagulant was also assessed, by definition without controlling for the other covariates. These associations were assessed using relative risk estimation by modified Poisson regression with robust error variance. These associations are presented in **Table 19** with "non-switching" as the referent group for each anticoagulant comparison. These associations were conducted on both the new user and prevalent user cohorts using the same methodology as Aim 1a.

Table 19. Bivariate association between anticoagulant switching and baseline sociodemographic and clinical characteristics in the 12-month baseline period

	Warfarin New Users		Dabigatran New Users		Prevalent Users	
Baseline Characteristic	**RR**	**95% CI**	**RR**	**95% CI**	**RR**	**95% CI**
Demographic						
Age (ref: <55 years)						
55-64 years	1.23	1.07-1.40*	1.23	1.02-1.48*	1.13	1.04-1.22*
65-74 years	1.09	0.95-1.24	1.35	1.12-1.63*	1.05	0.97-1.14
≥ 75 years	0.85	0.75-0.97*	1.60	1.34-1.90**	0.74	0.68-0.80**
Gender (ref: Female)	1.02	0.95-1.09	0.83	0.75-0.91**	1.09	1.05-1.13**
Region (ref: Northeast)						
North Central	1.02	0.92-1.13	1.00	0.86-1.16	0.82	0.78-0.87**
South	1.29	1.17-1.43**	1.09	0.95-1.26	1.35	1.29-1.42**
West	1.10	0.98-1.24	1.15	0.97-1.36	1.07	1.01-1.14*
Insurance plan (ref: Comprehensive)						
HMO	0.57	0.50-0.67**	0.92	0.75-1.12	0.40	0.37-0.43**
POS	1.23	1.06-1.43*	0.78	0.62-0.98*	1.27	1.17-1.37**
PPO	1.18	1.10-1.27**	0.91	0.82-1.01	1.23	1.19-1.28**
CDHP	1.23	0.96-1.58	0.86	0.60-1.24	1.12	0.95-1.31
Prescription generosity (ref: None/Poor)						
Fair coverage	1.06	0.86-1.31	1.73	0.45-6.59	1.58	1.32-1.89**
Good coverage	1.23	1.00-1.52	1.66	0.44-6.33	2.00	1.67-2.40**
Clinical (ref: 0/None unless specified)						
Ischemic Stroke	0.99	0.88-1.12	0.75	0.60-0.93*	1.00	0.93-1.07
Congestive Heart Failure	0.82	0.75-0.89**	1.00	0.88-1.13	0.88	0.84-0.92**
VTE	0.50	0.43-0.59**	1.13	0.85-1.50	0.60	0.55-0.66**
Hyperlipidemia	0.96	0.90-1.03	1.06	0.96-1.17	1.11	1.07-1.15**
Hypertension	1.00	0.92-1.07	1.10	0.99-1.23	1.04	1.00-1.08*
Myocardial infarction	0.80	0.66-0.99*	0.92	0.65-1.29	0.91	0.77-1.08
Coronary artery disease	0.92	0.85-0.99*	1.13	1.02-1.25*	1.05	1.01-1.09*
Peripheral vascular disease	0.88	0.77-1.02	1.15	0.95-1.40	0.91	0.85-0.98*
Renal impairment	0.61	0.52-0.70**	1.13	0.92-1.39	0.76	0.71-0.82**
Diabetes	0.97	0.90-1.05	1.04	0.93-1.16	0.97	0.93-1.01
Major bleeding	0.88	0.79-0.99*	1.00	0.85-1.18	1.03	0.98-1.09
Anemia	0.67	0.60-0.74**	1.11	0.95-1.30	0.85	0.81-0.90**
Peptic Ulcer disease	0.66	0.38-1.14	0.53	0.18-1.58	1.02	0.79-1.31
Sleep Apnea	1.22	1.10-1.35**	1.09	0.94-1.26	1.36	1.29-1.43**
Cognitive deficiency	0.77	0.48-1.25	1.05	0.55-2.01	0.94	0.75-1.17
CCI (ref: 0)						
1-2	1.02	0.94-1.11	1.11	0.99-1.24	0.98	0.94-1.02
3-5	0.82	0.74-0.90**	1.20	1.05-1.38*	0.89	0.85-0.93**
6-8	0.61	0.50-0.74**	1.14	0.85-1.52	0.77	0.69-0.85**
≥ 9	0.67	0.48-0.94*	0.87	0.48-1.58	0.79	0.65-0.97*
$CHADS_2$ (ref: 0)						
1	0.94	0.84-1.05	1.10	0.94-1.29	0.96	0.91-1.03
≥2	0.83	0.74-0.92**	1.29	1.11-1.49*	0.81	0.77-0.86**

CHA_2DS_2-VASc (ref: 0)						
1	1.06	0.92-1.23	1.07	0.87-1.31	1.19	1.08-1.29**
≥2	0.85	0.74-0.96*	1.38	1.16-1.64**	0.88	0.82-0.95*
ATRIA (ref: 0-3)						
4	0.89	0.79-1.01	0.95	0.78-1.16	0.96	0.89-1.02
≥5	0.59	0.52-0.66**	1.21	1.03-1.42*	0.75	0.71-0.79**
HAS-BLED (ref: 0-2)						
≥3	0.83	0.76-0.89**	1.04	0.92-1.17	0.94	0.90-0.98*
Hospitalizations						
≥1	0.89	0.83-0.96*	0.90	0.82-1.00*	1.03	0.99-1.07
Catheter ablation	0.95	0.66-1.34	0.24	0.12-0.50**	1.77	1.57-2.00**
Medication use						
Antiplatelet therapy	1.05	0.95-1.17	0.98	0.84-1.13	1.02	0.94-1.11
Gastroprotective agent	0.99	0.89-1.10	1.04	0.89-1.22	1.06	1.01-1.12*
Antiarrhythmic	1.17	1.08-1.26**	1.03	0.92-1.15	1.33	1.28-1.39**
Digoxin	1.01	0.92-1.10	1.00	0.87-1.15	0.97	0.93-1.09
Beta-blocker	1.02	0.95-1.10	1.22	1.10-1.36**	1.06	1.02-1.10*
Calcium channel blocker	1.06	0.99-1.14	1.06	0.96-1.17	1.13	1.09-1.17**
ACEI/ARB	1.12	1.04-1.20*	1.00	0.91-1.11	1.12	1.08-1.16**
Statin	1.06	0.99-1.14	0.98	0.89-1.09	1.13	1.09-1.17**
Hormone	1.40	1.21-1.63**	1.09	0.87-1.35	1.18	1.09-1.29**

*p<0.05
**p<0.001
Abbreviations: RR, Relative risk; ref, referent group; CI, confidence interval; HMO, health maintenance organization; POS, point of service; PPO, preferred provider organization; CDHP, consumer driven health plan; VTE, venous thromboembolism; CCI, Charlson comorbidity index; ACEI/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blockers

In these bivariate associations, many of the baseline sociodemographic and clinical characteristics were statistically significantly associated with anticoagulant selection, as seen in Table 19. These suggested that the switchers and non-switchers for each type of anticoagulant may significantly differ from each other in the 12-month baseline period. When examining the warfarin new user cohort, being from the South region and being 55-64 years of age, having a PPO plan, sleep apnea and using antiarrhythmics, ACEI/ARB or hormone therapies were significantly associated with switching from warfarin in the 12-month follow-up period. Patients were less likely to switch if they were ≥ 75 years of age, had an HMO plan, had CHF, VTE, anemia or renal impairment, had higher comorbidity burden, higher risk of ischemic stroke or bleeding, and had a previous hospitalization.

When examining the patients initiating dabigatran, patients greater than 55 years of age, with coronary artery disease, moderate comorbidity burden, higher ischemic stroke risk or bleeding risk and using beta-blocker therapies were more likely to switch from dabigatran. Patients were less likely to switch from dabigatran if they were male, had a POS plan, had previous ischemic stroke, were previously hospitalized or had a catheter ablation procedure. By comparison, patients with bleeding risk or ischemic stroke risk or congestive heart failure, VTE, renal impairment, anemia or PVD were less likely to switch if they were prevalent users. However, prevalent user patients with hypertension, hyperlipidemia and sleep apnea were more likely to switch. There was a significant amount of geographic variation between the regions, particularly among the prevalent users.

Lastly, among new users, newly-diagnosed AF was significantly associated with switching for warfarin in the 12-month follow-up period (warfarin RR: 1.32, 95% CI: 1.24-1.42; dabigatran RR: 1.03, 95% CI: 0.94-1.14), and a new diagnosis of AF was also adjusted for in the multivariate analyses discussed in the next section.

4.2.3. Multivariate analyses

4.2.3.1. Main analyses

The associations between ischemic stroke and bleeding risk scores and anticoagulant switching were also assessed using multivariable relative risk estimation by modified Poisson regression with robust error variance (**Table 20**). In this model, the independent variables were CHA_2DS_2-VASc and ATRIA risk scores, with the dependent variable being selection for a particular anticoagulant. Non-switchers were used as the referent group for all analyses using both the new user and the prevalent user cohorts and the methods described in Aim 1a. The associations with the other baseline characteristics are shown in **Appendix table 6**.

Compared with non-switchers, patients initiating warfarin were significantly less likely to switch therapies with high bleeding risk (RR: 0.69, 95% CI: 0.61-0.79). By comparison, patients initiating dabigatran were significantly more likely to switch with high ischemic stroke risk (RR: 1.35, 95% CI: 1.09-1.66) compared with non-switchers. Comparatively, patients who are newly-initiating dabigatran are more likely to switch with high baseline ischemic stroke risk, which appears to be driven by advanced age.

By contrast, in the prevalent users of warfarin, having a high ischemic stroke risk was associated with an 8% reduction in the likelihood of switching anticoagulants, while intermediate ischemic stroke risk was paradoxically associated with a 12% increase in switching. Similar to the new users of warfarin, however, high bleeding risk in the 12-month baseline was associated with a lower risk of switching (RR: 0.82, 95% CI: 0.77-0.87).

Table 20. Multivariable association between ischemic stroke and bleeding risk prediction scores and anticoagulant switching

	All Warfarin New Users		All Dabigatran New Users		Prevalent Users	
Risk Score	**RR**	**95% CI**	**RR**	**95% CI**	**RR**	**95% CI**
Demographic						
CHA_2DS_2-VASc (ref: 0)						
1	1.01	0.87-1.17	1.06	0.86-1.31	1.12	1.03-1.22*
≥2	0.88	0.76-1.02	1.35	1.09-1.66*	0.91	0.84-0.99*
ATRIA (ref: 0-3)						
4	0.95	0.83-1.08	0.91	0.74-1.12	0.96	0.90-1.03
≥5	0.69	0.61-0.79**	1.12	0.94-1.33	0.82	0.77-0.87**

*p<0.05
**p<0.001
Abbreviations: RR, Relative risk; ref, referent group; CI, confidence interval
NOTE: Adjusted for all other measured baseline covariates, except for those already included in risk scores, as shown in Appendix table 2

4.2.3.2. Model fit diagnostics

Just as in Aim 1a, the Quasilikelihood under the Independence model Criterion (QIC) was used to compare the insertion of $CHADS_2$ and the HAS-BLED score as possible predictors instead of the CHA_2DS_2-VASc and ATRIA risk scores. The model possibilities and resultant QICs are shown in **Appendix table 8** and again indicate that indeed the inclusion of the ATRIA risk score leads to a better model fit across both the warfarin and prevalent user models, as that model possibility had lower QICs than HAS-BLED. However, the models incorporating $CHADS_2$ and ATRIA (instead of CHA_2DS_2-VASc) had slightly lower QICs. The QICs were, indeed, marginally higher for the model including CHA_2DS_2-VASc and ATRIA, but the directionality and significance of the findings were similar. Moreover, intermediate ischemic stroke risk was associated with a reduction in the likelihood of switching – not just high ischemic stroke risk, but this difference was seen more strongly in the $CHADS_2$ models compared with the CHA_2DS_2-VASc models. These slight differences are likely due to differentiation differences in patients at intermediate risk between the two scores. Despite this slight difference, CHA_2DS_2-VASc and ATRIA were determined appropriate to be used in further analyses, because current

clinical guidelines are emphasizing the use of the CHA_2DS_2-VASc score instead of the $CHADS_2$ and the ATRIA score is better measured in this data source.

The relative risks and 95% confidence intervals for the baseline covariates included in the model are shown in the Appendix (Appendix table 6). Key interactions (e.g., age and gender) were also examined. As discussed in the previous section, age was examined via restriction to the commercially-insured and Medicare supplement patients, and some slight differences were noted. As with Aim 1a, gender was also investigated as an interaction term, and the term was not found to significantly interact with either score.

4.2.3.3. Sensitivity analyses

Just as in Aim 1a, the cohorts were also stratified based on the data sources into commercially-insured and Medicare supplemental claims (**Appendix table 7**). In the analysis of the new user cohort, the directions and significance of the associations between bleeding prediction risk scores and anticoagulant switching were largely similar to the original results for both warfarin and dabigatran. However, the strength of the associations did differ somewhat between the groups, with a stronger association between bleeding risk and switching seen in the CCAE group. Some differences with regard to ischemic stroke risk were also seen between the CCAE and Medicare supplement, however. Specifically, for warfarin initiators, no difference was seen between ischemic stroke risk and switching in the CCAE population, but higher ischemic stroke risk was associated with a slightly lower likelihood of switching in the Medicare Supplement group. These differences could possibly be due to age influencing switching. There were no differences in ischemic stroke risk and switching in the dabigatran initiators, however.

When examining the prevalent user cohort, there was one difference from the primary results when stratifying on insurance status. Intermediate and high ischemic stroke risk was, in

fact, associated with a reduction in the risk of switching within the 12-month follow-up period among Medicare beneficiaries, but not in the commercially-insured patients. However, there were few major differences in bleeding risk associations with switching between both the CCAE and Medicare supplement population – bleeding risk just had a slightly stronger association with not switching in the CCAE arm. Overall, the direction of the estimates was similar even when examining the two groups separately.

4.3. AIM 2: COMPARATIVE EFFECTIVENESS OF ANTICOAGULANTS

4.3.1. Descriptive statistics

4.3.1.1. Cohort identification

A total of 64,935 patients were included in the new user cohort, which was the primary analysis. Newly-diagnosed new users were also examined as a secondary analysis. The clinical and demographic characteristics of the cohort were previously shown in Aim 1a. In Aim 2, patients were followed from anticoagulant initiation until they experienced an outcome of interest, lost continuous eligibility, or were censored administratively on 12/31/2012 (the end of available data). The mean patient follow-up time from initiation was 323 days with an interquartile range of 113 days to 513 days. For the warfarin new users, the mean follow-up time was 311 days; for dabigatran new users, the mean follow-up time was 349 days.

4.3.1.2. Crude outcome rates

The unadjusted rates of outcomes in the new user cohort were also examined. The identification of clinical effectiveness and harm outcomes were previously discussed in Chapter 3 (Methods). **Table 21** shows the observed rate of the clinical effectiveness and harm outcomes by the type of anticoagulant initiated, standardized by 1,000 person-years of anticoagulant exposure. The overall incidence of ischemic stroke, TIA, and VTE was 177.36 per 1,000 person-years (PYs). As shown below in Table 21, the overall unadjusted outcome rates were higher among warfarin users compared with dabigatran users across both the new users and newly-diagnosed new users. For the effectiveness outcome endpoints, 54,667 (84.3%) of the patients were censored either administratively on 12/31/2012 at the end of the data collection period or

because of loss of continuous eligibility. For the harm outcome composites, 42,473 of the patients were censored (65.4%) for these same reasons (administratively on 12/31/2012 or loss of continuous eligibility).

Table 21. Outcome rates per 1,000 person-years by anticoagulant initiated

	New Users		Newly-diagnosed new users	
Outcome Type	**Warfarin**	**Dabigatran**	**Warfarin**	**Dabigatran**
Clinical Effectiveness				
Ischemic stroke	108.6	66.0	95.8	60.5
TIA	12.9	9.7	11.6	7.7
VTE	131.0	30.7	111.8	30.7
Composite	222.7	93.3	195.3	88.2
Harm				
Hemorrhagic stroke/ intracranial hemorrhage	16.3	7.1	14.4	6.2
Gastrointestinal hemorrhage	90.8	70.8	84.9	69.7
Other bleeding event	121.5	90.0	119.0	87.1
Hospitalization	391.7	310.8	375.3	309.6
Composite	419.1	338.6	401.6	337.4
Myocardial infarction	21.8	13.1	22.9	13.4

Abbreviations: TIA, Transient Ischemic Attack; VTE, Venous thromboembolism

4.3.2. Preliminary assessment of model specifications

As described in Chapter 3, the association between anticoagulant and the hazard of experiencing an outcome was examined using Cox proportional hazards regression via bivariate models, multivariable models, and propensity-score adjusted models. First, the baseline characteristics and their associations with anticoagulant exposure and outcomes were assessed for whether they are confounders and should be included (or not included) in the models. This process was previously shown in the Analytic Diagram (Chapter 3, Figure 3) and the Cox proportional hazards model (Chapter 3, Equation 2).

These baseline characteristics and their associations with exposure and the composite outcomes are shown in **Appendix table 9**. These tests were done in order to determine which covariates should be considered confounder variables (X3) for the analysis and thus included in statistical adjustments. Overall, these tests indicated that there was only one variable (i.e., hormone use) that statistically should be considered an X1 variable, a variable statistically associated solely with exposure that should not be included in propensity score analysis.[238]

Accordingly, this variable was not included in the propensity score analyses. Other variables were still included in the propensity score analysis as they were specified a priori based on associations seen in the literature and were seen to be confounders.[189]

In addition to multivariable adjustment, inverse-probability treatment weighting (IPTW) (with stabilized weights) was used as the primary propensity score adjustment method to control for measured confounding to estimates of the average effect of treatment in the study population. The kernel densities for the propensity score plots are shown in **Appendix figure 1**. After examining individual covariates included in the propensity score model, the ones most contributing to the non-overlap seen in the warfarin group (solid line) were the baseline prescription benefits' generosity and venous thromboembolism covariates. Applying stabilized weights, the mean probabilities of receiving anticoagulation with dabigatran and warfarin (referent) were 1.01 (SD: 1.25) and 1.00 (SD: 0.23), respectively. For the newly-diagnosed new users, after applying stabilized weights, the groups' mean probabilities were 1.00 (SD: 0.78) for dabigatran and 1.00 (SD: 0.24) for warfarin, respectively. The balance of the covariates for the new user groups following the IPTW is shown in **Appendix table 10.** Based on absolute standardized differences (whereby >10 indicates imbalance), there was no imbalance in covariates after weighting in the IPTW propensity score, which indicates good balance. The c-statistic for the propensity score for the new user group was 0.69, indicating good fit.

Standardized mortality ratio (SMR) propensity score weighting was also conducted as another adjustment method to estimate the comparative effectiveness of anticoagulants. As previously described in Chapter 3, in SMR weighting, weights are applied standardized to the treated group, estimating the average treatment effects among treated patients (e.g., in this setting, dabigatran patients). The mean SMR weight for the warfarin new user group was 0.48 (SD: 0.34) (as by definition, the dabigatran group's mean was 1 with SD equal to 0).

4.3.3. Main Results

4.3.3.1. Composite outcomes

These comparative effectiveness and safety of dabigatran and warfarin among new anticoagulant initiators is shown in **Table 22** for unadjusted, multivariable-adjusted, and propensity score-adjusted models. The estimated treatment effects comparing new users of dabigatran to warfarin on risk of outcomes among only outcomes that occurred in the inpatient setting are shown in **Appendix table 11.**

For the primary analyses, applying propensity scores using IPTW yielded a point estimate closer to the null, yielding a 30% reduction in the hazard of experiencing one of the clinical effectiveness outcomes (adjusted HR: 0.70, 95% CI: 0.67-0.73). By contrast, dabigatran users were no less likely to experience one of the harm outcomes included in the composite endpoint (adjusted HR: 1.02, 95% CI: 0.99-1.05) compared with warfarin, after multivariable adjustment.

For the multivariate analysis, compared with warfarin, dabigatran showed a 38% reduction in the hazard of experiencing one of the clinical effectiveness composite outcomes (adjusted [Hazard Ratio] HR: 0.62, 95% CI: 0.59-0.66). Multivariable models included adjustment for the covariates that were described in Appendix table 10. The full model results are shown in **Appendix table 12** for the multivariable analyses among new users. Applying SMR weighting moved the effect estimates slightly closer to the null, but the estimates of the risk of harm were still similar as multivariable-adjusted and IPTW-weighted analyses. The testing of assumptions, functional forms and model diagnostics are shown in Section 4.3.3.3.

In addition, applying trimming (5%) to the propensity scores did not appreciably change the effect estimates. Applying trimming to the IPTW propensity scores resulted in an adjusted HR of 0.68 (95% CL: 0.65-0.71) for the clinical effectiveness composite and an adjusted HR of

1.01 (95% CL: 0.98-1.04) for the harm outcome composite in the survival analysis regresssion. These findings are very similar to the original stabilized IPTW estimates shown in Table 22 below.

Table 22. Multivariable Cox models comparing dabigatran and warfarin use and outcomes in atrial fibrillation

Outcome Type	Unadjusted HR (95% CI)	MV Adjusted HR (95% CI)	PS-IPTW HR (95% CI)	PS-SMR HR (95% CI)
Clinical Effectiveness				
Ischemic stroke	0.66 (0.62-0.70)**	0.85 (0.80-0.91)**	0.92 (0.87-0.98)*	0.90 (0.83-0.96)*
TIA	0.83 (0.70-0.97)*	0.97 (0.82-1.16)	1.07 (0.92-1.25)	1.00 (0.82-1.22)
VTE	0.25 (0.23-0.27)**	0.41 (0.38-0.45)**	0.51 (0.47-0.54)**	0.52 (0.47-0.56)**
Composite	0.43 (0.41-0.45)**	0.62 (0.59-0.66)**	0.70 (0.67-0.74)**	0.74 (0.69-0.78)**
Harm				
Hemorrhagic stroke/intracranial hemorrhage	0.47 (0.40-0.57)**	0.62 (0.51-0.74)**	0.64 (0.54-0.75)**	0.65 (0.53-0.80)**
GI hemorrhage	0.85 (0.80-0.90)**	1.08 (1.01-1.15)*	1.19 (1.12-1.26)**	1.08 (1.00-1.15)
Other bleeding	0.80 (0.76-0.84)**	0.91 (0.86-0.96)**	0.91 (0.86-0.96)**	0.91 (0.86-0.97)*
Hospitalization	0.84 (0.81-0.86)**	0.97 (0.94-1.01)	1.00 (0.97-1.02)	0.98 (0.95-1.01)
Composite	0.85 (0.83-0.88)**	1.00 (0.97-1.03)	1.02 (0.99-1.05)	1.00 (0.97-1.03)
AMI	0.66 (0.57-0.76)**	0.86 (0.74-0.99)*	0.88 (0.77-1.00)	0.87 (0.74-1.02)

*p<0.05; **p<0.001

Abbreviations: HR, Hazard Ratio; CI, Confidence interval; MV, multivariable model; PS, Propensity score; IPTW, Inverse probability treatment weighting; SMR, Standardized Mortality Ratio; TIA, Transient ischemic attack; VTE, venous thromboembolism; GI, gastrointestinal; AMI, Acute Myocardial Infarction

4.3.3.2. Cause-specific outcomes

The cause-specific survival analyses yielded similar results. In these analyses, patients were followed from anticoagulant initiation until any outcome was experienced, they lost continuous eligibility or they were censored administratively at 12/31/2012. In these primary analyses using IPTW, initiating dabigatran resulted in a statistically significant reduction in the hazard of VTE (adjusted HR: 0.51, 95% CI: 0.47-0.54), ischemic stroke (adjusted HR: 0.92, 95% CI: 0.87-0.98), hemorrhagic stroke (adjusted HR: 0.64, 95% CI: 0.54-0.76), other bleeding (adjusted HR: 0.91, 95% CI: 0.86-0.96), and myocardial infarction (adjusted HR: 0.88, 95% CI: 0.77-1.00) compared with warfarin initiation. However, dabigatran was also associated with an increased hazard of GI hemorrhage (adjusted HR: 1.19, 95% CI: 1.12-1.26). Hospitalizations and TIAs did not differ between the anticoagulant groups.

4.3.3.3. Model diagnostics

The deviance residuals showed appropriate distribution for the main covariates assessed. Proportional hazards assumptions were also tested for both the composite of effectiveness and composite of harm outcomes. These tests did not reveal any violations of the assumption for the models. These tests are shown here in the Kaplan Meier plots (**Appendix figure 2**) for the association of anticoagulation with the clinical effectiveness and harm composites among new users**.** In addition, examining the Schoenfeld residuals also did not yield any violations of the proportional hazards assumptions. Including an interaction term for time in the models also did not indicate a violation of the proportional hazards assumption. In addition, supremum tests for heterogeneity of treatment effect were non-significant. The AICs were lower for the full multivariable model compared with other models.

4.3.4. Sensitivity analyses

4.3.4.1. Subgroup analyses

4.3.4.1.1. *Newly-diagnosed new users*

The effect estimates for the comparative effectiveness and safety of anticoagulation among newly-diagnosed new users as a sensitivity analysis are shown in **Table 23**. Similar to new users, the subgroup of newly-diagnosed new users also showed a significant reduction in the hazard of experiencing a clinical effectiveness outcome when initiating dabigatran compared with warfarin. The overall associations are very similar; in fact, a stronger reduction in clinical outcomes was observed when examining the newly-diagnosed new users (e.g., the HR is further away from the null). Thus, if there was unmeasured confounding, it would be likely to bias the estimates down and away from the null (as the warfarin group would likely have higher rates of frailty compared with dabigatran as seen in Aim 1). This suggests that perhaps unmeasured

confounding may be more present among the newly-diagnosed new users than the overall new user sample (or that dabigatran is more beneficial in newly-diagnosed patients). When examining the comparative safety of the agents via the safety composite, dabigatran and warfarin appeared to be no different in reducing the hazard of experiencing an adverse outcome. These results were also similar to the overall new user subgroup.

Table 23. Multivariable Cox models comparing the use of dabigatran with warfarin and outcomes in newly-diagnosed AF patients

Outcome Type	Unadjusted HR (95% CI)	MV Adjusted HR (95% CI)	PS-IPTW HR (95% CI)	PS-SMR HR (95% CI)
Clinical Effectiveness				
Ischemic stroke	0.68 (0.62-0.74)**	0.86 (0.78-0.94)**	0.89 (0.82-0.97)*	0.90 (0.81-1.00)
TIA	0.73 (0.57-0.93)*	0.84 (0.65-1.09)	0.86 (0.68-1.10)	0.83 (0.63-1.11)
VTE	0.29 (0.26-0.32)**	0.45 (0.40-0.51)**	0.45 (0.40-0.50)**	0.55 (0.49-0.63)**
Composite	0.46 (0.43-0.50)**	0.65 (0.60-0.70)**	0.67 (0.62-0.71)**	0.75 (0.69-0.82)**
Harm				
Hemorrhagic stroke/intracranial hemorrhage	0.46 (0.35-0.60)**	0.58 (0.44-0.76)**	0.58 (0.45-0.75)**	0.62 (0.46-0.83)*
GI hemorrhage	0.88 (0.81-0.96)*	1.08 (0.99-1.19)	1.10 (1.01-1.19)**	1.09 (0.98-1.21)
Other bleeding	0.78 (0.72-0.84)**	0.86 (0.79-0.93)**	0.86 (0.80-0.93)**	0.85 (0.78-0.93)**
Hospitalization	0.86 (0.83-0.90)**	0.98 (0.94-1.02)	0.98 (0.94-1.02)	0.98 (0.93-1.03)
Composite	0.88 (0.84-0.91)**	1.00 (0.96-1.04)	1.00 (0.96-1.04)	1.00 (0.95-1.05)
AMI	0.63 (0.52-0.76)**	0.80 (0.66-0.98)*	0.85 (0.71-1.01)	0.82 (0.66-1.02)

Abbreviations: AF, Atrial Fibrillation; HR, Hazard Ratio; MV, Multivariate; PS, Propensity score; IPTW, Inverse probability treatment weighting; SMR, Standardized Mortality Ratio; TIA, transient ischemic attack; VTE, venous thromboembolism; GI, gastrointestinal; AMI, Acute Myocardial Infarction

4.3.4.1.2. *Stratification by commercial insurance and Medicare patients*

The analyses were also conducted separately among commercially-insured beneficiaries and Medicare supplement beneficiaries (**Appendix table 13**) for both new users and newly-diagnosed new users. No statistically significant differences in the harm composite were seen between the users of dabigatran compared with warfarin for any subgroup. However, dabigatran was seen to be even more protective in terms of the clinical effectiveness endpoint compared with warfarin within commercially-insured beneficiaries (adjusted HR: 0.46, 95% CI: 0.42-0.51 for new users). While still statistically significant, the effect of dabigatran in reducing the hazard of experiencing a clinical effectiveness outcome was less pronounced among only the Medicare supplement beneficiaries (adjusted HR: 0.77, 95% CI: 0.73-0.81). All in all, the associations were similar across the groups, only the strength of the associations slightly differed for the clinical effectiveness endpoint.

4.3.4.1.3. *Stratification by dabigatran strengths*

The comparative effectiveness and safety of the two dabigatran strengths (75mg and 150mg) were also studied in separate survival analyses using warfarin as the referent group. These results are shown in **Appendix table 14**. Using both multivariable and PS-adjustment, dabigatran 150mg showed a statistically significant reduction in the hazard of experiencing one of the composite outcomes compared with warfarin. However, the comparative safety of dabigatran 150mg did not differ compared to warfarin. By contrast, there was no statistical difference in clinical effectiveness seen between dabigatran 75mg and warfarin; however, dabigatran 75mg showed an increased hazard of experiencing one of the harm outcomes, which could possibly be due to some unmeasured confounding.

4.3.4.2. Sensitivity analyses

4.3.4.2.1. *Influence of mortality*

A known limitation of the Truven Health MarketScan® is that when patients lose continuous eligibility, it is unknown whether they are changing plans or whether they have actually died. Death occurrences, outside of the hospital setting, within these data are unknown. First, to attempt to explore this limitation, the discharge location of the patients who experienced a hospital admission as their censoring outcome for the harm outcome composite was examined. Of the 14,219 warfarin patients who were hospitalized in the follow-up period after initiation, 381 (2.7%) patients were coded as "Died" or "Other died status" upon discharge from their hospitalization outcome. By contrast, of the 5,932 dabigatran patients who were hospitalized, 95 (1.6%) were coded with "Died" or "Other died status" for their discharge dispensation location. Crude test statistics on this difference in the proportion of hospitalizations associated with

mortality yielded a chi-square of 22.44 ($p<0.001$), suggesting that there was a significant difference in the proportion of hospitalizations in the follow-up period that resulted in death.

Secondly, the proportion of patients who were lost to follow-up (and not censored administratively on 12/31/2012) was also examined. In sum, 5,543 (12.6%) of warfarin patients and 2,314 (11.0%) of dabigatran patients were lost to follow-up (chi-square 35.97, $p<0.001$), suggestive of possible significant differences in the proportion of patients who were lost to follow-up. These patients, by definition, did not experience any one of the composite outcomes.

Finally, this limitation was explored by again conducting the multivariable survival analysis between anticoagulant initiation and the hazard of experiencing one of the composite outcomes – this time applying a statistical assumption that every patient who lost continuous eligibility actually died. In other words, those who were lost to follow-up were included in the composite endpoints as another outcome, censored at the date they were lost to follow up. These findings, along with the other sensitivity analyses in this section are shown in **Table 24**. The sensitivity analyses on mortality suggest that dabigatran only slightly reduced the hazard of experiencing both a clinical effectiveness and harm outcomes when assuming that all patients who lost continuous eligibility actually died. These results were in contrast to the primary findings particularly when considering magnitude, whereby in the original results, no significant difference in the reduction of the harm outcomes was found.

Table 24. Sensitivity analyses comparing the use of dabigatran with warfarin and outcomes in AF patients initiating anticoagulation

Outcome Type	Effectiveness composite HR (95% CI)	Harm composite HR (95% CI)
Original results		
MV-adjusted	0.62 (0.59-0.66)**	1.00 (0.97-1.03)
PS-IPTW	0.70 (0.67-0.74)**	1.02 (0.99-1.05)
Sensitivity analysis 1		
MV-adjusted	0.96 (0.93-0.99)*	0.92 (0.89-0.96)*
PS-IPTW	0.92 (0.89-0.96)**	0.97 (0.94-0.99)*
Sensitivity analysis 2		
MV-adjusted	0.63 (0.60-0.66)**	N/A
PS-IPTW	0.71 (0.68-0.74)**	N/A
Sensitivity analysis 3		
MV-adjusted	0.63 (0.60-0.66)**	N/A
PS-IPTW	0.71 (0.68-0.74)**	N/A

*p<0.05; **p<0.001

Abbreviations: AF, Atrial Fibrillation; HR, Hazard Ratio; MV, Multivariate; PS, Propensity score; IPTW, Inverse probability treatment weighting; SMR, Standardized Mortality Ratio; TIA, transient ischemic attack; VTE, venous thromboembolism; GI, gastrointestinal; AMI, Acute Myocardial Infarction

NOTE: Sensitivity analysis 1: Influence of mortality by including patients lost-to-follow-up; Sensitivity analysis 2: Inclusion of transient ischemic attack; Sensitivity analysis 3: Inclusion of hemorrhagic stroke

Overall, these explorations suggest that there could be some differential effects of dabigatran on the risk of mortality compared with warfarin, in that dabigatran may lead to slightly lower mortality risk. Specifically, there were fewer dabigatran patients who experienced morality upon hospitalization, and fewer dabigatran patients were lost to follow-up – outside of being censored administratively on 12/31/2012. However, none of these explorations were direct measures, and the re-analyses of the Cox proportional hazards regression relied on the very unlikely assumption that everyone who was lost to follow-up actually died. Thus, it could be reasonably assumed that not being able to have mortality as part of the composite outcomes may not have significantly affected the results, but it is still a possible limitation of the Truven Health MarketScan® database.

4.3.4.2.2. *Inclusion of transient ischemic attacks (TIAs)*

While some algorithms have recommended including transient ischemic attacks as part of the composite endpoint for the effectiveness of anticoagulants, the specificity of identifying them in claims data has been called into question. To test the robustness of results, TIA was removed as part of the composite clinical effectiveness endpoint, which reduced the overall number of events by 186 in the composite endpoint. Because the overall event rate was almost the exact same, the multivariate-adjusted survival analysis yielded the exact same hazard ratios, which were the same as the initial results without including TIA (Table 24). Among the newly-diagnosed new users, the results were similar: adjusted HR: 0.65, 95% CL: 0.61-0.70) and PS-IPTW HR: 0.67 (95% CL: 0.63-0.71). These findings suggest that the overall results were robust to the removal of TIA in the clinical effectiveness composite.

4.3.4.2.3. *Inclusion of hemorrhagic stroke*

To perhaps provide a closer analog to the RE-LY trial that was used for FDA-approval of dabigatran, an outcome of hemorrhagic stroke was also included in the primary clinical effectiveness endpoint. Specifically, the RE-LY trial included hemorrhagic stroke in the primary stroke or systemic embolism in their primary endpoint. In our study's sensitivity analysis, patients were then followed from anticoagulation initiation until they experienced either ischemic stroke, VTE, TIA, or hemorrhagic stroke/intracranial hemorrhage or were censored due to loss of continuous eligibility or administratively on 12/31/2012. In total, an additional 283 events were identified in our study and included in the composite clinical effectiveness endpoint. The multivariable survival analysis and analysis using IPTW were very similar to the primary results (Table 24). Among newly-diagnosed new users, the adjusted HR was 0.65 (95% CI: 0.61-

0.70). These findings suggest that the overall results were robust to the inclusion of hemorrhagic stroke in the clinical composite of effectiveness.

4.3.4.2.4. *Heterogeneity of treatment effects*

When examining the IPTW propensity score deciles, a little underlying heterogeneity for the estimated treatment effects was seen, particularly for the composite of the risk of harm outcomes (**Appendix figure 3**). However, there does appear to be some treatment effect heterogeneity in the lower IPTW propensity score deciles, indicating that dabigatran treatment was more beneficial in patients less likely to be treated with dabigatran. Said another way, anticoagulation with warfarin was less beneficial in patients who were more likely to be treated with warfarin. These finding suggest there could still be some imbalance in covariates, although covariate distributions post-propensity score weighting were similar (Appendix table 10). There were, however, few individuals treated with dabigatran contrary to prediction, as can be seen in the kernel density plots.

As previously described, subgroup analyses stratifying by baseline characteristics were also conducted to examine any treatment effect heterogeneity. Specifically, strata of patients with ischemic stroke, VTE, CHF, AMI and levels of prescription benefits' generosity, ATRIA, CHA_2DS_2-VASc, and ages were examined using stratum-specific propensity scores and Cox proportional hazards regression (**Appendix table 15**). Some treatment effect heterogeneity was noted in the hazard of experiencing the clinical effectiveness composite of dabigatran compared with warfarin, particularly among patients with previous VTE (HR: 0.50, 95% CI: 0.35-0.72), ATRIA $\geq$ 5 (HR: 0.73, 95% CI: 0.60-0.90), CHA_2DS_2-VASc $\geq$ 2 (HR: 0.84, 95% CI: 0.77-0.92), and age $\geq$ 75 years (HR: 0.89, 95% CI: 0.79-1.01). Dabigatran patients with higher ATRIA ($\geq$ 5), CHA_2DS_2-VASc $\geq$ 2 and age $\geq$ 75 years were also noted to have a slightly lower hazard of

experiencing the harm composite compared with patients on warfarin with the same characteristics.

4.3.4.3. Exploratory analyses

4.3.4.3.1. *Assessment of International Normalized Ratios (INRs)*

The International Normalized Ratio laboratory results were collected from the laboratory data files in the Truven Health MarketScan® database for the AF patients included in the cohort. The Laboratory Observation Identifiers Names and Codes (LOINC) identifier for the INR test was "5902-2", describing a coagulation assay that included an INR test. CPT procedure codes known to be associated with INR test were assessed, and the code "85610" was found to be the only one in the laboratory files. Of these, the only LOINC identifier associated with INRs was the 5902-2. Of the available INRs in the database, INRs were captured when they occurred on or after the index prescription fill date, before one of the outcomes included in the composite, and before loss of continuous eligibility or administrative censoring on 12/31/2012.

In total, 463 warfarin initiators had any INR laboratory values available within the follow-up period for a total of 1,816 INRs measured. The mean INR laboratory value was 2.24 (SD: 0.91). Each patient's available measured INRs were summed, averaged, and calculated for the proportion of INRs which were in therapeutic range (2.0-3.0). Two-hundred and three warfarin initiators had only 1 INR measured in the eligible follow-up period; the mean number of INRs measured for each patient was 3.92 (SD: 5.03). For these 463 warfarin patients, the average mean INR value over the follow-up period was 2.10 (SD: 0.87). Of the 260 warfarin patients with at least 2 INRs measured in the data, more than 56.2% had <60% of their measured INRs within the therapeutic range of 2.0-3.0 for anticoagulation in atrial fibrillation.

4.3.4.3.2. *Medication adherence*

Medication adherence and refill patterns were also examined descriptively. The proportion of patients refilling their anticoagulation therapy at least once was also calculated post-initiation. Of the 43,865 patients initiating warfarin, 81.8% refilled their warfarin prescription at least once. Of the 21,070 patients initiating dabigatran, 77.7% refilled their prescription at least once. Comparing the two anticoagulants using multivariate logistic regression, adjusting for the measured baseline characteristics, demonstrated that the dabigatran patients were indeed significantly less likely to refill their prescription. Specifically, initiating dabigatran was associated with a 20% lower odds of refilling dabigatran (OR: 0.80, 95% CI: 0.76-0.83). The bivariate OR comparing dabigatran refill likelihood to warfarin refill likelihood was also very similar before adjusting for the baseline characteristics (OR: 0.78, 95% CI: 0.74-0.81).

Adherence to each anticoagulant was calculated as the proportion of days covered (PDC) by the prescription supply calculated from refill records in the claims in the 12-months post-anticoagulation initiation. Conforming to current literature, if the patient had ≥80% of days covered with prescription supply, a patient was defined as adherent. In total, 33,711 patients were continuously enrolled for at least 12 months post-anticoagulation initiation and had their medication adherence patterns assessed. Among these patients, the mean PDC was 0.62 (SD: 0.33) and 0.64 (SD: 0.35) for warfarin and dabigatran initiators, respectively. In total, 41.3% were adherent to warfarin, and 48.6% were adherent to dabigatran. Multivariable logistic regression was used to compared the odds of being adherent to dabigatran compared with warfarin over the 12-months post anticoagulation initiation, adjusting for the measured baseline characteristics. This analysis indicated that patients filling dabigatran had a higher (45%) likelihood of being adherent (OR: 1.45, 95% CI: 1.38-1.52). Notably, patients were more likely

to be adherent with high ischemic stroke risk (OR: 1.57, 95% CI: 1.21-1.50) compared with those with low ischemic stroke risk. However, elevated bleeding risk was not statistically associated with adherence.

4.4. AIM 3: CLINICAL EFFECTS ASSOCIATED WITH SWITCHING

4.4.1. Descriptive statistics

4.4.1.1. Cohort identification

In total, 64,935 AF patients were treatment-naïve and met overall study criteria. Of the 43,865 patients who initiated warfarin, 42,752 patients were included in the cohort. For this study, only patients switching to dabigatran or warfarin were assessed, so 1,113 patients were excluded as switchers because they switched from warfarin to rivaroxaban in the follow-up period. In total, 2,373 warfarin initiators also contributed follow-up time as "switchers", because they switched to dabigatran after initiating warfarin before they experienced any of the measured outcomes, lost continuous eligibility or were censored administratively. These patients are characterized as "warfarin switchers" throughout this aim. Of the 20,070 patients who initiated dabigatran, 19,799 patients were included in the cohort; 1,271 patients were excluded because they switched from dabigatran to rivaroxaban in the follow-up period. In addition, 959 dabigatran initiators also contributed follow-up time as "switchers" and are characterized as "dabigatran switchers" through this aim. Of the patients who switched, warfarin patients switched in a mean 114.5 days (SD: 125.0), and dabigatran patients switched in a mean 116.8 days (SD: 134.6).

4.4.1.2. Baseline characteristics

Baseline characteristics are shown in **Table 25**. Patients were only included once in the descriptive statistics. If patients contributed any follow-up time as "switchers", they were classified as "switchers" and not as "non-switchers" for the numbers and percentages of the

baseline characteristics, because these are baseline characteristics measured in the 12-month period prior to the first anticoagulant initiation.

As expected, the distribution of the baseline characteristics concur with the findings in Aim 1b, which examined characteristics associated with switching over the 12-month follow-up period in patients who retained continuous eligibility for 12 months. Here in Aim 3, patients who initiated warfarin and switched to dabigatran were younger, have slightly better prescription benefits generosity, and were less likely to have had ischemic stroke, congestive heart failure, or other comorbidities. Patients who switched from warfarin to dabigatran also had lower baseline ischemic stroke risk and bleeding risk. In addition, warfarin switchers were slightly more likely to be using concomitant antiarrhythmic therapies compared with non-switchers.

Similarly to Aim 1b, patients who initiated dabigatran and then switched to warfarin were mostly similar to those who did not switch to warfarin – with some small exceptions. Patients who switched were slightly more likely to be older, female and have higher ischemic stroke risk compared with non-switchers. However, patients who switched were also slightly less likely to have ischemic stroke, congestive heart failure, acute myocardial infarction, or higher bleeding risk at baseline compared with non-switchers. Overall, the characteristics were more descriptively similar among dabigatran switchers and non-switchers compared with warfarin switchers and non-switchers.

Table 25. Baseline characteristics of warfarin and dabigatran switchers and non-switchers

Baseline Characteristic	Warfarin switcher, N (%)	Warfarin non-switcher, N (%)	Absolute SD	Dabigatran switcher, N (%)	Dabigatran non-switcher, N (%)	Absolute SD
Demographic						
Age						
< 55 years	224 (9.4)	3,557 (8.8)	2.8	100 (10.3)	2,728 (14.5)	18.3
55-64 years	681 (28.7)	9,143 (22.6)	17.1	283 (29.2)	5,812 (30.9)	4.6
65-74 years	600 (25.3)	8,914 (22.1)	9.4	235 (24.3)	4,290 (22.8)	4.5
≥ 75 years	868 (36.6)	18,765 (46.5)	24.6	350 (36.2)	6,001 (31.9)	10.9
Male Gender	1,435 (60.5)	23,467 (58.1)	5.5	534 (55.2)	12,082 (64.2)	20.8
Region						
Northeast	337 (14.2)	7,090 (17.6)	12.7	156 (16.1)	3,177 (16.9)	2.8
North Central	726 (30.6)	14,373 (35.6)	13.3	282 (29.1)	5,509 (29.3)	0.5
South	782 (33.0)	10,982 (27.2)	15.3	357 (36.9)	6,971 (37.0)	0.3
West	440 (18.5)	7,099 (17.6)	3.0	162 (16.7)	2,874 (15.3)	4.9
Insurance plan						
Comprehensive	863 (36.4)	14,439 (35.8)	1.5	334 (34.5)	6,030 (32.0)	6.4
HMO	192 (8.1)	6,086 (15.1)	34.0	89 (9.2)	1,543 (8.2)	4.7
POS	150 (6.3)	1,762 (4.4)	10.8	60 (6.2)	1,083 (5.8)	2.3
PPO	1,000 (42.1)	15,398 (38.1)	9.7	423 (43.7)	8,766 (46.6)	6.9
CDHP	47 (2.0)	635 (1.6)	4.0	21 (2.2)	422 (2.2)	0.0
Benefits generosity						
No/poor coverage	77 (3.2)	1,508 (3.7)	3.9	3 (0.3)	55 (0.3)	0.0
Fair coverage	1,108 (46.7)	19,762 (49.0)	5.4	458 (47.3)	8,748 (46.5)	1.9
Good coverage	1,188 (50.1)	19,079 (47.3)	6.5	507 (52.4)	10,028 (53.3)	2.1
Clinical						
Ischemic Stroke	141 (5.9)	4,476 (11.1)	29.7	43 (4.4)	1,366 (7.3)	19.3
Congestive Heart Failure	488 (20.6)	11,676 (28.9)	25.9	162 (16.7)	3,480 (18.5)	6.3
VTE	71 (3.0)	5,236 (13.0)	78.5	28 (2.9)	480 (2.6)	2.5
Hyperlipidemia	1,094 (46.1)	20,074 (49.7)	8.4	488 (50.4)	9,344 (49.6)	1.8
Hypertension	1,660 (70.0)	2,980 (73.3)	7.9	684 (70.7)	12,991 (69.0)	4.0
Myocardial infarction	59 (2.5)	1,898 (4.7)	19.5	16 (1.7)	457 (2.4)	7.6
Coronary artery disease	674 (28.4)	13,971 (34.6)	16.9	294 (30.4)	5,264 (28.0)	20.2
Peripheral vascular disease	136 (5.7)	3,680 (9.1)	19.9	55 (5.7)	1,011 (5.4)	1.8
Renal impairment	149 (6.3)	5,299 (13.1)	37.4	57 (5.9)	1,089 (5.8)	0.6
Diabetes	702 (29.6)	12,913 (32.0)	6.5	239 (24.7)	5,016 (26.6)	5.6
Major bleeding	236 (10.0)	5,608 (13.9)	17.3	81 (8.4)	1,760 (9.4)	4.9
Anemia	281 (11.8)	8,301 (20.6)	35.4	96 (9.9)	2,028 (10.8)	4.1
Peptic Ulcer disease	9 (0.4)	306 (0.8)	8.9	3 (0.3)	88 (0.5)	5.2
Sleep Apnea	279 (11.8)	4,137 (10.3)	6.3	115 (11.9)	2,271 (12.1)	0.8
Cognitive deficiency	8 (0.3)	420 (1.0)	18.0	3 (0.3)	111 (0.6)	7.7
CCI						
0	715 (30.1)	9,014 (22.3)	21.5	329 (34.0)	6,362 (33.8)	0.5
1-2	1,051 (44.3)	16,123 (39.9)	10.5	419 (43.3)	8.068 (42.8)	21.8
3-5	514 (21.7)	11,107 (27.5)	17.8	187 (19.3)	3,549 (18.9)	1.3
6-8	73 (3.1)	3,045 (7.5)	34.7	23 (2.4)	636 (3.4)	9.1

≥ 9	20 (0.8)	1,090 (2.7)	29.8	10 (1.0)	216 (1.2)	2.8
$CHADS_2$						
0	318 (13.4)	3,963 (9.8)	14.2	141 (14.6)	3,022 (16.1)	5.6
1	743 (31.3)	10,275 (25.5)	15.7	330 (34.1)	6,331 (33.6)	1.3
≥2	1,312 (55.3)	26,141 (64.7)	21.8	497 (51.3)	9,478 (50.3)	2.3
CHA_2DS_2-VASc						
0	209 (8.8)	2,629 (6.5)	11.1	96 (9.9)	2,234 (11.9)	9.0
1	468 (19.7)	5,684 (14.1)	18.6	209 (21.6)	4,203 (22.3)	2.2
≥2	1,696 (71.5)	32,066 (79.4)	19.7	663 (68.5)	12,394 (65.8)	6.3
ATRIA						
0-3	1,927 (81.2)	27,852 (69.0)	30.2	817 (84.4)	15,715 (83.5)	2.6
4	193 (8.1)	3,882 (9.6)	7.4	68 (7.0)	1,341 (7.1)	0.5
≥5	253 (10.7)	8,645 (21.4)	44.9	83 (8.6)	1,775 (9.4)	3.9
HAS-BLED						
0-2	2,207 (93.0)	35,020 (86.7)	21.5	914 (94.4)	17,511 (93.0)	5.9
≥3	166 (7.0)	5,359 (13.3)	32.9	54 (5.6)	1,320 (7.0)	8.3
Hospitalizations						
≥1	1,119 (47.2)	23,546 (58.3)	26.0	413 (42.7)	8,530 (45.3)	6.2
Catheter ablation	17 (0.7)	364 (0.9)	3.4	11 (1.1)	431 (2.3)	16.1
Medication Use						
Antiplatelet therapy	268 (11.3)	5,305 (13.1)	7.6	106 (11.0)	2,409 (12.8)	7.7
Gastroprotective agent	262 (11.0)	5,162 (12.8)	7.7	109 (11.3)	2,009 (10.7)	2.5
Antiarrhythmic	577 (24.3)	9,116 (22.6)	5.1	247 (25.5)	4,788 (25.4)	0.3
Digoxin	406 (17.1)	6,848 (17.0)	0.3	142 (14.7)	2,650 (14.1)	2.2
Beta-blocker	1,554 (65.5)	27,194 (67.4)	4.4	667 (68.9)	12,595 (66.9)	4.7
Calcium channel blocker	1,047 (44.1)	17,009 (42.1)	4.8	410 (42.4)	7,634 (40.5)	19.4
ACEI/ARB	1,413 (59.5)	22,909 (56.7)	6.4	535 (55.3)	10,628 (56.4)	2.5
Statin	1,275 (53.7)	22,073 (54.7)	2.3	517 (53.4)	10,006 (53.1)	0.7
Hormone	120 (5.1)	1,445 (3.6)	9.5	60 (6.2)	832 (4.4)	10.3

Abbreviations: HMO, Health maintenance organization; POS, Point-of-service; PPO, Preferred provider organization; CDHP, consumer-driven health plan; CCI, Charlson Comorbidity Index; ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker

4.4.1.3. Crude outcome rates

The outcome rates of patients who switched anticoagulation following initiation were also examined standardized by 1,000 person-years of exposure in the cohort. These rates are shown in **Table 26** for the clinical effectiveness composite, harm composite, and AMI below; just as in Aim 2, AMI was not included in either of the aforementioned composites but was followed separately as an outcome. As described in Chapter 3, patients were not censored for the other two outcomes if they experienced the outcome of interest for each analysis. Said another way, patients who experienced an ischemic stroke were censored for the clinical effectiveness

composite but not for the harm composite or the acute myocardial infarction outcome. As seen in the table, the crude outcome rates were higher among patients who were non-switchers compared with switchers for both warfarin and dabigatran switchers. For instance,, patients who did not switch from warfarin to dabigatran had a crude clinical effectiveness outcome rate of 238.5 events/1,000 person-years compared with those who switched (51.2 events/1,000 person years).

Table 26. Outcome rates per 1,000 person-years by warfarin and dabigatran switching groups

	Warfarin		Dabigatran	
Outcome Type	**Switchers[§]**	**Non-switchers**	**Switchers[§]**	**Non-switchers**
Clinical effectiveness composite	51.2	238.5	66.8	92.7
Harm Composite	273.0	495.7	345.5	408.2
Acute myocardial infarction	8.8	19.5	9.4	11.9

[§] Warfarin switchers: patients who switched from warfarin to dabigatran; Dabigatran switchers: patients who switched from dabigatran to warfarin

4.4.2. Main Results

4.4.2.1. Composite outcomes

The associations between anticoagulant switching and outcome composites were also assessed using multivariable Cox proportional hazards regression (**Table 27**), using the aforementioned methods and model specifications in Chapter 3. As previously described, patients were censored at their first outcome, whether it was a clinical effectiveness or harm outcome, or acute myocardial infarction.

Multivariable models were adjusted for the measured baseline characteristics in the 12-months prior to anticoagulant initiation that were previously described in Chapter 3. The full model results are shown in **Appendix table 16** for warfarin analyses and **Appendix table 17** for dabigatran analyses. Patients who switched from warfarin to dabigatran were 32% less likely to experience a clinical effectiveness outcome (adjusted HR: 0.68, 95% CI: 0.66-0.71), 32% less likely to experience a harm composite outcome (adjusted HR: 0.68, 95% CI: 0.65-0.71), and 32% less likely to experience an AMI (HR: 0.68, 95% CI: 0.66-0.70). Patients who switched from dabigatran to warfarin were no more likely to experience a clinical effectiveness outcome (adjusted HR: 1.02, 95% CI: 0.97-1.08), a harm outcome (adjusted HR: 1.06, 95% CI: 0.97-1.15), or an AMI (adjusted HR: 0.99, 95% CI: 0.94-1.04).

Table 27. Multivariable Cox models of the association between anticoagulant switching and clinical effectiveness and harm outcomes

Anticoagulant groups (referent: non-switchers)	Clinical effectiveness composite HR (95% CI)	Harm composite HR (95% CI)	Acute myocardial infarction HR (95% CI)
Warfarin to dabigatran switchers			
Unadjusted	0.67 (0.65-0.70)**	0.67 (0.64-0.70)**	0.66 (0.64-0.68)**
MV-adjusted	0.68 (0.66-0.71)**	0.68 (0.65-0.71)**	0.68 (0.66-0.70)**
Dabigatran to warfarin switchers			
Unadjusted	1.02 (0.97-1.08)	1.05 (0.97-1.14)	0.99 (0.94-1.04)
MV-adjusted	1.02 (0.97-1.08)	1.06 (0.97-1.15)	0.99 (0.94-1.04)

*p<0.05; **p<0.001
Abbreviations: HR, Hazard Ratio; CI, Confidence interval; MV, multivariable model
REF: Non-switching

4.4.2.2. Model diagnostics and specifications

Categories of covariates with fewer than 2% of patients with that characteristic were combined with another relevant level (e.g., "No", "Poor", and "Fair" prescription benefits generosity) or omitted from the model adjustments (e.g., consumer-driven health plan, cognitive deficiency, and peptic ulcer disease), when possible. These were done to ensure that very small cell sizes for certain categories would not affect the model dispersion or the positivity assumption. The deviance residuals showed appropriate distributions. Proportional hazards assumptions were tested for both composite outcomes and the AMI for the models. These tests did not reveal any violations of the assumptions for the models, using either Schoenfeld residuals or including an interaction term for time.

4.4.3. Sensitivity analyses

4.4.3.1. Primary analysis: Stratification by commercial insurance and Medicare beneficiaries

Just as in Aim 1a, the cohorts were also stratified based on the data sources into commercially-insured and Medicare supplemental claims, and the analyses were conducted

separately (**Appendix table 18**). The associations between switching anticoagulants were similar to the main results. Switching from dabigatran to warfarin trended towards an increased risk of the harm composite compared with non-switching when examining the Medicare supplement group separately. Despite the small sample sizes, dabigatran switching was seen to be slightly more harmful among Medicare beneficiaries compared with commercially-insured patients alone. The other associations were very similar when analyzing the subgroups individually.

CHAPTER 5: DISCUSSION

The goal of the dissertation was to examine the utilization, comparative effectiveness and safety, and clinical effects of switching anticoagulation among patients with atrial fibrillation (AF) in real-world US clinical practice. These three aims document the results of this research. In summary, in Aim 1, we sought to examine the utilization and switching of anticoagulation among patients initiating anticoagulation for the prevention of ischemic stroke and systemic embolism in atrial fibrillation, focusing in particular on how predictions of ischemic stroke and bleeding risk influenced anticoagulant selection. In Aim 2, we examined the comparative effectiveness of dabigatran and warfarin among patients with non-valvular atrial fibrillation newly-initiating anticoagulation. In Aim 3, we examined the clinical effects of switching anticoagulation and whether switching to a different anticoagulant was associated with a higher risk of stroke and other clinical effects. This concluding chapter synthesizes the findings from these three aims, discusses the findings' implications, highlights the strengths and weaknesses of the study, and provides suggestions for further work in this area.

5.1. SUMMARY OF FINDINGS

5.1.1. Aim 1: Patterns of use and switching of anticoagulants

5.1.1.1. Aim 1a: Patterns of anticoagulant utilization

In this large study of 64,935 AF patients initiating anticoagulation, we found that demographic and clinical characteristics differed strongly between new users of warfarin and dabigatran. Patients using warfarin for the first time were more likely to be older and have

previous clinical comorbidities, particularly ischemic stroke, congestive heart failure and venous thromboembolism. Patients initiating warfarin were also more likely to have higher ischemic stroke risk (as assessed by the $CHADS_2$ or CHA_2DS_2-VASc scores), higher bleeding risk (as assessed by the HAS-BLED or ATRIA scores), and lower prescription benefits' generosity, which measures how much patients paid for their prescription medications relative to how much their insurance paid. The lower the prescription benefits' generosity, the higher the patient's relative out-of-pocket prescription drug cost burden.

When adjusting for patient baseline characteristics using multivariable regression, we still found that the strong associations with ischemic stroke risk and bleeding risk between warfarin initiators compared with dabigatran initiators persisted. Patients using dabigatran were 8% less likely to have high ischemic stroke risk and 28% less likely to have high bleeding risk compared with warfarin users. Other patient characteristics were also still associated with anticoagulant selection, including prescription benefits' generosity which was one of the strongest predictors of initiation of dabigatran in this analysis. Patients with good prescription benefits' coverage (<20% paid out of pocket in the previous 12 months) were 10 times more likely to initiate dabigatran compared with warfarin.

5.1.1.2. Aim 1b: Anticoagulant switching patterns

In Aim 1b, among the 33,712 patients with atrial fibrillation initiating anticoagulation who were still enrolled in their insurance plans 12 months later, we found that approximately 12% switched their initial anticoagulant therapy. Approximately 30% of the patients who switched anticoagulants did so within 60 days of initiation. Notably, dabigatran initiators and warfarin initiators switched anticoagulants at relatively equal rates. However, characteristics of switchers compared with non-switchers of the two anticoagulants differed drastically.

Patients who switched away from warfarin had fewer comorbidities, low ischemic stroke risk, and low bleeding risk. By contrast, on most other measures, dabigatran switchers did not appear to differ systematically from non-switchers, with the exception of age, gender, coronary artery disease and increased ischemic stroke risk. After controlling for baseline patient characteristics, dabigatran patients were 35% more likely to switch with higher baseline ischemic stroke risk but were no different than non-switchers with regard to baseline bleeding risk. Prevalent users of warfarin followed similar switching patterns to new initiators of warfarin in that they were more likely to switch if they had lower rates of comorbidities, lower ischemic stroke, and lower bleeding risk.

These results suggest that patients initiating warfarin may be more concerned with the risk of harm (bleeding) of dabigatran and may be less likely to switch to dabigatran with higher bleeding risk. These findings are in concert with the patterns of use observed by new initiators in Aim 1, in which dabigatran patients were less likely to have higher bleeding risk. Of all the clinical and prognostic characteristics associated with dabigatran switching, the association between high ischemic stroke risk and not switching from dabigatran to warfarin was the greatest. These findings could suggest two possibilities: 1) patients with high ischemic stroke risk may be more likely to persist with initial therapy because of the high possibility of stroke, or 2) patients with high ischemic stroke risk may have been more likely to see a noticeable benefit in dabigatran altogether compared with patients with low ischemic stroke risk (and thus not experienced therapeutic failure leading to the need to switch). Either way, now that there are more treatment options for non-valvular atrial fibrillation, a significant number of patients are switching anticoagulation options within the first year of treatment, but there were equal proportions of patients switching their initial anticoagulants.

5.1.2. Aim 2: Comparative effectiveness and safety of anticoagulants

In Aim 2, in this large study of 64,935 patients with non-valvular atrial fibrillation, after multivariable adjustment using survival analysis, we found that patients initiating dabigatran were approximately 30% less likely to experience ischemic stroke, venous thromboembolism, or transient ischemic attacks compared with patients initiating warfarin. However, when examining the comparative safety of experiencing an adverse event, patients initiating dabigatran were equally likely to experience one of the harm outcomes (e.g., hemorrhage, bleeding, or hospitalization) with two notable exceptions. First, dabigatran patients were approximately 40% and 15% less likely to experience a hemorrhagic stroke and other bleeding event compared with warfarin patients. However, dabigatran patients were also 10% more likely to experience a gastrointestinal bleeding event after initiating anticoagulation. Notably, myocardial infarction risk also did not differ between the two anticoagulant groups. These results were also confirmed among a subset of patients who were newly-diagnosed with atrial fibrillation. Overall, these results suggest that dabigatran has better comparative effectiveness and safety compared with warfarin among non-valvular atrial fibrillation patients in real-world clinical practice in the US.

We also found some potential areas of treatment effect heterogeneity among patients receiving different strengths of dabigatran. The comparative effectiveness in preventing ischemic stroke or VTE did not differ between warfarin initiators and dabigatran 75mg initiators; however, patients using the lower dabigatran dose were more likely to experience harmful outcomes compared with warfarin initiators. By contrast, when stratifying on dose, the comparative effectiveness and safety of dabigatran 150mg was even more pronounced compared with warfarin initiators.

Certain characteristics known to be associated with comparative effectiveness in the real-world were also noted in this aim. For instance, medication adherence and refill patterns were

also seen to notably differ across the anticoagulant groups. Patients initiating dabigatran had a 20% lower likelihood of refilling dabigatran after the initial prescription compared with warfarin initiators. Overall medication adherence was also low in this study (<50% PDC in the 12-months post-anticoagulation initiation). Even though they were less likely to refill initially, patients filling dabigatran were found to have 45% higher likelihood of being adherent (PDC ≥ 80%) compared with warfarin initiators, even after adjustment for patient baseline characteristics. However, patients with high ischemic stroke risk were more likely to be adherent compared with those with low ischemic stroke risk.

5.1.3. Aim 3: Clinical effects of switching anticoagulants

In Aim 3, the goal was to examine whether patients who switched anticoagulants were at a higher risk of adverse events compared with patients who remained on one medication. We were particularly interested in isolating patients who switched for reasons unlikely to be associated with therapeutic failure, motivating the use of a time-varying exposure design that censored patients if they had experienced a clinical outcome prior to the switch.

In this study, we found notable differences in clinical outcomes among patients who switched anticoagulants (and had not experienced an outcome prior to the switch) compared with those who did not switch anticoagulation. After adjustment for patient baseline characteristics, we also found that patients who switched from warfarin to dabigatran were 32% less likely to experience ischemic stroke, VTE, or TIA compared with non-switchers. However, these warfarin switchers were also 32% less likely to experience a harm outcome, including bleeding, hemorrhage or hospitalization. Overall, these results suggest the risk of switching between anticoagulants is unlikely to result in any clinically-significant increases in clinical effectiveness or harm outcomes.

5.2. IMPLICATIONS OF FINDINGS

These results concur in part with previous research suggesting that some selection (or channeling) away from dabigatran has occurred, particularly away from patients with high ischemic stroke and bleeding risk.[40,241] Specifically, patients at higher risk of clinical outcomes like ischemic stroke or bleeding were much more likely to initiate the standard of care, warfarin. While these studies were generally small in sample size or limited to younger patients, they too found that patients who were newly-initiating dabigatran had lower bleeding risk and fewer comorbidities. However, in contrast to a recent study published by Steinberg et al, we found that bleeding risk was more strongly associated with initial anticoagulant selection than ischemic stroke risk.[242] In our study, we found that patients with higher bleeding risk initiated dabigatran more often than warfarin. Moreover, the associations with initial anticoagulation selection were higher in magnitude for the risk of bleeding compared with the risk of ischemic stroke in our study. Their study found an overall lack of familiarity with bleeding risk guidelines by physicians for patients enrolled in the ORBIT-AF registry; however, the study was limited by participants enrolling through October 2011 and did not examine either rivaroxaban or the contribution of patients' prescription benefits. By comparison, the results in our study suggest that there may be selective use of dabigatran for patients at lower risk of bleeding. Concerns over lack of a bleeding antidote may indeed prevail in this risk-benefit paradox.[40,241]

Our findings suggest that clinicians may be differentially choosing warfarin in real-world clinical practice for patients with both high stroke risk and bleeding risk, which may indicate possible concerns about the complications with the lack of a convenient reversal agent for the NOACs in general. In addition, these findings are in contrast to some other studies examining newly-approved pharmaceuticals. In other contexts, patients using newly-approved pharmaceuticals have tended to be sicker than those on the comparator medication; our findings

were opposite, which may have implications for studying comparative effectiveness.[181,243] If patients using the newly-approved therapies are more likely to be sicker (and these confounders are not properly controlled for), then the new therapy is more likely to appear inferior to the standard of care. For our study, the patients using the newly-approved therapy were healthier, in which case the new therapy is more likely to appear superior. These observations could have implications for the process and outcomes of treatment decision-making in clinical practice in that researchers should strive to consider which way their estimates are likely to skew and control for confounding using the best possible methodologies.

Further, providers appear to base anticoagulant selection on factors other than predictions of treatment benefit, which has implications for studying the anticoagulants' comparative effectiveness. At the time of this research, clinical guidelines had recommended continuing with warfarin in currently-treated patients but have been less clear with anticoagulant selection in treatment-naïve patients, which were the focus of this dissertation.[2-4] Until early 2014, warfarin was still considered the preferred agent in the US; however, as early as 2012, European guidelines had begun to prefer the novel agents for anticoagulant-naïve patients with non-valvular atrial fibrillation.[3] On the other hand, recent guidelines from the American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) published in March 2014 suggested that clinical equipoise may exist between all the anticoagulants for patients at high risk of stroke.[5]

These guidelines also recommend that clinicians weigh the balance of benefit with the risk of harm of available treatment options, but also consider that treatment selection may be in large part influenced by clinicians through preferences or other factors unrelated to patient clinical or prognostic characteristics.[244] In our study, while both ischemic stroke risk and bleeding risk were associated with overall anticoagulant selection, other clinical and

demographic factors, including prescription benefits' generosity were also strongly associated with selection. Because there is some clinical equipoise in our study, this finding may be exploited when assessing the comparative effectiveness of these anticoagulants. Because factors not clinical and prognostic may be related to initial anticoagulant selection and may lessen potential bias, we can have more faith in our estimates.

Comorbidity and co-medications may also play a role in anticoagulation switching. We saw in this study that patient comorbidity burden may play a role in lessening the likelihood of switching in that patients with more cardiovascular comorbidities were less likely to switch. Moreover, using antiarrhythmic or beta-blocker medications at baseline was also associated with switching from warfarin but not dabigatran. These factors together suggest that patients who are frailer are less likely to switch anticoagulants. It is also possible that patients using warfarin may have higher comorbidities at baseline and be more cautious with switching to avoid side effects, as has been seen in previous studies.[40,41,245] All in all, switching anticoagulants does not appear to be consistent across anticoagulants and may be due to the underlying reasons why the patients were initially placed on those medications to begin with.[224] Most recent guidelines and commentaries have recommended maintaining patients on warfarin if they were previously stabilized using warfarin, and these findings can be reassuring that indeed most patients are remaining on their initial anticoagulant as is recommended.[5] Either way, switching medications generally requires more time from the provider, pharmacist, and health care system to ensure the patient has the adequate knowledge to manage the new medication, which is enough reason to be cautious to avoid unnecessary switching.[224]

When considering the anticoagulants' clinical effectiveness, the large randomized-controlled trials used for initial approval of dabigatran and the other NOACs broadly found similar or better efficacy in preventing ischemic stroke and systemic embolism compared with

warfarin but significantly better safety, particularly in reducing intracranial bleeding and hemorrhagic stroke.[13,15,18] The results of this study concur with the RE-LY trial, in that dabigatran appears to be more effective than warfarin in preventing ischemic stroke and systemic embolism.[13] Just as in the RE-LY trial, gastrointestinal bleeding was higher among dabigatran patients compared with warfarin patients, but there were otherwise no general differences in the risk of harm or adverse outcomes. A very recent report by the FDA of a very large cohort of Medicare patients with atrial fibrillation found similar associations with lower risk of clot-related strokes, intracranial bleeding and death compared with warfarin.[246]

Our study also found a similar risk for AMI compared with warfarin and an increased risk of major gastrointestinal bleeding. Overall, while the use of dabigatran should be cautioned in patients at high bleeding risk, high risk of gastrointestinal bleeding or in renal insufficiency, dabigatran should otherwise be considered a safe and effective alternative to warfarin, even in real-world clinical practice.[17,122] We did note some underlying treatment effect heterogeneity among certain characteristics of AF patients, particularly patients with prior VTE and higher bleeding risk, which warrants further exploration. In addition, sensitivity analyses on the outcome definition and the subgroups yielded similar associations with slightly differing magnitudes, but the overall conclusions were robust to these modifications. Either way, insurers and policy-makers alike can have some reassurance that dabigatran users are no more likely to have worsened clinical outcomes compared with warfarin users, even outside the tightly-monitored clinical trials, particularly once underlying comorbidity differences are controlled for, as in this study.

Unlike the RE-LY trial, patients in our study were not regularly followed up as part of a protocol; in our study, these were patients in real-world practice. Some have felt that the clinical efficacy in the RE-LY trial was largely due to the regular monitoring of dabigatran that would

not necessarily take place in the real world but was done in the study to maintain blinding with warfarin, and a recent article by the *BMJ* in July 2014 raised some concerns about the trial's conduct and possible underrepresentation of bleeding events.[247,248] In addition, the rates of adverse events submitted to the FDA have also been higher for dabigatran compared with warfarin since dabigatran's market availability, but the FDA has since found that more events were likely to be reported, because dabigatran is a newer medication.[138] For both these concerns, the results of Aim 2 could be used to reassure patients and providers, because the results do indicate that dabigatran can be considered a safe and possibly more effective alternative to warfarin, even in patients outside clinical trials. Moreover, the fact that in Aim 1b, there were no differences in the rates of switching away from dabigatran compared with switching away from warfarin bolsters this assumption. Had there been major differences in switching, one could attribute those differences in switching to differences in therapeutic failure or adverse complications, but this was not the case in our study.

Due to the dependence on adherence and persistence to warfarin and dabigatran for the prevention of ischemic stroke and thrombosis, the low rate of adherence to both warfarin and dabigatran is concerning. Dabigatran patients were less likely to refill their medication again, but warfarin patients were less likely to be adherent over a 12-month period (even taking into account switching to a different anticoagulant). In this way, discontinuation would not be inappropriately attributed to not continuing anticoagulation altogether. While this study did not specifically examine persistence or discontinuation to warfarin, the low overall rate of adherence (less than 50%) to anticoagulation is troubling. Indeed, Tsai et al recently found that 40% of beneficiaries discontinued dabigatran within 6 months among a cohort of 17,000 US beneficiaries, most of whom did not continue any anticoagulation.[248] Our finding of adherence less than 50% at 12-months post-initiation concur with their results. These results continue to

suggest a need for healthcare professionals to provide additional support with these medications, particularly if the need for weekly face-to-face interactions through INR monitoring is no longer necessary in the novel oral anticoagulants. In addition, dabigatran is also dosed twice-daily, compared with warfarin's once-daily dosing, which could play a role in medication adherence and potential adverse events with a missed dosed.

Further, the findings from Aim 3 could possibly be attributed to physiologic differences between the agents. Warfarin's half-life is much longer than dabigatran's half-life..[5] As a result, switching from warfarin to dabigatran could be less problematic for both clinical effectiveness and harm outcomes compared with switching from dabigatran to warfarin. Indeed, switching to dabigatran was associated with similar (or lower) risk of harmful outcomes compared with remaining on warfarin. By comparison, switching to warfarin from dabigatran resulted in no clinically-significant differences in risk for the outcomes studied. While guidelines are clearer about how to bridge to dabigatran from warfarin (initiate dabigatran once INR<2.0) compared with vice versa, neither switching direction resulted in clinically or statistically significant increases in outcomes, which is generally the largest concern in switching medications. While guidelines recommended maintaining prevalent users of warfarin on warfarin, these findings can be reassure that switching anticoagulants is unlikely to results in any large risk of outcomes.

Further, the analysis of switching anticoagulants also poses an interesting question. In Aim 2, we found that the comparative effectiveness of dabigatran was superior to warfarin. However, how can one adequately measure the actual "risk" of switching anticoagulant altogether compared with the advantages in comparative safety of switching to the new agent? Indeed, we found that the clinical effects of switching from warfarin to dabigatran were superior to staying on warfarin – at least unilaterally in terms of reducing ischemic stroke and systemic embolisms. Had we been only measuring the comparative effectiveness of the agents (and not

the effects of switching), we would have seen a corresponding increase in the risk of adverse outcomes when switching from dabigatran to warfarin. However, we saw no difference in the risk of outcomes when examining switching from dabigatran to warfarin.

We know that incident user designs are usually preferred when measuring comparative effectiveness and safety, because prevalent user designs are more fraught with biases such as survivor bias and confounding by indication.[189,199,249] However, in the real world, patients are not always incident users, and warfarin has been thought to have major issues with switching between manufacturers – let alone different agents. The design employed in Aim 3 is intended to disentangle this question and point to why examining "switching" – as compared with just prevalent or incident use – can be useful in its own right. Indeed, studying prevalent users is not the same as examining switching between medications. Despite the comprehensive literature search for this dissertation, there was a relative lack of literature examining methods to address medication switching itself as an exposure and resulting outcomes. More attention should be paid towards developing methods to try to better assess medication switching.

5.3. STRENGTHS AND WEAKNESSES

As previously described in the Chapter 3 (Methods), our study has several limitations. First, prescription refill records from commercial claims databases may not fully reflect medication use. However, prescription refill records have been shown to have good validity, correlation, and similar sensitivity and specificity as other measurements, including self-report, pill counts, and electronic records.[209,250] Some warfarin prescriptions may also not be captured due to concomitant market influences, such as the low-cost generic prescription programs available in community pharmacies; however, these patients would merely not be included in this study.[201] The ATRIA score has also been used less frequently in research; however, it has

shown to be better validated in administrative claims data compared with other measures of bleeding risk.[107,113] In addition, the use of a 12-month baseline period for covariate identification, while standard in the literature and avoids unnecessary sample size truncations, may have led to some underidentification of covariates, although this was unlikely to be differential between the anticoagulant groups.[251] While this study could not measure mortality, the recent findings from the FDA and the sensitivity analyses help reduce the likelihood this impacted the study results.[246]

In addition, as previously discussed, unmeasured confounding, especially healthy user biases, may impact the study's findings. While underlying characteristics were adjusted for in the regression analyses, warfarin patients may be sicker (or frailer) in other confounding characteristics that could not be measured. The fact that the unadjusted analyses were down and away from the null and adjusting through multivariate analyses and propensity scores move the estimates closer to the null indicates that some residual confounding may exist. Provider-level and health-system level covariates could also not be measured due to the limitations of the database.

The findings from Aim 3 may also be impacted, because technically the "switcher" follow-up time may have led to some survivor bias, as the switchers had to avoid an outcome in order to be considered an anticoagulant switcher. While this censoring may also have impacted generalizability of the findings, it also limited confounding by indication. Ideally, marginal structural models could be an approach to address this issue and could be considered in future research to address issues of time-varying exposure and time-varying covariates.

In addition, in Aim 3, by virtue of the design and the intention-to-treat approach, patients were not removed from the cohort if they discontinued medications or had poor medication adherence. Our study found that patients who switched medications were no less likely to experience a harm outcome compared with patients who did not switch. If patients had actually

discontinued the medication, they would have contributed exposure time to the "non-switching" group. In theory, that could have actually made the "non-switching" group slightly less at risk of a harmful outcome; however, it also could have left the "non-switching" group at higher risk of ischemic stroke and systemic embolism (because of the discontinuation). In actuality, this finding was only noted in the warfarin switcher group and not in the dabigatran switcher group. If this assumption was to have hugely biased the study, it likely would have biased both the warfarin switchers and the dabigatran switchers.

There are, however, also several strengths of this study. This research used a large database of nationally-representative commercially-insured patients, including some Medicare beneficiaries in the United States. To our knowledge, most previous research examining the use of the novel anticoagulants has been conducted in Europe, in smaller, less representative databases, or by synthesizing results from randomized-controlled trials in meta-analyses. In addition, this study assessed general patterns of use and effectiveness of dabigatran a full two years after NOACs have been available, which have not been previously published. Lastly, while the clinical prediction risk scores have been thought to be only moderately associated with true risk of the outcomes in atrial fibrillation, the use of the CHA_2DS_2-VASc in particular has been thought to have better real-world concordance than the $CHADS_2$ and could also be considered a strength of our study compared with previous analyses.

5.4. RECOMMENDATIONS FOR FUTURE RESEARCH

First and foremost, due to the availability of data, this dissertation focuses on dabigatran. While dabigatran is now just one of the (currently) three FDA-approved NOACs for the prevention of stroke and systemic embolism, rivaroxaban and apixaban have more recently been available. Much work will be needed in general in this growing area – examining not just

dabigatran but the other NOACs as well. Early evidence indicates that each of the NOACs could have slightly different advantages and disadvantages. Dabigatran, in particular, may lead to more gastrointestinal side effects, and may be more problematic for patients with renal insufficiency. On the other hand, dabigatran may have fewer drug-drug interactions than either rivaroxaban or apixaban, because it is not metabolized via CYP3A4 and may be better for patients with hepatic disease. Either way, the clearest recommendation for future research lies in the need to disentangle the advantages and disadvantages of the NOACs, as most research to date in the real-world setting has examined dabigatran exclusively.

Relatedly, another trend worth noting is that the number of patients initiating warfarin decreased somewhat over time, while the number of patients initiating dabigatran increased from baseline in late 2010 and peaked in early 2012. Beginning in the 1st quarter of 2012, dabigatran initiation too began to decline. The introduction of rivaroxaban in late 2011 for the prevention of ischemic stroke and systemic embolism may have affected trends in anticoagulation use over the study time period. Future research should examine how utilization patterns of rivaroxaban (and other NOACs such as apixaban and edoxaban) have influenced medication selection and how they fare in comparative effectiveness and safety. Head-to-head studies are unlikely due to cost and feasibility issues, and salient and sound observational research studies in a variety of populations will be needed to ascertain not only how these medications are really being used clinically but also how safe and effective they are for different populations. Beyond the need to generalize the study of NOACs beyond dabigatran, when examining dabigatran specifically, this dissertation research points to a few other clear directions for future research.

First of all, this research was not designed to directly examine heterogeneity in effectiveness and safety of the differing dabigatran strengths, and these doses were FDA-approved with different target populations in mind. Dabigatran 75mg is intended for patients

with renal insufficiency; however, dabigatran 110mg was actually studied in clinical trials. Even if it was not our intention, some secondary findings in our research have several implications for patients with renal insufficiency. First, in Aim 1a, this research found that almost 10% of patients receiving dabigatran 150mg had diagnosed chronic kidney disease for whom the 150mg dose is neither FDA-approved nor recommended per clinical guidelines, and 22% of patients were using the 75mg dose without an indication of any kidney disease. Both groups of these patients could be subject to additional adverse events or harmful outcomes, because of the inappropriate doses; however, this has not yet been examined. In Aim 2, this research suggested that dabigatran 75mg was similarly effective as warfarin in the prevention of ischemic stroke and systemic embolism but that it was slightly more harmful. By contrast, patients using the dabigatran 150mg strength were less likely to experience an ischemic stroke or systemic embolic event without any increased risk of a harmful outcome. Even less work has been done examining how anticoagulation should be managed in patients undergoing dialysis, and none of the new oral anticoagulants are currently recommended. In sum, further examining this sub-population and the utilization patterns and comparative effectiveness and safety is highly relevant.

Secondly, this research was not originally designed to examine other types of treatment effect heterogeneity, including the comparative effectiveness and safety among patients with different types of comorbidity patterns. Before the application of propensity-score weighting, the largest absolute differences between baseline characteristics of warfarin and dabigatran initiators were renal impairment, anemia, venous thromboembolism, and congestive heart failure. These clinical comorbidities are known to be associated with ischemic stroke risk in patients with atrial fibrillation. While this research did explore some heterogeneity among subgroups, further examining the comparative effectiveness among strata of patients with atrial fibrillation

combined with one of these comorbidities may yield some potential areas for treatment effect heterogeneity and patients who may benefit more or less from certain anticoagulants.

Similarly, this study was not designed to specifically examine how medication adherence differed between the different users of anticoagulants, to some degree because a previous study undertaken by the authors had noticed potential missing warfarin prescription in the MarketScan® database.[201] Because dabigatran, the comparator, is a brand-name medication and more expensive for patients, prescriptions are likely to be less frequent in the warfarin group, resulting in differences in fill rates between the groups affecting the relative medication adherence calculations. Medication adherence has been known to be disentangled with comparative effectiveness, because medications traditionally work better in patients who take them regularly. Initiating an appropriate "as-treated" analysis in addition to the "intention-to-treat" approach used here would be warranted in the examination of anticoagulants; however, using medication adherence as an "exposure" and measuring resultant outcomes can be difficult methodologically.

Lastly, in addition to assessing the comparative effectiveness and safety of these new oral anticoagulants, which was one of the primary purposes of this dissertation, further work still needs to be done to examine and understand the cost implications of the agents. Particularly, analyses are needed that incorporate both the increased cost of the NOACs as well as the potential cost savings resulting from the prevention of outcomes and the avoidance of the need for INR measurements. Because of the current lack of an approved, affordable reversal agent in the event of a bleeding incident for the NOACs, these cost implications could also change over time once one does become available. Vigilance to developments in this area and the management of complications will also be an area where research will be much warranted.

5.5. CONCLUSION

In this large, nationwide cohort of non-valvular patients initiating anticoagulation from 2010-2012, we found that the uptake and utilization of dabigatran since its market entry has differed drastically from warfarin. Despite the rapid uptake of dabigatran, patients initiating dabigatran were healthier than those initiating warfarin and had lower risk of adverse outcomes. When examining the comparative effectiveness and safety of the medications, dabigatran was found to equally safe and even more effective than warfarin, even after adjusting for these differences in comorbidities and risk of outcomes. These results can provide some reassurance for patients, clinicians, and policymakers that dabigatran may be considered a safe and effective alternative to warfarin, even when used in real-world clinical practice and outside tightly-controlled clinical trials.

APPENDIX TABLES AND FIGURES

Appendix Table 1. Sensitivity analyses: Bivariate associations of continuous covariates with dabigatran and warfarin selection

	New users		Newly-diagnosed new users	
Baseline Characteristic (Assessed as continuous value)	**RR**	**95% CI**	**RR**	**95% CI**
Age	0.99	0.98-0.99**	0.99	0.98-0.99**
CCI	0.89	0.89-0.90**	0.90	0.89-0.90**
$CHADS_2$	0.85	0.84-0.86**	0.85	0.84-0.87**
CHA_2DS_2-VASc	0.87	0.86-0.88**	0.87	0.86-0.88**
ATRIA	0.88	0.87-0.88**	0.88	0.87-0.89**
HAS-BLED	0.84	0.83-0.86**	0.84	0.83-0.86**
Number of hospitalizations	0.77	0.76-0.78**	0.74	0.72-0.76**

Abbreviations: RR, Relative risk; ref, referent group; CI, confidence interval; CCI, Charlson comorbidity index
NOTE: Warfarin: referent group

Appendix Table 2. Multivariable associations between dabigatran compared with warfarin and other baseline covariates in the 12-month baseline period

	New Users		Newly-diagnosed new users	
Baseline Characteristic	**RR**	**95% CI**	**RR**	**95% CI**
Demographic				
Region (ref: Northeast)				
North Central	0.93	0.90-0.96**	0.89	0.85-0.93**
South	1.20	1.16-1.24**	1.14	1.10-1.19**
West	1.01	0.97-1.05	0.86	0.82-0.91**
Insurance plan (ref: Comprehensive)				
HMO	0.65	0.62-0.68**	0.59	0.55-0.63**
POS	1.00	0.95-1.05	0.95	0.89-1.01
PPO	0.99	0.97-1.02	0.96	0.93-0.99*
CDHP	0.89	0.82-0.95*	0.85	0.77-0.93**
Prescription generosity (ref: None/Poor)				
Fair coverage	9.18	7.18-11.74**	7.44	5.50-10.05**
Good coverage	10.30	8.07-13.21**	8.21	6.07-11.10**
Clinical (ref: 0/None unless specified)				
VTE	0.32	0.30-0.35**	0.34	0.30-0.38**
Hyperlipidemia	1.04	1.02-1.06*	1.07	1.04-1.11**
Peptic Ulcer disease	0.93	0.78-1.11	0.87	0.67-1.12
Sleep Apnea	1.06	1.03-1.10**	1.08	1.03-1.13*
Cognitive deficiency	0.98	0.85-1.14	0.82	0.64-1.04
CCI (ref: 0)				
1-2	0.92	0.90-0.95**	0.95	0.92-0.98*
3-5	0.81	0.78-0.84**	0.84	0.80-0.88**
6-8	0.67	0.63-0.73**	0.71	0.64-0.79**
≥ 9	0.71	0.63-0.79**	0.79	0.67-0.92*
≥1 hospitalizations	0.87	0.85-0.89**	0.81	0.79-0.84**
Catheter ablation	1.30	1.22-1.38**	1.28	1.05-1.56*
Medication use				
Antiplatelet therapy	1.12	1.08-1.16**	1.02	0.97-1.07
Gastroprotective agent	0.95	0.92-0.99*	0.93	0.89-0.98*
Antiarrhythmic	1.04	1.01-1.06*	1.01	0.97-1.05
Digoxin	0.91	0.88-0.94**	0.91	0.87-0.96**
Beta-blocker	1.04	1.01-1.06*	0.97	0.94-1.00*
Calcium channel blocker	1.01	0.99-1.03	0.96	0.93-0.98*
ACEI/ARB	1.04	1.02-1.07*	1.03	1.00-1.06
Statin	0.99	0.97-1.01	0.97	0.94-1.00
Hormone	1.13	1.07-1.19**	1.09	1.02-1.17*

NOTE: For covariates not already included in ischemic stroke or bleeding risk scores

*p<0.05

**p<0.001

Abbreviations: RR, Relative risk; ref, referent group; CI, confidence interval; HMO, health maintenance organization; POS, point of service; PPO, preferred provider organization; CDHP, consumer driven health plan; VTE, venous thromboembolism; CCI, Charlson comorbidity index; ACEI/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker

Appendix table 3. Ischemic stroke and bleeding risk score model predictor options and associations with dabigatran use compared with warfarin use

		New Users		Newly-diagnosed new users	
Model Option: QIC	**Baseline Characteristic**	**RR**	**95% CI**	**RR**	**95% CI**
1:	CHA_2DS_2-VASc (ref: 0)				
NU: 125,890.05	1	0.97	0.94-1.01	0.97	0.92-1.02
Ndx: 71,272.10	≥2	0.91	0.87-0.95**	0.92	0.87-0.98*
	ATRIA (ref: 0-3)				
	4	0.86	0.82-0.89**	0.85	0.80-0.91**
	≥5	0.72	0.69-0.76**	0.71	0.67-0.76**
2:	CHA_2DS_2-VASc (ref: 0)				
NU: 126,253.76	1	0.97	0.93-1.00	0.97	0.92-1.02
Ndx: 71,395.15	≥2	0.91	0.87-0.95**	0.93	0.87-0.99*
	HAS-BLED (ref: 0-2)				
	≥5	0.80	0.76-0.85**	0.78	0.73-0.85**
3:	$CHADS_2$ (ref: 0)				
NU: 125,957.39	1	0.98	0.95-1.01	0.99	0.95-1.04
Ndx: 71,272.46	≥2	0.94	0.90-0.98*	0.98	0.92-1.03
	ATRIA (ref: 0-3)				
	4	0.85	0.82-0.89**	0.85	0.80-0.90**
	≥5	0.72	0.69-0.76**	0.71	0.67-0.76**
4:	$CHADS_2$ (ref: 0)				
NU: 126,227.92	1	0.97	0.94-1.01	0.99	0.95-1.03
Ndx: 71,398.17	≥2	0.94	0.90-0.98*	0.98	0.93-1.03
	HAS-BLED (ref: 0-2)				
	≥5	0.80	0.76-0.85**	0.78	0.73-0.85**

Abbreviations: RR, Relative risk; Ref, referent group; CI, confidence interval; QIC, Quasilikelihood under the Independence model Criterion; NU, new user; Ndx, Newly-diagnosed new user

Appendix table 4. Sensitivity analyses: Multivariable associations between dabigatran compared with warfarin and ischemic stroke and bleeding risk scores

	New Users		Newly-diagnosed new users	
	Commercial	Medicare	Commercial	Medicare
Baseline Characteristic	**RR (95% CI)**	**RR (95% CI)**	**RR (95% CI)**	**RR (95% CI)**
Demographic				
CHA_2DS_2-VASc (ref=0)				
1	0.99 (0.95-1.03)	1.01 (0.95-1.07)	0.99 (0.94-1.04)	1.04 (0.96-1.13)
≥2	0.94 (0.89-0.99)*	0.98 (0.91-1.05)	0.95 (0.88-1.02)	1.04 (0.95-1.14)
ATRIA (ref: 0-3)				
4	0.80 (0.75-0.86)**	0.90 (0.85-0.95)**	0.80 (0.73-0.87)*	0.91 (0.84-0.99)*
≥5	0.57 (0.50-0.65)**	0.75 (0.72-0.79)**	0.53 (0.43-0.64)**	0.75 (0.70-0.80)**

*p<0.05

**p<0.001

NOTE: By definition, Medicare supplement beneficiaries cannot have CHA_2DS_2-VASc=0. For these patients, $CHADS_2$ was calculated and used in the relative risk estimations. Warfarin is the referent group.

Abbreviations: RR, Relative risk; ref, referent group; CI, confidence interval

Appendix table 5. Patient prescription cost-sharing of index anticoagulation and switching characteristics

	All Warfarin New Users			All Dabigatran New Users		
Index prescription generosity	**Switcher, N (%)**	**Non-Switcher, N (%)**	**Absolute SD**	**Switcher, N (%)**	**Non-Switcher, N (%)**	**Absolute SD**
No coverage	1,023 (36.5)	7,247 (37.8)	3.3	3 (0.21)	30 (0.29)	2.5
Poor coverage	224 (8.0)	1635 (8.5)	2.5	1 (0.07)	7 (0.07)	0.0
Fair coverage	742 (26.5)	4,805 (25.0)	4.3	295 (20.8)	2,398 (23.3)	7.9
Good coverage	811 (29.0)	5,502 (28.7)	0.8	1,117 (78.9)	7,872 (76.4)	6.4

	Prevalent Users		
	Switcher, N (%)	**Non-Switcher, N (%)**	**Absolute SD**
No coverage	2,997 (28.4)	24,288 (34.7)	17.2
Poor coverage	572 (5.4)	4982 (7.1)	10.3
Fair coverage	3,671 (34.8)	24,689 (35.3)	1.3
Good coverage	3,321 (31.4)	15,969 (22.8)	23.4

Abbreviations: SD, Standardized Differenced

Appendix table 6. Multivariable associations between anticoagulant switching and the other baseline covariates in the 12-month follow-up period

	Warfarin New Users		Dabigatran New Users		Prevalent Users	
Baseline Characteristic	**RR**	**95% CI**	**RR**	**95% CI**	**RR**	**95% CI**
Demographic						
Region (ref: Northeast)						
North Central	0.95	0.86-1.06	0.99	0.85-1.15	0.80	0.75-0.84**
South	1.17	1.06-1.30*	1.09	0.95-1.26	1.23	1.17-1.29**
West	1.16	1.03-1.31*	1.13	0.96-1.34	1.17	1.10-1.24**
Insurance plan (ref: Comprehensive)						
HMO	0.54	0.46-0.62**	0.94	0.76-1.16	0.38	0.35-0.42**
POS	1.12	0.96-1.31	0.80	0.63-1.01	1.11	1.03-1.20*
PPO	1.09	1.01-1.18*	0.95	0.85-1.06	1.09	1.05-1.14**
CDHP	0.96	0.75-1.24	0.97	0.67-1.39	0.88	0.75-1.03
Prescription generosity (ref: None/Poor)						
Fair coverage	1.07	0.86-1.32	1.66	0.43-6.37	1.43	1.19-1.71**
Good coverage	1.24	1.00-1.53*	1.57	0.41-6.01	1.71	1.43-2.04**
Clinical (ref: 0/None unless specified)						
VTE	0.56	0.48-0.66**	1.11	0.83-1.48	0.61	0.56-0.67**
Hyperlipidemia	0.98	0.91-1.05	1.08	0.97-1.20	1.12	1.08-1.17**
Peptic Ulcer disease	0.78	0.45-1.34	0.5	0.17-1.48	1.11	0.86-1.44
Sleep Apnea	1.22	1.10-1.36**	1.12	0.97-1.30	1.24	1.18-1.31**
Cognitive deficiency	0.93	0.58-1.50	0.98	0.51-1.89	0.99	0.80-1.24
≥1 hospitalizations	0.95	0.88-1.03	0.84	0.75-0.93*	1.09	1.04-1.13*
Catheter ablation	0.89	0.62-1.29	0.26	0.12-0.55**	1.31	1.16-1.48**
Newly-diagnosed AF	1.29	1.20-1.39**	1.05	0.95-1.16	N/A	N/A
Medication use						
Antiplatelet therapy	1.06	0.95-1.18	0.93	0.80-1.09	1.12	1.05-1.20**
Gastroprotective agent	1.01	0.91-1.13	1.06	0.90-1.24	1.02	0.96-1.07
Antiarrhythmic	1.16	1.07-1.26**	1.11	0.99-1.25	1.23	1.18-1.28**
Digoxin	1.02	0.93-1.12	0.97	0.84-1.12	0.98	0.94-1.02
Beta-blocker	1.01	0.94-1.09	1.26	1.12-1.41**	1.09	1.05-1.14**
Calcium channel blocker	1.04	0.97-1.12	1.06	0.96-1.18	1.13	1.09-1.17**
ACEI/ARB	1.11	1.03-1.19*	0.91	0.82-1.01	1.07	1.03-1.12*
Statin	1.06	0.99-1.15	0.9	0.81-1.00	1.05	1.01-1.09*
Hormone	1.36	1.17-1.57**	1.06	0.85-1.31	1.12	1.03-1.22*

NOTE: For covariates not already included in ischemic stroke or bleeding risk scores; REF: Non-switching; *p<0.05 **p<0.001

Abbreviations: RR, Relative risk; ref, referent group; CI, confidence interval; HMO, health maintenance organization; POS, point of service; PPO, preferred provider organization; CDHP, consumer driven health plan; VTE, venous thromboembolism; AF, Atrial Fibrillation; ACEI/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker

Appendix table 7. Ischemic stroke and bleeding risk score model predictor options and associations with anticoagulant switching

		Warfarin New User	Dabigatran New User	Prevalent User
Model Option: QIC	**Risk Score**	**RR (95% CI)**	**RR (95% CI)**	**RR (95% CI)**
1:	CHA_2DS_2-VASc (ref: 0)			
WNU: 19153.8948	1	1.01 (0.87-1.17)	1.07 (0.86-1.31)	1.12 (1.02-1.22)*
DNU: 10000.1665	≥2	0.88 (0.76-1.02)	1.35 (1.09-1.66)*	0.91 (0.84-0.99)*
PU: 71836.1822	ATRIA (ref: 0-3)			
	4	0.95 (0.83-1.08)	0.91 (0.74-1.12)	0.96 (0.90-1.03)
	≥5	0.69 (0.61-0.79)**	1.12 (0.94-1.33)	0.82 (0.77-0.87)**
2:	CHA_2DS_2-VASc (ref: 0)			
WNU: 19215.4250	1	1.00 (0.86-1.16)	1.05 (0.85-1.30)	1.12 (1.03-1.22)*
DNU: 9984.9208	≥2	0.86 (0.74-0.99)*	1.32 (1.07-1.62)*	0.90 (0.83-0.98)*
PU: 71903.7451	HAS-BLED (ref: 0-2)			
	≥5	0.94 (0.85-1.05)	0.95 (0.82-1.10)	1.00 (0.95-1.05)
3:	$CHADS_2$ (ref: 0)			
WNU: 19156.6780	1	0.92 (0.81-1.04)	1.06 (0.90-1.26)	0.94 (0.89-1.00)
DNU: 9988.5815	≥2	0.91 (0.80-1.03)	1.20 (0.99-1.44)	0.83 (0.78-0.88)**
PU: 71825.2560	ATRIA (ref: 0-3)			
	4	0.95 (0.83-1.08)	0.91 (0.74-1.12)	0.97 (0.91-1.04)
	≥5	0.69 (0.61-0.78)**	1.11 (0.93-1.33)	0.83 (0.78-0.88)**
4:	$CHADS_2$ (ref: 0)			
WNU:19220.4114	1	0.91 (0.80-1.02)	1.07 (0.90-1.26)	0.94 (0.88-1.00)*
DNU:9980.0506	≥2	0.99 (0.78-1.01)	1.21 (1.01-1.46)*	0.81 (0.76-0.87)**
PU: 71884.1138	HAS-BLED (ref: 0-2)			
	≥5	0.94 (0.85-1.03)	0.96 (0.82-1.11)	1.01 (0.96-1.06)

*p<0.05
**p<0.001
NOTE: REF: Non-switching
Abbreviations: QIC, Quasilikelihood under the Independence model Criterion; RR, Relative risk, ref, referent group; CI, confidence interval; WNU, Warfarin new user; D, Dabigatran new user; P, Prevalent user

Appendix table 8. Sensitivity analyses: Multivariable associations between anticoagulant switching and ischemic stroke and bleeding risk scores

Risk Score	Warfarin New Users		Prevalent Users	
	Commercial RR (95% CI)	Medicare RR (95% CI)	Commercial RR (95% CI)	Medicare RR (95% CI)
CHA_2DS_2-VASc (ref=0)				
1	1.04 (0.88-1.22)	0.83 (0.68-1.00)*	1.13 (1.03-1.25)*	0.85 (0.78-0.93)**
≥2	1.10 (0.89-1.35)	0.83 (0.69-1.00)*	1.06 (0.93-1.20)	0.76 (0.69-0.82)**
ATRIA (ref: 0-3)				
4	0.87 (0.70-1.08)	1.00 (0.86-1.18)	0.78 (0.70-0.90)*	1.03 (0.95-1.11)
≥5	0.51 (0.34-0.78)*	0.72 (0.63-0.83)**	0.81 (0.66-1.00)*	0.86 (0.80-0.91)**
	Dabigatran New Users			
	Commercial RR (95% CI)	Medicare RR (95% CI)		
CHA_2DS_2-VASc (ref=0)[§]				
>0	1.09 (0.87-1.36)	1.05 (0.82-1.35)		
ATRIA (ref: 0-3)[§]				
≥3	0.75 (0.54-1.06)	1.10 (0.95-1.28)		

*p<0.05

**p<0.001

[§]Due to small cell size issues (and non-convergence of the original model), the risk score levels were combined and some non-significant covariates omitted (e.g., prescription benefits generosity, peptic ulcer disease)

NOTE: By definition, Medicare supplement beneficiaries are unlikely to have CHA_2DS_2-VASc=0 (due to age). For these patients, $CHADS_2$ was calculated and used in the relative risk estimations; REF: Non-switching

Abbreviations: RR, Relative risk; ref, referent group; CI, confidence interval

Appendix table 9. Propensity score assessments: Testing variables' crude associations with risk of effectiveness and harm outcomes in new users

	Exposure association	Outcome association		Variable classification			
Baseline Characteristic	**RR (95% CI)**	**Effectiveness RR (95% CI)**	**Harm HR (95% CI)**	**X1**	**X2**	**X3**	**None**
Demographic							
Age (ref: <55 years)							
55-64 years	0.90 (0.87-0.93)	1.05 (0.96-1.14)	1.13 (1.07-1.20)		-		
65-74 years	0.76 (0.74-0.79)	1.16 (1.07-1.26)	1.27 (1.20-1.34)		-		
≥ 75 years	0.59 (0.57-0.61)	1.58 (1.46-1.70)	1.55 (1.48-1.63)		X		
Gender (ref: Female)	1.16 (1.13-1.19)	0.73 (0.70-0.76)	0.86 (0.84-0.88)		X		
Region (ref: Northeast)							
North Central	0.92 (0.89-0.95)	1.01 (0.95-1.06)	1.04 (1.00-1.08)		-		
South	1.27 (1.23-1.31)	0.92 (0.87-0.98)	0.95 (0.91-0.98)		-		
West	0.96 (0.92-0.99)	0.98 (0.92-1.05)	0.89 (0.85-0.93)		X		
Insurance plan (ref: Comprehensive)							
HMO	0.70 (0.67-0.73)	0.83 (0.78-0.88)	0.87 (0.83-0.90)		-		
POS	1.25 (1.20-1.32)	0.74 (0.67-0.82)	0.83 (0.78-0.88)		-		
PPO	1.20 (1.17-1.23)	0.84 (0.80-0.87)	0.81 (0.78-0.83)		-		
CDHP	1.30 (1.21-1.39)	0.59 (0.49-0.71)	0.70 (0.63-0.78)		X		
Prescription generosity (ref: None/Poor)							
Fair coverage	8.66 (6.77-11.09)	1.18 (1.04-1.34)	1.30 (1.18-1.43)		-		
Good coverage	9.69 (7.57-12.40)	1.35 (1.18-1.53)	1.43 (1.31-1.58)		X		
Clinical (ref: 0/None unless specified)							
Ischemic Stroke	0.72 (0.69-0.76)	6.26 (6.01-6.53)	1.35 (1.30-1.41)		X		
Congestive Heart Failure	0.67 (0.65-0.69)	1.31 (1.26-1.37)	1.67 (1.62-1.72)		X		
VTE	0.26 (0.24-0.28)	7.83 (7.51-8.17)	1.35 (1.29-1.41)		X		
Hyperlipidemia	1.00 (0.98-1.03)	0.99 (0.95-1.03)	0.98 (0.95-1.00)				X
Hypertension	0.88 (0.86-0.90)	1.35 (1.29-1.42)	1.21 (1.18-1.25)		X		
Myocardial infarction	0.61 (0.56-0.66)	1.40 (1.28-1.52)	1.50 (1.41-1.59)		X		
Coronary artery disease	0.83 (0.80-0.85)	1.14 (1.10-1.19)	1.40 (1.36-1.44)		X		
PVD	0.69 (0.58-0.83)	1.81 (1.71-1.92)	1.56 (1.49-1.63)		X		
Renal impairment	0.53 (0.50-0.56)	1.45 (1.37-1.53)	1.67 (1.61-1.74)		X		
Diabetes	0.84 (0.82-0.86)	1.05 (1.00-1.09)	1.27 (1.23-1.30)		X		
Major bleeding	0.74 (0.71-0.77)	1.69 (1.61-1.78)	1.47 (1.41-1.52)		X		
Anemia	0.59 (0.56-0.61)	1.70 (1.62-1.78)	1.61 (1.56-1.66)		X		
Peptic Ulcer disease	0.69 (0.58-0.83)	1.91 (1.59-2.30)	1.68 (1.46-1.94)		X		
Sleep Apnea	1.11 (1.08-1.15)	0.95 (0.91-1.00)	1.15 (1.10-1.20)			X	
Cognitive deficiency	0.69 (0.59-0.80)	4.15 (3.67-4.68)	1.35 (1.18-1.54)		X		
CCI (ref: 0)							
1-2	0.82 (0.80-0.84)	1.79 (1.69-1.91)	1.37 (1.32-1.42)		-		
3-5	0.61 (0.59-0.63)	2.91 (2.74-3.10)	1.99 (1.92-2.07)		-		
6-8	0.43 (0.40-0.46)	4.11 (3.80-4.45)	2.69 (2.55-2.84)		-		
≥ 9	0.42 (0.37-0.47)	5.32 (4.78-5.91)	3.19 (2.94-3.46)		X		
CHA_2DS_2-VASc (ref: 0)							
1	0.93 (0.90-0.97)	1.08 (0.96-1.21)	1.09 (1.03-1.17)		-		
≥2	0.63 (0.61-0.65)	2.24 (2.03-2.47)	1.67 (1.58-1.77)		X		

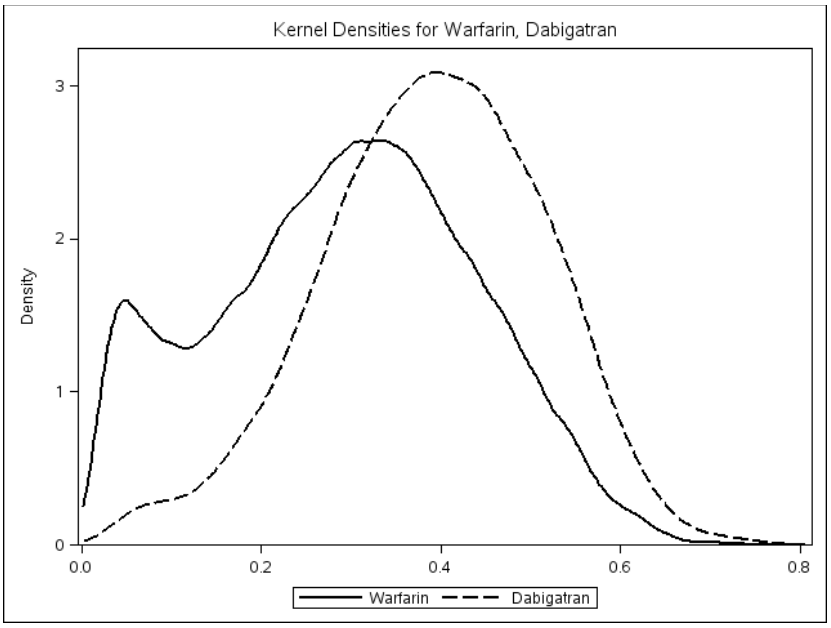
ATRIA (ref: 0-3)							
4	0.73 (0.70-0.76)	1.58 (1.49-1.69)	1.37 (1.31-1.43)		X		
≥5	0.49 (0.47-0.51)	1.86 (1.78-1.95)	1.84 (1.79-1.90)		X		
≥1 hospitalizations	0.71 (0.69-0.72)	2.89 (2.76-3.02)	1.56 (1.52-1.60)		X		
Catheter ablation	1.68 (1.58-1.79)	0.48 (0.37-0.62)	0.72 (0.63-0.82)		X		
Medication use							
Antiplatelet therapy	0.98 (0.95-1.01)	1.49 (1.42-1.57)	1.50 (1.45-1.55)			X	
Gastroprotective agent	0.88 (0.85-0.91)	1.41 (1.33-1.48)	1.30 (1.25-1.35)			X	
Antiarrhythmic	1.10 (1.07-1.13)	0.88 (0.84-0.92)	1.09 (1.06-1.12)			X	
Digoxin	0.86 (0.83-0.89)	0.95 (0.90-0.99)	1.16 (1.12-1.20)			X	
Beta-blocker	0.99 (0.97-1.02)	1.00 (0.96-1.04)	1.16 (1.13-1.19)			X_H	X_E
Calcium channel blocker	0.96 (0.94-0.99)	1.04 (1.00-1.08)	1.17 (1.14-1.20)		X		
ACEI/ARB	0.98 (0.96-1.01)	1.00 (0.95-1.03)	1.15 (1.12-1.19)			X_H	X_E
Statin	0.96 (0.94-0.98)	1.15 (1.10-1.19)	1.11 (1.08-1.14)		X		
Hormone	1.15 (1.09-1.21)	1.05 (0.95-1.16)	1.00 (0.94-1.07)	X			

Abbreviations: HMO, Health maintenance organization; POS, Point-of-service; PPO, Preferred provider organization; CDHP, consumer-driven health plan; CCI, Charlson Comorbidity Index; ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker; VTE, venous thromboembolism; PVD, Peripheral vascular disease

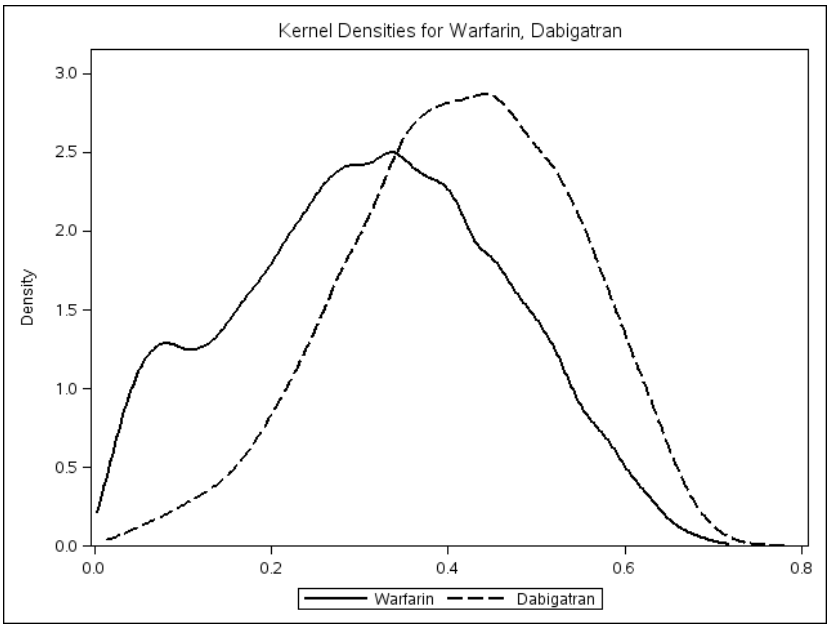
NOTE: E: Effectiveness Outcome; H: Harm Outcome; X1: variable only associated with exposure; X2: variable associated with both exposure and outcome; X3: variable associated with only outcome; None: variable associated with neither exposure nor outcome

Appendix figure 1. Estimated propensity score kernel densities among new users of anticoagulation

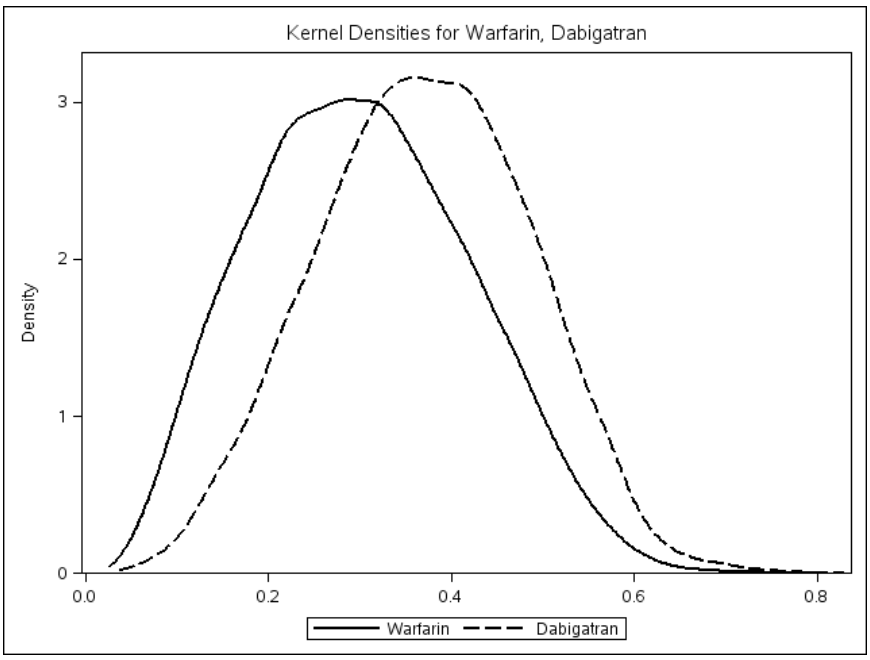
A. New Users



B. Newly-diagnosed new users



C. New Users excluding venous thromboembolism and prescription benefits generosity



Appendix table 10. Balance of covariates after applying the stabilized IPTW propensity scores among new users of dabigatran and warfarin

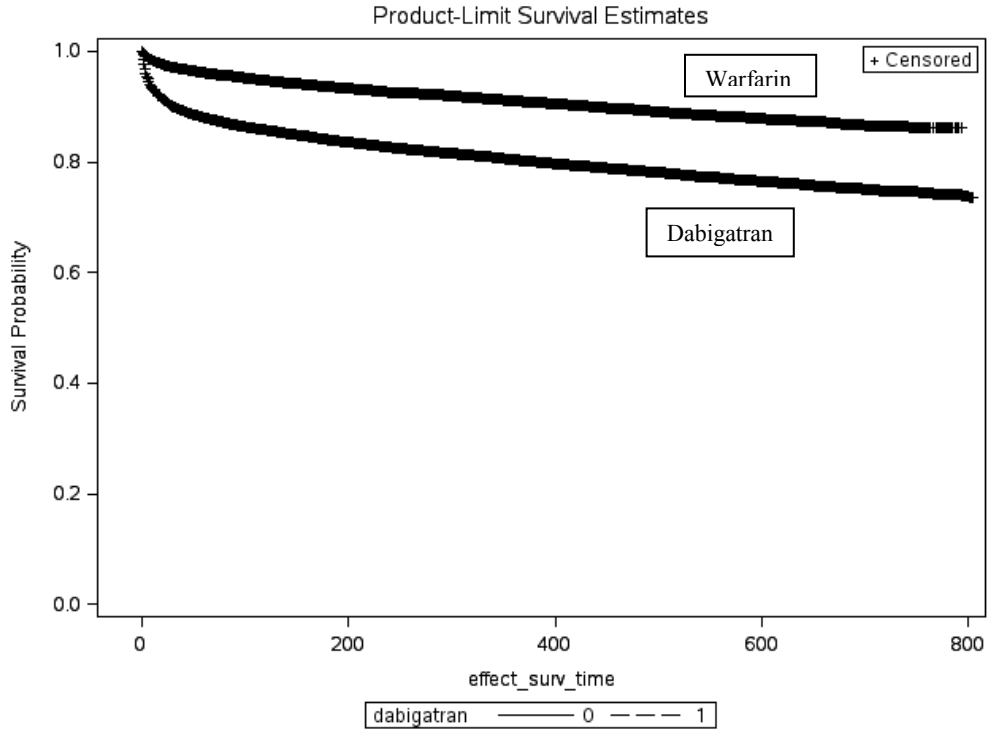
Baseline Characteristic	Warfarin, %	Dabigatran, %	Absolute SD
Demographic			
Age			
< 55 years	10.51%	10.07%	1.9
55-64 years	25.57%	25.40%	0.5
65-74 years	22.55%	23.35%	2.4
≥ 75 years	41.37%	41.18%	0.5
Male Gender	59.91%	59.18%	1.7
Region			
Northeast	16.76%	17.10%	1.2
North Central	33.12%	33.11%	0.0
South	30.91%	31.43%	1.4
West	16.93%	16.92%	0.0
Insurance plan			
Comprehensive	34.43%	35.59%	3.0
HMO	12.39%	12.02%	1.5
POS	4.93%	4.78%	1.0
PPO	41.02%	41.49%	1.1
CDHP	1.80%	1.92%	1.3
Benefits generosity			
No/poor coverage	2.60%	3.13%	4.6
Fair coverage	48.00%	48.08%	0.2
Good coverage	49.41%	48.79%	1.4
Clinical			
Ischemic Stroke	9.59%	10.30%	3.2
Congestive Heart Failure	25.10%	26.69%	4.6
VTE	9.13%	10.76%	7.6
Hyperlipidemia	49.57%	49.65%	0.2
Hypertension	71.82%	72.63%	1.9
Myocardial infarction	3.86%	3.91%	0.4
Coronary artery disease	32.32%	32.94%	1.6
Peripheral vascular disease	7.79%	9.12%	6.7
Renal impairment	10.36%	11.20%	3.7
Diabetes	30.12%	30.88%	2.1
Major bleeding	12.26%	13.31%	4.3
Anemia	16.90%	17.90%	3.5
Peptic Ulcer disease	0.64%	1.18%	9.5
Sleep Apnea	10.95%	11.31%	1.5
Cognitive deficiency	0.86%	0.89%	0.5
CCI			
0	26.37%	25.56%	2.3
1-2	41.13%	40.36%	1.9
3-5	24.49%	25.07%	1.7
6-8	5.93%	6.39%	2.7
≥ 9	2.09%	2.62%	5.2
CHA_2DS_2-VASc			
0	8.26%	7.85%	2.0

1	16.96%	16.69%	0.9
≥2	74.78%	75.46%	1.7
ATRIA			
0-3	74.32%	73.19%	2.8
4	8.72%	8.83%	0.5
≥5	16.96%	17.98%	3.5
≥1 hospitalizations	53.35%	54.11%	1.7
Catheter ablation	1.31%	1.31%	0.0
Medication Use			
Antiplatelet therapy	13.03%	14.05%	4.0
Gastroprotective agent	12.04%	11.72%	1.3
Antiarrhythmic	23.68%	23.68%	0.0
Digoxin	16.09%	16.71%	2.2
Beta-blocker	67.22%	68.11%	2.1
Calcium channel blocker	41.81%	42.19%	0.9
ACEI/ARB	56.88%	57.09%	0.5
Statin	54.18%	54.29%	0.3

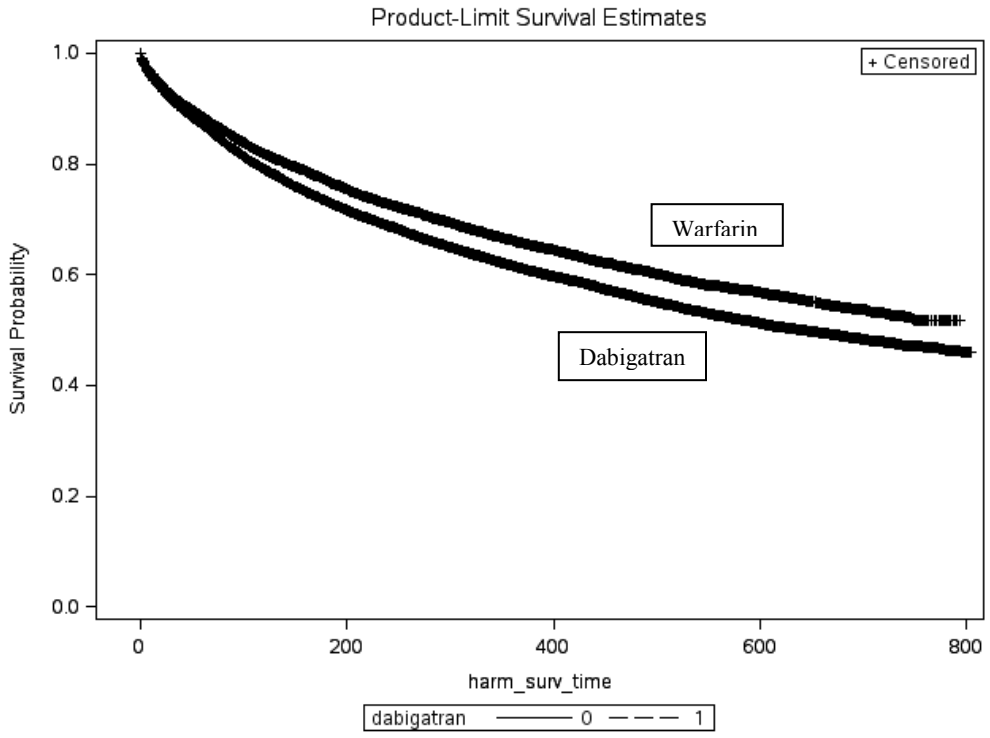
Abbreviations: SD, Standardized difference; HMO, Health maintenance organization; POS, Point-of-service; PPO, Preferred provider organization; CDHP, consumer-driven health plan; CCI, Charlson Comorbidity Index; ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker

Appendix figure 2. Kaplan-Meier curves of anticoagulant initiators

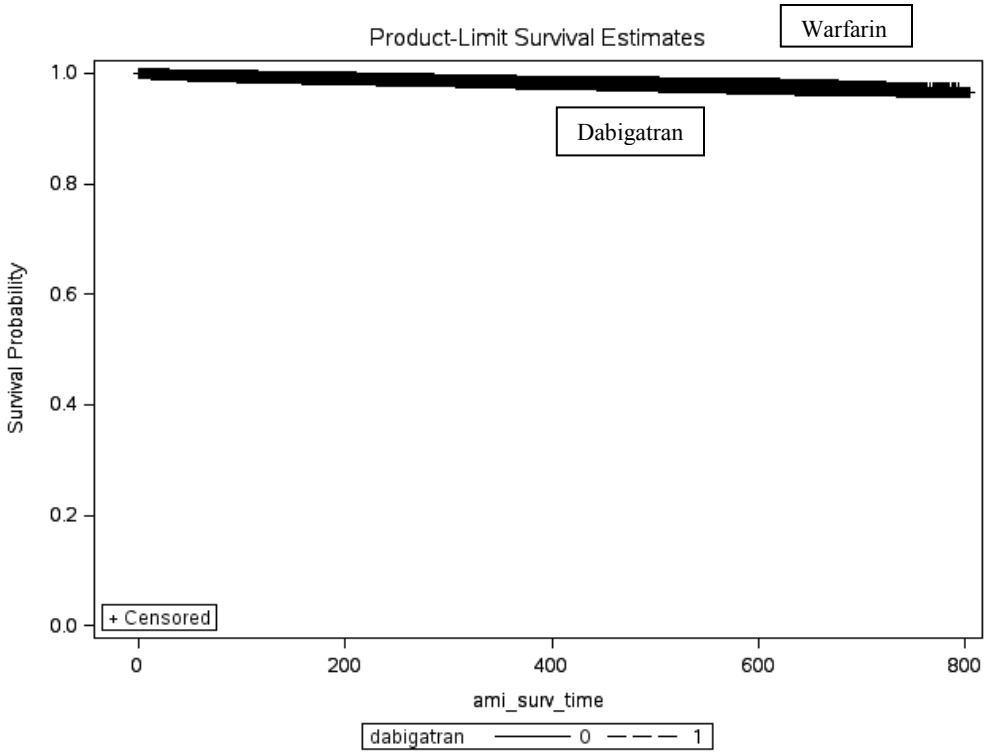
A. Composite of clinical effectiveness outcomes



B. Composite of risk of harm outcomes

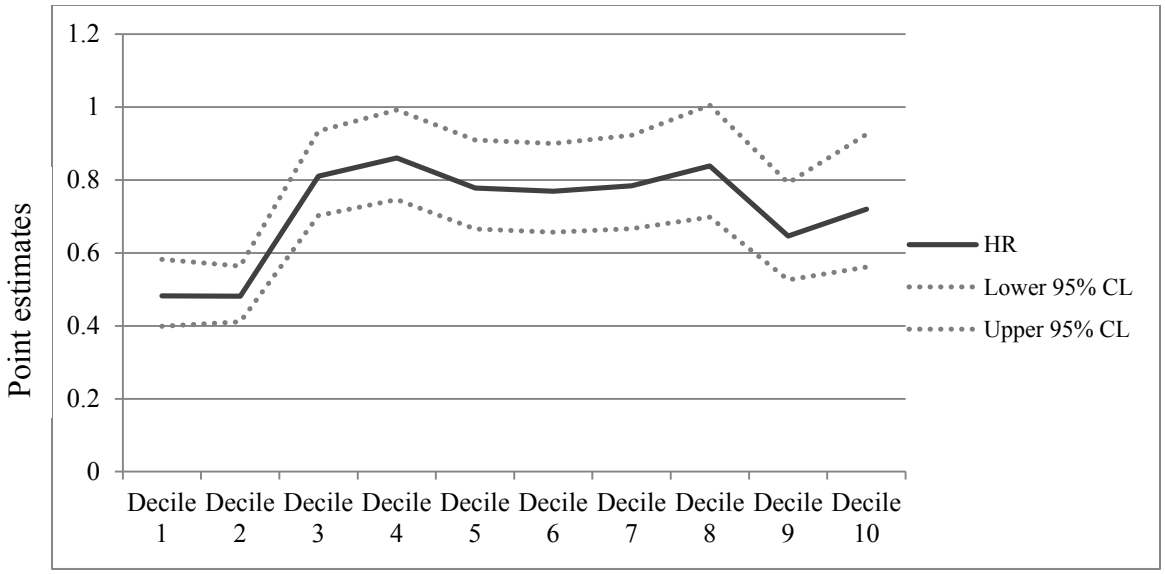


C. Acute myocardial infarction outcome

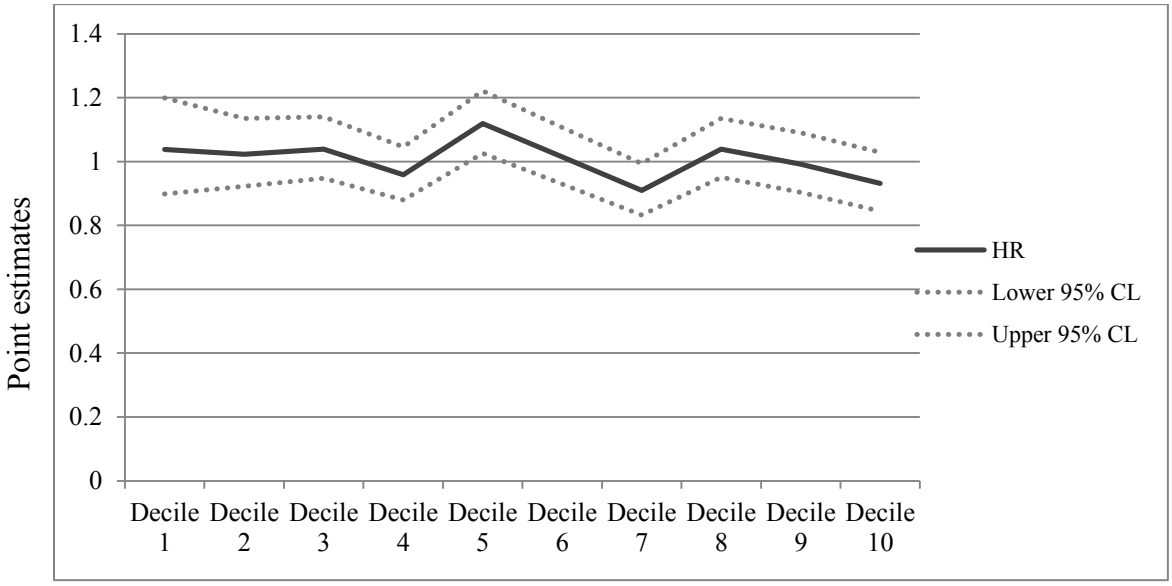


Appendix figure 3. Estimated treatment effects and 95% confidence Interval bounds for deciles of the estimated propensity scores for new users

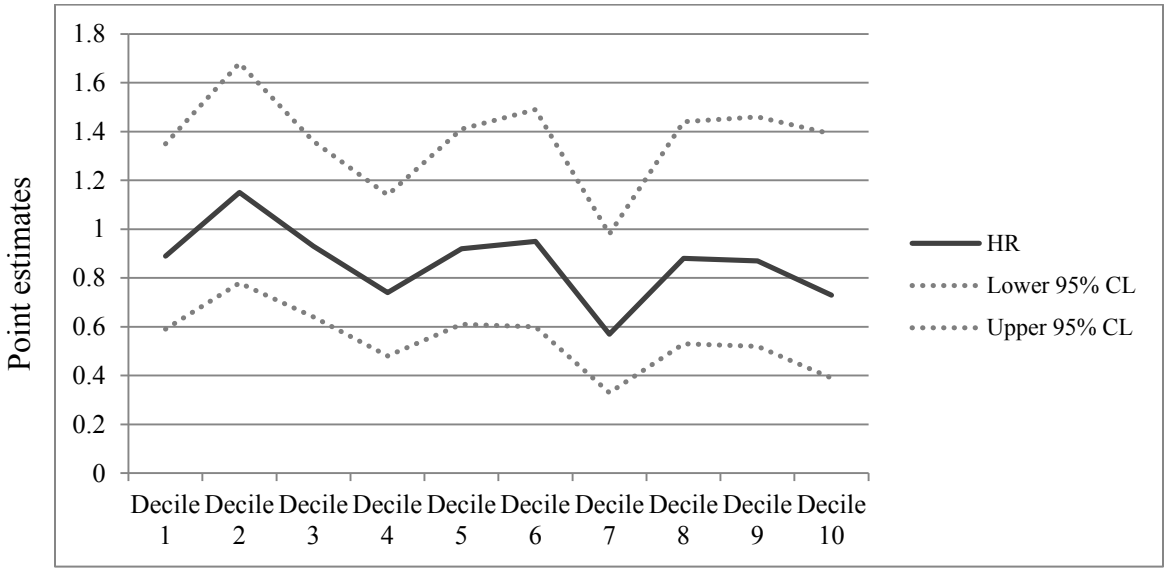
A. Effectiveness composites



B. Harm composites



C. Acute myocardial infarction



Appendix Table 11. Estimated treatment effects comparing new users of dabigatran to warfarin on risk of outcomes: Inpatient outcomes only

Outcome Type	Original PS-IPTW HR (95% CI)	Inpatient-only PS-IPTW HR (95% CI)	Warfarin Events/1,000 person-years (Inpatient-only)	Dabigatran Events/1,000 person-years (Inpatient-only)
Effectiveness				
Ischemic stroke	0.92 (0.87-0.98)*	0.91 (0.81-1.02)	35.6	17.3
TIA	1.07 (0.92-1.25)	1.07 (0.91-1.25)	11.3	9.2
VTE	0.51 (0.47-0.54)**	0.70 (0.60-0.80)**	20.4	9.1
Composite	0.70 (0.67-0.74)**	0.86 (0.79-0.93)**	48.6	30.2
Harm				
Hemorrhagic stroke	0.64 (0.54-0.75)**	0.51 (0.40-0.65)**	8.0	3.3
GI hemorrhage	1.19 (1.12-1.26)**	1.11 (1.02-1.22)*	32.1	21.8
Other bleeding	0.91 (0.86-0.96)**	0.76 (0.65-0.89)**	14.4	8.1
Hospitalization	1.00 (0.97-1.02)	0.99 (0.97-1.02)	343.4	295.8
Composite	1.02 (0.99-1.05)	0.99 (0.97-1.02)	343.4	295.8
AMI	0.88 (0.77-1.00)*	0.88 (0.77-1.00)*	19.1	13.1

*p<0.05; **p<0.001

Abbreviations: AF, Atrial Fibrillation; HR, Hazard Ratio; MV, Multivariate; PS, Propensity score; IPTW, Inverse probability treatment weighting; SMR, Standardized Mortality Ratio; TIA, transient ischemic attack; VTE, venous thromboembolism; GI, gastrointestinal; AMI, Acute Myocardial Infarction

Appendix table 12. Full multivariable survival analysis model results comparing dabigatran with warfarin use among new users of anticoagulation

	Effectiveness Composite		Harm Composite		Acute Myocardial Infarction	
	HR	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
Dabigatran (ref: Warfarin)	0.62	0.59-0.66**	1.00	0.97-1.03	0.86	0.74-0.99*
Baseline Demographic Characteristic						
Age (ref: <55 years)						
55-64 years	0.99	0.91-1.08	1.03	0.98-1.09	1.39	1.00-1.92*
65-74 years	0.84	0.77-0.92**	1.01	0.95-1.08	1.42	1.01-2.00*
≥75 years	0.94	0.86-1.03	1.13	1.06-1.21**	1.62	1.15-2.29*
Male Gender (ref: Female)	0.91	0.87-0.95**	0.91	0.89-0.94**	1.00	0.97-1.13
Region (ref: Northeast)						
North Central	1.04	0.98-1.10	1.02	0.95-1.03	0.84	0.71-0.99*
South	1.01	0.95-1.07	0.99	0.95-1.03	0.83	0.69-0.98*
West	1.06	1.00-1.14	0.93	0.89-0.98*	1.02	0.84-1.25
Insurance plan (ref: Comprehensive)						
HMO	0.96	0.90-1.03	0.99	0.95-1.04	0.78	0.63-0.96*
POS	0.92	0.83-1.02	0.99	0.93-1.06	0.69	0.49-0.97*
PPO	1.02	0.97-1.06	0.93	0.90-0.96**	0.80	0.69-0.93*
CDHP	0.81	0.67-0.98*	0.91	0.81-1.01	0.89	0.50-1.56
Prescription generosity (ref: None/Poor)						
Fair coverage	0.95	0.84-1.09	1.07	0.97-1.17	0.68	0.46-1.01
Good coverage	1.01	0.89-1.15	1.11	1.01-1.22*	0.72	0.49-1.07
Baseline Clinical Characteristic (ref: 0/None)						
Ischemic stroke	4.07	3.88-4.27**	1.02	0.97-1.06	0.93	0.76-1.12
Congestive Heart Failure	0.81	0.77-0.85**	1.21	1.17-1.25**	1.38	1.20-1.59**
Acute Myocardial infarction	0.87	0.80-0.96*	0.99	0.93-1.06	3.64	3.06-4.32**
Coronary artery disease	0.89	0.85-0.93**	1.11	1.08-1.15**	1.44	1.25-1.66**
Hypertension	1.06	1.00-1.12*	1.01	0.97-1.05	1.03	0.88-1.22
Peripheral vascular disease	0.97	0.81-1.03	1.10	1.05-1.15**	0.96	0.79-1.17
Diabetes Mellitus	0.80	0.76-0.84**	1.00	0.97-1.03	1.13	0.98-1.31
VTE	5.82	5.56-6.09**	1.06	1.01-1.11*	0.83	0.68-1.02
Renal insufficiency	0.90	0.82-0.96*	1.05	1.00-1.11	1.30	1.04-1.63*
Hyperlipidemia	0.97	0.93-1.01	0.93	0.90-0.95**	0.82	0.72-0.93*
Anemia	1.07	1.00-1.15	1.16	1.09-1.22**	0.92	0.74-1.14
Peptic Ulcer disease	1.00	0.83-1.20	1.17	1.01-1.34*	1.13	0.60-2.11
Sleep Apnea	1.02	0.96-1.09	1.13	1.08-1.18**	1.01	0.83-1.24
Cognitive deficiency	1.22	1.08-1.38	1.02	0.89-1.17	1.32	0.78-2.26
Major bleeding	1.05	0.99-1.11	1.18	1.14-1.23**	0.95	0.80-1.15
CHA_2DS_2-VASc						
1	1.02	0.90-1.16	0.97	0.91-1.05	1.40	0.85-2.28
≥2	1.25	1.10-1.42**	1.01	0.93-1.09	1.65	0.99-2.74
ATRIA						
4	1.00	0.93-1.08	1.01	0.96-1.07	1.04	0.82-1.31
≥5	0.92	0.84-1.01	1.06	0.99-1.13	1.02	0.77-1.34
CCI (ref: 0)						
1-2	1.30	1.21-1.40**	1.16	1.11-1.21**	1.25	1.00-1.56

3-5	1.62	1.50-1.76**	1.41	1.34-1.48**	1.41	1.08-1.83*
6-8	2.02	1.81-2.25**	1.59	1.47-1.71**	1.50	1.05-2.12*
≥ 9	1.87	1.64-2.12**	1.87	1.70-2.05**	1.56	1.00-2.42
≥1 hospitalizations	1.64	1.56-1.73**	1.18	1.15-1.22**	1.31	1.13-1.53**
Catheter ablation	0.67	0.53-0.89*	0.80	0.70-0.92*	1.01	0.52-1.95
Baseline Medication Use (ref: None)						
Antiplatelet therapy	1.05	1.00-1.11	1.16	1.12-2.21**	1.29	1.11-1.51*
Gastroprotective agent	1.05	0.99-1.11	1.11	1.07-1.15**	1.11	0.94-1.31
Antiarrhythmic	0.89	0.85-0.94**	1.05	1.01-1.08*	0.90	0.78-1.04
Digoxin	0.88	0.83-0.93**	1.05	1.02-1.09*	1.05	0.90-1.22
Beta-blocker	0.94	0.90-0.98*	1.03	1.00-1.06	1.14	0.98-1.33
Calcium channel blocker	0.91	0.88-0.95**	1.08	1.05-1.11**	0.87	0.76-0.98*
ACEI/ARB	0.94	0.90-0.98*	1.00	0.97-1.03**	1.08	0.84-1.24
Statin	1.05	1.00-1.10*	0.96	0.93-0.98*	1.10	0.95-1.26

*p<0.05

**p<0.001

Abbreviations: HR, Hazard Ratio; ref, referent group; CI, confidence interval; HMO, health maintenance organization; POS, point of service; PPO, preferred provider organization; CDHP, consumer driven health plan; VTE, venous thromboembolism; CCI, Charlson comorbidity index; ACEI/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker

Appendix table 13. Stratification by insurance status: Clinical effectiveness and safety of dabigatran compared with warfarin

	Commercially-insured (CCAE)		Medicare Supplement (MDCR)	
	Effectiveness Composite HR (95% CI)	Harm Composite HR (95% CI)	Effectiveness Composite HR (95% CI)	Harm Composite HR (95% CI)
New Users				
Unadjusted	0.28 (0.25-0.31)**	0.87 (0.83-0.91)**	0.55 (0.52-0.58)**	0.89 (0.86-0.92)**
MV-adjusted	0.46 (0.41-0.50)**	0.99 (0.94-1.04)	0.72 (0.68-0.77)**	1.00 (0.97-1.04)
PS-IPTW	0.46 (0.42-0.51)**	0.98 (0.94-1.03)	0.77 (0.73-0.81)**	1.02 (0.98-1.05)
PS-SMRW	0.60 (0.53-0.67)**	0.99 (0.93-1.04)	0.81 (0.75-0.87)**	1.00 (0.96-1.05)
Newly-diagnosed new users				
Unadjusted	0.31 (0.27-0.35)**	0.89 (0.83-0.95)**	0.58 (0.54-0.64)**	0.91 (0.86-0.95)**
MV-adjusted	0.47 (0.41-0.54)**	1.00 (0.94-1.08)	0.76 (0.70-0.83)**	1.00 (0.95-1.05)
PS-IPTW	0.52 (0.46-0.59)**	1.00 (0.94-1.07)	0.72 (0.67-0.79)**	0.99 (0.94-1.04)
PS-SMRW	0.61 (0.52-0.71)**	0.99 (0.92-1.06)	0.83 (0.76-0.93)**	1.00 (0.94-1.06)

*p<0.05; p<0.001

Abbreviations: MV, Multivariable; IPTW, Inverse-probability treatment weighting; HR, Hazard Ratio; CI, Confidence interval; SMRW, Standardized Mortality Ratio Weighting

Appendix table 14. Dabigatran strength subgroups: Association between anticoagulation and outcomes compared with warfarin

Outcome Type	Unadjusted HR (95% CI)	MV Adjusted HR (95% CI)	PS-IPTW HR (95% CI)
Dabigatran 75mg			
Effectiveness Composite	0.80 (0.71-0.90)**	0.93 (0.82-1.05)	0.96 (0.86-1.08)
Harm Composite	1.17 (1.09-1.26)**	1.03 (0.96-1.12)	1.19 (1.10-1.28)**
Dabigatran 150mg			
Effectiveness Composite	0.40 (0.38-0.42)**	0.59 (0.56-0.63)**	0.67 (0.64-0.71)**
Harm Composite	0.83 (0.80-.0.85)**	0.99 (0.96-1.02)	1.00 (0.97-1.03)

*p<0.05; p<0.001

Abbreviations: MV, Multivariable; IPTW, Inverse-probability treatment weighting; HR, Hazard Ratio; CI, Confidence interval

Appendix Table 15. Estimated treatment effects among strata of new user AF patients with certain characteristics

Patient Subgroups	Effectiveness HR (95% CI)	Harm Outcome HR (95% CI)
Original	0.86 (0.79-0.93)**	0.99 (0.97-1.02)
Ischemic stroke	0.85 (0.70-1.02)	1.07 (0.97-1.17)
VTE	0.50 (0.35-0.72)**	1.04 (0.91-1.20)
CHF	0.88 (0.75-1.03)	0.98 (0.93-1.04)
AMI	0.95 (0.63-1.43)	1.06 (0.91-1.22)
ATRIA < 4	0.89 (0.80-0.99)*	1.01 (0.98-1.05)
ATRIA = 4	0.84 (0.64-1.09)	0.97 (0.88-1.07)
ATRIA ≥ 5	0.73 (0.60-0.90)*	0.93 (0.86-1.00)*
CHA_2DS_2-VASc =1	1.01 (0.77-1.31)	1.00 (0.93-1.08)
CHA_2DS_2-VASc ≥2	0.84 (0.77-0.92)**	0.96 (0.93-1.00)*
Age <55 years	0.94 (0.70-1.26)	0.95 (0.86-1.05)
Age 55-64 years	0.59 (0.57-0.84)**	1.01 (0.95-1.07)
Age 65-74 years	0.79 (0.65-0.96)*	1.04 (0.98-1.11)
Age ≥75 years	0.89 (0.79-1.01)	0.91 (0.87-0.95)**
Fair prescription generosity	0.85 (0.75-0.96)*	1.02 (0.97-1.06)
Good prescription generosity	0.91 (0.81-1.02)	0.98 (0.94-1.02)

*p<0.05; **p<0.001

Appendix table 16. Full multivariable survival analysis model results comparing warfarin switchers to dabigatran versus warfarin non-switchers

	Effectiveness HR (95% CI)	Harm HR (95% CI)	AMI HR (95% CI)
Switcher (ref: non-switcher)	0.68 (0.66-0.71)**	0.68 (0.65-0.71)**	0.68 (0.66-0.70)**
Demographic baseline characteristic			
Age (ref: <55 years)			
55-64 years	1.06 (1.02-1.11)*	1.07 (1.02-1.12)*	1.06 (1.02-1.10)*
65-74 years	1.01 (0.96-1.06)	1.01 (0.96-1.07)	1.00 (0.95-1.04)
≥75 years	1.04 (0.99-1.09)	1.03 (0.97-1.08)	1.04 (1.00-1.09)
Male Gender (ref: Female)	0.98 (0.96-1.00)	0.98 (0.95-1.00)	0.99 (0.97-1.01)
Region (ref: Northeast)			
North Central	1.03 (1.00-1.06)	1.03 (1.00-1.07)	1.04 (1.01-1.07)*
South	0.99 (0.96-1.03)	0.99 (0.96-1.03)	1.00 (0.97-1.03)
West	0.99 (0.96-1.02)	0.98 (0.94-1.02)	1.00 (0.97-1.03)
Insurance plan (ref: Comprehensive)			
HMO	1.13 (1.09-1.17)**	1.15 (1.11-1.20)**	1.11 (1.08-1.15)*
POS	1.06 (1.01-1.12)*	1.08 (1.02-1.14)*	1.06 (1.01-1.11)*
PPO	1.18 (1.15-1.21)**	1.20 (1.16-1.22)**	1.17 (1.14-1.20)**
CDHP	1.09 (1.00-1.19)*	1.12 (1.02-1.23)*	1.12 (1.03-1.21)*
Prescription generosity (ref: None/Poor)			
Fair coverage	0.88 (0.83-0.93)**	0.88 (0.83-0.94)**	0.89 (0.85-0.94)**
Good coverage	0.87 (0.82-0.92)**	0.86 (0.81-0.92)**	0.87 (0.83-0.92)**
Clinical baseline characteristic (ref: 0/None)			
Ischemic stroke	1.00 (0.95-1.05)	1.05 (1.00-1.09)*	1.06 (1.03-1.10)*
Congestive Heart Failure	1.05 (1.02-1.08)*	1.04 (1.01-1.08)*	1.05 (1.02-1.07)*
Acute Myocardial infarction	1.04 (0.98-1.10)	1.07 (1.00-1.15)*	1.02 (0.97-1.08)
Coronary artery disease	0.99 (0.96-1.01)	0.99 (0.97-1.02)	0.98 (0.96-1.01)
Hypertension	1.08 (1.05-1.11)*	1.09 (1.05-1.12)*	1.08 (1.05-1.11)*
Peripheral vascular disease	1.03 (0.99-1.07)	1.03 (0.95-1.08)	1.01 (0.97-1.04)
Diabetes Mellitus	0.97 (0.95-1.00)	0.97 (0.94-1.00)	0.97 (0.95-1.00)*
VTE	1.03 (0.98-1.07)	1.05 (1.01-1.09)*	1.06 (1.02-1.09)*
Renal insufficiency	1.01 (0.96-1.06)	0.99 (0.93-1.04)	0.99 (0.95-1.04)
Hyperlipidemia	1.09 (1.07-1.12)**	1.11 (1.08-1.14)**	1.10 (1.07-1.12)**
Anemia	1.03 (0.99-1.08)	1.01 (0.96-1.06)	1.03 (0.99-1.07)
Peptic Ulcer disease	1.00 (0.87-1.15)	1.02 (0.88-1.19)	0.98 (0.88-1.09)
Sleep Apnea	1.03 (0.99-1.06)	1.01 (0.97-1.05)	1.01 (0.98-1.05)
Cognitive deficiency	1.23 (1.08-1.41)*	1.26 (1.11-1.42)**	1.20 (1.09-1.33)**
Major bleeding	1.00 (0.96-1.03)	1.02 (0.98-1.06)	1.00 (0.97-1.03)
CHA_2DS_2-VASc			
1	0.95 (0.90-1.00)*	0.95 (0.89-1.00)	0.95 (0.91-1.00)
≥2	0.94 (0.88-0.99)*	0.94 (0.88-1.01)	0.95 (0.90-1.00)
ATRIA			
4	1.02 (0.97-1.06)	1.05 (1.00-1.11)*	1.03 (0.99-1.07)
≥5	1.04 (0.98-1.10)	1.07 (1.00-1.14)*	1.03 (0.98-1.08)
CCI (ref: 0)			

1-2	1.06 (1.03-1.09)*	1.04 (1.01-1.08)*	1.05 (1.02-1.07)*
3-5	1.11 (1.06-1.15)*	1.09 (1.04-1.14)*	1.10 (1.06-1.14)*
6-8	1.16 (1.08-1.24)**	1.15 (1.06-1.24)*	1.18 (1.12-1.25)**
≥ 9	1.46 (1.33-1.60)**	1.34 (1.21-1.48)**	1.42 (1.33-1.54)**
≥1 hospitalizations	1.00 (0.98-1.03)	1.00 (0.97-1.03)	1.01 (0.99-1.03)
Catheter ablation	0.88 (0.79-0.98)*	0.78 (0.69-0.88)**	0.86 (0.78-0.95)*
Baseline Medication characteristic (ref: None)			
Antiplatelet therapy	1.00 (0.96-1.04)	1.00 (0.96-1.04)	1.00 (0.97-1.03)
Gastroprotective agent	1.04 (1.00-1.07)*	1.04 (1.01-1.08)*	1.05 (1.02-1.08)*
Antiarrhythmic	1.01 (0.99-1.04)	1.02 (1.00-1.06)	1.01 (0.99-1.03)
Digoxin	0.97 (0.94-0.99)*	0.95 (0.92-0.98)*	0.97 (0.95-1.00)*
Beta-blocker	1.04 (1.01-1.06)*	1.02 (0.99-1.04)	1.03 (1.01-1.06)*
Calcium channel blocker	1.02 (1.00-1.04)*	1.03 (1.00-1.06)*	1.02 (1.00-1.04)*
ACEI/ARB	0.97 (0.95-1.00)*	0.97 (0.95-1.00)*	0.98 (0.96-1.00)*
Statin	0.99 (0.97-1.01)	0.99 (0.97-1.02)	0.98 (0.96-1.00)
Hormone	0.98 (0.92-1.04)	0.97 (0.91-1.03)	0.99 (0.94-1.04)

*p<0.05

**p<0.001

Abbreviations: AMI, Acute Myocardial infarction; HR, Hazard Ratio; ref, referent group; CI, confidence interval; HMO, health maintenance organization; POS, point of service; PPO, preferred provider organization; CDHP, consumer driven health plan; VTE, venous thromboembolism; CCI, Charlson comorbidity index; ACEI/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker

Appendix table 17. Full multivariable survival analysis model results comparing dabigatran patients switching to warfarin versus dabigatran non-switchers

	Effectiveness HR (95% CI)	Harm HR (95% CI)	AMI HR (95% CI)
Switcher (ref: non-switcher)	1.02 (0.97-1.08)	1.06 (0.97-1.15)	0.99 (0.94-1.04)
Demographic baseline characteristic			
Age (ref: <55 years)			
55-64 years	1.04 (0.99-1.09)	1.07 (1.01-1.12)	1.04 (1.00-1.09)
65-74 years	0.94 (0.88-0.99)*	0.98 (0.91-1.05)	0.95 (0.90-1.01)
≥75 years	0.89 (0.83-0.95)*	0.92 (0.86-1.00)*	0.92 (0.86-0.98)*
Male Gender (ref: Female)	0.96 (0.93-1.00)*	0.96 (0.92-0.99)*	0.96 (0.93-0.99)
Region (ref: Northeast)			
North Central	1.05 (1.01-1.10)*	1.05 (1.00-1.11)*	1.06 (1.02-1.10)*
South	0.90 (0.87-0.94)*	0.90 (0.86-0.94)*	0.91 (0.88-0.95)*
West	0.97 (0.92-1.02)	0.96 (0.90-1.02)	0.97 (0.93-1.02)
Insurance plan (ref: Comprehensive)			
HMO	1.19 (1.12-1.27)**	1.22 (1.14-1.31)**	1.18 (1.11-1.25)**
POS	0.98 (0.92-1.05)	0.99 (0.91-1.06)	0.99 (0.93-1.05)
PPO	1.07 (1.03-1.11)*	1.09 (1.04-1.13)*	1.07 (1.03-1.11)*
CDHP	1.12 (1.01-1.24)*	1.14 (1.01-1.28)*	1.09 (0.99-1.20)
Prescription generosity (ref: None/Poor)			
Fair coverage	1.07 (0.85-1.36)	1.05 (0.81-1.37)	1.08 (0.84-1.38)
Good coverage	1.08 (0.85-1.37)	1.06 (0.81-1.38)	1.08 (0.84-1.39)
Clinical baseline characteristic (ref: 0/None)			
Ischemic stroke	0.99 (0.92-1.07)	1.01 (0.94-1.08)	1.01 (0.95-1.07)
Congestive Heart Failure	1.05 (1.00-1.09)*	1.06 (1.01-1.12)*	1.05 (1.01-1.10)*
Acute Myocardial infarction	1.02 (0.92-1.13)	1.04 (0.92-1.17)	1.01 (0.92-1.12)
Coronary artery disease	1.01 (0.98-1.05)	1.01 (0.97-1.05)	1.00 (0.97-1.04)
Hypertension	1.06 (1.02-1.11)*	1.09 (1.03-1.14)*	1.06 (1.02-1.10)*
Peripheral vascular disease	0.99 (0.92-1.05)	0.96 (0.88-1.04)	1.00 (0.94-1.06)
Diabetes Mellitus	0.98 (0.94-1.02)	0.97 (0.93-1.02)	0.99 (0.95-1.03)
VTE	0.88 (0.80-0.97)*	0.89 (0.79-1.00)*	0.93 (0.85-.101)
Renal insufficiency	0.95 (0.87-1.04)	1.01 (0.90-1.13)	0.97 (0.89-1.05)
Hyperlipidemia	1.05 (1.02-1.09)*	1.08 (1.04-1.12)*	1.05 (1.02-1.09)*
Anemia	1.04 (0.96-1.12)	1.04 (0.95-1.14)	1.04 (0.97-1.11)
Peptic Ulcer disease	0.98 (0.76-1.26)	1.00 (0.79-1.28)	0.99 (0.78-1.23)
Sleep Apnea	1.03 (0.98-1.07)	1.02 (0.96-1.07)	1.01 (0.97-1.05)
Cognitive deficiency	1.15 (0.89-1.48)	1.24 (0.98-1.57)	1.18 (0.97-1.43)
Major bleeding	0.92 (0.87-0.97)*	0.95 (0.89-1.02)	0.92 (0.87-0.97)*
CHA_2DS_2-VASc			
1	0.99 (0.93-1.05)	0.97 (0.91-1.04)	0.99 (0.92-1.06)
≥2	1.00 (0.92-1.08)	0.94 (0.86-1.03)	0.98 (0.90-1.05)
ATRIA			
4	1.00 (0.93-1.08)	0.99 (0.91-1.09)	0.99 (0.92-1.06)
≥5	1.09 (0.99-1.20)	1.07 (0.95-1.21)	1.07 (0.97-1.17)
CCI (ref: 0)			

1-2	1.02 (0.98-1.06)	1.03 (0.98-1.08)	1.03 (0.99-1.07)
3-5	1.08 (1.02-1.14)*	1.07 (1.00-1.14)	1.09 (1.03-1.15)*
6-8	1.14 (1.02-1.28)*	1.14 (1.00-1.30)*	1.14 (1.02-1.26)*
≥ 9	1.37 (1.18-1.59)**	1.21 (1.02-1.44)*	1.44 (1.26-1.65)**
≥1 hospitalizations	1.04 (1.01-1.07)*	1.04 (1.00-1.08)*	1.04 (1.01-1.07)*
Catheter ablation	1.02 (0.93-1.12)	1.21 (1.02-1.44)*	1.03 (0.94-1.13)
Baseline Medication characteristic (ref: None)			
Antiplatelet therapy	0.89 (0.85-0.94)*	0.89 (0.84-0.94)*	0.90 (0.86-0.94)*
Gastroprotective agent	1.01 (0.97-1.06)	1.01 (0.95-1.07)	1.01 (0.97-1.06)
Antiarrhythmic	1.01 (0.98-1.05)	1.00 (0.96-1.04)	1.01 (0.98-1.04)
Digoxin	0.98 (0.94-1.02)	0.96 (0.91-1.10)	0.97 (0.93-1.01)
Beta-blocker	1.04 (1.00-1.07)*	1.02 (0.99-1.06)	1.03 (1.00-1.06)*
Calcium channel blocker	1.01 (0.98-1.05)	1.01 (0.98-1.05)	1.01 (0.98-1.04)
ACEI/ARB	0.98 (0.95-1.01)	0.98 (0.95-1.02)	0.98 (0.95-1.01)
Statin	0.95 (0.92-0.99)*	0.94 (0.90-0.97)	0.95 (0.92-0.98)*
Hormone	0.95 (0.89-1.02)	0.93 (0.86-1.01)	0.95 (0.89-1.02)

*p<0.05

**p<0.001

Abbreviations: AMI, Acute Myocardial infarction; HR, Hazard Ratio; ref, referent group; CI, confidence interval; HMO, health maintenance organization; POS, point of service; PPO, preferred provider organization; CDHP, consumer driven health plan; VTE, venous thromboembolism; CCI, Charlson comorbidity index; ACEI/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker

Appendix table 18. Stratification by insurance status: Clinical effectiveness and safety of switching anticoagulants

Outcome Type	Effectiveness Composite HR (95% CI)	Harm Composite HR (95% CI)	AMI HR (95% CI)
Commercially-insured (CCAE)			
Warfarin switchers (ref: non-switchers) [§]			
Unadjusted	0.71 (0.67-0.75)**	0.71 (0.67-0.76)**	0.71 (0.67-0.74)**
MV-adjusted	0.70 (0.67-0.74)**	0.70 (0.66-0.75)**	0.71 (0.67-0.74)**
Dabigatran switchers (ref: non-switchers) [§]			
Unadjusted	1.04 (0.95-1.14)	1.03 (0.90-1.18)	0.99 (0.91-1.07)
MV-adjusted	1.03 (0.94-1.12)	1.02 (0.90-1.17)	0.97 (0.90-1.06)
Medicare Supplement (MDCR)			
Warfarin switchers (ref: non-switchers) [§]			
Unadjusted	0.65 (0.62-0.68)**	0.64 (0.60-0.68)**	0.64 (0.62-0.66)**
MV-adjusted	0.67 (0.64-0.70)**	0.66 (0.63-0.70)**	0.66 (0.64-0.69)**
Dabigatran switchers (ref: non-switchers) [§]			
Unadjusted	1.03 (0.95-1.10)	1.09 (0.98-1.21)	1.01 (0.94-1.07)
MV-adjusted	1.02 (0.95-1.09)	1.08 (0.97-1.19)	1.00 (0.94-1.07)

[§] Warfarin switchers: patients who switched from warfarin to dabigatran; Dabigatran switchers: patients who switched from dabigatran to warfarin

NOTE: REF: Non-switching

*p<0.05; p<0.001

Abbreviations: MV, Multivariable; HR, Hazard Ratio; CI, Confidence interval

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