The Thesis Committee for Sarah Elizabeth Hulvershorn
Certifies that this is the approved version of the following thesis:

Outcomes and direct treatment costs with novel oral anticoagulants compared to clinic-monitored warfarin for stroke prevention in atrial fibrillation

APPROVED BY
SUPERVISING COMMITTEE:

Supervisor:

Karen L. Rascati, Supervisor

James P. Wilson, Co-Supervisor

Ola O. Oyetayo

Paul J. Godley

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by

Sarah Elizabeth Hulvershorn, B.S., Pharm.D.

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Abstract

Outcomes and direct treatment costs with novel oral anticoagulants compared to clinic-monitored warfarin for stroke prevention in atrial fibrillation

Sarah Elizabeth Hulvershorn, M.S.P.S.

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Supervisor: Karen L. Rascati; James P. Wilson

Objectives: To describe patient characteristics and evaluate costs and outcomes of novel oral anticoagulants compared to clinic-monitored warfarin for the prevention of stroke and systemic embolism in patients with atrial fibrillation within the Scott & White Healthcare system.

Methods: Patients with atrial fibrillation, $CHADS_2$ score ≥ 1, and a prescription claim for dabigatran, rivaroxaban, or warfarin between 2010 and 2012 were evaluated over 12 months. Patients in the warfarin cohort were enrolled in an Anticoagulation Clinic. Patients were matched 1:1 for age, $CHADS_2$, and gender for comparisons between groups. Baseline characteristics, medication adherence, occurrence of adverse events, and treatment costs were compared using inferential statistics. Anticoagulation control was assessed for patients in the warfarin cohort.

Results: 141 and 471 patients met criteria for the novel cohort group and the warfarin group, respectively. After matching, 136 remained in each cohort. Prior to matching,

compared to the warfarin cohort, the novel anticoagulant cohort had a higher proportion of male patients (63% versus 49%), and lower average $CHADS_2$ score (2.65 versus 3.30), while average age in both cohorts was similar (75 years). Matched cohorts had similar adherence rates (88% for novel versus 87% for warfarin). After matching, annual medication cost in 2014 US dollars for dabigatran or rivaroxaban averaged $2,658 (SD $1,494) compared to $1,066 (SD $633) for warfarin, including monitoring costs. Annual total all-cause healthcare costs averaged $23,711 (SD $22,910) for dabigatran or rivaroxaban, compared to $18,248 (SD $24,184) for warfarin. For the 96 warfarin patients with INR values, time in therapeutic range averaged 70.4%.

Conclusion: Compared to clinic-monitored warfarin, more men than women were prescribed new oral anticoagulants and these patients averaged a lower $CHADS_2$ score. After matching, patient adherence was high and comparable between groups. Anticoagulation control for warfarin patients was similar to clinical trials. Annual medication cost was significantly greater for new oral anticoagulants than clinic-monitored warfarin, including INR monitoring costs. Total annual all-cause healthcare costs were significantly greater for patients taking new oral anticoagulants compared to warfarin, although too few adverse events occurred to draw conclusions regarding event rates and costs of ischemic stroke and major bleeds.

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CHAPTER 1: INTRODUCTION

Atrial Fibrillation

Atrial fibrillation is the most common sustained cardiac arrhythmia, estimated to affect 2.2 million Americans. [1] Atrial fibrillation occurs more often in men, patients with more severe heart failure, and incidence increases dramatically with age, with an 8% incidence rate in patients >80 years old.[1,2] Due to the aging population and improved survival of patients with cardiovascular disease, it is projected that the prevalence of atrial fibrillation in the United States will climb to over 12 million by the year 2050.[1,2]

Physiologically, atrial fibrillation is characterized by rapid, disorganized electrical activity (400 to 600 beats per minute) in the atria of the heart, leading to an irregularly irregular supraventricular heart rhythm.[1] The etiology of atrial fibrillation is often cardiogenic in nature, occurring frequently in patients with ischemic heart disease, heart failure, hypertension, congenital abnormalities, and valvular heart disease.[1] Noncardiogenic causes of atrial fibrillation include states of high adrenergic tone such as hyperthyroidism, acute infection, alcohol withdrawal, or post-surgery.[1] Atrial fibrillation may be asymptomatic, but patients can also experience clinical manifestations such as rapid heart rate, palpitations, fatigue, dizziness, shortness of breath, and worsening heart failure.[1]

Thromboembolic Events

Patients with atrial fibrillation are at increased risk of thromboembolic events, due to pooling of blood in the atria leading to subsequent thrombus formation.[1] Stroke is the most concerning of thromboembolic events associated with atrial fibrillation. Atrial fibrillation is a

strong independent predictor for ischemic stroke, and is associated with a fivefold increase in risk.[2] The use of oral antithrombotic agents is the mainstay of therapy in the prevention of stroke and systemic embolism in patients with atrial fibrillation. However, antithrombotic therapy is associated with increased risk of bleeding, therefore the underlying benefit of antithrombotic therapy depends on the risk of stroke.[3,4] Although there are several indices available to estimate baseline risk of stroke in patients with atrial fibrillation, the $CHADS_2$ score has been widely adopted by clinicians and is currently the most validated risk scheme, as it has been tested in at least 10 different cohorts since its original development.[4] $CHADS_2$ is an acronym for the risk factor criteria used to determine the score (**C**ongestive heart failure, **H**ypertension **A**ge, **D**iabetes, and prior **S**troke). The $CHADS_2$ score consists of a summary score of 0-6 based on risk factors for stroke in patients with atrial fibrillation, with 1 point each given for congestive heart failure, history of hypertension, age ≥75, and diabetes mellitus, and 2 points assigned for history of stroke or transient ischemic attack.[3] The Antithrombotic Therapy and Prevention of Thrombosis, 9th edition, American College of Chest Physicians (ACCP) Evidence-Based Clinical Practice Guidelines published in 2012 recommend aspirin as the antithrombotic agent of choice for atrial fibrillation patients at low risk of stroke ($CHADS_2 = 0$), and oral anticoagulant therapy for patients at intermediate to high risk of stroke ($CHADS_2 \geq 1$).[4]

Warfarin Therapy

The use of oral anticoagulation is the mainstay of therapy in the prevention of stroke and systemic embolism in patients with atrial fibrillation.[1] For over 50 years, warfarin was the only oral anticoagulant available for clinical use in the U.S.[5] Warfarin acts as a vitamin K antagonist, inhibiting the production of vitamin K-dependent clotting factors (factor VII, IX, X, and

prothrombin), thereby preventing initial thrombus formation and development.[1] A major limitation of warfarin is a wide inter-patient variability in dose-response due to a variety of factors.[1,5] Therapeutic response to warfarin is affected by genetic variability in both the CYP2C9 enzyme, affecting hepatic metabolism of warfarin, as well as vitamin K epoxide reductase (VKOR), which affects the pharmacodynamics of warfarin.[1,5] Variations in oral intake of dietary vitamin K impacts the effectiveness of warfarin.[1] Warfarin has numerous drug-drug interactions caused by a variety of mechanisms, including other drugs that induce or inhibit CYP2C9.[1] The primary adverse effect of warfarin (and the result of over-anticoagulation) is hemorrhage, such as gastrointestinal bleeding, bruising, and most severe, intracranial hemorrhage.[1]

Due to variability in therapeutic response and the narrow therapeutic index of the drug, warfarin requires frequent laboratory monitoring and dosing adjustments. The anticoagulation effect of warfarin is measured by prothrombin time (PT), which measures the amount of time required for clot formation upon addition of a reagent to a plasma sample.[1] Due to variability in the sensitivity of the reagent used to measure PT, the World Health Organization (WHO) developed a reference reagent in the 1970s and recommended the use of a corrected prothrombin-time ratio called the International Normalized Ratio (INR) to monitor warfarin therapy.[1] For stroke prevention in atrial fibrillation, the recommended therapeutic INR range is typically 2.0 – 3.0, with a target INR of 2.5.[6] INR testing is frequent upon initiation of warfarin therapy or upon dose adjustment (i.e., every few days to weekly), occurs every 4 weeks once INRs and dosing are stable, but may extend up to 12 week intervals in patients with consistently stable INRs.[6] The management of patients experiencing elevated INRs or bleeding depends on severity, and ranges from warfarin dose reduction or omission to administration of oral vitamin

K, intravenous vitamin K, fresh frozen plasma, prothrombin complex, or Recombinant Factor VIIa.[6]

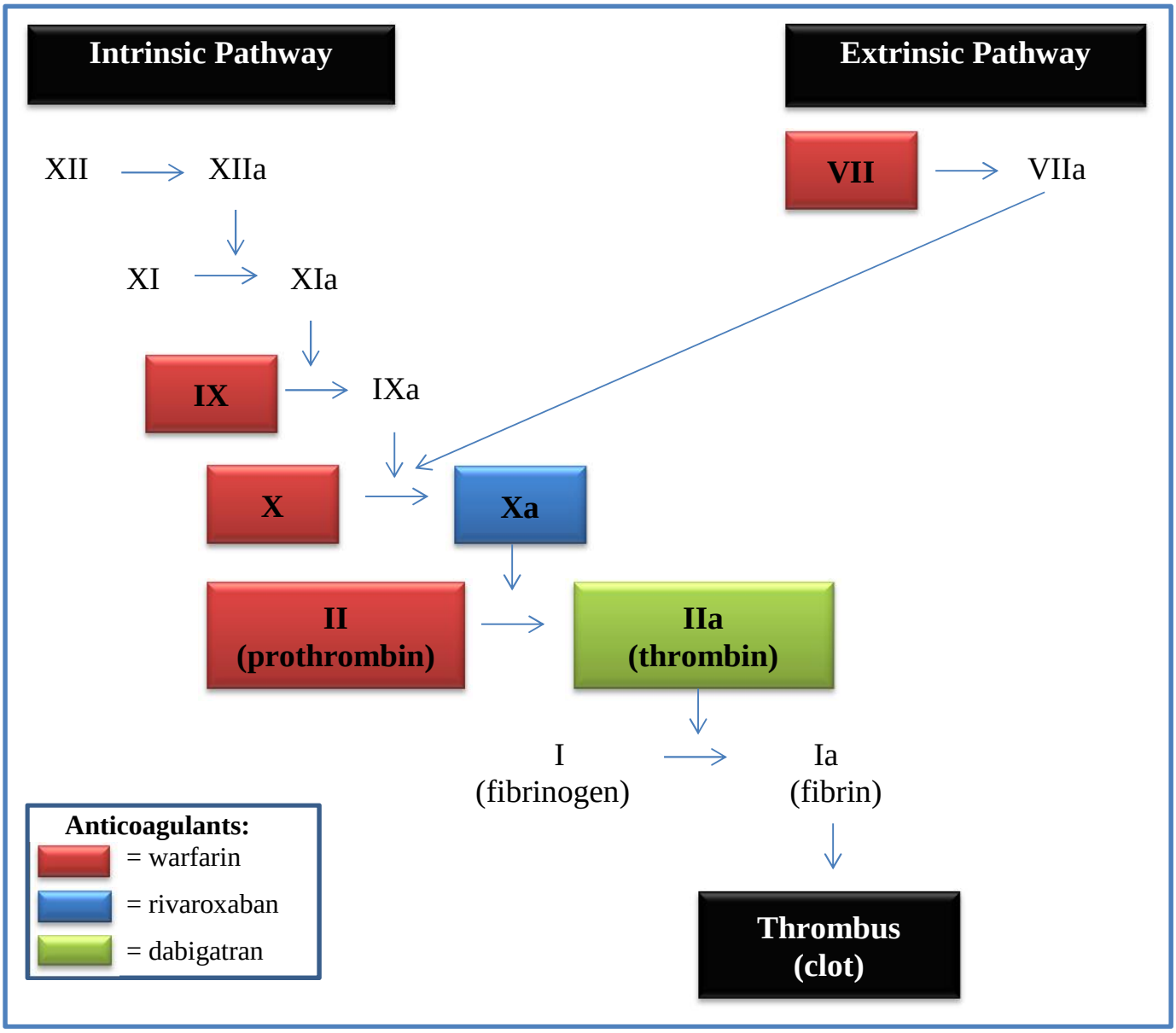
Sorensen and colleagues demonstrated that clinical and cost outcomes of warfarin are strongly dependent on the quality of anticoagulation, and as INR control improves, stroke rates decrease, quality-adjusted life years (QALYs) increase, and per-patient costs decrease.[7] The quality of a patient's anticoagulation management can be assessed by examining INRs over time. Time in Therapeutic Range (TTR) is often calculated as the proportion of days a patient's INR is in therapeutic range over the total number of days in the follow-up period, as proposed by Rosendaal et. al.[8] TTR has been reported in clinical trials ranging from 55-66%, although studies in community settings have reported TTRs closer to 50%.[9]

New Oral Anticoagulants

Dabigatran and rivaroxaban are new oral anticoagulants that became available in 2010 and 2012, respectively, as alternative therapy to warfarin for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation. Pharmacologically, dabigatran and rivaroxaban target different areas of the anticoagulation pathway than warfarin (Figure 1.1). These novel oral anticoagulants provide the advantage of fixed dosing and no laboratory monitoring, potentially leading to improved patient compliance.[10]

Dabigatran exerts its action as a direct thrombin inhibitor that prevents thrombin-induced platelet aggregation, thereby reducing the ability of thrombin to form a clot.[5] The pivotal study for dabigatran was the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) study, which was a randomized clinical trial of 18,113 patients with atrial fibrillation and risk of

Figure 1.1: Site of Action of Oral Anticoagulants in the Coagulation Cascade[11]



stroke comparing fixed-dose dabigatran to dose-adjusted warfarin.[12] The primary outcome of RE-LY was stroke or systemic embolism, with major hemorrhage as the primary safety outcome.[12] Warfarin was adjusted to an INR of 2.0-3.0, with a reported TTR of 64%. The mean $CHADS_2$ score for patients in RE-LY was 2.1. Dabigatran showed decreased annual rates of stroke and systemic embolism compared to warfarin (1.11% versus 1.69%, respectively, $p<0.001$ for superiority).[12] Dabigatran was shown to have similar annual rates of major hemorrhage compared to warfarin (3.11% versus 3.36%, respectively, $p=0.31$).[12] However, dabigatran had lower annual rates of intracranial bleeding and life-threatening bleeding compared to warfarin (0.74% versus 0.30%, and 1.80% versus 1.45%, respectively) ($p<0.05$ for all comparisons).[12] Dabigatran was found to have higher annual rates of gastrointestinal bleeding than warfarin (1.51% versus 1.02% respectively, $p<0.001$).[12]

Rivaroxaban is a direct factor Xa inhibitor, and exerts its action by reducing the production of thrombin, thus inhibiting thrombin-induced platelet activation and fibrin clot formation.[5] The pivotal study for rivaroxaban was the Rivaroxaban Once Daily Oral Direct Factor Xa inhibition Compared with Vitamin K Antagonist for the Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) study. ROCKET-AF was a double-blind, randomized clinical trial of 14,264 patients with atrial fibrillation plus two additional risk factors for embolic events, comparing fixed-dose rivaroxaban to dose-adjusted warfarin.[13] The primary outcome of ROCKET-AF was stroke or systemic embolism, and the primary safety endpoint was clinically relevant bleeding.[13] Warfarin was adjusted to an INR of 2.0-3.0, with a reported TTR of 55%. The mean $CHADS_2$ score for patients in ROCKET-AF was 3.5. Rivaroxaban was shown to be non-inferior to warfarin in annual rates of stroke and systemic embolism (1.7%

versus 2.2%, respectively, $p<0.001$ for noninferiority).[13] Rivaroxaban was shown to have similar annual rates of major hemorrhage compared to warfarin (3.6% versus 3.4%, respectively, $p=0.58$).[13] However, rivaroxaban had lower annual rates of intracranial bleeding and fatal bleeding compared to warfarin (0.5% versus 0.7%, and 0.2% versus 0.5%, respectively) ($p<0.05$ for all comparisons).[13] Rivaroxaban was found to have higher annual rates of gastrointestinal bleeding than warfarin (3.2% versus 2.2% respectively, $p<0.001$).[13]

In summary, clinical trials showed dabigatran to be clinically superior to warfarin in decreased rate of stroke and systemic embolism in patients with atrial fibrillation, while rivaroxaban was shown to be similar in efficacy compared to warfarin.[12,13] Both dabigatran and rivaroxaban were shown to have similar rates of major hemorrhage compared to warfarin, but less risk of intracranial bleeding.[12,13] The advantages of these agents include the convenience of fixed dosing due to more predictable pharmacology, less dietary restrictions and drug-drug interactions than warfarin, and no laboratory monitoring. However, the new oral anticoagulants are not without limitations. There are currently no widely available laboratory tests to correlate drug concentration and level of anticoagulation. This is due to insensitivity or oversensitivity of the new oral anticoagulants to currently available laboratory tests, nonlinear relationships to drug concentrations, and lack of clinical trial data linking clinical outcomes to drug concentration levels or clotting results.[5] There is currently no antidote to dabigatran or rivaroxaban for management of major bleeding, overdose, or urgent surgery or invasive procedures. Current management of major bleeding includes empirical strategies, such as discontinuation of the drug, volume or red blood cell replacement, local measures such as pressure or cautery, or activated charcoal to reduce gastrointestinal absorption.[5,9] Dabigatran is dialyzable, presenting another

potential management option, but rivaroxaban is highly plasma protein bound and dialysis would not be an appropriate option.[9] Additionally, the new oral anticoagulants have a rapid pharmacokinetic onset and offset, which may be attractive, but also makes patient compliance imperative.[9] In fact, the FDA has issued black box warnings on dabigatran and rivaroxaban warning that premature discontinuation of the drugs can increase risk of thromboembolic events. Additionally, dabigatran and rivaroxaban are priced at significantly higher acquisition costs compared to warfarin.

Cost-Effectiveness Studies

Using data from published clinical trials, several economic analyses have been conducted in hypothetical patient populations to evaluate the cost-effectiveness of dabigatran or rivaroxaban compared to warfarin in patients with nonvalvular atrial fibrillation.

The cost-effectiveness of dabigatran was examined in a Markov decision analysis model by Freeman, et al. and showed dabigatran provided an additional 0.56 quality-adjusted life years (QALYs) over warfarin in patients age 65 and older with nonvalvular atrial fibrillation and at an increased risk of stroke ($CHADS_2 \geq 1$).[14] The incremental cost-effectiveness ratio showed that dabigatran costs $45,372 (in 2008 U.S. dollars) per QALY gained compared to warfarin, with cost-effectiveness improving with increased risk of stroke and intracranial bleeding.[14] Assuming a willingness-to-pay threshold of $50,000 per QALY gained, this finding suggests that dabigatran may be a cost-effective alternative to dose-adjusted warfarin in this population. However, it is important to note the model was sensitive to dabigatran costs, as costs in the analysis were estimated from pricing in the United Kingdom.[14] Additionally, event rates used in this analysis were primarily derived from the RE-LY trial.[14]

Shah et al. conducted a Markov decision analysis model comparing various antithrombotic therapies for the treatment of atrial fibrillation and showed that for 70-year-old patients at moderate risk of stroke, dabigatran provided additional 0.25 QALYs over warfarin at a cost of $86,000 (in 2010 U.S. dollars) per QALY gained.[15] Although the base-case scenario estimate is higher than the commonly used willingness-to-pay threshold of $50,000 per QALY gained, the model was found to be sensitive to risk of stroke, bleed, and INR control of warfarin. For patients with moderate risk of stroke ($CHADS_2$ = 1 or 2), warfarin was cost-effective, unless the risk of hemorrhage was high (6%/year) or INR control was poor (TTR <57.1%).[15] For patients with high risk of stroke ($CHADS_2 \geq 3$), dabigatran was cost-effective, unless INR control was excellent (TTR >72.6%), in which case warfarin was cost-effective.[15] Dabigatran efficacy for this analysis was solely based on the RE-LY trial.

The cost-effectiveness of rivaroxaban was examined by Lee et al.[16] Their Markov decision analysis model utilized ROCKET-AF study data and found that for 65-year-old atrial fibrillation patients at high risk for stroke ($CHADS_2$ = 3), rivaroxaban provided an additional 0.22 QALYs over warfarin for an additional lifetime treatment cost of $5,912 (in 2011 U.S. dollars).[16] This results in an incremental cost-effectiveness ratio of $27,498 per QALY gained.[16] Although this is below the willingness to pay threshold of $50,000, the model was sensitive to rates of intracranial hemorrhage, stroke, and cost of rivaroxaban, as well as time horizon. Rivaroxaban was found to be cost-effective in 80% of 10,000 Monte Carlo iterations at a willingness-to-pay threshold of $50,000 per QALY.[16]

Deitelzweig and colleagues conducted an economic analysis using data from both the RE-LY and ROCKET-AF study, estimating one-year medical costs to be lower for atrial

fibrillation patients taking dabigatran or rivaroxaban (-$179 and -$89, respectively, in 2010 U.S. dollars) compared to warfarin.[17] Of 10,000 Monte-Carlo iterations, one-year medical costs were shown to be less than warfarin 92.6% of the time with dabigatran and 79.8% of the time with rivaroxaban.[17] Of note, this study demonstrated increased one-year medical cost of major bleedings (excluding hemorrhagic stroke) with dabigatran and rivaroxaban (+$31 and +$108, respectively) compared to warfarin.[17] Medical costs in this study were driven by clinical outcomes, as drug costs and monitoring costs were excluded from the analysis.

Harrington et al. also used data from the RE-LY and ROCKET-AF studies to conduct a Markov model decision analysis in nonvalvular atrial fibrillation patients age 70 at an increased risk of stroke ($CHADS_2 \geq 1$).[18] Warfarin was found to have the lowest lifetime costs ($77,813, in 2012 U.S. dollars) followed by rivaroxaban ($78,738) and dabigatran ($82,719).[18] Dabigatran provided an additional 0.44 QALY over warfarin while rivaroxaban provided an additional 0.29 QALY.[18] Both dabigatran and rivaroxaban were shown to be cost-effective compared to warfarin, with incremental cost-effectiveness ratios of $3,190 and $11,150, respectively.[18] Monte Carlo simulation showed dabigatran to be cost-effective in 40% of iterations, rivaroxaban in 14% of iterations, and warfarin in 0% iterations.[18] Cost-effectiveness in this model was dependent on the cost of the novel oral anticoagulants and on neurological events associated with rivaroxaban.[18]

Study Rationale

Oral anticoagulants are the mainstay of prevention of stroke in patients with atrial fibrillation. For over 50 years, warfarin was the only oral anticoagulant available for clinical use in the U.S. Limitations of warfarin include wide inter-patient variability in dose response and a

narrow therapeutic index requiring frequent INR monitoring. Novel oral anticoagulants have recently become available on the market that are similar in safety and efficacy to warfarin but have the advantage of more predictable pharmacokinetic profiles and no laboratory monitoring. Limitations to the new oral anticoagulants include lack of specific antidotes and significantly higher acquisition costs compared to warfarin. Several studies have shown potential cost-effectiveness of novel oral anticoagulants compared to warfarin in certain patient populations based on economic modeling from clinical trial data. However, the current literature is deficient in the evaluation of the cost-effectiveness of novel oral anticoagulants compared to warfarin in "real-world settings", which may differ from results seen in clinical trials due to more inclusive patient populations, and real-world patient compliance and INR control. The findings of this study will contribute significantly to the literature by describing patient characteristics, quantifying the incidence of major bleeds, rates of ischemic stroke, and the costs of treatment of novel oral anticoagulants compared to clinic-monitored warfarin for stroke prevention in patients with atrial fibrillation in a real-world healthcare system. Results may be incorporated into future models.

CHAPTER 2: METHODS

Study Objectives and Hypotheses

This study evaluated the cost-effectiveness of novel oral anticoagulants compared to clinic-monitored warfarin for prevention of stroke and systemic embolism in patients with atrial fibrillation within the Scott & White Healthcare system. The specific objectives of this study were:

1.) To determine if patient characteristics (age, gender, or $CHADS_2$ score) differ between patients taking novel oral anticoagulants (dabigatran or rivaroxaban) versus clinic-monitored warfarin.

2.) To determine if patient adherence to oral anticoagulant medication differs between patients taking novel oral anticoagulants (dabigatran or rivaroxaban) versus clinic-monitored warfarin.

3.) To determine if incidence of major bleeds (defined as requiring inpatient hospitalization) differs between patients taking novel oral anticoagulants (dabigatran or rivaroxaban) versus clinic-monitored warfarin.

4.) To determine if incidence of ischemic stroke differs between patients taking novel oral anticoagulants (dabigatran or rivaroxaban) versus clinic-monitored warfarin.

5.) To assess direct treatment costs with novel oral anticoagulants (dabigatran or rivaroxaban) compared to clinic-monitored warfarin.

6.) To assess INR control in patients taking clinic-monitored warfarin within the Scott & White Healthcare System.

This study addressed the following hypotheses:

$H_0$1: There is no statistical difference in patient characteristics (age, gender, or $CHADS_2$ score) between patients taking novel oral anticoagulants (dabigatran or rivaroxaban) versus clinic-monitored warfarin.

$H_0$2: There is no statistical difference in patient adherence to oral anticoagulant medication between patients taking novel oral anticoagulants (dabigatran or rivaroxaban) versus clinic-monitored warfarin.

$H_0$3: There is no statistical difference in the incidence of major bleeds (requiring inpatient hospitalization) between patients taking novel oral anticoagulants (dabigatran or rivaroxaban) versus clinic-monitored warfarin.

$H_0$4: There is no statistical difference in the incidence of ischemic stroke between patients taking novel oral anticoagulants (dabigatran or rivaroxaban) versus clinic-monitored warfarin.

$H_0$5: There is no statistical difference in total all-cause direct treatment costs for cohorts with novel oral anticoagulants (dabigatran or rivaroxaban) compared to clinic-monitored warfarin.

Data Source

Retrospective data were obtained from Scott & White Healthcare. Scott & White Healthcare is an integrated health system in Central Texas. The regional healthcare system is a 1,200 physician staff-model group practice which includes 12 hospitals and over 45 regional clinics (Scott & White Clinics) with 2 million patient visits annually. Scott & White Health Plan is a 220,000 covered lives staff-model nonprofit health plan, including 20,000 Medicare Part D

members and covering 50 counties in the Central Texas Region. Scott & White operates its own pharmacy benefit management (PBM) program, which includes an additional 45,000 member lives. Additionally, Scott & White operates a regional network of retail pharmacies.

The Scott & White Anticoagulation Clinic has been in operation since 1995 and focuses on outpatient management of warfarin therapy for patients across Central Texas. The multi-disciplinary clinic is staffed by pharmacists, nurses, and nurse practitioners who have been specially trained in anticoagulation therapy. Physician medical directors provide medical and administrative guidance for the Anticoagulation Clinic, which included an internal medicine physician and a hematologist during the time period of this study (January 2010 through December 2013). In addition to outpatient clinic operations, the Anticoagulation Clinic also provides a hospital service for clinic patients to smooth the transition of care from the inpatient to outpatient setting.

Patients are enrolled in the Anticoagulation Clinic upon physician referral for management of warfarin therapy for a variety of indications. Anticoagulation therapy monitoring and dose adjustments are based on a physician-approved protocol, and include patient education, screening for drug-drug interactions, drug-food interactions, and changes in health status affecting anticoagulation, prothrombin time (PT) and International Normalized Ratio (INR) monitoring, and subsequent dose adjustments to optimize therapy. PT and INR monitoring is performed by fingerstick in the office at point-of-care in about 70% of patients. Nursing home, home health, and out-of-town patients are monitored for PT/INR remotely via laboratory venipuncture and comprise 30% of patients.

This study was approved via expedited review by the Scott & White and The University of Texas Institutional Review Boards.

Study Design

The study was an intent-to-treat, retrospective, quasi-experimental design utilizing matched cohorts to allow for between-group comparisons of clinical and economic outcomes. Pharmacy claims, medical claims, electronic medical records, and health plan enrollment data were evaluated from January 1, 2010 to December 31, 2013.

Study Population

Patients were required to be 18 years or older with at least one diagnosis code for atrial fibrillation (ICD-9 427.31) and a $CHADS_2$ score ≥ 1 in order to be included in the analysis. Patients with at least one pharmacy claim for dabigatran or rivaroxaban between January 1, 2010 and December 31, 2012 were included in the novel oral anticoagulant cohort. Patients included in the warfarin cohort must have had at least one pharmacy claim for warfarin between January 1, 2010 and December 31, 2012 and be enrolled in the Scott & White Anticoagulation Clinics located in the cities of Temple, Gatesville, Taylor, or Killeen, Texas.

The date of the first claim for dabigatran, rivaroxaban, or warfarin between January 1, 2010 and December 31, 2012 was considered the index date. Patients were required to have continuous enrollment in Scott & White Health Plan for at least 12 months post-index.

Patients in the novel oral anticoagulant cohort were matched 1:1 to patients meeting criteria for the warfarin cohort, based on gender, age at index, and $CHADS_2$ score.

Outcome Measures

1.) Patient characteristics were evaluated based on age at index (continuous variable), gender (male or female), and baseline $CHADS_2$ stroke-risk index (score of 0 – 6) based on ICD9 codes (see Appendix A) from historical data in electronic medical records.

2.) Medication possession ratio (MPR) was calculated from prescription claims data to assess patient adherence to the index drug. MPR is a continuous variable defined as the number of days of medication supplied divided by the number of days from the first prescription of index drug filled to the date of the last index drug refilled during the 12 months post-index period[19] and was calculated as follows:

$$\text{MPR} = \frac{\text{total days supply of medication dispensed}}{\text{last prescription date} - \text{first prescription date} + \text{last prescription days of supply}}$$

3.) Incidence of major bleeds was extracted from inpatient claims with a primary ICD-9 code for hemorrhagic events (See Appendix B) within 12 months post-index.

4.) Incidence of stroke was extracted from inpatient claims with a primary ICD-9 code for ischemic stroke (ICD-9 433.xx – 435.xx) within 12 months post-index.

5.) Direct treatment costs were summed for the 12 months post-index follow-up period using the following cost parameters:

   a. Cost of index medication from pharmacy claims adjusted to 2014 U.S. dollars based on average wholesale price (AWP) from Medi-Span®

   b. Cost of monitoring warfarin via anticoagulation clinic as a sum of the following parameters per documented point-of-care laboratory INR testing:

- 2014 Centers for Medicare and Medicaid Services (CMS) reimbursement rate for CPT 85620 “prothrombin time” and CPT 99213 “15 minute office visit”
- 2014 cost of one iStat INR testing cartridge
- 20 minutes of staff labor cost for a registered nurse, as estimated by the 2012 median pay reported by the Bureau of Labor Statistics[20] adjusted to 2014 dollars using a 4% average medical inflation rate.[21]

c. Costs to treat clinical adverse events estimated from the total cost for each claim with an inpatient visit with a primary ICD-9 code for ischemic stroke (ICD-9 433.xx – 435.xx) or bleed (Appendix B). Costs were adjusted to 2014 U.S. dollars at a 4% annual medical inflation rate.[21]

6.) Time in therapeutic range (TTR) was calculated to assess INR control for patients in the warfarin cohort. TTR is a continuous variable defined as the proportion of time that the international normalized ratio (INR) was within therapeutic range. For the purposes of this study, the therapeutic range was assumed to be an INR between 2.0 and 3.0, consistent with 2012 ACCP guidelines.[6] TTR was calculated by the method proposed by Rosendaal et. al,[8] whereby INR values between two INR assessments are estimated using linear interpolation, and the TTR is defined as follows:

$$\text{Proportion of TTR} = \frac{\text{\# of patient days within specified range}}{\text{total patient days in follow-up period}}$$

Statistical Analysis

- Descriptive statistics (mean and standard deviation or median and interquartile range) will be used to characterize demographic data before and after matching.
- Chi-square analyses will be conducted for categorical variable comparisons between groups (e.g., incidence of major bleeds and ischemic stroke).
- Mann-Whitney U tests will be conducted for nonparameteric continuous variable comparisons between groups (e.g., direct treatment costs).
- Statistical analyses will be computed using SAS 9.2 (SAS Institute Inc, Cary, North Carolina) and IBM SPSS Statistics Version 21 for Windows.
- A value of $p<0.05$ will be used to determine statistical significance.

Feasibility Analysis

- Sample size calculations were performed using G*Power 3.1.9.2 software:
    - Using a conventional estimation for small effect size ($w = 0.1$), a total sample size of **785** would be required to determine a difference in rate of stroke or major bleed between treatment groups using Chi-Square analyses, assuming an alpha of 0.05 and power of 0.80.
    - Using published annual stroke rates from RE-LY yielded an effect size of $w = 0.05$, which would require a total sample size of **3,140** to detect a difference in rate of stroke between treatment groups using Chi-Square analyses, assuming an alpha of 0.05 and power of 0.80.

- Using published annual bleed rates from RE-LY yielded an effect size of w = 0.01, which would require a total sample size of **19,623** to detect a difference in rate of major bleed between treatment groups using Chi-Square analyses, assuming an alpha of 0.05 and power of 0.80.

- Preliminary sample sizes (prior to application of inclusion/exclusion criteria):
  - **254** unique Scott & White Health Plan members initiated dabigatran or rivaroxaban between January 1, 2010 and December 31, 2012.
  - **899** unique Scott & White Health Plan members had a claim for warfarin and were enrolled in Scott & White Anticoagulation Clinics in the cities of Temple, Gatesville, Taylor, and Killeen, Texas between January 1, 2010 and December 31, 2012.
- Preliminary event rates (prior to application of inclusion/exclusion criteria):
  - Of the 254 members with a claim for dabigatran or rivaroxaban:
    - **34** had an inpatient medical claim with a primary diagnosis of bleed between January 1, 2010 and December 31, 2013.
    - **30** had an inpatient medical claim with a primary diagnosis of ischemic stroke between January 1, 2010 and December 31, 2013.
  - Of the 899 unique members with a claim for warfarin and enrolled in anticoagulation clinic:
    - **114** had an inpatient medical claim with a primary diagnosis of bleed between January 1, 2010 and December 31, 2013.

        - **109** had an inpatient medical claim with a primary diagnosis of ischemic stroke between January 1, 2010 and December 31, 2013.

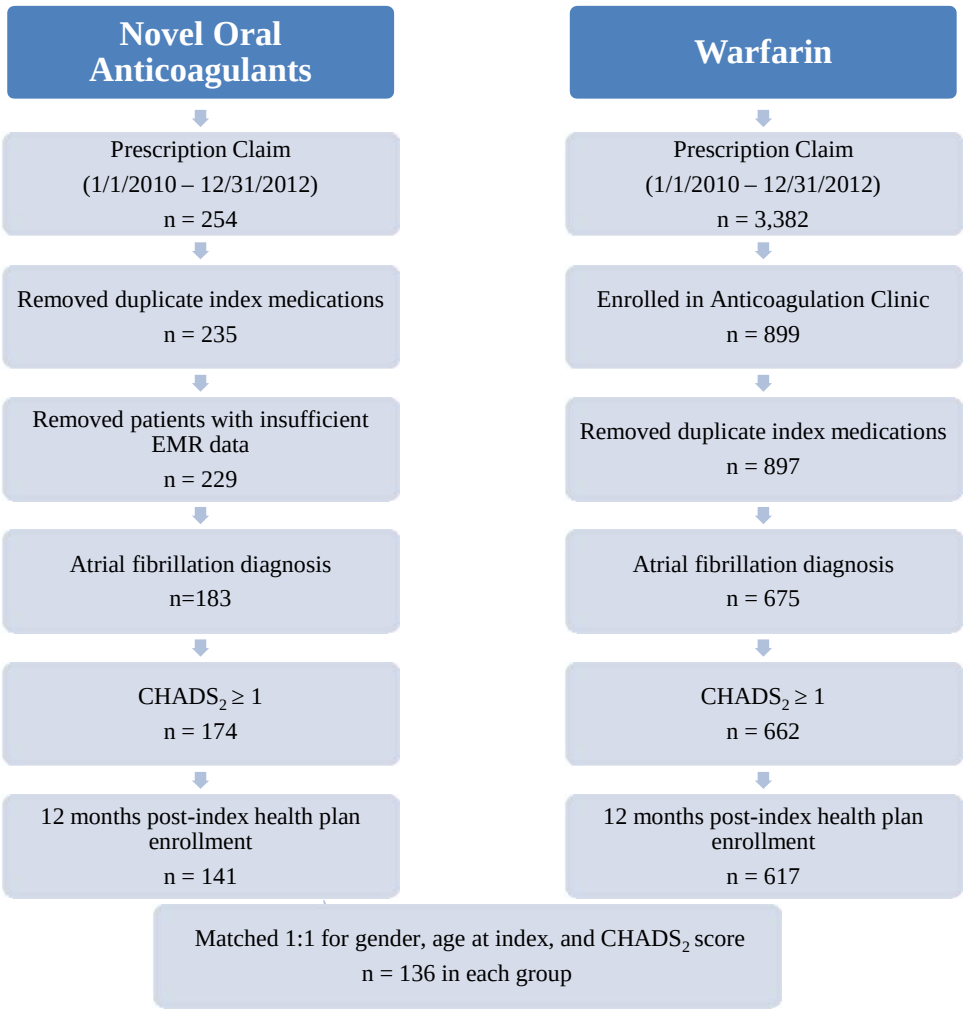
- Although sample size may be a limitation in this study for the statistical comparison of rare events (e.g., incidence of major bleeds and ischemic stroke), this study will still contribute to the literature with regards to comparison of direct treatment costs, adherence rates (MPR), and patient characteristics (e.g., age, gender, $CHADS_2$ score) between novel oral anticoagulants and clinic-monitored warfarin patients, as well as assessing INR control (TTR) of clinic-monitored warfarin patients in a real-world population.

CHAPTER 3: RESULTS

Patient Selection

A total of 758 patients met the inclusion criteria for this study. Among these, 141 patients met criteria for inclusion in the novel oral anticoagulant cohort, and 617 met criteria for inclusion in the warfarin cohort. After conducting a 1:1 match based on gender, age at index, and $CHADS_2$ score, the final study cohort included 136 patients in each group (Figure 3.1).

Figure 3.1: Flow-chart of patient identification



Demographic Characteristics

Demographic information for the 758 patients meeting inclusion criteria prior to matching is described in Table 3.1. An independent groups t-test showed no significant difference in mean age at index (in years) between patients taking novel oral anticoagulants (75.1, SD = 10.0) and warfarin (76.1, SD = 9.7) (t = 1.116; df = 203.963; p = 0.266).

A chi-square analysis revealed a significant relationship between patient gender and medication cohort (X^2 = 9.443; df = 1; p = 0.002). A greater proportion of males (63.1%) comprised the novel anticoagulant cohort than females (36.9%). In the warfarin cohort, gender proportions were almost equal (males = 48.8%; females = 51.2%).

A Mann-Whitney U test showed a significant difference in $CHADS_2$ score between patients taking novel oral anticoagulants (median = 2.0; mean = 2.65; SD = 1.24) and warfarin (median = 3.0; mean = 3.30; SD = 1.35) (Z = -5.317; p < 0.001).

Table 3.1: Baseline Characteristics by Cohort Prior to Matching

	Novel Anticoagulant (n = 141)	**Warfarin (n = 617)**	***p*-value**
Age at index (years) mean (SD)	75.06 (10.029)	76.10 (9.688)	0.266[a]
Gender			
Male, n (%)	89 (63.1)	301 (48.8)	0.002[b]
Female, n (%)	52 (36.9)	316 (51.2)	
$CHADS_2$ score			
1, n (%)	22 (15.6)	54 (8.8)	
2, n (%)	57 (40.4)	127 (20.6)	
3, n (%)	26 (18.4)	185 (30.0)	<0.001[c]
4, n (%)	22 (15.6)	117 (19.0)	
5, n (%)	12 (8.5)	97 (15.7)	
6, n (%)	2 (1.4)	37 (6.0)	

[a] Independent sample t-test (t = 1.116; df = 203.963)
[b] Chi-Square analysis (X^2 = 9.443; df = 1)
[c] Mann-Whitney U (Z = -5.317)

To form the final study cohort, patients in the novel anticoagulant cohort were matched 1:1 with patients in the warfarin cohort based on gender and $CHADS_2$ score, and a difference of ≤2 years of age at index. Demographic information for the 272 patients meeting inclusion criteria after matching is described in Table 3.2. An independent groups t-test showed no significant difference in mean age at index (in years) between patients taking novel oral anticoagulants (75.4, SD = 9.4) and warfarin (75.1, SD = 9.1) (t = -0.275; df = 269.785; p = 0.784). After matching, the proportions of patients by gender and in each $CHADS_2$ category were identical. Average $CHADS_2$ score for both cohorts after matching was 2.71.

Table 3.2: Baseline Characteristics by Cohort After Matching

	Novel Anticoagulant (n = 136)	**Warfarin (n = 136)**	***p*-value**
Age at index (years) mean (SD)	75.43 (9.401)	75.13 (9.140)	0.784[a]
Gender			
Male, n (%)	85 (62.5)	85 (62.5)	1.0[b]
Female, n (%)	51 (37.5)	51 (37.5)	
$CHADS_2$ score			
1, n (%)	18 (13.2)	18 (13.2)	
2, n (%)	56 (41.2)	56 (41.2)	
3, n (%)	26 (19.1)	26 (19.1)	1.0[c]
4, n (%)	22 (16.2)	22 (16.2)	
5, n (%)	12 (8.8)	12 (8.8)	
6, n (%)	2 (1.5)	2 (1.5)	

[a] Independent sample t-test (t = -0.275; df = 269.785)
[b] Chi-Square analysis (X^2 = 0.000; df = 1)
[c] Mann-Whitney U (Z = 0.000)

Anticoagulant Adherence

Medication Possession Ratio (MPR) was calculated from prescription claims data over the 12 months post-index period to assess patient adherence to the index drug. Overall MPR was found to be fairly normally distributed, with a similar overall mean (0.876, SD = 0.188) and median (0.930). An independent groups t-test showed no significant difference in MPR between patients taking novel oral anticoagulants (0.880, SD = 0.182) and warfarin (0.873, SD = 0.194) (t = -0.290; df = 268.948; p = 0.772).

Incidence of Major Bleeds

Incidence of major bleed (defined as a primary diagnosis code for a hemorrhagic event on an inpatient medical claim) was assessed 12 months post-index. Four patients (2.9%) in the novel oral anticoagulant cohort experienced a major bleed 12 months post-index, while 7 patients (5.1%) in the warfarin cohort experienced a major bleed. A chi-square analysis showed no statistically significant relationship between incidence of major bleed and medication cohort (X^2 = 0.853; df = 1; p = 0.356).

Incidence of Ischemic Stroke

Incidence of ischemic stroke (defined as a primary diagnosis code for ischemic stroke on an inpatient medical claim) was assessed 12 months post-index. Three patients (2.2%) in the novel oral anticoagulant cohort experienced an ischemic stroke 12 months post-index, while 1 patient (0.7%) in the warfarin cohort experienced an ischemic stroke. A chi-square analysis showed no statistically significant relationship between incidence of ischemic stroke and medication cohort (X^2 = 1.015; df = 1; p = 0.314). However, in this analysis, 50% of cells had

expected values less than 5, so the observed significance level based on chi-square distribution cannot be relied upon.[22]

Direct Treatment Costs

Treatment costs analyzed for the 12 months post-index period are described in Table 3.3. The sum of the total cost of the index medication was assessed during the 12 month post-index period. Overall, the sum of the index medication cost was found to be positively skewed with a bimodal distribution pattern. A Mann-Whitney U test showed a significant difference in the sum of the index medication costs between patients taking novel oral anticoagulants (median = $3,051; mean = $2,658; SD = $1,494) and warfarin (median = $259; mean = $315; SD = $229) (Z = -13.093; p <0.001).

Of the 136 patients meeting inclusion criteria for the warfarin cohort, costs of monitoring warfarin via anticoagulation clinic in the 12 month post-index period were estimated from point-of-care laboratory INR testing data retrievable from medical records. Each claim for INR testing was multiplied by the estimated cost of $70.44. Of the 136 patients, the range for the number of tests was zero to 30, the mean number of tests was 10.6 and the median was 14. About 30 % (n = 40) of the warfarin patients did not have a claim for INR testing. The total INR monitoring cost in the 12-month post-index period was found to be normally distributed with a mean of $751 (SD = $599) and a median of $986.

The sum of the total cost of the index medication plus INR monitoring cost was assessed during the 12 month post-index period. Overall, the sum of the index medication cost plus INR monitoring cost was found to be positively skewed with a bimodal distribution pattern. A Mann-Whitney U test showed a significant difference in the sum of the index medication cost plus INR

monitoring cost between patients taking novel oral anticoagulants (median = $3,084; mean = $2,658; SD = $1,494) and warfarin (median = $1,171; mean = $1,066; SD = $633) (Z = -8.210; p <0.001).

The sum of the costs to treat adverse events (based on primary diagnosis codes for ischemic stroke or major bleed on inpatient medical claims) was assessed in the 12 month post-index period. Overall, the sum of the costs to treat adverse events had a highly positively skewed distribution pattern. A Mann-Whitney U test showed no significant difference in the sum of the costs to treat an adverse event between patients taking novel oral anticoagulants (median = $0; mean = $237; SD = $1,232) and warfarin (median = $0; mean = $283; SD = $1,697) (Z = -0.269; p = 0.788). The range of estimated costs for the 8 patients in warfarin group who had an event was $43 to $13,580 (mean = $4,815; total = $38,524), while for the 7 patients in the novel agent group, the range was $31 to $8,325 (mean of $4,611; total = $32,283).

The sum of total costs of all-cause medical and pharmacy claims was assessed in the 12 month post-index period from Scott & White claims data. Overall, the sum of total costs had a positively skewed distribution pattern. A Mann-Whitney U test showed a significant difference total cost between patients taking novel oral anticoagulants (median = $14,589; mean = $23,711; SD = $22,910) and warfarin (median = $11,004; mean = $18,248; SD = $24,184) (Z = -3.603; p <0.001).

Table 3.3: Total Treatment Costs 12 Months Post-Index by Cohort (in 2014 U.S. dollars)

	Novel Anticoagulant (n = 136)	**Warfarin (n = 136)**	***p*-value**
Index Medication[a]			
mean (SD)	$2,658 ($1,494)	$315 ($229)	<0.001[b]
median	$3,084	$259	
range	$12 - $5,250	$40 - $1,767	
INR Monitoring[c]			
mean (SD)	N/A	$751 ($599)	N/A
median		$986	
range		$0 - $2,113	
Index Medication +INR Monitoring			
mean (SD)	$2,658 ($1,494)	$1,066 ($633)	<0.001[d]
median	$3,084	$1,171	
range	$12 - $5,250	$58 - $3,035	
Treating Adverse Events[e]			
mean (SD)	$237 ($1,232)	$283 ($1,697)	0.788[f]
median	$0	$0	
range	$0 - $8,325	$0 – $13,580	
Total All-cause Costs[g]			
mean (SD)	$23,711 ($22,910)	$18,248 ($24,184)	<0.001[h]
median	$14,589	$11,004	
range	$1,137 - $110,465	$1,762 - $201,057	

[a;] Estimated from 2014 per unit Average Wholesale Price (AWP) multiplied by unit quantity in claims
[b] Mann-Whitney U (Z = -13.093)
[c] Based on 2014 estimate of $70.44 total cost per claim for INR testing
[d] Mann-Whitney U (Z = -8.210)
[e] Based on total cost of inpatient claims for stroke or bleeds (n = 8 for warfarin cohort; n = 7 for novel anticoagulant cohort) adjusted to 2014 estimates
[f] Mann-Whitney U (Z = -0.269)
[g] Based on total cost of all-cause claims adjusted to 2014 estimates
[h] Mann-Whitney U (Z = -3.603)

INR Control

Time in Therapeutic Range (TTR) was calculated to assess INR control (assuming an INR theraputic range of 2.0 to 3.0) for the 136 patients who met inclusion criteria for the warfarin cohort for all point-of-care laboratory INR testing data retrievable from medical records. About 30% of patients (n = 40) did not have a claim for INR testing. For the other 70% (n = 96), TTR was found to range from 0% to 100% and was normally distributed with a mean of

70.4% (SD = 20.4%) and a median of 70.8%, with half of patients having a TTR falling between 61.0% and 83.8%.

Summary

A summary of the results for each hypotheis is provided in Table 3.4.

Table 3.4: Summary of Results by Hypothesis

Hypothesis	**Result**
$H_0$1: There is no statistical difference in patient characteristics (age, gender, or $CHADS_2$ score) between patients taking novel oral anticoagulants (dabigatran or rivaroxaban) versus clinic-monitored warfarin.	**Age:** not rejected **Gender**: rejected: Higher proportion males in novel cohort **$CHADS_2$** = rejected; Lower $CHADS_2$ score for novel cohort
$H_0$2: There is no statistical difference in patient adherence to oral anticoagulant medication between patients taking novel oral anticoagulants (dabigatran or rivaroxaban) versus clinic-monitored warfarin.	**MPR:** not rejected
$H_0$3: There is no statistical difference in the incidence of major bleeds (requiring inpatient hospitalization) between patients taking novel oral anticoagulants (dabigatran or rivaroxaban) versus clinic-monitored warfarin.	**Major bleed*** = not rejected
$H_0$4: There is no statistical difference in the incidence of ischemic stroke between patients taking novel oral anticoagulants (dabigatran or rivaroxaban) versus clinic-monitored warfarin.	**Ischemic Stroke*** = not rejected
$H_0$5: There is no statistical difference in total all-cause direct treatment costs with novel oral anticoagulants (dabigatran or rivaroxaban) compared to clinic-monitored warfarin.	**Direct treatment costs** = rejected; overall novel cohort costs higher

*Low cell size, interpret with caution

CHAPTER 4: DISCUSSION

Demographic Characteristics

The results of this study showed that prior to matching, patients taking dabigatran or rivaroxaban were comparable in age to those taking warfarin. Average age in this study was 76 years old, consistent with atrial fibrillation being a cardiac arrhythmia with increasing incidence with age. There was a substantial difference in gender between the study cohorts, with about two-thirds of patients taking dabigatran or rivaroxaban being male, while gender proportions were nearly equal in the warfarin cohort. The study cohorts also differed in $CHADS_2$ score, with a mean $CHADS_2$ of 2.65 in patients taking dabigatran or rivaroxaban compared with a mean $CHADS_2$ of 3.30 in patients taking warfarin, indicating that patients prescribed warfarin tended to be at a greater risk of stroke based on past medical history. Baseline demographics were comparable between study cohorts after matching, with 96% of patients in the novel oral anticoagulant cohort having a comparable match in the warfarin cohort based on age, gender, and $CHADS_2$ score.

Anticoagulant Adherence

The results of this study showed comparable medication adherence between patients taking dabigatran or rivaroxaban compared to patients taking warfarin. This is in contrast to the notion that the advantage of fixed dosing and lack of laboratory monitoring with the newer oral anticoagulants may lead to improved patient compliance. However, it's important to note that the warfarin patients in this study were followed by an Anticoagulation Clinic and may be more motivated to be adherent to warfarin compared to patients not enrolled in an Anticoagulation Clinic. Additionally, compared to relatively fixed dosing with dabigatran and rivaroxaban

therapy, days' supply in the MPR calculation for warfarin is particularly affected by complex dose regimens and regular dose adjustments with warfarin therapy and may therefore represent a more rough estimation of patient adherence.

Incidence of Major Bleeds

The results of this study showed comparable incidence of major bleeds 12 months post-index between patients taking dabigatran or rivaroxaban compared to patients taking warfarin. This study found incidence of major bleeds to be 2.9% for patients taking dabigatran or rivaroxaban, which is slightly less than the incidence found in the pivotal clinical trials for these drugs; RE-LY showed an annual rate of major hemorrhage of 3.11% in dabigatran, and ROCKET-AF showed an annual rate of major hemorrhage of 3.6% for rivaroxaban.[12,13] This study found an incidence of major bleeds to be 5.1% for patients taking warfarin, which is greater than annual rate of major hemorrhage for warfarin found in the RE-LY and ROCKET-AF trials (3.36% and 3.4%, respectively), although the definition of major bleeds in these studies was based upon prospective clinical observation rather than administrative claims data.[12,13] The incidence of major bleeds found in this study more closely mirror those of Darkow, et al., who conducted a study with a similar definition of major bleeds based on ICD-9 codes on inpatient administrative claims data, and found the occurrence of major hemorrhage with warfarin therapy to be 4.4% within a 720-day follow-up period.[23]

However, the authors of this study note that the sample size was underpowered to detect a difference between groups, therefore inferential statistics cannot be relied upon to draw conclusions regarding incidence of major bleeds in this study.

Incidence of Ischemic Stroke

The results of this study showed comparable incidence of ischemic stroke 12 months post-index between patients taking dabigatran or rivaroxaban compared to patients taking warfarin. This study found incidence of ischemic stroke to be 2.2% for patients taking dabigatran or rivaroxaban, which is slightly more than the incidence found in the pivotal clinical trials for these drugs; RE-LY showed an annual rate of stroke and systemic embolism of 1.11% in dabigatran, and ROCKET-AF showed an annual rate of stroke and systemic embolism of 1.7% for rivaroxaban.[12,13] This study found incidence of ischemic stroke to be 0.7% for patients taking warfarin, which is less than annual rate of ischemic stroke for warfarin found in RE-LY, ROCKET-AF, and less than the occurrence of ischemic stroke over a 720 day follow-up period in an administrative claims study by Darkow et. al. (1.69%, 2.2%, and 3.7%, respectively).[12,13,23] A meta-analysis of clinical trial data (including RE-LY and ROCKET-AF) showed an annual risk of stroke or systemic embolism of 1.66% for patients with atrial fibrillation taking warfarin.[9]

However, the chi-square analysis in this study showed 50% of cells had expected values less than 5, so the observed significance level based on chi-square distribution cannot be relied upon.[22] Additionally, the authors of this study note that the sample size was underpowered to detect a difference between groups, therefore inferential statistics cannot be relied upon to draw conclusions regarding incidence of ischemic stroke in this study.

Direct Treatment Costs

As expected, this study showed a significant difference in the annual cost of the oral anticoagulant medications based on average wholesale price (AWP), with warfarin approximately one-tenth the cost of the newer agents, dabigatran and rivaroxaban. Cost of INR monitoring was estimated from the perspective of the healthcare system, including the laboratory fee, office visit fee, cost of INR testing supplies, and staff labor costs. Total cost per patient per visit was estimated at $70.44 in 2014 U.S. dollars. Applying this charge to each documented INR visit in the warfarin cohort yielded an average annual monitoring cost of $751 per patient. Due to inconsistencies in included cost parameters, annual INR monitoring costs vary widely in previous studies, ranging from $291 to $943 in 2011 U.S. dollars.[10] The results of this study demonstrate that the annual cost of dabigatran or rivaroxaban is significantly greater than that of warfarin, even when accounting for both medication and monitoring costs.

The results of this study showed comparable costs to treat adverse events (ischemic stroke or major bleed) between patients taking dabigatran or rivaroxaban compared to patients taking warfarin. However, the number of events in this study was too few for true comparison between groups.

The results of this study show that patients taking dabigatran or rivaroxaban had greater total annual healthcare costs (including all pharmacy and medical claims) compared to patients taking warfarin. Given that there were too few adverse events to detect differences in related costs between medication cohorts, and given that patients in this study were matched based on age and $CHADS_2$ score, it can be assumed that a substantial portion of this difference in total annual healthcare costs is attributable to the significant difference in cost of the oral anticoagulant medication.

INR Control

The requirement of warfarin therapy to include frequent laboratory INR monitoring can be burdensome to both clinicians and patients. However, assessing the Time in Therapeutic Range (TTR) of INRs for warfarin patients is an essential component of evaluating "real-world" management of warfarin therapy, as the clinical and economic outcomes of warfarin therapy are strongly dependent on the quality of anticoagulation control, as demonstrated by Sorensen et al.[7] The model developed by Sorensen and colleagues showed that improved INR control lead to decreased stroke rates and decreased per-patient costs.[7] Additional studies have shown that decreased TTR results in poorer outcomes, such as mortality, ischemic stroke, thromboembolism, and major bleeding.[4]

The results of this study showed a mean TTR for warfarin patients was 70.4%. This "real-world" TTR is greater than the typical TTR reported in controlled clinical trials ranging from 55-66%, including the TTR found in RE-LY of 64% and the TTR in ROCKET-AF of 55%.[9,12,13] Studies in community settings often report TTRs closer to 50%.[9] The TTR found in this study more closely mirrors the "trial-like control" TTR of 68% used in the model by Sorensen et.al versus the "real-world control" TTR of 48%.[7] The results of this study indicate patients enrolled in the Scott & White Anticoagulation Clinics are particularly well managed on warfarin therapy compared to previously reported findings in community settings, and the TTR mirrors the anticoagulation control typically seen in clinical trial conditions. However, 30% of patients in the warfarin cohort of this study did not have a claim for INR testing, presumably due to INR monitoring occurring outside the Scott & White EMR system.

Study Limitations

Caution should be exercised when interpreting the results of this study due to several limitations. Data were limited to a regional health system in a geographically distinct area, which may limit the external validity of this study. Due to the retrospective nature of this study, the results were reliant upon administrative claims data and EMR documentation. Mis-coding of ICD-9 codes or lack of submission of medical claims could limit the validity of results but would not be expected to occur more frequently in one cohort over the other. Similarly, prescription medication provided by physician offices as samples or purchased out-of-pocket by patients (e.g., $4 generic drug lists) would not be captured in prescription claims data, and could have affected cohort development and adherence calculations. INR laboratory data were extracted from the EMR for an integrated healthcare system, and INR monitoring that occurred outside of the system was not captured, possibly affecting TTR calculations.

Conclusions

The findings of this study demonstrate that significantly more men than women were prescribed dabigatran or rivaroxaban compared to clinic-monitored warfarin, and patients prescribed the newer oral anticoagulants averaged a lower $CHADS_2$ score compared to warfarin patients. Patient adherence to dabigatran or rivaroxaban was comparable to clinic-monitored warfarin in this population. Anticoagulation control in this study was greater than previously reported findings in community settings, with a TTR similar to clinical trials.

Annual medication cost of dabigatran or rivaroxaban was found to be significantly greater than that of clinic-monitored warfarin, even when accounting for INR monitoring costs with warfarin. Total annual healthcare costs were also significantly greater for patients taking

dabigatran or rivaroxaban compared to warfarin, although there were too few adverse events in this study to draw conclusions regarding event rates and treatment costs of ischemic stroke and major bleeds.

Although the sample sizes and incidence rates of adverse events were low, comparison to previous clinical trial and 'real-world' data is useful for future studies. As more novel oral anticoagulants become available in the U.S. market as alternatives to warfarin for treatment of atrial fibrillation, future studies will need to evaluate long-term clinical and economic outcomes of these medications in larger patient populations. Decreased burden of INR monitoring is an advantage of the new oral anticoagulants, and future research is needed to assess impact of these agents on perceived quality of life. Additionally, this study focused on patients actively enrolled in an Anticoagulation Clinic, and patient self-monitoring or physician monitoring was not addressed.

Appendix A:

$CHADS_2$ Stroke-Risk Index – weights, diagnoses, and ICD-9 codes:

Weight[a]	**Diagnoses**[a]	**ICD-9 codes**[b]
1	Congestive heart failure	428.xx
1	Hypertension	401.xx – 405.xx
1	Age 75 years or older	N/A
1	Diabetes mellitus	250.xx
2	History of stroke or transient ischemic attack	433.xx – 435.xx

ICD-9: The International Classification of Diseases, 9th Revision, Clinical Modification

[a] Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA*. 2001; 285:2864 –2870.

[b] Rothendler JA, Rose AJ, Reisman JI, et al. Choices in the use of ICD-9 codes to identify stroke risk factors can affect the apparent population-level risk factor prevalence and distribution of $CHADS_2$ scores. Am J Cardiovasc Dis. 2012; 2(3):184-191.

Appendix B:

Diagnosis Codes for Hemorrhagic Event

ICD-9 codes[a]	Diagnosis Description[a]
246.3	Hemorrhage and infarction of thyroid
285.1	Acute posthemorrhagic anemia
286.5	Hemorrhagic disorder due to circulating anticoagulants
331.3	Communicating hydrocephalus
362.81	Retinal hemorrhage
363.61, 363.62	Choroidal hemorrhage
372.72	Conjunctival hemorrhage
376.32	Orbital hemorrhage
379.23	Vitreous hemorrhage
380.31	Hematoma of auricle or pinna
423.0	Hemopericardium
430	Subarachnoid hemorrhage
431	Intracerebral hemorrhage
432.xx	Other and unspecified intracranial hemorrhage
456.0, 456.20	Esophageal varices with bleeding
459.0	Hemorrhage, unspecified
530.82	Esophageal hemorrhage
531.0x, 531.2x	Acute gastric ulcer with hemorrhage
531.4x, 531.6x	Chronic or unspecified gastric ulcer with hemorrhage
532.0x, 532.2x	Acute duodenal ulcer with hemorrhage
532.4x, 532.6x	Chronic or unspecified duodenal ulcer with hemorrhage
533.0x, 533.2x	Acute peptic ulcer with hemorrhage
533.4x, 533.6x	Chronic or unspecified peptic ulcer with hemorrhage
534.0x, 534.2x	Acute gastrojejunal ulcer with hemorrhage
534.4x, 534.6x	Chronic or unspecified gastrojejunal ulcer with hemorrhage
535.x1	Gastritis and duodenitis with hemorrhage
537.83	Angiodysplasia of stomach and duodenum with hemorrhage
562.02, 562.03	Diverticulosis and diverticulitis of small intestine with hemorrhage
562.12, 562.13	Diverticulosis and diverticulitis of colon with hemorrhage
568.81	Hemoperitoneum
569.3	Hemorrhage of rectum and anus
569.85	Angiodysplasia of intestine with hemorrhage
578.x	Gastrointestinal hemorrhage
596.7	Hemorrhage into bladder wall
602.1	Hemorrhage of prostate
621.4	Hematometra
623.6	Vaginal hematoma

626.6	Metorrhageia
719.1x	Hemarthrosis
782.7	Spontaneous ecchymoses
784.7	Epistaxis
784.8	Hemorrhage from throat
786.3	Hemoptysis
997.02	Iatrogenic cerebrovascular infarction or hemorrhage
E934.2	Adverse effects related to therapeutic use of anticoagulants

ICD-9: The International Classification of Diseases, 9th Revision, Clinical Modification

[a] Darkow T, Vanderplas AM, Lew KH, et al. Treatment patterns and real-world effectiveness of warfarin in nonvalvular atrial fibrillation within a managed care system. *Curr Med Res Opin*. 2005; Oct:21(10):1583-94.

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