COMPARATIVE EFFECTIVENESS AND SAFETY OF ANTICOAGULANTS IN THE PREVENTION OF VENOUS THROMBOEMBOLISM IN ELECTIVE HIP AND KNEE REPLACEMENT SURGERY PATIENTS

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ABSTRACT

Mrudula Borse Glassberg: Comparative effectiveness and safety of anticoagulants in the
prevention of venous thromboembolism in elective hip and knee replacement surgery patients
(Under the direction of Stacie Dusetzina)

One of the serious complications after elective hip or knee replacement surgery

is venous thromboembolism and use of anticoagulants is recommended for prophylaxis.

Rivaroxaban is a newer oral anticoagulant and offers multiple benefits over standard

anticoagulants. However, the safety and effectiveness of rivaroxaban beyond clinical

trials is unknown. This study examined the comparative effectiveness and safety of

rivaroxaban versus warfarin in elective hip and knee replacement patients.

A retrospective cohort of commercial and Medicare patients newly initiating

rivaroxaban or warfarin after hip or knee replacement surgery between January 1, 2011

and December 31, 2015 was identified. Patients who were new users of treatment,

continuously enrolled for 6 months during the baseline period and three months after

the surgery, and older than 18 years were included. Logistic regression with IPTW was

used to examine the association between the choice of anticoagulant and VTE,

bleeding and post-operative joint infection risk.

Of the 117,393 commercially insured patients undergoing elective total hip

replacement, 12,876 and 10,892 were new users of warfarin and rivaroxaban

respectively. Of the 67,207 Medicare patients undergoing total hip replacement, 7,416

and 4,739 were new users of warfarin and rivaroxaban respectively. Of the 212,808

commercially insured knee replacement patients, 24,856 initiated warfarin and 21,398

initiated rivaroxaban. Of the 132,073 Medicare knee replacement patients, 15,483 and

8,997 were new users of warfarin and rivaroxaban respectively. Among total hip

replacement patients, warfarin users had significantly higher odds of deep vein

thrombosis (OR 2.63,95%CI 1.97-3.50 in commercial cohort and OR 1.78,95%CI 1.38-

2.29 in Medicare cohort) and pulmonary embolism (OR 2.60,95%CI 2.04-3.31 in

commercial cohort and OR 2.09,95%CI 1.66-2.65 in Medicare cohort). The odds of

deep vein thrombosis (OR 2.06,95%CI 1.76-2.42 in commercial cohort and OR

2.21,95%CI 1.84-2.65 in Medicare cohort) and pulmonary embolism (OR 2.03,95%CI

1.78-2.33 in commercial cohort and OR 2.16,95%CI 1.84-2.55 in Medicare cohort) were

also higher among warfarin users in the total knee replacement cohorts. There were no

statistically significant differences in the bleeding risk among rivaroxaban and warfarin

users. The odds of postoperative joint infection (OR 1.57,95%CI 1.16 -2.13 in

commercial cohort and OR 1.79,95%CI 1.14-2.81 in Medicare cohort) were significantly

higher in warfarin users compared to rivaroxaban users.

The results from this dissertation suggest that treatment with rivaroxaban may

help reduce the risk of incident VTE events without any significant increase in the risk of

bleeding or post-operative joint infection compared to warfarin in patients with hip or

knee replacement.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AMI	Acute myocardial infarction
CCAE	Commercial claims and encounters
CCI	Charlson's comorbidity index
CDHP	Consumer driven health plan
CHF	Congestive heart failure
CI	Confidence interval
COB	Coordination of benefits
CPT	Current procedural terminology
DVT	Deep vein thrombosis
EPO	Exclusive provider organization
FDA	Food and Drug Administration
FFS	Fee for service
GI	Gastrointestinal
HDHP	High deductible health plan
HMO	Health maintenance organization
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICD-10-PCS	International Classification of Diseases, Tenth Revision, Procedure Coding System
ICH	Intracranial hemorrhage
INR	International normalized ratio
IPTW	Inverse probability treatment weighting
LMWH	Low molecular weight heparin
NDC	National drug code
NOAC	New oral anticoagulants
OAC	Oral anticoagulants

OR	Odds ratio
PE	Pulmonary embolism
PJI	Post-operative joint infection
POS	Point of service
PPO	Preferred provider organization
PS	Propensity scores
RCT	Randomized clinical trial
RR	Relative risk
SD	Standard deviation
THR	Total hip replacement
TKR	Total knee replacement
TTR	Time within therapeutic range
UFH	Unfractionated heparins
VTE	Venous thromboembolism

Chapter 1 : INTRODUCTION

1.1 Overview

Deep vein thrombosis and pulmonary embolism, collectively known as venous thromboembolism (VTE), is one of the most serious complications after major orthopedic surgery, including total knee replacement and total hip replacement surgery.[1-3] It is often associated with significant morbidity and mortality.[4] Standard pharmacological prophylaxis includes use of unfractionated heparin, low molecular weight heparin (LMWH), fondaparinux, and warfarin.[5] Although these standard therapies are effective in preventing VTE, they have several limitations. LMWHs and fondaparinux require injection or infusion, which may cause discomfort among patients and can therefore lead to non-compliance.[6,7] Warfarin has a narrow therapeutic window and requires diet and international normalized ratio (INR) monitoring.[7]

Due to the limitations of standard anticoagulants, recently approved oral anticoagulants like dabigatran, apixaban, and rivaroxaban (known as "novel oral anticoagulants" or "target-specific oral anticoagulants") are emerging as potential alternatives in VTE prevention. Randomized clinical trials have demonstrated that novel oral anticoagulants are superior or non-inferior compared to standard therapy for prophylaxis of VTE after hip and knee replacement surgeries. [8] Moreover, novel oral anticoagulants provide the additional benefit of oral administration and do not require INR monitoring or dietary restrictions.[6] These benefits may lead to better treatment

compliance and VTE prevention than the standard anticoagulation regimen in a routine

practice setting. However, uncertainty remains about their relative safety, because,

unlike warfarin, most of these newer anticoagulants lack a direct reversal agent in the

event of bleeding complications. [6] Regardless, the utilization and clinical effectiveness

of novel oral anticoagulants in the prevention of VTE compared with standard therapy

such as warfarin remains unclear in real-world clinical practice.

Examining the comparative effectiveness of anticoagulants also necessitates

understanding the factors associated with the choice of a particular treatment,

especially new pharmaceuticals. If certain characteristics are significantly associated

with the use of one therapy versus another, the apparent comparative effectiveness

could be affected, particularly if those characteristics also affect outcomes. Optimal

treatment selection may also differ in specific patient populations and understanding the

risk of clinical outcomes among subgroups can help patients and providers in deciding

between anticoagulants. Hence, it is also important to understand the factors associated

with the choice of anticoagulant for these patients.

1.2 Significance

Each year, there are more than 719,000 total knee replacements and 332,000

total hip replacements performed in the United States.[9] Among these commonly

performed procedures, the incidence rate of VTE is 42-57% in hip arthroplasty and 41-

85% in knee arthroplasty. [10] VTE is the third most prevalent cardiovascular condition

and is associated with significant morbidity, mortality, and use of healthcare resources.[4]

In fact, VTE is the leading cause of all preventable hospital deaths.[4,11,12] The cumulative

risk of recurrent VTE among those who do not receive treatment after a primary episode

of VTE increases from 11% in one year up to 40% within 10 years.[13] The annual direct medical cost of patients who have VTE is $32,918, while the direct medical cost of those who have recurrent VTE events is $82,110, costing the U.S. healthcare system approximately $15.5 billion each year.[14,15] Optimizing anticoagulation after a hip or knee replacement surgery is a critical public health need.[4]

Although various clinical guidelines recommend prophylactic anticoagulation therapy after hip or knee replacement surgery, real-world treatment patterns in these patients have yet to be examined.[16,17] Understanding the factors associated with the use of anticoagulants in these patients may help future patient-centered research by examining areas where treatment-effect heterogeneity may exist. Comparative effectiveness research is thought to be affected by changing patterns of use in newly-launched therapies.[18,19] Furthermore, the effectiveness and safety of novel oral anticoagulants compared with standard prophylaxis after hip and knee replacement surgeries has not been studied extensively outside of randomized-clinical trials (RCTs) or meta-analyses of these RCTs. Moreover, the RCTs evaluating efficacy of novel oral anticoagulants among patients undergoing hip and knee replacement surgery are based on average 10-14 days and up to 35 days of anticoagulation, respectively.[20-31] Literature suggests that the cumulative risk of venous thromboembolism lasts for up to three months after hip surgery and for one month after total knee replacement.[32] There is no clear evidence of how newer oral anticoagulants perform compared to standard anticoagulants for prolonged VTE prophylaxis in actual practice.

Additionally, patients enrolled in RCTs may not be true representatives of the actual population and may not represent variation in the length of therapy, follow up

time, or physician practice. Given the variation in administration and burden associated with treatment regimens, conducting an observational study to compare the effectiveness of available anticoagulants is a novel element.[33] As of now, there are no observational studies that have used real world data to compare the effectiveness of novel oral anticoagulants in the prevention of VTE after hip or knee replacement surgery. Recent use of electronic medical records and large healthcare databases has gained importance to assessing comparative effectiveness.[34] This will be the first study that will use large insurance claims data to assess the real world effectiveness of these agents in hip and knee replacement surgery patients.

We will analyze data from Truven's MarketScan Commercial Claims and Encounters and Medicare Supplemental and Coordination of Benefits for the years 2010-2016 for this study. The MarketScan database contains claims submitted from health plans which have contracts with large private employers or public organizations in the United States. This longitudinal database covers all inpatient, outpatient, and prescription claims for individual patients for as long as they remain enrolled in the health plan.

The goal of this study is to investigate the factors associated with new use of anticoagulants after hip and knee replacement surgeries, and to study the comparative effectiveness and safety of novel oral anticoagulants with standard anticoagulants in these patients. Because of the increasing use of newer anticoagulants, understanding their comparative effectiveness and safety is of critical importance. The contribution of the proposed research is expected to help inform patients, clinicians, researchers, and

third-party payers of the real-world utilization and comparative effectiveness in order to help improve clinical practice.

1.3 Specific Aims

Aim 1: <u>To examine trends and predictors of anticoagulant use following elective total knee replacement or elective total hip replacement surgery.</u>

Aim 1a: To analyze market trends in the utilization of anticoagulants in patients undergoing an elective total hip or knee replacement surgery.

We will analyze the change in uptake of various anticoagulants for VTE prophylaxis in elective hip and knee replacement surgery patients after the introduction of newer oral anticoagulants. This will help us understand the change in treatment patterns in clinical practice over time.

Aim 1b: To identify factors influencing the choice of anticoagulation therapy in patients undergoing an elective total hip or knee replacement surgery.

We will also design a retrospective cohort study to evaluate the influence of various population characteristics on the choice of anticoagulation therapy in patients undergoing an elective total hip or knee replacement surgery. We will use the Andersen's Behavioral Model for health service use to guide variable selection for the analysis.[35] Andersen's Model is a multi-level model that incorporates both individual and contextual determinants of health care use. In this model, predisposing factors like patient's age, sex, timing of surgery and geographic location influence patients' ability (measured through enabling factors like health insurance type and prescription drug benefit generosity) to obtain health care. These factors, when added to the need for treatment (measured through need factors like past clinical events, concomitant

5

therapies and comorbidities), predict the use of health care services. In order to understand the impact of various predictors on the type of anticoagulation therapy, logistic regression models will be used.

Aim 2: <u>To compare the real world effectiveness of novel oral anticoagulant rivaroxaban with standard oral anticoagulant warfarin in venous thromboembolism prevention among patients with elective total hip and knee replacement surgery.</u>

In this specific aim, a cohort study will be designed to compare the effectiveness of rivaroxaban with standard therapy (warfarin) in the prevention of venous thromboembolism in elective total hip and knee replacement surgery patients. We chose to only include rivaroxaban as the novel oral anticoagulant comparator because it was the first approved novel oral anticoagulant in the United States for prevention and treatment of VTE after a hip or knee replacement and shares almost forty percent of the market share of oral anticoagulants. Furthermore, apixaban and dabigatran had too small sample sizes to sufficiently power their individual comparisons to warfarin. Multiple logistic regression will be used to estimate the odds ratios controlling for potential confounders identified in specific aim 1.

Aim 3: <u>To compare the safety of novel oral anticoagulant rivaroxaban with standard oral anticoagulant warfarin among patients with elective total hip or knee replacement surgery.</u>

In this specific aim, we will examine the association between the use of rivaroxaban and warfarin and the risk of adverse events such as major bleeding,

intracranial hemorrhage, gastrointestinal bleeding and perioperative wound infection in patients undergoing elective total hip or knee replacement surgery.

Research implications:

The results of our aim 1 can improve our understanding of the utilization patterns and choice of anticoagulation treatment in patients undergoing elective total hip or knee replacement surgery. This can help identify factors and target patient subgroups for anticoagulation treatment initiation to maximize treatment benefit from these agents. Results from aims 2 and 3 can add unique information to the literature by providing information on whether the novel oral anticoagulants are more effective in the real world in improving VTE outcomes and preventing major bleed events among patients undergoing elective hip and knee replacement surgery. These findings will guide therapeutic decision-making to improve the quality of care provided to patients having elective knee and hip transplants.

Chapter 2 : BACKGROUND AND LITERATURE REVIEW

In section 2.1, we provide an overview of elective total hip or knee replacement surgery. Section 2.2 provides a review of the literature on the relationship between hip and knee replacement surgery and venous thromboembolism (VTE). In section 2.3, we present a review of the current treatment options for VTE prophylaxis after hip and knee replacement surgeries. In section 2.4, we provide a review of the current evidence regarding effectiveness and safety of VTE treatment in arthroplasty patients. Section 2.5 identifies the gaps in current literature and provides a rationale for the proposed study. In section 2.6, we describe the significance of this study and the potential implications of our findings. Finally, in section 2.7, we propose a theoretical framework for this study.

2.1 Elective total hip and knee replacement surgery overview

Elective major orthopedic surgeries are now commonly performed in the United States, with approximately one million elderly operated every year.[36] Elective major orthopedic surgeries mainly encompass hip and knee arthroplasties, more commonly referred to as hip and knee replacements. Hip and knee replacements are surgical procedures in which the hip and the knee joints, respectively, are replaced by a prosthetic implant. They are generally performed to alleviate arthritic pain and inflammation. Depending on the prognosis, they can be performed as a total replacement or a partial replacement. These procedures are among the most successful and satisfactory interventions in relieving pain, restoring joint function, and

improving quality of life post-surgery in these patients.[37-43] With the aging of the baby boomer population, and higher numbers of younger patients opting for joint replacements, the number of hip and knee replacements are predicted to increase, and by 2030, there are expected to be more than 4 million replacement surgeries performed annually in the United States.[44] As the number of total joint arthroplasties performed continues to grow, a commensurate increase in the number of complications associated with these surgeries, including venous thromboembolism (VTE) events, can be anticipated. As such, it important to further our understanding of the effectiveness of prevention strategies, especially in populations excluded from the clinical trials.

2.2 Risk of venous thromboembolism in elective hip and knee replacement surgery

Venous thromboembolism is one of the serious complications after hip and knee arthroplasties, and is associated with significant morbidity and mortality.[45] Without any prophylactic measures, the overall risk of VTE after joint replacement surgery ranges from 33% to 46%.[45-47] Venous thromboembolism is a combination of deep vein thrombosis and pulmonary embolism. Deep vein thrombosis is the formation of a blood clot (thrombus) within a deep vein, predominantly in the legs or pelvis, causing total or partial blockage of blood flow. Pulmonary embolism is caused by the detachment (embolization) of the blood clot which then travels through the bloodstream to the lungs, resulting in blockage of the pulmonary arteries. Based on the level of blockage, pulmonary embolism is a potentially life-threatening complication.[48]

The pathophysiology of VTE and the associated risk factors were first explained by pathologist Rudolph Virchow in 1856.[48,49] Three main pathophysiological factors,

9

commonly referred to as the Virchow's triad, are thought to contribute to thrombosis. These factors are: 1) venous stasis, 2) endothelial injury and 3) hypercoagulability.[50] All of these factors are closely linked to orthopedic surgeries, particularly major ones, like hip and knee arthroplasties, thereby increasing the risk for occurrence of venous thromboembolism post-surgery.[51,52] The positioning of the limb during surgery, localized post-operative edema, and limited ambulation, both during and immediately after surgery, all play significant roles in venous stasis and the consequent reduction of blood flow.[52,53] Surgical lesions also increase the release of thromboplastins from damaged endothelial lining and bone, thereby activating the clotting cascade.[52] Because of all of these factors, the risk of VTE after hip or knee replacement surgery is particularly high.[54]

2.3 Prophylactic measures for postoperative venous thromboembolism

The risk of VTE after joint replacement can be reduced by early mobilization and a combination of one or more of the following preventive strategies: 1) mechanical agents, 2) injectable agents, 3) older oral anticoagulants, and 4) newer or novel oral anticoagulants.[45] Mechanical prevention involves the use of mechanical compression devices such as graduated compression stockings, intermittent pneumatic compression devices, and plantar venous pumps.[55] They reduce venous congestion and stasis by squeezing the lower extremities.[56,57] Mechanical devices can help prevent VTE in some patients and are appealing to surgeons as they do not cause hemorrhagic side effects, like pharmacological agents can. However, they are expensive, have low rates of compliance, and are impractical when the patient starts to mobilize.[58] They are also

contraindicated in conditions such as exposed fracture, cardiac insufficiency, infection, and ulceration of the lower limbs.[59]

Several pharmacological agents are available to surgeons for VTE prophylaxis after joint replacement surgeries. While mechanical devices prevent clots from travelling through the blood stream and reaching the lungs, anticoagulants are used to prevent clot formation. Pharmacological agents prevent VTE by targeting hypercoagulability, activating anti-coagulation factors, and preventing platelet aggregation (Figure 2-1).[60] These include injectable agents, older oral anticoagulants, and newer oral anticoagulants. A brief summary of the different pharmacological agents and their recommended dosage for VTE prophylaxis after replacement surgery is provided in Table 2-1.

Figure 2-1 Clotting cascade and mechanism of action of pharmacological agents
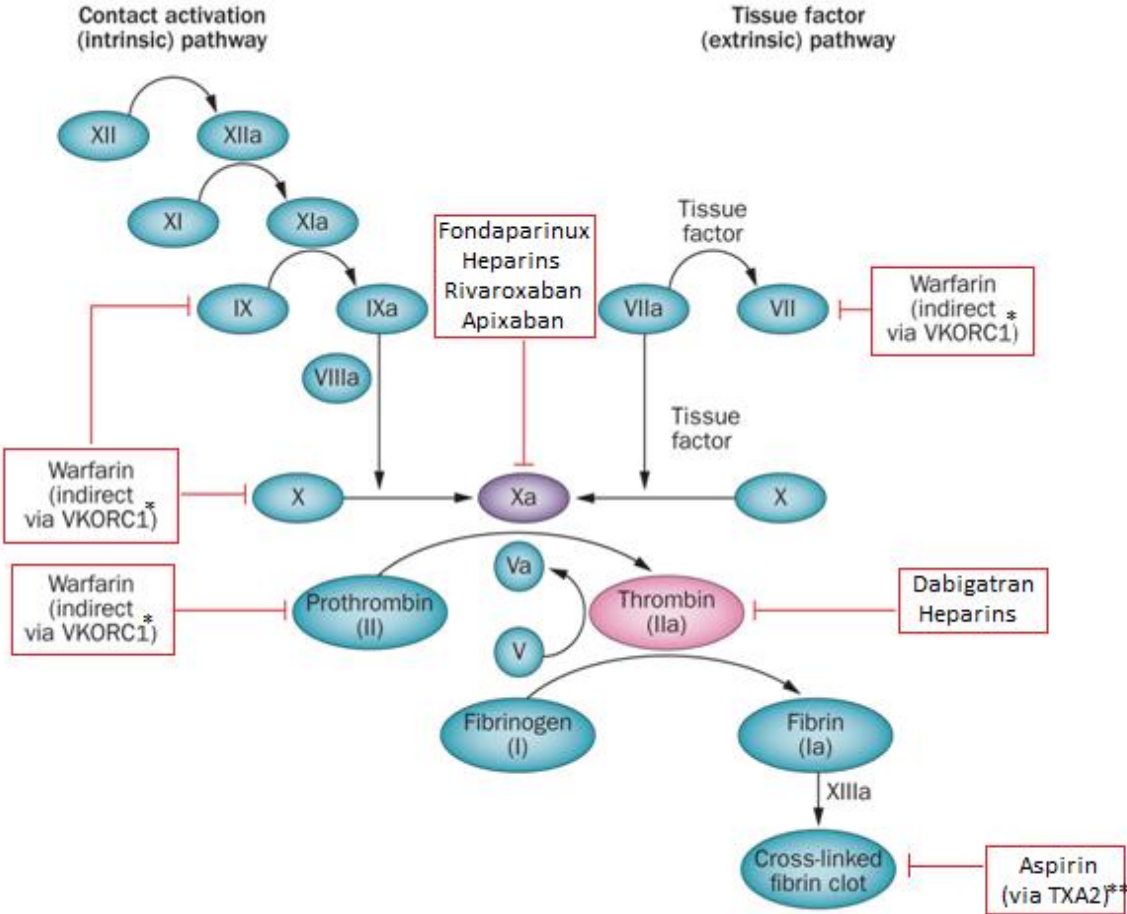
Source: Sabir, et al.[61] (Adapted)

Table 2-1 Pharmacological prophylaxis for VTE after replacement surgery

Pharmacological agent	Recommended dosing	Duration
Fondaparinux	2.5 mg/day, subcutaneously Started 6-8 hours after surgery	28 days
Unfractionated heparins	5,000 IU two to three times daily, subcutaneously or IV bolus Start preoperatively	9 days or until hospital discharge
LMWHs Dalteparin	 5,000 IU daily, subcutaneously Start preoperatively, up to 2 hours before surgery	 9 days or until hospital discharge
Enoxaparin	30 mg twice daily, subcutaneously Start up to 12 hours before surgery	28 days
Tinzaparin	3500 IU daily, subcutaneously	
Warfarin	2-5 mg daily, orally Adjusted to target INR of 2.0-3.0	21 days or until hospital discharge
Rivaroxaban	10 mg daily, orally Started 6-10 hours after surgery	12-14 days for TKR 35 days for THR
Dabigatran	220 mg daily, orally 150 mg daily, orally if age>75 Started 1-4 hours after surgery	10 days for TKR 28-35 days for THR
Apixaban	2.5 mg twice daily, orally Started 12-24 hours after surgery	12 days for TKR 35 days for THR

*IU- international unit, IV- intravenous, LMWHs – low molecular weight heparins, INR- international normalized ratio, TKR- total knee replacement, THR- total hip replacement

Source: Gross, et al.[62] (Adapted)

Injectable agents mainly include fondaparinux and heparins – particularly unfractionated heparin (UFH) and low molecular weight heparins (LMWH).[5] Fondaparinux is an indirect inhibitor of the clotting factor Xa.[63] It is administered subcutaneously about 6-8 hours after surgery as a daily dose of 2.5 milligrams. Some studies suggest that fondaparinux is more effective than LMWHs in preventing VTE after hip and knee replacements.[64,65] However, its use may be associated with an increased risk of bleeding.[64] Moreover, the subcutaneous administration of fondaparinux on a daily basis can be painful and can lead to non-compliance with the therapy.[66] UFH is administered intravenously or subcutaneously a few hours before surgery and every 8-12 hours for VTE prophylaxis after surgery. It is typically only used while the patient is in the hospital because it requires continuous monitoring and dosing adjustments due to inter-patient variability in dose response and changes in patient response over time.[67-69]

LMWHs are more effective than UFH in VTE prophylaxis and have better bioavailability, longer half-life, and predictable dose-response relationship.[67,70] Because of these clinical advantages, LMWHs have gradually replaced UFH for most indications.[67] Heparins are inexpensive and effective in preventing VTE after surgery.[67] However, patients on heparin may experience some serious side effects, including heparin-induced thrombocytopenia, bleeding, renal failure, low blood platelets, and pain at the injection site. Heparin-induced thrombocytopenia is caused by the formation of abnormal antibodies after heparin administration which activates platelets resulting in the formation of blood clots. These blood clots can travel through the blood stream and increase the risk of VTE and stroke. [68] Like all other injectable agents, the main disadvantage of heparins is the inconvenience in route of administration and poor

patient compliance. Compliance with therapy is especially challenging after patients are discharged from the hospital.[71] This is particularly concerning because most venous thrombotic events manifest clinically after discharge from the hospital.[72,73]

Oral anticoagulants offer the benefit of ease of administration over injectable agents and are preferable in patients experiencing difficulty in self-administration. Oral anticoagulants can be broadly classified as older oral anticoagulants (OACs) and newer or novel oral anticoagulants (NOACs). Warfarin is the most commonly used older oral anticoagulants. Warfarin indirectly inhibits various blood clotting factors (factors II, VII, IX, X, and proteins C and S) through vitamin K epoxide reductase complex subunit 1. It does not act on the circulating clotting factors, but rather on their synthesis in the liver, explaining its delayed effect. Although effective in preventing VTE, warfarin has several drawbacks. Warfarin has a narrow therapeutic index, requiring frequent dose adjustments. Variations in patient genotype have also been shown to affect warfarin dose requirements.[16] In addition, warfarin is highly susceptible to interactions with prescription and non-prescription drugs, herbal and other natural products, as well as food and alcohol.[74] Therefore, warfarin dose and its therapeutic effect must be determined by frequent laboratory monitoring of prothrombin time, expressed as international normalized ratio (INR). This can be expensive and time consuming. Warfarin therapy is also associated with bleeding complications.[16] If started too close to surgery or at a higher dose, there is an increased risk of bleeding. However, if started too late and at a lower dose, there is an interval of unprotected time during which the patient is susceptible to VTE.[45]

The new oral anticoagulants, which include rivaroxaban, dabigatran, and apixaban, are poised to simplify the treatment of venous thromboembolism by eliminating the need for initial parenteral anticoagulant therapy and laboratory monitoring. In July 2011, rivaroxaban (Xarelto®) was the first novel oral anticoagulant that was approved by the FDA to reduce the risk of VTE from occurring after knee or hip replacement surgery. Soon after, in March 2014 and April 2014, respectively, apixaban (Eliquis®) and dabigatran (Pradaxa®) also received FDA approval for VTE prophylaxis in patients with arthroplasty. New oral anticoagulants act by inhibiting factor Xa or thrombin and have a rapid onset of action.[75] Peak plasma levels are achieved within 1 to 4 hours after oral administration, thereby eliminating the need for a parenteral anticoagulant. They also have a wide therapeutic window, little or no interaction with food and other drugs, minimal inter-patient variability, and display similar pharmacokinetics in different patient populations. The convenience of the new OACs has translated into improvements in efficacy and safety as shown in phase III randomized trials.

2.4 Current evidence on the safety and efficacy of anticoagulants in management of venous thromboembolism in orthopedic surgery patients

Two important factors that are considered when selecting anticoagulant therapy are their effectiveness and safety. Clinicians weigh in the benefits and risks of different anticoagulants and the patient's medical history when initiating anticoagulants and selecting the type of anticoagulant.[76] Effectiveness is a measure of preventing VTE events after initiating anticoagulant therapy. The main safety concern for anticoagulants is the risk of bleeding, especially major bleeding, intracranial hemorrhage and

gastrointestinal bleeding. Some surgeons are also concerned with an increased risk of peri-prosthetic infection with the use of anticoagulants.[77]

Before the introduction of oral anticoagulants, low molecular weight heparins (LMWHs) have been the standard of care for patients undergoing orthopedic surgery.[78] A systematic review of randomized controlled trials demonstrated that LMWHs reduce symptomatic deep vein thrombosis (RR, 0.80; 95% CI, 0.73-0.88) without increasing the risk of major bleeding when compared with unfractionated heparins (RR, 0.91; 95% CI, 0.75-1.09).[79] The pooled result of clinical trials comparing LMWHs and fondaparinux failed to demonstrate or exclude a beneficial or detrimental effect of fondaparinux on the event rate of pulmonary embolism (RR, 1.32; 95%, 0.37-4.74) or deep vein thrombosis (RR, 1.31; 95% CI, 0.47-3.7). However, there was a statistically significant increase in the rate of hemorrhagic events (RR, 1.85; 95 % CI, 1.1-3.11) with use of fondaparinux compared to LMWHs.[79] When LMWHs were compared to warfarin, the pooled result of clinical trials demonstrated that LMWHs significantly reduced the risk of symptomatic deep vein thrombosis (RR, 0.68; 95 % CI, 0.6-0.78), but also increased the risk of major bleeding (RR, 1.56; 95% CI, 1.23-2.0). However, while none of the hemorrhagic events in the LMWH group were fatal, there were two fatal bleeding events in the warfarin group which raises the safety concerns with warfarin therapy.[79]

Various phase III trials have compared the effectiveness and safety of new oral anticoagulants. Four large phase III trials were conducted to compare rivaroxaban and enoxaparin in patients who had total hip replacement and total knee replacement surgery. Rivaroxaban (10 mg once daily) demonstrated superiority in reducing VTE after hip arthroplasty compared with enoxaparin (40 mg once daily) and a similar bleeding-

event profile to that of enoxaparin in both, RECORD 1 and 2 studies.[23,80] RECORD 2 and 3 trials compared the efficacy of rivaroxaban after knee replacement surgery and also demonstrated superiority compared to enoxaparin (40 mg once daily-RECORD 3) and enoxaparin (30 mg twice daily-RECORD 4).[81,82] Rates of bleeding events were the same in both groups in RECORD 3 and higher with rivaroxaban, but not statistically significant in RECORD 4 study.[81,82]

The utility of dabigatran for VTE prophylaxis after hip or knee replacement has been investigated in four phase III studies. Dabigatran (150 mg or 220 mg once daily) demonstrated non-inferior efficacy and a similar safety profile to enoxaparin (40 mg once daily) for 28 to 35 days after THR (total hip replacement) surgery in RE-NOVATE and RE-NOVATE II and for 6 to 10 days after TKR (total knee replacement) surgery in RE-MODEL.[25,27,83] There was no significant difference in the rates of major bleeding between the treatment groups in either study for dabigatran 150 mg once daily, dabigatran 220 mg once daily, and enoxaparin 40 mg once daily, respectively:[25,27]

Three phase III trials investigated apixaban in patients who had total hip replacement or total knee replacement surgery. In the ADVANCE-2 and ADVANCE-3 trials, apixaban (2.5 mg twice daily) demonstrated superiority in reducing the number of VTE events compared with enoxaparin (40 mg once daily) in patients who had undergone total knee replacement and total hip replacement surgery, respectively.[28,29] As with dabigatran in RE-MOBILIZE, however, apixaban (2.5 mg twice daily) failed to demonstrate non-inferiority to enoxaparin (30 mg twice daily) in ADVANCE-1.[30] Apixaban was not associated with increased rates of major bleeding events, compared with enoxaparin, in any of the three studies.[28-30]

2.5 Research Gap

Although randomized controlled trials are considered the "gold standard" in establishing efficacy of pharmacological agents, practitioners often require evidence of comparative effectiveness using observational data for understanding and establishing treatment recommendations in populations beyond the clinical trials.[34,84] Randomized controlled trials are conducted in a very controlled and monitored setting, meaning their findings may not always reflect the same effect in real life.[84] Patients enrolled in the RCTs may not be a true representative of the actual population and may not represent variation in the length of therapy, follow up time, or physician practice. For example, older patients were often excluded from RCTs of novel oral anticoagulants. Given the variation in patient population, route of administration and burden associated with treatment regimens, conducting an observational study to compare the effectiveness of available anticoagulants is itself a novel element. This is especially important in VTE prophylactic agents like warfarin, in which the safety and effectiveness of the therapy is dependent on adherence to therapy, diet, and INR monitoring.[85] In warfarin patients, the percentage of time within therapeutic range (TTR) has been shown to strongly correlate with clinical outcomes.[86] And although there is lack of real world data on time spent in therapeutic range for warfarin patients after major orthopedic surgery, estimates of TTR in atrial fibrillation patients show that the mean time in TTR is only 48% in the first six months of starting therapy.[87] This is significantly lower than that observed for warfarin patients in the clinical trials for newer oral anticoagulants and can affect the real world effectiveness of warfarin therapy.[88,89] Similarly, with injectable agents like heparins, the real world compliance and effectiveness of standard anticoagulants could be different

compared to randomized controlled trials which require complete compliance with therapy.[33] No published literature has reported the real world effectiveness and safety of newer oral anticoagulants with standard anticoagulation therapies in patients with hip and knee replacement surgery.

Furthermore, the phase III trials assessing efficacy and safety of newer oral anticoagulants among total knee and hip arthroplasty patients were mostly based on 10-14 days, and in one study, up to 35 days of anticoagulation.[21,23-25,27,80,90] However, research suggests that the risk of VTE persists for up to 3 months after surgery.[91] There is no clear evidence on how long a patient undergoing hip and knee replacement surgery is anticoagulated with newer OACs in actual practice and what are the risks and benefits with varying the length of therapy. Understanding the real-world safety and effectiveness could help establish guideline recommendations through the use of targeted interventions to increase the effectiveness of pharmacological agents.

There are also considerable gaps in literature related to safety of anticoagulants. Although the clinical trials for newer oral anticoagulants reported the risk of bleeding, it is not possible to compare safety data from trial to trial because there is no standardized definition of bleeding that has been used uniformly in all randomized controlled trials. Differences in reported major bleeding rates among pivotal trials for various anticoagulant agents are driven to a large extent by the actual definitions of bleeding, which were much stricter and limited in scope in the RECORD trials, driven partially by the regimens utilized and partially by the properties of the agents themselves. Furthermore, although reported as a concern by orthopedic surgeons, the differential risk for peri-prosthetic infection between anticoagulants has not been studied before.

Our study hopes to fill some of these gaps in literature by using real-world healthcare data.

2.6 Significance of this research

Randomized controlled trials often do not adequately reflect patient heterogeneity due to selective inclusion criteria, and therefore fall short of informing "real-world" clinical practice. Randomized controlled trials also may not represent variation in the length of therapy, follow up time, or physician practice. Given the variation in route of administration and burden associated with treatment regimens, conducting an observational study to compare the real-world effectiveness and safety of available anticoagulants is important. There are currently no observational studies that have used real world data to compare the effectiveness and safety of new OACs in the prevention of VTE in patients with orthopedic surgery. Recently, use of electronic medical records and large healthcare databases has gained importance to assess real-world comparative effectiveness. In this study, we will explore the real world effectiveness and safety of anticoagulants using a claims database. We will use a retrospective cohort study design, which is the strongest study design, to establish casual inference when observational data is used.[92] This dissertation will use the data from administrative claims submitted from health plans which have contracts with large private employers or with public organizations in the United States for the years between 2010 and 2016. The use of this recent data from the "real-world" will strengthen the external validity of the study by inclusion of patients with multiple comorbid conditions in the study cohort, which cannot be achieved through RCTs.

Results from our specific aim 1 may be useful in accessing and targeting the most important factors that facilitate anticoagulant treatment initiation. Results from Specific Aims 2 and 3 may help in guiding therapeutic decision-making to improve the quality of care provided to patients with orthopedic surgery.

2.7 Conceptual Model

The following section describes the theoretical framework used to guide this dissertation by identifying factors that contribute to utilization of anticoagulants. A conceptual model forms the basis for consideration of appropriate variables in any research study. The proposed conceptual framework for this dissertation was adapted from Andersen's Emerging Behavioral Model of Health Services Use.[93] According to the model, the use of healthcare services and subsequent health outcomes are influenced by a set of population characteristics. More specifically, these characteristics are divided into three groups: 1) predisposing factors, 2) need factors, and 3) enabling factors. Predisposing factors include patient characteristics that predispose them to the utilization of health services (e.g. race, age, gender, geographical factors). Need factors represent both the perceived and the actual health state of patients that necessitate the utilization of health services (e.g. comorbid conditions, severity of illness, use of other medications). Enabling factors include variables representing patients' ability to secure the healthcare services (e.g. health insurance type, prescription drug coverage generosity).

Based on these principles, this model was adapted to fit our research needs. Figure 2-2 shows Andersen's model with our variables of interest.

Figure 2-2 Andersen's Emerging Behavioral Model of Health Services Use (Adapted)

```
┌─────────────────────────────┐
│ Predisposing factors        │
│   • Age                     │
│   • Sex                     │
│   • Geographic location     │
│   • Metropolitan area       │
│     indicator               │                ┌──────────────────┐      ┌──────────────────┐
│   • Year of surgery         │                │ Anticoagulation  │      │   Incident VTE   │
│                             │ ─────────────▶ │ treatment        │ ───▶ │   events and     │
│                             │                │ initiation       │      │ bleeding events  │
│ Enabling factors            │                └──────────────────┘      └──────────────────┘
│   • Health benefit plan     │
│   • Prescription drug       │                  Drug utilization          Health outcomes
│     benefit generosity      │
│                             │
│                             │
│ Need based factors          │
│   • Past clinical events    │
│   • Comorbidities           │
│   • Concurrent therapy      │
│                             │
│                             │
└─────────────────────────────┘
     Population characteristics
```

We included age, gender, year of surgery and geographical location as the predisposing factors in our model. Some studies suggest that the risk of intracranial hemorrhage increases with age in warfarin patients.[94,95] This could affect the prescription of warfarin in older patients. Clinicians might be more likely to prescribe relatively safer-perceived anticoagulants such as LMWHs for older patients. The incidence of VTE is higher in elderly men compared to women which could result in different gender-based anticoagulant prescribing patterns.[96,97] Similarly, geographic variation has been reported in the risk of VTE. [98] Patients residing at higher altitudes have a reported predisposition for hypercoagulable state and are at an increased risk

for VTE. Based on regional differences, prescribing patterns may vary which will be explored in our model. We also included the year of surgery as a variable in our model because prescription patterns change over time, especially with the introduction of new therapies, availability of new clinical information, and change in therapeutic guidelines.[99-101]

Enabling factors are factors that facilitate obtaining health care. In our model, we translated this into an individual's ability to obtain the more expensive, newer oral anticoagulants. A study reported that privately insured patients or patients with a higher insurance index are more likely to receive new drugs than others.[102] We examined this association in our model and its effect on the type of anticoagulant received by including the type of health benefit plan and prescription drug benefit generosity index in the model. We hypothesized that patients with more generous prescription drug benefit will be more likely prescribed one of the newer oral anticoagulants over warfarin.

Need based factors are clinical factors that necessitate the utilization of health care services. Bleeding risk is often weighed along with a concurrent VTE risk assessment in deciding the choice of anticoagulant. We included known risk factors for bleeding and VTE as the clinical need factors in the model such as past clinical events, comorbidities and concurrent therapy. Comorbidities and past clinical events such as previous venous thromboembolism (VTE), ischemic stroke, and acute myocardial infarction (AMI) are considered risk factors for VTE and were included in the model.[110] Bleeding risk is often weighed along with a concurrent VTE risk assessment and presence of any previous major bleeding event was included in the model. Bleeding risk may be increased by surgery, medications, or factors inherent to the patient. A recent

observational study by the IMPROVE investigators reported on factors found to be most

predictive of in-hospital bleeding in medical patients.[61] Active peptic ulcer, active

bleeding within 3 months prior to admission, hepatic failure, age ≥85 years, and male

gender were the strongest independent risk factors. We included these variables along

with presence of gastritis, esophagitis, and duodenitis which are also known risk

factors[111] for bleeding in the model. Other patient comorbidities including diabetes

mellitus, atrial fibrillation, congestive heart failure (CHF), cardiovascular diseases,

hypertension, hyperlipidemia, renal impairment, sleep apnea, cancer, dementia and

anemia are also associated with the choice of anticoagulants in patients with atrial

fibrillation and were also included in our model.[103] Body mass index is also a known

predictor of choice of anticoagulant therapy. However due to the nature of

administrative claims data, we did not have access to this information. We used

clinically diagnosed obesity as a proxy for body mass index. Concomitant therapies

including antiplatelet therapy, antiarrhythmics, rate control therapies (eg, digoxin, beta-

blockers, calcium channel blockers), statins, gastroprotective agents, ACE inhibitors,

and hormonal contraceptives are contraindicated in certain anticoagulants[104] and can

affect the choice of anticoagulant prescribed. Concomitant use of these medications

with the anticoagulant was also included in the model. The Charlson Comorbidity Index

(CCI) is a commonly-used composite measure of overall disease burden which serves

as a proxy for patient health status; the higher the score, the greater the comorbidity

burden.[115, 116] 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.[105-107]

We also included hospitalization and the type of surgery setting (outpatient vs. inpatient)

in the model. All the covariates were measured in the 180 days baseline period. We

assessed the association of baseline covariates and the choice of anticoagulant using

logistic regression model.

Chapter 3 : METHODS

In section 3.1, the data source used for this dissertation is described. In section 3.2, methods used are described in detail by specific aims and finally in section 3.3, issues related to statistical power are discussed.

3.1 Data Source

The Truven Health MarketScan Commercial Claims and Encounters (CCAE) and Medicare Supplemental and Coordination of Benefits (COB) data were used for this study. The Truven MarketScan database contains de-identified patient level information on health care utilization, health care expenditure, insurance enrollment and plan benefit for commercially insured patients and Medicare-eligible retirees. The CCAE database consists of employer and health plan sourced data containing medical and prescription drug claims from over 100 nationwide insurers for around 40 million individuals annually. Enrollees include active employees, their spouses, early retirees, COBRA continuees, and their dependents insured by employer-sponsored private health insurance plans (ie, non-Medicare eligibles). Healthcare for these individuals is provided under a variety of fee-for-service (FFS), fully capitated, and partially capitated health plans, including preferred and exclusive provider organizations (PPOs and EPOs), point of service (POS) plans, indemnity plans, and health maintenance organizations (HMOs).

The MarketScan Medicare Supplemental and Coordination of Benefits (Medicare Supplemental) database contains claims data for Medicare-eligible retirees with supplemental insurance plans offered by their former employers. There are approximately 4.3 million enrollees annually included in the database. The Medicare Supplemental Database provides detailed utilization and health outcomes (e.g. adverse events) data for healthcare services performed in both, the inpatient and outpatient settings. Beneficiaries in the MarketScan Medicare database also have drug coverage; and therefore provide additional valuable information. Claims include the Medicare-covered portion of payment (represented as Coordination of Benefits Amount, or COB).

Both databases include patient specific inpatient and outpatient service claims, physician office visits, outpatient prescription drug and enrollment information. Additionally, the data can be linked to track detailed patient information across sites, types of providers, and over time thereby reflecting a true continuum of care.[108] Due to its substantial size, longitudinal integrity, and unique data links, this database provides an ideal opportunity to conduct pharmacoepidemiologic research. In this particular analysis, data from inpatient services file, outpatient services file, prescription drug claims file and enrollment file were merged using unique patient identifiers.

3.2 Methods by Specific Aim

The plan for patient population, study design, measurement of variables and statistical analyses is detailed below by Specific Aim.

3.2.1 Specific Aim 1a: To analyze market trends in the utilization of anticoagulants in patients undergoing an elective total hip or knee replacement surgery.

Study population

Time frame for the trend analysis was from January 1, 2010 to December 31, 2015. We chose this time frame to analyze the change in utilization of anticoagulants after the introduction of novel oral anticoagulants to the US market. Dabigatran was the first non-Vitamin K oral anticoagulant approved by the US FDA on October 19, 2010. However, it was approved for stroke prevention indication in patients with atrial fibrillation. On November 23, 2015, dabigatran received approved for VTE prevention after hip replacement surgery. Rivaroxaban was the first approved novel oral anticoagulant for VTE prophylaxis after knee and hip replacement surgeries and received FDA approval on July 1, 2011. Apixaban was introduced to the US market on December 28, 2012, but received approval for VTE prophylaxis indication following hip and knee replacement surgery on March 18, 2014.

Patients undergoing a total knee replacement surgery or a total hip replacement surgery during the study period were identified using inpatient and outpatient claims data. International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes, International Classification of Diseases, Tenth Revision, Procedure Coding System (ICD-10-PCS) and Current Procedural Terminology (CPT) medical billing codes were used to identify total hip replacement and total knee replacement and

are reported in table 3-1. We extracted and analyzed their prescription drug claims data for an anticoagulant prescription fill from seven days before their surgery date until three months after their surgery date. A seven-day pre-surgery period was used to identify patients that could have filled the prescription in preparation for their surgery. National drug codes (NDCs) were used to identify the different types of anticoagulants. These were categorized as low molecular weight heparins, warfarin, dabigatran, rivaroxaban, and apixaban. We analyzed quarterly prescription volumes in patients undergoing surgery from January 2010 to December 2015 to understand patterns in treatment utilization. A quarter was defined as a three-month interval. Prescription volume included new fills for these medications during the three-month post-surgery window. We segregated the analysis by the type of surgery – total hip replacement or total knee replacement, and the type of insurance – commercially insured cohort and Medicare cohort due to the inherent differences in these populations.

Table 3-1 Procedure codes for elective total hip and knee replacement surgery

ICD-9 CM	ICD – 10 PCS	CPT code	Category description
81.51			Total hip replacement
	0SR90J9		Replacement of Right Hip Joint with Synthetic Substitute, Cemented, Open Approach
	0SR90JA		Replacement of Right Hip Joint with Synthetic Substitute, Uncemented, Open Approach
	0SR90JZ		Replacement of Right Hip Joint with Synthetic Substitute, Open Approach
	0SRB0J9		Replacement of Left Hip Joint with Synthetic Substitute, Cemented, Open Approach
	0SRB0JA		Replacement of Left Hip Joint with Synthetic Substitute, Uncemented, Open Approach
	0SRB0JZ		Replacement of Left Hip Joint with Synthetic Substitute, Open Approach
		27130	Arthroplasty, acetabular and proximal femoral prosthetic replacement (total hip arthroplasty), with or without autograft or allograft
81.54			Total knee replacement
	0SRC07Z		Replacement of Right Knee Joint with Autologous Tissue Substitute, Open Approach
	0SRC0JZ		Replacement of Right Knee Joint with Synthetic Substitute, Open Approach
	0SRC0J9		Replacement of Right Knee Joint with Synthetic Substitute, Open Approach, Cemented
	0SRC0KZ		Replacement of Right Knee Joint with Nonautologous Tissue Substitute, Open Approach
	0SRC0LZ		Replacement of Right Knee Joint with Unicondylar Synthetic Substitute, Open Approach
	0SRD07Z		Replacement of Left Knee Joint with Autologous Tissue Substitute, Open Approach
	0SRD0JZ		Replacement of Left Knee Joint with Synthetic Substitute, Open Approach
	0SRD0J9		Replacement of Left Knee Joint with Synthetic Substitute, Open Approach, Cemented
	0SRD0KZ		Replacement of Left Knee Joint with Nonautologous Tissue Substitute, Open Approach

	0SRD0LZ		Replacement of Left Knee Joint with Unicondylar Synthetic Substitute, Open Approach
	0SRT07Z		Replacement of Right Knee Joint, Femoral Surface with Autologous Tissue Substitute, Open Approach
	0SRT0JZ		Replacement of Right Knee Joint, Femoral Surface with Synthetic Substitute, Open Approach
	0SRT0KZ		Replacement of Right Knee Joint, Femoral Surface with Nonautologous Tissue Substitute, Open Approach
	0SRU07Z		Replacement of Left Knee Joint, Femoral Surface with Autologous Tissue Substitute, Open Approach
	0SRU0JZ		Replacement of Left Knee Joint, Femoral Surface with Synthetic Substitute, Open Approach
	0SRU0KZ		Replacement of Left Knee Joint, Femoral Surface with Nonautologous Tissue Substitute, Open Approach
	0SRV07Z		Replacement of Right Knee Joint, Tibial Surface with Autologous Tissue Substitute, Open Approach
	0SRV0JZ		Replacement of Right Knee Joint, Tibial Surface with Synthetic Substitute, Open Approach
	0SRV0KZ		Replacement of Right Knee Joint, Tibial Surface with Nonautologous Tissue Substitute, Open Approach
	0SRW07Z		Replacement of Left Knee Joint, Tibial Surface with Autologous Tissue Substitute, Open Approach
	0SRW0JZ		Replacement of Left Knee Joint, Tibial Surface with Synthetic Substitute, Open Approach
	0SRW0KZ		Replacement of Left Knee Joint, Tibial Surface with Nonautologous Tissue Substitute, Open Approach
		27447	Arthroplasty, knee, condyle and plateau; medial and lateral compartments with or without patella resurfacing (total knee arthroplasty)

3.2.1.b Specific Aim 1b: To identify factors influencing the choice of anticoagulation therapy in patients undergoing an elective total hip or knee replacement surgery.

<u>Patient population</u>

The time frame for our study was from January 1, 2011 to December 31, 2015. This time frame was selected because the first newer oral anticoagulant, dabigatran, was approved in United States by the Food and Drug Administration (FDA) on October 19, 2010. To allow for 180 days of baseline and at least 90 days of follow up period for everyone, the subject identification period started from July 1, 2011 and ended on September 1, 2015. Patients undergoing a total hip replacement (THR) or a total knee replacement (TKR) surgery during this time period were eligible for inclusion in the cohort. We built four separate cohorts based on the type of surgery and type of insurance: (1) commercially insured total hip replacement patients, (2) Medicare total hip replacement patients, (3) commercially insured total knee replacement patients, and (4) Medicare total knee replacement patients. The patient population was separated accordingly because the risk of outcomes was assumed to be different in each of these cohorts due to inherent baseline differences in these cohorts. Total knee replacement and total hip replacement were identified by an inpatient or outpatient claim using medical billing codes as described in table 3-1. These operational definitions to identify TKR and THR are based on previously published literature and mapped to include ICD-10 PCS.[109,110] The date of discharge from hospital was considered as the index date.

Patients younger than 18 years were excluded from this study because hip or knee replacement under 18 years is generally due to trauma induced injuries and differs

systematically from total joint replacement in regards with disease progression and treatment. We further limited the inclusion to patients continuously enrolled in their health plan for at least 180 days prior to and 90 days after their index date. This was done because intermittent enrollment may result in incompleteness of the data in our analytic dataset; which in turn could lead to misinterpretation of our effect estimates. The 180 days of continuous enrollment period prior to the index date was defined as the baseline period. In addition, patients were excluded from the study if they had an anticoagulant prescription fill in the baseline period until seven days prior to the surgery to examine new users of anticoagulation. We excluded prevalent users because if the hazard function associated with the use of anticoagulants varies with time, it can introduce substantial bias. However, we restricted this criterion to seven days before the surgery due to the assumption that treatment-naïve patients that filled the anticoagulant prescription just prior to surgery were most likely filling it for use after surgery. The effect of this assumption was further explored by running a sensitivity analysis for dates of fill around the surgery date. We also excluded patients who had a previous major orthopedic surgery in the baseline period to avoid potential confounding factors associated with previous surgeries and medication use. Figure 3-1 summarizes the inclusion and exclusion criteria for our study cohort.

Figure 3-1 Inclusion-exclusion criteria for aim 1b

```
┌─────────────────────────────────────────────────────────────────────┐
│ Total joint replacement identification: THR or TKR diagnosis (using   │
│ ICD 9 CM, ICD 10 PCS and CPT codes) recorded on either inpatient or   │
│ outpatient service claims between July 1, 2011 to September 30, 2015  │
│ (4 cohorts: commercially insured THR, Medicare THR, commercially      │
│ insured TKR, Medicare TKR                                             │
└─────────────────────────────────────────────────────────────────────┘
                    │
                    │              ┌──────────────────────────────────┐
                    │              │ Exclude: Age < 18, not            │
                    │              │ continuously enrolled             │
                    │              └──────────────────────────────────┘
                    ▼
┌─────────────────────────────────────────────────────────────────────┐
│ Eligibility requirements: Patients >18 yrs with 210 days continuous   │
│ enrollment (180 days pre-index + 90 days post-index) in their health  │
│ plan                                                                  │
└─────────────────────────────────────────────────────────────────────┘
                    │
                    │              ┌──────────────────────────────────┐
                    │              │ Exclude: Patients not on warfarin │
                    │              │ or rivaroxaban or using multiple  │
                    │              │ anticoagulants following surgery  │
                    │              └──────────────────────────────────┘
                    ▼
┌─────────────────────────────────────────────────────────────────────┐
│ Patients using rivaroxaban or warfarin following surgery              │
└─────────────────────────────────────────────────────────────────────┘
                    │
                    │              ┌──────────────────────────────────┐
                    │              │ Exclude: Prevalent users of       │
                    │              │ rivaroxaban or warfarin           │
                    │              └──────────────────────────────────┘
                    ▼
┌─────────────────────────────────────────────────────────────────────┐
│ New users of anticoagulants following surgery                         │
│ Final sample                                                          │
└─────────────────────────────────────────────────────────────────────┘
```

We designed a retrospective cohort study to evaluate factors influencing the choice of anticoagulant for this particular aim. Patients included in the study cohort (See Figure 3-1) were followed for 30 days from the index date for determining anticoagulant treatment exposure. Figure 3-2 shows a schematic diagram of study design for aim 1.

Figure 3-2 Study design for Aim 1
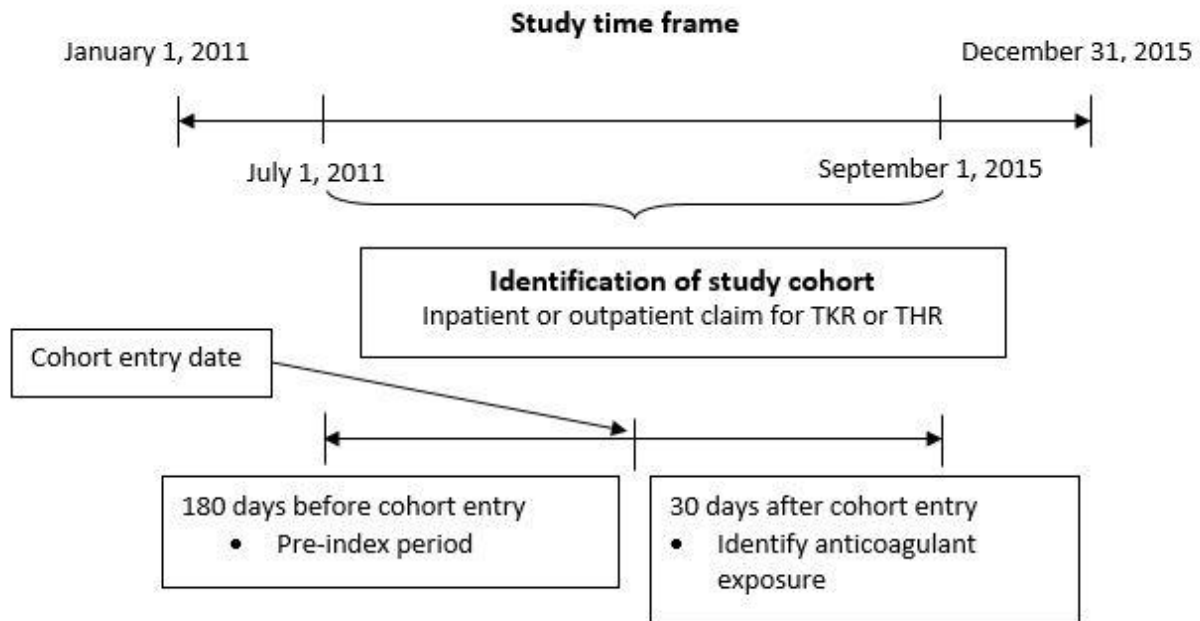
Measurement of variables

Covariates: In this specific aim, we evaluated factors influencing the choice of anticoagulant treatment in total joint replacement surgery patients (Table 3-2). All the patient factors were independent variables of interest and were measured during the 180 days baseline period preceding their index date.

Table 3-2 Covariate descriptions and coding strategies for patient characteristics in baseline period

Patient Characteristics	Covariate Coding	Covariate Definition
Predisposing Characteristics		
Age at the time of surgery	Continuous	Age in years at time of orthopedic surgery
Sex	1=Male, 2=Female	Sex from enrollment file
Geographic Region	1=Northeast, 2=North central, 3= South, 4=West, 5=Unknown	Region from enrollment file
Metropolitan statistical area indicator	First three digits of zip code	Three digit zip code indicator from enrollment file
Time of surgery	Year of surgery	Year of surgery from inpatient file
Enabling Resources		
Type of health benefit plan	1=Basic/major medical 2=Comprehensive 3=EPO 4=HMO 5=POS 6=PPO 7=POS with capitation 8=CDHP 9=HDHP	Type of health benefit plan from enrollment file
Prescription benefits generosity	1=No/Poor coverage 2=Fair coverage 3=Good coverage 4=Unknown	Ratio of patient cost-sharing for prescription payments relative to total payments for prescriptions
Need Characteristics		
Past clinical events		

Previous venous thromboembolism (VTE)	0=Absent, 1=Present	VTE diagnosis
Previous ischemic stroke	0=Absent, 1=Present	Ischemic stroke diagnosis
Previous myocardial infarction	0=Absent, 1=Present	Myocardial infarction diagnosis
Previous major bleeding	0=Absent, 1=Present	Diagnosis of hemorrhagic or gastrointestinal bleeding
Comorbidities		
Charlson Comorbidity Index (CCI)	Categorical (0, 1, 2-4, ≥5)	Patient disease severity
Atrial Fibrillation	0=Absent, 1=Present	Atrial fibrillation diagnosis
Cardiovascular disease	0=Absent, 1=Present	Cardiovascular disease diagnosis
Congestive Heart Failure	0=Absent, 1=Present	Congestive heart failure diagnosis
Hepatic failure	0=Absent, 1=Present	Liver failure diagnosis
Renal Impairment	0=Absent, 1=Present	Chronic kidney disease or End Stage Renal Disease diagnosis
Peptic Ulcer disease	0=Absent, 1=Present	Diagnosis of peptic ulcer disease
Gastritis	0=Absent, 1=Present	Diagnosis of gastritis
Duodeniitis	0=Absent, 1=Present	Diagnosis of duodenitis
Esophagitis	0=Absent, 1=Present	Diagnosis of esophagitis
Hyperlipidemia	0=Absent, 1=Present	Hyperlipidemia diagnosis
Hypertension	0=Absent, 1=Present	Hypertension diagnosis
Diabetes Mellitus	0=Absent, 1=Present	Diabetes Mellitus diagnosis
Anemia	0=Absent, 1=Present	Diagnosis of anemia
Sleep apnea	0=Absent, 1=Present	Diagnosis of sleep apnea
Cancer	0=Absent, 1=Present	Diagnosis of cancer
Dementia	0=Absent, 1=Present	Diagnosis of dementia
Obesity	0=Absent, 1=Present	Diagnosis of obesity

Number of hospitalizations	Categorical (0, ≥1)	Number of hospitalizations in baseline
Type of Surgery Setting	0=Outpatient procedure, 1=Inpatient procedure	Type of surgery setting
Concomitant therapies		
Antiplatelet therapy (aspirin excluded)	0=Non-use, 1=Use	Prescription fill for clopidogrel or Aggrenox
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
Hormonal contraceptive use	0=Non-use, 1=Use	Prescription fill for oral contraceptive
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)

The details of variables to be measured are provided below.

1. **Predisposing factors:** Patients' age on their index date was measured as a continuous variable. Proportions of male and female patients in each anticoagulant group were reported. Two variables for the geographic location were included, 1) geographic region, in which the patients were placed in one of the following groups based on US census region: Northeast, Midwest, South and West (Refer to Table 3-3 for the regional assignment) and 2) a metropolitan

statistical area indicator. The year of surgery was also included as a proxy for time.

Table 3-3 Geographic Region Definitions

Region	States
Northeast	Connecticut, Maine, Massachusetts, New Hampshire, Vermont, Rhode Island, New Jersey, New York, and Pennsylvania
Midwest	Illinois, Indiana, Michigan, Ohio, Wisconsin, Iowa, Kansas, Minnesota, Missouri, Nebraska, North Dakota, and South Dakota
South	Delaware, District of Columbia, Florida, Georgia, Maryland, North Carolina, South Carolina, Virginia, Alabama, Kentucky, Mississippi, Tennessee, West Virginia, Arkansas, Louisiana, Oklahoma, and Texas
West	Arizona, Colorado, Idaho, Montana, Nevada, New Mexico, Utah, Wyoming, Alaska, California, Hawaii, Oregon, and Washington

Source: http://www.census.gov/geo/www/geo_defn.html#GeographicCode

2. **Enabling factors:** We included type of health benefit plan and a measure of the generosity of the prescription drug benefit as enabling factors.[111] Type of health benefit plan was a categorical variable indicating capitated plans such as health maintenance organization, or point-of-service plans and non-capitated plans such as basic major medical, comprehensive, exclusive provider organization, preferred provider organization, non-capitated point-of-service, consumer-driven health plan or high deductible health plan. Drug benefit generosity was approximated by creating a 'generosity index' using payment information from all the prescriptions filled by patients in the baseline period. This index was calculated as a continuous scale in the range of 0-1 and was defined as patients' cost-sharing proportions for all prescriptions in the baseline period prior to anticoagulant initiation divided by the total net drug payments as a benefits' generosity measure. Based on this index, patients were classified into three

ratio levels of drug benefit generosity to facilitate interpretation: >0.80 paid by

patients ("No/Poor coverage"), 0.20 to 0.80 ("Fair coverage), and ≤0.20 ("Good

coverage"). Similar methods have been successfully used in prior studies.[111]

Patients with prescription drug benefits but with no measured prescription fills in

the baseline period were assigned an unknown status. We reported the number

of patients with unknown information in prescription drug benefits.

3. **Clinical need factors:** We measured the risk factors for VTE, patients'

comorbidity profile and concurrent therapy in the baseline period. Details for

measurement are as follows,

    a. Past clinical events: Relevant clinical events were identified in the 180

       days baseline period using ICD-9 and ICD-10 codes in the outpatient and

       inpatient medical claims files based on previous literature.[105] These

       included known risk factors for VTE and bleeding such as previous

       venous thromboembolism, ischemic stroke, acute myocardial infarction

       (AMI), and bleeding

    b. Comorbidity profile: Patient comorbidities including atrial fibrillation,

       cardiovascular diseases, diabetes mellitus, congestive heart failure

       (CHF), hypertension, hyperlipidemia, renal impairment, peptic ulcer

       disease, gastritis, duodenitis, esophagitis, hepatic failure, anemia, sleep

       apnea, obesity, cancer and dementia were also measured using ICD-9

       and ICD-10 codes in the outpatient and inpatient medical claims files.

       Charlson's comorbidity index was also calculated as an overall measure

of patient comorbidity burden. Previous hospitalization and setting of

surgery was also included as covariates.

c. Use of co-medications: We measured the utilization of concomitant

therapies in the baseline period including antiplatelet therapy,

antiarrhythmics, rate control therapies (eg, digoxin, beta-blockers,

calcium channel blockers), statins, gastroprotective agents, ACE

inhibitors and hormonal contraceptives because of known associations

with anticoagulation. These products were identified using the national

drug code (NDC) numbers from the outpatient pharmacy files.

Dependent (Outcome) variable: The outcome variable of interest was type of

anticoagulant initiated during the 30 days of follow up period beginning on the index

date or seven days in the pre-index period. Type of anticoagulant was categorized as

warfarin and rivaroxaban. The use of these anticoagulants was identified using NDC

numbers from outpatient pharmacy files for filled prescriptions. Patients who were

exposed to more than one anticoagulant were excluded from the analysis.

Statistical analysis

Descriptive statistics were used to summarize and compare patient factors in

warfarin and rivaroxaban users. For dichotomous and categorical variables, the results

were presented as numbers and proportions. For continuous variables, the results were

presented as mean (± SD). The patient factors were then compared between warfarin

users and rivaroxaban users using standardized differences. This method was used to

avoid statistically significant but clinically meaningless differences between our two groups owing to the large sample size.

The equation for standardized differences can be given as follows:

Standardized difference = $\dfrac{\text{Treatment improvement} - \text{Comparator improvement}}{\text{Pooled standard deviation}}$

Standardized difference of zero means that the treatment and the comparator have equivalent effects. Standardized differences greater than 0.2 mean smaller effect size; greater than 0.5 is considered medium and greater than 0.8 is considered a large effect.[112] To understand the impact of various covariates on the choice of anticoagulant therapy, logistic regression models were used. Although a common approach to statistical model building is minimization of variables until the most parsimonious model is obtained, methodologists argue that it could lead to eliminating relevant confounders from the model as well as potentially overfitting the data. To overcome this issue, some epidemiologists suggest inclusion of all clinical and other relevant variables in the model regardless of their significance in order to control for confounding. We used this approach to include all the relevant clinical and demographics variables that have been previously found to be associated with the choice of anticoagulant after a hip or knee replacement.

The logistic regression equation used was:

$$y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \ldots \beta_n X_n + \varepsilon$$

y= type of anticoagulant treatment (warfarin or rivaroxaban)

β=regression co-efficient for the independent variables

X= Independent variable

ε= error

Sensitivity analysis:

One of the limitations of including all theoretical confounders irrespective of their significance is that it can lead to numerically unstable estimates and large standard errors. To understand the effect of including such confounders in our model, we ran a sensitivity analysis to obtain the most parsimonious model through purposeful selection as suggested by Bursac et al.[113] In this sensitivity analysis, we began the model building and variable selection by univariate analysis of each variable as previously identified. Any variable having a significant univariate test at p-value cut-off point of 0.25 was selected as a candidate to be included in the model. In the iterative process of variable selection, covariates were removed from the model if they were non-significant and not a confounder. Significance was evaluated at the 0.1 alpha level and confounding was defined as a change in any remaining parameter estimate greater than 15% as compared to the full model. These cut off ranges were based on the recommended values by the authors.[113] A change in the parameter estimate above the specified level indicates that the excluded variable was important in providing a needed adjustment for one or more of the variables remaining in the model. At the end of this iterative process of deleting, refitting, and verifying, the model contained significant covariates and confounders. Any variable not selected for the original multivariate model was then added back one at a time, with significant covariates and confounders retained earlier. This step is helpful in identifying variables that, by themselves, are not significantly related to the outcome but make an important contribution in the presence of other

variables. Those that are significant at the 0.15 level were put in the model, and the model was iteratively reduced as before but only for the variables that were additionally added.

3.2.2 Specific Aim 2: To compare the real world effectiveness of novel oral anticoagulant rivaroxaban with standard oral anticoagulant warfarin in venous thromboembolism prevention among patients with elective total hip or knee replacement surgery.

<u>Patient population and study design</u>

For this aim, we designed a retrospective cohort study to study the effectiveness of warfarin and rivaroxaban for VTE prevention in patients with total hip or knee replacement surgery. All the patients identified as the members of the hip or knee replacement surgery population in aim 1 (figure 3-3) comprised of the base cohort for aim 2.

<u>Inclusion- exclusion criteria</u>

To be considered for the comparative effectiveness analysis, patients in the base cohort had to meet the following inclusion criteria:

1) Patients with an inpatient or outpatient claim for an elective total hip replacement or elective total knee replacement surgery.

2) At least 18 years of age at the time of the surgery

3) Continuous enrollment in their health plans during the 180 days of the baseline period and 90 days post index period to ensure completeness of data

4) No use of any anticoagulants in the baseline period because when the risk of

outcome is altered with the course of treatment, the internal validity of the study

is compromised if we fail to account for duration of the treatment. This issue can

be circumvented by exclusion of prevalent drug users and constructing a clean

cohort of only the new drug users.[114]

5) No previous history of hip or knee replacement surgery. We also excluded

patients with partial hip or knee replacement surgery.

Follow up period was defined as the 90 day period following discharge after orthopedic

surgery.

Figure 3-3 Study design for Aim 2
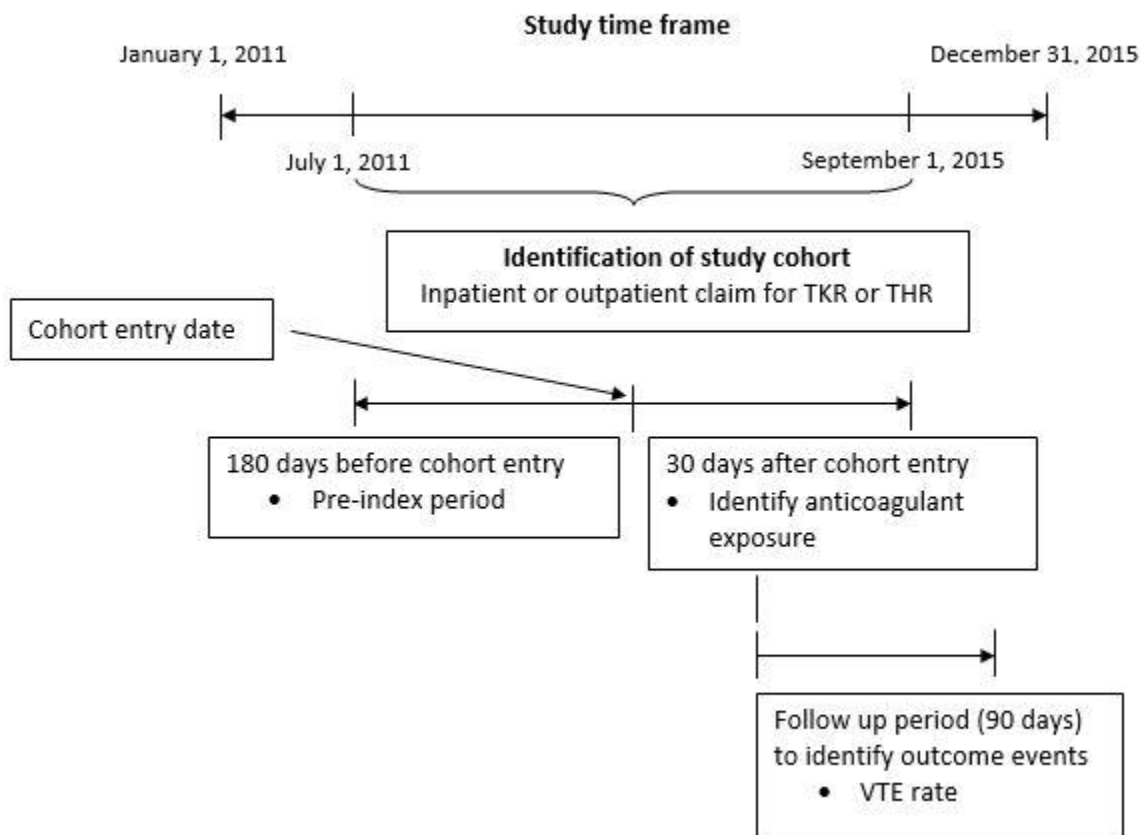
The outcome of interest was venous thromboembolism which was a measure of the occurrence of pulmonary embolism and deep vein thrombosis in the follow-up period. Outcomes were assessed based on the presence of inpatient or outpatient claims with a primary diagnosis. Validated ICD-9 coding algorithms (Table 3-4) and mapped ICD 10 codes were used to measure the outcome events, which are based on published studies found in the literature.[115,116]

Table 3-4 Medical diagnosis codes for outcomes in aim 2

ICD-9 CM	ICD – 10 PCS	Category description
451.1x		Phlebitis and thrombophlebitis of deep veins of lower extremities
451.2		Phlebitis and thrombophlebitis of lower extremities unspecified
453.4x		Acute venous embolism and thrombosis of deep vessels of lower extremity
453.8		Acute venous embolism and thrombosis of other specified veins
453.9		Embolism and thrombosis of unspecified site
	I82.40X	Acute embolism and thrombosis of unspecified deep veins of lower extremity
	I82.401	Acute venous embolism and thrombosis of deep vessels of right lower extremity
	I82.402	Acute venous embolism and thrombosis of deep vessels of left lower extremity
	I82.403	Acute venous embolism and thrombosis of deep vessels of lower extremity, bilateral
	I82.409	Acute venous embolism and thrombosis of deep vessels of unspecified lower extremities
	I82.419	Acute embolism and thrombosis of unspecified femoral vein
	I82.429	Acute embolism and thrombosis of unspecified iliac vein
	I82.439	Acute embolism and thrombosis of unspecified popliteal vein
	I82.4Y9	Acute embolism and thrombosis of unspecified proximal lower extremity
	I82.449	Acute embolism and thrombosis of unspecified tibial vein

	I82.499	Acute embolism and thrombosis of other specified deep vein of unspecified lower extremity
	I82.4Z9	Acute embolism and thrombosis of unspecified deep veins of unspecified distal lower extremity
	I82.62X	Acute embolism and thrombosis of deep veins of upper extremity
	I82.621	Acute embolism and thrombosis of deep veins of right upper extremity
	I82.622	Acute embolism and thrombosis of deep veins of left upper extremity
	I82.623	Acute embolism and thrombosis of deep veins of upper extremity, bilateral
	I82.629	Acute embolism and thrombosis of deep veins of unspecified upper extremity
415.1x		Pulmonary embolism and infarction
	I26.99	Acute pulmonary embolism
	I26.01	Septic pulmonary embolism with acute cor pulmonale
	I26.90	Septic pulmonary embolism without acute cor pulmonale
	I26.02	Saddle embolus of pulmonary artery with acute cor pulmonale
	I26.92	Saddle embolus of pulmonary artery without acute cor pulmonale
	I26.09	Other pulmonary embolism with acute cor pulmonale

Baseline covariates included in the propensity model were age, gender, year of surgery, census region of residence, type of health benefit plan, measure of the generosity of the prescription drug benefit, CCI, history of DVT or PE, ischemic stroke, myocardial infarction, atrial fibrillation, diabetes, dementia, hypertension, anemia, cardiovascular diseases, congestive heart failure, hepatic failure, renal impairment, sleep apnea, cancer, obesity, number of hospitalizations, type of surgery setting, antiplatelet therapy, antiarrythmics, rate control therapy, ACE inhibitors, hormone use and statins. The number of events in the follow up period were reported as VTE event rate.

Statistical analysis

Descriptive statistics were generated including the VTE rates in each anticoagulant group and distributions of baseline characteristics. We estimated odds ratios (OR) and 95% confidence intervals (CIs) using logistic regression models with stabilized inverse probability treatment weighting (IPTW).[117] IPTW was used to adjust for baseline differences among warfarin and rivaroxaban users.

Inverse probability treatment weighting:

Establishing causal inference using observational data is often disputed because the study subjects are not randomly allocated, which may result in selection bias. However, advanced techniques such as propensity score adjustment can be used to reduce these confounding biases.[118] Propensity score (PS) methods attempt to control for lack of randomization in observational studies by balancing covariate distributions between treatment groups.[118,119] Estimates of the average treatment effect in the treated group can be obtained by PS matching between two comparable groups, such that pairs of matched individuals have similar values of the propensity score. 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). Our study will use IPTW 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. We used the IPTW method because the number of warfarin users were almost the same as the number of rivaroxaban users. Regression models can be

weighted by the inverse probability of treatment to estimate the average treatment effect of receiving the treatment.

Propensity score weights were estimated using logistic regression that included all variables identified from aim 1 as covariates. The propensity score distributions were examined by exposure status for overlap to assess factors associated with overall treatment selection and comparability of the covariate distributions. We then estimated the treatment effects using propensity score weighting, including IPTW approaches, trimming for non-overlapping regions. Because weights may be unstable for individuals with very low probabilities of receiving treatment, stabilizing weights and 'trimming' subjects are methods often used. IPTW uses weights based on the propensity score to create a synthetic sample in which the distribution of measured baseline covariates is independent of treatment assignment. Weights are computed that denote the probability of receiving the treatment that was actually received. If e denotes the estimated propensity score, then the original sample is weighted by: $\dfrac{Z}{e} + \dfrac{(1-Z)}{(1-e)}$
 (i.e. treated subjects are assigned a weight equal to the reciprocal of the propensity score, while control subjects are assigned a weight equal to the reciprocal of one minus the propensity score). Since, the weights may be inaccurate or unstable for subjects with a very low probability of receiving the treatment received, the use of stabilizing weights has been proposed in literature.[120] We limited the weighting thresholds such that weights exceeding the 1st and 99th percentile were set to that threshold. The estimated weights were incorporated into the logistic regression models that only included the anticoagulant treatment variable.

Sensitivity analysis:

We conducted sensitivity analysis by restricting the use of anticoagulants in the

first seven days after surgery to compare real world results to clinical trials where

patients received anticoagulation within the first 7 days.

3.2.3 Specific Aim 3: To compare the safety of novel oral anticoagulant rivaroxaban with standard oral anticoagulant warfarin among patients with elective total hip or knee replacement surgery.

<u>Study population and study design</u>

For this aim, we designed a retrospective cohort study to study the effect of type of anticoagulant use on the safety in patients with elective total hip or knee replacement surgery. All the patients identified as the members of the comparative effectiveness cohort for aim 2 were included in the analysis for this aim. We applied the same inclusion exclusion criteria as aim 2 for this cohort (Figure 3-4). Follow up period began from the discharge date after the orthopedic surgery and patients were followed for 90 days after discharge.

Figure 3-4 Study design for Aim 3
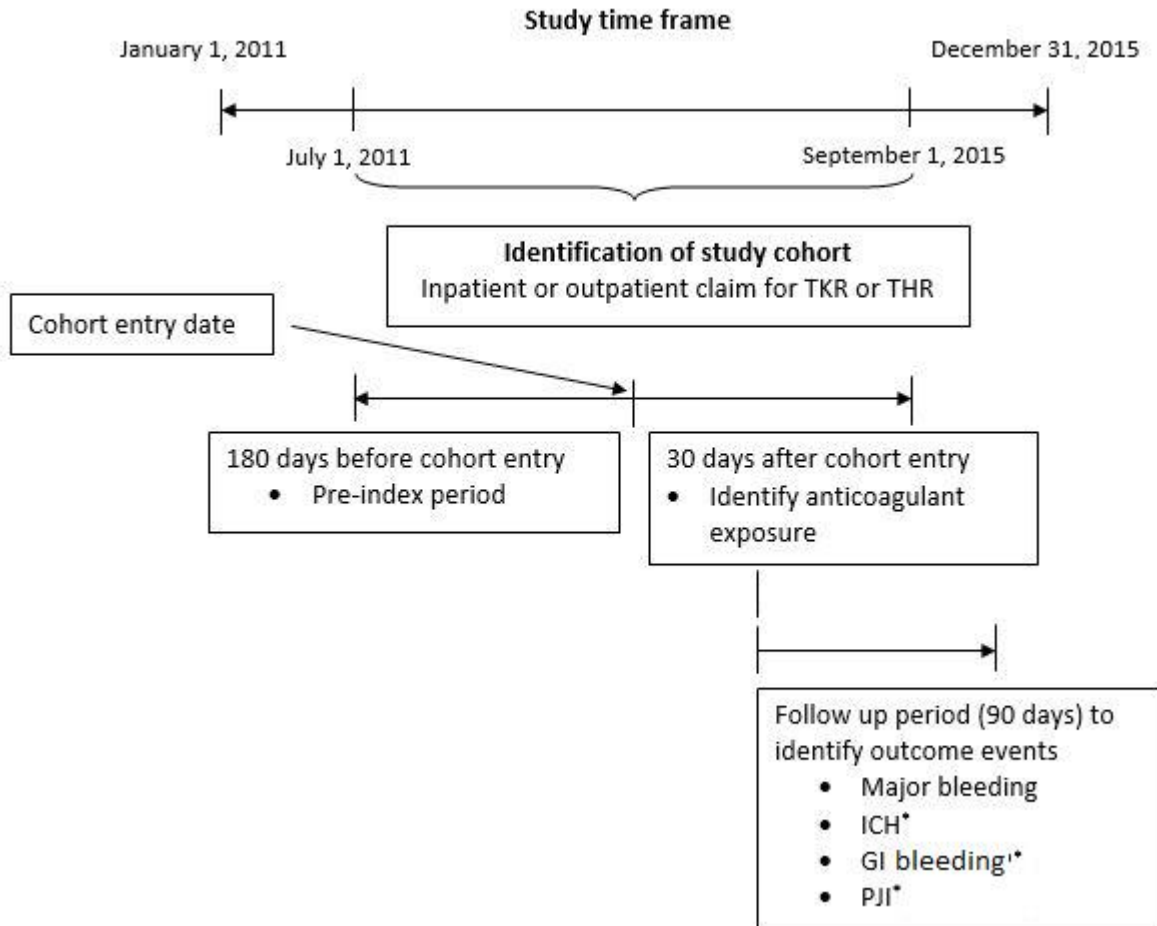
Measurement of variables

     The outcomes of interest were the occurrence of major bleeding, intracranial

hemorrhage (ICH), gastrointestinal (GI) bleeding and peri-prosthetic infection in the

follow-up period. Outcomes were assessed based on the presence of inpatient or

outpatient claims with a primary diagnosis. Validated ICD-9 coding algorithms and

mapped ICD 10 codes (Table 3-5) were used to measure the bleeding events and

periprosthetic infection, which are based on published studies found in the literature.[121]

Baseline covariates included in the propensity model were age, gender, year of surgery,

census region of residence, type of health benefit plan, measure of the generosity of the

prescription drug benefit, CCI, previous bleeding, peptic ulcer, gastritis, duodenitis, esophagitis, atrial fibrillation, diabetes, dementia, hypertension, cardiovascular diseases, congestive heart failure, hepatic failure, renal failure, sleep apnea, anemia, number of hospitalizations, type of surgery setting, gastroprotective agents, antiplatelet therapy, ACE inhibitors and statins. The number of events were used to calculate bleeding and PJI rates in the two user cohorts.

Table 3-5 Medical diagnosis codes for outcomes in aim 3

Diagnosis	ICD-9 CM and ICD-10 CM
Major bleeding	360.43, 362.81, 372.72, 376.32, 379.23, 423.0, 430, 431, 432, 568.81, 719.1,852, 853, 854, 363.61
Gastrointestinal bleeding event	530.82, 531.2, 531.4, 531.6, 532.2, 532.4, 532.6, 533.2, 533.4, 533.6, 534.2, 534.4, 534.6, 535.x1, 537.83, 562.02, 562.03, 562.12, 562.13, 569.3, 578.x, K92.2, K29.x
Intracranial bleeding event	430.x, 431.x, 432.0, 432.1, 432.2, 432.9, or 851-854, I61.9, I62
Any bleeding	360.43, 362.81, 363.61, 372.72, 376.32, 379.23, 423.0, 430, 431, 432, 852.0, 852.2, 852.4, 853.0, 455.2, 455.5, 455.8, 456.0, 456.20, 459.0, 530.7, 530.82, 531.00, 531.01, 531.20, 531.21, 531.40, 531.41, 531.60, 531.61, 533.01, 533.20, 533.21, 533.40, 533.41, 533.60 , 533.61 , 534.00 , 534.01, 534.20, 534.21 , 534.40, 534.41, 531.01, 534.60, 534.61, 535.11, 535.21 , 535.31 , 535.41 , 535.51, 535.61, 537.83, 562.02, 562.03 , 562.12 , 562.13, 568.81, 569.3, 569.85, 578, 578.0 , 578.1 , 578.9 , 593.81, 599.7 , 719.10, 719.11, 719.12 , 719.13 , 719.14, 719.15, 719.16, 719.17, 719.18, 719.19, 784.7, 784.8, 786.3, R58
Prosthetic joint infection	996.66, T84.5

Statistical analysis

Descriptive statistics were generated including the event rates in each anticoagulant group and distributions of baseline characteristics. We estimated odds ratios (ORs) and 95% confidence intervals (CIs) using logistic regression models with stabilized inverse probability treatment weighting (IPTW).[117] Propensity score weights were estimated using logistic regression. The propensity score distributions were

examined by exposure status for overlap to assess factors associated with overall treatment selection and comparability of the covariate distributions. We then estimated the treatment effects using propensity score weighting, including IPTW approaches, trimming for non-overlapping regions. The estimated weights were incorporated into the logistic regression models that only included the anticoagulant treatment variable.

Sensitivity analysis:

Similar to aim 2, we conducted a sensitivity analysis by restricting the use of anticoagulants in the first seven days after surgery to compare real world results to clinical trials where patients received anticoagulation within the first 7 days.

3.3 Power calculations

Power and sample size calculations were based on previous literature. [1] The power calculation in RE-LY trial indicated 1,275 patients should be included in each study arm to demonstrate non-inferiority between dabigatran and warfarin. We will require the same number of subjects in each anticoagulant drug class that would be needed in order to have power of 80% to detect statistically significant differences between those exposed to standard therapy compared to those exposed to newer oral anticoagulants for experiencing the primary outcome.

Chapter 4 : RESULTS

This chapter presents the three main findings of this study. In this chapter, we analyzed the utilization patterns of anticoagulants in real-world clinical practice and evaluated the factors influencing the choice of preventive anticoagulant therapy in patients undergoing an elective hip or knee replacement surgery using health insurance claims from Marketscan databases during the period of 2011 to 2015. We also compared the effectiveness and safety of rivaroxaban and warfarin in elective orthopedic surgery patients.

4.1 Aim 1a Real world utilization of anticoagulants after an elective total hip or knee replacement

Trends in the utilization pattern of anticoagulants after an elective total hip or knee replacement surgery were examined between January 1, 2010 and December 31, 2015. This time period was chosen to reflect the effect of introduction of novel anticoagulants in the US market. Dabigatran was the first non-Vitamin K oral anticoagulant approved by the US FDA on October 19, 2010. However, it was approved for stroke prevention indication in patients with atrial fibrillation. On November 23, 2015, dabigatran received approved for VTE prevention after hip replacement surgery. Rivaroxaban was the first approved novel oral anticoagulant for VTE prophylaxis after knee and hip replacement surgeries and received FDA approval on July 1, 2011.

Apixaban was introduced to the US market on December 28, 2012, but received approval for VTE prophylaxis indication following hip and knee replacement surgery on March 18, 2014.

The number of patients having total hip replacement each quarter and the number of prescriptions for each anticoagulant are represented in Figure 4-1 and Figure 4-2 for commercially insured and Medicare populations respectively.

Figure 4-1 Market trend for anticoagulant utilization in commercially insured total hip replacement patients
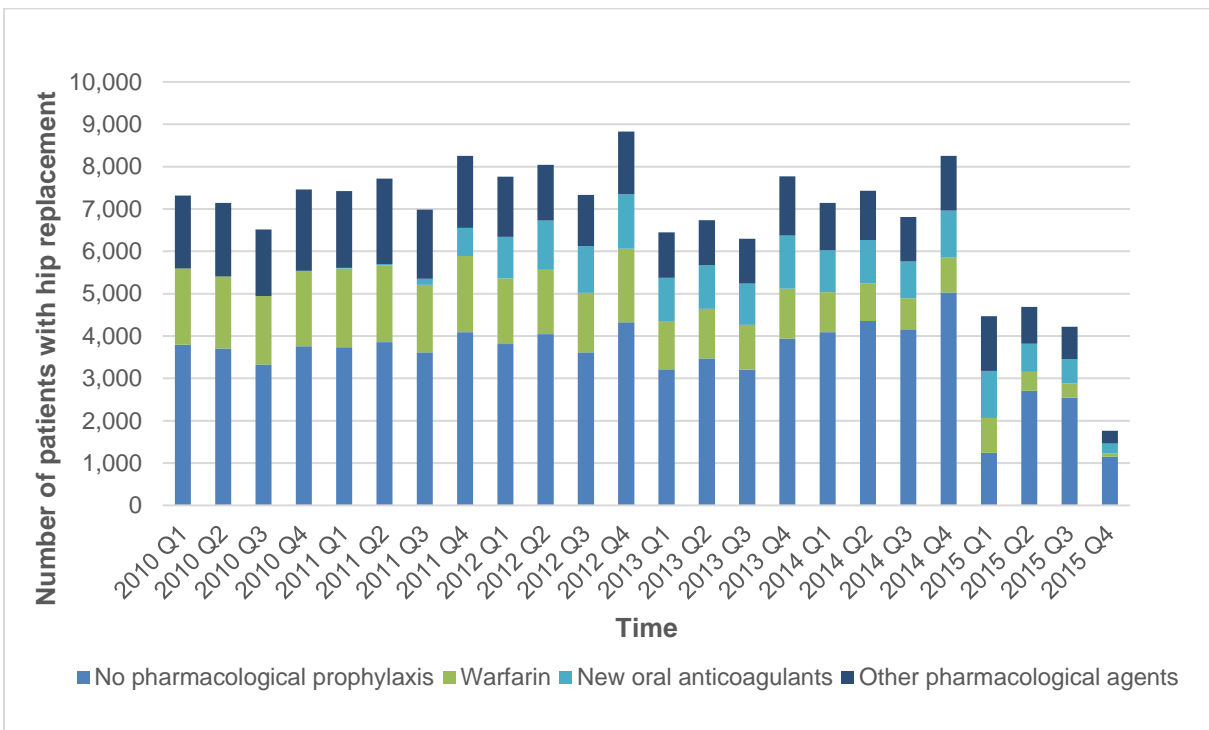
No pharmacological prophylaxis was defined as lack of claims on pharmacological agents in the follow up period; new oral anticoagulants included rivaroxaban, apixaban and dabigatran; other pharmacological agents included heparins, prescription aspirin, and fondaparinux

Figure 4-2 Market trend for anticoagulant utilization in Medicare total hip replacement patients
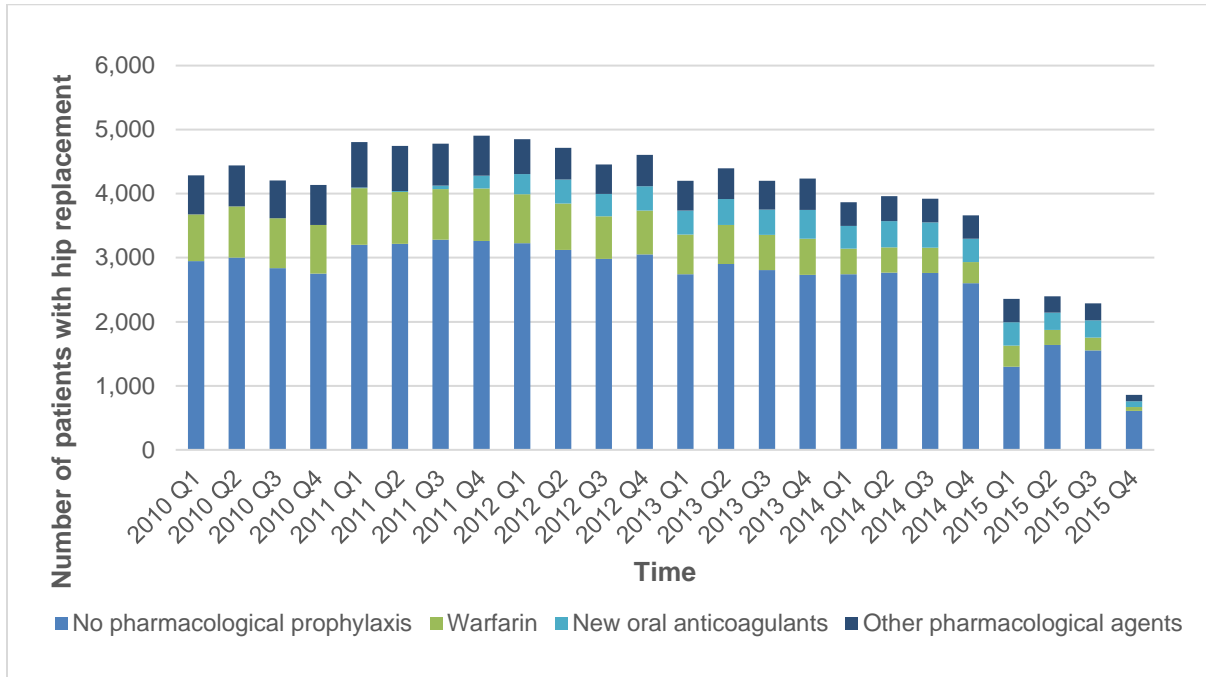
No pharmacological prophylaxis was defined as lack of claims on pharmacological agents in the follow up period; new oral anticoagulants included rivaroxaban, apixaban and dabigatran; other pharmacological agents included heparins, prescription aspirin, and fondaparinux

Figures 4-3 and 4-4 represent the number of patients having total knee replacement each quarter and the number of prescriptions for each anticoagulant in commercially insured and Medicare populations respectively.

Figure 4-3 Market trend for anticoagulant utilization in commercially insured total knee replacement patients
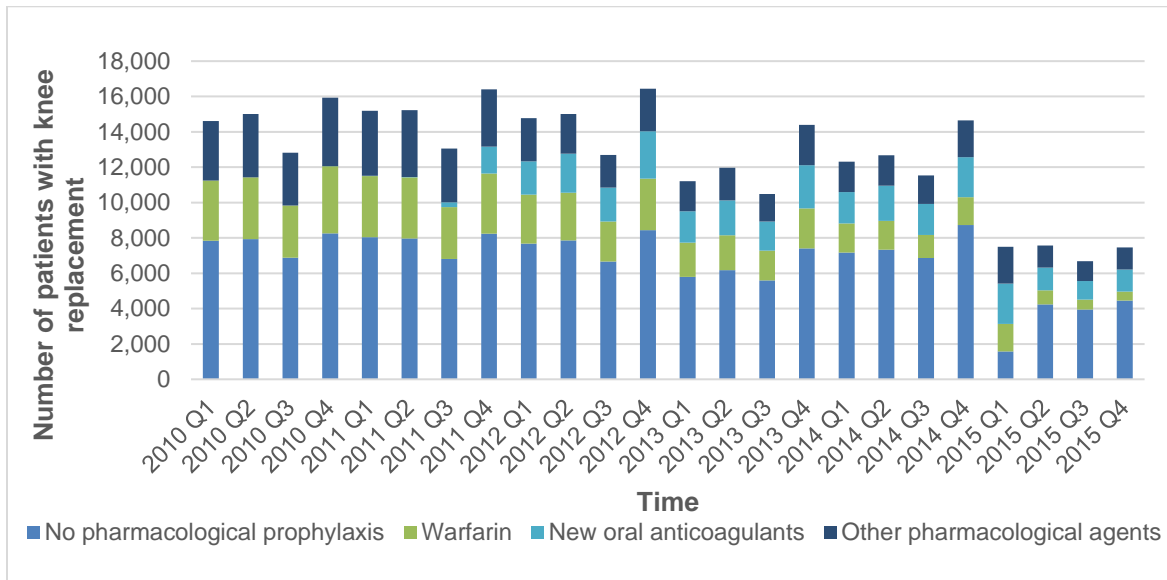
No pharmacological prophylaxis was defined as lack of claims on pharmacological agents in the follow up period; new oral anticoagulants included rivaroxaban, apixaban and dabigatran; other pharmacological agents included heparins, prescription aspirin, and fondaparinux

Figure 4-4 Market trend for anticoagulant utilization in Medicare total knee replacement patients
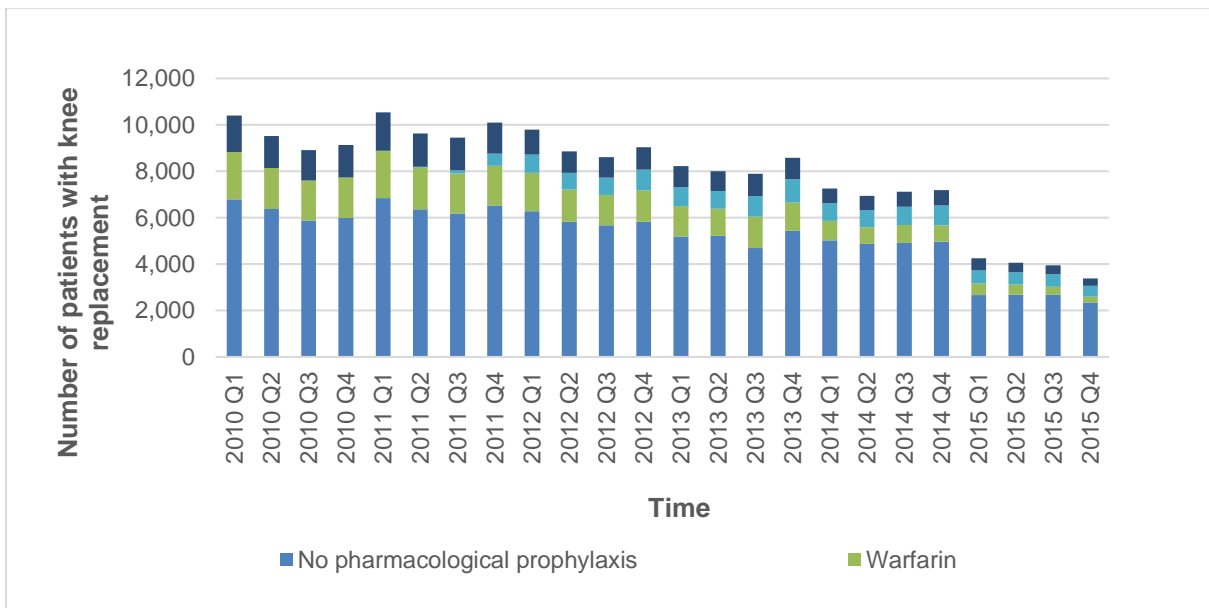
No pharmacological prophylaxis was defined as lack of claims on pharmacological agents in the follow up period; new oral anticoagulants included rivaroxaban, apixaban and dabigatran; other pharmacological agents included heparins, prescription aspirin, and fondaparinux

Market share of different anticoagulants used by total hip replacement patients is represented in Figure 4-5 and by total knee replacement patients in Figure 4-6. We segregated the utilization patterns by type of insurance, commercially insured and Medicare patients.

Figure 4-5 Market share of anticoagulants in total hip replacement patients
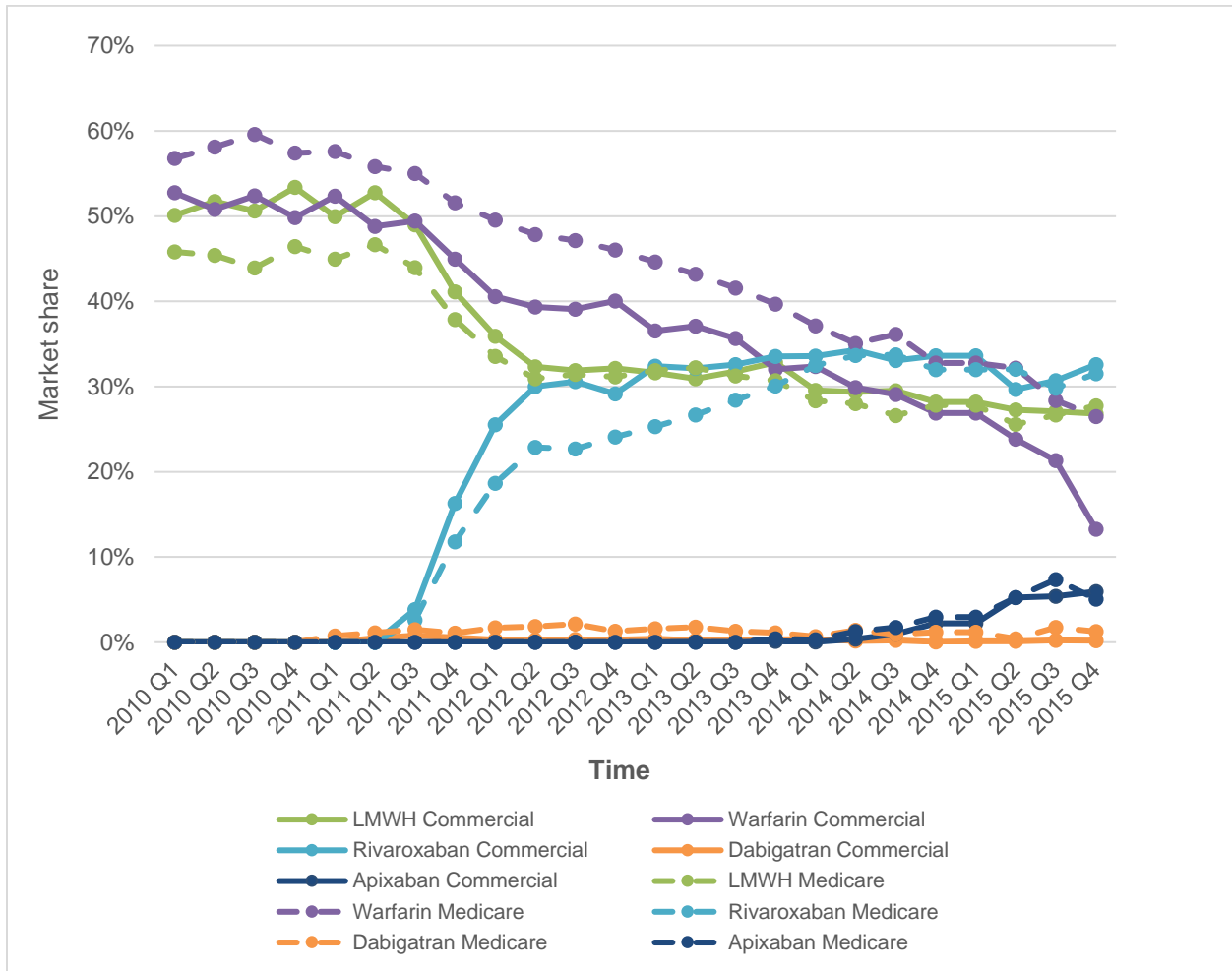
Figure 4-6 Market share of anticoagulants in total knee replacement patients
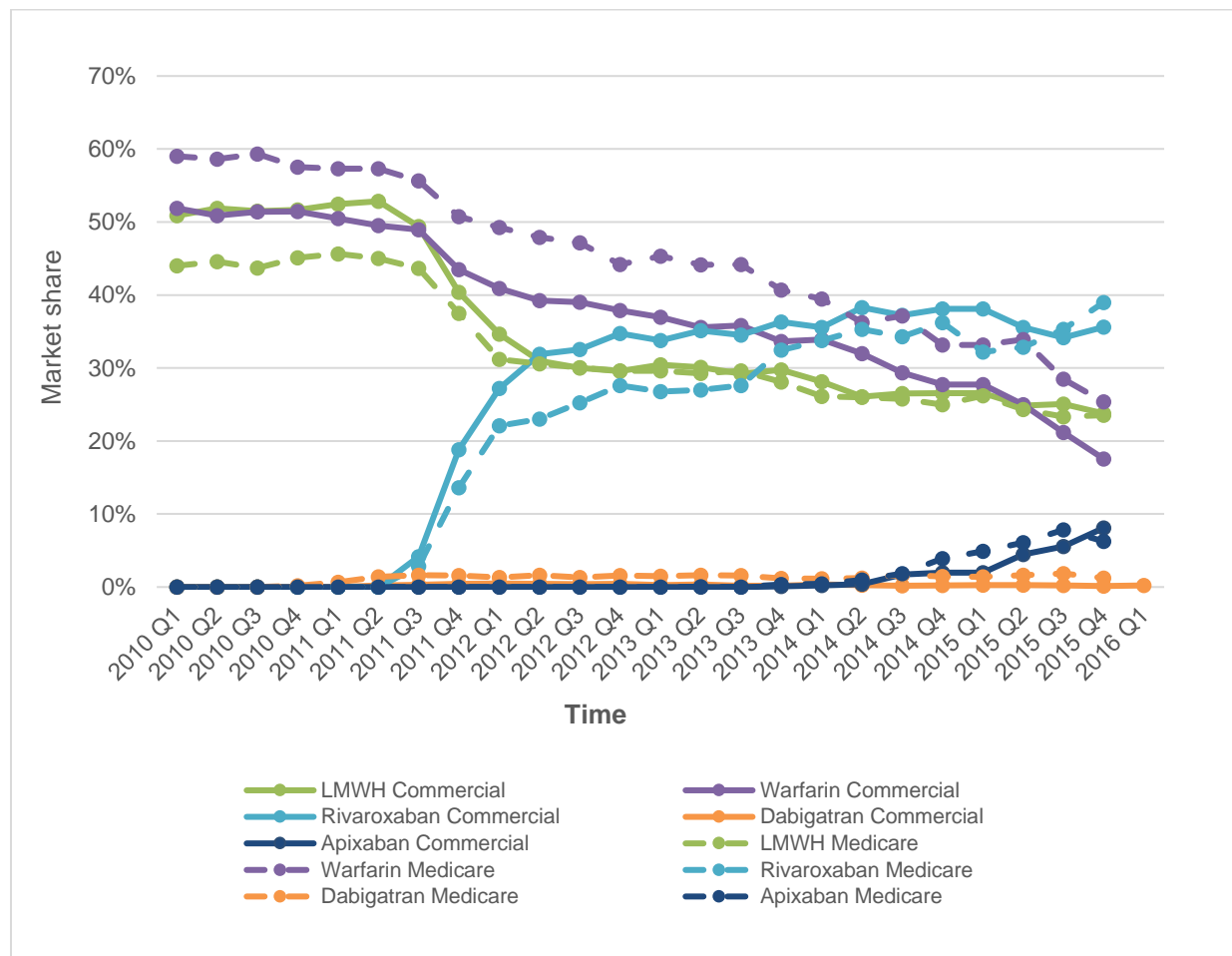
Until the approval of rivaroxaban, warfarin and low molecular weight heparins shared the majority of the market share in both, hip and knee replacement surgery patients. Warfarin utilization was a little higher in the Medicare population compared to commercially insured populations in both, hip and knee replacement surgery patients. With rivaroxaban gaining US FDA approval in July 1, 2011, market share for warfarin and LMWH dropped substantially with a simultaneous increase in the market share for rivaroxaban. By 2nd quarter of 2012, rivaroxaban was utilized by almost a third of patients on anticoagulants after hip and knee replacement surgery.

Dabigatran, which was approved for stroke prevention in atrial fibrillation patients in October, 2010, was also prescribed for an off-label VTE prevention indication in some patients, although its use remained less than 1%. Dabigatran received approval for VTE prophylaxis indication in hip replacement patients on November 23, 2015 and is reflected by a short spike in its use in Medicare patients in 3rd quarter of 2015. Apixaban is the newest addition to the non-Vitamin K oral anticoagulants and received US FDA approval for VTE prophylaxis after hip and knee replacement surgeries in March, 2014. Use of apixaban has steadily increased since 3rd quarter of 2014 which may explain why the proportion of warfarin users seems to further decrease in 2015.

4.2 Aim 1b Predictors of choice of anticoagulant after elective total hip and knee replacements

Due to the insufficient sample size of newer oral anticoagulants- dabigatran and apixaban in our data, we decided to only include rivaroxaban as the newer oral anticoagulant comparator in all the subsequent aims.

4.2.1 Descriptive statistics

A total of 117,393 commercially insured patients and 67,207 Medicare patients were identified as undergoing elective total hip replacement surgery between June 1, 2011 and September 30, 2015. Of these, 12,876 warfarin new users and 10,892 rivaroxaban users were included in the final commercially insured cohort (Figure 4-7) and 7,416 new warfarin users and 4,739 rivaroxaban new users were included in the final Medicare cohort (Figure 4-8).

Figure 4-7 Sample derivation flow chart for commercially insured elective total hip replacement surgery patients

```
┌─────────────────────────────────────────────────────────┐
│ THR diagnosis (using ICD 9 and 10 and CPT codes) recorded on │
│ either inpatient or outpatient service claims between July 1, 2011 to │
│ September 30, 2015 (n=117,393) │
└─────────────────────────────────────────────────────────┘
              │
              │         ┌───────────────────────────────────┐
              │         │ Exclude: Age < 18 (n=151) │
              │         │ Continuous enrollment (n=34,063) │
              ▼         └───────────────────────────────────┘
┌─────────────────────────────────────────────────────────┐
│ Eligibility requirements: Patients >18 yrs with 270 days continuous │
│ enrollment (180 days pre-index + 90 days post-index) in their health │
│ plan (n=83,179) │
└─────────────────────────────────────────────────────────┘
              │
              │         ┌───────────────────────────────────┐
              │         │ Exclude: No use of anticoagulants or use of more │
              │         │ than 1 anticoagulants following surgery (n=57,534) │
              ▼         └───────────────────────────────────┘
┌─────────────────────────────────────────────────────────┐
│ Patients using rivaroxaban or warfarin following surgery (n=25,645) │
└─────────────────────────────────────────────────────────┘
              │
              │         ┌───────────────────────────────────┐
              │         │ Exclude: Prevalent users of rivaroxaban or warfarin │
              │         │ (n=1,877) │
              ▼         └───────────────────────────────────┘
┌─────────────────────────────────────────────────────────┐
│ New users of anticoagulants following surgery │
│ Final sample │
│ 23,768 │
│ (Warfarin users: 12,876 Rivaroxaban users: 10,892) │
└─────────────────────────────────────────────────────────┘
```

Figure 4-8 Sample derivation flow chart for Medicare elective total hip replacement surgery patients

THR diagnosis (using ICD 9 and 10 and CPT codes) recorded on either inpatient or outpatient service claims between July 1, 2011 to September 30, 2015
n=67,207

Exclude: Age < 18 (n=41)
Continuous enrollment (n=17,018)

Eligibility requirements: Patients >18 yrs with 210 days continuous enrollment (180 days pre-index + 90 days post-index) in their health plan (n=50,148)

Exclude: Patients not on warfarin or rivaroxaban or using multiple anticoagulants following surgery (n=35,913)

Patients using rivaroxaban or warfarin following surgery (n=14,235)

Exclude: Prevalent users of rivaroxaban or warfarin (n=2,080)

New users of anticoagulants following surgery
Final sample
12,155
(Warfarin users: 7,416 Rivaroxaban users: 4,739)

A total of 212,808 commercially insured patients and 132,073 Medicare patients were identified as undergoing elective total knee replacement surgery between June 1, 2011 and September 30, 2015. Of these, 24,856 were new users of warfarin and 21,398 were new users of rivaroxaban in the final commercially insured cohort (Figure 4-9) and 15,483 were new users of warfarin and 8,997 were new users of rivaroxaban in the final Medicare cohort (Figure 4-10).

Figure 4-9 Sample derivation flow chart for commercially insured elective total knee replacement surgery patients

```
┌─────────────────────────────────────────────────────┐
│   TKR diagnosis (using ICD 9 and 10 and CPT codes)   │
│   recorded on either inpatient or outpatient service │
│   claims between July 1, 2011 to September 30, 2015   │
│                    n=212,808                          │
└─────────────────────────────────────────────────────┘
        │              ┌──────────────────────────────────┐
        │              │  Exclude: *42 with second surgery │
        │              │         Age < 18 (n=165)          │
        │              │  Continuous enrollment (n=59,571) │
        ▼              └──────────────────────────────────┘
┌─────────────────────────────────────────────────────┐
│ Eligibility requirements: Patients >18 yrs with 270   │
│ days continuous enrollment (180 days pre-index + 90   │
│ days post-index) in their health plan (n=153,072)     │
└─────────────────────────────────────────────────────┘
        │              ┌──────────────────────────────────┐
        │              │ Exclude: No use of anticoagulants │
        │              │  or use of more than 1            │
        │              │  anticoagulants following surgery │
        │              │           (n=103,545)             │
        ▼              └──────────────────────────────────┘
┌─────────────────────────────────────────────────────┐
│ Patients using rivaroxaban or warfarin following      │
│ surgery (n=49,527)                                    │
│                                                       │
└─────────────────────────────────────────────────────┘
        │              ┌──────────────────────────────────┐
        │              │ Exclude: Prevalent users of       │
        │              │ rivaroxaban or warfarin           │
        │              │           (n=3,273)               │
        ▼              └──────────────────────────────────┘
┌─────────────────────────────────────────────────────┐
│ New users of anticoagulants following surgery         │
│                   **Final sample**                    │
│                     **46,254**                        │
│ (Warfarin users: 24,856 Rivaroxaban users: 21,398)    │
└─────────────────────────────────────────────────────┘
```

Figure 4-10 Sample derivation flow chart for Medicare elective total knee replacement surgery patients

```
┌─────────────────────────────────────────────────────────────┐
│ TKR diagnosis (using ICD 9 and 10 and CPT codes) recorded on │
│ either inpatient or outpatient service claims between July 1,│
│                   2011 to September 30, 2015                  │
│                        n=132,073                             │
└─────────────────────────────────────────────────────────────┘
            │          ┌──────────────────────────────────┐
            │          │ Exclude:                         │
            │          │ Age < 18 (n=94)                  │
            │          │ Continuous enrollment (n=33,137) │
            ▼          └──────────────────────────────────┘
┌─────────────────────────────────────────────────────────────┐
│ Eligibility requirements: Patients >18 yrs with 270 days     │
│ continuous enrollment (180 days pre-index + 90 days          │
│ post-index) in their health plan (n=98,842)                  │
└─────────────────────────────────────────────────────────────┘
            │       ┌──────────────────────────────────────┐
            │       │ Exclude: No use of anticoagulants or │
            │       │ use of other anticogulants following │
            │       │ surgery (n=66,463)                   │
            ▼       └──────────────────────────────────────┘
┌─────────────────────────────────────────────────────────────┐
│ Patients using rivaroxaban or warfarin following surgery     │
│ (n=28,379)                                                   │
└─────────────────────────────────────────────────────────────┘
            │       ┌──────────────────────────────────────┐
            │       │ Exclude: Prevalent users of          │
            │       │ rivaroxaban or warfarin (n=3,899)    │
            ▼       └──────────────────────────────────────┘
┌─────────────────────────────────────────────────────────────┐
│ New users of anticogulants following surgery                 │
│                     Final sample                             │
│                        24,480                                │
│ (Warfarin users: 15,483 Rivaroxaban users: 8,997)           │
└─────────────────────────────────────────────────────────────┘
```

4.2.2 Baseline characteristics

     Patient sociodemographic characteristics among new users of warfarin and rivaroxaban after an elective hip replacement surgery are shown in table 4-1, including the absolute standardized differences for comparing baseline characteristics between the two groups of anticoagulant users. Comparison of the baseline variables suggested that new users of rivaroxaban after total hip replacement were more likely to live in the southern region (43.08% vs 32.15%, absolute standardized difference 0.29 in the commercial population and 32.39% vs 23.49%, absolute standardized difference 0.23 in the Medicare population) and were more likely to have surgeries in the later years (30.25% vs 24.55% in 2013, 24.65% vs 15.9% in 2014 and 9.43% vs 5.5% in 2015, standardized difference 0.50 in commercially insured population and 29.54% vs 25.05% in 2013, 26.23% vs 14.74% in 2014 and 11.67% vs 5.77% in 2015, standardized difference 0.58 in Medicare population).

Table 4-1 Baseline characteristics of patients with elective total hip replacement surgery

Baseline Characteristic	Commercially insured			Medicare insured		
	Warfarin N=12,876 N (%)	Rivaroxaban N=10,892 N (%)	Standardized difference+	Warfarin N=7,416 N (%)	Rivaroxaban N=4,739 N (%)	Standardized difference+
Predisposing Characteristics						
Patient Age (Mean (SD))	55.98 (6.92)	56.04 (6.81)	0.01	74.27 (6.54)	73.70 (6.44)	-0.09
Female	6,568 (51.01)	5,380 (49.39)	-0.02	4,4452 (60.03)	2,766 (58.37)	-0.09
Region Northeast	2,742 (21.3)	1,357 (12.46)	0.29	1,861 (25.09)	866 (18.27)	0.23
North Central	3,737 (29.02)	2,942 (27.01)		2,557 (34.48)	1,618 (34.14)	
South	4,139 (32.15)	4,692 (43.08)		1,742 (23.49)	1,535 (32.39)	
West	2,176 (16.9)	1,862 (17.10)		1,229 (16.57)	706 (14.9)	

Unknown	82 (0.64)	39 (0.36)		27 (0.36)	14 (.3)	
MSA	10,992 (85.37)	9,251 (84.93)	-0.01	6,204 (83.66)	4,073 (85.95)	0.06
Time of Surgery			0.50			0.58
2011	2,707 (21.02)	684 (6.28)		1,499 (20.21)	231 (4.87)	
2012	4,246 (32.98)	3,201 (29.39)		2,538 (34.22)	1,312 (27.69)	
2013	3,161 (24.55)	3,295 (30.25)		1,858 (25.05)	1,400 (29.54)	
2014	2,047 (15.9)	2,685 (24.65)		1,093 (14.74)	1,243 (26.23)	
2015	715 (5.5)	1,027 (9.43)		428 (5.77)	553 (11.67)	
Enabling Resources						
						0.10
Insurance plan			0.13			
Basic Medical	458 (3.56)	311 (2.86)		93 (1.25)	47 (0.99)	
Comprehensive	490 (3.81)	414 (3.80)		2,657 (35.83)	1,733 (36.57)	
EPO	133 (1.03)	98 (0.90)		13 (0.18)	13 (0.27)	
HMO	1,408 (10.94)	925 (8.49)		888 (11.97)	437 (9.22)	
POS	937 (7.28)	671 (6.16)		249 (3.36)	193 (4.07)	
PPO	8,031 (62.37)	7,135 (65.51)		3,449 (46.51)	2,273 (47.96)	
POS with capitation	93 (0.72)	35 (0.32)		18 (0.24)	9 (0.19)	
CDHP	866 (6.73)	849 (7.79)		40 (0.54)	27 (0.57)	
HDHP	460 (3.57)	454 (4.17)		9 (0.12)	7 (0.15)	
Prescription benefits generosity			0.05			
No/poor coverage (> 0.80 and ≤ 1)	1,633 (12.68)	1,359 (12.48)		494 (6.66)	323 (6.82)	0.12
Fair coverage (> 0.20 and ≤ 0.80)	6,928 (53.81)	5,661 (51.97)		4,936 (66.56)	2,900 (61.19)	
Good coverage (≥ 0 and ≤ 0.20)	3,35 (26.06)	3,073 (21.28)		1,815 (24.47)	1,381 (29.14)	
Unknown	960 (7.46)	799 (7.34)		171 (2.31)	135 (2.85)	
Need characteristics						
DVT	104 (0.81)	63 (0.58)	-0.03	117 (1.58)	40 (0.84)	-0.07
PE	104 (0.81)	61 (0.56)	-0.03	139 (1.87)	61 (1.29)	-.0.05
DVT and PE	39 (0.30)	20 (0.18)	-0.02	51 (0.69)	16 (0.34)	-0.05
Ischemic Stroke	164 (1.27)	142 (1.30)	0.00	423 (5.70)	282 (5.95)	0.01
Myocardial Infarction	114 (0.89)	94 (0.86)	0.00	150 (2.02)	97 (2.05)	0.00
Major Bleeding	482 (3.74)	434 (3.98)	0.01	447 (6.03)	274 (5.78)	-0.01
Charlson Comorbidity Index (CCI)			0.03			0.02
0	10,309 (80.06)	8,796 (80.76)		4,775 (64.39)	3,104 (65.50)	
1	1,419 (11.02)	1,198 (11.0)		1,235 (16.65)	772 (16.29)	

2-4	1,040 (8.08)	832 (7.64)		1,293 (17.44)	794 (16.75)	
≥5	108 (0.84)	66 (0.61)		113 (1.52)	69 (1.46)	
Atrial fibrillation	241 (1.87)	157 (1.44)	-0.03	515 (6.94)	230 (4.85)	-0.09
Cardiovascular Diseases	1,002 (7.78)	870 (7.99)	0.01	1,875 (25.28)	1,132 (23.89)	-0.03
Congestive Heart Failure	188 (1.46)	158 (1.45)	0.00	357 (4.81)	188 (3.97)	-0.04
Hepatic Failure	267 (2.07)	242 (2.22)	0.01	129 (1.74)	86 (1.81)	0.01
Renal Impairment	288 (2.24)	185 (1.7)	-0.04	479 (6.46)	246 (5.19)	0.05
Peptic Ulcer	20 (0.16)	14 (0.13)	-0.01	24 (0.32)	9 (0.19)	-0.03
Gastritis	87 (0.68)	87 (0.80)	0.01	84 (1.13)	61 (1.29)	0.01
Duodeniitis	21 (0.16)	22 (0.2)	0.01	19 (0.26)	15 (0.32)	0.01
Esophagitis	43 (0.33)	50 (0.46)	0.02	37 (0.50)	29 (0.61)	0.02
Hyperlipidemia	2,891 (22.45)	2,544 (23.36)	0.02	2,247 (30.3)	1,525 (32.18)	0.04
Hypertension	5,434 (42.2)	4,843 (44.46)	0.05	4,637 (62.53)	2,983 (62.95)	0.01
Diabetes Mellitus	1,528 (11.87)	1,257 (11.54)	-0.01	1,379 (18.59)	828 (17.47)	-0.03
Anemia	1,013 (7.87)	858 (7.88)	0.00	787 (10.61)	480 (10.13)	-0.02
Sleep Apnea	864 (6.71)	736 (6.76)	0.00	457 (6.16)	299 (6.31)	-0.01
Cancer	578 (4.49)	442 (4.06)	-0.02	783 (10.56)	502 (10.59)	0.00
Dementia	3 (0.02)	1 (0.01)	-0.01	17 (0.23)	15 (0.32)	0.02
Obesity	1,066 (8.28)	887 (8.14)	0.00	382 (5.15)	267 (5.63)	0.02
Number of hospitalizations	460 (3.57)	380 (3.49)	0.00	458 (6.18)	285 (6.01)	-0.01
Outpatient Surgery Setting	251 (1.95)	205 (1.88)	0.00	306 (4.13)	190 (4.01	0.01
Antiplatelet Therapy	266 (2.07)	179 (1.64)	-0.03	453 (6.11)	285 (6.01)	0.00
Gastroprotective Agents	2,598 (20.18)	2,114 (19.41)	-0.02	2,013 (27.14)	1,220 (25.74)	-0.03
Antiarrhythmics	86 (0.67)	61 (0.56)	-0.01	159 (2.14)	98 (2.07)	-0.01
Rate Control Therapy	3,447 (26.77)	2,769 (25.42)	-0.03	3,670 (49.49)	2,119 (46.40)	-0.06
Hormone Use	153 (1.19)	117 (1.07)	-0.01	2 (0.03)	0 (0.00)	-0.02
Statins	3,679 (28.57)	3,005 (27.59)	-0.02	3,588 (48.38)	2,214 (46.72)	-0.03
ACE Inhibitors	4,467 (34.69)	3,868 (35.51)	0.02	3,679 (49.61)	2,320 (48.96)	-0.01

[†]Standardized difference is the difference in means or proportions divided by standard error; imbalance is defined as absolute value greater than 0.20[112] (≥0.2 - <0.5: small effect size; ≥0.5 - <0.8: medium effect size; and ≥0.8: large effect size)

Table 4-2 shows patient sociodemographic characteristics among new users of warfarin and rivaroxaban after an elective knee replacement surgery, including the absolute standardized differences for each characteristic category between the two anticoagulants. Comparison of the baseline variables suggested that new users of rivaroxaban after total knee replacement were more likely to live in the southern region (48.54% vs 34.23%, absolute standardized difference 0.37 in the commercial population and 40.19% vs 26.08%, absolute standardized difference 0.36 in the Medicare population) and were more likely to have surgeries in the later years (28.61% vs 23.91% in 2013, 25.16% vs 16.54% in 2014 and 10.01% vs 6.02% in 2015, standardized difference 0.47 in commercially insured population and 30.50% vs 25.56% in 2013, 25.29% vs 14.68% in 2014 and 10.16% vs 5.25% in 2015, standardized difference 0.55 in Medicare population).

Table 4-2 Baseline characteristics of patients with elective total knee replacement surgery

Baseline Characteristic	Commercially insured			Medicare insured		
	Warfarin N=24,856 N (%)	Rivaroxaban N=21,398 N (%)	Standardized difference[+]	Warfarin N=15,483 N (%)	Rivaroxaban N=8,997 N (%)	Standardized difference[+]
Predisposing Characteristics						
Patient Age (Mean (SD))	57.73 (5.28)	57.35 (5.52)	-0.07	73.45 (5.99)	72.70 (5.78)	-0.13
Female	15,206 (61.18)	12,888 (60.23)	-0.07	9,536 (61.59)	5,310 (59.02)	-0.13
Region Northeast	4,963 (19.97)	1,995 (9.32)	0.37	3,645 (23.54)	1,169 (12.99)	0.36
North Central	7,645 (30.76)	5,702 (26.65)		5,554 (35.87)	3,000 (33.34)	
South	8,507 (34.23)	10,386 (48.54)		4,038 (26.08)	3,616 (40.19)	
West	3,563 (14.33)	3,230 (15.09)		2,201 (14.22)	1,187 (13.19)	
Unknown	178 (0.72)	85 (0.4)		45 (0.29)	25 (0.28)	
MSA	20,618 (82.95)	17,443 (81.52)	-0.04	13,026 (84.13)	7,500 (83.36)	-0.02
Time of Surgery			0.47			0.55
2011	5,327 (21.43)	1,497 (7.00)		3,183 (20.56)	503 (5.59)	
2012	7,981 (32.11)	6,254 (29.23)		5,527 (33.95)	2,561 (28.47)	
2013	5,942 (23.91)	6,121 (28.61)		3,957 (25.56)	2,744 (30.50)	
2014	4,110 (16.54)	5,384 (25.16)		2,273 (14.68)	2,275 (25.29)	
2015	1,496 (6.02)	2,142 (10.01)		813 (5.25)	914 (10.16)	
Enabling Resources						
Insurance plan			0.11			0.13
Basic Medical	980 (3.94)	636 (2.97)		199 (1.29)	96 (1.07)	
Comprehensive	1,152 (4.63)	946 (4.42)		5,868 (37.90)	3,689 (41.00)	
EPO	239 (0.96)	182 (0.85)		19 (0.12)	16 (0.18)	
HMO	2,542 (10.23)	1,677 (7.84)		1,652 (10.67)	659 (7.32)	
POS	1,797 (7.23)	1,475 (6.89)		610 (3.94)	409 (4.55)	
PPO	15,663 (52.76)	14,026 (47.24)		7,033 (45.42)	4,042 (44.93)	
POS with capitation	151 (0.61)	79 (0.37)		29 (0.19)	14 (0.16)	
CDHP	1,592 (6.40)	1,631 (7.62)		59 (0.38)	60 (0.67)	
HDHP	740 (2.98)	746 (3.49)		14 (0.09)	12 (0.13)	

Prescription benefits generosity			0.06			
No/poor coverage (> 0.80 and ≤ 1)	2,701 (10.87)	2,385 (11.15)		1,040 (6.72)	603 (6.70)	0.12
Fair coverage (> 0.20 and ≤ 0.80)	14,274 (57.43)	11,757 (54.94)		10,239 (66.13)	5,480 (60.91)	
Good coverage (≥ 0 and ≤ 0.20)	6,457 (25.98)	6,114 (28.57)		3,802 (24.56)	2,679 (25.68)	
Unknown	1,424 (5.73)	1,142 (5.34)		402 (2.60)	235 (2.61)	
Need characteristics						
DVT	249 (1.00)	137 (0.64)	-0.04	258 (1.67)	68 (0.76)	-0.08
PE	315 (1.27)	143 (0.67)	-0.06	244 (1.58)	94 (1.04)	-0.05
DVT and PE	88 (0.35)	36 (0.17)	-0.04	78 (0.50)	17 (0.19)	-0.05
Ischemic Stroke	344 (1.38)	298 (1.39)	0.00	786 (5.08)	445 (4.95)	-0.01
Myocardial Infarction	189 (0.76)	155 (0.72)	0.00	283 (1.83)	149 (1.66)	-0.01
Major Bleeding	1,107 (4.45)	940 (4.39)	0.00	855 (5.52)	463 (5.15)	-0.02
Charlson Comorbidity Index (CCI)			0.03			0.05
0	19,364 (77.90)	16,932 (79.13)		10,236 (66.11)	6,120 (68.02)	
1	3,289 (13.23)	2,700 (12.62)		2,535 (16.37)	1,472 (16.36)	
2-4	2,104 (8.46)	1,688 (7.89)		2,586 (16.70)	1,341 (14.90)	
≥5	99 (0.40)	78 (0.36)		126 (0.81)	64 (0.71)	
Atrial fibrillation	476 (1.92)	356 (1.66)	-0.02	927 (5.99)	380 (4.22)	-0.08
Cardiovascular Diseases	2,257 (9.08)	1,857 (8.68)	-0.01	3,845 (24.83)	2,006 (22.30)	-0.06
Congestive Heart Failure	372 (1.50)	288 (1.35)	-0.01	650 (4.20)	272 (3.02)	-0.06
Hepatic Failure	609 (2.45)	520 (2.43)	0.00	263 (1.70)	153 (1.17)	0.00
Renal Impairment	539 (2.17)	381 (1.78)	-0.03	863 (5.57)	425 (4.72)	-0.04
Peptic Ulcer	27 (0.11)	22 (0.10)	0.00	21 (0.14)	22 (0.24)	0.03
Gastritis	236 (0.95)	218 (1.02)	0.01	171 (1.10)	107 (1.19)	0.01
Duodeniitis	32 (0.13)	29 (0.14)	0.00	25 (0.16)	14 (0.16)	0.00
Esophagitis	144 (0.58)	99 (0.46)	-0.02	106 (0.68)	56 (0.62)	-0.01
Hyperlipidemia	6,437 (25.90)	5,516 (25.78)	0.00	4,761 (30.75)	2,736 (30.41)	-0.01
Hypertension	12,556 (50.51)	11,202 (52.35)	0.04	10,092 (65.18)	5,845 (64.97)	0.00
Diabetes Mellitus	4,544 (18.28)	3,797 (17.74)	-0.01	3,540 (22.86)	2,051 (22.80)	0.00
Anemia	2,053 (8.26)	1,699 (7.94)	-0.01	1,515 (9.78)	816 (9.07)	-0.02
Sleep Apnea	2,529 (10.17)	2,212 (10.34)	0.01	1,217 (7.86)	743 (8.25)	0.02
Cancer	1,021 (4.11)	801 (3.74)	-0.01	1,480 (9.56)	822 (9.14)	-0.01
Dementia	5 (0.02)	5 (0.02)	0.00	29 (0.19)	7 (0.08)	-0.03
Obesity	2,918 (11.74)	2,499 (11.68)	0.00	1,039 (6.71)	637 (7.08)	0.01

Number of hospitalizations	763 (3.07)	646 (3.02)	0.00	697 (4.50)	335 (3.72)	-0.04
Outpatient Surgery Setting	518 (2.08)	389 (1.82)	0.02	587 (3.79)	348 (1.87)	0.00
Antiplatelet Therapy	583 (2.35)	404 (1.89)	-0.03	946 (6.11)	506 (5.62)	0.02
Gastroprotective Agents	6,376 (25.65)	5,451 (25.47)	0.00	4,678 (30.21)	2,687 (29.87)	-0.01
Antiarrhythmics	205 (0.82)	154 (0.72)	-0.01	351 (2.27)	167 (1.86)	-0.03
Rate Control Therapy	7,924 (31.88)	6,637 (31.02)	-0.01	7,993 (51.62)	4,502 (50.04)	-0.03
Hormone Use	143 (0.58)	145 (0.68)	0.01	2 (0.01)	0 (0.00)	-0.02
Statins	8,473 (32.09)	7,089 (31.13)	-0.02	7,890 (50.96)	4,558 (50.66)	-0.01
ACE Inhibitors	10,544 (42.42)	9,281 (43.37)	0.02	8,307 (53.65)	4,839 (53.78)	0.00

+Standardized difference is the difference in means or proportions divided by standard error; imbalance is defined as absolute value greater than 0.20 (small effect size)

4.2.3 Multivariate analyses of anticoagulant selection

The results of our multivariate model that evaluated the influence of various baseline characteristics on the choice of anticoagulant treatment in total hip replacement patients are presented in table 4-3. Warfarin was used as the referent group for all analyses. In the commercial cohort, sex, geographic region and time of surgery were found to be significant predisposing predictors of choice of anticoagulant therapy. Females had lower odds of being prescribed rivaroxaban than males (OR 0.92, 95% CI 0.87-0.97). Patients in the western region had significantly higher odds of rivaroxaban prescription compared to patients in northeast (OR 2.34, 95% CI 2.16-2.54). Patients having surgery in 2015 had higher odds of being prescribed rivaroxaban than ones having a surgery in 2011 (OR 5.86, 95% CI 5.14-6.67). In the Medicare cohort, age, geographic region and time of surgery were found to be significant predisposing predictors. Each year increase in age reduced the odds of rivaroxaban initiation by 1.3% (OR 0.99, 95% CI 0.98-0.99). Patients in the western region had

significantly higher odds of rivaroxaban prescription compared to patients in northeast (OR 1.95, 95% CI 1.74-2.18). Patients having surgery in 2015 had higher odds of being prescribed rivaroxaban than ones having a surgery in 2011 (OR 9.09, 95% CI 7.50-11.02).

In the commercial cohort, type of health plan was found to a significant enabling variable in the choice of anticoagulant, with patients with point of service with capitation plan having the lowest odds of rivaroxaban initiation (OR 0.40, 95% CI 0.26-0.62). Comorbidities such as cardiovascular diseases, renal impairment, and hypertension also significantly affected the odds of rivaroxaban initiation in these patients. Patients with a history of cardiovascular diseases had higher odds of being prescribed rivaroxaban than those without (OR 1.14, 95% CI 1.01-1.28) and those with renal impairment had lower odds of rivaroxaban prescription (OR 0.71, 95% CI 0.58-0.87). Patients with hypertension also had higher odds of being initiated on rivaroxaban (OR 1.13, 95% CI1.05-1.21).

In the Medicare population, patients with previous deep vein thrombosis (OR 0.51, 95% CI 0.31-0.83) or pulmonary embolism (OR 0.66, 95% CI 0.45-0.97) or atrial fibrillation (OR 0.65, 95% CI 0.54-0.78) had lower odds of being prescribed rivaroxaban. Patients with renal impairment also had lower odds of rivaroxaban initiation than ones without (OR 0.78, 95% CI 0.64-0.94). Compared to no history of use in the pre-index period, use of antiplatelet agents and rate control agents decreased the odds of rivaroxaban initiation in the commercial cohort by 26% (OR 0.74, 95% CI 0.60-0.92) and 9% (OR 0.91, 95% CI 0.85-0.97) respectively.

Table 4-3 Odds of receiving rivaroxaban versus warfarin in total hip replacement patients

Patient Characteristics	Commercially insured OR (95% CI)	Medicare OR (95% CI)
Predisposing Characteristics		
Age at the time of surgery	1.00 (1.00-1.00)	0.99* (0.98-0.99)
Sex		
Male	1	1
Female	0.92* (0.87-0.97)	0.94 (0.87-1.02)
Geographic Region		
Northeast	1	1
North central	1.64* (1.50 -1.79)	1.30* (1.17-1.45)
West	2.34* (2.16-2.54)	1.95* (1.74-2.18)
South	1.81* (1.64 -1.99)	1.38* (1.21-1.58)
Metropolitan Statistical Area		
MSA	1.02 (0.94-1.10)	1.21* (1.09-1.35)
Non MSA	1	1
Time of surgery		
2011	1	1
2012	3.01* (2.74-3.32)	3.47* (2.97-4.05)
2013	4.25* (3.85-4.69)	5.07* (4.34-5.94)
2014	5.37* (4.84-5.95)	7.78* (6.60-9.18)
2015	5.86* (5.14-6.67)	9.09* (7.50-11.02)
Enabling Resources		
Type of health benefit plan		
Basic Medical	1	1
Comprehensive	0.77* (0.62-0.95)	1.00 (0.87-1.47)
EPO	0.77 (0.56-1.06)	1.36 (0.55-3.35)
HMO	0.59* (0.49-0.71)	0.84 (0.57-1.24)
POS	0.67* (0.55-0.80)	1.03 (0.68-1.57)
PPO	0.78* (0.66-0.92)	1.01 (0.67-1.47)
POS with capitation	0.40* (0.26-0.62)	0.66 (0.27-1.64)
CDHP	0.73* (0.61-0.89)	0.68 (0.36-1.26)
HDHP	0.80* (0.65-0.99)	0.61 (0.21-1.81)
Prescription benefits generosity		
No/poor coverage	1	1
Fair coverage	1.00 (0.92-1.08)	0.90 (0.70-1.05)
Good coverage	0.97 (0.88 -1.06)	0.94 (0.79-1.11)
Need Characteristics		
Past clinical events		

Previous VTE events		
DVT	0.70 (0.47-1.04)	0.51* (0.31-0.83)
PE	0.72 (0.48-1.09)	0.66* (0.45-0.97)
DVT and PE	1.12 (0.50-2.49)	1.35 (0.58-3.15)
Previous ischemic stroke	1.14 (0.89-1.45)	1.10 (0.93-1.30)
Previous myocardial infarction	0.96 (0.71-1.30)	1.04 (0.78-1.38)
Previous major bleeding	1.07 (0.93 -1.23)	0.98 (0.82-1.15)
Comorbidities		
Charlson Comorbidity Index (CCI)		
0	1	1
1	1.03 (0.94-1.12)	1.01 (0.90-1.13)
2-4	0.85 (0.70-1.02)	1.05 (0.84-1.31)
≥5	0.64* (0.44-0.95)	1.09 (0.70-1.69)
Atrial Fibrillation	0.82 (0.65-1.04)	0.65* (0.54-0.78)
Cardiovascular Diseases	1.14 (1.01-1.28)	0.99 (0.89-1.09)
Congestive Heart Failure	1.25 (0.95-1.66)	0.87 (0.67-1.13)
Hepatic failure	1.21 (0.96-1.51)	1.02 (0.74-1.42)
Renal Impairment	0.71* (0.58-0.87)	0.78* (0.64-0.94)
Peptic Ulcer	0.85 (0.42-1.76)	0.55 (0.24-1.23)
Gastritis	1.15 (0.83-1.59)	1.20 (0.83-1.71)
Duodeniitis	1.23 (0.64-2.36)	0.97 (0.47-2.01)
Esophagitis	1.50 (0.97-2.33)	1.27 (0.75-2.15)
Hyperlipidemia	1.04 (0.97-1.12)	1.02 (0.93-1.11)
Hypertension	1.13* (1.05-1.21)	1.07 (0.98-1.17)
Diabetes Mellitus	0.98 (0.90-1.07)	0.92 (0.83-1.03)
Anemia	1.01 (0.91-1.12)	0.94 (0.82-1.17)
Sleep Apnea	0.97 (0.87-1.08)	0.98 (0.84-1.16)
Cancer	1.12 (0.90-1.41)	0.96 (0.76-1.22)
Dementia	0.28 (0.03-2.77)	1.55 (0.73-3.29)
Obesity	0.91 (0.83-1.01)	0.94 (0.79-1.12)
Previous Hospitalization		
No hospitalization	1	1
At least 1 hospitalization	1.11 (0.95-1.29)	1.15 (0.97-1.37)
Outpatient Surgery Setting		
Inpatient	1	1
Outpatient	0.91 (0.75-1.10)	1.07 (0.87-1.30)
Concomitant therapy		

Antiplatelet Therapy	0.74[*] (0.60-0.92)	1.08 (0.91-1.28)
Gastroprotective Agents	0.95 (0.88-1.02)	0.94 (0.86-1.03)
Antiarrhythmics	0.97 (0.67-1.40)	1.29 (0.97-1.72)
Rate Control Therapy	0.91[*] (0.85-0.97)	0.96 (0.88-1.04)
Hormone Use	0.92 (0.71-1.19)	-
Statins	0.94 (0.88-1.01)	0.95 (0.87-1.03)
ACE Inhibitors	0.97 (0.90-1.04)	0.99 (0.91-1.08)

[*] denotes a significant statistical difference

Table 4-4 presents the results of our logistic regression model that evaluated the influence of various predictors on the type of anticoagulant initiated after a total knee replacement. The predisposing variables patient age at the time of surgery, sex, geographic region, and year of surgery were found to be significant predictors of type of anticoagulant initiated. Each year increase in age reduced the odds of rivaroxaban initiation by 1.6% in the commercial cohort (OR 0.98, 95% CI 0.98-0.99) and by 2.6% in the Medicare cohort (OR 0.98, 95% CI 0.97-0.98). Females were less likely to be initiated on rivaroxaban compared to males (OR 0.94, 95% CI 0.90-0.93 in the commercial cohort and OR 0.89, 95% CI 0.84-0.94 in the Medicare cohort). Patients in the western region had significantly higher likelihood of rivaroxaban prescription compared to patients in northeast (OR 3.16, 95% CI 2.97-3.37 in the commercial cohort and OR 2.88, 95% CI 2.65-3.13 in the Medicare cohort). Patients having surgery in 2015 were more likely to be prescribed rivaroxaban than ones having a surgery in 2011 (OR 5.48, 95% CI 5.01-5.99 in commercially insured patients and OR 7.83, 95% CI 6.82-8.99 in Medicare patients). In the commercial cohort, type of health plan was found to a significant enabling variable in the choice of anticoagulant, with patients with point of service with capitation plan having the lowest likelihood of rivaroxaban initiation (OR 0.52, 95% CI 0.38-0.71).

Several of the need variables were found to be associated with the choice of anticoagulant. Compared to no previous history of deep vein thrombosis in the pre-index period, deep vein thrombosis decreased the odds of rivaroxaban initiation by 29% in the commercial cohort (OR 0.71, 95% CI 0.55-0.92) and 49% in the Medicare cohort (OR 0.51, 95% CI 0.37-0.70). Also, patients with pulmonary embolism in the commercial cohort had lower odds of rivaroxaban initiation (OR 0.53, 95% CI 0.42-0.67). In the Medicare cohort, patients with atrial fibrillation or cardiovascular disease or hyperlipidemia had lower odds of rivaroxaban initiation than those without (OR 0.72, 95% CI 0.63-0.83, OR 0.92, 95% CI 0.85-0.99, and OR 0.94, 95% CI 0.88-0.99 respectively). Also, patients with renal impairment in both the cohorts had a lower likelihood of rivaroxaban initiation (OR 0.79, 95% CI 0.68-0.92 in the commercial cohort and OR 0.85, 95% CI 0.74-0.98 in the Medicare cohort). In the commercial cohort, patients that had the knee replacement surgery performed in an outpatient setting had 16% lower odds (OR 0.84, 95% CI 0.73-0.97) of rivaroxaban initiation than those who had an inpatient surgery. Also, compared to no use of antiplatelet agents in the pre-index period, use of antiplatelet agents decreased the odds of rivaroxaban initiation by 17% (OR 0.83, 95% CI 0.72-0.96).

Table 4-4 Odds of receiving rivaroxaban versus warfarin in total knee replacement patients

Patient Characteristics	Commercially insured OR (95% CI)	Medicare OR (95% CI)
Predisposing Characteristics		
Age at the time of surgery	0.98* (0.98-0.99)	0.98* (0.97-0.98)
Sex		
Male	1	1
Female	0.94* (0.90-0.93)	0.89* (0.84-0.94)
Geographic Region		
Northeast	1	1
North central	1.95* (1.83-2.09)	1.63* (1.50-1.78)
West	3.16* (2.97-3.37)	2.88* (2.65-3.13)
South	2.43* (2.26-2.62)	1.93* (1.74-2.14)
Metropolitan Statistical Area		
MSA	0.95 (0.91-1.00)	0.98 (0.91-1.06)
Non MSA	1	1
Time of surgery		
2011	1	1
2012	2.89* (2.70-3.09)	3.17* (2.85-3.53)
2013	3.79* (3.54-4.06)	4.61* (4.14-5.14)
2014	4.91* (4.57-5.28)	6.95* (6.20-7.80)
2015	5.48* (5.01-6.00)	7.83* (6.82-8.99)
Enabling Resources		
Type of health benefit plan		
Basic Medical	1	1
Comprehensive	0.71* (0.61-0.82)	1.07 (0.83-1.39)
EPO	0.69* (0.55-0.87)	1.35 (0.63-2.88)
HMO	0.54* (0.48-0.62)	0.78 (0.59-1.03)
POS	0.70* (0.61-0.79)	0.95 (0.71-1.27)
PPO	0.70* (0.63-0.79)	0.98 (0.76-1.28)
POS with capitation	0.52* (0.38-0.71)	0.66 (0.32-1.35)
CDHP	0.69* (0.60-0.79)	1.17 (0.75-1.85)
HDHP	0.74* (0.63-0.86)	0.86 (0.37-2.01)
Prescription benefits generosity		
No/poor coverage	1	1
Fair coverage	0.96 (0.90-1.02)	0.88* (0.79-0.99)
Good coverage	0.96 (0.90-1.03)	0.93 (0.83-1.05)
Need Characteristics		
Past clinical events		
Previous VTE events		
DVT	0.71* (0.55-0.92)	0.51* (0.37-0.70)
PE	0.53* (0.42-0.67)	0.81 (0.61-1.08)
DVT and PE	1.23 (0.72-2.12)	0.94 (0.47-1.90)

Previous ischemic stroke	1.10 (0.93-1.30)	1.11 (0.98-1.27)
Previous myocardial infarction	0.98 (0.77-1.24)	1.01 (0.81-1.26)
Previous major bleeding	1.02 (0.93-1.12)	0.98 (0.87-1.11)
Comorbidities		
Charlson Comorbidity Index (CCI)		
0	1	1
1	0.95 (0.90-1.01)	1.01 (0.94-1.10)
2-4	1.00 (0.87-1.14)	0.95 (0.81-1.12)
≥5	0.98 (0.68-1.40)	0.92 (0.62-1.38)
Atrial Fibrillation	0.92 (0.78-1.08)	0.72[*] (0.63-0.83)
Cardiovascular Diseases	1.08[*] (1.00 – 1.17)	0.92[*] (0.85-0.99)
Congestive Heart Failure	0.94 (0.77-1.16)	0.84 (0.68-1.03)
Hepatic failure	1.02 (0.87-1.19)	0.98 (0.77-1.24)
Renal Impairment	0.79[*] (0.68-0.92)	0.85[*] (0.74-0.98)
Peptic Ulcer	0.89 (0.49-1.62)	1.88 (0.97-3.62)
Gastritis	1.08 (0.88-1.31)	1.14 (0.87-1.49)
Duodeniitis	1.21 (0.70-2.06)	0.94 (0.46-1.92)
Esophagitis	0.93 (0.71-1.23)	0.94 (0.66-1.33)
Hyperlipidemia	1.01 (0.96-1.06)	0.94[*] (0.88-1.00)
Hypertension	1.10[*] (1.05-1.15)	1.01 (0.94-1.08)
Diabetes Mellitus	0.97 (0.92-1.02)	0.99 (0.93-1.07)
Anemia	0.96 (0.89-1.03)	0.97 (0.88-1.07)
Sleep Apnea	0.96 (0.90-1.03)	0.93 (0.84-1.04)
Cancer	0.96 (0.81-1.13)	1.06 (0.88-1.26)
Dementia	1.29 (0.33-4.99)	0.63 (0.27-1.52)
Obesity	0.93[*] (0.87-0.99)	1.01 (0.90-1.13)
Previous Hospitalization		
No hospitalization	1	1
At least 1 hospitalization	1.14[*] (1.01-1.28)	0.96 (0.83-1.12)
Outpatient Surgery Setting		
Inpatient	1	1
Outpatient	0.84[*] (0.73-0.97)	1.15 (0.99-1.34)
Concomittant therapy		
Antiplatelet Therapy	0.83 (0.72-0.96)	0.99 (0.88-1.13)
Gastroprotective Agents	1.01 (0.96-1.06)	0.97 (0.91-1.03)
Antiarrhythmics	0.92 (0.72-1.17)	1.01 (0.82-1.24)
Rate Control Therapy	0.96 (0.92-1.00)	1.02 (0.96-1.08)

Hormone Use	1.05 (0.82-1.35)	-
Statins	0.98 (0.93-1.02)	1.03 (0.97-1.09)
ACE Inhibitors	1.01 (0.97-1.06)	0.99 (0.94-1.06)

[*] denotes a statistically significant difference

We also performed a sensitivity analysis using the purposeful selection method by Bursac et al to understand the effect of variable selection on the model fit.[113] In this analysis, variables were included in the model only if they had univariate associations at the significance level of 0.25 or higher with the outcome. In the iterative process of variable selection, covariates were removed from the model if they were non-significant (significance was evaluated at the 0.1 alpha level) and not a confounder (confounding was defined as a change in any remaining parameter estimate greater than 15% as compared to the full model). This process of parsimonious model building was repeated for each of the four cohorts.

The c-statistics for the commercially insured hip replacement cohort, Medicare hip replacement cohort, commercially insured knee replacement cohort, and Medicare knee replacement cohort were 0.653, 0.673, 0.665 and 0.686, respectively. Results from these models are presented in Appendix 1. The parsimonious model for commercially insured hip replacement patients found that geographic region, type of insurance plan, prescription drug plan generosity, year of surgery, previous history of deep vein thrombosis, pulmonary embolism, atrial fibrillation, vascular diseases, end stage renal disease and concurrent use of statins were significantly associated with the choice of anticoagulant. The parsimonious model for Medicare total hip replacement patients found age, geographic region, type of insurance plan, prescription drug plan generosity, year of surgery, previous history of deep vein thrombosis, pulmonary

embolism, atrial fibrillation, diabetes, end stage renal disease and previous hospitalizations were significantly associated with the choice of anticoagulant.

Age, sex, geographic region, health insurance plan, prescription drug plan generosity, year of surgery, previous history of deep vein thrombosis, pulmonary embolism, diabetes, vascular diseases, end stage renal disease, clinically diagnosed obesity, concurrent use of statins, type of surgery setting and previous hospitalizations were found to be significantly associated with the choice of anticoagulant in commercially insured total knee replacement patients. The parsimonious model for Medicare total knee replacement cohort found that age, sex, geographic region, health insurance plan, prescription drug plan generosity, year of surgery, previous history of deep vein thrombosis, pulmonary embolism, vascular diseases, end stage renal disease, congestive heart failure, atrial fibrillation and the of surgery setting were significantly associated with the choice of anticoagulant.

4.3 Aim 2: To compare the real world effectiveness of novel oral anticoagulant rivaroxaban with standard oral anticoagulant warfarin in venous thromboembolism prevention among patients with elective total hip or knee replacement surgery

A total of 12,876 warfarin users and 10,892 rivaroxaban users with an elective total hip replacement were included in the commercially insured cohort (Figure 4-7) and 7,416 warfarin users and 4,739 rivaroxaban users were included in the Medicare cohort (Figure 4-8). The baseline patient characteristics and standardized differences between warfarin and rivaroxaban users of the two hip replacement cohorts are presented in

83

Table 4-1. A total of 24,856 warfarin users and 21,398 rivaroxaban users with an elective total knee replacement were included in the commercially insured cohort (Figure 4-9) and 15,483 warfarin users and 8,997 rivaroxaban users were included in the Medicare cohort (Figure 4-10). The baseline patient characteristics and standardized differences between warfarin and rivaroxaban users of the two knee replacement cohorts are presented in Table 4-2. A detailed description of the baseline differences among the users is provided in section 4.2.2.

VTE event rates were captured over 90 days following surgery and compared between patients initiating warfarin versus rivaroxaban. Table 4-5 shows the unadjusted results for VTE rates for patients initiating warfarin compared to rivaroxaban following an elective total hip or knee replacement surgery. Patients initiating rivaroxaban had, on average, lower rates of VTE in the 90 days following surgery. The unadjusted relative risks for DVT, PE and DVT and PE in the commercially insured elective hip replacement cohort and Medicare cohort were lower for rivaroxaban users compared to warfarin users (0.44 RR for DVT, 0.46 RR for PE and 0.53 RR for DVT and PE in commercial and 0.43 RR for DVT, 0.46 RR for PE and 0.32 RR for DVT and PE in Medicare cohorts, respectively).

Among the total knee replacement cohorts, the unadjusted relative risks of DVT, PE and DVT and PE were lower in rivaroxaban users compared to warfarin users (0.35 RR for DVT, 0.35 RR for PE and 0.39 RR for DVT and PE in commercial and 0.58 RR for DVT, 0.46 RR for PE and 0.44 RR for DVT and PE in Medicare cohorts, respectively

Table 4-5 Unadjusted VTE outcomes during 90 days post index period by therapy

	Commercially insured			Medicare		
	Warfarin n (%)	Rivaroxaban n (%)	P value	Warfarin n (%)	Rivaroxaban n (%)	P value
Total hip replacement	n=12,876	n=10,892		n=7,416	n=4,739	
DVT	198 (1.54)	59 (0.54)	<0.001	223 (3.01)	82 (1.73)	<0.001
PE	273 (2.12)	80 (0.73)	<0.001	303 (4.09)	89 (1.88)	<0.001
DVT and PE	36 (0.28)	12 (0.11)	<0.01	74 (1.00)	21 (0.44)	<0.001
Total knee replacement	n=24,856	n=21,398		n=15,483	n=8,997	
DVT	537 (2.16)	204 (0.95)	<0.001	557 (3.60)	139 (1.54)	<0.001
PE	747 (3.01)	293 (1.37)	<0.001	664 (4.29)	177 (1.97)	<0.001
DVT and PE	132 (0.53)	60 (0.28)	<0.001	168 (1.09)	31 (0.34)	<0.001

Model fit:

The c, or concordance, statistic is often cited as a measure of the fit of the propensity score. It can take on values between 0.5 (classification no better than flipping a coin) and 1.0 (perfect classification). The c-statistic measures the ability of a model to predict treatment status using the observed covariates. Several reviews have reported a c-statistic greater than 0.90 indicates very good ability of the propensity score model to predict treatment status. The c-statistic for the THR commercial and Medicare models were 0.76 and 0.78 and for the TKR commercial and Medicare models were 0.77 and 0.79. Although a c-statistic is often reported, it provides no certainty that all measured confounders have been balanced between treatment groups. Therefore, rather than letting the c-statistic guide selection of covariates into the propensity score model selection was informed by the conceptual model used to identify potentially important predictors of treatment selection (Figure 2-2). After model fit was evaluated,

the distribution of the propensity scores for patients initiating rivaroxaban vs. warfarin was evaluated using histograms. PS significantly overlapped between patients who initiated rivaroxaban and those who initiated warfarin except at the tails (Appendix 2). We used trimming (1st and 99th percentile) for the non-overlapping region.

A logistic regression model was used to evaluate the association between initiation of rivaroxaban versus warfarin and having a VTE event during the follow-up period (Table 4-6). As reflected in Table 4-6, among total hip replacement patients, warfarin users had significantly higher odds of deep vein thrombosis (OR 2.63, 95% CI 1.97-3.50 in commercial cohort and OR 1.78, 95% CI 1.38-2.29 in Medicare cohort) and pulmonary embolism (OR 2.60, 95% CI 2.04-3.31 in commercial cohort and OR 2.09, 95% CI 1.66-2.65 in Medicare cohort). The odds of deep vein thrombosis (OR 2.06, 95% CI 1.76-2.42 in commercial cohort and OR 2.21, 95% CI 1.84-2.65 in Medicare cohort) and pulmonary embolism (OR 2.03, 95% CI 1.78-2.33 in commercial cohort and OR 2.16, 95% CI 1.84-2.55 in Medicare cohort) was also higher in the warfarin users in the total knee replacement commercial and Medicare cohorts.

Table 4-6 Association between initiating warfarin versus rivaroxaban and VTE event in propensity score adjusted cohort

	Commercially insured OR (95% CI)	Medicare OR (95% CI)
Total hip replacement		
DVT	2.63[*] (1.98, 3.50)	1.78[*] (1.38-2.29)
PE	2.60[*] (2.04, 3.31)	2.09[*] (1.66-2.65)
DVT and PE	2.33[*] (1.25-4.37)	2.23[*] (1.39-3.58)
Total knee replacement		
DVT	2.06[*] (1.76-2.42)	2.21[*] (1.84-2.65)
PE	2.03[*] (1.78-2.33)	2.16[*] (1.84-2.55)
DVT and PE	1.59[*] (1.17-2.14)	2.75[*] (1.92-3.96)

DVT- Deep vein thrombosis, PE – pulmonary embolism, OR – odds ratio, CI – confidence interval
[*] denotes a statistically significant difference

Sensitivity analysis:

To understand the effect of our assumption of prescription fills before the surgery, we restricted new users to only include those filling the prescription within 7 days of the surgery (index date + 7). This reduced our sample size to 4,896 warfarin new users and 3,857 rivaroxaban new users in the commercially insured hip replacement cohort and 2,456 warfarin users and 947 rivaroxaban users in the hip replacement Medicare cohort. There were 10,459 warfarin users and 9,674 rivaroxaban users in the commercially insured total knee replacement cohort and 6,753 warfarin users and 2,989 rivaroxaban users in the Medicare cohort. Estimates from the sensitivity analysis are reported in table 4-7 and were found to be consistent with the primary model.

Table 4-7 Sensitivity analysis: Association between warfarin use versus rivaroxaban and VTE events in propensity score adjusted cohort

	Commercially insured OR (95% CI)	Medicare OR (95% CI)
Total hip replacement		
DVT	2.74* (1.87, 3.68)	2.10* (1.56-2.45)
PE	2.58* (1.87, 3.29)	2.32* (1.78-2.71)
DVT and PE	2.34* (1.19-3.12)	1.98* (1.54-2.67)
Total knee replacement		
DVT	2.53* (1.87-2.86)	2.42* (1.96-2.97)
PE	2.32* (1.86-3.20)	2.56* (1.65-3.21)
DVT and PE	2.01* (1.56-2.39)	2.38* (1.64-2.76)

DVT- Deep vein thrombosis, PE – pulmonary embolism, OR – odds ratio, CI – confidence interval
* denotes a statistically significant difference

4.4 Aim 3: To compare the safety of novel oral anticoagulant rivaroxaban with standard oral anticoagulant warfarin in venous thromboembolism prevention among patients with elective total hip or knee replacement surgery

A total of 12,876 warfarin users and 10,892 rivaroxaban users with an elective total hip replacement were included in the commercially insured cohort (Figure 4-7) and 7,416 warfarin users and 4,739 rivaroxaban users were included in the Medicare cohort (Figure 4-8). The baseline patient characteristics and standardized differences between warfarin and rivaroxaban users of the two hip replacement cohorts are presented in Table 4-1. A total of 24,856 warfarin users and 21,398 rivaroxaban users with an elective total knee replacement were included in the commercially insured cohort (Figure 4-9) and 15,483 warfarin users and 8,997 rivaroxaban users were included in the Medicare cohort (Figure 4-10). The baseline patient characteristics and standardized differences between warfarin and rivaroxaban users of the two knee replacement cohorts are presented in Table 4-2. A detailed description of the baseline differences among the users is provided in section 4.2.2.

Bleeding event rates were captured over 90 days following surgery and compared between patients initiating warfarin versus rivaroxaban. Table 4-8 shows the unadjusted results for bleeding rates for patients initiating warfarin compared to rivaroxaban following an elective hip or knee replacement surgery. The unadjusted relative risks for any bleeding in the commercially insured elective hip replacement cohort and Medicare cohort were the same for rivaroxaban users compared to warfarin users (relative risk 1.01 RR). The unadjusted relative risk of gastrointestinal bleeding was lower in rivaroxaban users compared to warfarin users (RR 0.95 and RR 0.97 in

commercial and Medicare cohorts, respectively). The unadjusted relative risk of intracranial hemorrhage was lower in the commercial cohort but higher in the Medicare cohort (RR 0.59 in commercial cohort, RR 1.34 in Medicare cohort). The unadjusted relative risk of major bleeding was almost the same across warfarin and rivaroxaban users (RR 1.07 in commercial cohort and RR 1.13 in Medicare cohort). The unadjusted relative risk of post-operative infection was lower in rivaroxaban users compared to warfarin users (RR 0.70 in commercial cohort and 0.57 in Medicare cohort)

Among the total knee replacement commercial cohort, unadjusted relative risks of any bleeding, GI bleeding and ICH were lower in rivaroxaban users compared to warfarin users (0.84 RR for any bleeding, 0.78 RR for GI bleeding, and 0.44 RR for ICH). In the Medicare cohort, the unadjusted risk of bleeding was the same between warfarin and rivaroxaban users (RR 0.99), but the risk of GI bleeding was slightly higher (RR 1.13) and that of intracranial hemorrhage was lower (RR .65). The unadjusted relative risk of major bleeding was lower in both the cohorts (RR 0.89 in commercial cohort and RR 0.81 in Medicare cohort). The unadjusted risk of perioperative joint infection was also slightly lower in the rivaroxaban cohorts (RR 0.92 in commercial cohort and 0.95 in Medicare cohort).

Table 4-8 Unadjusted bleeding outcomes during 90 days post index period by therapy

	Commercially insured			Medicare		
	Warfarin n (%)	Rivaroxaban n (%)	P value	Warfarin n (%)	Rivaroxaban n (%)	P value
Total hip replacement	n=12,876	n=10,892		n=7,416	n=4,739	
Any bleeding	68 (0.53)	58 (0.53)	0.96	87 (1.17)	56 (1.18)	0.97
GI bleeding	35 (0.27)	28 (0.26)	0.83	58 (0.78)	36 (0.76)	0.89
ICH	4 (0.03)	2 (0.02)	-	7 (0.09)	6 (0.13)	0.60
Major bleeding	33 (0.26)	30 (0.28)	0.77	29 (0.39)	21 (0.44)	0.66
PJI	113 (0.88)	67 (0.62)	0.02	63 (0.85)	23 (0.49)	0.02
Total knee replacement	n=24,856	n=21,398		n=15,483	n=8,997	
Any bleeding	173 (0.70)	125 (0.58)	0.13	211 (1.36)	121 (1.34)	0.91
GI bleeding	79 (0.32)	53 (0.25)	0.16	117 (0.76)	77 (0.86)	0.39
ICH	16 (0.06)	6 (0.03)	0.07	16 (0.1)	6 (0.07)	0.36
Major bleeding	94 (0.38)	72 (0.34)	0.45	94 (0.61)	44 (0.49)	0.23
PJI	175 (0.70)	139 (0.65)	0.48	103 (0.67)	57 (0.63)	0.77

*GI bleeding– gastrointestinal bleeding, ICH – intracranial hemorrhage, PJI – postoperative joint infection

As shown in Table 4-9, among total hip replacement patients, warfarin users had slightly lower odds of any bleeding compared to rivaroxaban users (OR 0.91, 95% CI 0.65-1.28 in commercial cohort and OR 0.91, 95% CI 0.66 -1.27 in Medicare cohort). However, these were statistically insignificant. The odds of GI bleeding (OR 0.99, 95% CI 0.61 -1.64 in commercial cohort and OR 0.92, 95% CI 0.62 -1.37 in Medicare cohort), intracranial hemorrhage (OR 0.78, 95% CI 0.26 -2.37 in Medicare cohort) and major bleeding (OR 0.84, 95% CI 0.52-1.35 in commercial cohort and OR 0.86, 95% CI 0.49-1.51 in Medicare cohort), although statistically insignificant, were also lower in warfarin users. The odds of postoperative joint infection (OR 1.57, 95% CI 1.16 -2.13 in commercial cohort and OR 1.79, 95% CI 1.14-2.81 in Medicare cohort) was significantly higher in the warfarin users compared to rivaroxaban users.

Table 4-9 Association between initiating warfarin versus rivaroxaban and bleeding event in propensity score adjusted cohort

	Commercially insured OR (95% CI)	Medicare OR (95% CI)
Total hip replacement		
Any bleeding	0.91 (0.65-1.29)	0.91 (0.66-1.27)
GI bleeding	0.99 (0.61 -1.64)	0.92 (0.62 -1.37)
ICH	N/A†	0.78 (0.26 -2.37)
Major bleeding	0.84 (0.52-1.35)	0.86 (0.49-1.51)
PJI	1.57* (1.16 -2.13)	1.79* (1.14-2.81)
Total knee replacement		
Any bleeding	1.26* (1.00-1.57)	1.00 (0.81-1.24)
GI bleeding	1.39 (0.98-1.97)	0.86 (0.65-1.13)
ICH	2.70* (1.05-6.91)	1.43 (0.59-3.47)
Major bleeding	1.17 (0.87-1.56)	1.27 (0.90-1.80)
PJI	1.07 (0.86-1.33)	0.98 (0.72-1.34)

GI bleeding– gastrointestinal bleeding, ICH – intracranial hemorrhage, PJI – postoperative joint infection, OR – odds ratio, CI – confidence interval
* denotes a statistically significant difference
† the number of events was less than 5 and was not modelled due to power considerations

Among total knee replacement patients, warfarin users had the same odds of any bleeding compared to rivaroxaban users (OR 1.26, 95% CI 1.00-1.57 in commercial cohort and OR 1.00, 95% CI 0.81 -1.24 in Medicare cohort). The odds of GI bleeding (OR 1.39, 95% CI 0.98 -1.97 in commercial cohort and OR 0.86, 95% CI 0.65 -1.13 in Medicare cohort), intracranial hemorrhage (OR 2.70, 95% CI 1.05 -6.91 in commercial cohort and OR 1.43, 95% CI 0.59-3.47 Medicare cohort) and major bleeding (OR 1.17,

95% CI 0.87-1.56 in commercial cohort and OR 1.27, 95% CI 0.90-1.80 in Medicare

cohort), although statistically insignificant, were slightly higher in warfarin users. The

odds of postoperative joint infection (OR 1.07, 95% CI 0.86 -1.33 in commercial cohort

and OR 0.98, 95% CI 0.72-1.34 in Medicare cohort) was the same among warfarin

users compared to rivaroxaban users.

Sensitivity analysis:

    To understand the effect of our assumption of prescription fills before the

surgery, we restricted new users to only include those filling the prescription within 7

days of the surgery (index date + 7). This reduced our sample size to 4,896 warfarin

new users and 3,857 rivaroxaban new users in the commercially insured hip

replacement cohort and 2,456 warfarin users and 947 rivaroxaban users in the hip

replacement Medicare cohort. There were 10,459 warfarin users and 9,674 rivaroxaban

users in the commercially insured total knee replacement cohort and 6,753 warfarin

users and 2,989 rivaroxaban users in the Medicare cohort. The rate of intracranial

hemorrhage in the sensitivity cohort was too low to perform sensitivity analysis.

Estimates from the sensitivity analysis are reported in table 4-10 and were found to be

consistent with the primary model.

Table 4-10 Sensitivity analysis: Association between warfarin use versus rivaroxaban and bleeding events in propensity score adjusted cohort

	Commercially insured OR (95% CI)	Medicare OR (95% CI)
Total hip replacement		
Any bleeding	1.02 (0.68-1.23)	0.98 (0.658-1.267)
GI bleeding	0.98 (0.67 -1.39)	0.97 (0.56-1.62)
Major bleeding	0.99 (0.62-1.23)	0.96 (0.56-1.24)
PJI	1.23* (1.01 -1.87)	1.21* (1.08-1.89)
Total knee replacement		
Any bleeding	1.10 (0.76 -1.45)	0.99 (0.78-1.21)
GI bleeding	1.40 (0.87-2.10)	1.02 (0.66-1.45)
Major bleeding	1.23 (0.89-1.84)	1.02 (0.78-1.34)
PJI	1.02 (0.67-1.48)	1.01 (0.89-1.53)

GI bleeding– gastrointestinal bleeding, ICH – intracranial hemorrhage, PJI – postoperative joint infection, OR – odds ratio, CI – confidence interval

* denotes a statistically significant difference

Chapter 5 : Discussion

This study describes the trends in utilization of anticoagulants after an elective total hip or knee replacement surgery over time. Additionally, it explores the association of different patient characteristics with the type of anticoagulant prescribed. It also analyses the comparative effectiveness and safety of the newer oral anticoagulant, rivaroxaban with the standard oral anticoagulant, warfarin.

This study has four main findings. First, since their introduction in the US market in 2011, newer oral anticoagulants, particularly rivaroxaban, have been quickly adopted into clinical practice in post-surgery in orthopedic patients. Rivaroxaban replaced 21% of warfarin prescriptions in under a year and up to 50% in three years. This could be attributed to the perceived benefits of newer oral anticoagulants over warfarin by physicians. A recent study conducted in atrial fibrillation patients regarding physician and patient preferences for oral anticoagulants showed that almost half of the surveyed physicians spontaneously stated rivaroxaban as their preferred agent for anticoagulation.[122] It is interesting to note that this study did not show any patient preferences between warfarin, rivaroxaban and apixaban. We also notice a steady decline in the use of non-oral anticoagulants such as heparins over time. The extent to which newer oral anticoagulants will replace current therapies and continue to expand their market share depends upon the balance between benefits such as greater dosing convenience and fewer drug-drug interactions and the risks such as uncertainties

regarding their comparative safety and effectiveness, established beyond the clinical trials used to gain their market approval.

Second, we found that the choice of anticoagulant was influenced by a mix of predisposing, enabling and need factors. Females were less likely to be prescribed rivaroxaban compared to males. One study found that women have fewer DVT events and more bleeds than men during the course of anticoagulation therapy.[123] If bleeding is a safety concern in patients, warfarin is preferred over rivaroxaban due to the availability of reversal agents. This could explain some of the reasons for the differences in prescribing by gender. Patients having surgeries in the recent years had higher odds of rivaroxaban use compared to those having surgery closer to 2011. Over time, more studies have been published establishing the comparative effectiveness and safety of newer anticoagulants through meta-analysis of clinical trials. This shift in prescribing pattern over time could be due to more evidence generation. Type of health plan was also found to be a significant predictor of rivaroxaban initiation in these patients. Plans with capitated health plans had a lower rate of rivaroxaban prescription and could be due to plans trying to keep their costs lower. Previous research has shown that capitated payment plans encourage underuse of expensive services.[124] However, this finding should be interpreted with caution as a very small percentage of our sample size (<1%) was enrolled in the capitated plan which could result in insufficient power to support these findings.

In addition to these factors, our analyses found clinical comorbidities such as a history of deep vein thrombosis, pulmonary embolism, cardiovascular diseases and renal impairment also affected the choice of anticoagulant. Patients with renal

impairment were less likely to be prescribed rivaroxaban in both, commercially insured as well as Medicare cohorts. Physicians are advised to use caution when using rivaroxaban in patients with kidney disease due increased half-life and lack of reversal agents.[125] While the presence of deep vein thrombosis, pulmonary embolism and cardiovascular diseases was associated with an increased use of rivaroxaban in commercially insured patients, it was associated with a decreased use of rivaroxaban in Medicare patients. This difference between the two cohorts could be due to other differences in these patient populations such age and overall health status. Physicians have been reported to use less aggressive treatment strategies in elder people in other therapeutic areas such as rheumatoid arthritis.[126] This also corresponds to on average, relatively lower uptake of rivaroxaban in the Medicare population compared to commercially insured population as observed in aim 1a over time. Future research should be conducted to examine the efficacy and safety of anticoagulants in elderly patients to address physician concerns.

Our study used real-world claims data from a US population to compare the safety and effectiveness of rivaroxaban with warfarin therapy in patients with elective total hip and knee replacements. Our analyses show that the odds of deep vein thrombosis and pulmonary embolism were significantly lower among rivaroxaban users compared to warfarin users. To our knowledge, no studies have directly compared the safety and effectiveness of rivaroxaban with warfarin following hip or knee replacement surgery. However, clinical trials that have compared the efficacy of heparins (enoxaparin and dalteparin) found them to be superior to warfarin in terms of

efficacy.[127,128] Also, clinical trials in elective orthopedic surgery patients found rivaroxaban to be superior in preventing VTE compared to enoxaparin.[129]

Orthopedic surgery practice in the area of venous thromboembolism prophylaxis has often been guided by concerns over bleeding, especially with the newer oral anticoagulants.[130] Our study found that the risk of bleeding among rivaroxaban users was not significantly different than warfarin users. Different clinical trials have evaluated the bleeding risk of rivaroxaban, but have different conclusions.[131-135] It is not possible to compare safety data from different clinical trials because there is no standardized definition of bleeding that has been used uniformly in all randomized controlled trials. Differences in reported major bleeding rates among pivotal trials for the newer anticoagulants are driven to a large extent by the definitions of bleeding used in the trials, by the regimens utilized and partially by the properties of the anticoagulants themselves. Another concern that orthopedic surgeons often have with anticoagulants after a hip or knee replacement surgery is their effect on the rate of postoperative joint infection. We observed that the risk of postoperative joint infection is significantly lower in rivaroxaban users compared to warfarin users. No previous study has analyzed the risk of perioperative joint infection among rivaroxaban and warfarin users. One study that compared rivaroxaban to enoxaparin found similar rates of infection between the two agents.

Limitations:

The findings of our study should be viewed in light of its limitations and strengths. To assess the treatment exposure, we required the patient to survive the surgical hospitalization which could induce survival bias. Therefore, we can generalize our

findings only to those who survive initial hip or knee replacement surgery related hospitalization. To understand the effect of survival bias on our findings, we analyzed the number of people lost to follow up (as defined by disenrollment in the three months following the surgery) in the rivaroxaban group versus the warfarin group in each of the surgery cohorts. We found no patients lost in either the warfarin or the rivaroxaban group among the total hip replacement surgery patients. Among the total knee replacement Medicare cohort, we found 1 person (0.004%) dis-enrolled in the month following the surgery in the warfarin cohort compared to no loss during follow up period in the rivaroxaban cohort. There were no patients lost to follow up in either of the two treatment groups in the commercially insured total knee replacement cohort. Based on this analysis, we assumed that there was little chance of differential survival among the two treatment options in either of the surgery cohorts.

Our results are based on patients in the TruvenHealth Marketscan databases and may not be generalizable to the entire commercially insured or general population. Our study also only included patients with supplemental Medicare insurance and these individuals are not representative of the entire Medicare population. Furthermore, there are several limitations of claims databases that must be acknowledged. Since, the primary function of claims data is collection and adjudication of insurance claims, they do not contain any information about over-the-counter drug use or medication use through secondary sources such as physician samples or mail order pharmacies. Since aspirin is a newly emerging anticoagulant that is available over-the-counter, there is a potential for concurrent use or switching from other pharmacological agents that was

unobservable in our data. Claims data relies on accuracy in medical coding and errors

in billing codes could lead to inaccuracies in the event rate.

Lastly, the observed differences in the risk of the outcome (or lack thereof)

between the two treatment groups could be due to confounding caused by imbalance of

other covariates. To overcome this limitation, we used IPTW to balance covariates in

the baseline period. However, this was only limited to observable confounders. We did

not have access to some of the known potential confounders such as body mass index.

Despite these limitations, our study provides a comprehensive overview of the

utilization pattern of anticoagulants that helps us understand the changes in clinical

practice over time. It also helps us quantify the uptake of newer oral anticoagulants in

these patients and tries to provide meaningful answer to the important clinical question

related to the best strategies of reducing VTE and bleeding risk in patients with hip or

knee replacement. Lastly, our study provides us with an insight into the real-world VTE

and symptomatic bleeding complication rates among the different anticoagulants.

Conclusion:

The results from this dissertation suggest that treatment with rivaroxaban may

help in reducing the risk of incident VTE events without any significant increase in the

risk of bleeding or post-operative joint infection compared to warfarin treatment in

patients with a hip or knee replacement surgery. Future studies with larger sample size

are recommended to confirm findings from our study.

APPENDICES

Appendix 1: SAS output for purposeful selection of variables

FINAL MODEL FOR COMMERCIALLY INSURED TOTAL HIP REPLACEMENT COHORT

Model Information

Response Variable   rivaroxaban
Number of Response Levels 2
Model   binary logit
Optimization Technique Fisher's scoring

Number of Observations Read 23768
Number of Observations Used 23768

   Response Profile

Ordered Value	rivaroxaban	Total Frequency
1	1	10892
2	0	12876

Probability modeled is rivaroxaban=1.

Final main effects model - some significant noncandidates

The LOGISTIC Procedure

   Model Convergence Status

  Convergence criterion (GCONV=1E-8) satisfied.

  Deviance and Pearson Goodness-of-Fit Statistics

Criterion	Value	DF	Value/DF	Pr > ChiSq
Deviance	2626.4265	2035	1.2906	<.0001
Pearson	2179.1469	2035	1.0708	0.0133

Number of unique profiles: 2057

  Model Fit Statistics

Hosmer and Lemeshow Goodness-of-Fit Test

Chi-Square	DF	Pr > ChiSq
45.4705	8	<.0001

AIC	32785.640	30856.969
SC	32793.716	31066.948
-2 Log L	32783.640	30804.969

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	1978.6707	25	<.0001
Score	1862.7941	25	<.0001
Wald	1695.2225	25	<.0001

Analysis of Maximum Likelihood Estimates

Parameter		DF	Standard Estimate	Wald Error	Chi-Square	Pr > ChiSq
Intercept		1	-1.1695	0.3358	12.1337	0.0005
rxgen	1	1	-0.00855	0.0633	0.0182	0.8926
rxgen	2	1	-0.0286	0.0542	0.2785	0.5977
rxgen	3	1	-0.0537	0.0573	0.8803	0.3481
Statin	0	1	0.0507	0.0313	2.6322	0.1047
DVT	0	1	0.3136	0.1760	3.1739	0.0748
PE	0	1	0.2814	0.1780	2.4988	0.1139
indexyr	2011	1	-1.7623	0.0659	715.1200	<.0001
indexyr	2012	1	-0.6611	0.0550	144.3466	<.0001
indexyr	2013	1	-0.3190	0.0556	32.9672	<.0001
indexyr	2014	1	-0.0837	0.0576	2.1082	0.1465
AF	0	1	0.2055	0.1083	3.6013	0.0577
REGION	1	1	-0.0167	0.2078	0.0065	0.9358
REGION	2	1	0.4722	0.2068	5.2126	0.0224
REGION	3	1	0.8280	0.2063	16.1052	<.0001
REGION	4	1	0.5630	0.2074	7.3685	0.0066
PLANTYP	0	1	0.2250	0.1065	4.4588	0.0347
PLANTYP	2	1	-0.0346	0.0984	0.1238	0.7250
PLANTYP	3	1	-0.0344	0.1566	0.0482	0.8262
PLANTYP	4	1	-0.3124	0.0835	13.9829	0.0002
PLANTYP	5	1	-0.1904	0.0882	4.6620	0.0308
PLANTYP	6	1	-0.0278	0.0720	0.1484	0.7001
PLANTYP	7	1	-0.6968	0.2231	9.7563	0.0018

```
PLANTYP  8    1   -0.0918   0.0851    1.1630   0.2809
ESRD    0     1    0.3560   0.0990   12.9178   0.0003
Vascular 0    1   -0.0890   0.0518    2.9532   0.0857
```

Odds Ratio Estimates

Effect		Point Estimate	95% Wald Confidence Limits	
rxgen	1 vs 4	0.991	0.876	1.122
rxgen	2 vs 4	0.972	0.874	1.081
rxgen	3 vs 4	0.948	0.847	1.060
Statin	0 vs 1	1.052	0.989	1.119
DVT	0 vs 1	1.368	0.969	1.932
PE	0 vs 1	1.325	0.935	1.878
indexyr	2011 vs 2015	0.172	0.151	0.195
indexyr	2012 vs 2015	0.516	0.464	0.575
indexyr	2013 vs 2015	0.727	0.652	0.811
indexyr	2014 vs 2015	0.920	0.821	1.030
AF	0 vs 1	1.228	0.993	1.518
REGION	1 vs 5	0.983	0.654	1.478
REGION	2 vs 5	1.603	1.069	2.405
REGION	3 vs 5	2.289	1.527	3.429
REGION	4 vs 5	1.756	1.169	2.637
PLANTYP	0 vs 9	1.252	1.016	1.543
PLANTYP	2 vs 9	0.966	0.797	1.171
PLANTYP	3 vs 9	0.966	0.711	1.313
PLANTYP	4 vs 9	0.732	0.621	0.862
PLANTYP	5 vs 9	0.827	0.695	0.983
PLANTYP	6 vs 9	0.973	0.845	1.120
PLANTYP	7 vs 9	0.498	0.322	0.771
PLANTYP	8 vs 9	0.912	0.772	1.078
ESRD	0 vs 1	1.428	1.176	1.733
Vascular	0 vs 1	0.915	0.826	1.013

Association of Predicted Probabilities and Observed Responses

```
Percent Concordant    65.0   Somers' D   0.306
Percent Discordant    34.4   Gamma       0.307
Percent Tied           0.5   Tau-a       0.152
Pairs            140245392   c           0.653
```

FINAL MODEL FOR TOTAL HIP REPLACEMENT IN MEDICARE PATIENTS

Final main effects model - some significant noncandidates

The LOGISTIC Procedure

Model Information

Response Variable   rivaroxaban
Number of Response Levels   2
Model   binary logit
Optimization Technique   Fisher's scoring

Number of Observations Read   12155
Number of Observations Used   12155

Response Profile

Ordered Value	rivaroxaban	Total Frequency
1	1	4739
2	0	7416

Probability modeled is rivaroxaban=1.

Model Convergence Status

Convergence criterion (GCONV=1E-8) satisfied.

Deviance and Pearson Goodness-of-Fit Statistics

Criterion	Value	DF	Value/DF	Pr > ChiSq
Deviance	6441.2121	5408	1.1911	<.0001
Pearson	5302.4193	5408	0.9805	0.8451

Number of unique profiles: 5430

Model Fit Statistics

Criterion	Intercept Only	Intercept and Covariates
AIC	16257.968	15120.248
SC	16265.374	15320.196
-2 Log L	16255.968	15066.248

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	1189.7204	26	<.0001
Score	1097.6999	26	<.0001

Wald   974.1887   26   <.0001

Type 3 Analysis of Effects

            Wald
Effect   DF   Chi-Square   Pr > ChiSq

agevar   1   17.2672   <.0001
REGION   4   147.0847   <.0001
PLANTYP   8   11.3678   0.1817
rxgen   3   5.5685   0.1346
indexyr   4   769.5827   <.0001
Diabetes 1   3.0902   0.0788
DVT   1   7.9440   0.0048
PE   1   4.4031   0.0359
AF   1   21.5116   <.0001
ESRD   1   7.6644   0.0056
cat_hosp 1   2.7171   0.0993

Analysis of Maximum Likelihood Estimates

                 Standard   Wald
Parameter   DF Estimate   Error   Chi-Square   Pr > ChiSq

Intercept   1   -1.0814   0.7126   2.3028   0.1291
agevar   1   -0.0128   0.00308   17.2672   <.0001
REGION   1   1   0.3037   0.3398   0.7989   0.3714
REGION   2   1   0.5622   0.3389   2.7511   0.0972
REGION   3   1   0.9665   0.3394   8.1099   0.0044
REGION   4   1   0.6378   0.3408   3.5024   0.0613
PLANTYP 0   1   0.4452   0.5486   0.6584   0.4171
PLANTYP 2   1   0.4531   0.5162   0.7706   0.3800
PLANTYP 3   1   0.8198   0.6632   1.5282   0.2164
PLANTYP 4   1   0.2901   0.5193   0.3121   0.5764
PLANTYP 5   1   0.4931   0.5245   0.8840   0.3471
PLANTYP 6   1   0.4654   0.5160   0.8137   0.3670
PLANTYP 7   1   0.0344   0.6670   0.0027   0.9589
PLANTYP 8   1   0.0598   0.5745   0.0108   0.9171
rxgen   1   1   -0.1188   0.1422   0.6979   0.4035
rxgen   2   1   -0.2305   0.1235   3.4838   0.0620
rxgen   3   1   -0.1830   0.1273   2.0671   0.1505
indexyr 2011 1   -2.2052   0.0975   511.7599   <.0001
indexyr 2012 1   -0.9695   0.0746   168.8098   <.0001
indexyr 2013 1   -0.5827   0.0748   60.6383   <.0001
indexyr 2014 1   -0.1575   0.0777   4.1127   0.0426
Diabetes 0   1   0.0904   0.0514   3.0902   0.0788
DVT   0   1   0.5704   0.2024   7.9440   0.0048
PE   0   1   0.3605   0.1718   4.4031   0.0359

105

```
AF       0    1    0.3999    0.0862    21.5116    <.0001
ESRD     0    1    0.2389    0.0863     7.6644    0.0056
cat_hosp 0    1   -0.1388    0.0842     2.7171    0.0993
```

Odds Ratio Estimates

Effect	Point Estimate	95% Wald Confidence Limits	
agevar	0.987	0.981	0.993
REGION 1 vs 5	1.355	0.696	2.637
REGION 2 vs 5	1.755	0.903	3.409
REGION 3 vs 5	2.629	1.352	5.112
REGION 4 vs 5	1.892	0.970	3.691
PLANTYP 0 vs 9	1.561	0.533	4.575
PLANTYP 2 vs 9	1.573	0.572	4.326
PLANTYP 3 vs 9	2.270	0.619	8.328
PLANTYP 4 vs 9	1.337	0.483	3.699
PLANTYP 5 vs 9	1.637	0.586	4.577
PLANTYP 6 vs 9	1.593	0.579	4.379
PLANTYP 7 vs 9	1.035	0.280	3.825
PLANTYP 8 vs 9	1.062	0.344	3.273
rxgen 1 vs 4	0.888	0.672	1.173
rxgen 2 vs 4	0.794	0.623	1.012
rxgen 3 vs 4	0.833	0.649	1.069
indexyr 2011 vs 2015	0.110	0.091	0.133
indexyr 2012 vs 2015	0.379	0.328	0.439
indexyr 2013 vs 2015	0.558	0.482	0.647
indexyr 2014 vs 2015	0.854	0.734	0.995
Diabetes 0 vs 1	1.095	0.990	1.211
DVT 0 vs 1	1.769	1.190	2.630
PE 0 vs 1	1.434	1.024	2.008
AF 0 vs 1	1.492	1.260	1.766
ESRD 0 vs 1	1.270	1.072	1.504
cat_hosp 0 vs 1	0.870	0.738	1.027

Association of Predicted Probabilities and Observed Responses

```
Percent Concordant     67.3   Somers' D   0.347
Percent Discordant     32.7   Gamma       0.347
Percent Tied            0.0   Tau-a       0.165
Pairs            35144424   c           0.673
```

<u>FINAL MODEL FOR COMMERCIALLY INSURED TOTAL KNEE REPLACEMENT COHORT</u>

Model Information

Response Variable   rivaroxaban
Number of Response Levels   2
Model   binary logit
Optimization Technique   Fisher's scoring
Number of Observations Read   46254
Number of Observations Used   46254

Response Profile

Ordered Value	rivaroxaban	Total Frequency
1	1	21398
2	0	24856

Probability modeled is rivaroxaban=1.

Model Convergence Status

Convergence criterion (GCONV=1E-8) satisfied.

Deviance and Pearson Goodness-of-Fit Statistics

Criterion	Value	DF	Value/DF	Pr > ChiSq
Deviance	30567.9857	24E3	1.2623	<.0001
Pearson	24022.8002	24E3	0.9920	0.8110

Number of unique profiles: 24247

Model Fit Statistics

Criterion	Intercept Only	Intercept & Covariates
AIC	63864.894	59595.863
SC	63873.636	59858.120
-2 Log L	63862.894	59535.863

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	4327.3441	30	<.0001

```
Score              4077.4448      30      <.0001
Wald               3717.6778      30      <.0001
```

Type 3 Analysis of Effects

```
                    Wald
Effect      DF    Chi-Square    Pr > ChiSq

agevar       1      76.0972       <.0001
SEX          1       9.9260        0.0016
REGION       4     1431.6074       <.0001
PLANTYP      8      104.5396       <.0001
rxgen        3       2.6590        0.4472
indexyr      4     2218.6674       <.0001
DVT          1       6.5044        0.0108
PE           1      30.1100        <.0001
Diabetes     1       0.7106        0.3992
Vascular     1       1.5429        0.2142
ESRD         1      11.8820        0.0006
Obese        1       5.0734        0.0243
INPATIENT    1       5.8450        0.0156
cat_hosp     1       4.2508        0.0392
Statin       1       0.5446        0.4605
```

Analysis of Maximum Likelihood Estimates

```
                    Standard     Wald
Parameter     DF   Estimate    Error   Chi-Square   Pr > ChiSq

Intercept      1    -0.3881    0.2514     2.3843      0.1226
agevar         1    -0.0162    0.00186   76.0972      <.0001
SEX      1     1     0.0639    0.0203     9.9260      0.0016
REGION   1     1    -0.1208    0.1434     0.7095      0.3996
REGION   2     1     0.5478    0.1422    14.8459      0.0001
REGION   3     1     1.0329    0.1417    53.1420      <.0001
REGION   4     1     0.7613    0.1429    28.3654      <.0001
PLANTYP  0     1     0.3110    0.0792    15.4015      <.0001
PLANTYP  2     1    -0.0401    0.0717     0.3129      0.5759
PLANTYP  3     1    -0.0724    0.1178     0.3781      0.5386
PLANTYP  4     1    -0.3063    0.0647    22.4233      <.0001
PLANTYP  5     1    -0.0588    0.0668     0.7731      0.3793
PLANTYP  6     1    -0.0440    0.0564     0.6087      0.4353
PLANTYP  7     1    -0.3462    0.1626     4.5310      0.0333
PLANTYP  8     1    -0.0640    0.0656     0.9509      0.3295
rxgen    1     1     0.0533    0.0514     1.0759      0.2996
rxgen    2     1     0.00111   0.0444     0.0006      0.9800
rxgen    3     1     0.00726   0.0464     0.0244      0.8758
indexyr  2011  1    -1.7018    0.0460  1366.0887      <.0001
indexyr  2012  1    -0.6424    0.0390   271.9377      <.0001
indexyr  2013  1    -0.3707    0.0394    88.5279      <.0001
indexyr  2014  1    -0.1098    0.0405     7.3380      0.0068
```

```
DVT       0    1    0.2958    0.1160    6.5044    0.0108
PE        0    1    0.5997    0.1093    30.1100   <.0001
Diabetes  0    1    0.0224    0.0265    0.7106    0.3992
Vascular  0    1   -0.0441    0.0355    1.5429    0.2142
ESRD      0    1    0.2463    0.0715    11.8820   0.0006
Obese     0    1    0.0697    0.0309    5.0734    0.0243
INPATIENT 0    1   -0.1714    0.0709    5.8450    0.0156
cat_hosp  0    1   -0.1201    0.0583    4.2508    0.0392
Statin    0    1    0.0162    0.0220    0.5446    0.4605
```

Odds Ratio Estimates

```
                    Point        95% Wald
Effect              Estimate    Confidence Limits

agevar                0.984     0.980    0.988
SEX      1 vs 2       1.066     1.024    1.109
REGION   1 vs 5       0.886     0.669    1.174
REGION   2 vs 5       1.729     1.309    2.285
REGION   3 vs 5       2.809     2.128    3.709
REGION   4 vs 5       2.141     1.618    2.833
PLANTYP  0 vs 9       1.365     1.168    1.594
PLANTYP  2 vs 9       0.961     0.835    1.106
PLANTYP  3 vs 9       0.930     0.738    1.172
PLANTYP  4 vs 9       0.736     0.649    0.836
PLANTYP  5 vs 9       0.943     0.827    1.075
PLANTYP  6 vs 9       0.957     0.857    1.069
PLANTYP  7 vs 9       0.707     0.514    0.973
PLANTYP  8 vs 9       0.938     0.825    1.067
rxgen    1 vs 4       1.055     0.954    1.166
rxgen    2 vs 4       1.001     0.918    1.092
rxgen    3 vs 4       1.007     0.920    1.103
indexyr  2011 vs 2015   0.182   0.167    0.200
indexyr  2012 vs 2015   0.526   0.487    0.568
indexyr  2013 vs 2015   0.690   0.639    0.746
indexyr  2014 vs 2015   0.896   0.828    0.970
DVT      0 vs 1       1.344     1.071    1.687
PE       0 vs 1       1.822     1.470    2.257
Diabetes 0 vs 1       1.023     0.971    1.077
Vascular 0 vs 1       0.957     0.892    1.026
ESRD     0 vs 1       1.279     1.112    1.472
Obese    0 vs 1       1.072     1.009    1.139
INPATIENT 0 vs 1      0.843     0.733    0.968
cat_hosp 0 vs 1       0.887     0.791    0.994
Statin   0 vs 1       1.016     0.973    1.061
```

Association of Predicted Probabilities and Observed Responses

```
Percent Concordant     66.5   Somers' D   0.329
Percent Discordant     33.5   Gamma       0.329
Percent Tied            0.0   Tau-a       0.164
```

109

Pairs   531868688   c   0.665

FINAL MODEL FOR TOTAL KNEE REPLACEMENT IN MEDICARE PATIENTS

Model Information

Data Set   WORK.T4
Response Variable   rivaroxaban
Number of Response Levels   2
Model   binary logit
Optimization Technique   Fisher's scoring

Number of Observations Read   24480
Number of Observations Used   24480

Response Profile

Ordered Value	rivaroxaban	Total Frequency
1	1	8997
2	0	15483

Probability modeled is rivaroxaban=1.

Model Convergence Status

Convergence criterion (GCONV=1E-8) satisfied.

Deviance and Pearson Goodness-of-Fit Statistics

Criterion	Value	DF	Value/DF	Pr > ChiSq
Deviance	12811.3177	11E3	1.1727	<.0001
Pearson	10844.9813	11E3	0.9927	0.7048

Number of unique profiles: 10947

Model Fit Statistics

Criterion	Intercept Only	Intercept and Covariates
AIC	32199.321	29621.706
SC	32207.427	29800.029

110

-2 Log L   32197.321   29577.706

Testing Global Null Hypothesis: BETA=0

Test	Chi-Square	DF	Pr > ChiSq
Likelihood Ratio	2624.9126	28	<.0001
Score	2413.9701	28	<.0001
Wald	2152.7215	28	<.0001

Type 3 Analysis of Effects

Effect	DF	Wald Chi-Square	Pr > ChiSq
agevar	1	70.6097	<.0001
SEX	1	16.1877	<.0001
REGION	4	673.4663	<.0001
PLANTYP	8	38.4849	<.0001
rxgen	3	6.4331	0.0923
indexyr	4	1364.9215	<.0001
DVT	1	22.6813	<.0001
PE	1	3.0334	0.0816
Vascular	1	5.9776	0.0145
ESRD	1	7.7005	0.0055
CHF	1	8.1579	0.0043
AF	1	23.8872	<.0001
INPATIENT	1	3.3041	0.0691

Analysis of Maximum Likelihood Estimates

Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept		1	-0.5562	0.5627	0.9770	0.3229
agevar		1	-0.0204	0.00243	70.6097	<.0001
SEX	1	1	0.1167	0.0290	16.1877	<.0001
REGION	1	1	-0.3199	0.2602	1.5110	0.2190
REGION	2	1	0.1678	0.2593	0.4187	0.5176
REGION	3	1	0.7374	0.2592	8.0944	0.0044
REGION	4	1	0.3319	0.2609	1.6186	0.2033
PLANTYP	0	1	0.1560	0.4315	0.1307	0.7177
PLANTYP	2	1	0.2228	0.4116	0.2932	0.5882
PLANTYP	3	1	0.4290	0.5491	0.6104	0.4346
PLANTYP	4	1	-0.1035	0.4144	0.0623	0.8028
PLANTYP	5	1	0.0973	0.4163	0.0546	0.8152
PLANTYP	6	1	0.1316	0.4115	0.1023	0.7491
PLANTYP	7	1	-0.2648	0.5327	0.2472	0.6190
PLANTYP	8	1	0.3103	0.4528	0.4695	0.4932
rxgen	1	1	0.1412	0.1017	1.9298	0.1648

```
rxgen      2    1    0.0154    0.0881    0.0305    0.8613
rxgen      3    1    0.0645    0.0907    0.5058    0.4769
indexyr  2011   1   -2.0442    0.0701   850.4822   <.0001
indexyr  2012   1   -0.8945    0.0559   256.4636   <.0001
indexyr  2013   1   -0.5238    0.0558    88.0464   <.0001
indexyr  2014   1   -0.1148    0.0580     3.9176    0.0478
DVT      0    1    0.7033    0.1477    22.6813    <.0001
PE       0    1    0.2330    0.1338     3.0334    0.0816
Vascular  0    1    0.0837    0.0342     5.9776    0.0145
ESRD     0    1    0.1788    0.0644     7.7005    0.0055
CHF      0    1    0.2237    0.0783     8.1579    0.0043
AF       0    1    0.3235    0.0662    23.8872    <.0001
INPATIENT 0    1    0.1343    0.0739     3.3041    0.0691
```

Odds Ratio Estimates

Effect		Point Estimate	95% Wald Confidence Limits	
agevar		0.980	0.975	0.984
SEX	1 vs 2	1.124	1.062	1.189
REGION	1 vs 5	0.726	0.436	1.209
REGION	2 vs 5	1.183	0.712	1.966
REGION	3 vs 5	2.090	1.258	3.474
REGION	4 vs 5	1.394	0.836	2.324
PLANTYP	0 vs 9	1.169	0.502	2.723
PLANTYP	2 vs 9	1.250	0.558	2.800
PLANTYP	3 vs 9	1.536	0.524	4.505
PLANTYP	4 vs 9	0.902	0.400	2.031
PLANTYP	5 vs 9	1.102	0.487	2.493
PLANTYP	6 vs 9	1.141	0.509	2.555
PLANTYP	7 vs 9	0.767	0.270	2.180
PLANTYP	8 vs 9	1.364	0.561	3.313
rxgen	1 vs 4	1.152	0.944	1.406
rxgen	2 vs 4	1.016	0.854	1.207
rxgen	3 vs 4	1.067	0.893	1.274
indexyr	2011 vs 2015	0.129	0.113	0.149
indexyr	2012 vs 2015	0.409	0.366	0.456
indexyr	2013 vs 2015	0.592	0.531	0.661
indexyr	2014 vs 2015	0.892	0.796	0.999
DVT	0 vs 1	2.020	1.513	2.699
PE	0 vs 1	1.262	0.971	1.641
Vascular	0 vs 1	1.087	1.017	1.163
ESRD	0 vs 1	1.196	1.054	1.357
CHF	0 vs 1	1.251	1.073	1.458
AF	0 vs 1	1.382	1.214	1.573
INPATIENT	0 vs 1	1.144	0.990	1.322

Association of Predicted Probabilities and Observed Responses

Percent Concordant   68.6   Somers' D   0.371

Percent Discordant   31.4   Gamma   0.371
Percent Tied   0.0   Tau-a   0.173
Pairs   139300551   c   0.686

Appendix 2: Distribution of propensity scores
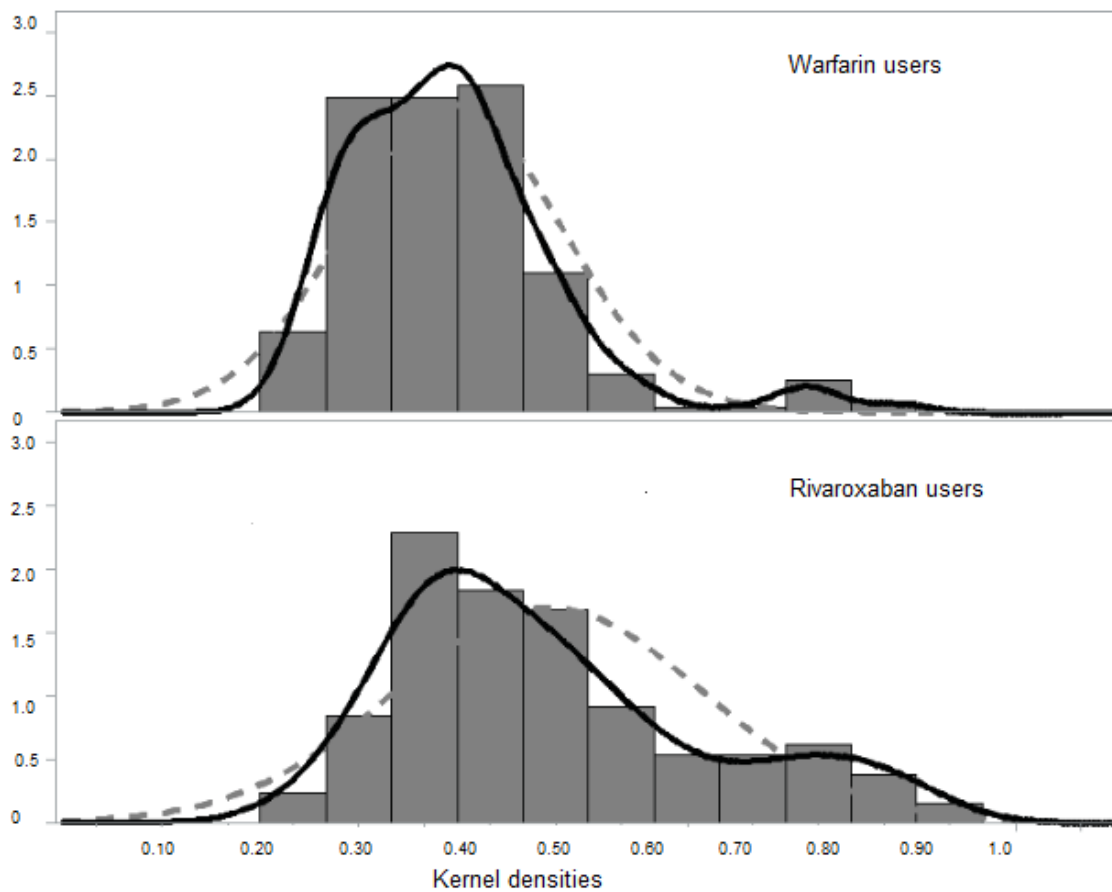
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