Patient Outcomes with Warfarin Therapy after Hip and Knee Replacement: Comparison of Two Models of Care

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THESIS

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This thesis is dedicated to my dearest parents for their love and support through this journey. Thank you, Daddy for being my inspiration to persevere in the pursuit of learning. Thank you, Ma for your unconditional love and faith in me.

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LIST OF ABBREVIATIONS

US	United States
VTE	Venous thromboembolism
DVT	Deep Vein Thrombosis
PE	Pulmonary Embolism
INR	International Normalized Ratio
TTR	% Time in Therapeutic Range
ICD-9	International Classification of Diseases, 9th Edition
ACC	Specilialized Anticoagulation Clinic
RMC	Routine Model of Care
ATE	Average Treatment Effect
ATT	Average Treatment Effect for Treated
ORadj	Adjusted Odds Ratio
95% CI	95% Confidence Interval
Std Err	Standard Error
WHO	World Health Organization

SUMMARY

According to National Hospital Discharge Survey, the number of surgeries performed in the year 2007 in United States (U.S.) was 543,000 total knee replacement (TKR) and 230,000 total hip replacement (THR). Patients undergoing THR and TKR surgeries are at a high risk for venous thromboembolism (VTE). To reduce the risk of VTE post-surgery, evidence-based guidelines by American College of Chest Physicians (ACCP) recommend different anticoagulant therapies, such as fixed doses of subcutaneous low molecular weight heparin (LMWH), fixed doses of subcutaneous fondaparinux, adjusted doses of oral warfarin, to maintain a target international normalized ratio (INR) of 2.5 (range 2 – 3) OR newer oral anticoagulants.

Warfarin is the most commonly used drug for patients undergoing hip and knee replacement surgery. Although the effectiveness of warfarin has been established, management of patients on warfarin therapy has been a challenge in clinical practice settings. Warfarin related adverse events contribute significantly to the economic and clinical burden. The three models of anticoagulation management that exist in the U.S. are (i) routine care provided by general practitioners or nurses (ii) systematic and coordinated care provided by trained pharmacists or physicians at specialized anticoagulation clinics and (iii) patient self-management (PSM) or patient self-testing (PST).

While the findings of various comparison studies found that pharmacist-managed anticoagulation clinic shows improved outcomes for patients as compared to routine care, these studies largely consisted of patients having an indication such as atrial fibrillation which requires long-term therapy. Warfarin therapy and related clinical outcomes have not been compared between two models of care for patients receiving post-surgery VTE prophylaxis which requires a short-term therapy. In addition, most of the previous studies had enrolled relatively stable patients who had been on warfarin therapy for at least 3 months. The post-surgical VTE

prophylaxis for patients undergoing THR and TKR has been recommended from 10 days to 35 days by ACCP. Therefore, achieving an adequate anticoagulation control by maintaining INR within therapeutic range early on in these patients is essential.

Although data are available on comparing management in different care settings, the published evidence lacks information regarding the referral patterns post-surgery to anticoagulation clinic and routine care. The first objective of the study was to examine association between race and referral patterns for anticoagulation management in patients who have undergone THR and TKR surgery. The second objective of this study was to investigate the association between type of anticoagulation clinic and TTR in patients undergoing THR and TKR.

We conducted a retrospective, observational study of patients who underwent hip or knee replacement surgery at University of Illinois Hospital and Health Sciences System (UIHHSS) between the years 2000 and 2009 and were referred to either anticoagulation clinic or orthopedic clinic at UIC for post-surgical prophylaxis. The association between race and type of clinic was expressed in odds ratios (OR) with 95% confidence interval (95% CI) was determined using multivariate logistic regression. The treatment effect of anticoagulation clinic on TTR was expressed as % change in TTR using several matching and propensity score methods. We conducted several sensitivity analyses to evaluate the robustness of our results.

There were 873 patients that met the criteria for inclusion in cohort. Within this cohort, there 294 were referred to anticoagulation clinic and 573 to orthopedic clinic. The majority of the study cohort patients were female (68.3%) and average age of the cohort was 59 years. Compared to Caucasian patients, African American (ORadj=1.543, 95% CI =0.929-2.563) and Hispanic (ORadj=4.244, 95% CI =2.378-7.574) patients were more likely to be referred to

Anticoagulation clinic whereas other race patients (ORadj=0.164, 95% CI =0.050-0.545) were less likely to be referred to anticoagulation clinic adjusting for the covariates.

The adjusted mean TTR was 8.96 % higher after matching on propensity scores and 8.79 % higher after matching covariates for patients who were referred to anticoagulation clinic. For the overall group, the weight adjusted mean TTR was higher by 6.60% and for those referred to anticoagulation clinic as compared to those being followed at orthopedic clinic and was 9.02% higher for patients who received warfarin therapy at the anticoagulation clinic. For overall group, mean TTR was higher by 7.1% for anticoagulation clinic compared to orthopedic clinic on using inverse probability weighting combined with regression adjustment and 9.08% higher for patients referred to anticoagulation clinic.

First, this study adds to the existing body of literature that compares anticoagulation models of care for patients receiving warfarin therapy. We found that race adjusting for socio-economic status and disease severity influences the patient referral pattern to outpatient clinics for receiving VTE prophylaxis after undergoing hip and knee replacement surgery. Hispanic patients, patients with Medicare and >4 risk factors for VTE receive warfarin therapy at specialized anticoagulation clinic. Second, the study demonstrates that anticoagulation clinic had an association with better TTR for a short-term therapy of VTE prophylaxis post hip and knee replacement surgery. Patients in anticoagulation clinic had a higher TTR as compared to those in orthopedic clinic if we assume that patients were randomly referred to either of the two clinics. It is important to note that this was a single center study. Future research needs to be done to understand the impact of specialized anticoagulation care as compared to routine model of care in a larger diverse sample of patients receiving warfarin therapy.

1 INTRODUCTION

1.1 Background and Problem Statement

Total joint replacement surgeries have been recommended for severe cases of joint pain, mainly osteoarthritis. These surgeries result in reduction of pain, improvement of mobility and quality of life.[1,2] According to National Hospital Discharge Survey, the number of surgeries performed in the year 2007 in United States (U.S.) were 543,000 total knee replacement (TKR) and 230,000 total hip replacement (THR).[3] Moreover, the demand for THR surgery is projected to grow by 174% from 208,600 in 2005 to 572,000 in 2030 and the demand for TKR surgery by 673% from 450,000 in 2005 to 3.48 million procedures in 2030.[4]

Patients undergoing THR and TKR surgeries are at a high risk for venous thromboembolism (VTE) which comprises of two conditions - deep vein thrombosis (DVT) and pulmonary embolism (PE). Venous thromboembolism is a post-surgical complication that results in increased morbidity, mortality and economic burden.[5] For example, Ollendorf et al. examined the discharge summaries and itemized bills of 105,562 patients from 220 U.S. acute care hospitals. They found that patients with VTE spend ten times longer time in the intensive care unit and incur approximately twice the costs for inpatient care compared with patients without VTE. The mortality rate in patients with PE was the highest at 19.49% , followed by 2.51% in patients with DVT and 1.02% for patients without VTE.[5,6] To reduce the risk of VTE post-surgery, evidence-based guidelines by American College of Chest Physicians (ACCP) recommend different anticoagulant therapies, such as fixed doses of subcutaneous low molecular weight heparin (LMWH), fixed doses of subcutaneous fondaparinux, adjusted doses of oral warfarin, to maintain a target international normalized ratio (INR) of 2.5 (range 2 – 3) or newer available oral anticoagulants.[7]

Warfarin is the most commonly used drug for patients undergoing hip and knee replacement surgery.[8] For example, a survey conducted by the American Association of Hip and Knee Surgeons reported that 66% of patients undergoing THR and 59% of patients undergoing TKR are given warfarin prophylaxis.[8] Although the effectiveness of warfarin has been established, management of patients on warfarin therapy has been a challenge in clinical practice settings. Warfarin related adverse events contribute significantly to the economic and clinical burden. Using data from National Electronic Injury Surveillance System (2007 through 2009), Budnitz et al. showed that the highest frequency and rates of hospitalization after emergency department visits in patients aged 65 years old or older for adverse drug events were due to warfarin.[9] Most of the estimated 21,010 hospitalizations (95% CI, 10,126 to 31,894) were attributed to overdose of warfarin.[9] Warfarin has a narrow therapeutic index. The dose response varies by race/ethnicity, disease states or genetic constitution, and many known food and drug interactions. Therefore, patients on warfarin therapy require constant monitoring and dose adjustments.[10,11] Consequently, inadequate management of warfarin may lead to bleeding or thromboembolic events.[12] Thromboembolism is associated with sub-therapeutic INR values for patients on warfarin therapy and bleeding with supra-therapeutic INR values.[10,13] The three models of anticoagulation management that exist in the U.S. are (i) routine care provided by general practitioners or nurses (ii) systematic and coordinated care provided by trained pharmacists or physicians at specialized anticoagulation clinics and (iii) patient self-management (PSM) or patient self-testing (PST).[14] According to available evidence, routine care is currently the predominant model of care in the US.[15,16] Specialized anticoagulation clinics have evolved to standardize the care available for patients receiving anticoagulation therapy. The management for warfarin therapy is fairly complex compared to the available subcutaneous alternatives. The specialized anticoagulation clinics offer an optimal level of care for patients receiving warfarin therapy by adequate monitoring of diet and concomitant drugs and providing education to patients on warfarin therapy.[15,17] In addition, pharmacist-managed

anticoagulation clinics have demonstrated better management of patients on oral anticoagulant therapy compared to routine model of care offered by family practitioners. Patients in anticoagulation clinic have better anticoagulation control [18-26] and reduced thromboembolic and bleeding events as compared to routine model of care.[18-20] Pharmacist- managed anticoagulation clinics have reported cost savings from $860 to $162,058 per 100 patients annually.[17-19] However, the anticoagulation clinics in the U.S. provide care for approximately 30-40% of the patients on oral anticoagulation therapy.[15]

Although data are available on comparing management in different care settings, the published evidence lacks information regarding the referral patterns post-surgery to anticoagulation clinic and routine model of care. In our study, University of Illinois Hospital and Health Sciences System (UIHHSS) hospital did not follow a specific protocol for referring patients to either anticoagulation clinic or routine model of care. Patients in anticoagulation clinic were monitored by pharmacists via face-to-face visits whereas those in orthopedic clinic which functions as routine model of care were monitored by physician assistants or nurses via phone follow up. Patients referred to routine model of care were expected to have access to home care or home nursing. The probable reasons for being referred to anticoagulation clinic would be if the patients were sicker, lived closer to the clinic or had a better socioeconomic status. In addition, through anecdotal clinical resources in the clinical setting at UIHSSS, African American and Hispanic patients were more likely to be referred to pharmacist managed anticoagulation clinic as compared to routine model of care. This study aims to examine association between race and referral patterns for anticoagulation management in patients who have undergone THR and TKR surgery.

While the findings of various comparison studies found that pharmacist-managed anticoagulation clinic shows improved outcomes for patients as compared to routine model of care, these studies largely consisted of patients having an indication such as atrial fibrillation

which requires long-term therapy.[22-25] Warfarin therapy and related clinical outcomes have not been compared between two models of care for patients receiving post-surgery VTE prophylaxis which requires a short-term therapy. In addition, most of the previous studies had enrolled relatively stable patients who had been on warfarin therapy for at least 3 months.[22-25] A case of symptomatic VTE in reported within 3 months for 1.3% - 10% of the patients undergoing orthopedic surgeries.[27] The post-surgical VTE prophylaxis for patients undergoing THR and TKR has been recommended from 10 days to 35 days by ACCP.[27] Therefore, achieving an adequate anticoagulation control by maintaining INR within therapeutic range early on in these patients is essential. Notably, the literature has a gap with regards to comparison of different models of care in patients receiving VTE prophylaxis warfarin therapy after having undergone THR or TKR surgery. One of the most significant predictive factors for VTE is race. African Americans are at a higher risk of post-surgery complications as compared to Caucasians.[28-30] In the light of these facts, there is a need to evaluate the referral patterns to different models of care followed by the impact of model of care for VTE prophylaxis with warfarin therapy on anticoagulation control.

1.2 Purpose of the Study

One of the aims of this study is to examine the association of race on being referred to anticoagulation clinic post hip and knee replacement surgery and to compare time in therapeutic range (TTR) in patients receiving VTE prophylaxis at pharmacist-managed anticoagulation clinic compared to those at orthopedic clinic. Rudd et al. conducted a study with predominantly Caucasian patient populations (99%).[31] In addition, the other published comparisons of the two models of care have not specified a racial breakdown for the enrolled patients.[19,20,22,25] Literature suggests that African Americans have 30-60% higher incidence of VTE as compared to Caucasians and 2 to 3 folds higher compared to Asians, Native Americans and Hispanics.[29,32] Bhandari et al., in a 6-year study conducted in patients primarily with atrial fibrillation or

prosthetic heart valve reported that the time spent in therapeutic range was lower in African Americans compared to Caucasians.[33] This research aims to evaluate time in therapeutic range in a patient population which comprises of Caucasians, African Americans, Hispanics and other race. Additionally, our study will examine for disparities by race in being referred to a specialized clinic compared to routine model of care. The observational studies that have compared routine care and anticoagulation model of care do not adjust for confounding bias or selection bias[22,34] although several emerging methods are available. Comparisons between outcomes of patients in these two models of care may be biased due to differences in baseline characteristics and unobserved selection biases. This study attempts to reduce this bias by using the available propensity score methods to adjust for the selection bias and compare TTR between the two clinics. Propensity score in this study is defined as the predicted probability of being referred to anticoagulation clinic compared to orthopedic clinic.

The anticoagulation clinic as a model of care has not been made mandatory, but its practice has been promoted by the National Quality Forum in conjunction with Agency for Healthcare and Research Quality.[15] Results of this study could potentially add to the body of evidence supporting the anticoagulation clinic model of care.

1.3 Objectives and Hypotheses

1. To examine the association of race in patients undergoing THR and TKR on the likelihood of them being referred to anticoagulation clinic or orthopedic clinic

   H_0: There is no difference by race in the likelihood of being referred to anticoagulation clinic or orthopedic clinic.

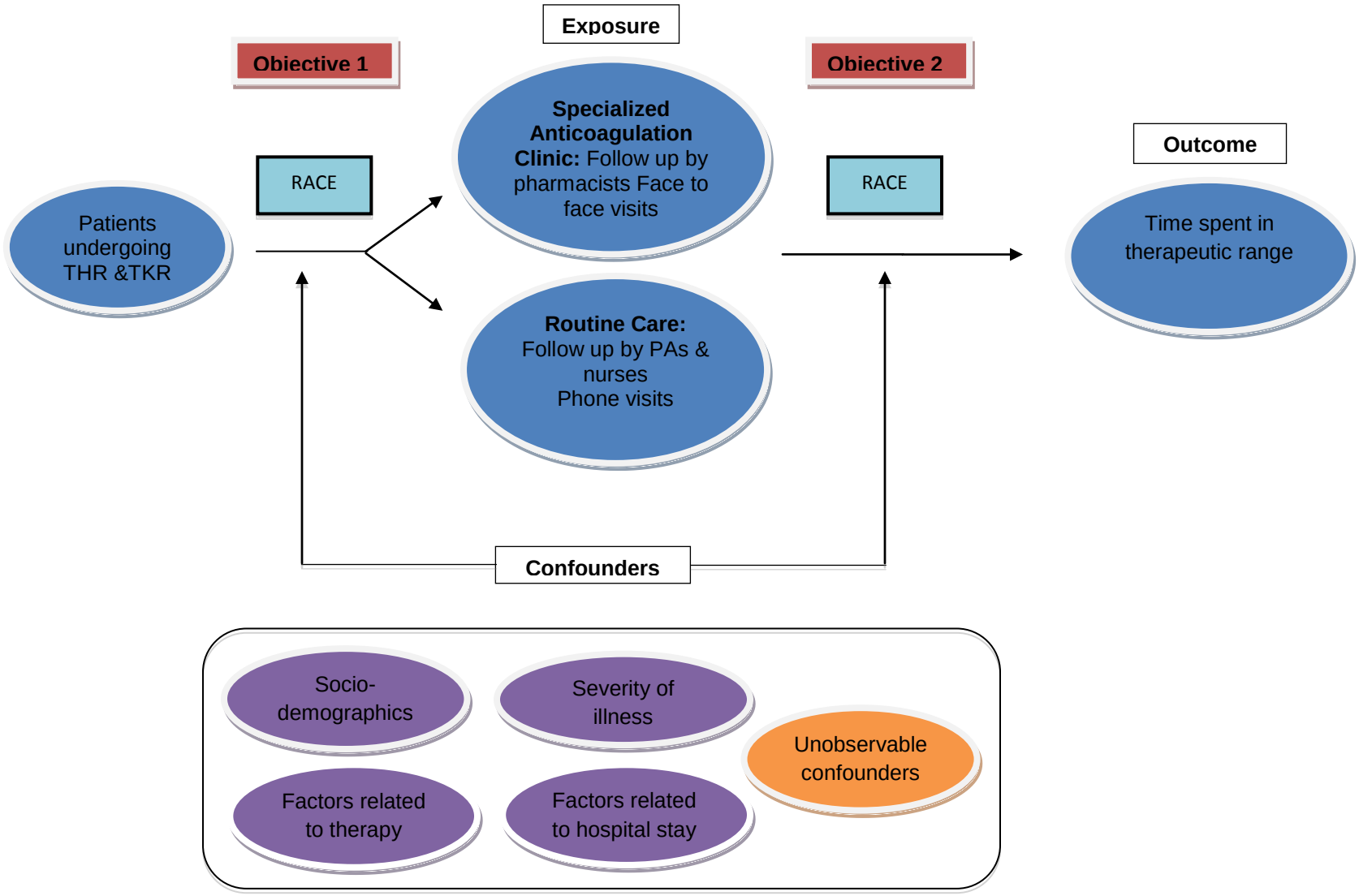
   H_A: African Americans and Hispanics compared to Caucasians are more likely to be referred to anticoagulation clinic.

2. To compare time in therapeutic range between the two clinics.

H_0: There is no difference in time in therapeutic range in patients managed in anticoagulation clinic compared to orthopedic clinic.

H_A: Time in therapeutic range is positively associated with patients managed in anticoagulation clinic compared to orthopedic clinic.

Figure 1. Conceptual Framework



1.4 Significance of the Study

Previous studies have compared anticoagulation clinic and routine model of care for patients with indications such as atrial fibrillation, aortic or mechanical heart valve replacement, cardiovascular disease and pulmonary and deep vein thromboembolism. However, none of these comparisons have focused specifically on patients undergoing THR or TKR surgeries who receive prophylaxis for VTE. Additionally, these studies have assessed patient outcomes after they have been relatively stabilized on warfarin therapy. The aim of the study is to examine patients from the initiation of warfarin therapy to understand how two different models of care are effective in maintaining the target INR for patients. Warfarin management of patients will be compared between anticoagulation clinic and routine model of care for the duration of therapy recommended by ACCP. This study aims to control for treatment selection by using different available propensity score methods. In addition, a sensitivity analyses is performed for patients who had at least 3 INR recordings. This would allow TTR to be calculated based on minimum of three readings of INR.

First, the results from this study will demonstrate whether race/ethnicity is associated with referral pattern. Second, the study will suggest the model of care that provides better management of patients on warfarin therapy and add to the existing body of knowledge on models of anticoagulation care. This research will lay the foundation for larger studies in anticoagulation practice external to UIC.

2 LITERATURE REVIEW

2.1 Total Joint Replacement

2.1.1 Definition and Epidemiology

"Osteoarthritis causes wearing of cartilage thereby exposing bone surfaces to each other leading to friction and pain".[35] It can be detected by joint symptoms, by structural pathology, or by the combination of the two. When pharmacological treatments fail to relieve the pain, patient is recommended to undergo a joint replacement surgery.[36]

The numbers of knee and hip replacement surgeries have been on the rise and they have shown to reduce pain and improve quality of life. [2] From 1990 to 2002, primary hip and knee procedures increased by 62% and 200%, respectively.[37] A nationwide inpatient sample (NIS) which is a part of Healthcare Cost and Utilization project database showed a 37% increase in THR and 53% increase in TKR performed from 2000 to 2004.[38] This study showed an increasing trend for number of surgeries for age group of 45-64 while highest number of surgeries was performed for the age group of 65-84 through 2004. Women were shown to have more number of surgeries as compared to men.[38] Using NIS data between 1993 and 2006, it showed that demand for surgeries for age group less than 65 has been projected to increase by 50% for THA by 2011 and for TKA by 2016.[4] From 2000 to 2006, TKR procedures amongst U.S. Medicare enrollees increased by 58% from 145,242 in 2000 to 248,267 in 2006.[39]

2.1.2 Clinical and Economic Burden

According to ACCP, patients undergoing these surgical procedures are recommended anticoagulation prophylaxis as they are at a particularly high risk for VTE.[27] In the absence of adequate prophylaxis, up to 60% of these patients may develop asymptomatic objectively confirmed DVT, and up to 5% may develop symptomatic VTE following surgery. Even though,

prophylaxis does not completely eliminate the possibility of VTE, it causes a significant reduction in its occurrence as it has been reported patients who receive prophylaxis may have in 1 to 10% chance of having VTE.[27] There is a significant economic burden associated with post hip or knee replacement surgery due to complications that follow.[40] According to a literature based model for THR, long-term costs associated for recurrent DVT were projected to be $3817 and for recurrent PE to be $6604. Caprini et al also showed that more than 70% of costs of VTE complications post-surgery were attributed to DVT as compared to PE.[41] As a consequence, it is important that appropriate prophylaxis against VTE is given to patients with adequate monitoring and follow-up. Data from a healthcare claims database for patients undergoing THR showed that estimated mean billed charges for the index admission were $36,705 in patients with no VTE, $62,558 in patients with in-hospital VTE, and $34,970 for post-discharge VTE.[40,42] They estimated costs for TKR as well which were $35,601 in patients with no VTE, $44,898 in patients with in-hospital VTE, and $31,774 for post-discharge VTE.[40,42]

2.1.3 Treatment and Prophylaxis

Three pharmacological options have been recommended by ACCP:

1) Low molecular weight heparin (LMWH) at a usual high-risk dose, started 12 h before surgery or 12 to 24 h after surgery, or 4 to 6 h after surgery at half the usual high-risk dose and then increasing to the usual high-risk dose the following day);

2) Fondaparinux (2.5 mg started 6 to 24 h after surgery); or

3) adjusted dose VKA started preoperatively or the evening of the surgical day (INR target, 2.5; INR range, 2.0 to 3.0).

4) Aspirin

5) Newer oral anticoagulants- dabigatran, rivaroxaban, apixaban.[7]

2.2 Warfarin

Warfarin has been most commonly prescribed in North America for the following indications: atrial fibrillation, myocardial infarction, prevention and treatment of VTE and mechanical heart valves.[10] Approximately, 4 million patients in United States are on warfarin therapy.[43] It has a narrow therapeutic index and numerous interactions with diet and drugs.[10] Hence, adequate monitoring and patient education is of paramount importance.

2.2.1 Mechanism of Action

Warfarin functions by blocking the regeneration of vitamin K epoxide by inhibiting the C1 subunit of the vitamin K epoxide reductase (VKORC1) enzyme which is required for carboxylation of the clotting factors and proteins C and S. Even though it suppresses the formation of biologically active clotting factors, it does not affect the factors which have been synthesized. Since, different factors, and proteins C and S have different half lives, it takes 3-4 days for a therapeutic effect of warfarin to be seen.[10,44,45] The starting dose of warfarin needs to be adjusted taking many factors into consideration and should be as individualized as possible.

2.2.2 Pharmacokinetics and Pharmacodynamics

Warfarin is a highly protein bound drug mainly albumin.[37] Warfarin is quickly absorbed from the gastrointestinal tract and is metabolized by the CYP450 liver enzymes. It has a bioavailability of more than 90% on oral administration.[10,44,45] Dose requirements need to be adjusted frequently due to the wide inter-individual differences in hepatic metabolism. Concurrent medications prescribed may increase or decrease the metabolism of warfarin and also need to be taken into account while determining the correct dose.[46]

2.2.3 Pharmacogenomics and Race

The metabolism of warfarin is affected by genetic factors like variations in the CYP2C9 isozyme in the liver. Genetic polymorphisms of the enzyme Vitamin K epoxide

reductase also play a role when health care providers decide the warfarin dose.[10,44,47] The metabolism of warfarin is affected by genetic factors like variations in the CYP2C9 isozyme in the liver. Genetic polymorphisms of the enzyme Vitamin K epoxide reductase also play a role when health care providers decide the warfarin dose.[10,44,47] Generally, patients with different CYP2C9 expressions have higher risk for over anticoagulation and hence are given lower warfarin doses. Genetic variation differs by races, 20% Caucasians, 5% African Americans and 2% Asians carry at least one variant of CYP2C9 and 27% Caucasians, 14% African Americans and 89% Asians carry at least one variant of Vitamin K epoxide reductase complex subunit 1. This difference leads to different dose requirements of warfarin.[48,49] These genes variation does not explain low dose requirements in Hispanics as compared to Caucasians and Asian population.[46] Some recent studies have shown that gene-based dosing does not necessarily improve clinical outcomes.[49-51] A study in older population showed that gene-based dosing over-estimated the dose of warfarin to this population.[51] Another study that focused on patients undergoing THR and TKR, gene-based dosing did not improve INR outcomes.[50]

2.2.4 Factors to be Considered during Initiation of Warfarin Therapy

Patient specific characteristics such as age, weight, height, race, concomitant medications, and co-morbidities are to be taken in consideration when selecting the warfarin dose. Although, from the literature we know that genotyping could play a role in determining the dose, there has not been incorporated into practice.

Age: Increased age has shown to be associated with increased bleeding risk with warfarin therapy particularly during the initial 3 months of the therapy. The dose requirements decrease

for patients >60 years.[10,46,52,53] Other probable factors such as increase in number of co morbidities and medications are associated with elderly patients which affect the INR or dose requirements. A dose of ≤ 5mg with close monitoring has been recommended in these patients by American College of Chest Physicians (ACCP).[10,46,54]

BMI: Some trials have demonstrated that BMI is positively associated with warfarin dose[52,55] while some do not show any association of BMI with warfarin dose.[46,56] The effect of BMI on warfarin dosing remains uncertain.[46]

Co-morbidities: Warfarin dose has to be adjusted with caution in patients with co-morbidities such as live impairment, renal impairment, thyroid disease, congestive heart failure and acute illnesses.[46] Warfarin is metabolized by enzyme P450 in the liver and hence its impairment causes reduction in formation of metabolites with reduced activity. This lack of functioning in its usual capacity leads to supratherapeutic INRs thereby increasing the risk of hemorrhage.[46,57] Renal disease is a risk for bleeding for patients on warfarin therapy.[46] Although, warfarin is metabolized to its minimally active form in the liver and excreted through kidney, a recent study suggests that patients with severe kidney impairment require lesser daily dose of 3.9 mg warfarin as compared to 4.8 mg in patients with mild impairment.[46,58] Hyperthyroidism has been associated with increased warfarin sensitivity.[46] The probable reasons could be reduced production of vitamin K-dependent clotting factors or increased catabolism of prothrombin and factor VII. Hence, lower doses would be given to these patients whereas patients with hypothyroidism require higher doses. [46] Congestive heart failure has been associated with a decrease in warfarin dose requirements in all regression analyses examining patient-specific variables on warfarin response. There is more evidence required to establish this finding firmly. Some studies have shown fever to be associated with increased INR values. [46 59]

Drugs: There is adequate evidence which confirms several drug interactions with warfarin can affect INR and cause serious adverse events. Drugs may either potentiate or inhibit the effect if warfarin. Clinical significance of herbal interactions is yet to be established even though growing

emerging evidences suggests possibility of an interaction between certain herbal medications and warfarin.[60] Holbrook et al. conducted a meta-analysis of the existing literature on drug interactions with warfarin and categorized them into highly probable, probable, possible and highly improbable clinically significant interactions.[61] For this study, we will be focusing on highly probable and probable clinically significant interactions only that include the following drugs.[61]

Highly probable potentiating: Ciprofloxacin, Cotrimoxazole, Erythromycin, Fluconazole, Isoniazid (600 mg/d), Metronidazole, Miconazole, Voriconazole, Amiodarone, Clofibrate, Diltiazem, Fenofibrate, Propafenone, Propranolol, Sulfinpyrazone (biphasic with later inhibition), Phenylbutazone, Piroxicam, Alcohol (if concomitant liver disease), Citalopram, Entacapone, Sertraline.

Probable potentiating: Amoxicillin/clavulanate, Azithromycin, Clarithromycin, Itraconazole, Levofloxacin, Ritonavir, Tetracycline, Acetylsalicylic acid, Fluvastatin, Quinidine, Ropinirole, Simvastatin, Acetaminophen, Acetylsalicylic acid, Celecoxib, Dextropropoxyphene, Interferon, Tramadol, Disulfiram Choral hydrate, Fluvoxamine, Phenytoin (biphasic with later inhibition).

Highly probable inhibiting: Griseofulvin, Nafcillin, Ribavirin, Rifampin, Cholestyramine, Mesalamine, Barbiturates, Carbamazepine.

Probable inhibiting: Dicloxacillin, Ritonavir, Bosentan, Azathioprine, Chlordiazepoxide.

2.2.5 International Normalized Ratio

This is a lab test that reports standardized values of prothrombin time (PT) ratio and is used to monitor patients who are on warfarin therapy.[62,63] PT represents time for clot formation of blood when thromboplastin along with adequate amounts of Calcium is added to the plasma. There is a variation observed in prothrombin time due to differences in sensitivity levels of thromboplastin reagents having different levels of sensitivity. Hence, World Health Organization (WHO) introduced a reference thromboplastin in order to obtain standardized values of prothrombin time using International Sensitivity Index(ISI). “ISI is a measure of thromboplastin

responsiveness compared to WHO's reference". INR is calculated by using the following formula: INR= (Prothrombin time of patient/mean of normal range) ^{ISI}.[44,63] For most of the indications including VTE, the recommended INR range is 2-3. It is crucial to monitor INR values as higher values would increase the risk of bleeding and lower values would pose a risk to thromboembolic events. During, initiation of warfarin therapy, patient's INR values are monitored frequently until a patient has been stabilized and their individualized dose regimen has been established.[44] Time in therapeutic range is an important as it delineates the stability of warfarin therapy and is calculated as total number of INR values in goal INR range/ Total number of INR values. A study reported that the annual incidence of recurrent VTE is 16% when TTR is less than 45% and 4.6% when TTR is greater than 65%.64.

2.3 Models of Care

It is crucial to reach and maintain the INR levels of patients within the goal range for effectiveness and safety of the warfarin therapy. There are three models of anticoagulation management that exist, routine care provided by general practitioners, systematic and coordinated care provided by specialized anticoagulation clinics, and patient self-management (PSM) or patient self-testing (PST).[14] Specialized anticoagulation clinics are managed by pharmacists, nurses and physicians assistant.[15] PST requires a patient to test at home and communicate the results to the provider via telephone or internet and PSM in addition requires management of doses using an algorithm.[14]. There are about 3000 anticoagulation clinics that exist in United States which manage about 30-40% of patients receiving oral anticoagulation[15,17] and about 1.6% of patients engage in self-testing[16]. Therefore, it is evident that majority of the patients are managed by routine model of care.

Specialized anticoagulation clinics have evolved in order to facilitate and optimize the delivery of care for patients on oral anticoagulation therapy. They have achieved high standards

by improving clinical outcomes such as maintaining time in therapeutic range and reducing thromboembolic and bleeding complications.[15,17] National Quality Forum in conjunction with Agency for Healthcare and Research Quality has encouraged practice of this model of care as one of the 30 National Safe Practices for Better Health care.[15] As evidence shows, routine model of care is currently the predominant model of care in United States.[15,16] Approximately, 60-70% of patients of oral anticoagulation are managed by this model of care. Family practitioners usually deliver care to patients in this model of care.[15] Patients could also adapt either to self-testing or self-management. Patients are trained on how to obtain INR results using the patient self-testing device at home. These results are then communicated via phone or internet to the health care provider who then modifies and recommends the dose of warfarin based on the reported result. In case of self-management, patients are trained in altering the self-dose and sometimes provided with an algorithm for adjusting the dose. In both cases, the health-provider supervises the anticoagulation management.[14] This model of care is significantly more predominant in Europe as compared to U.S.[14,64] Self-testing is expensive, however, it is covered by Medicare and some insurance groups for major indications which include VTE.[14] There are barriers that exist to this model of care which need to be addressed. Patient perceived barriers such as fear of pricking, concerns about safety and using PST device, concerns about adequate contact with the health-care provider and cost of the PST device have been identified.[14]

The summary of the published evidence is presented in Table I. Of the 8 studies, 7 of them found significantly higher %TTR in pharmacist managed anticoagulation clinics ranging from 40-83.6% as compared to routine model of care ranging from 37-71.1%. A study by Rudd et al showed a significant decrease in number of emergency room (ER) and hospitalization visits due to thromboembolic or bleeding event in the clinic managed by pharmacists as compared to routine model of care. In addition, 2 other studies showed reduction in number of

thromboembolic events in pharmacist managed anticoagulation group as compared to routine care. All of the above studies were conducted in patients who have been stabilized on warfarin and a majority of them involved warfarin therapy due to atrial fibrillation. None of them compared anticoagulation care from the inception of their therapy for patients who have undergone THR or TKR.

TABLE1: COMPARISON OF ANTICOAGULATION CLINIC TO ROUTINE MODEL OF CARE

No.	Author; Year	N, Country, Study Design, Length of study	International normalized ratios
1	Garton and Crosby; 2011	64, United States, Retrospective Randomized Chart Review; 1 year	**%INR within therapeutic range:** 81.1% ACC vs. 71.1% RMC; p < 0.0001 **Variance in average therapeutic INR rates:** 185.2 ACC vs. 365.7; p = 0.004 RMC
2	Young et al.; 2011	193, Canada, retrospective observational cohort study, 17 months	**%INR within therapeutic range:** 73% AC vs. 65% RMC; p< 0.0001 **Expanded TTR (±3):** 91% AC vs.85%RMC; p < 0.0001 **% INRS<1.5:** 0.7% AC vs. 1.9% RMC; p <0.0001 **% INRs > 5%:** 0.3% AC vs. 0.1% RMC (p < 0.0001)
3	Rudd et al.; 2010[31]	996, United States, retrospective medical cohort study, 1 year	**INR time in range (%)** 57.4 RMC vs. 71.8 NMC vs. 83.6 ACC ; p < 0.05 **INR values in range (%)** 49.4 RMC vs. 67.3 NMC vs. 74.9 ACC ; p < 0.05 **INR values > 5.0 (%)** 2.9 vs. 2.0 vs. 1.2 ; p < 0.05 (95% CI) = 2.70 (1.57- 4.63)
4	Lalonde et al.; 2008[23]	250, Canada, randomized, controlled, open, pragmatic clinical trial, 6 months	**INR time in range (%):** 77.3% vs. 76.7% **TTER (%)** 93%% ACC vs. 91.6% RMC **Time spent within the supratherapeutic range:** 0.4% ACC vs. 0.1% RMC **Number of INR tests, incidence of** were similar in both groups.
5	Chan et al.; 2006[24]	137, Hong Kong, prospective randomized clinical trial, 2 year	**INR time in range (%):** 59% RMC vs. 64% ACC; p < 0.001

TABLE1: COMPARISON OF ANTICOAGULATION CLINIC TO ROUTINE MODEL OF CARE (CONTINUED)

No.	Author; Year	N, Country, Study Design, Length of study	International normalized ratios
6	Witt et al; 2005[20]	6645, US, Retrospective observational cohort study, 6 months	**Therapeutic INR control, %** **Days below INR target:** 24.7 (ACC) vs. 30.3 (RMC); p< 0.001 **Days within INR target:** 63.5 (ACC) vs. 55.2 (RMC); p < 0.001 **Days above INR target:** 11.8 (ACC) vs. 14.5 (RMC); p < 0.001 **Mean interval to next INR following INR:** **≥4.0 or ≤ 1.5, d (SD):** 12.0 (12.2) ACC vs. 13.5 (15.4) RMC; p < 0.03 **Total INRs**: **≥4.0 or ≤ 1.5 :** **%** 15.1 ACC vs. 20.4% p < 0.001
7	Chamberlain et al; 2001[22]	96, US, Retrospective observational cohort study, 1 year	**INRs outside target range:** 40.4%RMC vs. 47.3%ACC; p = 0.022 No significant difference in TTR.
8	Chiquette et al; 1998[19]	328, US, Retrospective observational cohort study, 3 years 5 months	**TTR:** **For lower target range (2-3):** 40.0% ACC vs. 37% RMC, p < 0.001 **For higher target range (2.5-4.5):** 64% ACC vs. 51% RMC; p < 0.001

3 METHODS

3.1 Study Design and Description of Data Source

This was a retrospective, observational study of patients who underwent hip or knee replacement surgery at UIHHSS between the years 2000 and 2009 and were referred to either anticoagulation clinic or orthopedic clinic at UIC for post-surgical prophylaxis.

3.2 Data Collection

Patient records were obtained through the medical charts from Cerner electronic medical record system using ICD 9 codes: 81.51(THR), 81.53 (revision of hip replacement), 81.54 (TKR) and 81.55 (revision of knee replacement). Each record was reviewed and eligibility was determined based on inclusion and exclusion criteria stated below:

Inclusion Criteria

- Patients who had their post-prophylaxis follow up at ATC or orthopedic Clinic at UIC.
- Patients who received warfarin for their post-prophylaxis during their follow up.

Exclusion criteria

- Patients who had a bleeding or VTE event before starting their therapy at the outpatient clinics.
- Patients with missing data on the variables that were collected.

Data including sociodemographic variables, INRs (from the time of admission in the hospital until the patients received a follow up for VTE prophylaxis at the outpatient clinics), thromboembolic and bleeding events (from the time of admission in the hospital until 90 days post-surgery) and different factors that are associated with the INR discussed in the section 2.2

were extracted from the patient records by trained personnel at UIC. Data was obtained and maintained in an excel sheet. A 10% validity check was performed on all the variables. Specifically, for a randomly selected 10% of the observations, we compared values for each variable in the data set to those in the original medical chart. The only errors found in the variables were in the coding of concomitant drugs. With respect to concomitant drugs, we observed that aspirin was often missed; however, the other variables were found to be highly valid.

3.3 Study Variables

The coding for the variables used in the analysis is summarized in Table II below. For objective 1, to examine the association of race on the likelihood of being referred to the anticoagulation clinic or the orthopedic clinic, variables were coded as described below.

Dependent variable: The dependent variable was an indicator for being referred to the anticoagulation clinic.

Key exposure variable: Race was the key exposure variable, where indicators for Caucasian, African American, Hispanic and other race were used. Asians and other race categories were combined because no Asian patient was referred to anticoagulation clinic. Also, Asians are typically at low risk of VTE. Therefore, our primary interest was to evaluate impact of being an African American or a Hispanic patient compared to being a Caucasian patient on referral to anticoagulation clinic.

Covariates: Several variables were collected for use as covariates as described below-

a) Sociodemographic variables: Controls included years of age, an indicator variable for being male, and indicator variables for marital status (having private insurance, Medicare, Medicaid or no insurance). In addition, we controlled for insurance status using indicator variables for having

private, Medicare, Medicaid or no insurance. The insurance status would serve as a proxy for socioeconomic status. Distance in miles between a patient's residence and the anticoagulation clinic was added as a covariate. Zip codes for patient's residential address were obtained from medical chart and distance between their home and clinic was calculated using Google maps. Patients staying in the vicinity of clinic would make better candidates for being referred to anticoagulation clinic.

b) Seasonal variation: Controls included indicator variables for season (spring, summer, fall and winter). Season was defined using the date of admission to the hospital obtained from medical chart.[65,66]

c) Factors related to hospital stay: We controlled for the length of inpatient stay measured in days. Inpatient stay was calculated using the date of admission to the hospital and the date of discharge from the hospital acquired from medical chart. Indicator variables were created for the type of orthopedic surgery a patient had at the hospital. They were as follows-THR, TKR, revision hip replacement and revision knee replacement. These categories were created using ICD 9 codes (81.51-THR, 81.53 - revision hip surgery, 81.54 - TKR and 81.55 - revision knee surgery). Additionally, controls included indicator variables for INR being within range (2-3) on the day of discharge from the hospital, and for having an extended stay at the hospital. Extended stay at the hospital for a patient was defined as re-admission on the next day after discharge for rehabilitation.

d) Disease severity: Indicator variables for number of bleeding risk factors- 0, 1, 2, ≥ 3[67] and number of VTE risk factors – 1,2,3, ≥ 4.[68] Stroke, gastrointestinal bleeding, age > 65, coronary artery disease, congestive heart failure, renal insufficiency, liver disease, malignancy, diabetes and genetic defects were recorded as the bleeding risk factors from the medical chart.[67,69] Surgery, trauma, immobility, cancer, cancer therapy, venous compression, previous VTE, age > 40, pregnancy and post partum, oral contraceptives, selective estrogen receptor modulator, erythropoiesis stimulation agents, acute medical illness, inflammatory bowel disease, nephrotic

syndrome, myeloproliferative disorders, paroxysmal nocturnal hemoglobinuria, obesity (BMI > 30), central venous catheterization and thrombophilia recorded as the VTE risk factors from the medical chart.[69] In addition, an indicator variable was created for being a smoker (yes or no).[46] Smoking status during the duration of therapy was self-reported by the patient.[46] Indicator variable for having thyroid disease[46] (yes or no) was created based on information obtained from medical chart.

e) Concomitant use of interacting medications: A continuous variable defined as the total number of probably and highly probable interacting drugs.[61]

For the analysis of objective 2, to compare time in therapeutic range (TTR) between patients who were referred to anticoagulation clinic and those referred to orthopedic clinic, variables were coded as below.

Dependent variable: TTR was measured as the percent of observed INR values that were within range as follows: (Total number of INR values within therapeutic INR range/Total number of INR values measured)*100. Therapeutic INR range for patients receiving warfarin therapy was defined as 2≤INRs≤3.

Key exposure variable: Exposure was defined via an indicator variable for being in the anticoagulation clinic.

Covariates: Race and the covariates mentioned above were used.

TABLE II: STUDY VARIABLES

Variable	Type	Description
Key outcome variables		
Anticoagulation clinic vs. Orthopedic Clinic	Categorical	Indicator variables for being referred to anticoagulation clinic
TTR	Continuous	Percentage of INRs in Therapeutic Range
Other outcome variables		
Thromboembolic event	Discrete	Indicator variables for experiencing a VTE event within 90 days of the surgery
Major bleed	Discrete	Indicator variables for experiencing a major bleed within 90 days of the surgery
Key exposure variables		
Type of outpatient clinic	Categorical	Indicator variables for being referred to anticoagulation clinic
Race	Categorical	Indicator variables for being Caucasian, African American, Hispanic or other race
Covariates		
Age	Continuous	Values in years obtained from the medical records
Gender	Categorical	Indicator variable for being male
Marital Status	Categorical	Indicator variables for being married, single, divorced, widowed or separated
Insurance Status	Categorical	Indicator variables for having private, Medicare, Medicaid or no insurance
Distance	Continuous	Distance in miles calculated using zip codes
Season during the surgery	Categorical	Indicator variables for being admitted in Summer, Spring, Fall or winter
Type of surgery	Categorical	Indicator variables for TKA, THA, Revised TKA, Revised THA
Duration of inpatient stay	Continuous	Date of discharge- date of admission from medical charts
State of INR at the end of therapy	Categorical	Indicator variable for INR being within target range on the day of discharge
Extended stay	Categorical	Indicator variable for having an extended stay at the rehabilitation post-discharge
Number of bleeding risk factors	Categorical	Indicator variables for having 0, 1, 2 or ≥ 3 factors
Number of VTE risk factors	Continuous	Indicator variables for having 1, 2, 3 or ≥ 4 factor
Smoking Status	Categorical	Indicator variable for being a smoker
Thyroid disease	Categorical	Indicator variable for having thyroid disease
Concomitant interacting drugs	Continuous	Total number of drugs that may interact with warfarin

3.4 Power Analysis

For objective 1, to examine the effect of race in patients undergoing THR and TKR on being referred to anticoagulation clinic or orthopedic clinic, a range of sample sizes were calculated using G*Power 3.1.3. Sample sizes were estimated based on a Type 1 error $\alpha = 0.05$ and a power $(1-\beta) = 0.8$. We used one-sided tests because we were testing for a positive association between being African American or Hispanic on being referred to anticoagulation clinic. No literature is available for evaluating referral pattern for patients who have undergone hip and knee replacement surgery. Therefore, we calculated a range of sample sizes by varying the proportion of patients in anticoagulation clinic and odds of being referred to anticoagulation clinic. The proportion of patients in anticoagulation clinic was varied from 0.2-0.8. We varied odds of being referred to anticoagulation clinic from .2 to 4. The squared multiple correlation of the anticoagulation clinic with all the covariates described in section 3.3 was assumed to be 0. Table III summarizes the results for sample size calculation for the effect of race on being referred to the anticoagulation clinic.

TABLE III: SAMPLE SIZE CALCULATION FOR THE EFFECT OF RACE ON BEING REFERRED TO THE ANTICOAGULATION CLINIC

OR / P	1.2	1.4	1.6	1.8	2	4
0.2	4416	1247	620	387	273	64
0.4	3055	891	456	292	211	58
0.6	3168	953	501	328	242	76
0.8	4926	1526	822	550	413	144

For objective 2, a range of sample sizes were calculated using SAS software 9.2 (SAS Institute Inc., Cary, NC) to detect a difference in TTR in patients receiving care at anticoagulation clinic and those at orthopedic clinic. Because this is a new study, effect sizes were not available. We varied the effect sizes from 0.2 to 0.8 and calculated the corresponding sample sizes.[70] For a one-tailed t-test with significance (alpha) set to 0.05 and power set to 80%, the required sample size to detect a small effect of 0.2 was 1084. For a medium effect of 0.5 it was 128, and for a large effect of 0.80 it was 70.

3.5 Data Analysis

All analyses were carried out in SAS version 9.2 (SAS Institute, Cary, NC) and STATA, version 11.0 (STATA Corp., College Station, TX).

Baseline cohort characteristics

Descriptive statistics were performed to compare the patient characteristics between the two clinics. Means for continuous variables were compared by using t-test and frequencies for categorical variables were compared by using chi-squared test between the two clinics.

Evaluation of objective 1: Association between race of a patient and being referred to anticoagulation clinic

A logistic regression analysis was performed. The following equation (1) is a general representation of logistic regression model where Y_i = probability of an outcome given X_1= 1 when adjusted for p covariates for observation i (i= 1, 2,…., N).

$$\mathbf{ln\ (Y_i|X_1=1) = X_{i\times p}\ \beta_{p\times 1} + e_i}$$

Where $y_i = n_i x1$ vector of responses for i

$X_i = n_i \times (p+1)$ covariate matrix

β = (p+1) x 1 vector of regression coefficients

$e_i = n_i$ x 1 vector of residuals.

An indicator for being in the anticoagulation clinic was regressed on race adjusting for the covariates mentioned in section3.3. The statistical significance of the coefficients (β) was tested using Wald chi-square statistic.

The likelihood ratio test was used to evaluate goodness of fit of the model. The statistical significance of the model was tested using a chi-square statistic. A p value of > 0.05 was used indicate a good model fit to the data.

Evaluation of objective 2: Comparison of time in therapeutic range in patients between anticoagulation clinic and orthopedic clinic

A key issue in evaluating objective 2 was the potential for being selected into anticoagulation clinic compared to orthopedic clinic. Several methods are available in the literature to adjust for selection bias. Several strategies for controlling for selection were applied in measuring the treatment effect. First, a general framework for understanding treatment effect in context of our study is presented, followed by assumptions considered for analysis, and the different methods used to adjust for selection bias and estimate the impact of anticoagulation clinic on TTR.

General framework for the analysis

The treatment effect we seek to measure is a causal effect of a given treatment. This means that a difference between the TTR for a patient in an anticoagulation clinic and a TTR for the same patient in an orthopedic clinic would be required to estimate true treatment effect. It is not possible to obtain the true treatment effect at the patient level since a patient would have a TTR for being referred either to an anticoagulation clinic or to an orthopedic clinic at a given

point in time. Hence, we focus on determining the effect of treatment on outcomes using what is referred to as the average treatment effect (ATE) and the average treatment effect on the treated (ATT). The ATE is the expected effect for a randomly selected individual patient from the population and the ATT is the average effect from treatment for those who actually were treated. To estimate the ATE and ATT, we will calculate the potential unobserved outcomes by using matching and propensity score methods which are described below.

Throughout the analysis, we use the unconfoundedness assumption which relies upon an assumption that the being referred to the anticoagulation clinic is independent of TTR given the available baseline covariates. This assumption is supported by the fact that variables that were most likely to confound any comparison between patients referred to an anticoagulation clinic and those referred to an orthopedic clinic were used in the analysis. In addition, we assume that the conditional probability (propensity score) for being referred to an anticoagulation clinic is always positive.

ATE and ATT were estimated using the following methods: nearest neighbor matching method using propensity scores and covariates, inverse probability weighting, regression adjustment, and inverse probability weighting combined with regression adjustment.

3.5.1 Nearest Neighbor Matching using Propensity Scores

Using this approach, a patient in the orthopedic clinic was matched to a patient in anticoagulation clinic on similar values of propensity scores without replacement. Propensity scores were constructed using results from logistic regression. Log values of these propensity scores were calculated. The patients were matched using the using the logit of propensity scores using 1:1 match.[71-73] The matching was performed by specifying a caliper value which is a pre-specified maximum distance by which the two treatment groups are allowed to differ. The formula used to calculate the caliper value was[71-73] –

= 0.2 * √σ2 of the logit of the propensity score

= 0.2*1.95

We chose a caliper of 0.2 based on a recent study that showed that caliper width of 0.2 removed 98% of the bias from the crude estimator.[74] Rosenbaum and Rubin have suggested that logit of a propensity score has approximately normal distribution.[75] Histograms were generated using the estimated propensity scores to compare the overlap between the two clinics and non-overlapping portions were trimmed. Comparison of the two matched treatment groups was done using a t-test. In addition, reduction in overall bias was estimated in the matched sample to support the results obtained from t-test.[76] A t-test by itself may not be reliable estimate as the groups may appear to be balanced because of the reduction in sample size.[76] ATT was calculated using STATA for the continuous outcome.

3.5.2 Nearest Neighbor Matching using Selected Covariates

This approach was used to match patients from orthopedic clinic to those in anticoagulation clinic with similar values for the selected covariates with replacement.[77] These covariates used for matching the two groups were selected by calculating the difference in means of covariates between the two clinics and retaining variables with a |t-statistic > 2|.[78] This method is based on minimizing distance between vectors of the covariates. All the covariates were divided by inverse of their variance in order to scale them prior to matching the patients between two clinics.[77] Distance was defined as the distance square root of difference between the two vectors. For every observation in the anticoagulation clinic, 4 observations were matched from orthopedic clinic. Abadie and Imbens recommend matching 4 observations to one in order to use more information to create appropriate match.[77] Bias introduced due to inexact matching on covariates was adjusted by using a bias corrected matching estimator suggested by Abadie and Imbens.[77] This method uses results of a regression of the outcome on the covariates in a simple matched sample to adjust the outcomes of the group to be used as

matches for remaining differences in the covariates after matching. This estimator adjusts for difference in the matches due to difference in their covariate values.[77] The OLS regression function is run on matched observations and every observation is weighted by the number of times the unit is used as a match.[77]

3.5.3 Inverse Probability Weighting Based on Propensity Score

Propensity scores constructed from the results of the logistic regression were used as inverse weights. A weight of 1/propensity scores (1/ps) was given to patients referred to anticoagulation clinic (t=1) and 1/1-propensity scores (1/1-ps) to those referred to orthopedic clinic (t=0) to estimating ATE given x covariates.[72,78,79]

$$\omega\,(t,x) = t/ps + (1-t)/1-ps \quad \ldots\ldots\ldots \quad (1)$$

A weight of unity was used for the patients in anticoagulation clinic and ps/1-ps for orthopedic group for estimating ATT.[78]

$$\omega\,(t,x) = t + (1-t) * ps/1-ps \quad \ldots\ldots\ldots \quad (2)$$

These weights were normalized and histograms were generated using these normalized weights to compare the overlap between the two clinics. Comparison of the two weighted treatment groups was done using a t-test. Non-overlapping observations and observations with extreme weights were trimmed. These weights were used to estimate treatment effects using in a weighted linear regression.[80]

3.5.4 Regression Adjustment with Weighting Based on Propensity Score

This method is based on the principle that supposing that at least one of the two models: treatment assignment given the covariates or conditional mean given the covariates is correctly specified, the estimated ATE and ATT obtained will be robust.[78,81]

A variable selection process recommended by Imbens [78] was performed to select the variables to be included in the logistic regression with the type of outpatient clinic as an outcome. We calculated the difference in means of covariates between the two clinics and retained variables with a |t-statistic > 2|. The selected set of covariates was orthogonalized to address the concern related to collinearity. These orthogonalized variables were used to estimate a logistic regression to construct propensity scores. Histograms were generated using the propensity scores that were estimated using the subset of variables with a t statistic >2 from the two groups.[78] Weights were calculated using the equations 2 and 3 mentioned in section 3.5. These weights were normalized and weights > 10 were set to 10 and those < 0.1 were set to 0.1.

The subsequent variable selection procedure was performed to select confounders for regression adjustment. We ran separate linear regression models to test each potential covariate with TTR as an outcome and clinic as an exposure. Variables with |t statistic > 2| were selected to be in the model. These selected set of covariates were orthogonalized to improve numerical stability.[78]

Two separate regression models with the adjusted covariates were used to estimate ATE and ATT using a weighted regression based on the equation below.

$$Yi = \alpha 0 + \tau * Ti + \alpha 1'iXi + \alpha 2'* (Xi - mean(X)i) * Ti + ei \quad \ldots..(3)$$

The covariates were centered by adjusting the overall means ((adjusted_X = X – mean (X)) for estimating ATE and means of patients in anticoagulation clinic (adjusted_X = X – mean (X|treatment = 1)) for estimating ATT. The centering of variables was performed to minimize collinearity.[78]

3.5.5 Sensitivity Analysis

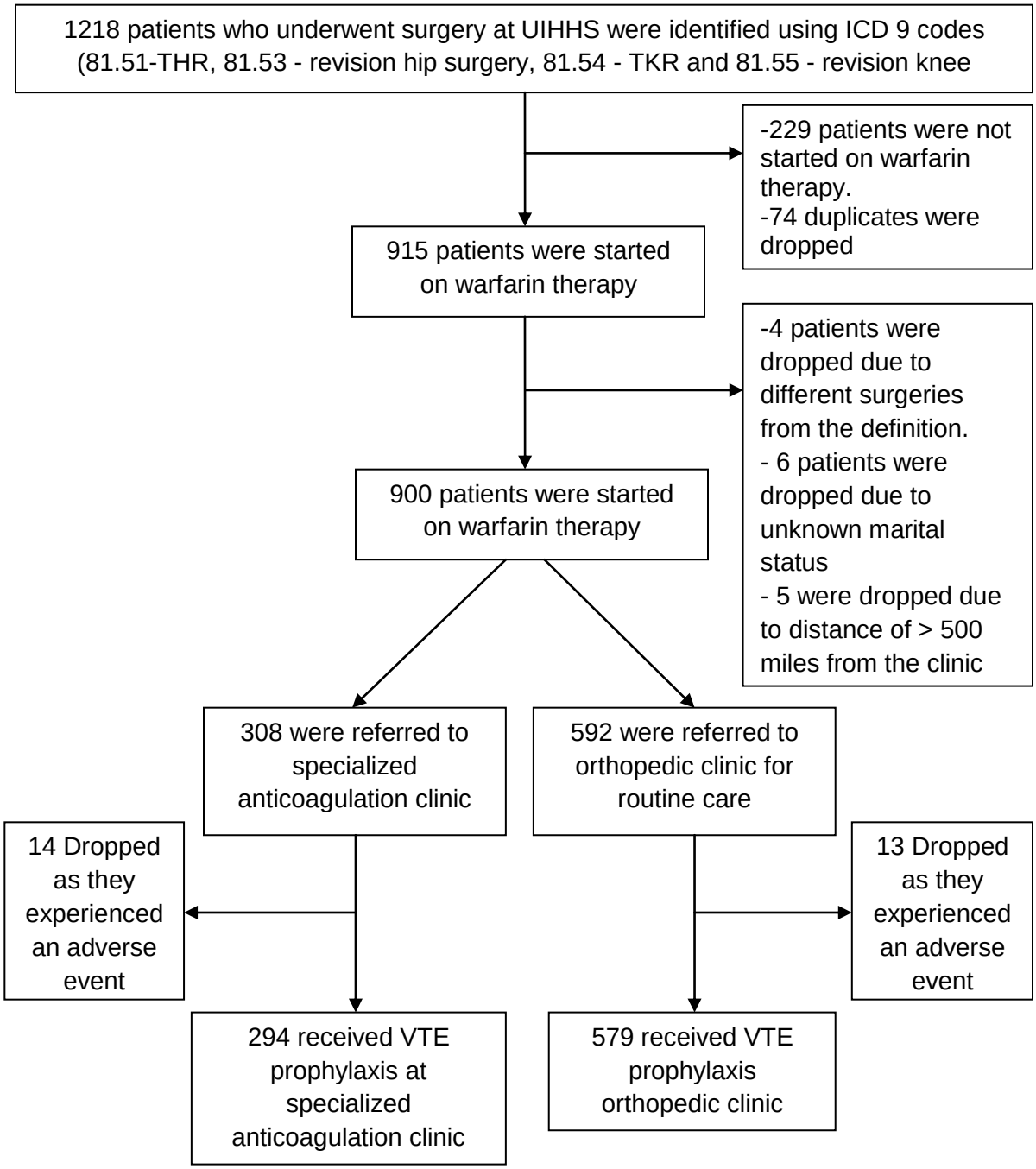
We conducted two sensitivity analyses to examine the robustness of our results. First, we limited the number of observations to those with less than three INR measurements. The methods described above were used to estimate ATE and ATT for the new cohort with observations that has at least three INR readings. Second, we included length of therapy and number of outpatient INRs measured for the two clinics in the analysis. a) We matched patients on length of therapy and number of INR measurements only and estimated ATT using matching on covariates with replacement method. b) We matched patients on significantly different covariates (refer to Table VIII) in addition to length of therapy and number of outpatient INR. WE estimated ATT for using matching on covariates method with replacement to calculate ATT.

4 RESULTS

4.1 Study Cohort

We identified 1218 patients between Jan 1, 2000 and December, 2009 using ICD 9 codes (81.51-THR, 81.53 - revision hip surgery, 81.54 - TKR and 81.55 - revision knee surgery). Within this cohort, 132 patients received fondaparinux, 63 patients received enoxaparin, 4 patients received heparin and 20 patients bridged therapy (combination of the two aforementioned drugs) and 915 patients received warfarin therapy. Figure 2 illustrates the different stages at which patients were dropped for meeting the exclusion criteria that lead to a study cohort with 873 patients. Of 873 patients, 579 were referred to orthopedic clinic and 294 were referred to anticoagulation clinic to receive warfarin therapy as a post-surgery VTE prophylaxis at UIHHS.

Figure 2. Study Cohort Entry



4.2 Baseline Cohort Characteristics

The majority of patients were female (68.3%) and average age of the cohort was 59 years. Majority of patients were African Americans (54.74%), followed by Hispanics (21.72%), Caucasians (18.04%) and other race (8.19%). Table IV presents baseline characteristics of patients stratified by the two outpatient clinics: orthopedic clinic and anticoagulation clinic. In regards with socio-demographic factors, nearly 69% female patients were referred to both anticoagulation clinic and orthopedic clinic. The average age of patients in anticoagulation clinic was lower compared to orthopedic clinic (58.51±12.73 vs. 60.24 ± 12.15). Anticoagulation clinic had a higher proportion of African American (51.99% vs. 57.48%) and Hispanic patients (28.23% vs.15.20%), a higher proportion of Medicare patients (53.40% vs. 42.14%), a higher proportion of single (39.80% vs. 37.13%), divorced (12.24% vs. 5.70%) and separated patients (4.42% vs. 2.59%). Patients living at a distance closer from the hospital were referred to anticoagulation clinic (10.28 ± 9.17 vs.14.26 ± 14.19). A higher proportion of patients were referred to anticoagulation clinic during spring (33.33% vs. 26.77%**)** and summer seasons (29.25% vs. 25.91%). In regards with clinical factors, a higher proportion of patients with >4 risk factors for VTE (16.67% vs. 3.97%) and a higher proportion of patients with no bleeding risk factors (47.96% vs. 43.18%) were referred to anticoagulation clinic. A higher proportion of smokers (18.37% vs. 5.53%) were referred to anticoagulation clinic. Patients with greater length of hospital stay (4.57% vs. 3.32%) were referred to anticoagulation clinic.

Table V presents clinical characteristics of patients stratified by the two outpatient clinics: orthopedic clinic and anticoagulation clinic. Compared to orthopedic clinic, outpatient TTR was higher in anticoagulation clinic (40.90 ± 28.93 vs. 34.20 ± 26.65). Time to reach 1st therapeutic INR in the outpatient clinics was not significantly different but patients with a greater time to therapeutic INR (n days) during their inpatient stay were referred to anticoagulation clinic (4.45 ± 2.56 vs. 3.98 ± 2.52). Bleeding and VTE events did not significantly differ in the two clinics.

TABLE IV: BASELINE CHARACTERISTICS OF THE STUDY COHORT BY CLINIC

Patient Characteristics	Orthopedic Clinic (n=579)	Anticoagulation Clinic (n=294)	P value
Age (mean, SD)	60.24 (12.15)	58.51 (12.73)	0.0509
Gender (n, %)			0.8713
Male	182 (31.43)	94 (31.97)	
Female	397 (68.57)	200 (68.03)	
Race (n, %)			
Caucasian	134 (23.14)	38 (12.93)	<.0001
African American	301 (51.99)	169 (57.48)	
Hispanic	88 (15.20)	83 (28.23)	
Asian	31 (5.35)	0 (0.00)	
Other	25 (4.32)	5 (1.36)	
Insurance Status (n, %)			
Self pay	9 (1.55)	11 (3.74)	0.0001
Private	173 (29.88)	52 (17.69)	
Medicare	244 (42.14)	157 (53.40)	
Medicaid	153 (26.42)	74 (25.17)	
Marital Status (n, %)			
Single	215 (37.13)	117 (39.80)	0.0012
Married	195 (33.68)	83 (28.23)	
Divorced	33 (5.70)	36 (12.24)	
Widowed	121 (20.90)	45 (15.31)	
Separated	15 (2.59)	13 (4.42)	
Type of surgery (n, %)			0.5861
TKR	316 (54.58)	160 (54.42)	
THR	203 (35.06)	105 (35.71)	
Revision TKR	18 (3.11)	13 (4.42)	
Revision THR	42 (7.25)	16 (5.44)	
Season (n, %)			0.0242
Spring	155 (26.77)	98 (33.33)	
Summer	150 (25.91)	86 (29.25)	
Fall	138 (23.83)	51 (17.35)	
Winter	136 (23.49)	59 (20.07)	
Risk factors for VTE (n, %)			<.0001
1	16 (2.76)	18 (6.12)	
2	212 (36.61)	129 (43.88)	
3	328 (56.65)	98 (33.33)	
4+	23 (3.97)	49 (16.67)	
Risk factors for bleeding (n, %)			0.2733
0	250 (43.18)	141 (47.96)	
1	212 (36.61)	108 (36.73)	
2	77 (13.30)	32 (10.88)	
3+	40 (6.91)	14 (4.42)	
Thyroid disease (n, %)	36 (6.22)	16 (5.44)	0.6473
Smoking status (n, %)	32 (5.53)	54 (18.37)	<.0001
Extended inpatient stay (n, %)	64 (11.05)	60 (20.41)	0.0002
Length of hospital stay in days (mean, SD)	6.38 (3.32)	7.04 (4.57)	0.0291
Length of therapy in days (mean, SD)	31.91 (10.70)	46.72 (20.29)	<0.0001
Total number of drugs (mean, SD)	1.05 (0.99)	0.96 (0.97)	0.1941
Distance in miles (mean, SD)	14.26 ± 14.19	10.28 ± 9.17	<0.0001

TABLE V: CLINICAL OUTCOMES OF THE STUDY COHORT BY CLINIC

Patient Characteristics	Orthopedic Clinic (n=579)	Anticoagulation Clinic (n=294)	P value
TTR (mean, SD)			
Inpatient	15.63 ± 21.36	17.99 ± 22.80	0.1318
Outpatient	34.20 ± 26.65	40.90 ± 28.93	0.0007
Therapeutic INR reached (n, %)			0.5226
Not reached	65 (11.23)	34 (11.56)	
Inpatient	231 (39.90)	128 (43.54)	
Outpatient	283 (48.88)	132 (44.90)	
Time to reach therapeutic INR (mean, SD)			
Inpatient	3.98 ± 2.52	4.45 ± 2.56	<0.0001
Outpatient	13.60 ± 7.05	15.88 ± 11.12	0.1756
Bleeding events (n, %)	0 (0.00)	2 (0.62)	
VTE events (n, %)			
DVT	4 (0.69)	0	
PE	0	1 (0.34)	

4.3 Association between Race and Referral to Anticoagulation Clinic

Results from the logistic regression analysis assessing the association between race and treatment assignment (type of clinic) are listed in Table VI. Compared to Caucasian patients, African American (OR_{adj}=1.543, 95% CI =0.929-2.563) and Hispanic (OR_{adj}=4.244, 95% CI =2.378-7.574) patients were more likely to be referred to anticoagulation whereas other race patients (OR_{adj}=0.164, 95% CI =0.050-0.545) were less likely to be referred to anticoagulation clinic adjusting for the relevant covariates.

There were significant associations observed between several covariates and treatment assignment. Compared to patients with private insurance, patients with Medicare were more likely to be referred to anticoagulation clinic. Widowed patients were more likely to be referred to anticoagulation clinic as compared to married patients. Patients with ≥ 3 bleeding risk factors as compared to no risk factors were less likely to be referred to anticoagulation clinic. Patients with >4 VTE risk factors were more likely to be referred to anticoagulation clinic as compared to

patient with one risk factor whereas patients with 3 VTE risk factors were less likely to be referred to anticoagulation clinic. Patients were less likely to be referred to anticoagulation clinic during fall season as compared to spring season. Smokers were more likely to be referred to anticoagulation clinic. Patients with extended length of stay in days at the hospital were more likely to be referred to anticoagulation clinic. With an increase in distance and total number of drugs were less likely to be referred to anticoagulation clinic.

Likelihood ratio test was used to examine the model fit. The log likelihood statistic is the difference between the two model fit,

- 2 Log L (Reduced model) – 2 Log L (Full Model) = 928.439– 869.855

= 58.584

The log likelihood statistic has a distribution with 1 degree of freedom with a p-value of <0.0001. Thus, the null hypothesis can be rejected at level 5%.

TABLE VI: LOGISTIC REGRESSION MODEL FOR BEING REFERRED TO ANTICOAGULATION CLINIC VS. AN ORTHOPEDIC CLINIC

Variable	Odds Ratio	OR (95% CI)	P value
Age	0.983	0.966 – 0.999	0.0418
Male	1.125	0.763 – 1.657	0.5524
African American vs. Caucasian	1.543	0.929 – 2.563	0.0233
Hispanic vs. Caucasian	4.244	2.378 – 7.574	<0.0001
Other vs. Caucasian	0.164	0.050 – 0.545	<0.0001
Self pay vs. private	3.740	1.229 – 11.381	0.0564
Medicare vs. private	2.030	1.267 – 3.251	0.3428
Medicaid vs. private	1.101	0.661 – 1.834	0.0298
Single vs. married	1.096	0.712 – 1.687	0.2850
Divorced vs. married	2.013	1.028 – 3.939	0.0920
Widowed vs. married	0.910	0.530 –1.563	0.0795
Separated vs. Married	1.906	0.727 – 4.996	0.3164
TKR vs. THR	1.230	0.840 - 1.801	0.8263
Rev TKR vs. TKR	2.273	0.898 – 5.752	0.0642
Rev THR vs. TKR	0.700	0.330 - 1.486	0.0758
Bleeding risk factor (1 vs. 0)	0.928	0.631 - 1.364	0.0419
Bleeding risk factor (2 vs. 0)	0.780	0.448 - 1.357	0.4796
Bleeding risk factor (3 vs. 0)	0.280	0.124 - 0.633	0.0041
VTE risk factor (2 vs. 1)	0.633	0.279 - 1.438	0.0729
VTE risk factor (3 vs. 1)	0.264	0.115 - 0.603	<0.0001
VTE risk factor (>4 vs. 1)	3.058	1.155 - 8.099	<0.0001
Smoker vs. Non-smoker	4.228	2.440 – 7.327	<0.0001
Thyroid disease	0.959	0.450 – 2.044	0.9139
Summer vs. Spring	0.947	0.616 - 1.457	0.2888
Fall vs. Spring	0.517	0.319 - 0.840	0.0049
Winter vs. Spring	0.904	0.565 - 1.448	0.5121
Last inpatient INR (In/out of range)	0.764	0.522 - 1.117	0.1644
Length of inpatient stay (in days)	1.015	0.961 - 1.072	0.7469
Extended stay	2.266	1.250 – 4.106	0.0070
Distance (in miles)	0.970	0.954 – 0.987	0.0005
Total number of drugs	0.835	0.700– 0.996	0.0455

4.4 Average Treatment Effect and Average Treatment Effect for Treated

4.4.1 Nearest Neighbor Matching Based on Propensity Scores

The distribution of estimated propensity scores in figure 3A shows that patients in anticoagulation clinic had higher propensity scores. Matching without replacement with a caliper of 0.196 (0.2*0.98) resulted in 287 matched pairs of patients. Figure 3B shows a sufficient overlap of propensity scores between the two clinics in the matched set.

Table VII reports the means of treated group and control group in matched set. The groups appear to be balanced and the bias decreased for majority of the covariates. Mean bias reduced from 15.9 to 7.3. The adjusted mean TTR was 8.96% (std err = 2.44, t= 3.12) higher after matching on propensity scores for patients who were referred to anticoagulation clinic.

Figure 3A. Distribution of Propensity Scores before Matching

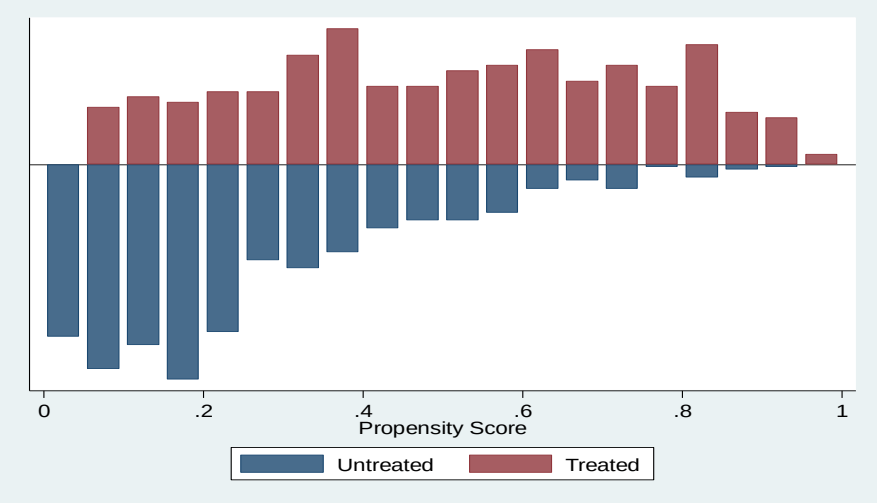


Figure 3B. Distribution of Propensity Scores after Matching

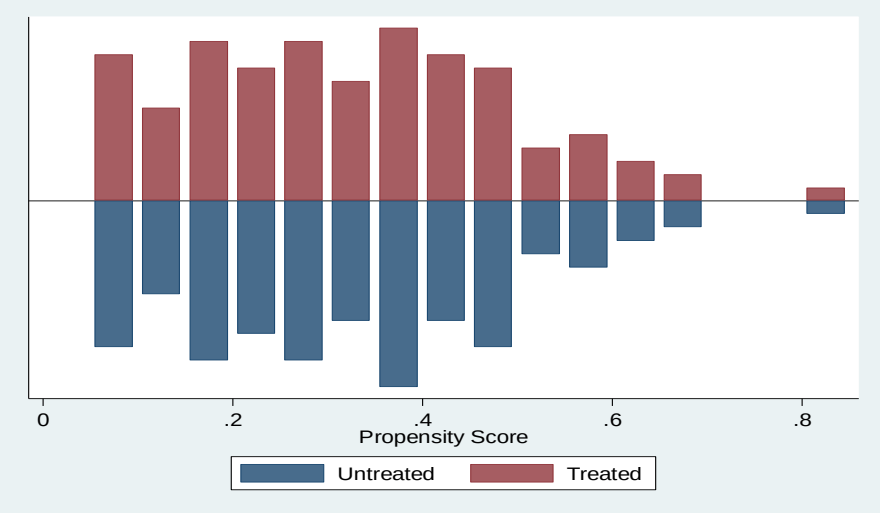


TABLE VII COVARIATE BALANCE AFTER MATCHING

Variable	Orthopedic clinic	Anticoagulation clinic	% bias reduction	t	p>|t|
Age in years	56.677	58.517	14.8	1.78	0.076
Length of inpatient stay	6.8673	7.0374	4.3	0.50	0.617
# Drugs	1.0204	0.9626	-6.0	-0.79	0.430
Distance in miles	10.703	10.283	-3.5	-0.53	0.595
Male	0.3367	0.3197	-3.7	-0.44	0.661
Black	0.5748	0.5748	0.0	-0.00	1.000
White	0.1599	0.1293	-8.0	-1.05	0.292
Hispanic	0.2449	0.2823	9.2	1.03	0.304
Other race	0.0204	0.0136	-3.0	-0.64	0.524
Single	0.4014	0.3980	-0.7	-0.08	0.933
Married	0.3231	0.2823	-8.8	-1.08	0.282
Widowed	0.1054	0.1531	12.4	1.72	0.086
Divorced	0.0986	0.1225	8.4	0.92	0.358
Separated	0.0714	0.0442	-14.8	-1.41	0.158
Private	0.1871	0.1769	-2.4	-0.32	0.749
Medicare	0.5748	0.5340	-8.2	-0.99	0.320
Medicaid	0.2007	0.2517	11.6	1.48	0.140
Self-pay	0.0374	0.0374	0.0	-0.00	1.000
THR	0.3401	0.3571	3.6	0.43	0.666
TKR	1.1088	1.0884	-2.0	-0.25	0.804
Rev. knee surgery	0.0272	0.0442	8.9	1.11	0.267
Rev. hip surgery	0.0782	0.0544	-9.8	-1.16	0.247
Spring	0.3980	0.3333	-14.1	-1.63	0.104
Summer	0.2959	0.2925	-0.8	-0.09	0.928
Fall	0.1157	0.1735	14.3	2.00	0.046
Winter	0.1905	0.2007	2.5	0.31	0.756
Thyroid	0.0408	0.0544	5.8	0.77	0.439
Smoking	0.1803	0.1837	1.1	0.11	0.915
Extended inpatient stay	0.1667	0.2041	10.3	1.17	0.244
State of INR on discharge (in vs. out)	0.2551	0.2551	0.0	0.00	1.000
VTE risk factor (n=1)	0.0850	0.0612	-11.6	-1.11	0.268
VTE risk factor (n=2)	0.4456	0.4388	-1.4	-0.17	0.868
VTE risk factor (n=3)	0.3197	0.3333	2.8	0.35	0.726
VTE risk factor (n=4)	0.1497	0.1667	5.7	0.56	0.573
Bleeding risk factor (n=1)	0.5680	0.4796	-17.8	-2.15	0.032
Bleeding risk factor (n=2)	0.2687	0.3674	20.4	2.58	0.010
Bleeding risk factor (n=3)	0.1497	0.1088	-12.5	-1.48	0.141
Bleeding risk factor (n=4)	0.0136	0.0442	13.2	2.22	0.027

4.4.2 Nearest Neighbor Matching Based on Selected Covariates

There were 25 of 40 covariates selected. Table VIII gives a list of variables that were selected. The adjusted mean TTR was 5.37% (standard error=2.53, t=2.12, p =0.0034) higher after matching on selected covariates for patients who were referred to anticoagulation clinic. The adjusted mean TTR was 8.79 % (std err = 2.42, Z = 3.63) higher after matching on propensity scores for patients who were referred to anticoagulation clinic.

TABLE VIII COVARIATES SELECTED BASED ON |T VALUE| > 2

Variables	Orthopedic clinic	Anticoagulation clinic	T value
White	0.2314	0.4221	3.88
Black	0.5199	0.5000	-1.54
Hispanic	0.1520	0.2823	-4.31
Other race	0.0967	0.0136	5.92
Single	0.3713	0.3980	-0.77
Married	0.3368	0.2823	1.63
Divorced	0.0570	0.1224	-3.05
Widowed	0.2090	0.1531	2.07
Separated	0.0259	0.0442	1.34
Self-pay	0.0155	0.0374	-1.79
Private	0.2988	0.1769	4.16
Medicare	0.4214	0.5340	0.0017
Medicaid	0.2642	0.2517	0.40
Spring	0.2677	0.3333	-2.02
Summer	0.2591	0.2925	-1.05
Fall	0.2383	0.1735	2.29
Winter	0.2349	0.2007	1.15
VTE risk factors (n=1)	0.0276	0.0612	-2.16
VTE risk factors (n=2)	0.3661	0.4388	-2.06
VTE risk factors (n=3)	0.5665	0.3333	6.67
VTE risk factors (n=4)	0.0397	0.1667	-5.46
Distance	14.26	10.28	5.00
Inpatient stay	6.380	3.3245	-2.19
Extended stay	0.1105	0.2041	-3.48
Smoking status	0.0553	0.1837	-5.23

4.4.3 Inverse Probability Weighting Based on Propensity Scores

For estimating ATE, the individual treatment weights ranged from 1.00 to 14.66 for orthopedic clinic and 1.02 to 17.72 for anticoagulation clinic. After normalizing, the new weights ranged from 0.66 to 9.7 for orthopedic clinic and 0.68 to 11.75 for anticoagulation clinic

For ATT, the individual inverse probability of treatment weights ranged from 0.0014 to 13.6635 for orthopedic clinic and unity for anticoagulation clinic. After normalizing, the new weights ranged from 0.0028 to 26.9200 for orthopedic clinic and 1.9702 for anticoagulation clinic. The stabilized weights were set to 0.10 if they were less than 0.1 and 10 if they were greater than 10.[80]

Table IX shows covariate balance of means of treated group and control group, with no adjustment, with weight adjustment for estimating ATE and ATT. The groups appear to be balanced as weight adjustment brings the means closer.

TABLE IX: COVARIATE BALANCE AFTER USING INVERSE PROBABILITY WEIGHTING

	Before applying weights				After applying weights for ATE				After applying weights for ATT			
Variable	T=0	T=1	t	p>|t|	T=0	T=1	t	p>|t|	T=0	T=1	t	p>|t|
AGE	60.25	58.52	1.93	0.0547	59.32	58.90	0.46	0.6443	58.52	57.49	-1.13	0.2589
Distance	14.26	10.28	5.00	<0.0001	13.22	12.52	0.83	0.4041	10.28	11.18	1.29	0.1992
# Drugs	1.05	0.96	1.32	0.1866	1.03	1.02	0.10	0.9225	0.96	0.98	0.30	0.7625
Male	0.31	0.32	-0.16	0.8718	0.34	0.36	-0.51	0.6127	0.32	0.39	1.94	0.0525
White	0.23	0.13	3.88	0.0001	0.20	0.20	0.07	0.9413	0.13	0.15	0.81	0.4154
Black	0.52	0.57	-1.54	0.1229	0.54	0.55	-0.35	0.7234	0.57	0.59	0.31	0.7559
Hispanic	0.15	0.28	-4.31	<0.0001	0.18	0.20	-0.43	0.6657	0.28	0.25	-1.04	0.2996
Other race	0.10	0.01	5.92	<0.0001	0.07	0.05	1.40	0.1618	0.01	0.02	0.24	0.8107
Single	0.37	0.40	-0.76	0.4464	0.37	0.38	-0.10	0.9194	0.40	0.38	-0.53	0.5938
Married	0.34	0.28	1.66	0.0976	0.33	0.35	-0.72	0.4746	0.28	0.30	0.67	0.5007
Divorced	0.06	0.12	-3.05	0.0024	0.07	0.09	-0.92	0.3596	0.12	0.09	-1.26	0.2099
Widowed	0.21	0.15	2.07	0.0387	0.18	0.15	1.16	0.2473	0.15	0.13	-0.81	0.4173
Separated	0.03	0.04	-1.34	0.1822	0.05	0.03	1.12	0.2648	0.04	0.09	2.71	0.0069
Self-pay	0.02	0.04	-1.79	0.0743	0.03	0.03	-0.42	0.6752	0.04	0.05	1.16	0.2472
Private	0.30	0.18	4.16	<0.0001	0.26	0.27	-0.43	0.6666	0.18	0.17	-0.10	0.9174
Medicare	0.42	0.53	-3.16	0.0017	0.47	0.47	-0.04	0.9677	0.53	0.57	1.02	0.3064
Medicaid	0.26	0.25	0.40	0.6886	0.24	0.22	0.68	0.4988	0.25	0.20	-1.67	0.0963
Spring	0.27	0.33	-1.98	0.0481	0.31	0.32	-0.48	0.6344	0.33	0.38	1.48	0.1406
Summer	0.26	0.29	-1.04	0.2997	0.26	0.26	0.06	0.9531	0.29	0.27	-0.57	0.5702
Fall	0.24	0.17	2.29	0.0224	0.21	0.19	0.71	0.4761	0.17	0.17	-0.17	0.8670
Winter	0.23	0.20	1.17	0.2434	0.21	0.22	-0.22	0.8271	0.20	0.17	-0.97	0.3304
TKR	1.09	1.09	0.04	0.9654	1.09	1.04	0.64	0.5226	1.09	1.09	-0.02	0.9810
THR	0.35	0.36	-0.19	0.8490	0.35	0.38	-0.97	0.3343	0.36	0.34	-0.59	0.5537
Rev. Knee	0.03	0.04	-0.94	0.3492	0.03	0.03	-0.29	0.7735	0.04	0.03	-0.97	0.3347
Rev. hip	0.07	0.05	1.06	0.2895	0.08	0.06	0.78	0.4330	0.05	0.09	1.95	0.0518
Thyroid	0.06	0.05	0.47	0.6411	0.05	0.05	0.13	0.8978	0.05	0.04	-0.95	0.3435
Smoking	0.06	0.18	-5.23	<0.0001	0.10	0.10	-0.05	0.9595	0.18	0.18	0.00	0.9995
Extend stay	0.11	0.20	-3.48	0.0006	0.14	0.14	0.11	0.9129	0.20	0.20	-0.16	0.8741
Inpatient stay	6.38	7.04	-2.19	0.0291	6.65	6.56	0.33	0.7446	7.04	7.19	0.49	0.6216
INR on discharge	0.29	0.26	1.16	0.2467	0.28	0.27	0.25	0.8015	0.26	0.25	-0.05	0.9634

TABLE IX: COVARIATE BALANCE AFTER USING INVERSE PROBABILITY WEIGHTING (CONTINUED)

	Before applying weights				After applying weights for ATE				After applying weights for ATT			
Variable	T=0	T=1	t	p>|t|	T=0	T=1	t	p>|t|	T=0	T=1	t	p>|t|
Bleeding risk=0	0.43	0.48	-1.34	0.1813	0.46	0.45	0.41	0.6820	0.48	0.52	1.10	0.2697
Bleeding risk=1	0.37	0.37	-0.03	0.9724	0.35	0.38	-0.77	0.4400	0.37	0.33	-1.14	0.2566
Bleeding risk=2	0.13	0.11	1.05	0.2949	0.13	0.12	0.34	0.7314	0.11	0.11	0.19	0.8527
Bleeding risk=3	0.07	0.04	1.56	0.1202	0.06	0.05	0.25	0.804	0.04	0.04	-0.33	0.7388
VTE risk=1	0.03	0.06	-2.16	0.0316	0.04	0.04	-0.15	0.8801	0.06	0.07	0.38	0.7016
VTE risk=2	0.37	0.44	-2.06	0.0398	0.40	0.40	-0.09	0.9246	0.44	0.45	0.38	0.7008
VTE risk=3	0.57	0.33	6.78	0.0000	0.48	0.47	0.33	0.7415	0.33	0.31	-0.55	0.5853
VTE risk =4	0.04	0.17	-5.46	0.0000	0.08	0.09	-0.31	0.7537	0.17	0.16	-0.08	0.9394

The results of weight adjusted ATE and ATT are described in Table X. Suppose that patients were randomly assigned to either of the two clinics then, the weight adjusted mean TTR was higher by 6.60% for those referred to anticoagulation clinic as compared to those being followed at orthopedic clinic. The weight adjusted mean TTR was 9.02% higher for patients who received VTE prophylaxis at anticoagulation clinic.

TABLE X: ATE AND ATT USING INVERSE PROBABILITY WEIGHTING

Method	N	Estimate	Standard error	T	P
Inverse Probability Weighting					
ATE	873	6.60	1.91	3.44	0.0004
ATT	873	9.02	1.94	4.67	<0.0001

4.4.4 Regression Adjustment with Weighting Based on Propensity Score

The variable selection criteria of selecting covariates with a t statistic ≥ 2 when compared between the two clinics led to inclusion of 25 covariates of 40. Table VIII above gives the list of variables that are selected. Propensity scores varied from 0.0014 to 0.93 for orthopedic clinic and from 0.056 to 0.97 for anticoagulation clinic. Figure 4A shows the distribution of estimated propensity scores. Figure 4B shows the distribution of the estimated propensity scores after variable selection. The weights were normalized and set to 0.10 if they were less than 0.1 and 10 if they were greater than 10.[80]

Table XI below shows balance on covariates for IPTW and regression adjustment after restriction was applied Variable selection leads to inclusion of 6 confounders in the model (black, white, Hispanic, other race, extended stay in the hospital and age).

Figure 4A. Distribution of estimated propensity scores before variable selection

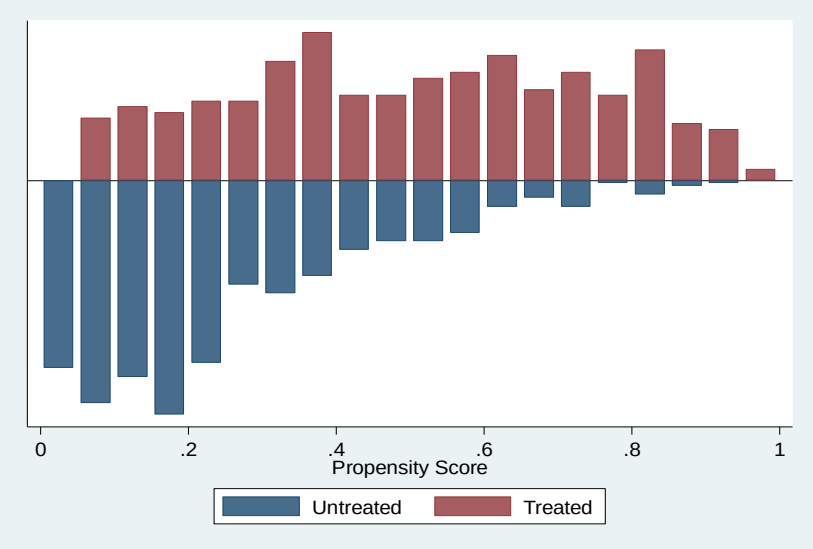


Figure 4B. Distribution of estimated propensity score after variable selection

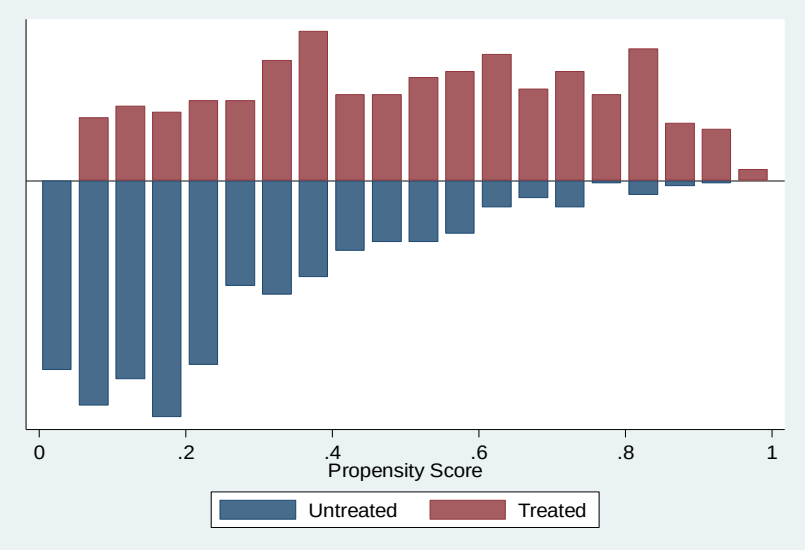


TABLE XI: COVARIATE BALANCE AFTER USING INVERSE PROBABILITY WEIGHTING AND REGRESSION ADJUSTMENT

	Before applying weights and regression adjustment				After applying weights and regression adjustment for ATE				After applying weights and regression adjustment for ATT			
Variable	T=0	T=1	t	p>|t|	T=0	T=1	t	p>|t|	T=0	T=1	t	p>|t|
Distance	14.26	10.28	4.36	<0.0001	12.07	12.59	-0.65	0.5135	10.36	11.22	1.19	0.2358
White	0.23	0.12	3.88	0.0001	0.19	0.20	-0.22	0.8367	0.15	0.13	1.28	0.2827
Black	0.52	0.57	-0.15	0.1229	0.56	0.56	0.25	0.7990	0.57	0.59	-0.57	0.5717
Hispanic	0.15	0.28	-4.31	<0.0001	0.20	0.19	0.43	0.6665	0.26	0.27	-0.20	0.8418
Other race	0.096	0.013	5.92	<0.0001	0.03	0.04	-1.07	0.2830	0.01	0.01	-0.02	0.9838
Single	0.37	0.39	-0.77	0.4443	0.39	0.38	0.27	0.7889	0.40	0.40	-0.16	0.8758
Married	0.34	0.28	1.63	0.1027	0.32	0.35	-0.85	0.4173	0.32	0.28	0.93	0.3540
Divorced	0.06	0.12	-3.41	0.0007	0.08	0.08	-0.41	0.6814	0.10	0.12	-0.63	0.5315
Widowed	0.20	0.15	2.07	0.0387	0.17	0.15	0.96	0.3364	0.14	0.16	-0.55	0.5804
Separated	0.02	0.04	-1.34	0.1822	0.03	0.03	0.07	0.9418	0.04	0.04	0.21	0.8263
Self-pay	0.02	0.04	-1.79	0.0743	0.03	0.03	-0.13	0.9037	0.06	0.04	1.46	0.1441
Private	0.30	0.17	4.16	<0.0001	0.24	0.27	-0.97	0.3329	0.18	0.18	-0.13	0.8967
Medicare	0.42	0.53	-3.17	0.0016	0.48	0.46	0.40	0.6920	0.55	0.52	1.45	0.4140
Medicaid	0.26	0.25	0.40	0.6900	0.24	0.22	0.59	0.5531	0.21	0.25	-1.52	0.1284
Spring	0.26	0.33	-2.02	0.0481	0.31	0.32	-0.23	0.8219	0.36	0.33	0.73	0.4654
Summer	0.25	0.29	-1.04	0.2997	0.28	0.26	0.40	0.6906	0.29	0.29	-0.19	0.8498
Fall	0.23	0.17	2.29	0.0224	0.19	0.20	0.25	0.8062	0.18	0.17	0.07	0.9415
Winter	0.23	0.20	1.17	0.2434	0.21	0.22	-0.43	0.6819	0.18	0.20	-0.73	0.4682
VTE risk factors (n=1)	0.02	0.06	-0.15	0.0316	0.05	0.04	0.09	0.9286	0.06	0.07	0.42	0.6723
VTE risk factors (n=2)	0.36	0.43	-2.08	0.0377	0.40	0.40	-0.22	0.8224	0.43	0.46	-0.83	0.4069
VTE risk factors (n=3)	0.56	0.33	6.67	<0.0001	0.47	0.47	-0.26	0.7896	0.33	0.35	-0.56	0.5756
VTE risk factors (n=4)	0.03	0.16	-5.46	<0.0001	0.09	0.07	-0.81	0.4186	0.17	0.13	1.62	0.1053
Smoking	0.05	0.18	-5.23	<.0001	0.09	0.10	-0.45	0.6558	0.14	0.19	-1.54	0.1237
Extend stay	0.11	0.20	-3.48	0.0006	0.13	0.12	0.12	0.9072	0.16	0.18	-0.87	0.3866
Inpatient stay	6.38	3.32	-2.19	0.0291	6.49	6.48	0.01	0.9904	6.62	6.84	-0.73	0.4677

Table XII shows results for inverse probability weighting, regression adjustment and both combined. Using inverse probability weighting method, the adjusted mean TTR was 9.02 % higher in patient referred to anticoagulation clinic. The adjusted mean TTR was higher by 6.47% for patients referred to anticoagulation using regression adjustment. Patients referred to anticoagulation clinic had 8.58% higher TTR using both the above methods combined.

If patients had been randomly assigned to either of the two clinics then, compared to patients in orthopedic clinic, those in anticoagulation clinic had a higher mean of 6.56 % TTR using inverse probability weighting, 6.85% using regression adjustment and 6.55% using the two methods combined.

TABLE XII: ATE AND ATT USING INVERSE PROBABILITY WEIGHTING, REGRESSION ADJUSTMENT AND BOTH COMBINED

Method	N	Estimate	Standard error	T	P
Inverse probability weighting					
ATE	873	6.56	1.91	3.43	0.0006
ATT	873	9.02	1.93	4.67	<.0001
Regression adjustment					
ATE	873	6.47	2.17	2.98	0.0030
ATT	873	6.41	2.07	3.09	0.0021
Weighting and regression adjustment					
ATE	873	7.10	1.88361	3.77	0.0002
ATT	873	9.08	1.91	4.76	<.0001

4.4.5 Sensitivity Analysis

Results from the first sensitivity analysis are shown in Table XIII after restricting the sample to patients with at least 3 readings in the outpatient setting.

On matching using propensity scores the adjusted mean TTR was 7.70 % higher in patient referred to anticoagulation clinic and 8.21% when matched using covariates. The adjusted mean TTR was higher by 10.94 % for patients referred to anticoagulation using inverse probability weighting. Patients referred to anticoagulation clinic had 8.99 % higher TTR using inverse probability weighting combined with regression adjustment. If patients had been randomly assigned to either of the two clinics then, compared to patients in orthopedic clinic, those in anticoagulation clinic had a higher mean of 7.53 % TTR using inverse probability weighting, and 7.96 % TTR using inverse probability weighting combined with regression adjustment.

TABLE XIII: ATE AND ATT WITH RESTRICTED NUMBER OF INRS

Method	N	Estimate	Standard error	T/Z	P
Matching					
ATT using propensity scores	360	7.70	3.21	T = 2.40	<.0001
ATT using covariates	873	8.21	2.46	Z = 3.34	0.0001
Weighting					
ATE	774	7.53	1.92	T = 3.92	<.0001
ATT	779	9.20	1.92	T = 4.80	<.0001
Imben's					
ATE	753	6.46	2.04	T = 3.17	<.0001
ATT	753	8.27	1.86	T = 4.46	<.0001

Results from the second sensitivity analysis are shown in table XIV. In a model that matched only upon length of therapy and number of outpatient INRs, the adjusted mean TTR was 7.21% higher in patient receiving warfarin therapy at anticoagulation clinic. After matching on length of therapy, number of INRs, and the other significant covariates from the previous analyses, the adjusted mean TTR was 5.44% higher for patients receiving warfarin therapy at anticoagulation clinic.

TABLE XIV: ATE AND ATT WITH RESTRICTED MATCHED LENGTH OF THERAPY IN DAYS AND NUMBER OF OUTPATIENT INRS

Method	N	Estimate	Standard error	Z	P
Matching on covariates					
Length of therapy in days and total number of outpatient INRs	873	7.21	3.77	1.91	0.056
Significant covariates + Length of therapy in days and total number of outpatient INRs	873	5.44	2.43	2.24	0.025

5 DISCUSSION

5.1 Discussion of the Study Results

Newer oral anticoagulants are available in the market as a convenient alternative for VTE prophylaxis. However, an evaluation of patient outcomes using warfarin therapy between different models of care would prove beneficial for several reasons. First, the newer drugs are expensive and lack observational data concerning safety and efficacy[14,82,83] whereas safety and efficacy profile of warfarin is well established and this drug has been around for more than 60 years. Of the different pharmacological approaches that have been suggested, warfarin has been most commonly used in practice. As reported in a survey conducted by the American Association of Hip and Knee Surgeons, 66% of patients undergoing THR and 59% of patients undergoing TKR are given warfarin prophylaxis.[7]

This study gives an insight on referral of patients undergoing hip and knee replacement surgery to outpatient clinic for VTE prophylaxis with warfarin therapy. An understanding of a referral pattern to specialized care compared to routine model of care is important as these decisions have an impact on the costs incurred, and quality of care received by patients. The results from our study show that for patients undergoing hip and knee replacement surgery at UIHHS, orthopedic surgeons were more inclined to refer Hispanic patients to specialized anticoagulation clinic as compared to Caucasian patients when adjusted for confounders. In contrast, they were less likely to refer other race patients including Asians patients to anticoagulation clinic. Even though results for African American patient referral were not significant, the results pointed in the hypothesized direction. The possible reasons for the Hispanics being referred to anticoagulation clinic could be because of the poor anticoagulation control compared to Caucasians.[33] Our data show that a higher number of patients with Medicare were referred to anticoagulation clinic as compared to patients with private insurance.

A possible reason could be that patients with private insurance could receive a routine model of care follow up as they were covered for home visits. In our study cohort, we found that a lower percentage of African Americans and Hispanics had private insurance as compared to Caucasians which could possibly be an influencing factor for referring African Americans and Hispanics to anticoagulation clinic. Patients with a lesser distance from the clinic may have been referred to anticoagulation clinic because of convenience as this model of care requires face to face visits. Most of our results supported that sicker patients were more likely to be referred to anticoagulation clinic as ≥ 4 VTE risk factors, an extended stay at the hospital, higher number of interacting medications or being a smoker was positively associated with being referred to anticoagulation clinic. Although patients who had a VTE event during their inpatient stay or after discharge were excluded from the final study cohort, a noteworthy point is that those patients were referred to anticoagulation clinic. Contrary to our expectations, patients with greater a bleeding risk were referred to orthopedic clinic.

The study results portray that patients receiving warfarin therapy for their VTE prophylaxis after hip and knee replacement surgeries in specialized anticoagulation clinic have a better TTR as compared to those in routine model of care. Our results are consistent with several studies that have concluded that pharmacist managed specialized care clinic has better clinical outcomes for patients receiving warfarin therapy. For example, a randomized control trial by Chan et al TTR was higher by 5% in anticoagulation clinic compared to routine model of care (64% vs. 59%, p value <0.001).[24] In a large cohort study where 6645 patients were randomized to either of the two clinics, Witt et al reported a better anticoagulation in anticoagulation clinic compared to routine model of care, with 63.5% TTR for anticoagulation clinic compared to 55.2 % TTR for routine model of care (p<0.001).[20] A few other cohort studies that were conducted in United States reported similarly reported improved patient outcomes for those receiving care at anticoagulation clinic. Garton et al reported a 10% higher TTR in anticoagulation clinic

compared to routine model of care (81.1% vs. 71.1%, p<0.0001).[25] In addition, a study by Chiquette et al reported a 3% higher TTR in anticoagulation clinic compared to routine model of care (40% vs. 37%, p value< 0.0001).[19] Rudd et al in another retrospective cohort study reported a 25.5 % higher TTR in anticoagulation clinic compared routine model of care and 7.6% higher TTR compared to a clinic managed by nurses.[31] Additionally, a study conducted by Chamberlain reported that TTR was 6.9% higher in anticoagulation clinic compared to routine model of care (47.3% vs. 40.4 %).[22] Lalonde et al. reported that the TTR between anticoagulation clinic and routine model of care was not significantly different, with 77.3% TTR in anticoagulation clinic and 76.7% in routine model of care.[23] According to a study conducted by Young et al, TTR was 8% higher for anticoagulation clinic compared to routine model of care (73% vs. 65%, p <0.0001). However, these studies had been conducted in patients who were relatively been stabilized on warfarin therapy. These patients received a long-term warfarin therapy mainly for indications such as atrial fibrillation, aortic or mechanical heart valve replacement, cardiovascular disease, and pulmonary and deep vein thromboembolism. Each of these retrospective cohort studies compared the unadjusted TTR between the two clinics and did not adjust for confounders or potential selection bias that may have existed.

Our study compared TTR between specialized anticoagulation clinic and routine model of care in patients that were initiated on short-term warfarin therapy. These patients received warfarin therapy as a VTE prophylaxis after hip and knee replacement surgeries. We also adjusted for potential selection bias by using different available methods. Different propensity score methods were used to adjust for difference baseline characteristics. The unadjusted difference was 6.6% TTR between the two clinics. Using different methods of creating balanced groups, we found a range of results for ATE (6.49- 6.82) and ATT (6.92-9.02). It was interesting to see that ATT estimates were approximately the same using matching on propensity scores, matching on selected covariates, inverse probability weighting, and inverse probability weighting

combined with regression adjustment for selected covariates. We found that, regression adjustment gave a lower bound estimate for ATT. On matching, 287 pairs were formed which lead to decrease in sample size by excluding 4 unmatched observations. Therefore, this method is not the most efficient method. Inverse probability weighting using all the covariates compared to with selected covariates did not alter the estimates. Only regression adjustment decreases the treatment effects and it is inefficient as it does not account for imbalance between the two groups and gives biased results by itself.

5.3 Study Limitations

There are several limitations to the study. First, there are concerns regarding the conclusion for understanding the effect of race of referral pattern. Due to small sample size, we collapsed Asians and other variable as no Asian patient had been referred to anticoagulation clinic. We suspect that the reason for this referral was due them having a low risk of VTE. The categorization of race in our study is different from those observed in the literature.[73] Even though the categorization is more simplified in our study, the categories of interest African American, Hispanic and Caucasians for comparisons were available.

Second, this is a retrospective cohort study that compared outpatient TTR in patients between the two clinics where patients were selectively being referred to anticoagulation clinic. In order to minimize this selection bias, we used different propensity score methods to reduce the differences in the baseline characteristics between the treatment and control groups. This method balances the two groups on observed covariates but it does not address the hidden bias.

Third, the results are not generalizable as this is a single center study. In addition, the external validity is limited because UIHHS serves primarily underserved minority patients. The

routine model of care in this study uses phone follow up method to monitor patients. Therefore, the results will not be generalizable to routine model of care with face-to-face visits.

Fourth, this study does not incorporate genetic variation in the construction of propensity scores that may have had an impact on the selection process in the analysis. Genetic variation is typically known to vary by race and we adjusted for race in our analysis.

5.4 Study Strengths

Our study had several strengths. This is the first study to our knowledge to compare the two predominant anticoagulation models of care for outcomes of patients receiving warfarin therapy as a post-prophylaxis to prevent VTE after undergoing hip or knee replacement surgery which is a short-term therapy.

Previous studies that have compared anticoagulation models of care have not adjusted for potential confounders or selection bias.[22-28] The inverse probability weighting alongwith regression adjustment method creates two balanced groups and adjust the remaining confounding in the regression model to give more robust estimates. This study calculates to two estimators ATE and ATT. ATE shows the estimate if patients were randomly assigned to the two treatments whereas ATT shows the benefit on receiving the treatment.

Also, this is the first study that evaluates racial disparities in referral to specialized clinic adjusting for potential confounders. Most of the previous studies do not describe racial distribution of their study sample. A study performed by Rudd et al. had over 97% Caucasians patients. Our study sample had a good racial mix which may reflect better of the patient population on warfarin therapy in United States.

Results from this study will serve as a good basis for further research in multiple settings to establish the external validity.

5.5 Conclusions

First, this study adds to the existing body of literature that compares anticoagulation models of care for patients receiving warfarin therapy. We found that race adjusting for socio-economic status and disease severity influences the patient referral pattern to outpatient clinics for receiving VTE prophylaxis after undergoing hip and knee replacement surgery. Hispanic patients, patients without private insurance and >4 risk factors for VTE receive warfarin therapy at specialized anticoagulation clinic.

Second, the study demonstrates that anticoagulation clinic had an association with better clinical outcomes for a short-term therapy of VTE prophylaxis post hip and knee replacement surgery. Patients in anticoagulation clinic had a higher TTR as compared to those in orthopedic clinic if we assume that patients were randomly referred to either of the two clinics. It is important to note that this was a single center study. Future research needs to be done to understand the impact of specialized anticoagulation care as compared to routine model of care in a larger diverse sample of patients receiving warfarin therapy.

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Member, Indian Pharmaceutical Association – Students forum (IPA-SF)

ABSTRACTS:

- Bathija S, Schumock GT,Sharp LK,Gerber BS, Fitzgibbon ML, Cavallari LH, Hellenbart E, Chevalier A, Drambarean B, Shapiro NL, Nutescu EA, Pharm.D. Factors affecting awareness and interest of patient-self-testing (PST) in patients on warfarin therapy in an inner-city underserved minority population. Accepted at Anticoagulation Forum 12th National Conference. Phoenix, Arizona, May 9-11, 2013.(Poster presentation)
- Bathija S, Walton S, Lau D, Nutescu EA. Warfarin management in patients who have undergone hip and knee replacement surgery. Submitted to Midwest Social and Administrative Pharmacy Conference, Madison, WI, August 8-10, 2012. (Podium presentation)
- Nutescu EA, DiDomenico R, Bathija S, Grim S, Mucksavage J, Tesoro E, Ohler K, Thielke J, Chan J, Shapiro N, Engle J. Balance of Academic Responsibilities of Clinical Track Pharmacy Faculty in the US. Submitted to 2012 ACCP Annual Meeting, Hollywood, FL, October 21-24, 2012. (Poster presentation)
- Bathija S, Schumock GT, Sharp L, Gerber B, Fitzgibbon ML, Cavallari LH, Nutescu EA. Patient factors affecting non-adherence to anticoagulation therapy in an inner-city underserved minority population. International Society for Pharmacoeconomics and Outcomes Research 17th Annual International Meeting. Washington, DC, June 2-6, 2012. (Poster presentation)
- Lee YM, Bathija S, DiDomenico R, Galanter W, Stamos T, Thambi M, Ruland S, Nutescu E. Impact of obesity on achieving anticoagulation therapy with heparin. College of Pharmacy Research Day. University of Illinois at Chicago (UIC), IL, March 8-9, 2012. (Poster presentation)

- Nutescu E, Sharp L, Bathija S, Dotiwala Z, Cavallari L, Schumock G, Meltzer D, Fitzgibbon M. Factors that Influence Adoption of Anticoagulation Self-Monitoring in Underserved Minority Patients. Anticoagulation Forum 11th National Conference. Boston, MA, May 5-7, 2011. Abstract published in: J Thromb Thrombolysis 2011;31:382-D8. (Poster presentation)

PUBLICATIONS:

- Bathija S, Walton S, Lau D, Nutescu E. Patient outcomes with warfarin therapy after Hip and Knee Replacement: Comparison of two Models of Care. (In progress)
- Nutescu EA, Bathija S, Sharp LK, Gerber BS, Schumock GT, Fitzgibbon ML Evaluating awareness and interest regarding self-monitoring in underserved minority patients. (In progress)
- Nutescu EA, Bathija S, Sharp LK, Gerber BS, Schumock GT, Fitzgibbon ML Barriers to current model of anticoagulation clinic care and factors influencing adoption of self-monitoring. (In progress)
- Nutescu EA, Bathija S, Sharp LK, Gerber BS, Schumock GT, Fitzgibbon ML. Anticoagulation patient self-monitoring in the United States: considerations for clinical practice adoption. Pharmacotherapy. 2011 Dec;31(12):1161-74