The Use of Warfarin for DVT Prophylaxis Following Hip and Knee Arthroplasty: How Often Are Patients Within Their Target INR Range?

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Abstract

The purpose of this study was to determine the percentage of time that patients are subtherapeutic, therapeutic, and supratherapeutic based on the recommended INR for therapeutic efficacy when prescribed warfarin for chemical thromboprophylaxis following a hip or knee arthroplasty procedure. One hundred eighty-four patients receiving warfarin for 4 weeks postoperatively, dosed using a web-application accounting for patient demographics, INR levels, and concomitant medication use, were included for analysis. On average, patients with a target INR range between 1.7-2.7 were therapeutic for only 54.4% of the time (32.5% subtherapeutic, 13.0 supratherapeutic) while patients with a target INR range between 2.0 and 3.0 were therapeutic for only 45.9% of the time (39.2% subtherapeutic, 14.8% supratherapeutic) of their warfarin regimen. This study confirms that patients receiving warfarin for chemical thromboprophylaxis are within their targeted INR range for only a limited period of time during their postoperative course.

Keywords

total knee arthroplasty; warfarin; coumadin; thromboprophylaxis

Introduction

One of the most important variables in post-operative care following a total joint arthroplasty (TJA) is the selection and management of mechanical and chemical thromboprophylaxis(1). Warfarin (coumadin) is the most notable FDA-approved vitamin K antagonist and is currently the most commonly prescribed oral anticoagulant medication for both orthopedic and non-orthopedic indications (2, 3). Following TJA, warfarin has been shown to be as effective at preventing pulmonary embolism (PE) as low molecular weight

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heparin (LMWH) (1), and several studies have demonstrated its improved efficacy in preventing proximal deep venous thrombosis (DVT) (4, 5). In addition, warfarin is administered orally (versus injectable medications) (6, 7), while also being a relatively inexpensive drug(7). However, a cost-analysis has shown that the frequent monitoring required when on warfarin may actually make its use more expensive than LMWH (8).

Several disadvantages are present with the use of warfarin for chemical thromboprophylaxis following TJA, including its relatively narrow INR therapeutic window and difficulty with dosing (9-11). Warfarin's pharmacokinetics can vary widely based on genetics, body mass index, drug interactions, as well as diet (7, 12-14). A delicate balance exists between avoidance of a subtherapeutic INR in which patients may be at risk of thromboembolic events, and a supratherapeutic INR which may increase the risk of bleeding and wound complications(15). Recently, McDougall et al. performed a retrospective case-control study comparing the outcomes of patients on warfarin following primary total hip arthroplasty (THA) versus a control group taking oral aspirin. They found patients on warfarin to have a significantly higher risk of deep joint infection (9% versus 2.2%), hematoma or wound ooze (28% versus 4%), and superficial infection (13.5% versus 2.2%) with 11% of patients having a supratherapeutic INR at the time of readmission based on the recommended INR for therapeutic efficacy (16). The increased risk of wound complications and hematoma noted in this study are similar to those reported with the use of LMWH, which has led to a decrease in its popularity following total joint arthroplasty (17, 18). Thus, tight regulation of INR is crucial for the prevention of thromboembolic events, but also more common complications that are devastating and costly to both the patient and hospital.

Recent trends toward accelerated recovery following TJA has demonstrated the average length of stay (LOS) to decrease from 9 days between 1991-1992, to between 2 to 4 days depending on the institution(19, 20). This relates directly to thromboprophylaxis with warfarin, as it potentially makes achieving an INR at discharge within the targeted range, along with understanding a patient's responsiveness to warfarin more difficult(20). Patients must be discharged with a projected dose of warfarin and have their INR levels monitored closely as outpatients. While several studies have explored potential complications with the administration of warfarin (19, 21-23), to our knowledge none have followed the percentage of time that patients are actually within their targeted INR range during their post-operative course. Knowing the percentage of time that patients are actually within the recommended INR for therapeutic efficacy may further clarify the role of warfarin in the prevention of post-TJA complications and readmissions. Therefore, the primary purpose of this study was to determine the percentage of time that patients are subtherapeutic, therapeutic, and supratherapeutic (based on the recommended INR for therapeutic efficacy) when prescribed warfarin for chemical thromboprophylaxis following a hip or knee arthroplasty procedure. Our hypothesis is that patients will be within their targeted INR range for only a limited period of time during their postoperative course.

Materials and Methods

This study was a retrospective, institutional review board-approved investigation performed at a single academic center. From January 2013 to December 2013, all patients who received

warfarin for pharmacologic thromboprophylaxis following a joint arthroplasty were reviewed. Inclusion criteria were patients undergoing a joint arthroplasty procedure (total hip arthroplasty (THA), revision THA, total knee arthroplasty (TKA), revision TKA, explantation of prosthesis and placement of antibiotic spacer, or unicompartmental knee arthroplasty (UKA)) who received a 4-week course of warfarin for pharmacologic thromboprophylaxis managed by one of two clinical nurse practitioners. Patients were excluded if they did not complete a 4-week course of warfarin therapy, received a different form of pharmacologic thromboprophylaxis, or were entered in a concurrent, multi-center randomized control trial in which our institution is participating to assess the effectiveness of pharmacogenetic warfarin dosing (Genetics Informatics Trial of Warfarin) (24). Over this time period, 287 patients underwent a joint arthroplasty procedure and received warfarin postoperatively. One hundred eighty-four patients met our inclusion criteria and were included for analysis.

Warfarin dosing was guided by http://www.WarfarinDosing.org, which is a nonprofit, decision-support web application available for public use (24). This web application incorporates laboratory and clinical data, including patient demographics (age, sex, ethnicity, weight, height), the baseline international normalized ratio (INR), target INR, and whether the patient currently smokes, has liver disease, or is currently taking medications known to affect warfarin metabolism (amiodarone, statin/HMG CoA reductase inhibitors, -azole medications, or sulfamethoxazole/septra/bactrim/cotrim/sulfatrim) to determine appropriate dosing (2, 13, 14, 24, 25). Following discharge, patient INR levels are checked two times a week to have their doses adjusted accordingly, but the frequency of INR checks can vary based on the presence of a subtherapeutic or supratherapeutic INR level. All INR levels and blood draws are ordered by a clinical nurse practitioner who then receives the results via telephone call or fax. The recommended dose is then ordered with all documentation being placed in the electronic medical record.

The majority of joint arthroplasty patients at our institution receive one of two postoperative protocols for deep venous thromboprophylaxis: 1) aspirin for pharmacologic thromboprophylaxis for a period of 6 weeks, along with the use of mobile compression devices for 10 days, or 2) warfarin for pharmacologic thromboprophylaxis for a period of 4 weeks, along with the use of mobile compression devices only during their inpatient stay (26). All patients in this study were determined to be at increased risk of venous thromboembolism (VTE) at the discretion of the surgeon, primary care physician (PCP), and medical subspecialist (when necessary), and thus were placed on warfarin postoperatively. Reasons for warfarin administration included having a prior VTE event, family history of DVT or PE, the potential for prolonged immobilization, cardiac history (atrial fibrillation, stents, cardiac valve), gastrointestinal disorder including a history of ulcers, among other potential risk factors. The target INR for each patient was either 2.20 or 2.50 based on the recommendation of the surgeon and is in adherence with national guidelines for the recommended INR for therapeutic efficacy (1, 27). Patients with a cardiac history requiring anticoagulation (i.e. mechanical valve, atrial fibrillation) or prior history of DVT or PE, were often dosed with a target INR of 2.50.

All procedures were performed by one of five surgeons specializing in joint arthroplasty. One hundred eighty of 184 patients received a preoperative dose of warfarin the night prior to surgery to hasten achievement of the target INR postoperatively. Four patients did not receive a preoperative dose as initially they were scheduled to receive aspirin for thromboprophylaxis, but were changed to warfarin at the surgeon's discretion. Intraoperatively, all patients had a mobile compression device pump placed on the contralateral, nonoperative lower extremity prior to procedure initiation. Postoperatively, all patients were mobilized on postoperative day 0 by a physical therapist, wore mobile compression device pumps on both lower extremities only during their inpatient stay, and received a daily dose of warfarin for thromboprophylaxis. INR levels were checked daily during the inpatient stay. Data collected included patient demographics, medical history, medication and smoking history, INR levels at discharge and during their postoperative course, patient readmissions, and any postoperative complications within 30 days of the index surgery. Patients were monitored throughout their inpatient stay and following discharge for any clinical signs or symptoms of VTE. All patients were called or seen for clinical follow-up at two weeks postoperatively and assessed for any clinical symptoms of DVT or PE including increased swelling or tenderness to palpation in the lower extremity, chest pain, or shortness of breath. All patients were also assessed with a clinical examination at four to six weeks postoperatively. Patients with clinical symptoms of DVT underwent duplex ultrasonography, while patients with clinical suspicion of a PE received a spiral computed tomography scan of the lungs for diagnosis. Routine screening for venous thromboembolism using ultrasonography is not performed at our institution.

Data Analysis

Patients with a target INR of 2.20 were considered to have a therapeutic INR if their INR was between 1.7-2.7, subtherapeutic if 1.69, and supratherapeutic if 2.71. For patients with a target INR of 2.50, the INR was considered therapeutic if between 2.0-3.0, subtherapeutic if 1.99, and supratherapeutic if 3.01. Statistical analysis was performed to determine the percentage of patients therapeutic at the time of hospital discharge, at each respective INR checked following discharge, and the mean percentage of time that patients were therapeutic during their 4- week postoperative treatment course. Pearson and Spearman correlation coefficients were performed to determine the association between patient demographics and the percentage of time that they were therapeutic during their postoperative course. Again, the terms therapeutic, subtherapeutic, and supratherapeutic are being used based on the recommended INR for therapeutic efficacy. Correlation coefficients were graded using a previously described semi-quantitative criteria: excellent for 0.9 r 1.0, good for 0.7 r 0.89, fair/moderate for 0.5 r 0.69, low for 0.25 r 0.49, and poor for 0.0 r 0.24 (28). We then conducted a forward stepwise multiple linear regression analysis to examine the association of patient demographics, medical history, and medication use on the percentage of time a patient is therapeutic on warfarin. All statistical analyses were performed using IBM® SPSS® software version 22 (IBM Corp., Armonk, NY, USA).

Results

Patient demographics, surgical procedures, and indications for warfarin use are presented in Table 1. The most common surgical procedures were a primary THA (40.2%) and a primary TKA (32.6%), and the most common indication for warfarin use was having a prior DVT or PE (33.7%) followed by a family history of DVT or PE (22.3%).

Seventeen of 184 patients (9.2%) were currently smoking during the time of the surgical procedure while 3 patients (1.6%) had a history of liver disease. The percentage of patients on medications potentially affecting warfarin metabolism is presented in Table 2.

Ninety-one patients (49.5%) had a target INR of 2.20. The mean length of hospital stay in these patients was 2.4 ± 1.9 days, and only 16.5% of patients were therapeutic at the time of discharge (77.9% of patients were subtherapeutic, 5.5% were supratherapeutic). The percentage of patients who had a therapeutic, subtherapeutic, or supratherapeutic INR level at each time their INR was checked postoperatively is presented in Figure 1. For example, at the first INR level checked following discharge, 27 of 91 patients (29.7%) had a therapeutic INR level. The percentage of patients who were therapeutic at each INR check postoperatively ranged from a low of 25.0% to a high of 72.0%. The mean percentage of time that each patient was therapeutic during the 4-week course of warfarin was also calculated. On average, patients had a therapeutic INR level for only 54.4% of the time that they were receiving warfarin postoperatively, were subtherapeutic 32.5% of the time, and supratherapeutic 13.0% of the time (Figure 2). Nine of 91 patients (9.9%) were subtherapeutic for greater than 70% of the time during their 4-week course of warfarin prophylaxis.

Ninety-three patients (50.5%) had a target INR of 2.50. The mean length of hospital stay in these patients was 2.6 days ± 2.0 days, and only 17.2% were therapeutic at the time of discharge (81.7% of patients were subtherapeutic, 1.1% were supratherapeutic). The percentage of patients who had a therapeutic, subtherapeutic, or supratherapeutic INR level at each time their INR was checked postoperatively is presented in Figure 3. The percentage of patients who were therapeutic at each INR check postoperatively ranged from a low of 24.7% to a high of 61.1%. On average, patients had a therapeutic INR level for only 45.9% of the time that they were receiving warfarin postoperatively, were subtherapeutic 39.2% of the time, and supratherapeutic 14.8% of the time (Figure 4). Fourteen of 93 patients (15.1%) were subtherapeutic for greater than 70% of the time during their 4-week course of warfarin prophylaxis.

Correlation coefficients revealed no significant associations between the percentage of time a patient is therapeutic on warfarin and their sex, age, body mass index, race, procedure performed, or indication for warfarin use (r= -0.05 to 0.12; all "poor"). Using stepwise multivariable linear regression analysis, a significant model emerged with an adjusted R square of .048, F= 10.1, and p-value= 0.002. However, the model was only able to account for approximately 4.8% of the variance in the percentage of time a patient was therapeutic, and smoking was the only significant independent variable in the model (β = -0.231, p=.

002). Being positive for smoking had a negative effect on the percentage of time a patient was therapeutic during their 4-week course.

There were a total of 22 postoperative complications noted (12.0% of procedures) within 30 days of the index surgery. The most common complication was prolonged wound drainage, which occurred in 11 patients (6.0%). We defined "prolonged" wound drainage as drainage continuing greater than four days following the index procedure, as per our institution's protocol, patients are discharged from the hospital with their surgical dressings in place. Four of 11 patients who experienced prolonged wound drainage had a supratherapeutic INR level at the time of diagnosis (range 3.5 to 3.6). A wound hematoma was diagnosed in 5 cases (2.7%), with 3 patients having a supratherapeutic INR at the time of diagnosis (range 3.7 to 4.0). There were 2 cases of superficial cellulitis that did not require repeat surgery, 1 case in which the INR level was 3.7, and the other in which the INR level was 3.0. There were 2 readmissions postoperatively within 30 days of the index surgery: one for a C. Difficile infection and one for an ischemic cerebrovascular accident resulting in mortality. In both readmissions, the INR was within therapeutic range. Lastly, 1 primary TKA and 1 revision TKA underwent manipulation under anesthesia (MUA) for stiffness. The primary TKA undergoing MUA was not diagnosed with a wound hematoma or prolonged drainage, but did have an INR of 4.0 on postoperative day 5 and INR of 3.6 on postoperative day 18 following the surgery. There were no incidences of DVT or PE diagnosed in this cohort of patients.

Discussion

The number of total joint arthroplasties performed in the United States is projected to increase to almost 4 million procedures annually by the year 2030(29), and thus optimization of perioperative care for TJA patients has become paramount. One of the most important variables in postoperative care is the selection and management of appropriate thromboprophylaxis during the postoperative course. The presence of a variety of regimens that comply with American Academy of Orthopaedic Surgeons' guidelines indicates a lack of consensus regarding the optimal regimen. Furthermore, the occurrence of "avoidable" complications following TJA will be increasingly scrutinized with evolving healthcare legislation. In a study of 591 unplanned readmissions following TJAs conducted over a 5-year period, Zmistowski et al. showed that superficial and deep wound infections comprised 25% of readmissions within 90 days, and venous thromboembolism comprised only 6% of readmissions. Similarly, Adelani et al. in a review of 128 readmissions following TKA noted wound complications to comprise 14% of readmissions, surgical site infection 9.9%, and bleeding 9.9%, while VTE only comprised 3.3% despite all patients being compliant with Surgical Care Improvement Project VTE guidelines(30). Several studies have demonstrated a positive association between a supratherapeutic INR, postoperative wound complications, and risk of infection in patients receiving warfarin therapy postoperatively (20-22). Thus, with the known difficulty in dosing and maintaining a therapeutic range with the use of warfarin(12-14), the purpose of this study was to evaluate how often patients are actually therapeutic during their postoperative course when receiving warfarin for chemical thromboprophylaxis, based on the recommended INR for therapeutic efficacy. Our results demonstrate that on average, patients with a target INR range between 1.7-2.7 were

therapeutic for only 54.4% of the time, while patients with a target INR range between 2.0 and 3.0 were therapeutic for only 45.9% of the time of their warfarin regimen.

There are several limitations of this study that must be recognized before interpreting our results. Due to the limited number of patients reviewed in this study, we lack the power to comment on the association of venous thromboembolism and wound complications with a subtherapeutic, therapeutic, and supratherapeutic INR. Furthermore, our study cannot comment on the ideal "target" INR range that would effectively prevent a VTE event. Large scale studies assessing various target INR ranges across cohorts of patients with similar risk factors, mobilization, and rehabilitation protocols, along with assurance that patients are within their intended INR range, would be necessary to potentially address this question. However, this was not the primary purpose of our study, as our goal was to simply determine the average amount of time that patients are actually therapeutic when receiving warfarin postoperatively. A second limitation of this study is that various factors can affect the ability to achieve a therapeutic INR, including medications, diet, and patient compliance. While we attempted to account for various medications and demographic factors, other potentially confounding variables were not considered. Lastly, our study was performed in a retrospective manner, and we are unable to draw conclusions regarding the effectiveness of warfarin therapy versus other thromboprophylaxis regimens.

This study demonstrates that although warfarin is commonly used for pharmacologic thromboprophylaxis following joint arthroplasty procedures, the ability to consistently maintain a target INR for each patient remains difficult. This raises significant concerns about the true effectiveness of the use of warfarin postoperatively, and whether it is worth taking the potential risks associated with a supratherapeutic INR (present for 13.0% and 14.8% of the time, respectively in our study). A consequence of shorter length of stays following TJA may be an increased difficulty in gauging a patient's responsiveness to warfarin, along with obtaining a therapeutic INR prior to discharge (19, 20). Therefore, practitioners will have a more difficult time effectively dosing warfarin for patients following discharge, when INR levels are no longer checked on a daily basis. Our institution's protocol calls for a dose of warfarin the night prior to surgery to hasten achievement of a therapeutic INR postoperatively. Recently, Aynardi et al. reported that 80% of patients were subtherapeutic at the time of discharge when prescribed warfarin, using a definition of "therapeutic" to be an INR between 2.0-2.5 (20). Despite administration of a preoperative dose and use of a broader definition of "therapeutic", the vast majority of patients in our study (76.9% to 81.7%) remained subtherapeutic at the time of discharge.

The relationship between postoperative wound complications and subsequent infection is well described (22, 31), and thus it is concerning that the overall incidence of wound hematoma or prolonged drainage in this cohort was 8.7% (16 of 184 patients), and the overall complication rate was 12.0% (22 of 184 patients). Fifty percent of patients experiencing prolonged wound drainage or diagnosed with a wound hematoma had an associated supratherapeutic INR. While our retrospective results do not allow us to comment on causation regarding these complications, their association with supratherapeutic INR levels and the known difficulty in maintaining a therapeutic INR remain relevant concerns.

Regarding the inability to consistently maintain a therapeutic INR level, there are several potential ways in which this data can be interpreted and influence our practice. First, the ideal target INR for prevention of venous thromboembolism (VTE) following TJA remains controversial. Kearon et al. found that an INR of 2-3 was more effective than an INR of 1.5-1.9 in preventing VTE occurrence and equally safe(11), while other studies have demonstrated that target INR values of <2.5 are safe and effective following orthopaedic procedures(7, 10). Thus, there is the potential that targeting a higher therapeutic range may incur an unnecessary, greater risk of wound and bleeding complications, and perhaps our target ranges of INR should be re-evaluated in future studies. Future studies Furthermore, in this study, the only factor elucidated that decreased the ability to obtain an INR recommended for therapeutic efficacy was the patient's smoking history. This is not surprising as Nithusawan et al., in a systematic review of 13 studies, found evidence that smoking increases the rate of warfarin clearance, thus reducing its effectiveness (32). Thus, potential risk factors that may cause difficulty in obtaining the recommended INR for therapeutic efficacy should also continue to be evaluated.

A second potential interpretation is that given our limited success in consistently maintaining an INR level within the targeted range, perhaps the routine use of warfarin following TJA should be reevaluated and be reserved for patients with a documented DVT or PE or cardiac history requiring its use. Botteman et al. used economic models demonstrating the use of low-molecular weight heparin to be more cost-effective than warfarin in part due to the administrative costs of monitoring INR levels postoperatively (8). Recently, oral direct factor Xa inhibitors such as rivaroxaban and apixaban, and the direct factor IIa inhibitor dabigatran have been introduced as potential forms of VTE prophylaxis following joint arthroplasty. These medications are simple to use, as they are prescribed in fixed doses not requiring blood monitoring. However, significant concerns remain with their use due to potential drug interactions and studies demonstrating rates of bleeding similar to that of enoxaparin (33). In addition, Colwell et al., in a randomized controlled trial comparing mobile compression devices with or without aspirin to LMWH following primary THA, found the rate of major bleeding events to be 0% in the mobile compression group versus 6% in the LMWH cohort, and no difference between the groups with regard to the prevalence of venous thromboembolism (26). Thus, patient mobilization and mechanical compression may be the true keys to VTE prevention.

Therefore, while the results of this study provide discrete data regarding the percentage of time that patients achieve INR levels within the recommended range for therapeutic efficacy following joint arthroplasty procedures, several questions still remain. Future directions should focus on prospective studies assessing the effect of being therapeutic, subtherapeutic, and supratherapeutic (based on the recommended ranges for therapeutic efficacy) while taking warfarin, and perhaps definitively determine whether a lower target INR or a standardized dose (i.e. 1mg daily) for all patients may be equally effective. In addition, future studies must identify factors that may predict whether patients will be responsive or overly sensitive to warfarin therapy. Currently, a multi-center, prospective, randomized-controlled trial is being performed to assess both the effectiveness of pharmacogenetic dosing (accounting for genetic, single nucleotide polymorphisms that affect warfarin metabolism) and also targeting a lower INR versus a higher INR (24). In conclusion, this

study confirms our hypothesis that patients receiving warfarin for chemical thromboprophylaxis are within their targeted INR range for only a limited period of time during their postoperative course.

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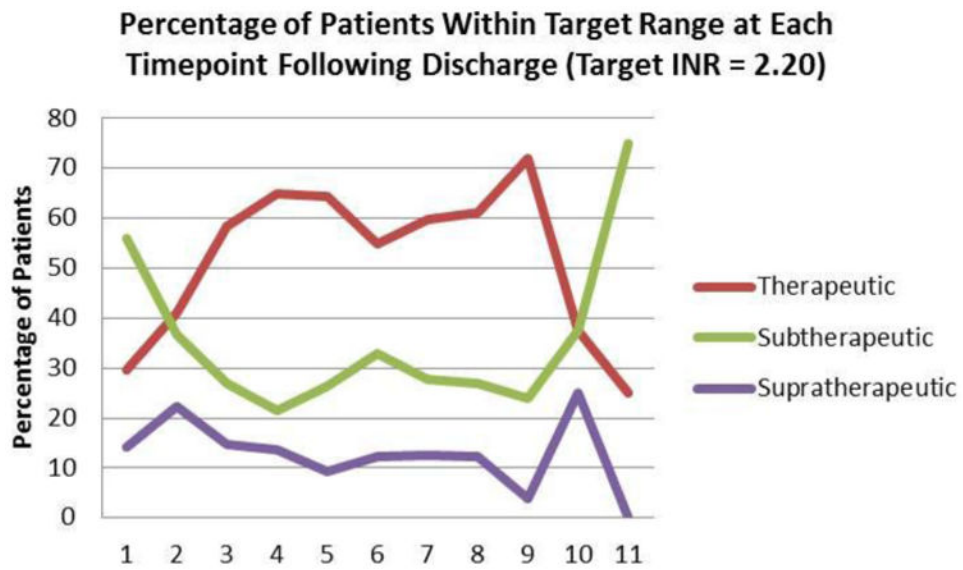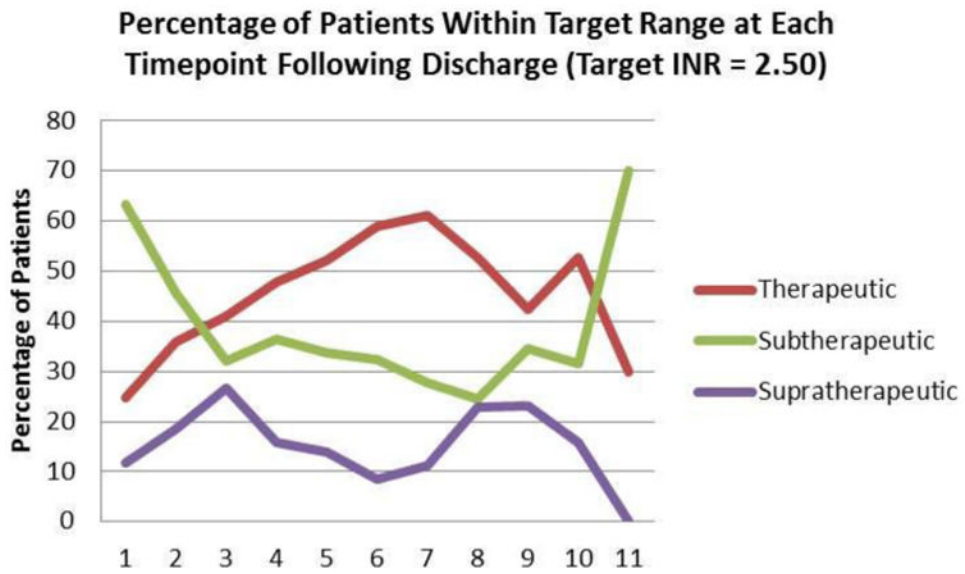
Figure 1.
Graph depicting the percentage of patients who were therapeutic, subtherapeutic, and suratherapeutic at each time their INR was checked postoperatively with a target INR of 2.20. Timepoint 1 corresponds with the first INR level checked following discharge, while timepoint 11 corresponds with the eleventh INR level checked following discharge.

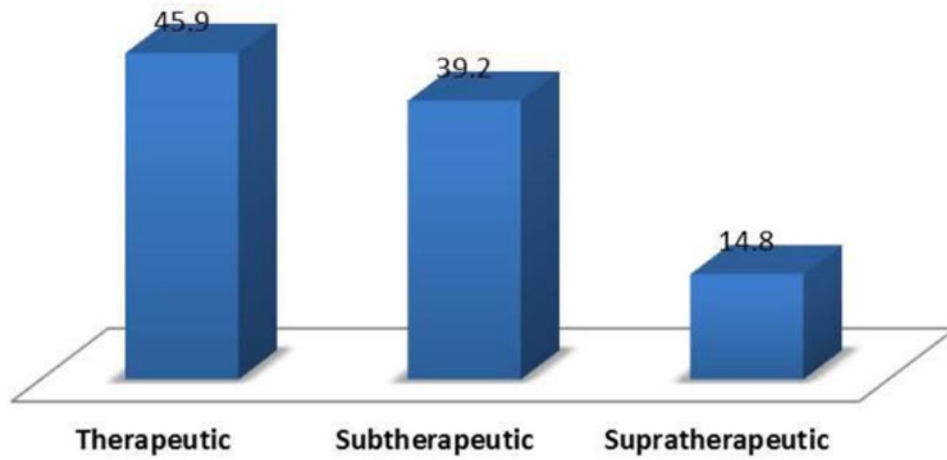## Mean Percentage of Time Patients Within Target Range During Their Treatment Course (Target INR = 2.20)
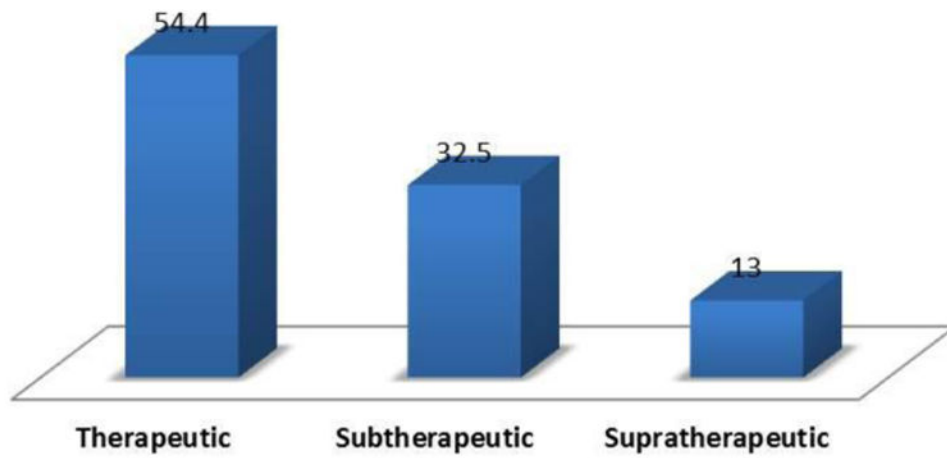
Figure 2.
Graph demonstrating the mean percentage of time that patients were therapeutic, subtherapeutic, or supratherapeutic over their 4-week warfarin course with a target INR of 2.20.

Figure 3.
Graph depicting the percentage of patients who were therapeutic, subtherapeutic, and supratherapeutic at each time their INR was checked postoperatively with a target INR of 2.50. Timepoint 1 corresponds with the first INR level checked following discharge, while timepoint 11 corresponds with the eleventh INR level checked following discharge.

Mean Percentage of Time Patients Within Target Range During Their Treatment Course (Target INR = 2.50)

Figure 4.
Graph demonstrating the mean percentage of time that patients were therapeutic, subtherapeutic, or supratherapeutic over their 4-week warfarin course with a target INR of 2.50.

Table 1

Patient demographics, surgical procedures, and indication for warfarin use. THA= total hip arthroplasty, TKA = total knee arthroplasty, UKA = unicompartmental knee arthroplasty

Mean Age at Surgery (years)	64.0 ± 12.3
Sex	
Male	65
Female	119
Mean Body Mass Index (kg/m²)	31.5 ± 6.3
Patient's Race (frequency/percent of total)	
African American or Black	15 (8.2)
Asian or Indian Subcontinent	1 (0.5)
White, Caucasian, or Middle Eastern	165 (89.7)
Not recorded	3 (1.6)
Surgical Procedure (frequency/percent of total)	
THA	74 (40.2)
Revision THA	17 (9.2)
TKA	60 (32.6)
Revision TKA	17 (9.2)
Infection – Explant of Prosthesis	13 (7.1)
UKA	3 (1.6)
Indication for Warfarin Use (frequency/percent of total)	
Prior DVT or PE	62 (33.7)
Family History of DVT or PE	41 (22.3)
Prolonged Immobilization	5 (2.7)
Atrial Fibrillation, Cardiac Valve, Stent, etc.	31 (16.8)
Hx of Gastric Ulcers	10 (5.4)
Other	35 (19.0)

Table 2

Factors potentially affecting warfarin metabolism.

Currently Smoking (frequency/percent of total)	17 (9.2)
History of Liver Disease (frequency/percent of total)	3 (1.6)
On the Following Medications: (frequency/percent of total)	
Amiodarone	0 (0)
Statin or HMG CoA Reductase Inhibitor	64 (34.8)
-azole (i.e. Fluconazole)	18 (9.8)
Sulfa/Septra/Bactrim/Cotrim/or Sulfatrim	47 (25.5)