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Original Article

Majority of Total Joint Arthroplasties Are Subtherapeutic on Warfarin at Time of Discharge: Another Reason to Avoid Warfarin as a Venous Thromboembolism Prophylaxis?

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ABSTRACT

Background: Warfarin has been used as prophylaxis against venous thromboembolism (VTE) after total joint arthroplasty (TJA) for over 60 years. With trends of shorter hospital stays for TJA patients, it is important to examine how many patients achieve therapeutic international normalized ratio (INR) at time of discharge. We aimed at elucidating the proportion of patients discharged at therapeutic INR and whether this is affected by inpatient specialty anticoagulation management service (AMS) involvement.
Methods: We conducted a retrospective review of 2927 primary TJA patients who received warfarin as postoperative VTE chemoprophylaxis from 2011 to 2016. An electronic chart query determined AMS input, length of stay (LOS), INR at discharge, and in-hospital complications. INR results were categorized as subtherapeutic (INR < 2.0), therapeutic (2.0 ≤ INR < 3.0), and supratherapeutic (INR ≥ 3.0). Descriptive statistics, chi-square, and *t*-tests were performed for analysis.
Results: At discharge, 93.9% of patients had subtherapeutic INR. Average INR was 1.41 with average LOS of 2.53 days. Factors associated with being subtherapeutic included male gender, shorter LOS, fewer comorbidities, reduced in-hospital complications, and higher body mass index. AMS supervised postoperative warfarin dosing in 64.9% of patients. Patients managed by AMS were less likely to be subtherapeutic at discharge compared to those without AMS input; however, the absolute difference in INR may not be clinically significant. There were 19 VTEs, of which 13 had prolonged hospitalization to achieve therapeutic INR.
Conclusion: The majority of patients are discharged at subtherapeutic INR levels despite management by AMS. Patients may not be adequately anticoagulated with warfarin at time of discharge, raising significant patient safety concerns as well as medicolegal implications.

Originally developed as a potent rodenticide, warfarin has been used as a chemical prophylaxis against venous anticoagulation for total joint arthroplasty (TJA) since its approval by Food and Drug Administration in 1954 [1]. Warfarin as an anticoagulation agent has been studied extensively and shown to be relatively effective in preventing pulmonary embolism (PE) and deep vein thrombosis (DVT) [2–5]. Despite over 6 decades of use, the administration of warfarin remains a challenge because of the very narrow therapeutic window. Hence, warfarin has been falling out of favor as a perioperative venous thromboprophylaxis for patients undergoing TJA [6].

The American College of Chest Physicians recommends a target international normalized ratio (INR) of 2.5 with a range of 2.0-3.0 when warfarin is used as a chemoprophylaxis agent for patients undergoing TJA [7]. Successfully navigating this therapeutic window is essential as subtherapeutic therapy may predispose patients to venous thromboembolic (VTE) events, while supratherapeutic therapy can lead to serious and sometimes fatal bleeding [1,8]. Recent efforts to optimize warfarin therapy based on genetic factors have shown some improvement in reducing supratherapeutic INRs, but have not demonstrated a significant reduction in PE or DVT [9,10]. Furthermore, warfarin is the most cited reason for drug-

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related mortality [11] and the second leading cause of drug-related emergency room visits [12].

Alongside the evolution in postoperative TJA management over the past 25 years, the choice of VTE prophylaxis also requires reexamination. With average length of stay (LOS) decreasing to between 2 and 4 days for patients following TJA, achieving therapeutic INR at discharge has become more and more unlikely [13–15]. This study will focus on the in-hospital management of warfarin in patients undergoing TJA. It is our hypothesis that the majority of patients undergoing TJA receiving warfarin as VTE chemoprophylaxis are not therapeutic at the time of discharge from hospital. We further postulate that involvement of a specialized in-hospital anticoagulation service provides limited benefit with regard to achieving a therapeutic INR at discharge.

Materials and Methods

After institutional review board approval, a retrospective review of patients undergoing primary TJA at a single institution from 2011 to 2016 was performed. An electronic chart query was used to identify patients who received warfarin as VTE prophylaxis throughout their hospital stay. Inclusion criteria for this study comprised of patients undergoing elective primary TJA with warfarin as monoprophylaxis against VTE postoperatively. Patients who were taking warfarin before hospital admission were excluded from the study. Additionally, patients who were bridged or switched to a different VTE prophylactic medication during their hospital stay were excluded. All patients received mechanical prophylaxis during their hospital course.

An electronic query was then performed for date of admission, date of discharge, in-hospital complications, INR value at discharge, VTE prophylaxis management service involvement, comorbidities, and demographic information. There were 2926 patients who met the inclusion criteria with primary total knee arthroplasty representing 52.1% (1523/2926) and primary total hip arthroplasty representing 47.9% (1403/2926) of the final cohort. Demographic data are shown in Table 1.

The target INR for VTE prophylaxis of orthopedic patients is 2.0-3.0 at our institution. Patients with subtherapeutic INR (INR < 2.0), therapeutic INR (2.0 ≤ INR < 3.0), and supratherapeutic INR (INR ≥ 3.0) were identified. In-hospital complications (VTE, cardiac, pulmonary, gastrointestinal, cerebral, vascular, infection, intraoperative, and renal adverse events) were assessed within the subtherapeutic, therapeutic, and supratherapeutic INR groups. Patients were divided into 2 groups: one group had their warfarin administered by a specialized anticoagulation management service (AMS), while patients in the other group had their anticoagulation managed solely by the admitting orthopedic team. Criteria for management by the AMS service was determined by patient's medical history of VTE event, family history of VTE, and at the discretion of the admitting orthopedic team. VTE events were diagnosed using either computed tomography angiography of the chest (for PE) or ultrasound of the extremity of concern (for DVT). Patients were tested at the discretion of the ordering provider based on clinical suspicion, which was based on a combination of clinical symptoms (such as dyspnea or extremity pain), physical examination (such as extremity swelling), and laboratory values (such as D-dimer).

Table 1
Demographic Data.

Demographics	Overall (N = 2926)	AMS (N = 1899)	No AMS (N = 1027)	*P* Value
Age, mean (SE)	64.41 (0.20)	64.48 (0.25)	64.28 (0.34)	$P = .631$
Male gender, number (%)	1214 (41.49)	774 (40.76)	440 (42.84)	$P = .275$
BMI, mean (SE)	30.32 (0.11)	30.69 (0.13)	29.63 (0.18)	$P < .001$
Elixhauser, mean (SE)	1.74 (0.03)	1.80 (0.03)	1.62 (0.04)	$P = .001$

Data are presented as mean (SE) or number (percentage).
BMI, body mass index; AMS, anticoagulation management service; SE, standard error.

Statistical Analysis

Descriptive statistics are presented throughout the text as mean (standard error), number (percentage), or percentage (numerator/denominator). Comparative statistics were made between the group of patients managed by AMS and those not managed by them. Chi-square analysis was used to compare between dichotomous variables and a *t*-test was used to compare between continuous variables. Variables associated with having a therapeutic INR at discharge within the univariate analysis ($P < .1$) were included in a multiple regression analysis.

Results

In the 2926 patients undergoing TJA who received warfarin monoprophylaxis, the average INR at the time of hospital discharge was 1.41 (SE = 0.01) and the average LOS was 2.53 days (SE = 0.03). At the time of discharge, 93.9% (2747/2926) of patients had subtherapeutic INR (Fig. 1). Factors significantly associated with being subtherapeutic at discharge were male gender (42.19% vs 30.73%; $P < .001$), shorter length of hospital stay (2.43 days vs 4.08 days; $P < .001$), lower in-hospital complication rates ($P < .001$), fewer comorbidities (Elixhauser score: 1.70 vs 2.24; $P < .001$), younger age (64.20 vs 67.66; $P < .001$), and higher body mass index (BMI) (30.39 vs 29.28; $P = .011$). Of note, 0.24% of patients (7/2926) had supratherapeutic INR at time of discharge.

When stratified by joint, total hip arthroplasty patients had a shorter LOS (2.32 days vs 2.72 days, $P < .001$), lower INR at discharge (1.38 vs 1.44, $P < .001$), and were more likely to be discharged with a subtherapeutic INR (1333 [95.01%] vs 1414 [92.84%], $P < .001$) than patients undergoing total knee arthroplasty.

Management by Anticoagulation Service

The specialized anticoagulation management service managed 64.9% (1899/2926) of patients undergoing primary TJA in this cohort. Patients managed by AMS achieved a higher average INR at discharge (1.43 vs 1.38; $P < .001$) and had decreased mean LOS (2.45 days vs 2.67 days; $P = .01$) compared to the cohort managed by the admitting orthopedic service (Table 2); however, the absolute difference in INR at discharge may not be clinically significant. Additionally, patients managed by the AMS had fewer comorbidities ($P = .001$), lower BMI ($P < .001$), and were significantly more likely to be discharged with therapeutic INR ($P < .0001$). This remained significant in a multivariate regression analysis (odds ratio, 2.24; confidence interval, 1.83-2.74; $P < .0001$) after adjusting for age, gender, BMI, LOS, in-hospital complications, and Elixhauser comorbidity score.

Postoperative Complications

There were 19 VTE events (16 PEs, 3 isolated DVTs) in 17 patients. Of these 17 patients, 12 patients were managed by AMS. Four patients (3 PEs, 1 isolated DVT) had a prolonged hospital course due to other additional postoperative complications. For the remaining 13 patients with VTEs, mean time to event was 2.11 days (SE = 0.21). These patients consisted of 9 women and 4 men with an average age of 69.9 years (SE = 2.57), BMI of 31.2 kg/m^2 (SE = 1.57),