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Thromboembolic and Bleeding Outcomes of Extended Duration Low-Intensity Warfarin Following Elective Total Knee Arthroplasty

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ABSTRACT

Introduction: The purpose of this study was to describe the incidence of symptomatic venous thromboembolism (VTE), clinically-relevant bleeding, and death among a real-world population receiving warfarin prophylaxis targeting an international normalized ratio (INR) of 1.5 to 2.5 for four weeks following total knee arthroplasty (TKA).
Materials and Methods: This retrospective, observational study included patients receiving warfarin following a TKA between August 1, 2005 and July 31, 2009 identified in the Kaiser Permanente Total Joint Replacement Registry. Patients <18 years, receiving warfarin for another indication, or without continuous KPCO membership during the study period were excluded.
Results: There were 1487 patients with TKA included in the analysis. Mean patient age was 67.7 years and 61.7% were female. The median percent of time in therapeutic INR range during follow-up was 55% (interquartile range = 35%-75%). Nineteen cases of symptomatic VTE [1.3%; 95% confidence interval (CI) 0.8%-2.0%] including ten pulmonary emboli (PE) (0.7%) were identified within 90 days of surgery. Clinically-relevant bleeding occurred in 1.7% (95% CI 1.1%-2.5%) of patients during warfarin prophylaxis and there were no deaths within 90 days of surgery.
Conclusions: The rates of symptomatic VTE and clinically-relevant bleeding following TKA in patients receiving warfarin prophylaxis with a target INR of 1.5 to 2.5 were low. Additional studies should include low-intensity warfarin to identify the regimen that optimally balances risks of bleeding and symptomatic VTE after major orthopedic surgery.

Introduction

Venous stasis, endothelial injury, inflammation, and subsequent hypercoagulability during and following total knee arthroplasty (TKA) collectively increase the risk of post-surgical venous thromboembolism (VTE) [1–3]. The estimated baseline risk for clinically significant symptomatic VTE without thromboprophylaxis is 4.3% during the first 35 days following joint arthroplasty, with risk being greatest during the first seven days after surgery [1]. Consensus guidelines, including the 9th edition of the American College of Chest Physicians (ACCP) and the American Academy of Orthopaedic Surgeons (AAOS) guidelines, recommend pharmacologic thromboprophylaxis following TKA to reduce the risk and incidence of symptomatic deep vein thrombosis (DVT) and pulmonary embolism (PE) and prevent potentially life-threatening outcomes [1,4].

Historically, the ACCP and AAOS guidelines disagreed regarding the optimal intensity of prophylaxis with vitamin K antagonists (VKAs), including warfarin. The ACCP (2008) guidelines previously emphasized preventing VTE outcomes and recommended dose-adjusted warfarin targeting a conventional international normalized ratio (INR) range of 2.0 to 3.0 [5]. Past AAOS (2009) guidelines supported a low intensity INR target of ≤ 2.0 due to concern for post-surgical bleeding complications [6]. The most recent AAOS (2011) and ACCP (2012) guidelines no longer recommend a specific INR target for warfarin therapy [1,4]. The ACCP guidelines comment that morbidity associated with symptomatic VTE is comparable to that of major post-operative bleeding following total joint arthroplasty [1].

Abbreviations: TKA, total knee arthroplasty; VTE, venous thromboembolism; ACCP, American College of Chest Physicians; AAOS, American Academy of Orthopaedic Surgeons; DVT, deep vein thrombosis; PE, pulmonary embolism; VKA, vitamin K antagonist; INR, International Normalized Ratio; KPCO, Kaiser Permanente Colorado; CPAAS, Clinical Pharmacy Anticoagulation and Anemia Service; EMR, electronic medical record; LMWH, low-molecular-weight heparin; TJRR, total joint replacement registry; TTR, time spent within the therapeutic INR range ICD-9 - International Classification of Diseases, Ninth Revision

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Warfarin prophylaxis targeting lower INRs is commonly used in clinical practice. A recent survey of orthopedic surgeons in the United States found that only 23% of respondents using warfarin thromboprophylaxis reported targeting an INR range of 2.0 to 3.0 [7]. A survey of American Association of Hip and Knee Surgeons found that more than 90% of respondents reported targeting an INR range lower than 2.0 to 3.0 (e.g. target INR $\leq$ 2.0) [8].

Despite widespread use of low-intensity warfarin thromboprophylaxis following TKA, studies reporting symptomatic VTE and bleeding with this intervention are limited. Available publications have evaluated abbreviated VKA prophylaxis durations, provide limited detail regarding anticoagulation control, report outcomes in populations intermixed with total hip and knee replacement surgeries, and do not report follow-up for VTE outcomes extending to 90 days [9–13]. The purpose of this study is to describe the incidence of symptomatic VTE, clinically-relevant bleeding, and death in a cohort of patients receiving low intensity warfarin (INR targeted to 1.5 to 2.5) for four weeks after TKA.

Materials and Methods

Study Design and Setting

This retrospective, single group, observational study was conducted at Kaiser Permanente Colorado (KPCO), a not-for-profit integrated healthcare delivery system providing health care to over 520,000 patients in Colorado. At KPCO, orthopedic surgeons prefer warfarin with an INR target of 1.5 to 2.5 for thromboprophylaxis following TKA. Warfarin is initiated the evening of the procedure and typically continued for four weeks.

Pharmacists in the KPCO Clinical Pharmacy Anticoagulation and Anemia Service (CPAAS) centrally monitor and manage over 8,000 patients receiving outpatient anticoagulants. At any given time 7% to 9% of the CPAAS census is patients receiving low-intensity warfarin after total joint arthroplasty. Orthopedic surgeons refer patients for anticoagulation management to CPAAS where clinical pharmacists practice under collaborative drug therapy management agreements and document all direct patient care activities (including warfarin dose titration and lab monitoring) in an electronic medical record (EMR) and anticoagulation tracking software program (Dawn-AC; 4S Systems, Ltd., Cumbria, United Kingdom) [14]. All study activities were reviewed and approved by the KPCO Institutional Review Board.

Study Population

The study included patients who 1) were age $\geq$18 years at the time of TKA; 2) had a TKA between August 1, 2005 and July 31, 2009; 3) had continuous KPCO membership in the six months prior and three months following TKA; and 4) received warfarin targeted to an INR 1.5 to 2.5 for post-TKA thrombopropylaxis. Patients who did not receive low-intensity warfarin (defined as warfarin prophylaxis targeting INR 1.5 to 2.5) or had concurrent warfarin indication(s) other than post-TKA thromboprophylaxis were excluded. Only a patient's first TKA during the study period was included in the analysis.

Study Outcomes

Primary outcomes were the rates of symptomatic VTE (DVT and/or PE), all-cause mortality during the 90-day post-TKA and clinically-relevant bleeding during the four-week warfarin prophylaxis time periods. Clinically-relevant bleeding was defined as any unexpected bleeding following surgery documented during the index hospitalization or bleeding that resulted in rehospitalization or emergency department (ED) visit after discharge. Secondary outcomes included the rate of major hemorrhage during the four-week warfarin prophylaxis time period as defined by the International Society of Thrombosis and Haemostasis (i.e. bleeding that was fatal, symptomatic bleeding into a critical organ, bleeding that resulted in a hemoglobin decrease of greater than or equal to 2 g/dL or led to transfusion of 2 or more units of packed red blood cells) [15,16]. In addition, time spent within the therapeutic INR range (TTR) starting from the day of surgery through completion of warfarin thromboprophyalxis and rate of post-operative infection during the 90-day post-TKA time period were assessed [16].

Data Collection

The KPCO study cohort was identified from the Total Joint Replacement Registry (TJRR) which includes >90,000 joint replacement procedures from all of the Kaiser Permanente regions [17]. The TJRR was developed and maintained through administrative databases queries, physician intake forms, and manual review of EMRs. In addition to demographic data, the TJRR provides thromboprophylaxis details, intra-operative outcomes, and post-procedural complications.

Bleeding, VTE and fatal outcomes were initially identified either within the TJRR or through queries of the KPCO electronic inpatient claims (for VTE, bleeding, infection outcomes) and outpatient record (for VTE outcomes) administrative databases using predefined International Classification of Diseases, Ninth Revision (ICD-9) diagnosis codes (see Appendix). Manual chart review was also undertaken for the entire sample to ensure VTE events managed in the outpatient setting were not missed. Membership datasets were used to identify fatal outcomes. Potential outcomes identified through either the TJR, administrative database queries, or manual chart review were examined and validated by at least two study team members using a standardized chart abstraction form (SEC and DMW). Any disagreements were adjudicated by a 3rd reviewer (NPC). Post-TKA target INR range and INR values during the four-week warfarin thromboprophylaxis course were obtained from the Dawn-AC database.

Patient membership during the study period was identified through queries of the electronic KPCO membership database. Comorbidities (hypertension, diabetes mellitus, renal insufficiency, hepatic disease, previous VTE, and cancer [solid tumor and metastatic]) in the six months prior to TKA were identified via query of the KPCO outpatient record database using predefined ICD-9 codes. The KPCO electronic pharmacy database was used to identify prescription purchase history of nonsteroidal anti-inflammatory drugs, estrogen, and corticosteroids during the 90 days prior to and 28 days following TKA and unfractionated heparin, low-molecular-weight heparin (LMWH), or fondaparinux in the 90 days following TKA.

Data Analysis

Patient characteristics are reported with descriptive statistics (means, medians, standard deviations, interquartile ranges, and percentages). Venous thromboembolism, clinically-relevant bleeding, death, and infection rates were calculated by dividing the frequency of the outcome by the total count of included surgeries and reported as percentages with 95% confidence intervals.

Results

There were 1,725 TKA procedures identified from the TJRR during the study period. Of these, 238 procedures (13.8%) were excluded: 119 for patients with multiple procedures, 94 for chronic warfarin use prior to elective TKA, 11 received LMWH or fondaparinux instead of warfarin, eight received standard intensity warfarin (targeted INR range of 2 to 3), three for miscoded surgery type, and one each for: warfarin treatment refused, dabigatran clinical trial participation, and thromboprophylaxis being prohibited by intraoperative bleeding. Of the eight patients with INR target of 2.0 to 3.0, two cases had post-operative atrial fibrillation, five cases had history of VTE or known thrombophilia, and no rationale was readily apparent in one case. In