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The risk of venous thromboembolism with aspirin compared to anticoagulants after hip and knee arthroplasty

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ABSTRACT

Background: Recent guidelines include aspirin as an option to prevent venous thromboembolism (VTE) in selected patients undergoing hip or knee replacement surgery. However, the efficacy of aspirin after arthroplasty has not been well-defined, particularly in more contemporary patient populations. We compared rates of post-operative VTE between patients who received aspirin-only versus anticoagulants after hip or knee arthroplasty, using data from a large US-based administrative database.

Materials and methods: We conducted a retrospective cohort study of 231,780 adults who underwent total knee arthroplasty and 110,621 who underwent total hip arthroplasty in 2009–2012 and who received pharmacologic VTE prophylaxis (aspirin or anticoagulant) within the first 7 days after surgery. We compared the risk of post-operative VTE between patients receiving aspirin-only vs. anticoagulants, controlling for clinical and hospital characteristics using multivariable logistic regression with propensity score adjustment.

Results: Aspirin-only prophylaxis was administered to 7.5% of patients after knee arthroplasty and 8.0% after hip arthroplasty. Post-operative VTE was diagnosed in 2217 (0.96%) patients after knee arthroplasty and 454 (0.41%) after hip arthroplasty. Compared to anticoagulants, aspirin was not associated with a higher risk for post-operative VTE either after knee arthroplasty (adjusted odds ratio and 95% confidence interval [OR] 0.34 [0.24–0.48]) or hip arthroplasty (OR 0.82 [0.45–1.51]).

Conclusions: Aspirin was uncommonly administered as the sole prophylactic agent after hip or knee arthroplasty in this study. However, patients who received aspirin-only had similar rates of post-operative VTE compared to patients who received anticoagulants. Further research should focus on distinguishing which patients benefit more from anticoagulants versus aspirin after arthroplasty.

1. Background

Post-operative venous thromboembolism (VTE), primarily deep vein thrombosis (DVT) or pulmonary embolism (PE), are well-documented and potentially preventable complications of major orthopedic surgery [1,2]. Anticoagulants such as low-molecular-weight heparins (LMWH), warfarin, fondaparinux, and direct oral anticoagulants have been shown to reduce the risk of post-operative VTE after hip or knee arthroplasty [3]. However, the benefits of using anticoagulants to prevent VTE must be weighed against an increased risk of hemorrhage [1].

National guidelines, including from the American Association of Orthopedic Surgeons (AAOS) and the American College of Chest Physicians (ACCP) recommend the administration of pharmacologic agents or mechanical compressive methods to prevent VTE in patients undergoing elective hip and knee arthroplasty [4,5]. Although warfarin and LMWHs are the most widely used agents for VTE prophylaxis after arthroplasty, guidelines recently included aspirin as an option for VTE prophylaxis after joint arthroplasty, particularly for patients who are at increased risk for adverse bleeding events [4,5]. Aspirin is an appealing alternative to anticoagulants because of its lower cost and ease of administration. However, the evidence base supporting the efficacy and safety of aspirin after arthroplasty is only weak to moderate in quality, with few randomized clinical trials addressing the topic in more contemporary patient populations [6–11]. In the absence of high quality clinical trial evidence, observational studies can provide important insights in trends in medication utilization and outcomes.

Our study used a large administrative database to describe rates of aspirin use in patients undergoing elective hip or knee arthroplasty

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and compared their rates of post-operative VTE to patients who received anticoagulants.

2. Methodology

We conducted a retrospective cohort study using data from the Perspective (Premier, Inc.) database, an ongoing database representing >700 mostly small to mid-size hospitals in the US serving a largely urban patient population. Developed to measure health care quality and utilization, the Perspective database contains hospital discharge file data, date-stamped records of charges for devices, materials, medications, procedures, hospital level data (including number of beds and region), and de-identified patient level data (including demographics, admission type, and discharge diagnosis) [12].

Patients were included in our analysis if they were aged 18 years or older and hospitalized during the time period January 1, 2009 and March 31, 2012 with a principal diagnosis of primary total hip arthroplasty or total knee arthroplasty (*International Classification of Diseases*, *Ninth Revision*, *Clinical Modification* [ICD-9] diagnosis codes 81.51 or 81.54). Only hospitals with 12 months or more of data were included. We next restricted the analysis to patients who received a charge for a medication used for VTE prevention after surgery, specifically, aspirin or anticoagulants. Patients who were admitted from emergency departments or as transfers from other acute care facilities were excluded because our focus was on elective hip or knee arthroplasty.

We obtained data on patient demographic data, including patient age, gender, race/ethnicity, primary health insurance payer, as well as hospital data, including geographic region, bed size, and teaching status. We also searched for secondary ICD-9 discharge diagnosis codes for specific medical diagnoses considered risk factors for VTE, such as malignancy, congestive heart failure, chronic obstructive pulmonary disease (COPD), and myocardial infarction [13] as well as for clinical factors comprising the validated VTE risk score developed by Caprini et al., which has been previously validated in other surgical settings [14,15]. ICD-9 codes were also used to calculate an Elixhauser comorbidity risk score, a validated measure of hospital comorbidity [16].

2.1. Pharmacologic prophylaxis for VTE

The primary predictor of the analysis was type of pharmacologic VTE prophylaxis administered after surgery. We searched for itemized charges for specific antithrombotic agents used for VTE prophylaxis administered at any time within the first seven days after the index hip or knee surgery. VTE prophylaxis was considered any of the following anticoagulant medications: warfarin sodium (any dose); injectable heparin sodium at doses between 5000 and 7500 units; prophylactic doses of LMWH (enoxaparin at doses of 30 mg or 40 mg, dalteparin at doses of 2500 or 5000 units, or tinzaparin at doses of 3500 or 4500 units); fondaparinux at a dose of 2.5 mg; or prophylactic doses of direct oral anticoagulants (dabigatran at doses of 75 mg or 150 mg, rivaroxaban at a dose of 10 mg, or apixaban at a dose of 2.5 mg). Receipt of aspirin for VTE prophylaxis was defined as a charge for aspirin (at any dose) in non-combination formulations.

Patients were grouped into three separate categories: 1) patients who received aspirin-only after surgery; 2) patients who received anticoagulants alone; and 3) patients who received both aspirin and anticoagulants.

2.2. Post-operative VTE and hemorrhagic outcomes

The primary outcome of the study was VTE that occurred during the index hospitalization or within 30 days of the index surgery, ascertained through a combination of ICD-9 and "present-on-admission" codes [17]. VTE events that occurred during the index hospitalization were identified by searching for discharge diagnosis codes for lower extremity DVT or PE during the index hospitalization (ICD-9 codes: 415.11, 415.19, 451.11, 451.19, 451.2, 451.81, 451.9, 453.40, 453.41, 453.42, 453.8, 453.9) combined with a present-on-admission code of "no" [17]. VTE events that occurred after discharge and within 30 days were identified as a readmission to a hospital participating in the Premier consortium with a principal diagnosis code of DVT or PE.

We also examined as a secondary clinical outcome the rate of post-operative bleeding complications, defined using ICD-9 codes 998.1, 998.11, 998.12, 998.13, 852.4, 432.0, 578.9, 39.98, 39.99, 83.14, 83.19, 83.39, 83.44, 83.49, 578.xx, 86.04, 86.22, 86.28, 96.58, 96.59, 97.15, 97.16, in combination with a present-on-admission code of "no" [10]. These codes encompassed gastrointestinal and extradural hemorrhages; wound hemorrhage/hematoma/or seromas; and procedures related to management of wound complications such as fasciotomy, incision/drainage, debridement, or wound packing.

2.3. Statistical analysis

We first described the distribution of antithrombotic prophylaxis (aspirin-only, anticoagulants-only, and aspirin plus anticoagulants) used after surgery in our study population, stratified by hip and knee arthroplasty. Using bivariable analysis, we tested the association of individual risk factors, including demographics, hospital factors, and medical conditions, with the primary clinical outcome of post-operative VTE using Chi-squared tests for categorical variables and *t*-tests for continuous variables.

In order to account for the potential risk of allocation bias in this observational study where patients were not randomly assigned VTE prophylaxis strategies, we developed propensity scores to model the likelihood of a patient receiving aspirin-only therapy [18]. Using all available baseline clinical and hospital variables, we developed a propensity score for patients undergoing hip arthroplasty and a separate score for knee arthroplasty. The initial development step involved testing bivariable associations between individual risk factors and the likelihood of receiving aspirin-only. Variables were retained in the final propensity score if the bivariate association was significant at a P of <0.1. Then, each cohort (hip or knee) was stratified by quintiles of propensity score and the distribution of covariates between aspirin-only and anticoagulant groups was examined to determine whether they were more equally distributed.

The propensity scores for receiving aspirin-only were then included in the multivariable logistic regression models testing the association of VTE with aspirin-only exposure. Variables corresponding to patient demographics, hospital characteristics, Elixhauser comorbidity, and the Caprini VTE risk score were included in the model as potential adjustors. PROC GENMOD was used to account for potential effects of clustering at the individual hospital level. All analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC). This study was approved by the institutional review board of the University of California, San Francisco.

3. Results

We identified 399,696 elective primary total hip and knee arthroplasty procedures performed between January 1, 2009 and March 31, 2012 at 323 and 327 hospitals, respectively. Pharmacologic VTE prophylaxis, either aspirin-only, anticoagulant-only, or anticoagulants plus aspirin, was administered to 342,401 (85.7%) of hospitalized patients within the first 7 days after surgery; this constituted our analytic cohort. Among the 231,780 patients undergoing knee arthroplasty, most received anticoagulants-only (79.7%), while 7.5% received aspirin-only, and 12.8% received both anticoagulants and aspirin. Among the 110,621 patients undergoing hip arthroplasty, most received anticoagulants-only (79.9%), while 8.0% received aspirin-only and 12.1% received both anticoagulants and aspirin. The most common antithrombotic medication prescribed post-operatively was warfarin only, given to 29.6% of patients undergoing knee arthroplasty and 30.8% undergoing hip arthroplasty. Enoxaparin only was the next