Venous Thromboembolism in Total Hip and Total Knee Arthroplasty

Samantha J. Simon, BA; Rushad Patell, MD; Jeffrey I. Zwicker, MD; Dhruv S. Kazi, MD; Brian L. Hollenbeck, MD

Abstract

IMPORTANCE The optimal pharmacologic thromboprophylaxis agent after total hip and total knee arthroplasty is uncertain and consensus is lacking. Quantifying the risk of postoperative venous thromboembolism (VTE) and bleeding and evaluating comparative effectiveness and safety of the thromboprophylaxis strategies can inform care.

OBJECTIVE To quantify risk factors for postoperative VTE and bleeding and compare patient outcomes among pharmacological thromboprophylaxis agents used after total hip and knee arthroplasty.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study used data from a large health care claims database. Participants included patients in the United States with hip or knee arthroplasty and continuous insurance enrollment 3 months prior to and following their surgical procedure. Patients were excluded if they received anticoagulation before surgery, received no postsurgical pharmacological thromboprophylaxis, or had multiple postsurgery thromboprophylactic agents. In a propensity-matched analysis, patients receiving a direct oral anticoagulant (DOAC) were matched with those receiving aspirin.

EXPOSURES Aspirin, apixaban, rivaroxaban, enoxaparin, or warfarin.

MAIN OUTCOMES AND MEASURES The primary outcome was 30-day cumulative incidence of postdischarge VTE. Other outcomes included postdischarge bleeding.

RESULTS Among 29,264 patients included in the final cohort, 17,040 (58.2%) were female, 27,897 (95.2%) had inpatient admissions with median (IQR) length of stay of 2 (1-2) days, 10,948 (37.4%) underwent total hip arthroplasty, 18,316 (62.6%) underwent total knee arthroplasty, and median (IQR) age was 59 (55-63) years. At 30 days, cumulative incidence of VTE was 1.19% (95% CI, 1.06%-1.32%) and cumulative incidence of bleeding was 3.43% (95% CI, 3.22%-3.64%). In the multivariate analysis, leading risk factors associated with increased VTE risk included prior VTE history (odds ratio [OR], 5.94 [95% CI, 4.29-8.24]), a hereditary hypercoagulable state (OR, 2.64 [95% CI, 1.32-5.28]), knee arthroplasty (OR, 1.65 [95% CI, 1.29-2.10]), and male sex (OR, 1.34 [95% CI, 1.08-1.67]). In a propensity-matched cohort of 7,844 DOAC-aspirin pairs, there was no significant difference in the risk of VTE in the first 30 days after the surgical procedure (OR, 1.14 [95% CI, 0.82-1.59]), but postoperative bleeding was more frequent in patients receiving DOACs (OR, 1.36 [95% CI, 1.13-1.62]).

CONCLUSIONS AND RELEVANCE In this cohort study of patients who underwent total hip or total knee arthroplasty, underlying patient risk factors, but not choice of aspirin or DOAC, were associated with postsurgical VTE. Postoperative bleeding rates were lower in patients prescribed aspirin. These results suggest that thromboprophylaxis strategies should be patient-centric and tailored to individual risk of thrombosis and bleeding.


Key Points

Question Are thromboprophylactic agents and patient risk factors associated with venous thromboembolism (VTE) and bleeding rates after lower extremity arthroplasty?

Findings In this cohort study of 29,264 patients who underwent total hip arthroplasty or total knee arthroplasty, VTE occurred in 1.19% and bleeding in 3.43% at 30 days. A history of VTE or hereditary hypercoagulable state was associated with a higher rate of VTE.

Meaning VTE risk following arthroplasty was primarily associated with underlying patient risk factors; these results suggest that thromboprophylaxis strategies should be patient-centric and tailored to individual risk of thrombosis and bleeding.
Introduction

An estimated 1.5 million lower extremity arthroplasty procedures are performed in the United States annually.\(^1\) Deep vein thrombosis (DVT) and pulmonary embolism (PE) occur in 0.6% to 3.0% of total hip arthroplasty (THA) and total knee arthroplasty (TKA) cases\(^2,3\) and contribute to postoperative mortality, morbidity, and health care spending.\(^4-10\) Venous thromboembolism (VTE) risk is determined by patient demographics, comorbidities, and thromboprophylaxis strategy.\(^11-14\) Although pharmacologic thromboprophylaxis strategies in orthopedic patients is often procedure specific, underlying risk factors that mediate thrombotic and bleeding risk can make decision-making more nuanced.\(^15\)

Different thromboprophylaxis strategies to reduce postoperative VTE after THA or TKA have been proposed, with variable levels of supporting literature.\(^2,16-19\) All thromboprophylaxis medications have potential for postoperative bleeding, especially in patients with additional risk factors for hemorrhage.\(^20-22\) The optimal choice and selection of thromboprophylaxis in patients after THA or TKA remains unclear and consensus among clinical societies is lacking.\(^23-27\) In particular, how aspirin compares with more contemporary prophylactic anticoagulants is not well established. Regardless, the use of aspirin after THA or TKA in the United States is frequent, although the lack of comparative data are acknowledged.\(^28-30\)

We analyzed a national health care claims–based database to compare the incidence of VTE and bleeding risk after THA or TKA by underlying risk factors. In a propensity-matched approach we further compared the risk of postoperative VTE and bleeding with the use of direct oral anticoagulants (DOACs) and aspirin.

Methods

MarketScan Database

This cohort study used data from the MarketScan Commercial Claims and Encounters databases and MarketScan Medicare Supplemental and Coordination of Benefits databases from January 1, 2017, to December 31, 2019. It includes coverage of the United States and uses private health insurance claims and billing codes to report data on more than 245 million patients. The Medicare supplemental database was used to include those with health care that is employer-paid Medicare.

Study Population

The study was reviewed and deemed exempt by the New England Baptist Hospital institutional review board, thus informed consent was not needed in accordance with 45 CFR §46. We identified patients undergoing primary THA or TKA between March 1, 2017, and September 30, 2019, using Current Procedural Terminology codes (THA: 27130; TKA: 27447). This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies. The study cohort included patients with continuous insurance enrollment 3 months prior to and following arthroplasty. Among patients who had contralateral surgical procedures during the study period, only the first procedure was included. To ensure we only included patients receiving anticoagulants or antiplatelets for thromboprophylaxis, we excluded patients prescribed an anticoagulant medication 14 to 90 days prior to the surgical procedure. Patients prescribed greater than 1 or no postoperative thromboprophylactic medication were also excluded.

Comorbidities

We identified the following comorbidities (coded up to 36 months prior to the index surgical procedure) based on likelihood to influence risk of postsurgical thrombotic and bleeding risk using appropriate International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) codes: obesity, chronic kidney disease (CKD), antiphospholipid antibody, lupus...
anticoagulant, history of VTE, factor V Leiden, antithrombin deficiency, prothrombin gene mutation, protein C or S deficiency, and cancer (eTable 1 in Supplement 1).5

Pharmacological Thromboprophylaxis
We collected data on thromboprophylactic medication using national drug codes for prescription aspirin, rivaroxaban, apixaban, warfarin, and enoxaparin (eTable 2 in Supplement 1). We used the first prescription for a thromboprophylactic medication between 10 days prior to the index surgical procedure, up to 14 days following the procedure. Aspirin prescriptions included 81 mg and 325 mg both once and twice a day.

Outcomes
The primary outcome was cumulative incidence of VTE (including postdischarge DVT and PE) at 30 days.8,16 Secondary outcomes were 90-day cumulative incidence of VTE and 30-day and 90-day postdischarge bleeding events. The ICD-10 codes used to identify these VTE (including lower extremity DVT and PEs) and bleeding events (including intracranial, intraocular, gastrointestinal, genitourinary, and intraarticular bleeding) in the claims data were modified from previously validated studies (eTable 3 and eTable 4 in Supplement 1).19,31-33

Statistical Analysis
Main Analysis
Cumulative incidences of VTE and bleeding were calculated individually without censoring for other outcomes. We performed univariate χ² and regression analysis to identify risk factors and compare thromboprophylactic agents for 30-day VTE events. Statistical significance was set at 2-sided P < .05. Multivariable logistic regression was performed to identify independent risk factors for the 30-day VTE or bleeding events, adjusting for sex, age, THA or TKA, length of stay (LOS), obesity, cancer, CKD, antiphospholipid antibody or lupus anticoagulant, history of VTE, and a hereditary hypercoagulable state (factor V Leiden, antithrombin deficiency, prothrombin gene mutation, protein C deficiency, or protein S deficiency). We included LOS as a surrogate for uncontrolled comorbidities, complexity of surgical procedure, or immediate postoperative complications. Data are presented as odds ratios (OR) with 95% CI. Statistical analysis was performed using SAS software version 9.4 (SAS Institute) from December 7, 2021, to September 23, 2023.

Propensity score matching was done to compare bleeding and thrombotic outcomes in patients prescribed aspirin or DOACs. We included only rivaroxaban and apixaban in the DOAC group as other DOACs were infrequent. Propensity for receiving a DOAC was calculated for each patient based on age, sex, year procedure was performed, inpatient or outpatient arthroplasty, LOS, THA or TKA, hereditary hypercoagulable state, obesity, CKD, cancer, antiphospholipid antibody or lupus anticoagulant, and history of VTE. Patients receiving aspirin or DOAC were matched in 1:1 ratio, with the allowable difference in propensity scores set at 0.01% using greedy nearest neighbor matching without replacement. Standardized mean differences (SMDs) were calculated to compare the matched groups. We calculated 30-day and 90-day cumulative incidence of bleeding and VTE for the aspirin and DOAC groups. We also calculated the OR and 95% CI on the matched data for primary and secondary outcomes.

Sensitivity Analyses
We performed sensitivity analyses to assess the robustness of our findings in the primary analyses. E-values (defined as the minimum strength of association that an unmeasured confounder would need to have to fully explain away a specific association, conditional on the measured covariates) were calculated for VTE ORs.34-36 To assess for residual confounding after propensity score matching, we compared bleeding rates 90 days prior to surgical procedure. To detect potential bias, we compared the rates of negative (unrelated) control outcomes, cholecystitis and motor vehicle accidents, between the aspirin and DOAC groups in the matched analysis.
Secondary Analyses

To further refine our definition of VTE in our matched cohort, we performed the following analysis: 30-day PE rates, odds of VTE in the 30- to 60-day and 60- to 90-day postoperative windows, VTE rates in THA and TKA separately, and VTE and bleeding cumulative incidences stratified by aspirin doses.

Results

Patient Overview

Of the 132,237 patients who underwent THA or TKA between 2017 and 2019 and had continuous insurance enrollment, we excluded 6,688 patients with chronic anticoagulation, 774 patients prescribed at least 2 anticoagulants, and 95,511 patients with no medication prescription recorded. Among 29,264 patients with complete data included in the final cohort, 17,040 (58.2%) were female, 27,897 (95.2%) had inpatient admissions with median (IQR) LOS of 2 (1-2) days, 10,948 (37.4%) had THA; and median (IQR) age was 59 (55-63) years (Table). Common comorbidities included 8,212 patients with obesity.
(28.1%), 1142 with CKD (3.9%), and 1328 with cancer (4.5%). Missing data accounted for a small percentage overall. For example, 7 patients (<0.1%) did not have location of surgical procedure coded, and for these patients we assumed that if their LOS was greater than 0 days, then they had inpatient surgical procedures, otherwise they had outpatient surgical procedures.

**Use of Thromboprophylaxis Medications**

Aspirin was prescribed most frequently to 10 082 patients (34.5%), followed by 7068 (24.2%) receiving rivaroxaban, 5764 (19.7%) receiving enoxaparin, 3253 (11.1%) receiving apixaban, and 3097 (10.6%) receiving warfarin (Table). The median (IQR) durations of prescriptions were 31 (31-32) days for aspirin, 17 (14-31) days for rivaroxaban, 15 (12-22) days for enoxaparin, 18 (14-31) days for apixaban, and 31 (24-33) days for warfarin.

**VTE and Bleeding Rates**

The cumulative incidence of VTE was 1.19% (95% CI, 1.06-1.32%) at 30 days and 1.86% (95% CI, 1.70-2.02%) at 90 days (Figure 1). The cumulative incidence of bleeding was 3.43% (95% CI, 3.22-3.64%) at 30 days and 5.33% (95% CI, 5.07-5.59%) at 90 days. When stratified by the presence of a thrombotic risk factor (including obesity, cancer, CKD, history of VTE, antiphospholipid antibody or lupus anticoagulant, and hereditary hypercoagulable state), the cumulative incidence of VTE remained higher through the 90-day postoperative period for those with a prothrombotic risk factor (2.45% [95% CI, 2.15%-2.75%]) than for those without a thrombotic risk factor (1.53% [95% CI, 1.35%-1.71%]).

**VTE Risk Factors**

In the univariate analysis, hereditary hypercoagulable state and history of thrombosis had the highest unadjusted VTE risk (eTable 5 in Supplement 1). On multivariate analysis, factors associated with significant higher odds of 30-day VTE included a history of VTE (OR, 5.94 [95% CI, 4.29-8.24]), hereditary hypercoagulable state (OR, 2.64 [95% CI, 1.32-5.28]), TKA (OR, 1.65 [95% CI, 1.29-2.10]), and male sex (OR, 1.34 [95% CI, 1.08-1.67]) (Figure 2). For 30-day bleeds, an LOS of at least 3 days, antiphospholipid antibody or lupus anticoagulant, CKD, age greater than or equal to 65 years, and TKA were associated with increased odds of a postoperative bleed.

For 30-day VTE, adjusted for patient and surgical risk factors, patients prescribed aspirin had lower VTE rates when compared with those prescribed enoxaparin or rivaroxaban. There was no statistically significant difference in 30-day VTE rates between those prescribed aspirin and those prescribed warfarin or apixaban. Aspirin was associated with less bleeding than other agents.

**Figure 1. Cumulative Incidence of Venous Thromboembolism (VTE) and Bleeding 0 to 90 Days After Surgical Procedure**

Figure shows the cumulative incidence of VTE and bleeding 0 to 90 days after total hip arthroplasty and total knee arthroplasty surgical procedures. Shaded areas represent 95% CIs.
Multivariable analysis for 90-day outcomes also favored aspirin as having lower VTE and bleeding rates (eTable 6 in Supplement 1).

Propensity-Matched Analysis
In the unmatched cohort, patients prescribed DOACs had higher incidences of VTE risk factors, including history of VTE, CKD, and hereditary hypercoagulable state. This was associated with the higher median (IQR) propensity score in the DOAC group (0.54 [0.42-0.61]) compared with the aspirin group (0.44 [0.40-0.59]) (eFigure 1 in Supplement 1). The propensity-matched analysis included 15,688 patients (7,844 matched pairs; eTable 7 in Supplement 1). Propensity for receiving a DOAC ranged from 32.1% to 94.5% in the matched cohort. Prior to matching, absolute SMDs between the DOAC and aspirin group ranged from less than 0.01 to 0.19. After matching, the absolute SMDs for all variables decreased to 0.00, eliminating detectable differences in risk factors between the groups (eFigure 2 in Supplement 1).

Thromboprophylaxis prescription duration was assessed in comparison with the occurrence of VTE and bleeding events (Figure 3). In our matched cohort the median (IQR) duration a patient was prescribed was 31 (31-32) days for aspirin and 18 (14-31) days for DOACs; 43.6% (3,189 of 7,844) of the aspirin group and 20.6% (1,616 of 7,844) of the DOAC group were prescribed medication for more than 31 days.

In the propensity-matched cohort, 30-day VTE cumulative incidences were 0.92% (95% CI, 0.83%-1.05%) for the DOAC group and 0.83% (95% CI, 0.73%-0.93%) for the aspirin group. At 90 days, the cumulative incidence was 1.63% (95% CI, 1.49%-1.77%) for the DOAC group and 1.29% (95% CI, 1.16%-1.42%) for the aspirin group.

Patients receiving a DOAC had similar odds of VTE at 30 days compared with patients receiving aspirin (OR, 1.14 [95% CI, 0.82-1.59]), but odds of bleeding were higher in the DOAC group (OR, 1.36 [95% CI, 1.13-1.62]). Similarly, at 90 days, the odds of VTE were not statistically different between the DOAC and aspirin groups (OR, 1.28 [95% CI, 0.98-1.66]), but odds of bleeding were higher in patients receiving DOACs (OR, 1.27 [95% CI, 1.10-1.47]). The only difference in odds of VTE was seen between days 30 to 60 where the odds of VTE were higher in the DOAC group compared with the aspirin group (OR, 1.89 [95% CI, 1.09-3.30]).

Figure 2. Multivariable Analysis of 30-Day Postoperative Venous Thromboembolism and Bleeding

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio (95% CI)</th>
<th>P value</th>
<th>Odds ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥65 y vs &lt; 65 y</td>
<td>1.14 (0.88-1.47)</td>
<td>.10</td>
<td>1.19 (1.02-1.39)</td>
<td>.02</td>
</tr>
<tr>
<td>Male vs female</td>
<td>1.34 (1.08-1.67)</td>
<td>.007</td>
<td>0.95 (0.83-1.08)</td>
<td>.41</td>
</tr>
<tr>
<td>Length of stay, d</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2 vs 0</td>
<td>0.89 (0.63-1.25)</td>
<td>.49</td>
<td>0.98 (0.79-1.23)</td>
<td>.88</td>
</tr>
<tr>
<td>3-4 vs 0</td>
<td>1.02 (0.76-1.38)</td>
<td>.88</td>
<td>1.50 (1.24-1.82)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>≥5 vs 0</td>
<td>1.46 (0.83-2.58)</td>
<td>.19</td>
<td>2.33 (1.68-3.24)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Knee vs hip arthroplasty</td>
<td>1.65 (1.29-2.10)</td>
<td>&lt;.001</td>
<td>1.17 (1.03-1.35)</td>
<td>.02</td>
</tr>
<tr>
<td>Obesity</td>
<td>0.81 (0.63-1.03)</td>
<td>.09</td>
<td>0.92 (0.80-1.07)</td>
<td>.28</td>
</tr>
<tr>
<td>Cancer</td>
<td>1.43 (0.94-2.19)</td>
<td>.10</td>
<td>1.22 (0.94-1.60)</td>
<td>.14</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>1.47 (0.95-2.27)</td>
<td>.08</td>
<td>1.33 (1.01-1.76)</td>
<td>.04</td>
</tr>
<tr>
<td>History of venous thromboembolism</td>
<td>5.94 (4.29-8.24)</td>
<td>&lt;.001</td>
<td>1.26 (0.89-1.79)</td>
<td>.20</td>
</tr>
<tr>
<td>Antiphospholipid antibody or lupus anticoagulant</td>
<td>1.85 (1.07-3.93)</td>
<td>.11</td>
<td>1.70 (1.02-2.85)</td>
<td>.04</td>
</tr>
<tr>
<td>Hereditary hypercoagulable state</td>
<td>2.64 (1.32-5.28)</td>
<td>.006</td>
<td>1.45 (0.72-2.89)</td>
<td>.30</td>
</tr>
<tr>
<td>Rivaroxaban vs aspirin</td>
<td>2.00 (1.47-2.74)</td>
<td>&lt;.001</td>
<td>1.38 (1.15-1.66)</td>
<td>.001</td>
</tr>
<tr>
<td>Apixaban vs aspirin</td>
<td>1.21 (0.87-1.68)</td>
<td>.24</td>
<td>1.28 (1.07-1.53)</td>
<td>.007</td>
</tr>
<tr>
<td>Enoxaparin vs aspirin</td>
<td>2.26 (1.59-3.21)</td>
<td>&lt;.001</td>
<td>1.33 (1.07-1.66)</td>
<td>.01</td>
</tr>
<tr>
<td>Warfarin vs aspirin</td>
<td>1.25 (0.83-1.86)</td>
<td>.28</td>
<td>1.43 (1.16-1.77)</td>
<td>.001</td>
</tr>
</tbody>
</table>

Figure shows odds of developing a venous thromboembolism and odds of developing a bleed.
Sensitivity Analyses
The E-values calculated for the 30-day VTE OR of the 2 statistically significant prophylactic medications were 3.95 for enoxaparin and 3.41 for rivaroxaban. This was higher than any OR calculated for the known risk factors of 30-day VTE, with the exception of history of VTE.

For the propensity-matched patients, the bleeding rates 90 days prior to surgical procedure were not statistically significant between the aspirin and DOAC groups. Additionally, there was no statistical difference in the incidence of the 2 negative control outcomes, cholecystitis and motor vehicle accidents, between the aspirin and DOAC groups.

Secondary Analyses
The 30-day cumulative incidence of PE was not statistically significant between the aspirin and DOAC groups; and out of the matched cohort, patients who received THA alone and patients who received TKA alone both showed no difference in 30-day VTE rates. When stratifying by aspirin doses, there was no difference in 30-day VTE or bleeding rates.
Discussion

In this cohort study, the 30-day cumulative incidence for VTE after THA or TKA was low at 1.19%, with higher rates in patients with thrombotic risk factors. Aspirin was a common VTE thromboprophylaxis choice and was not associated with higher rates of VTE compared with other anticoagulants, however, rates of bleeding were significantly lower with aspirin. Furthermore, in the propensity-matched analysis, aspirin was shown to have a potentially longer lasting effect as odds of VTE were lower in the 30- to 60-day postoperative window with lower overall VTE rates at 90 days compared with patients receiving DOAC.

A similar study that used the same database from an older timeframe (2004-2013) demonstrated 6-month DVT rates ranging from 3.12% to 3.42% in a comparable population. This may reflect lower incidence of VTE after orthopedic surgical procedures at a population level over the last decade due to secular trends in management practices (eg, shorter LOS, outpatient arthroplasty, and earlier mobilization) or increasing use of DOACs. A recent report that included 363 530 patients who underwent THA or TKA from 2008 to 2016 in a national surgical quality database demonstrated an overall VTE rate of 0.6% to 1.4%, similar to rates observed in the current study. Acquired and hereditary conditions can increase thrombotic risk in patients through different mechanisms, and may be additive. In this large claims-based study, the risk remained statistically significant for male vs female, TKA vs THA, and known thrombotic risk factors.

Over the last decade, aspirin has become common for thromboprophylaxis after THA or TKA. In contemporary trials, aspirin showed noninferiority compared with low-molecular-weight heparin or rivaroxaban in reducing VTE in THA and TKA. However, a separate randomized clinical trial (RCT) that compared aspirin with enoxaparin in reducing symptomatic VTE after THA or TKA failed to meet noninferiority criteria for aspirin. A comparative clinical trial with aspirin and DOACs is ongoing. In this study based on clinical data, patients prescribed aspirin appear to have similar postoperative VTE rates and significantly less bleeding compared with patients prescribed DOACs, consistent with recent studies. While the effectiveness of aspirin when used as sole prophylaxis compared with DOACs has not been fully resolved, the existing evidence, convenience, and perceived lower bleeding risk have made aspirin VTE prophylaxis widespread in recent years.

Thromboprophylaxis selection involves balancing thrombotic risk with bleeding risk. We found aspirin was associated with significantly lower bleeding risk than other anticoagulants prescribed after THA and TKA. These results are supported by data from RCTs that have compared aspirin with other anticoagulants. A systematic review found a lower rate of bleeding with aspirin compared with anticoagulants after hip fracture repair and a trend toward lower rates of bleeding after lower extremity arthroplasty. In contrast, a recent meta-analysis that included 13 RCTs showed no difference in rates of bleeding complications. In our study, the favorable bleeding profile for aspirin may be drawn from a large population of patients who could be at higher risk of bleeding than the carefully selected participants of RCTs. Clinical data can support relative effectiveness and safety, which supplements efficacy data from well-designed randomized studies.

In addition to lower bleeding risk, our study found that the aspirin group had lower odds of VTE during days 30 to 60, which is the period when most patients discontinue prophylaxis. This illustrates how aspirin may continue to reduce VTE risk after the patient is no longer taking the medication. This could be by way of the inhibition of cyclooxygenase isoenzymes by aspirin, which irreversibly inhibits the action of platelets, thus extending the effect equal to the life of the platelet.

Limitations

This study had limitations. Although the use of an insurance database allowed us to capture a large sample that is reflective of patient populations and circumstances, it is inherently limited by the quality of billing information. We used previously validated algorithms for the outcome measurements to minimize biases introduced through inaccurate coding. However, there may be differences in strategies for diagnosing thrombotic events that could be influenced by the...
pharmacologic thromboprophylaxis which could influence the results. Additionally, national drug codes are unable to capture information about over-the-counter medications and reflect only what a patient was prescribed, not necessarily what was taken. Therefore, we could not verify that patients without a prescription did not actually receive over-the-counter aspirin for prophylaxis or that patients prescribed DOACs were also taking aspirin. We applied exclusion criteria to ensure we analyzed patients with sufficient data (including the absence of a script for thromboprophylaxis); however, it is notable that ultimately approximately 25% of the originally identified population were included. The MarketScan database includes only privately insured patients, thus the population in this study is younger than those enrolled in clinical trials. Therefore, data presented in this study may not be as generalizable to an older patient population. Retrospective studies are susceptible to residual confounding. For example, although we included several known acquired and hereditary risk factors for thrombosis and bleeding in the models, comorbidities such as CKD can influence the choice of pharmacologic thoromboprophylaxis as well as be associated with increased risk of thrombosis and bleeding. Similar rates of bleeding in the 90 days prior and similar rates of falsification end points (cholecystitis and motor vehicle accidents) in the 90 days after index surgical procedure suggest that the groups were adequately matched. We also calculated E-values to assess the presence of potential but unknown confounders. The ORs for such unknown confounders were shown to be greater than 3.0 (higher than most of the known risk factors included), which makes it unlikely that such unknown confounders exist. We note that the variability in the median prescription length of aspirin compared with DOACs could be an important contributing factor to the findings, however, we feel these data reflect clinical practice patterns and are thus important to elucidate.

Conclusions

In this cohort study of patients who received THA or TKA, we found that the risk of VTE was associated with underlying risk factors and preexisting diagnoses, rather than choice of thromboprophylactic medication. A propensity-matched subset of patients that compared aspirin with DOACs had equivalent rates of VTE at 30 days, but lower VTE rates at 90 days and lower bleeding rates. These results suggest a need for patient-centric thromboprophylaxis strategies tailored to individual risk of thrombosis and bleeding.
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Obtained funding: Hollenbeck.

Administrative, technical, or material support: Simon, Hollenbeck.

Supervision: Patell, Zwicker, Hollenbeck.

Conflict of Interest Disclosures: Dr Zwicker reported personal fees from Calyx, personal fees from CSL Berhing, personal fees from Sanofi, grants from Incyte, and grants from Quercegen outside the submitted work. No other disclosures were reported.

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Data Sharing Statement: See Supplement 2.

REFERENCES


SUPPLEMENT 1.
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eTable 3. International Classification of Diseases-10th Revision (ICD-10) Codes for Venous Thromboembolism
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SUPPLEMENT 2.
Data Sharing Statement