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BRIEF REPORT

# Aspirin thromboprophylaxis in joint replacement surgery

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## Abstract

**Background:** Aspirin is commonly used as the only pharmacologic agent for prevention of venous thromboembolism (VTE) after joint replacement surgery in the United States. Despite this, prospective studies investigating VTE events after aspirin-only thromboprophylaxis in joint replacement surgery are lacking in the real-world setting.

**Objectives:** The aim of this study was to estimate the risk of VTE with aspirin-only pharmacologic prophylaxis following joint replacement surgery.

**Methods:** We carried out a prospective observational study of 350 low-risk patients (no prior history of VTE and low cardiovascular risk factors) who underwent total knee and total hip arthroplasty and received only aspirin for thromboprophylaxis postoperatively.

**Results:** The observed risk of symptomatic VTE was 1.7% (95% confidence interval, 0.9%-3.3%) over 3 months of follow up, with only one major bleeding event and no surgical hematomas.

**Conclusion:** The risk of VTE with aspirin monotherapy for thromboprophylaxis in joint replacement surgery in this real-world cohort was higher than previously reported.

KEYWORDS
aspirin, bleeding, joint replacement surgery, thromboprophylaxis, venous thromboembolism

**Essentials**

- Prospective data on venous thromboembolism (VTE) with aspirin use after arthroplasty are lacking.
- This was a prospective observational study of 350 patients who underwent arthroplasty and received aspirin monotherapy.
- The risk of VTE with use of aspirin monotherapy as thromboprophylaxis was 1.7% (95% confidence interval, 0.9%-3.3%).
- VTE risk with aspirin monotherapy in arthroplasty is higher than previously reported.

## 1 | INTRODUCTION

Total knee arthroplasty (TKA) and total hip arthroplasty (THA) are associated with a high risk of postoperative venous thromboembolism (VTE).[1] Historically, the VTE rates associated with these surgeries without thromboprophylaxis were reported to be as high as 20% to 30% with 5% mortality, a dreaded complication of these procedures.[2] Consequently, postoperative pharmacologic prophylaxis, which extends after hospital discharge, became routine and led to the development of various anticoagulant prophylaxis regimens specific to these surgeries. This, together with modern-day surgical practice, near-universal use of mechanical prophylaxis, and the early initiation of physical therapy, however, has decreased symptomatic VTE rates to <1%. This field has also moved away from considering

asymptomatic clots diagnosed by routine postoperative imaging as being clinically relevant.

Use of aspirin for prevention of VTE following THA and TKA has gained popularity, especially among orthopedic surgeons, due to a low risk of surgical bleeding.[3,4] Both the American College of Chest Physicians and the American Academy of Orthopedic Surgeons (AAOS) support the use of aspirin-only regimens for prevention of postoperative VTE over no pharmacologic prophylaxis.[1,5] AAOS, in particular, recommends stratification of patients into low- and high-risk groups with regards to VTE, based on prior history of VTE, body mass index (BMI), active cancer, and cardiovascular risk factors, such as diabetes mellitus, coronary and cerebrovascular disease, and congestive heart failure.[3] No specific guidelines exist for risk stratification for this purpose, but criteria based on general risk factors for cardiovascular disease are in common use.[5] Aspirin is then recommended for low-risk patients. As a result, a significant proportion of patients undergoing joint replacement surgery in the United States receive aspirin for postoperative VTE prophylaxis without any anticoagulants.[4,6] The majority of the data supporting this strategy come from retrospective studies that suggest that aspirin may be noninferior to anticoagulants as prophylaxis.[4,7,8]

The available prospective data include the PEP trial, which showed a reduction in fatal pulmonary embolism (PE) and proximal deep vein thrombosis (DVT) with the use of aspirin following hip fracture surgery; joint replacement, however, formed a small proportion of the patients in this study, and >25% of the patients received unfractionated or low-molecular-weight heparin (LMWH) in addition to aspirin.[9] A recent systemic review also reported that the effectiveness of aspirin did not differ from other anticoagulant prophylaxis after joint replacement, but most modern trials included in this meta-analysis had an initial, at least 5 days, anticoagulant overlap with aspirin, or the studies were old, comparing aspirin to warfarin, or using larger daily doses of aspirin than in current use.[3] More recently, the EPCAT trials showed that aspirin was noninferior to anticoagulants as prophylaxis after an initial 5 to 10 days of LMWH or rivaroxaban after TKA and THA.[10,11] Still, the safety and efficacy of an aspirin-only regimen for VTE prophylaxis in the absence of any anticoagulant use in these surgeries remains unknown, particularly in the real-world setting. We therefore carried out a prospective observational study of patients undergoing TKA and THA who received only aspirin, without an anticoagulant, for thromboprophylaxis.

## 2 | METHODS

The study was approved by the institutional review board. Patients who underwent TKA and THA who were prescribed aspirin at a dose of 325 mg twice daily for 1 month as thromboprophylaxis by their orthopedic surgeons at the New England Baptist Hospital, without any other anticoagulants, were identified on postoperative day 1, and informed consent was obtained. All consecutive patients meeting the inclusion criteria were approached. The use of aspirin at this dose and schedule is the usual practice of orthopedic surgeons in the United States based on AAOS guidelines.[5] The study outcomes were symptomatic VTE and bleeding.

All patients started aspirin within 12 hours of the surgery also wore intermittent pneumatic compression devices on their lower extremities while hospitalized as per usual hospital practice. Relevant medical and surgical data were then collected. Study subjects were contacted by authors via telephone on postoperative day 30 (±3 days) and postoperative day 90 (±7 days), and a questionnaire regarding VTE and bleeding was conducted (Appendix S1). Major and minor bleeds were defined on the basis of the ISTH criteria.[12] All patient-reported VTEs and major bleeding events were confirmed by obtaining relevant medical records, such as hospital or clinic notes and radiology reports. Outside imaging was reviewed by radiology at our institution. The cumulative incidence of VTE up to postoperative day 90 was estimated and 95% confidence intervals (CIs) calculated.

## 3 | RESULTS AND DISCUSSION

A total of 350 patients (of 375 approached) provided informed consent and completed the study; 216 underwent TKA and 134 underwent THA. These patients were deemed low risk for VTE during their presurgical evaluation by their surgeons as per the institutional guidelines, detailed in Table 1. Table 2 summarizes the clinical characteristics of the total cohort. As shown, the rates of cardiovascular disease, tobacco use, and active cancer were low. Table 3 summarizes the total VTE and bleeding events in this cohort. No patients were lost to follow-up. No patients received prophylactic anticoagulants during follow-up. A total of six VTE events occurred during the study period, giving a VTE rate with aspirin-only thromboprophylaxis of 1.7% (95% CI, 0.9%-3.3%) up to postoperative day 90. There were

**TABLE 1** Criteria for low risk for postoperative VTE[a]

| Inclusion criteria | Exclusion criteria |
|---|---|
| No prior history of VTE | History of VTE |
| | Significant cardiovascular disease (≥2 of coronary artery disease, cerebrovascular disease, peripheral vascular disease and congestive heart failure) |
| | Body mass index >40 kg/m$^2$ |
| | Diabetes + smoking + body mass index >35 kg/m$^2$ |
| | Cancer diagnosis within 6 months of surgery (except localized breast and prostate cancers) |

Abbreviation: VTE, venous thromboembolism.

[a]According to the American Academy of Orthopedic Surgeons.[5]

**TABLE 2** Patient characteristics of the study cohort

| Characteristic | Total cohort | Patients with VTE |
|---|---|---|
| N | 350 | 6 |
| TKA, n (%) | 216 (61.7) | 3 (50.0) |
| Median age, y (interquartile range) | 67 (61-72) | 68 (62-75)* |
| Female sex, n (%) | 214 (62.5) | 4 (66.0) |
| Median BMI, kg/m$^2$ (interquartile range) | 29.83 (26.6-33.9) | 28.2 (25.4-35.4) |
| Tobacco use, n (%) | 20 (5.8) | 0 |
| History of VTE, n (%) | 0 (0) | 0 |
| Cardiovascular disease (hypertension, CAD, CVD, CHF), n (%) | 58 (16.5) | 2 (33.0) |
| Recent history of cancer (localized breast and prostate cancer), no. (%) | 12 (3.6) | 0 |

Abbreviations: BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; CVD, cerebrovascular disease; TKA, total knee arthroplasty.

*Range.

four PEs, one proximal (involving popliteal or femoral veins) DVT, and one isolated distal DVT. Three events occurred within 3 days of surgery and before hospital discharge, one on postoperative day 8, one on postoperative day 10, and the last on postoperative day 21. The characteristics of patients who experienced VTE were similar to the rest of the cohort (Table 2 right column). All events were treated with a direct oral anticoagulant (DOAC) (two rivaroxaban and four apixaban) with no reported surgical bleeds. Sixteen (4.5%) of the patients reported at least one minor bleeding episode, with bruising being the most common manifestation. Only one patient experienced a major bleed, a gastrointestinal bleed secondary to aspirin-induced gastritis diagnosed by esophagogastroduodenoscopy 4 weeks following surgery. No bleeds at the surgical site were reported.

**TABLE 3** Total VTE and bleeding events in the aspirin cohort

| | |
|---|---|
| Symptomatic VTE, n (%) | 6 (1.7) |
| Pulmonary embolism | 4 |
| Proximal DVT | 1 |
| Distal DVT | 1 |
| Bleeding, n (%) | 16 (4.5) |
| Major | 1 (GI) |
| Surgical hematoma | 0 |
| Minor | 15 |

Abbreviations: DVT, deep vein thrombosis; GI, gastrointestinal; VTE, venous thromboembolism.

The current rates of symptomatic VTE following TKA and THA are ≈1% or less based on recent trials comparing DOACs to LMWH.[13-17] The current baseline risk of VTE, in the absence of any pharmacologic prophylaxis, is not known. In this prospective observational study of 350 low-risk patients treated only with aspirin following TKA and THA, the risk of VTE up to postoperative day 90 was 1.7% (0.9%-3.3%), with a very low risk of bleeding. This rate is higher than that reported in recent studies that found use of aspirin monotherapy to be noninferior to anticoagulant prophylaxis, but these were retrospective studies primarily done using large-registry data.[4,8] For example, in a recent retrospective study using the US MedAssets database, Baumgartner et al.[4] found the risk of VTE to be 0.7% and 0.4% in TKA and THA, respectively, in a cohort of 20 047 patients. Although this study was large, their data were extracted from a billing database and performed retrospectively using International Classification of Diseases, Ninth Revision codes, which is known to be associated with many limitations in identification of VTE.[18] Similarly, in another retrospective study of joint replacement surgery in their center, Huang et al.[7] found the risk of VTE 0.2% in "lower-risk" patients and 0.6% in "higher-risk" patients. In addition to the biases associated with retrospective and database studies, many patients present to other health systems for complications, particularly VTE, that can be captured only with prospective follow-up.

Although, overall, the risk of VTE with aspirin monotherapy appears low, there are several important considerations to be made. First, as noted above, this was a cohort of patients with low risk for VTE, with no prior history of VTE, lower median BMI, and low rates of cardiovascular disease, whereas recent anticoagulant trials cited above did not exclude patients on the basis of their prior history of VTE, obesity, or other cardiovascular risk factors. Second, the majority of the thrombotic events in this cohort were proximal DVTs or PEs, which is different from what is known to be associated with these surgeries, that is, significantly more distal events. It is possible that distal DVTs, which may be less symptomatic, are more likely to be captured with close in-person follow-up as opposed to phone calls. Finally, this study was carried out in a high-volume specialty orthopedic hospital that has a low postoperative complication rate; rapid institution of physical therapy and early hospital discharge are routine. In this era of simpler, efficacious anticoagulants with a low risk of bleeding for VTE prophylaxis following joint replacement surgery, is a 1.7% risk of symptomatic VTE in a low-risk population using aspirin alone following TKA acceptable, and can it be reduced by using an anticoagulant? An appropriately powered head-to-head

trial comparing aspirin monotherapy to a DOAC, or a DOAC for a limited duration followed by aspirin will be required in TKA and THA to address this question.

To our knowledge, this is the only real-world prospective observational study of VTE rates with the use of aspirin alone following joint replacement surgery in the literature. The study, however, has several limitations. First, it was performed at a single institution, which is a high-volume orthopedic specialty hospital, which could lead to a lack of generalizability and selection bias. The latter was minimized by identifying and obtaining consent from consecutive patients postoperatively. These patients were identified as low risk and put on aspirin prophylaxis by their surgeons. Second, the lack of in-person follow-up visits may have led to failure to diagnose some VTE events manifested only by swelling or mild leg discomfort, particularly distal DVTs, as well as bleeding; however, this would only increase the event rate. Third, we do not have the exact proportion of patients who were eligible for this study, although ≈42% of all patients at this center receive aspirin monotherapy for thromboprophylaxis. Finally, the absence of a control group does not allow direct comparison of VTE rates in our aspirin-only cohort with a group receiving anticoagulant prophylaxis following joint replacement surgery. Finally, even if use of an anticoagulant for a limited duration of time followed by aspirin turns out to be superior to aspirin alone, it will not completely eliminate the risk of VTE.

## RELATIONSHIP DISCLOSURE

AVS and KF have no conflicts of interest to disclose. KAB is a consultant for Janssen.

## AUTHOR CONTRIBUTIONS

AVS designed the study, collected and analyzed the data, and wrote the manuscript. KF collected and analyzed the data, and KAB participated in the design of the study and writing of the manuscript.

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## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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