Aspirin Compared with Anticoagulation to Prevent Venous Thromboembolism After Knee or Hip Arthroplasty: a Large Retrospective Cohort Study

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BACKGROUND: Although guidelines now allow the use of aspirin as an alternative to anticoagulants for venous thromboembolism prophylaxis after knee or hip arthroplasty, there is limited data on contemporary use and outcomes with aspirin.

OBJECTIVE: To describe the use of pharmacologic thromboprophylaxis and to assess venous thromboembolic risk with aspirin compared with anticoagulation after knee or hip arthroplasty.

DESIGN: Retrospective cohort study using data from the US MedAssets database.

PATIENTS: Adults with a principal discharge diagnosis of knee or hip arthroplasty between January 1, 2013, and December 31, 2014.

MAIN MEASURES: We identified charges for medications used for thromboprophylaxis within 7 days after the index surgery from billing records. The primary outcome was postoperative venous thromboembolism identified by International Classification of Diseases, 9th edition codes, from the index hospitalization, rehospitalization within 30 days, or during an outpatient visit within 90 days postoperatively. We compared postoperative thromboembolic risk in patients receiving aspirin-only and those receiving anticoagulants using propensity score–adjusted multivariable logistic regression models.

KEY RESULTS: We identified 74,234 patients with knee arthroplasty and 36,192 with hip arthroplasty who received pharmacologic thromboprophylaxis. Aspirin-only was used in 27.9% of all patients, while 24.2% and 24.1% received warfarin or enoxaparin as prophylactic monotherapy, respectively. Postoperative venous thromboembolism occurred in 495 (0.67%) patients undergoing knee arthroplasty and 145 (0.40%) undergoing hip arthroplasty. Aspirin-only was not related to increased odds of postoperative venous thromboembolism compared with anticoagulants in multivariable adjusted analyses (odds ratio [OR] 0.70; 95% confidence interval [CI], 0.56–0.87, and OR 0.93; 95% CI, 0.62–1.38 for knee or hip arthroplasty, respectively).

CONCLUSIONS: More than a fourth of all patients received aspirin as the sole antithrombotic agent after knee or hip arthroplasty. Postoperative thromboprophylaxis with aspirin-only was not associated with a higher risk of postoperative venous thromboembolism compared with anticoagulants after hip or knee arthroplasty.

KEY WORDS: venous thromboembolism; arthroplasty; anticoagulation; aspirin.

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INTRODUCTION

Venous thromboembolism is a known complication after major orthopedic surgery including knee or hip arthroplasty.[1] More than 1 million knee or hip replacement procedures are performed in the USA each year and the number continues to rise,[2] emphasizing the need for optimal venous thromboembolism prevention strategies in this population.

For patients with elective knee or hip replacement surgery, subcutaneous or oral administration of anticoagulant agents have been the mainstay for venous thromboembolism prevention for years.[3] Guidelines now allow for the use of aspirin as an alternative to anticoagulants for thromboprophylaxis after knee or hip arthroplasty, particularly in patients at high risk of bleeding.[1] Advantages of aspirin over direct oral anticoagulants, warfarin, or low molecular weight heparin include its ease of administration, lack of monitoring need, and lower costs. However, evidence on the comparative efficacy of aspirin for venous thromboembolism prevention after joint arthroplasty in contemporary populations is limited and of low quality.[4, 5]

Previous studies found low rates of aspirin use for venous thromboembolism prevention in patients with knee or hip arthroplasty,[6] but the adoption of these new guideline recommendations might have led to changes in the use of aspirin for perioperative thromboprophylaxis in more recent cohorts, especially in light of a movement towards non-pharmacologic interventions that likely additionally reduce the rates of venous thromboembolism diagnoses, such as early mobility and recommendations against Doppler ultrasonography screening.[1]

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Therefore, our aim was to describe management strategies for pharmacologic thromboprophylaxis in a large contemporary cohort of patients undergoing knee or hip arthroplasty and to assess and compare the risk of postoperative venous thromboembolism in patients receiving aspirin and those receiving anticoagulation for thromboprophylaxis.

METHODS

Study Design and Setting

We conducted a retrospective cohort study using data from the MedAssets Health System database, which is a medical administrative database containing patient-level billing information from about 400 academic and community hospitals in the USA.[7, 8] The MedAssets Health System was developed to improve health care performance and collected de-identified data on patient demographics, hospital discharge diagnoses, admission type, outpatient diagnostic codes, dated charges for medications, materials, devices, and procedures. Data from contributing hospitals were extracted from billing systems, and de-identified and cleaned pooled records were uploaded to an analytic warehouse once a week.[8]

The study sponsors were not involved in the design and conduct of the study; collection, management, analysis, and interpretation of data; or preparation, review, or approval of the manuscript.

Study Population

We included adult patients aged 18 years or older with a principal hospital discharge diagnosis of primary total knee arthroplasty or primary total hip arthroplasty (International Classification of Diseases, Ninth Revision [ICD-9] procedure codes 81.51 or 81.54) between January 1, 2013 and December 31, 2014 and who received pharmacologic prophylaxis for venous thromboembolism. To capture outcomes during the inpatient stay and after discharge, we only included patients discharged from a hospital providing both in- and outpatient data. Patients from hospitals providing < 12 months of data to the MedAssets database were excluded to ensure sufficient information on patient and hospital characteristics. We also excluded patients who received knee or hip arthroplasty after an emergency admission or a transfer from another acute health care institution to restrict our analysis to patients with elective surgery. Patients with a venous thromboembolism diagnosis code and a present-on-admission indicator of "yes" were excluded to limit our analysis to individuals without known previous venous thromboembolism.[9] All patients were unique, and for patients receiving more than one arthroplasty within the defined time period, only the first procedure was considered.

The study was approved by the institutional review board of the University of California, San Francisco. A waiver of informed consent was obtained due to the nature of the study.

Primary Predictor: Pharmacologic Prophylaxis for Venous Thromboembolism

Detailed billing description records containing information on generic type, dose, strength, and day of administration for prescribed drugs were used to identify charges for medications used for postoperative thromboprophylaxis during the index hospitalization at any time within 7 days after the index knee or hip surgery. We considered following medications as pharmacologic prophylaxis for venous thromboembolism: low-dose aspirin (80 to 325 mg) in non-combination formulations, unfractionated heparin at doses of 5000 to 7500 units, low molecular weight heparin at prophylactic doses (enoxaparin 20 to 40 mg, dalteparin 2500 to 5000 units), fondaparinux 2.5 mg, warfarin sodium at any dose, and prophylactic doses of direct oral anticoagulants (apixaban 2.5 mg, rivaroxaban 10 mg). Dabigatran was not considered, because approval by the Food and Drug Administration for pharmacologic prophylaxis of venous thromboembolism was after the end of our study period. For patients with more than one prescription for pharmacologic thromboprophylaxis within the 7 days after the index surgery, information on all medications was extracted.

Outcomes

The primary outcome was postoperative venous thromboembolism occurring during the index hospitalization, or responsible for readmission within 30 days or an outpatient visit within 90 days after discharge, because an increased thromboembolic risk persists up to 3 months postoperatively.[10] Venous thromboembolism diagnoses included lower extremity deep vein thrombosis and pulmonary embolism events and were based on ICD-9 codes (online Supplemental Table 1).[6, 9, 11] Follow-up for thromboembolic events started at the day of surgery. Events that occurred after discharge and led to readmission within 30 days were based on primary diagnosis codes for venous thromboembolism, and we also considered outpatient encounters for venous thromboembolism within 90 days after discharge. If a patient experienced more than one thromboembolic event during the study period, only the first event was considered. Secondary outcomes were prosthetic complications and bleeding events during the index hospitalization (see online Supplemental Table 1 for definition of outcomes).

Covariates

Information on patient demographics, hospital characteristics (teaching status, number of beds, volume of surgeries, geographical region), and secondary hospital discharge diagnosis

Table 1 Characteristics of Participants with Knee Arthroplasty ($n = 74,234$)

Characteristic	Aspirin-only, $n = 20,047$ (27.0%)	Prophylactic anticoagulant–only, $n = 46,284$ (62.4%)	Both anticoagulant and aspirin, $n = 7903$ (10.7%)	*P* value
Patient baseline characteristics				
Age in years				< 0.001
18–64	8419 (42.0)	19,442 (42.0)	2611 (33.0)	
65–69	4093 (20.4)	9424 (20.4)	1710 (21.6)	
70–74	3444 (17.2)	7709 (16.7)	1509 (19.1)	
75–79	2334 (11.6)	5557 (12.0)	1164 (14.7)	
≥ 80	1757 (8.8)	4152 (9.0)	909 (11.5)	
Male gender	7996 (39.9)	17,212 (37.2)	3293 (41.7)	< 0.001
Comorbidities				
Congestive heart failure	392 (2.0)	1259 (2.7)	382 (4.8)	< 0.001
Valvular disease	559 (2.8)	1679 (3.6)	460 (5.8)	< 0.001
History of CAD	861 (4.3)	1573 (3.4)	361 (4.6)	< 0.001
Pulmonary circulation disease	128 (0.6)	519 (1.1)	158 (2.0)	< 0.001
Peripheral vascular disease	383 (1.9)	860 (1.9)	238 (3.0)	< 0.001
Hypertension	13,400 (66.8)	30,950 (66.9)	6015 (76.1)	< 0.001
Paralysis	59 (0.3)	114 (0.3)	32 (0.4)	0.04
Chronic pulmonary disease	2797 (14.0)	6723 (14.5)	1285 (16.3)	< 0.001
Diabetes	4260 (21.3)	10,029 (21.7)	2145 (27.1)	< 0.001
Renal failure	1019 (5.1)	2563 (5.5)	666 (8.4)	< 0.001
Liver disease	186 (0.9)	540 (1.2)	89 (1.1)	0.03
Lymphoma	44 (0.2)	122 (0.3)	20 (0.3)	0.58
Metastatic cancer	6 (0.03)	28 (0.06)	6 (0.08)	0.20
Rheumatoid arthritis/collagen vascular disease	724 (3.6)	1926 (4.2)	287 (3.6)	0.001
Coagulopathy	400 (2.0)	870 (1.9)	174 (2.2)	0.13
Obesity	4877 (24.3)	11,289 (24.4)	2112 (26.7)	< 0.001
Chronic blood loss anemia	130 (0.7)	381 (0.8)	80 (1.0)	0.005
Deficiency anemia	2009 (10.0)	4329 (9.4)	853 (10.8)	< 0.001
Alcohol/drug abuse	290 (1.5)	596 (1.3)	104 (1.3)	0.10
Elixhauser comorbidity measure,[15] mean (SD)	2.0 (1.5)	2.1 (1.5)	2.4 (1.6)	< 0.001
The Caprini VTE risk score,[13] mean (SD)	11.2 (0.9)	11.2 (0.9)	11.4 (0.9)	< 0.001
Compression stockings	5102 (25.3)	11,641 (24.9)	2748 (34.3)	0.047
Characteristics of hospitals				
Rural location*	473 (2.4)	1665 (3.6)	489 (6.2)	< 0.001
Area				< 0.001
Midwest	4621 (23.1)	5328 (11.5)	476 (6.0)	
Northeast	2763 (13.8)	7546 (16.3)	1194 (15.1)	
South	10,245 (51.1)	29,653 (64.1)	5476 (69.3)	
West	2418 (12.1)	3757 (8.1)	757 (9.6)	
Number of beds*				< 0.001
0–99	1039 (5.2)	3203 (6.9)	2193 (27.8)	
100–199	5286 (26.4)	6905 (14.9)	1768 (22.4)	
200–299	2323 (11.6)	7113 (15.4)	598 (7.6)	
300–499	4702 (23.5)	12,586 (27.2)	1612 (20.4)	
≥ 500	5964 (29.8)	14,795 (32.0)	1468 (18.6)	
Teaching hospital	8752 (43.7)	22,628 (48.9)	2997 (37.9)	< 0.001
Hospital annual volume of surgeries, median (IQR)	500 (250, 737)	430 (250, 848)	565 (269, 1143)	< 0.001
Characteristics of hospital stay				
Length of stay in days, mean (SD)	3.6 (1.3)	4.0 (1.4)	4.4 (2.1)	< 0.001
Disposition†				< 0.001
Home	14,114 (70.4)	29,003 (62.7)	4467 (56.5)	
Transfer to another acute care facility	175 (0.9)	448 (1.0)	91 (1.2)	
Skilled nursing facility/rehabilitation	3751 (18.7)	12,221 (26.4)	2354 (29.8)	
Died	7 (0.03)	12 (0.03)	8 (0.1)	
Other‡	2000 (10.0)	4600 (9.9)	983 (12.4)	

Numbers are presented as n (%), unless indicated otherwise. P values were derived from a chi-squared test for categorical and ANOVA for continuous variables

CAD, coronary artery disease; IQR, interquartile range; SD, standard deviation; VTE, venous thromboembolism

**Information on hospital location and number of hospital beds was missing for 2679 participants: 1682 (3.6%) in the group with anticoagulant-only, 733 (3.7%) in the group with aspirin-only, and 264 (3.3%) in the group with both anticoagulant and aspirin*

†Information on disposition was missing for 7507 participants: 4533 (9.8%) in the group with anticoagulant-only, 1995 (10.0%) in the group with aspirin-only, and 979 (12.4%) in the group with both anticoagulant and aspirin

‡Individuals that were transferred to a hospice, left the hospital against medical advice, or had missing data on disposition status

codes to identify relevant comorbid conditions were extracted from the database. We also collected information on length of stay and disposition status. Variables used to calculate the Caprini risk score (which is a tool to assess venous thromboembolic risk in surgical patients)[12, 13] were obtained, and we also calculated the Elixhauser comorbidity measure using ICD-9 codes[14, 15] to assess and compare perioperative risk among the exposure groups.

Table 2 Characteristics of Participants with Hip Arthroplasty ($n = 36,192$)

Characteristic	Aspirin-only, $n = 10,769$ (29.8%)	Prophylactic anticoagulant–only, $n = 22,055$ (60.9%)	Both anticoagulant and aspirin, $n = 3368$ (9.3%)	*P* value
Patient baseline characteristics				
Age				< 0.001
18–64	5260 (48.8)	10,760 (48.8)	1235 (36.7)	
65–69	1927 (17.9)	3683 (16.7)	618 (18.4)	
70–74	1472 (13.7)	3007 (13.6)	543 (16.1)	
75–79	1057 (9.8)	2258 (10.2)	442 (13.1)	
≥ 80	1053 (9.8)	2347 (10.6)	530 (15.7)	
Male gender	4869 (45.2)	9709 (44.0)	1582 (47.0)	0.002
Comorbidities				
Congestive heart failure	183 (1.7)	586 (2.7)	169 (5.0)	< 0.001
Valvular disease	314 (2.9)	819 (3.7)	180 (5.3)	< 0.001
History of CAD	346 (3.2)	725 (3.3)	190 (5.6)	< 0.001
Pulmonary circulation disease	43 (0.4)	187 (0.8)	47 (1.4)	< 0.001
Peripheral vascular disease	218 (2.0)	467 (2.1)	142 (4.2)	< 0.001
Hypertension	6226 (57.8)	13,018 (59.0)	2388 (70.9)	< 0.001
Paralysis	24 (0.2)	77 (0.4)	17 (0.5)	0.03
Chronic pulmonary disease	1357 (12.6)	3094 (14.0)	505 (15.0)	< 0.001
Diabetes	1544 (14.3)	3243 (14.7)	653 (19.4)	< 0.001
Renal failure	425 (4.0)	1188 (5.4)	256 (7.6)	< 0.001
Liver disease	107 (1.0)	285 (1.3)	36 (1.1)	0.05
Lymphoma	33 (0.3)	70 (0.3)	8 (0.2)	0.74
Metastatic cancer	11 (0.1)	47 (0.2)	5 (0.2)	0.07
Rheumatoid arthritis/collagen vascular disease	385 (3.6)	914 (4.1)	139 (4.1)	0.04
Coagulopathy	226 (2.1)	431 (2.0)	83 (2.5)	0.13
Obesity	1612 (15.0)	3825 (17.3)	600 (17.8)	< 0.001
Chronic blood loss anemia	96 (0.9)	206 (0.9)	37 (1.1)	0.55
Deficiency anemia	991 (9.2)	2199 (10.0)	372 (11.1)	0.004
Alcohol/drug abuse	251 (2.3)	513 (2.3)	70 (2.1)	0.12
The Elixhauser comorbidity measure,[15] mean (SD)	1.7 (1.4)	1.8 (1.5)	2.2 (1.6)	< 0.0001
The Caprini VTE risk score,[13] mean (SD)	11.0 (0.9)	11.1 (1.0)	11.3 (1.0)	< 0.001
Compression stockings	3254 (30.1)	6992 (31.3)	1334 (39.2)	< 0.001
Characteristics of hospitals				
Rural location*	185 (1.7)	623 (2.8)	174 (5.2)	< 0.001
Area				< 0.001
Midwest	2017 (18.7)	2896 (13.1)	263 (7.8)	
Northeast	1155 (10.7)	3200 (14.5)	464 (13.8)	
South	5739 (53.3)	13,909 (63.1)	2214 (65.7)	
West	1858 (17.3)	2050 (9.3)	427 (12.7)	
Number of beds*				< 0.001
0–99	469 (4.4)	1233 (5.6)	849 (25.2)	
100–199	2806 (26.1)	3113 (14.1)	591 (17.6)	
200–299	1501 (13.9)	3376 (15.3)	294 (8.7)	
300–499	2128 (19.8)	6844 (31.0)	704 (20.9)	
≥ 500	3471 (32.2)	6596 (29.9)	797 (23.7)	
Teaching	4382 (40.7)	11,161 (50.6)	1475 (43.8)	< 0.001
Hospital annual volume of surgeries, median (IQR)	271 (152, 477)	260 (131, 438)	350 (157, 451)	< 0.001
Characteristics of hospital stay				
Length of stay in days, mean (SD)	3.3 (1.4)	3.9 (2.2)	4.4 (2.2)	< 0.001
Disposition†				< 0.001
Home	8053 (74.8)	14,355 (65.1)	1930 (57.3)	
Transfer to another acute care facility	83 (0.8)	213 (1.0)	42 (1.3)	
Skilled nursing facility/rehabilitation	1616 (15.0)	5327 (25.2)	940 (27.9)	
Died	6 (0.06)	9 (0.04)	5 (0.15)	
Other‡	1011 (9.4)	2151 (9.8)	451 (13.4)	

Numbers are presented as n (%), unless indicated otherwise. P values were derived from a chi-squared test for categorical and ANOVA for continuous variables

CAD, coronary artery disease; IQR, interquartile range; SD, standard deviation; VTE, venous thromboembolism

**Information on hospital location and number of hospital beds was missing for 1420 participants: 893 (4.1%) in the group with anticoagulant-only, 394 (3.7%) in the group with aspirin-only, and 133 (4.0%) in the group with both anticoagulant and aspirin*

†Information on disposition was missing for 3590 participants: 2133 (9.7%) in the group with anticoagulant-only, 1006 (9.3%) in the group with aspirin-only, and 451 (13.4%) in the group with both anticoagulant and aspirin

‡individuals that were transferred to a hospice, left the hospital against medical advice, or had missing data on disposition status

Statistical Analysis

We divided all participants included in our analysis into three subgroups based on receipt of postoperative thromboprophylaxis: patients receiving aspirin-only, patients receiving anticoagulants, and those receiving both aspirin and anticoagulants. Patients in the two latter subgroups could have been prescribed more than one medication for thromboprophylaxis. Differences in patient and hospital characteristics between the three

groups were compared using chi-squared tests for categorical and ANOVA for continuous variables.

We used chi-squared tests to compare crude proportions of outcome events between the three exposure groups.

To account for potential bias introduced by systematic imbalance in covariates between the two treatment groups of patients who received aspirin-only or those who received an order for any anticoagulant, we used propensity score adjustment to compare the treatment effect for patients with similar conditional probabilities of receiving aspirin-only for postoperative thromboprophylaxis, given the pretreatment covariates.[16]

In a first step, propensity scores were estimated using a multivariable logistic regression model with receipt of aspirin as the dependent variable and baseline patient and hospital characteristics (that did not meet the clear criteria of being instrumental variables or colliders) as the independent variables (all patient baseline characteristics and characteristics of hospitals listed in Tables 1 and 2, and additional variables including hypothyroidism, neurological disease other than paralysis, peptic ulcer disease, AIDS, solid tumor without metastasis, weight loss, fluid and electrolyte disorders, psychoses, depression, prior myocardial infarction). Two separate propensity scores were developed for patients receiving knee or hip arthroplasty. We stratified patients by quintiles of the distribution of their propensity score, and there was sufficient quintile overlap.

In a second step, we developed a multivariable logistic regression to model the independent association between aspirin-only (versus anticoagulation) and the risk of postoperative venous thromboembolism. This model was adjusted for quintiles of the propensity to receive aspirin-only, and we additionally adjusted for the most important confounders (age, gender, venous thromboembolism risk score, metastatic cancer, obesity, congestive heart failure, paralysis, renal failure, coagulopathy, rheumatoid arthritis) to account for the potential of residual confounding due to the subdivision of propensity scores into five strata. We accounted for clustering by individual hospital using the PROC GENMOD command.

Two-sided P values of < 0.05 were considered statistically significant.

All analyses were conducted using SAS version 9.2 (SAS Institute Inc., Cary, NC).

RESULTS

A total of 110,426 participants who received pharmacologic thromboprophylaxis after joint replacement surgery were included in this study: 74,234 participants with knee arthroplasty from 268 hospitals and 36,192 individuals with hip arthroplasty from 243 hospitals. Overall, 27.9% of all patients had aspirin-only for postoperative thromboprophylaxis within the first 7 days after the surgery: 20,047 (27.0%) patients with knee arthroplasty and 10,769 (29.8%) with hip arthroplasty (Tables 1 and 2). The most frequently administered anticoagulant regimens were enoxaparin or warfarin monotherapy, each accounting for 24.1% and 24.2% of anticoagulation prescriptions in both groups of patients undergoing knee or hip arthroplasty (online Supplemental Table 2). We did not identify any patients who received monotherapy with prophylactically dosed rivaroxaban or apixaban during the time period.

Characteristics of included patients and their hospitals stratified by type of pharmacologic thromboprophylaxis are presented in Tables 1 and 2. In both groups of patients with knee or hip arthroplasty, those receiving both anticoagulation and aspirin were older and more likely to be male compared with those with anticoagulation-only or aspirin-only; they had more cardiovascular risk factors and heart disease and had a slightly higher mean Caprini risk score. Patients receiving aspirin-only were more likely to be discharged home and had fewer comorbidities and a shorter length of stay compared with the two other groups.

Among patients with knee or hip arthroplasty, 2778 (3.7%) and 1258 (3.5%) patients were readmitted to a hospital within 30 days, and 26,093 (35.1%) and 11,438 (31.6%) patients had an outpatient visit within 90 days postoperatively, respectively (Table 3). Overall, we identified a total of 495 postoperative venous thromboembolic events in patients undergoing knee arthroplasty (0.67%) during the index hospitalization or leading to a hospital readmission within 30 days or an outpatient visit within 90 days postoperatively, while there were 145 venous thromboembolic events (0.40%) in patients after hip arthroplasty. The crude numbers of postoperative thromboembolic events stratified by type of antithrombotic therapy and by dose of aspirin are presented in Table 3 and online Supplemental Table 3, respectively.

Results from the multivariable model adjusted for the propensity scores of receiving thromboprophylaxis with aspirin-only are shown in Table 4. For patients undergoing knee arthroplasty, those who received aspirin-only had a 30% lower odds of postoperative venous thromboembolism than patients who received any anticoagulants (odds ratio 0.70; 95% confidence interval, 0.56–0.87). The odds of postoperative venous thromboembolism did not significantly differ between patients on aspirin-only compared with those who had any anticoagulants for thromboprophylaxis after hip arthroplasty (odds ratio 0.93; 95% confidence interval, 0.62–1.38).

Overall, 77 (0.10%) patients with knee and 42 (0.12%) patients with hip arthroplasty had a diagnostic code for postoperative bleeding complications during the

Table 3 Postoperative Outcomes, Stratified by Type of Pharmacologic VTE Prophylaxis

Outcome	Total	Aspirin-only	Prophylactic anticoagulant–only	Both anticoagulant and aspirin	*P* value
Knee arthroplasty					
In-hospital postoperative complications*	*n* = 74,234	*n* = 20,047	*n* = 46,284	*n* = 7903	
DVT only	42 (0.06)	2 (0.01)	27 (0.06)	13 (0.16)	< 0.001
PE only	68 (0.09)	7 (0.03)	49 (0.11)	12 (0.15)	0.004
PE and DVT	5 (0.01)	0	4 (0.01)	1 (0.01)	0.36
Prosthetic complications†	117 (0.16)	64 (0.3)	43 (0.1)	10 (0.1)	< 0.001
Bleeding‡	77 (0.10)	16 (0.1)	54 (0.1)	7 (0.1)	0.36
Hospital readmission within 30 days§	*n* = 2778	*n* = 602	*n* = 1888	*n* = 288	
DVT	18 (0.65)	6 (1.0)	11 (0.6)	1 (0.4)	0.43
PE	60 (2.2)	14 (2.3)	40 (2.1)	6 (2.1)	0.95
Prosthetic complications†	290 (10.4)	61 (10.1)	202 (10.7)	27 (9.4)	0.76
Outpatient visit within 90 days	*n* = 26,093	*n* = 6245	*n* = 17,011	*n* = 2837	
DVT	263 (1.01)	65 (1.04)	180 (1.06)	18 (.67)	0.15
PE	39 (0.15)	7 (0.11)	28 (0.16)	4 (0.14)	0.65
Prosthetic complications†	360 (1.4)	115 (1.8)	213 (1.3)	32 (1.1)	< 0.001
Overall VTE events‖	495 (0.67)	101 (0.50)	339 (0.73)	55 (0.70)	0.004
Hip arthroplasty					
In-hospital postoperative complications*	*n* = 36,192	*n* = 10,769	*n* = 22,055	*n* = 3368	
DVT only	15 (0.04)	3 (0.03)	9 (0.04)	3 (0.09)	0.31
PE only	9 (0.02)	1 (0.01)	7 (0.03)	1 (0.03)	0.47
PE and DVT	2 (0.01)	0	2 (0.01)	0	0.53
Prosthetic complications†	85 (0.23)	21 (0.2)	52 (0.2)	12 (0.4)	0.24
Bleeding‡	42 (0.12)	6 (0.06)	27 (0.12)	9 (0.26)	0.006
Hospital readmission within 30 days§	*n* = 1258	*n* = 230	*n* = 898	*n* = 130	
DVT	10 (0.79)	5 (2.2)	5 (0.6)	0	0.027
PE	14 (1.1)	5 (2.2)	9 (1.0)	0	0.14
Prosthetic complications†	197 (15.7)	38 (16.5)	133 (14.8)	26 (20.0)	0.29
Outpatient visit within 90 days	*n* = 11,438	*n* = 2914	*n* = 7397	*n* = 1127	
DVT	75 (0.66)	20 (0.69)	49 (0.66)	6 (0.53)	0.86
PE	20 (0.17)	3 (0.10)	15 (0.20)	2 (0.18)	0.55
Prosthetic complications†	291 (2.5)	97 (3.3)	168 (2.3)	26 (2.3)	0.008
Overall VTE events‖	145 (0.40)	37 (0.34)	96 (0.44)	12 (0.36)	0.43

Numbers are presented as n (%). P values for unadjusted comparisons were derived from a chi-squared test. Only the first event for each patient was considered

DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism

**During index hospitalization*

†Prosthetic complications were defined as mechanical complications or infection of the joint implant, disruption, infection or non-healing of the wound, or persistent postoperative fistula (online Supplemental Table 1)

‡Bleeding outcomes were defined as gastrointestinal and extradural bleeding, hematoma/hemorrhage/seroma at the surgical site, or procedures related to the management of wound complications (online Supplemental Table 1)

§Outcomes refer to the primary diagnosis of a hospital readmission

‖Overall events are defined as all events during the index hospitalization plus primary diagnoses of a hospital readmission within 30 days plus primary diagnoses of an outpatient visit within 90 days postoperatively among all patients with a knee or hip arthroplasty, respectively

index hospitalization (Table 3). The crude number of patients with prosthetic complications is shown in Table 3 and was not higher in patients with any anticoagulants compared with aspirin.

DISCUSSION

In this large contemporary cohort of patients undergoing knee or hip arthroplasty, more than a quarter of those receiving any pharmacological thromboprophylaxis were prescribed aspirin-only. Patients who used aspirin-only did not have a higher risk of postoperative venous thromboembolism compared with those who received any prophylactic anticoagulant drug.

Compared with previous findings, the frequency of using aspirin-only for postoperativethromboprophylaxis in patients undergoing knee or hip arthroplasty was higher in our study.[6, 17] Our previous retrospective cohort study which similarly investigated thromboembolic risk in a large nationally representative sample of patients receiving aspirin compared with anticoagulation after knee or hip replacement surgery between 2009 and 2012 in the USA found that aspirin-only was administered in 7.5–8% of cases,[6] while this proportion increased to more than 27% in our current study that covered a timeframe after publication of the updated American College of Chest Physicians (ACCP) guidelines. Similarly, a recent retrospective chart review of 329 patients undergoing knee arthroplasty at 2 tertiary care centers found that the proportion of patients receiving monotherapy with aspirin for postoperative thromboprophylaxis increased from 4.6 to 44.4% in the periods before and after the publication of ACCP guidelines in 2012[18]; in these updated guidelines, the use of aspirin as a sole thromboprophylactic agent after knee or hip arthroplasty was newly endorsed and hence, consensus was reached with the recommendations made by the American Academy of Orthopedic Surgeons (AAOS).[1, 19, 20] It is notable that the

Table 4 Results of the Association between Type of Pharmacologic VTE Prophylaxis and Postoperative Venous Thromboembolism After Knee or Hip Arthroplasty

Analysis	Knee arthroplasty		Hip arthroplasty	
	Odds ratio (95% CI)*	*P* value	Odds ratio (95% CI)*	*P* value
Unadjusted				
Aspirin-only vs. any anticoagulant†	0.69 (0.56–0.86)	0.001	0.81 (0.56–1.17)	0.26
Multivariable adjusted‡				
Aspirin-only vs. any anticoagulant†	0.70 (0.56–0.87)	0.002	0.93 (0.62–1.38)	0.72

CI, confidence interval
**Odds ratio and 95% CI for postoperative VTE*
†VTE prophylaxis with anticoagulants refers to any prophylactic anticoagulant or combined anticoagulant and aspirin
‡Using a logistic regression model adjusted for quintiles of the propensity of receiving aspirin, as well as age, gender, the Caprini venous thromboembolism risk score, metastatic cancer, obesity, congestive heart failure, paralysis, renal failure, coagulopathy, and rheumatoid arthritis

proportion of patients with aspirin-only for thromboprophylaxis was very high in this retrospective chart review, but the lower proportion as found in our study (which used data from more than 200 hospitals across the USA) may better reflect national practice.

Comparatively few participants experienced postoperative venous thromboembolism in our study; these results are consistent with incidences found in previous studies ascertaining symptomatic venous thromboembolism in patients with joint arthroplasty.[6, 21–23] Our results suggest that patients with aspirin-only did not have a higher risk of venous thromboembolism than patients with anticoagulants, which is in line with previous findings. Two systematic reviews assessing aspirin compared with other chemoprophylactic agents to prevent postoperative venous thromboembolism after knee or hip arthroplasty concluded that thromboprophylaxis with aspirin-only after knee or hip arthroplasty may be a suitable alternative to anticoagulants, but that the overall quality of the available evidence is limited.[4, 5] To date, evidence from adequately powered randomized trials is lacking,[5, 23] but the ongoing Comparative Effectiveness of Pulmonary Embolism Prevention After Hip and Knee Replacement (PEPPER) trial, which is planned to terminate in 2021, aims to fill this gap by comparing venous thromboembolism outcomes in patients undergoing hip or knee arthroplasty that are randomly assigned to aspirin, warfarin, or rivaroxaban.[24] Data is limited from studies conducted in recent years, after the use of direct oral anticoagulants for thromboprophylaxis in patients undergoing arthroplasty has been approved in the USA.[5] A recently published large randomized trial did not find a difference in postoperative thromboembolic events at 90 days in patients following hip or knee arthroplasty randomized to aspirin or continued rivaroxaban after an initial 5-day course of rivaroxaban[25]; however, the question whether administration of aspirin-only for venous thromboembolism prevention after hip or knee arthroplasty has not exactly been answered with this study given the use of a direct oral anticoagulant within the first 5 postoperative days.

Strengths of our study include the large sample size and the extended follow-up beyond the index hospitalization to capture venous thromboembolic events that occurred in the outpatient setting or led to a hospital readmission.

Our study has several limitations. Patients who received aspirin-only after arthroplasty were generally healthier, as shown in our baseline Tables 1 and 2, giving rise to the potential of confounding by indication. Despite our effort to control for potential confounders of the relationship between type of pharmacologic thromboprophylaxis and subsequent venous thromboembolism using a propensity score model, we cannot exclude residual confounding, as this was an observational study without random assignment of patients to aspirin or anticoagulation. ICD-9 codes to identify covariates and outcomes might not be fully accurate,[26] and potential non-differential misclassification of the outcome might have resulted in an underestimation of the true association between thromboprophylactic agent and thromboembolic risk. It is also possible that we missed events from patients presenting to hospitals and outpatient centers outside the MedAssets Health System. Although we restricted our analysis to hospitals that contributed both inpatient and outpatient data to the MedAssets database, we could not be sure that individual patients returned to participating hospitals for their post-arthroplasty care. Thus, we were not able to assess the extent of missing data for postoperative readmissions and outpatient encounters, and the rates of postoperative venous thromboembolism may be underestimated. However, other recent studies examining thromboembolic risk in patients undergoing hip or knee arthroplasty found similarly low estimates, suggesting that the number of venous thromboembolism events missed in our study might not be relevant.[21, 22, 25] We assessed crude rates of prosthetic complications and in-hospital bleeding outcomes as potential and clinically important adverse effects associated with anticoagulant and antithrombotic use[27, 28]; however, these results must be interpreted with care, as bleeding events and prosthetic complications based on ICD-9 codes are likely to be underdocumented. Data on post-discharge

thromboprophylaxis and changes to the thromboprophylactic strategy were unavailable, so we are not able to assess duration of antithrombotic medication and whether differences in post-discharge management influenced observed venous thromboembolism rates after the index hospitalization. Even though these medications were approved for thromboprophylaxis after arthroplasty, none of the patients included in our study received rivaroxaban or apixaban as the sole thromboprophylactic agents postoperatively, which might not reflect current practice in other healthcare settings.

This study adds to the growing body of evidence that aspirin is a reasonable antithrombotic option after knee or hip arthroplasty for at least a sizable proportion of patients. Broader adoption of these recommendations to the appropriate population might be cost-effective,[29] which is particularly important given the increasing number of patients undergoing arthroplasty in the USA and the shift towards younger patients, which additionally entails an increase in revision arthroplasties.[2, 30] However, results from adequately powered randomized controlled trials such as the currently ongoing PEPPER trial (ClinicalTrials.gov NCT02810704) are needed to confirm the efficacy and safety of aspirin for thromboprophylaxis after joint replacement surgery, in comparison with not only parenteral anticoagulants or warfarin but also direct oral anticoagulants. Furthermore, validated and easy to use risk stratification tools should be developed to identify which patients are most suitable for postoperative thromboprophylaxis with aspirin.[31]

In conclusion, the proportion of patients receiving aspirin as the sole antithrombotic agent after knee or hip arthroplasty has dramatically increased in recent years. Postoperative thromboprophylaxis with aspirin-only may be a safe option in some patients, but further research is needed to identify those who derive greater benefit with anticoagulants.

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Compliance with Ethical Standards:

Conflict of Interest: *Dr. Auerbach receives honoraria from the Society of Hospital Medicine for his role as Editor in Chief of the Journal of Hospital Medicine. He also receives Royalties from UpToDate for his role as Editor; all remaining authors declare that they do not have a conflict of interest.*

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