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Original Research

Perioperative Tranexamic Acid Should Be Considered for Total Joint Arthroplasty Patients Receiving Apixaban for Thromboprophylaxis

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ABSTRACT

Background: This study aims to investigate if the perioperative administration of tranexamic acid (TXA) for total joint arthroplasty (TJA) patients receiving apixaban for thromboprophylaxis can reduce the risk of postoperative bleeding without increasing the rate of thromboembolic events.

Methods: The Premier Healthcare Database was utilized to identify all primary elective total knee arthroplasty (TKA) and total hip arthroplasty (THA) patients. Patients receiving apixaban during their in-hospital admission who received TXA on the day of surgery were compared to those who did not receive TXA. Differences in demographics, hospital characteristics, and comorbidities were assessed between groups. Univariate and multivariable regressions were utilized to assess differences in 90-day bleeding, thromboembolic, and medical postoperative outcomes between cohorts.

Results: In total, 118,219 TJA patients were identified (TKA: 65.3%; THA: 34.7%), of which 30,592 (25.9%) received apixaban alone, and 87,627 (74.1%) received apixaban and TXA. Multivariable analyses found that patients who received apixaban and TXA had a reduced risk of aggregate bleeding complications (adjusted odds ratio [aOR] 0.83, 95% confidence interval [CI]: 0.81-0.86, $P < .001$), transfusion (aOR 0.47, 95% CI: 0.43-0.52, $P < .001$), acute anemia (aOR 0.84, 95% CI: 0.81-0.87, $P < .001$), deep vein thrombosis (aOR 0.74, 95% CI: 0.66-0.83, $P < .001$), and pulmonary embolism (aOR 0.84, 95% CI: 0.72-0.96, $P = .012$). No differences between cohorts were observed for risk of stroke (aOR 1.09, 95% CI: 0.82-1.46, $P = .372$) and myocardial infarction (aOR 0.94, 95% CI: 0.76-1.16, $P = .564$).

Conclusions: Perioperative administration of TXA to TJA patients receiving apixaban reduces the risk of bleeding complications without increasing thromboembolic risk. Arthroplasty surgeons should strongly consider providing TXA to TJA patients receiving apixaban.

Introduction

Venous thromboembolism (VTE) in the early postoperative period following elective total joint arthroplasty (TJA) is a significant concern, leading to increased morbidity and mortality [1-3] In a retrospective cohort of 29,264 patients undergoing primary TJA, Simon et al. reported that the incidence of VTE in the 30-d postoperative period was 1.19%, with identified risk factors including a prior history of VTE and a hereditary hypercoagulable state [4] Older age, female sex, higher BMI, bilateral surgery, and surgery time >2 h have similarly been associated with an increased risk of VTE following TJA [5] In addition to increased morbidity and mortality, Ollendorf et al. found that the costs of inpatient care for individuals who developed symptomatic, in-hospital VTE were almost doubled, resulting in significant economic burden to the healthcare system [6,7]

Direct oral anticoagulants (DOACs) have recently gained popularity as safe and effective chemoprophylactic agents for lowering the risk of VTE following TJA [8,9] Apixaban, a direct factor X inhibitor commonly dosed at 2.5 mg BID, is the most frequently dispensed DOAC, accounting for 25% of all oral anticoagulation prescribed [10-13] In a double-blind, randomized controlled trial examining 3057 elective total knee arthroplasty (TKA), Lassen et al. found that individuals randomized to receive apixaban 2.5 mg BID

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had a significantly lower risk of developing major VTE than those receiving enoxaparin 40 mg once daily [14] Many patients also require apixaban on a chronic basis because of a history of atrial fibrillation, stroke, or VTE [15-17] However, despite the impressive antithrombotic benefits of apixaban and other DOACs, bleeding complications following major orthopedic surgery remain a significant concern [12,18]

Recently, tranexamic acid (TXA) has gained popularity as a means of reducing postoperative blood loss without increasing thromboembolic risk [19-23] While TXA's benefits are well-established in the arthroplasty literature, some surgeons selectively withhold it from patients they perceive to be at increased risk of thromboembolic disease. Many of these same high-risk patients receive chemoprophylactic agents such as apixaban. Despite the arthroplasty community recognizing the importance of TXA, it is frequently withheld from patients on apixaban. To date, insufficient data exist examining the potential upsides and downsides of this practice. As such, using a nationally representative database, this study sought to explore whether the combination of apixaban and TXA could safely mitigate the risk of postoperative bleeding events without increasing the risk of VTE in the early postoperative period.

Material and methods

All data in this study were obtained from the Premier Healthcare Database (PHD) (Premier, Inc., NC), a national, multi-center, all-payer claims repository containing approximately 25% of all inpatient admissions in the United States [24] The PHD contains information including Current Procedural Terminology codes, International Classification of Diseases 10th Revision codes, billing records, patient and hospital characteristics, medication history, and 90-d complications. This study was not subjected to institutional review board approval, as all patient information in the PHD is de-identified in compliance with the Health Insurance Portability and Accountability Act.

International Classification of Diseases 10th Revision and Current Procedural Terminology codes were utilized to identify all patients who underwent primary elective TKA and total hip arthroplasty (THA) between January 1, 2015, and December 31, 2021. Patient medication regimens were identified using charge codes that are specific to PHD. All TJA patients who received oral or intravenous TXA on the day of surgery and any dose of apixaban during the in-hospital admission were identified as our cohort of interest. Patients who did not receive TXA but received any dose of apixaban served as our control group. Patients <18 y old, those receiving additional antithrombotics during their in-hospital admission, and individuals who underwent TJA for non-elective indications were excluded from the study (Supplemental Table 1).

Information including patient demographics, hospital characteristics, and comorbidities was extracted for both cohorts. The primary outcome of interest was the 90-d risk of postoperative bleeding complications (transfusion, acute anemia, hematoma, hemorrhage, and aggregate bleeding complications). Secondary outcomes included the 90-d risk of postoperative thromboembolic complications [deep vein thrombosis (DVT), pulmonary embolism (PE), stroke, myocardial infarction], medical complications (acute renal failure, pneumonia, acute respiratory failure, urinary tract infection, periprosthetic joint infection, sepsis, wound dehiscence, seroma), hospital readmission, and mortality.

Differences in patient demographics, hospital characteristics, and comorbidity burden were assessed utilizing *chi*-square analyses for categorical variables and independent *t*-tests for continuous variables. Univariate regression was subsequently utilized to assess risk for all primary and secondary outcomes. Multivariable regression analyses were then performed to account for potential confounding variables, including any patient demographics, hospital characteristics, and comorbidities that displayed a significant difference between cohorts ($P < .100$). Statistical significance in the study was set at $P < .05$. All statistical analyses for this study were performed using STATA (version 18.0; StataCorp, College Station, TX).

Results

There were 118,219 TJA patients included in this study (TKA: 65.3%; THA: 34.7%), of which 30,592 (25.9%) received apixaban alone, and 87,627 (74.1%) received apixaban and TXA.

Demographics

While there were no significant differences in the gender composition between cohorts, patients who received apixaban and TXA were younger (67.7 y vs 68.8 y, $P < .001$) and more likely to be black (8.8% vs 8.1%, $P < .001$) and married (61.0% vs 52.3%, $P < .001$). Furthermore, patients receiving both apixaban and TXA were more likely to be treated in a teaching hospital (45.2% vs 37.5%, $P < .001$) and treated by a provider in the Midwest (30.1% vs 26.1%, $P < .001$; Table 1).

Comorbidities

Patients receiving apixaban alone had a higher prevalence in 30 of the 38 comorbidities assessed. Compared to patients receiving apixaban alone, patients receiving apixaban and TXA had significantly lower rates of congestive heart failure (6.6% vs 8.7%, $P < .001$), myocardial infarction (4.1% vs 5.1%, $P < .001$), coronary artery disease (13.4% vs 16.8%, $P < .001$), history of a prior stent (4.4% vs 5.8%, $P < .001$), renal failure (9.8% vs 12.0%, $P < .001$), cerebrovascular accident (5.5% vs 7.6%, $P < .001$), complicated diabetes (7.6% vs 8.9%, $P < .001$), and VTE (9.8% vs 14.6%, $P < .001$). Patients receiving apixaban and TXA were more likely to have hypertension (59.0% vs 57.8%, $P < .001$) and be obese (32.8% vs 31.8%, $P = .002$). No differences between cohorts were found when looking at prevalence of smoking, uncomplicated diabetes, rheumatic disease, and depression (Table 2).

Outcomes

Univariate regression analysis demonstrated that patients receiving apixaban and TXA had lower rates of aggregate bleeding complications (18.6% vs 23.0%, $P < .001$), transfusion (1.3% vs 3.6%, $P < .001$), and acute anemia (17.9% vs 22.0%, $P < .001$) within 90 d postoperatively. No significant differences were found when looking at rates of hematoma (0.4% vs 0.5%, $P = .056$) and hemorrhage (0.2% vs 0.3%, $P = .099$; Table 3).

Regarding thromboembolic complications, patients who received apixaban and TXA had significantly reduced rates of DVT (1.0% vs 1.7%, $P < .001$), PE (0.8% vs 1.2%, $P < .001$), stroke (0.2% vs 0.3%, $P = .043$), and myocardial infarction (0.3% vs 0.5%, $P < .001$; Table 4). In addition, when looking at medical complications, patients receiving both apixaban and TXA had reduced rates of acute renal failure (3.3% vs 5.2%, $P < .001$), pneumonia (0.8% vs 1.1%, $P < .001$), acute respiratory failure (1.5% vs 2.4%, $P < .001$), urinary tract infection (2.2% vs 2.6%, $P < .001$), sepsis (0.6% vs 0.8%, $P < .001$), and hospital readmission (5.8% vs 3.8%, $P < .001$). No significant differences were found between cohorts for rates of periprosthetic joint infection (0.6% vs 0.7%, $P = .115$), wound dehiscence (0.6% vs 0.7%, $P = .179$), seroma (0.1% vs 0.1%, $P = .939$), and 90-day mortality (0.1% vs 0.2%, $P = .293$; Table 5).

Table 1
Patient and Hospital characteristics of the apixaban and the apixaban + TXA cohorts.

Demographics	Apixaban (N = 30,592)		Apixaban + TXA (N = 87,627)		*P*-value
	Average	SD	Average	SD	
Age (years)	68.8	9.9	67.7	9.8	<.001
	Number	Percent	Number	Percent	
Gender					
Men	18,068	59.1%	52,355	59.7%	.101
Women	12,524	40.9%	35,272	40.3%	
Race					
Asian	25,803	84.3%	74,248	84.7%	<.001
Black	306	1.0%	653	0.7%	
Other	2466	8.1%	7688	8.8%	
Unknown	1343	4.4%	3932	4.5%	
Caucasian	674	2.2%	1106	1.3%	
Marital status					
Married	15,994	52.3%	53,442	61.0%	<.001
Single	9884	32.3%	31,076	35.5%	
Other	4622	15.1%	2868	3.3%	
Unknown	92	0.3%	241	0.3%	
Bed size					
<100	1549	5.1%	5887	6.7%	<.001
100-199	6833	22.3%	14,135	16.1%	
200-299	5883	19.2%	19,079	21.8%	
399-399	5269	17.2%	13,948	15.9%	
400-499	3397	11.1%	12,210	13.9%	
>500	7661	25.0%	22,368	25.5%	
Urban vs. Rural					
Rural	3371	11.0%	9830	11.2%	.342
Urban	27,221	89.0%	77,797	88.8%	
Teaching status					
No	19,113	62.5%	48,006	54.8%	<.001
Yes	11,479	37.5%	39,621	45.2%	
Region					
Midwest	7979	26.1%	26,340	30.1%	<.001
Northeast	5761	18.8%	13,463	15.4%	
South	13,415	43.9%	41,583	47.5%	
West	3437	11.2%	6241	7.1%	

TXA, tranexamic acid.

Multivariable models controlling for confounding variables found that patients in the apixaban and TXA cohort continued to have a significantly reduced risk of aggregate bleeding complications (adjusted odds ratio [aOR] 0.83, 95% confidence interval [CI]: 0.81-0.86, $P < .001$), transfusion (aOR 0.47, 95% CI: 0.43-0.52, $P < .001$), acute anemia (aOR 0.84, 95% CI: 0.81-0.87, $P < .001$), DVT (aOR 0.74, 95% CI: 0.66-0.83, $P < .001$), PE (aOR 0.84, 95% CI: 0.72-0.96, $P = .012$), acute renal failure (aOR 0.82, 95% CI: 0.76-0.88, $P < .001$), and acute respiratory failure (aOR 0.87, 95% CI: 0.78-0.96, $P = .005$; Tables 3-5).

Multivariable regression showed no significant differences were found for risk of hematoma, hemorrhage, stroke, myocardial infarction, pneumonia, urinary tract infection, periprosthetic joint infection, sepsis, wound dehiscence, seroma, hospital readmission, and mortality (Tables 3-5).

Post hoc power analysis using G*Power version 3.1.9.7 demonstrated a power greater than 80% for all outcomes within this study, indicating sufficient statistical power [25].

Discussion

Perioperative administration of TXA has been shown to be highly effective, decreasing rates of bleeding and transfusion for TJA patients [22,23,26] Similarly, apixaban has been shown to reduce the risk of symptomatic VTE events [27-29] Despite the frequency at which these medications are prescribed, no studies have investigated the combined perioperative use of these medications in arthroplasty patients. Our study shows that patients receiving both apixaban and TXA demonstrate a decreased risk of bleeding complications, without any increased risk of thromboembolic complications compared to patients receiving apixaban alone.

Apixaban has emerged as a highly effective thromboprophylactic agent for TJA patients, with advantages compared to those of traditional anticoagulants including oral administration and reduced need for extensive laboratory monitoring [8,11,27,30,31]. Similarly, TXA has gained popularity among arthroplasty surgeons for its ability to prevent postoperative bleeding complications [19,20,32]. Despite historical concerns about the increased VTE risk associated with the perioperative administration of TXA, recent studies have determined that these concerns are unfounded [22,23,33,34] In a retrospective study involving 70,759 TJA patients with a history of VTE, Richardson et al. demonstrated that patients who received TXA had lower rates of PE and similar rates of myocardial infarction, stroke, and DVT compared to patients who did not receive TXA [22]. However, it is unknown if the perioperative administration of TXA to TJA patients receiving apixaban affects the thromboprophylactic potential of apixaban. Our study shows that administering TXA in the perioperative period does not negate the robust anti-thrombotic potency of apixaban, with patients receiving both TXA and apixaban displaying a 0.736-times reduced risk of developing DVT and a 0.835-times decreased risk of developing PE compared to patients on apixaban alone. This lower risk of DVT and PE may occur as TXA significantly mitigates the risk of transfusion, a known risk factor for thromboembolic complications [22,35] Furthermore, similar to Richardson et al., we found that patients who received TXA were at no increased risk of 90-d medical complications, readmission, or mortality [22]. Our

Table 2
Comorbidity differences between the apixaban and the apixaban + TXA cohorts.

Comorbidities	Apixaban (N = 30,592)		Apixaban + TXA (N = 87,627)		% difference	*P*-value
	N	%	N	%		
Congestive heart failure	2652	8.7%	5810	6.6%	−2.1%	<.001
Myocardial infarction	1562	5.1%	3625	4.1%	−1.0%	<.001
Valvular disease	307	1.0%	607	0.7%	−0.3%	<.001
Coronary artery disease	5135	16.8%	11,772	13.4%	−3.4%	<.001
Prior stent	1762	5.8%	3813	4.4%	−1.4%	<.001
Smoking	1682	5.5%	4986	5.7%	0.2%	.210
Thrombophilia	487	1.6%	835	1.0%	−0.6%	<.001
Hemophilia	66	0.2%	103	0.1%	−0.1%	<.001
Pulmonary hypertension	541	1.8%	1119	1.3%	−0.5%	<.001
Chronic pulmonary disease	5642	18.4%	15,305	17.5%	−0.9%	<.001
Peripheral vascular disease	1488	4.9%	3171	3.6%	−1.3%	<.001
Hypertension	17,691	57.8%	51,662	59.0%	1.2%	<.001
Complicated hypertension	4818	15.8%	11,221	12.8%	−3.0%	<.001
Cerebrovascular accident	2312	7.6%	4830	5.5%	−2.1%	<.001
Hemiplegia/Paraplegia	45	0.2%	70	0.1%	−0.1%	<.001
Other neurological disorders	904	3.0%	2066	2.4%	−0.6%	<.001
Diabetes, uncomplicated	4401	14.4%	12,990	14.8%	0.4%	.063
Diabetes, complicated	2736	8.9%	6697	7.6%	−1.3%	<.001
Hypothyroidism	5702	18.6%	15,778	18.0%	−0.6%	.013
Renal failure	3657	12.0%	8584	9.8%	−2.2%	<.001
Liver disease	560	1.8%	1302	1.5%	−0.3%	<.001
Chronic peptic ulcer disease	97	0.3%	273	0.3%	0.0%	.882
Blood loss anemia	216	0.7%	711	0.8%	0.1%	.072
Deficiency anemia	587	1.9%	1328	1.5%	−0.4%	<.001
Coagulopathy	1192	3.9%	2350	2.7%	−1.2%	<.001
Venous thromboembolism	4457	14.6%	8606	9.8%	−4.8%	<.001
Fluid and electrolyte disorders	3088	10.1%	6424	7.3%	−2.8%	<.001
Rheumatic disease	1455	4.8%	4042	4.6%	−0.2%	.305
HIV/AIDS	21	0.1%	43	0.1%	0.0%	.205
Lymphoma	127	0.4%	198	0.2%	−0.2%	<.001
Obesity	9727	31.8%	28,708	32.8%	1.0%	.002
Weight loss	91	0.3%	184	0.2%	−0.1%	.006
Solid tumor	224	0.7%	524	0.6%	−0.1%	.011
Metastatic cancer	24	0.1%	51	0.1%	0.0%	.226
Alcohol abuse	282	0.9%	823	0.9%	0.0%	.785
Drug abuse	337	1.1%	828	0.9%	−0.2%	.017
Psychoses	70	0.2%	198	0.2%	0.0%	.928
Depression	4186	13.7%	12,112	13.8%	0.1%	.544

study adds to the growing body of literature confirming the safety profile of TXA, even when used perioperatively with apixaban.

DOAC use after TJA has been associated with an elevated risk of postoperative blood loss [8,12,18]. In a retrospective database study comparing outcomes of THA patients on various postoperative thromboprophylactic agents, Agaba et al. found that those given only apixaban exhibited a 4-times increased risk of hematoma and 3.5-times the risk of hemorrhage postoperatively compared to patients receiving other standard chemoprophylactic agents such as aspirin [36] Similar concerns regarding increased risk of postoperative bleeding accompany rivaroxaban, which like apixaban is a direct factor Xa inhibitor [8]. Several randomized controlled studies have looked at the utility of TXA to potentially offset postoperative bleeding complications for TJA patients given rivaroxaban, demonstrating that patients receiving TXA on the day of surgery and rivaroxaban for postoperative thromboprophylaxis experienced significantly less postoperative blood loss and risk of transfusion than patients using rivaroxaban alone [37,38]. Similarly, our study shows that TJA patients who received TXA and apixaban had a significantly decreased risk of bleeding than patients receiving apixaban alone, with a 0.471-times reduced risk of transfusion, a 0.840-times decreased risk of acute anemia, and a 0.834-fold reduction in aggregate bleeding complications. These outcomes underscore the robust hemostatic effects of TXA, which

Table 3
Bleeding complications.

90-Day postoperative outcomes	Apixaban (N = 30,592)		Apixaban + TXA (N = 87,627)		Univariate regression			Multivariable regression		
	N	%	N	%	OR	95% CI	*P*-value	aOR	95% CI	*P*-value
Aggregate bleeding complications	7036	23.0%	16,283	18.6%	0.76	0.74-0.79	<.001	0.83	0.81-0.86	<.001
Transfusion	1088	3.6%	1152	1.3%	0.36	0.33-0.39	<.001	0.47	0.43-0.52	<.001
Acute anemia	6728	22.0%	15,689	17.9%	0.77	0.75-0.80	<.001	0.84	0.81-0.87	<.001
Hematoma	142	0.5%	336	0.4%	0.83	0.68-1.00	.056	0.89	0.73-1.09	.255
Hemorrhage	75	0.3%	171	0.2%	0.80	0.61-1.04	.099	0.87	0.66-1.14	.312
Hospital readmission	1164	3.8%	5091	5.8%	0.85	0.80-0.90	<.001	0.95	0.89-1.02	.186
Mortality	50	0.2%	120	0.1%	0.84	0.60-1.17	.293	1.28	0.91-1.81	.157

Table 4
Thromboembolic complications.

90-Day postoperative outcomes	Apixaban (N = 30,592)		Apixaban + TXA (N = 87,627)		Univariate regression			Multivariate regression		
	N	%	N	%	OR	95% CI	*P*-value	aOR	95% CI	*P*-value
Deep vein thrombosis	520	1.7%	893	1.0%	0.60	0.53-0.66	<.001	0.74	0.66-0.83	<.001
Pulmonary embolism	375	1.2%	698	0.8%	0.65	0.57-0.73	<.001	0.84	0.72-0.96	.012
Stroke	83	0.3%	182	0.2%	0.77	0.59-0.99	.043	1.09	0.82-1.46	.561
Myocardial infarction	147	0.5%	269	0.3%	0.64	0.52-0.78	<.001	0.94	0.76-1.16	.564

are still preserved even when patients are given apixaban in the perioperative period. Furthermore, in vitro studies demonstrate no drug-drug interactions between apixaban and TXA, further highlighting the compatibility of utilizing both medications [39,40] The results of this study suggest that TJA patients on apixaban for postoperative thromboprophylaxis or due to a history of atrial fibrillation, stroke, or VTE should receive TXA perioperatively, given the potential of TXA to effectively mitigate the risk of bleeding complications.

There are several limitations to this study. Given its retrospective nature, this study is naturally prone to errors stemming from the source data. Also, while the PHD is one of the largest databases available, it still only captures 25% of all inpatient admissions in the United States, which may limit generalizability. Furthermore, the patients within our study who received TXA in addition to apixaban tended to be healthier and have fewer comorbidities than patients just receiving apixaban, which may be a reflection of selection bias and surgeons' hesitancy to provide TXA to sicker patients. However, we were able to account for these differences in medical comorbidities in our multivariable models. In addition, we were unable to account for differences in route and timing of TXA administration during the perioperative period. However, current clinical practice guidelines show that there are limited differences in patient outcomes when taking into consideration route, dosage, and the perioperative timing of TXA administration [41] Moreover, although the PHD provides detailed information regarding medications that patient receive during their in-patient stay, it lacks data preceding and following the index admission unless the patient is readmitted. Consequently, our ability to account for patients potentially receiving apixaban prior to surgery due to other coexisting comorbidities and to assess the duration of apixaban regimens and the timing of thromboembolic complications in relationship to apixaban cessation is limited. Lastly, as a retrospective study, causal relationships cannot be conclusively established between a particular intervention and an outcome. As such, future prospective studies are needed to provide additional high-quality data to help guide clinical practice guidelines.

This study has several notable strengths. To begin with, all patients within this study underwent TJA between 2015 and 2021, representing a modern cohort reflective of contemporary surgical practices. In addition, to our knowledge, there are no current studies in the arthroplasty literature comparing outcomes between patients receiving apixaban and patients receiving apixaban and TXA. Furthermore, the PHD is a multicenter national database, providing a robust representation of the arthroplasty patient population within the United States. Moreover, the PHD provides a high degree of granularity for each patient, including information such as demographics, hospital characteristics, and comorbidities. This allowed us to control for potential confounders and create robust multivariable models that are able to compare the true difference in outcomes between patients who were administered apixaban vs those given TXA and apixaban.

Conclusions

This study found that administering TXA perioperatively to TJA patients receiving apixaban for thromboprophylaxis reduces the risk of postoperative bleeding complications without increasing the risk of thromboembolic complications. Surgeons should strongly consider administering TXA to all TJA patients receiving apixaban for VTE thromboprophylaxis.

Conflicts of interest

NDH received royalties from Corin U.S.A.; is a paid consultant for Intellijoint Surgical, MicroPort Orthopedics, Corin U.S.A., and Zimmer; has stock or stock options in Intellijoint Surgical; and is a board member of AAOS, AJRR, and AAHKS. JRL receives royalties from and is a paid consultant for DePuy, a Johnson and Johnson Company; has stock or stock options in BD Surgiphor and Hip Innovations Technologies; received financial or material support from Saunders/Mosby Elsevier; and is a board member of AAOS, Hip Society, Musculoskeletal Transplant Foundation, and Western Orthopaedic Association. The remaining authors have no conflicts to disclose.

Table 5
Medical and other complications.

90-Day postoperative outcomes	Apixaban (N = 30,592)		Apixaban + TXA (N = 87,627)		Univariate regression			Multivariate regression		
	N	%	N	%	OR	95% CI	*P*-value	aOR	95% CI	*P*-value
Acute renal failure	1584	5.2%	2927	3.3%	0.63	0.59-0.67	<.001	0.82	0.76-0.88	<.001
Pneumonia	345	1.1%	687	0.8%	0.69	0.61-0.79	<.001	0.88	0.77-1.01	.068
Acute respiratory failure	723	2.4%	1350	1.5%	0.65	0.59-0.71	<.001	0.87	0.78-0.96	.005
Urinary tract infection	808	2.6%	1882	2.2%	0.81	0.74-0.88	<.001	0.96	0.88-1.05	.374
Periprosthetic joint infection	198	0.7%	497	0.6%	0.88	0.74-1.03	.115	0.95	0.80-1.12	.526
Sepsis	237	0.8%	515	0.6%	0.76	0.65-0.88	<.001	0.95	0.81-1.12	.534
Wound dehiscence	208	0.7%	534	0.6%	0.90	0.76-1.05	.179	0.99	0.84-1.16	.869
Seroma	24	0.1%	70	0.1%	1.02	0.64-1.62	.939	1.05	0.66-1.69	.830
Hospital readmission	1164	3.8%	5091	5.8%	0.85	0.80-0.90	<.001	0.96	0.90-1.02	.152
Mortality	50	0.2%	120	0.1%	0.84	0.60-1.17	.293	1.28	0.92-1.80	.149

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CRediT authorship contribution statement

Sagar Telang: Writing — review & editing, Writing — original draft, Validation, Investigation, Formal analysis. **Ryan Palmer:** Writing — review & editing, Writing — original draft, Validation, Investigation. **Andrew Dobitsch:** Writing — review & editing, Writing — original draft, Validation, Formal analysis. **Jacob R. Ball:** Writing — review & editing, Writing — original draft, Investigation. **Nathanael D. Heckmann:** Writing — review & editing, Validation, Supervision, Conceptualization. **Jay R. Lieberman:** Writing — review & editing, Validation, Supervision.

References

[1] Kirksey M, Chiu YL, Ma Y, Della Valle AG, Poultsides L, Gerner P, et al. Trends in in-hospital major morbidity and mortality after total joint arthroplasty: United States 1998-2008. Anesth Analg 2012;115:321–7.
[2] Colwell CW. The ACCP guidelines for thromboprophylaxis in total hip and knee arthroplasty. Orthopedics 2009;32:67–73.
[3] Deitelzweig S. Preventing venous thromboembolic events after total hip arthroplasty: new developments in clinical practice. Hosp Pract 2012;40:79–87.
[4] Simon SJ, Patell R, Zwicker JI, Kazi DS, Hollenbeck BL. Venous thromboembolism in total hip and total knee arthroplasty. JAMA Netw Open 2023;6:e2345883.
[5] Zhang Z-H, Shen B, Yang J, Zhou Z-K, Kang P, Pei F-X. Risk factors for venous thromboembolism of total hip arthroplasty and total knee arthroplasty: a systematic review of evidences in ten years. BMC Musculoskelet Disord 2015;16:24.
[6] Ollendorf DA, Vera-Llonch M, Oster G. Cost of venous thromboembolism following major orthopedic surgery in hospitalized patients. Am J Health Syst Pharm 2002;59:1750–4.
[7] Klemen ND, Feingold PL, Hashimoto B, Wang M, Kleyman S, Brackett A, et al. Mortality risk associated with venous thromboembolism: a systematic review and Bayesian meta-analysis. Lancet Haematol 2020;7:e583–93.
[8] Lieberman JR, Heckmann N. Venous thromboembolism prophylaxis in total hip arthroplasty and total knee arthroplasty patients: from guidelines to practice. J Am Acad Orthop Surg 2017;25:789–98.
[9] Rooney T, Barrack RL, Clohisy JC, Nunley RM, Lawrie CM. Is apixaban safe and effective for venous thromboembolism prophylaxis after primary total hip and total knee arthroplasties? J Arthroplasty 2021;36:S328–31.
[10] Colacci M, Tseng EK, Sacks CA, Fralick M. Oral anticoagulant utilization in the United States and United Kingdom. J Gen Intern Med 2020;35:2505–7.
[11] Gómez-Outes A, Terleira-Fernández AI, Suárez-Gea ML, Vargas-Castrillón E. Dabigatran, rivaroxaban, or apixaban versus enoxaparin for thromboprophylaxis after total hip or knee replacement: systematic review, meta-analysis, and indirect treatment comparisons. BMJ 2012;344:e3675.
[12] Piple AS, Wang JC, Kang HP, Mills ES, Mayfield CK, Lieberman JR, et al. Safety and efficacy of rivaroxaban in primary total hip and knee arthroplasty. J Arthroplasty 2023;38:1613–1620.e4.
[13] Lieberman JR, Bell JA. Venous thromboembolic prophylaxis after total hip and knee arthroplasty. J Bone Joint Surg Am 2021;103:1556–64.
[14] Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Hornick P, et al. Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial. Lancet 2010;375:807–15.
[15] Agnelli G, Buller HR, Cohen A, Madelyn C, Gallus AS, Johnson M, et al. Apixaban for extended treatment of venous thromboembolism. N Engl J Med 2013;368:699–708. n.d.
[16] Halvorsen S, Atar D, Yang H, De Caterina R, Erol C, Garcia D, et al. Efficacy and safety of apixaban compared with warfarin according to age for stroke prevention in atrial fibrillation: observations from the ARISTOTLE trial. Eur Heart J 2014;35:1864–72.
[17] Li XS, Deitelzweig S, Keshishian A, Hamilton M, Horblyuk R, Gupta K, et al. Effectiveness and safety of apixaban versus warfarin in non-valvular atrial fibrillation patients in "real-world" clinical practice. A propensity-matched analysis of 76,940 patients. Thromb Haemost 2017;117:1072–82.
[18] Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, et al. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med 2013;369:799–808.
[19] Poeran J, Rasul R, Suzuki S, Danninger T, Mazumdar M, Opperer M, et al. Tranexamic acid use and postoperative outcomes in patients undergoing total hip or knee arthroplasty in the United States: retrospective analysis of effectiveness and safety. BMJ 2014;349:g4829.
[20] Fillingham YA, Ramkumar DB, Jevsevar DS, Yates AJ, Shores P, Mullen K, et al. The efficacy of tranexamic acid in total hip arthroplasty: a network meta-analysis. J Arthroplasty 2018;33:3083–3089.e4.
[21] Yang Z-G, Chen W-P, Wu L-D. Effectiveness and safety of tranexamic acid in reducing blood loss in total knee arthroplasty: a meta-analysis. J Bone Joint Surg Am 2012;94:1153–9.
[22] Richardson MK, Liu KC, Mayfield CK, Kistler NM, Lieberman JR, Heckmann ND. Tranexamic acid is safe in patients with a history of venous thromboembolism undergoing total joint arthroplasty. J Bone Joint Surg Am 2024;106:30–8.
[23] Heckmann ND, Haque TF, Piple AS, Mayfield CK, Bouz GJ, Mayer LW, et al. Tranexamic acid and prothrombotic complications following total hip and total knee arthroplasty: a population-wide safety analysis accounting for surgeon selection bias. J Arthroplasty 2023;38:215–23.
[24] Premier Healthcare. Database White Paper. Data that informs and performs. Premier Applied Sciences®. Charlotte, NC: Premier Inc; 2020.
[25] Faul F, Erdfelder E, Buchner A, Lang A-G. Statistical power analyses using G*Power 3.1: tests for correlation and regression analyses. Behav Res Methods 2009;41:1149–60.
[26] Marra F, Rosso F, Bruzzone M, Bonasia DE, Dettoni F, Rossi R. Use of tranexamic acid in total knee arthroplasty. Joints 2016;4:202–13.
[27] Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Portman RJ. Apixaban or enoxaparin for thromboprophylaxis after knee replacement. N Engl J Med 2009;361:594–604.
[28] Lassen MR, Gallus A, Raskob GE, Pineo G, Chen D, Ramirez LM, et al. Apixaban versus enoxaparin for thromboprophylaxis after hip replacement. N Engl J Med 2010;363:2487–98.
[29] Klauser W, Dütsch M. Practical management of new oral anticoagulants after total hip or total knee arthroplasty. Musculoskelet Surg 2013;97:189–97.
[30] Nieto JA, Espada NG, Merino RG, González TC. Dabigatran, rivaroxaban and apixaban versus enoxaparin for thromboprophylaxis after total knee or hip arthroplasty: pool-analysis of phase III randomized clinical trials. Thromb Res 2012;130:183–91.
[31] Highcock AJ, As-Sultany M, Finley R, Donnachie NJ. A prospective cohort comparative study of rivaroxaban, dabigatran, and apixaban oral thromboprophylaxis in 2431 hip and knee arthroplasty patients: primary efficacy outcomes and safety profile. J Arthroplasty 2020;35:3093–8.
[32] Chauncey JM, Wieters JS. Tranexamic acid. Treasure Island, FL: StatPearls Publishing; 2023.
[33] Arnljots B, Wieslander JB, Dougan P, Salemark L. Importance of fibrinolysis in limiting thrombus formation following severe microarterial trauma: an experimental study in the rabbit. Microsurgery 1991;12:332–9.
[34] Wong J, Abrishami A, El Beheiry H, Mahomed NN, Roderick Davey J, Gandhi R, et al. Topical application of tranexamic acid reduces postoperative blood loss in total knee arthroplasty: a randomized, controlled trial. J Bone Joint Surg Am 2010;92:2503–13.
[35] Shohat N, Ludwick L, Goh GS, Sherman M, Paladino J, Parvizi J. Blood transfusions increase the risk for venous thromboembolism events following total joint arthroplasty. Sci Rep 2021;11:21240.
[36] Agaba P, Kildow BJ, Dhotar H, Seyler TM, Bolognesi M. Comparison of postoperative complications after total hip arthroplasty among patients receiving aspirin, enoxaparin, warfarin, and factor Xa inhibitors. J Orthop 2017;14:537–43.
[37] Wang J-W, Chen B, Lin P-C, Yen S-H, Huang C-C, Kuo F-C. The efficacy of combined use of rivaroxaban and tranexamic acid on blood conservation in minimally invasive total knee arthroplasty a double-blind randomized, controlled trial. J Arthroplasty 2017;32:801–6.
[38] Clavé A, Gérard R, Lacroix J, Baynat C, Danguy des Déserts M, Gatineau F, et al. A randomized, double-blind, placebo-controlled trial on the efficacy of tranexamic acid combined with rivaroxaban thromboprophylaxis in reducing blood loss after primary cementless total hip arthroplasty. Bone Joint Lett J 2019;101-B:207–12.
[39] Fernandez S, Lenoir C, Samer C, Rollason V. Drug interactions with apixaban: a systematic review of the literature and an analysis of VigiBase, the World Health Organization database of spontaneous safety reports. Pharmacol Res Perspect 2020;8:e00647.
[40] Sayani S, Iqbal O, Hoppensteadt D, Fareed J. Drug interactions of newer oral anticoagulants dabigatran, rivaroxaban, and apixaban with routinely used nonanticoagulant/antiplatelet drugs. Blood 2014;124:4267.
[41] Fillingham YA, Ramkumar DB, Jevsevar DS, Yates AJ, Bini SA, Clarke HD, et al. Tranexamic acid use in total joint arthroplasty: the clinical practice guidelines endorsed by the American association of hip and knee surgeons, American society of regional anesthesia and pain medicine, American academy of orthopaedic surgeons, hip society, and knee society. J Arthroplasty 2018;33:3065–9.

Supplemental Table 1
ICD-Tenth Revision (ICD-10) and Current Procedural Terminology (CPT) codes.

ICD-10 codes	Description
TJA	THA: 0SR90- + 0SRB0-; TKA: 0SRC0- + 0SRD0-
Neoplasm	C40.2, C40.8, C40.9, C41.4, C41.9, C76.3, C76.5, C79.5, C80.9
Trauma	M80.05, M80.06, M80.85, M80.86, M84.35, M84.36, M84.45, M84.46, M84.65, M84.66, M84.75, S32.3, S32.4, S32.5, S32.6, S32.8, S72, S79.0, S79.1, S82.0, S82.1, S82.2, S82.3, S82.4, S82.8, S82.9, S89.0, S89.1, S89.2, S89.3, M96.65, M96.66, M96.67, M96.69
Periprosthetic Fracture	M97.0, M97.1
Complication of Orthopedic Implants	T84.0, T84.116, T85.117, T84.124, T84.125, T84.126, T84.127, T84.194, T84.195, T84.196, T84.197, T84.218, T84.228, T84.3, T84.4, T84.8, T84.9
History of Venous Thromboembolism	Z86.71, I26
History of Myocardial Infarction	I21, I22, I25.2
History of Cerebrovascular Accident	G45, G46, I60, I69, H34.0, Z86.73
Peripheral Vascular Disease	Z95.8, Z95.9
CPT Codes	**Description**
TJA	THA: 27130; TKA: 27447