ANESTHESIOLOGY

Safety of Tranexamic Acid in Hip and Knee Arthroplasty in High-risk Patients

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- The use of tranexamic acid to decrease blood loss during lower-extremity arthroplasty is commonplace
- Safety concerns remain for patients with a history of thromboembolic, cardiovascular, renal, or neurologic comorbidities

What This Article Tells Us That Is New

- National administrative data from more than 500 hospitals and 40,000 patients demonstrate that approximately half of high-risk patients receive tranexamic acid, similar to non–high-risk patients
- Tranexamic acid use in high-risk patients undergoing lower-extremity arthroplasty is associated with fewer transfusions
- Tranexamic acid use is not associated with venous thromboembolism, myocardial infarction, seizures, ischemic strokes, or transient ischemic attacks

ABSTRACT

Background: With increasing use of tranexamic acid in total hip and knee arthroplasties, safety concerns remain. Using national claims data, this study examined tranexamic acid use in patients with preexisting comorbidities. The hypothesis was that tranexamic acid use is not associated with increased complication risk in hip and knee arthroplasty patients with comorbidities.

Methods: Among 765,011 total hip/knee arthroplasties (2013 to 2016, Premier Healthcare claims), tranexamic acid use was assessed in three high-risk groups: group I with patients with a history of venous thromboembolism, myocardial infarction, seizures, or ischemic stroke/transient ischemic attack (n = 27,890); group II with renal disease (n = 44,608); and group III with atrial fibrillation (n = 45,952). The coprimary outcomes were blood transfusion and new-onset "composite complications" (venous thromboembolism, myocardial infarction, seizures, and ischemic stroke/transient ischemic attack). Associations between tranexamic acid use and outcomes were measured separately by high-risk group. The odds ratios and Bonferroni-adjusted 99.9% CIs are reported.

Results: Overall, 404,974 patients (52.9%) received tranexamic acid, with similar frequencies across high-risk groups I (13,004 of 27,890 [46.6%]), II (22,424 of 44,608 [50.3%]), and III (22,379 of 45,952 [48.7%]). Tranexamic acid use was associated with decreased odds of blood transfusion in high-risk groups I (721 of 13,004 [5.5%] *vs.* 2,293 of 14,886 [15.4%]; odds ratio, 0.307; 99.9% CI, 0.258 to 0.366), group II (2,045 of 22,424 [9.1%] *vs.* 5,159 of 22,184 [23.3%]; odds ratio, 0.315; 99.9% CI, 0.263 to 0.378), and group III (1,325 of 22,379 [5.9%] *vs.* 3,773 of 23,573 [16.0%]; odds ratio, 0.321; 99.9% CI, 0.266 to 0.389); all adjusted comparisons $P < 0.001$. No increased odds of composite complications were observed in high-risk group I (129 of 13,004 [1.0%] *vs.* 239 of 14,886 [1.6%]; odds ratio, 0.89, 99.9% CI, 0.49 to 1.59), group II (238 of 22,424 [1.1%] *vs.* 369 of 22,184 [1.7%]; odds ratio, 0.98; 99.9% CI, 0.58 to 1.67), and group III (187 of 22,379 [0.8%] *vs.* 290 of 23,573 [1.2%]; odds ratio, 0.93; 99.9% CI, 0.54 to 1.61); all adjusted comparisons $P > 0.999$.

Conclusions: Although effective in reducing blood transfusions, tranexamic acid is not associated with increased complications, irrespective of patient high-risk status at baseline.

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Tranexamic acid, an antifibrinolytic agent, is widely used to reduce the overall magnitude of blood loss during total hip and knee arthroplasty.[1] Numerous trials and meta-analyses have shown its effectiveness in reducing blood loss and the need for blood transfusion in this cohort.[2–6] However, concerns exist regarding the occurrence of complications such as venous thromboembolism (VTE; including deep venous thrombosis or pulmonary embolism).[7] Moreover, several case reports have linked tranexamic acid use to acute renal failure,[8,9] while the risk of ischemic events such as myocardial infarction (MI), ischemic stroke, and transient ischemic attacks remains unclear.[10,11]

To date, no meta-analysis has demonstrated tranexamic acid use to be associated with increased risk of these

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complications in lower-extremity joint replacement surgery.[2–6] However, trials have mostly excluded patients with risk factors such as those with a history of cardiovascular disease, thromboembolic events, or renal disease.[7] This does not represent clinical practice, because there is a trend toward increasing comorbidity burden in patients selected for total hip and knee arthroplasty surgery.[12]

Crucially, large-scale data are lacking on the real-world use of tranexamic acid, specifically in patients with preexisting comorbidities such as a history of VTE.[13] Therefore, using national claims data on lower-extremity joint replacements, we aimed to study the association between tranexamic acid use and (1) blood transfusions and (2) complications when used in patients with preexisting comorbidities, focusing on patients with a history of VTE, MI, seizures, ischemic disease, renal disease, and atrial fibrillation. Additional outcomes were length and cost of hospitalization. A secondary study aim was the evaluation of utilization patterns of tranexamic acid across these high-risk groups. We hypothesized that tranexamic acid use would not be associated with an increased risk of complications in high-risk patients.

Materials and Methods

Study Design

The Mount Sinai Hospital Institutional Review Board approved this retrospective cohort study (Project No. 14-0067). Included data were extracted from the Premier Healthcare database,[14,15] a national all-payer claims database representing 20 to 25% of US hospital discharges. Hospitals participating in Premier Healthcare are mainly concentrated in the South of the United States (approximately 40%), with equal distributions of hospitals located in the Northeast, West, and Midwest (approximately 20% each). This data set contains detailed billing information on hospitalizations. International Classification of Diseases, Ninth Revision (ICD-9) procedure codes for total hip arthroplasty (81.51) and total knee arthroplasty (81.54) were used to define the study cohort including data from 2013 to 2016. Of note, the data set purchased from Premier Healthcare included only ICD-9 codes; International Classification of Diseases, Tenth Revision codes—introduced in the United States in October 2015—were converted to ICD-9 codes using a proprietary algorithm. Before any exclusion criteria, the Premier Healthcare data set included 820,816 total hip and knee arthroplasties performed between 2013 and 2016. Exclusion criteria pertained to patients who met one or more of the following criteria: unknown sex (n = 280), unknown discharge status (n = 457), classification as a nonelective procedure (n = 49,172), patient under 18 yr of age (n = 119), and classification as an outpatient procedure (n = 5,677).

Study Variables

Exposure. A data analysis and statistical plan was written, date-stamped, and recorded in the investigators' files before the data were accessed. The exposure of interest was the use of tranexamic acid in patients with preexisting comorbidities for which concerns existed of associated increased risks with tranexamic acid use. Tranexamic acid use was defined using pharmacy billing information, which also provided information on the dose (1,000 mg, 2,000 mg, 3,000 mg or more, or not specified) and the mode of administration, classified into "parenteral" or "other/not specified"; the latter likely represents intraarticular use. Tranexamic acid use was applied as a binary variable in analyses; however, information on the distribution of dose and mode of administration is presented as well.

High-risk Definitions. The main focus of this study is the use of tranexamic acid in high-risk patients. Thus, three separate definitions of high-risk patients were applied, based on preexisting comorbidities that were defined by ICD-9 codes in line with previous studies.[16–18] To distinguish between preexisting (comorbidities) and "new-onset" (complications during hospitalization), we applied the "present-on-admission" indicator provided in the Premier Healthcare data set.

The three separate high-risk definitions were based on the following:

1. Patients' history of VTE (including deep venous thrombosis and pulmonary embolism), MI, seizures, or ischemic stroke/transient ischemic attacks.
2. Patients' history of renal disease: Concerns have been noted on tranexamic acid administration in these patients in the context of cardiac surgery and other clinical contexts[19]; it has also been used as exclusion criterion in trials focusing on tranexamic acid in lower-extremity joint arthroplasty.[19–21]
3. Patients' history of atrial fibrillation: This was added after discussions flowing from presenting our preliminary results at the annual meeting of the American Association of Hip and Knee Surgeons on November 3, 2018, in Dallas, Texas. Here, atrial fibrillation was suggested to be included because it represents a thromboembolic risk factor. Likewise, it has also been evaluated in another recent study on safety of tranexamic acid using institutional data.[22]

Outcomes. The two coprimary outcomes were (1) blood transfusion use and (2) composite complication of new-onset VTE, MI, seizures, or ischemic stroke/transient ischemic attacks. Complications were evaluated separately as well as in a "composite complication" variable. Blood transfusion was defined as a patient having a billing charge description or ICD-9 code indicating the transfusion of any blood product during the hospital stay. The aforementioned clinical complications were only counted if they occurred during the hospital stay, given the short course of tranexamic acid treatment in these patients and the half-life of 2 h. Secondary outcomes included acute renal failure, 90-day readmission caused by the aforementioned clinical complications (based on the ICD diagnosis codes associated with the readmission), in-hospital mortality, length of

hospital stay, and cost of hospitalization. In total, these are 12 outcome variables.

Covariates. Patient demographics included age, sex, and race (White, Black, other). Healthcare-related variables included insurance type (commercial, Medicaid, Medicare, uninsured, other/unknown), hospital location (urban, rural), hospital size (less than 300, 300 to 499, 500 beds or more), teaching status, and annual number of total hip and knee arthroplasties performed per hospital. Procedure-related variables were year and type of procedure, type of anesthesia, use of patient-controlled analgesia, nonopioid analgesics (nonsteroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors, ketamine, pregabalin/gabapentin and acetaminophen), and use of peripheral nerve blocks. Comorbidity-related variables (in addition to the aforementioned comorbidity definitions of interest) included comorbidities from the Charlson Comorbidity Index,[23] history of substance use/abuse (including smoking), chronic pain conditions, psychiatric comorbidities, opioid use disorder, and obstructive sleep apnea. The latter five and postsurgical analgesic variables were included given their association with opioid use and perioperative complications. We additionally assessed anticoagulant/antiplatelet use, categorized into aspirin or other antiplatelets, heparin, warfarin, other anticoagulants, more than one of the preceding, and none. Any medication-related variable was defined as the patient having a billing charge (using descriptions of generic names) at any point during the hospital stay. ICD-9 codes used for definitions of outcomes and comorbidities are presented in the Supplemental Digital Content (supplemental table 1, http://links.lww.com/ALN/C584). Our study was not burdened by missing data as the main variables of interest were defined based on whether or not a patient record had the associated ICD code or billing description. If this was not the case, then they were considered not to have that outcome/exposure/confounder.

Statistical Analysis

First, univariable associations between tranexamic acid use and the aforementioned study variables were assessed; percentages and medians (with interquartile ranges) were compared. Univariable group differences easily reach statistical significance in large sample sizes; we therefore opted to report both standardized differences and *P* values (from chi-square and Mann–Whitney U test for categorical and continuous variables, respectively). A standardized difference of 0.1 (or 10%) generally indicates a meaningful difference in covariate distribution between groups.[24]

Mixed-effects models[25] measured associations between tranexamic acid use and outcomes. This was done separately for patients in high-risk and non–high-risk groups by applying interaction terms between the aforementioned high-risk definitions and tranexamic acid use. Given the focus on tranexamic acid use in high-risk patients, we only present effect estimates from high-risk groups in the article text; effect estimates from non–high-risk groups can be found in the Supplemental Digital Content (supplemental tables 2 through 4, http://links.lww.com/ALN/C584). Mixed-effects models account for correlation of patients within hospitals; this is important in this context as patients treated at the same hospital are more likely to receive similar treatment and care than a patient treated at another hospital. Given the large study sample size and decreased need for parsimony, models were adjusted for all covariates available. Additionally, as a sensitivity analysis, these same analyses were performed using a cohort only including hospitals with a high use of tranexamic acid (greater than or equal to 75% hospital-specific tranexamic acid use), to address the issue of potential selective use of tranexamic acid.

We report odds ratios and Bonferroni-adjusted 99.9% CIs taking into account the number of hypotheses tested for in the main analyses (72 hypotheses reflecting 12 outcomes and 6 (non–)high-risk groups of interest: three definitions of high-risk and their subsequent three complementary non–high-risk counterparts). The reported 99.9% CI values are computed from 1 - (0.05/72) = 99.9%. This was applied to reduce the risk of type I errors (false-positive associations); however, this step may increase the likelihood of type II errors (false-negative associations).[26] Given this conservative approach and our main interest in safety outcomes, we consider any association in multivariable analyses that demonstrates statistical significance (after applying the Bonferroni correction) as meaningful. For the continuous outcomes (length of stay and cost of hospitalization), instead of odds ratios, we report the percentage of change; as for these models, a γ distribution with a log link function was applied given that these variables are highly skewed.[27,28]

We additionally assessed trends in tranexamic acid use by the three aforementioned high-risk groups because it may provide information on differential use of tranexamic acid between those with and without comorbidities. Hypothesis testing was two-sided. All analyses were performed using SAS version 9.4 statistical software (SAS Institute, USA).

A Priori versus Post Hoc

During the peer-review process and presentation of preliminary results at national professional meetings, the following adjustments were made to our initial analyses:

- Addition of atrial fibrillation as an additional definition of high risk.
- Removal of analyses representing Charlson Comorbidity Index categories as a definition of high risk.
- Addition of a history of seizure(s) and new-onset seizure(s) as both a determinant of high-risk status and an outcome of interest, respectively.
- Restricting the study cohort to 2013 to 2016 (previously 2006 to 2016).

Table 1. Use of Tranexamic Acid in Elective Total Hip and Knee Arthroplasty Patients by Study Variables

Variables	Tranexamic Acid Use, n (%)		*P* Value	Standardized Difference
	Yes (n = 404,974)	No (n = 360,037)		
Patient demographics				
Age*	66 (59–73)	66 (59–73)	< 0.001	0.014
Sex			0.009	0.006
Female	242,031 (59.8%)	214,122 (59.5%)		
Male	162,943 (40.2%)	145,915 (40.5%)		
Race			< 0.001	0.129
White	336,050 (83.0%)	285,864 (79.4%)		
Black	30,953 (7.6%)	27,969 (7.8%)		
Other	37,971 (9.4%)	46,204 (12.8%)		
Healthcare-related				
Insurance type			< 0.001	0.059
Commercial	151,253 (37.3%)	125,434 (34.8%)		
Medicaid	15,769 (3.9%)	14,996 (4.2%)		
Medicare	224,523 (55.4%)	202,735 (56.3%)		
Uninsured	1,473 (0.4%)	1,602 (0.4%)		
Other/unknown	11,956 (3.0%)	15,270 (4.2%)		
Hospital location			0.005	0.007
Rural	41,817 (10.3%)	37,892 (10.5%)		
Urban	363,157 (89.7%)	322,145 (89.5%)		
Hospital size			< 0.001	0.155
Small (fewer than 300 beds)	167,263 (41.3%)	169,350 (47.0%)		
Medium (300–499 beds)	134,918 (33.3%)	92,476 (25.7%)		
Large (500 beds or more)	102,793 (25.4%)	98,211 (27.3%)		
Hospital teaching status			< 0.001	0.096
Nonteaching	241,648 (59.7%)	197,775 (54.9%)		
Teaching	163,326 (40.3%)	162,262 (45.1%)		
No. of annual hip/knee arthroplasties per hospital*	663 (430–1,215)	603 (338–1,128)	< 0.001	0.008
Procedure-related				
Year of procedure			< 0.001	0.728
2013	47,567 (11.7%)	132,435 (36.8%)		
2014	87,701 (21.7%)	101,232 (28.1%)		
2015	132,551 (32.7%)	72,419 (20.1%)		
2016	137,155 (33.9%)	53,951 (15.0%)		
Procedure type			< 0.001	0.313
Total hip arthroplasty	146,122 (36.1%)	119,036 (33.1%)		
Total knee arthroplasty	258,852 (63.9%)	241,001 (66.9%)		
Anesthesia type			< 0.001	0.167
General	216,991 (53.6%)	224,889 (62.5%)		
Neuraxial plus general	74,454 (18.4%)	59,363 (16.5%)		
Unknown	113,529 (28.0%)	75,785 (21.0%)		
Patient-controlled analgesia	22,512 (5.6%)	39,433 (11.0%)	< 0.001	0.197
Nonopioid analgesic modes				
NSAIDs	257,569 (63.6%)	167,918 (46.6%)	< 0.001	0.346
Cyclooxygenase-2 inhibitors	217,195 (53.6%)	145,179 (40.3%)	< 0.001	0.269
Ketamine	26,890 (6.6%)	17,172 (4.8%)	< 0.001	0.081
Pregabalin/gabapentin	160,238 (39.6%)	97,916 (27.2%)	< 0.001	0.265
Acetaminophen	293,162 (72.4%)	216,005 (60.0%)	< 0.001	0.264
Peripheral nerve block	71,374 (17.6%)	53,787 (14.9%)	< 0.001	0.073
High-risk group definitions				
History of deep venous thrombosis	**178 (0.0%)**	**263 (0.1%)**	**< 0.001**	**0.012**
History of pulmonary embolism	**52 (0.0%)**	**82 (0.0%)**	**0.001**	**0.007**
History of MI	**12,119 (3.0%)**	**13,967 (3.9%)**	**< 0.001**	**0.049**
History of seizures	**614 (0.2%)**	**564 (0.2%)**	**0.575**	**0.001**
History of ischemic stroke/transient ischemic attack	**83 (0.0%)**	**85 (0.0%)**	**0.359**	**0.002**
High-risk definition I: History of VTE, MI, seizures, or ischemic stroke/transient ischemic attack	**13,004 (3.2%)**	**14,886 (4.1%)**	**< 0.001**	**0.049**
High-risk definition II: History of renal disease	**22,424 (5.5%)**	**22,184 (6.2%)**	**< 0.001**	**0.027**
High-risk definition III: History of atrial fibrillation	**22,379 (5.5%)**	**23,573 (6.5%)**	**< 0.001**	**0.043**
Use of anticoagulants			< 0.001	0.484
Aspirin	136,169 (33.6%)	54,534 (15.1%)		
Other antiplatelet	714 (0.2%)	569 (0.2%)		
Heparin	68,483 (16.9%)	73,448 (20.4%)		
Warfarin	38,269 (9.4%)	54,238 (15.1%)		
Other anticoagulant	67,747 (16.7%)	66,596 (18.5%)		
> 1 of the above	76,820 (19.0%)	87,656 (24.3%)		
None	16,772 (4.1%)	22,996 (6.4%)		
History of substance use/abuse	38,809 (9.6%)	36,862 (10.2%)	< 0.001	0.022
Chronic pain conditions	75,374 (18.6%)	64,911 (18.0%)	< 0.001	0.015
Psychiatric comorbidities	87,615 (21.6%)	77,455 (21.5%)	0.197	0.003
Opioid use disorder	1,587 (0.4%)	1,309 (0.4%)	0.044	0.005
Obstructive sleep apnea	59,022 (14.6%)	51,457 (14.3%)	0.001	0.008
Charlson Comorbidity Index				
0	238,298 (58.8%)	202,956 (56.4%)	< 0.001	0.058
1	105,863 (26.1%)	96,851 (26.9%)		
2	37,320 (9.2%)	35,689 (9.9%)		
> 2	23,493 (5.8%)	24,541 (6.8%)		

Definitions of high-risk groups are emphasized in boldface text.

*Continuous variable, median and interquartile range instead of N and %.

MI, myocardial infarction; NSAID, nonsteroidal anti-inflammatory drug; VTE, venous thromboembolism, a composite of deep venous thrombosis and pulmonary embolism.

- Providing a preliminary "dose-response" analysis modeling tranexamic acid by dose categories and their association with "composite complications" among patients with a history of VTE, MI, seizures, or ischemic stroke/transient ischemic attacks receiving tranexamic acid. Here, the presence of a dose-response pattern of higher complication odds with a higher tranexamic acid dose would inform potential dose adjustment strategies in high-risk patients, whereas the absence of such a pattern would argue against higher risks associated with tranexamic acid use in these high-risk patients.
- Separating out renal comorbidities and renal complications from the rest of the preexisting comorbidities/complications.
- Application of Bonferroni adjustments.

Results

Overall, 765,011 (representing 589 hospitals) lower-extremity joint arthroplasties were included: 265,158 total hip arthroplasties and 499,853 total knee arthroplasties with an overall blood transfusion rate of 8.1% (n = 62,190). Tranexamic acid was utilized in 52.9% (n = 404,974) of procedures; of note, tranexamic acid was not used at all in 73 hospitals representing 37,148 cases. The majority of tranexamic acid (n = 381,943; 94.3%) was administered intravenously with billing for 2,000 mg the most common dose (n = 207,907 [51.3%]; n = 119,275 [29.5%], n = 54,761 [13.5%], and n = 23,031 [5.7%] for 1,000 mg, 3,000 mg or more, and unspecified dose categories, respectively). Tranexamic acid utilization, indicated by row totals, was particularly higher in more recent years, in total knee arthroplasties, and among those receiving most nonopioid analgesic modes (table 1). Interestingly, tranexamic acid use was lower among those receiving patient-controlled analgesia, and as expected, use of anticoagulants was highly associated with tranexamic acid use (standardized differences of more than 0.1; table 1). Tranexamic acid use differed minimally between patients in the various high-risk groups compared to those in the non–high-risk groups (table 1: indicated by boldface text; all standardized differences less than 0.1).

Table 2. Dosing Characteristics and Outcomes by Tranexamic Acid Use in Elective Total Hip and Knee Arthroplasty Patients with a History of VTE, MI, Seizures, or Ischemic Stroke/Transient Ischemic Attack

	High-risk Definition I: History of VTE, MI, Seizures, or Ischemic Stroke/Transient Ischemic Attack			
	Tranexamic Acid Use			
	Yes (n = 13,004)	No (n = 14,886)	*P* Value	Standardized Difference
Dose				
1,000 mg	4,032 (31.0%)			
2,000 mg	6,321 (48.6%)			
≥ 3,000 mg	1,923 (14.8%)			
Not specified	728 (5.6%)			
Outcomes				
Blood transfusion	721 (5.5%)	2,293 (15.4%)	< 0.001	0.326
Complications				
New-onset deep venous thrombosis	33 (0.3%)	50 (0.3%)	0.209	0.015
New-onset pulmonary embolism	25 (0.2%)	40 (0.3%)	0.187	0.016
New-onset MI	58 (0.4%)	121 (0.8%)	0.001	0.046
New-onset seizures	1 (0.0%)	3 (0.0%)	0.386	0.011
New-onset ischemic stroke/transient ischemic attack	18 (0.1%)	38 (0.3%)	0.030	0.026
New-onset VTE, MI, seizures, ischemic stroke/transient ischemic attack ("composite complications")	129 (1.0%)	239 (1.6%)	< 0.001	0.054
New-onset acute renal failure	379 (2.9%)	626 (4.2%)	< 0.001	0.070
90-day readmission caused by any of the above (new-onset VTE, MI, seizures, ischemic stroke/transient ischemic attack, or acute renal failure)	25 (0.2%)	42 (0.3%)	0.126	0.019
In-hospital mortality	10 (0.1%)	36 (0.2%)	0.001	0.041
Resource utilization				
Length of stay (days)*	2 (2–3)	3 (2–3)	< 0.001	0.283
Cost of hospitalization*	$15,894 ($13,119–$19,525)	$16,580 ($13,526–$20,676)	< 0.001	0.109

*Continuous variable, median and interquartile range instead of N and %.

MI, myocardial infarction; VTE, venous thromboembolism, a composite of deep venous thrombosis and pulmonary embolism.

Tables 2 through 4 show dosing characteristics and outcomes by tranexamic acid use, separately for the three high-risk groups: those with a history of VTE, MI, seizures, and ischemic stroke/transient ischemic attack (n = 27,890) in group I, renal disease (n = 44,608) in group II, or atrial fibrillation (n = 45,952) in group III. Of note, numbers for the non–high-risk groups (*i.e.*, patients without a history of the aforementioned comorbidities) can be found in the Supplemental Digital Content (supplemental tables 2 through 4, http://links.lww.com/ALN/C584). Minimal differences in tranexamic acid dosing were seen between high-risk and non–high-risk patients. Across high-risk groups, generally lower blood transfusion rates, complication rates, and resource utilization were observed in patients receiving tranexamic acid (compared to those that did not).

This pattern was further corroborated in the adjusted analyses presented in table 5; tranexamic acid use was associated with decreased odds of blood transfusion in high-risk group I (721 of 13,004 [5.5%] *vs.* 2,293 of 14,886 [15.4%]; odds ratio, 0.307; 99.9% CI, 0.258 to 0.366); group II (2,045 of 22,424 [9.1%] *vs.* 5,159 of 22,184 [23.3%]; odds ratio, 0.315; 99% CI, 0.263 to 0.378); and group III (1,325 of 22,379 [5.9%] *vs.* 3,773 of 23,573 [16.0%]; odds ratio, 0.321; 99% CI, 0.266 to 0.389); all adjusted comparisons $P < 0.001$. No increased odds of composite complications were observed: high-risk groups I (129 of 13,004 [1.0%] *vs.* 239 of 14,886 [1.6%]; odds ratio, 0.89; 99.9% CI, 0.49 to 1.59); group II (238 of 22,424 [1.1%] *vs.* 369 of 22,184 [1.7%]; odds ratio, 0.98; 99% CI, 0.58 to 1.67); and group III (187 of 22,379 [0.8%] *vs.* 290 of 23,573 [1.2%]; odds ratio, 0.93; 99% CI, 0.54 to 1.61); all adjusted comparisons $P > 0.999$. In addition, no increased odds were observed for the other complication outcomes when applying both Bonferroni-adjusted and -unadjusted (not shown in table 5) *P* values. To the contrary, tranexamic acid use was associated with *decreases* in length of stay (−3.2% to −4.4%) and cost of hospitalization (−2.8% to −4.2%); all $P < 0.01$. A *post hoc* analysis evaluating a potential dose–response effect (table 6) did not demonstrate a pattern of higher complication odds with a higher tranexamic acid dose in high-risk patients. All model c-statistics were 0.74 or higher (the majority was 0.80 or higher), indicating sufficient discrimination.

Finally, when evaluating tranexamic acid utilization trends, the overall increased utilization was observed with somewhat lower tranexamic acid use in high-risk (compared to non–high-risk) patients (fig. 1). Sensitivity analyses

Table 3. Dosing Characteristics and Outcomes by Tranexamic Acid Use in Elective Total Hip and Knee Arthroplasty Patients with a History of Renal Disease

	High-risk Definition II: History of Renal Disease			
	Tranexamic Acid Use			
	Yes (n = 22,424)	No (n = 22,184)	*P* Value	Standardized Difference
Dose				
1,000 mg	6,709 (29.9%)			
2,000 mg	11,440 (51.0%)			
≥ 3,000 mg	3,139 (14.0%)			
Not specified or not available	1,136 (5.1%)			
Outcomes				
Blood transfusion	2,045 (9.1%)	5,159 (23.3%)	< 0.001	0.391
Complications				
New-onset deep venous thrombosis	77 (0.3%)	115 (0.5%)	0.005	0.027
New-onset pulmonary embolism	55 (0.2%)	82 (0.4%)	0.018	0.023
New-onset MI	70 (0.3%)	146 (0.7%)	< 0.001	0.050
New-onset seizures	10 (0.0%)	8 (0.0%)	0.654	0.004
New-onset ischemic stroke/transient ischemic attack	43 (0.2%)	53 (0.2%)	0.283	0.010
New-onset VTE, MI, seizures, ischemic stroke/transient ischemic attack ("composite complications")	238 (1.1%)	369 (1.7%)	< 0.001	0.052
New-onset acute renal failure	2,120 (9.5%)	3,128 (14.1%)	< 0.001	0.145
90-day readmission caused by any of the above (new-onset VTE, MI, seizures, ischemic stroke/transient ischemic attack, or acute renal failure)	67 (0.3%)	71 (0.3%)	0.686	0.004
In-hospital mortality	17 (0.1%)	85 (0.4%)	< 0.001	0.064
Resource utilization				
Length of stay (days)*	3 (2–3)	3 (3–4)	< 0.001	0.294
Cost of hospitalization*	$16,304 ($13,355–$20,292)	$17,372 ($14,129–$22,161)	< 0.001	0.132

*Continuous variable, median and interquartile range instead of N and %.

MI, myocardial infarction; VTE, venous thromboembolism, a composite of deep venous thrombosis and pulmonary embolism.

including only hospitals with at least 75% tranexamic acid use (to address potential selective tranexamic acid use) found results similar to those in our main analyses (*i.e.*, no increased odds of complications with tranexamic acid use among high-risk patients; Supplemental Digital Content (supplemental table 4, http://links.lww.com/ALN/C584).

Discussion

In this cohort of 27,890 to 45,952 high-risk patients undergoing elective lower-extremity joint replacement surgery, we found an increase in tranexamic acid use over time. The utilization rate and dosing schemes did not meaningfully differ between high-risk and non–high-risk patients. Although consistently associated with decreased odds of blood transfusions, tranexamic acid use was not associated with increased odds of a variety of thromboembolic and ischemic complications among high-risk patients, using varying definitions of high risk. To the contrary, somewhat lower length and cost of hospitalization was observed with tranexamic acid use among high-risk patients. In addition, higher doses of tranexamic acid in high-risk patients did not demonstrate a pattern of higher complication odds; conversely, there was a trend toward lower odds of complications.

These results target a clinical challenge and prominent evidence gap on tranexamic acid use in high-risk patients, as previously noted.[13] Adding to this challenge is the fact that tranexamic acid is still considered "off label" for use in total hip and knee arthroplasty surgery, and safety concerns remain,[29,30] despite the availability of high-quality evidence supporting the use of tranexamic acid in this surgical cohort in terms of its beneficial impact on blood loss and transfusion risk.[2–6,13,29] Among several large meta-analyses and observational studies, none have demonstrated increased risks associated with the use of tranexamic acid,[2–6,18,22,31] for which main concerns include thromboembolic risk and renal failure caused by acute renal cortical necrosis.[7–9,30] These concerns may be exacerbated in patients considered at high risk because of preexisting comorbidities, a subgroup generally excluded from trials.[7,13,32]

Despite these concerns, our results demonstrate a minimal difference in tranexamic acid use among high-risk and non–high-risk patients, using various definitions, suggesting that high-risk status does not appear to be a main driver behind tranexamic acid use. Moreover tranexamic acid was

Table 4. Dosing Characteristics and Outcomes by Tranexamic Acid Use in Elective Total Hip and Knee Arthroplasty Patients with a History of Atrial Fibrillation

	High-risk Definition III: History of Atrial Fibrillation			
	Tranexamic Acid Use			
	Yes (n = 22,379)	No (n = 23,573)	*P* Value	Standardized Difference
Dose				
1,000 mg	6,712 (30.0%)			
2,000 mg	11,169 (49.9%)			
≥ 3,000 mg	3,250 (14.5%)			
Not specified or not available	1,248 (5.6%)			
Outcomes				
Blood transfusion	1,325 (5.9%)	3,773 (16.0%)	< 0.001	0.327
Complications				
New-onset deep venous thrombosis	66 (0.3%)	83 (0.4%)	0.281	0.010
New-onset pulmonary embolism	67 (0.3%)	79 (0.3%)	0.496	0.006
New-onset MI	38 (0.2%)	80 (0.3%)	< 0.001	0.034
New-onset seizures	1 (0.0%)	6 (0.0%)	0.069	0.017
New-onset ischemic stroke/transient ischemic attack	34 (0.2%)	56 (0.2%)	0.038	0.019
New-onset VTE, MI, seizures, ischemic stroke/transient ischemic attack ("composite complications")	187 (0.8%)	290 (1.2%)	< 0.001	0.039
New-onset acute renal failure	650 (2.9%)	1,119 (4.7%)	< 0.001	0.096
90-day readmission caused by any of the above (new-onset VTE, MI, seizures, ischemic stroke/transient ischemic attack, or acute renal failure)	30 (0.1%)	44 (0.2%)	0.160	0.013
In-hospital mortality	13 (0.1%)	62 (0.3%)	< 0.001	0.051
Resource utilization				
Length of stay (days)*	3 (2–3)	3 (2–4)	< 0.001	0.287
Cost of hospitalization*	$16,005 ($13,238–$19,659)	$16,726 ($13,706–$20,975)	< 0.001	0.150

*Continuous variable, median and interquartile range instead of N and %.

MI, myocardial infarction; VTE, venous thromboembolism, a composite of deep venous thrombosis and pulmonary embolism.

Table 5. Results from Multivariable Models in High-risk Definition Groups in Elective Total Hip and Knee Arthroplasty Patients

	High-risk Definition I: History of VTE, MI, Seizures, Ischemic Stroke/Transient Ischemic Attack		High-risk Definition II: History of Renal Disease		High-risk Definition III: History of Atrial Fibrillation	
	Tranexamic Acid Use [Reference: No Use]		Tranexamic Acid Use [Reference: No Use]		Tranexamic Acid Use [Reference: No Use]	
Outcomes	**Odds Ratio/% Change (99.9% CI)**	***P* Value**	**Odds Ratio/% Change (99.9% CI)**	***P* Value**	**Odds Ratio/% Change (99.9% CI)**	***P* Value**
Blood transfusion	0.307 (0.258 to 0.366)	< 0.001	0.315 (0.263 to 0.378)	< 0.001	0.321 (0.266 to 0.389)	< 0.001
Complications						
New-onset deep venous thrombosis	1.03 (0.44 to 2.39)	> 0.999	1.01 (0.42 to 2.43)	> 0.999	1.20 (0.48 to 2.97)	> 0.999
New-onset pulmonary embolism	0.82 (0.309 to 2.16)	> 0.999	0.83 (0.300 to 2.31)	> 0.999	1.06 (0.393 to 2.87)	> 0.999
New-onset MI	1.00 (0.392 to 2.54)	> 0.999	1.07 (0.396 to 2.87)	> 0.999	0.94 (0.321 to 2.75)	> 0.999
New-onset seizures	1.74 (0.126 to 24.0)	> 0.999	2.06 (0.137 to 30.8)	>0.999	0.67 (0.020 to 22.8)	> 0.999
New-onset ischemic stroke/transient ischemic attack	1.91 (0.65 to 5.7)	> 0.999	2.11 (0.65 to 6.9)	> 0.999	1.42 (0.43 to 4.7)	> 0.999
New-onset VTE, MI, seizures, ischemic stroke/transient ischemic attack ("composite complications")	0.89 (0.49 to 1.59)	> 0.999	0.98 (0.58 to 1.67)	> 0.999	0.93 (0.54 to 1.61)	> 0.999
New-onset acute renal failure	0.80 (0.60 to 1.05)	0.432	0.81 (0.61 to 1.08)	> 0.999	0.73 (0.53 to 1.00)	0.043
90-day readmission caused by any of the above (new-onset VTE, MI, seizures, ischemic stroke/transient ischemic attack, or acute renal failure)	1.10 (0.49 to 2.49)	> 0.999	1.24 (0.52 to 2.93)	> 0.999	1.00 (0.353 to 2.83)	> 0.999
In-hospital mortality	0.57 (0.108 to 3.07)	> 0.999	0.58 (0.107 to 3.18)	> 0.999	0.62 (0.107 to 3.58)	> 0.999
Resource utilization						
Length of stay*	−3.3% (−5.0 to −1.6%)	< 0.001	−4.4% (−6.3 to −2.5%)	< 0.001	−3.2% (−5.0 to −1.3%)	< 0.001
Cost of hospitalization*	−2.8% (−4.9 to −0.6%)	< 0.001	−4.2% (−6.6 to −1.8%)	< 0.001	−2.4% (−4.8 to 0.0%)	0.058

The models are adjusted for age, sex, race, insurance type, hospital location, bed size, teaching status, annual volume of joint arthroplasty procedures, year and type of procedure, anesthesia type, use of patient-controlled analgesia, nonsteroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors, ketamine, pregabalin/gabapentin, acetaminophen, peripheral nerve blocks, history of VTE, MI, seizures, ischemic stroke/transient ischemic attack, renal disease, atrial fibrillation, Charlson comorbidities (not overlapping with aforementioned comorbidities), use of anticoagulants, history of substance use/abuse, chronic pain conditions, psychiatric comorbidities, opioid use disorder, and obstructive sleep apnea. *P* values are Bonferroni-adjusted and reflect testing of 72 hypotheses.

*Continuous variable, percent change instead of odds ratios.

MI, myocardial infarction; VTE, venous thromboembolism, a composite of deep venous thrombosis and pulmonary embolism.

consistently associated with decreased blood transfusion odds, whereas no increased odds of complications were observed among high-risk patients. These findings are in line with a recently published meta-analysis and an institutional study, although smaller sample sizes were assessed.[22,32] In the former, Fillingham *et al.*[32] used the American Society

Table 6. *Post Hoc* Analysis Evaluating a Potential Tranexamic Acid Dose–Response Relationship Modeling Tranexamic Acid Dosing Subgroups and Their Association with Combined Complications among Elective Total Hip and Knee Arthroplasty Patients with a History of VTE, MI, Seizures, or Ischemic Stroke/Transient Ischemic Attacks Receiving Tranexamic Acid

	Outcome: New-onset VTE, MI, Seizures, Ischemic Stroke, or Transient Ischemic Attack ("Composite Complications")					
Tranexamic acid dose	**Yes (n = 1,263)**	**No (n = 25,899)**	**Odds Ratio**	**95% CI**		***P* Value**
No tranexamic acid	239 (65.8%)	14,647 (54.7%)		Reference		
1,000 mg	40 (11.0%)	3,992 (14.9%)	0.74	0.51	1.06	0.100
2,000 mg	71 (19.6%)	6,250 (23.3%)	0.92	0.68	1.24	0.563
≥ 3,000 mg	13 (3.6%)	1,910 (7.1%)	0.52	0.288	0.92	0.025

The models are adjusted for age, sex, race, insurance type, hospital location, bed size, teaching status, annual volume of joint arthroplasty procedures, year and type of procedure, anesthesia type, use of patient-controlled analgesia, nonsteroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors, ketamine, pregabalin/gabapentin, acetaminophen, peripheral nerve blocks, history of VTE, MI, seizures, ischemic stroke/transient ischemic attack, Charlson comorbidities (not overlapping with aforementioned comorbidities), use of anticoagulants, history of substance use/abuse, chronic pain conditions, psychiatric comorbidities, opioid use disorder, and obstructive sleep apnea.

MI, myocardial infarction; VTE, venous thromboembolism, a composite of deep venous thrombosis and pulmonary embolism.

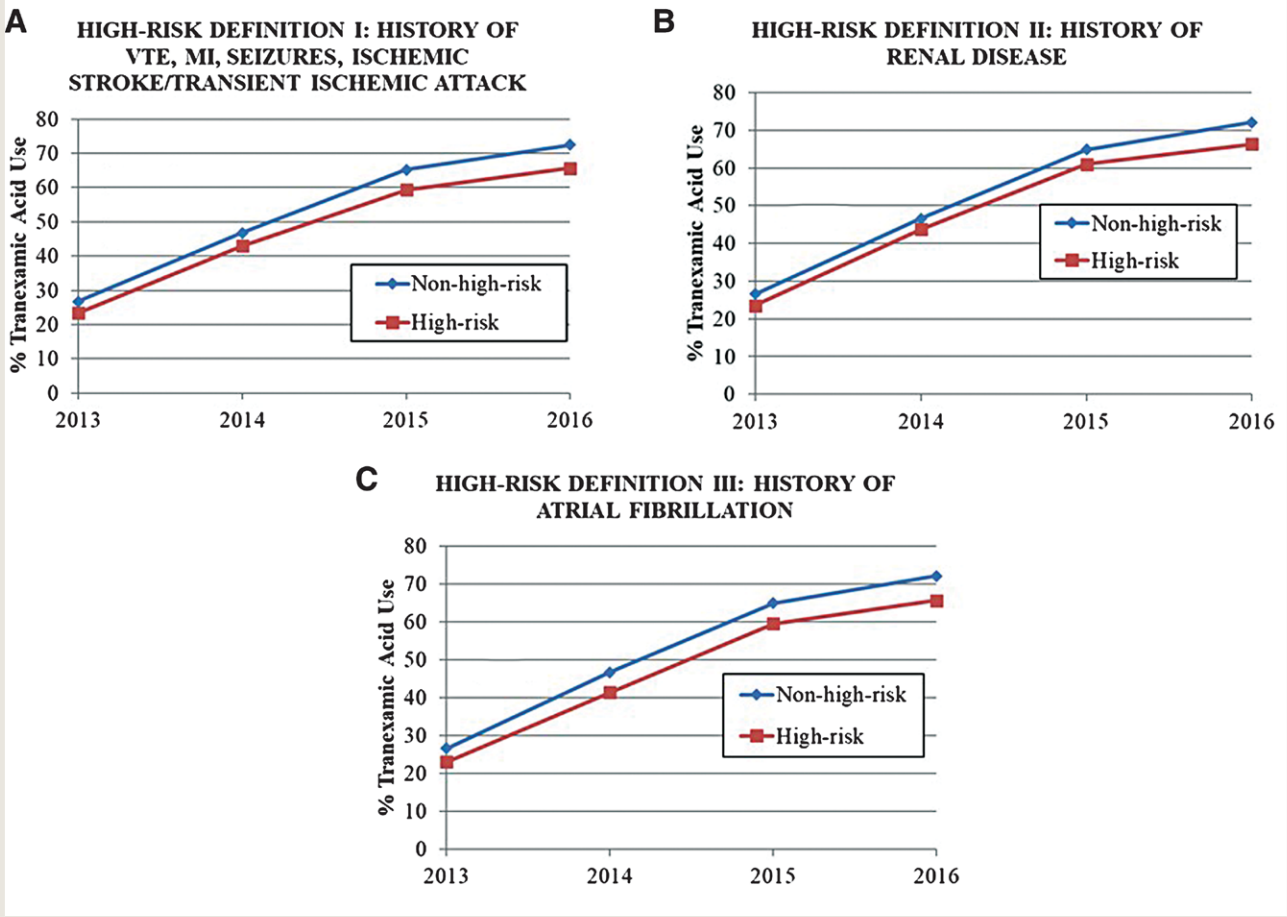

Fig. 1. Trends in tranexamic acid use by history of venous thromboembolism (a composite of deep venous thrombosis and pulmonary embolism; VTE), myocardial infarction (MI), seizures, ischemic stroke/transient ischemic attack (*A*), history of renal disease (*B*), and history of atrial fibrillation (*C*).

of Anesthesiologists (Schaumburg, Illinois) Physical Status score in definitions of high risk and found that patients with a higher ASA score receiving tranexamic acid were not at increased risk of VTE. Likewise, using single-institution data, Porter *et al.*[22] subgrouped 38,220 lower-extremity joint replacement patients based on the presence of prothrombotic conditions before surgery and found no statistically significant increased odds of complications among those with and without a high-risk status. The current study supplements the analysis by Porter *et al.*[22] by using a larger sample size and thus has the ability to detect smaller differences between groups regarding these rare complications. Moreover, the current study provides information on additional definitions of high risk, *i.e.*, renal disease and history of seizure, and additional outcomes such as new-onset seizures given the existence of official warnings.[33] The data used in the current study also allowed an assessment of various tranexamic acid doses in which we did not find a dose-response pattern of higher complication odds with a higher tranexamic acid dose, thus further supporting our main conclusions regarding the absence of an association between tranexamic acid use and complications in high-risk patients. Finally, we were able to address potential selective use of tranexamic acid in sensitivity analyses. Although these studies add to the existing body of literature suggesting no increased complication risk after tranexamic acid use among high-risk patients,[22,32,34,35] important future work may follow from prospective multi-institutional registries specifically geared toward tracking outcomes after administration of tranexamic acid, especially given the expected increased use in other surgeries and expected increases in joint arthroplasty demand.[36,37] Of note, even in the large sample size used in the current study, specific preexisting comorbidities represent relatively small samples, for example, 575 patients with a history of VTE. Thus, given that tranexamic use continues to increase, future work may also need to be focused on even more specific populations than the current study.

We observed somewhat lower length and cost of hospitalization with tranexamic acid use among high-risk

patients, whereas higher doses of tranexamic acid in high-risk patients also demonstrated a pattern toward lower odds of complications; some of these results mirror previous findings.[18,38] Although speculative, selective avoidance of tranexamic acid may occur in patients perceived to be at high risk for complications. This is, however, not supported by our results, because minimal differences were observed in tranexamic acid use across high-risk and non–high-risk groups. Other potential mechanisms may stem from the potential beneficial effects of avoidance of blood loss/transfusion,[39,40] which may exert a stronger impact than any potential negative effect of tranexamic acid. Given the seriousness of potential harm, we acknowledge the statements of Fillingham *et al.*[32] in that vigilance should be exercised, and each patient's individual risk profile should be considered together with the potential benefits of tranexamic acid.

Our study is burdened by various limitations. Despite the large overall sample size and generalizability, our high-risk groups were relatively small compared to those categorized as non–high-risk. Moreover, complications such as our composite complication variable are rare in this high-volume surgical cohort, further limiting reproducibility and reliability of observations; continuing monitoring efforts will therefore be crucial. We also lacked information on clinical variables such as hemoglobin values, blood loss, and local protocols on blood transfusion and tranexamic acid use. Particularly, missing information on local protocols may be partially addressed by the mixed-effects statistical modeling approach, which accounts for unspecified hospital-level effects. Additionally, no information was present on drivers of tranexamic acid use, for example, physician preferences or local protocols, specifically if avoidance was purposeful in high-risk patients. However, observed tranexamic acid utilization patterns and confirmatory results from sensitivity analyses suggest a minimal role of this limitation. Additionally, the majority of our subgroups and outcomes of interest were defined based on ICD-9 codes, which may have underestimated true comorbidity burden or complication risk. This may have been additionally burdened by potential inaccuracies or underestimations in "present-on-admission"[41] coding. However, we do not expect ICD-9 and present-on-admission coding to be dependent on billing for tranexamic acid. Last, although our data provide a unique look into tranexamic acid use in daily clinical practice, this remains an observational study, and therefore we can only infer associations and not causation. In conclusion, among 27,890 to 45,952 high-risk patients undergoing elective lower-extremity joint replacement surgery, we found that tranexamic acid use was not associated with increased odds of thromboembolic and ischemic complications.

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Competing Interests

The authors declare no competing interests.

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References

1. Jennings JD, Solarz MK, Haydel C: Application of tranexamic acid in trauma and orthopedic surgery. Orthop Clin North Am 2016; 47:137–43
2. Alshryda S, Sarda P, Sukeik M, Nargol A, Blenkinsopp J, Mason JM: Tranexamic acid in total knee replacement: A systematic review and meta-analysis. J Bone Joint Surg Br 2011; 93:1577–85
3. Sukeik M, Alshryda S, Haddad FS, Mason JM: Systematic review and meta-analysis of the use of tranexamic acid in total hip replacement. J Bone Joint Surg Br 2011; 93:39–46
4. Wei Z, Liu M: The effectiveness and safety of tranexamic acid in total hip or knee arthroplasty: A meta-analysis of 2720 cases. Transfus Med 2015; 25:151–62
5. Wu Q, Zhang HA, Liu SL, Meng T, Zhou X, Wang P: Is tranexamic acid clinically effective and safe to prevent blood loss in total knee arthroplasty?: A meta-analysis of 34 randomized controlled trials. Eur J Orthop Surg Traumatol 2015; 25:525–41
6. Chen S, Wu K, Kong G, Feng W, Deng Z, Wang H: The efficacy of topical tranexamic acid in total hip arthroplasty: A meta-analysis. BMC Musculoskelet Disord 2016; 17:81
7. Tengborn L, Blombäck M, Berntorp E: Tranexamic acid: An old drug still going strong and making a revival. Thromb Res 2015; 135:231–42
8. Ko DH, Kim TH, Kim JW, Gu JJ, Yoon BH, Oh JH, Hong SG: Tranexamic acid–induced acute renal cortical necrosis in post-endoscopic papillectomy bleeding. Clin Endosc 2017; 50:609–13
9. Koo JR, Lee YK, Kim YS, Cho WY, Kim HK, Won NH: Acute renal cortical necrosis caused by an antifibrinolytic drug (tranexamic acid). Nephrol Dial Transplant 1999; 14:750–2

10. Hunt BJ: The current place of tranexamic acid in the management of bleeding. Anaesthesia 2015; 70(suppl 1):50–7
11. Ker K, Edwards P, Perel P, Shakur H, Roberts I: Effect of tranexamic acid on surgical bleeding: Systematic review and cumulative meta-analysis. BMJ 2012; 344:e3054
12. Kirksey M, Chiu YL, Ma Y, Della Valle AG, Poultsides L, Gerner P, Memtsoudis SG: Trends in in-hospital major morbidity and mortality after total joint arthroplasty: United States 1998–2008. Anesth Analg 2012; 115:321–7
13. Fillingham YA, Ramkumar DB, Jevsevar DS, Yates AJ, Bini SA, Clarke HD, Schemitsch E, Johnson RL, Memtsoudis SG, Sayeed SA, Sah AP, Della Valle CJ: 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
14. Premier Healthcare Database: Data that informs and performs. 2020. Available at: https://learn.premierinc.com/white-papers/premier-healthcare-database-whitepaper. Accessed August 24, 2018.
15. Makadia R, Ryan PB: Transforming the premier perspective hospital database into the Observational Medical Outcomes Partnership (OMOP) common data model. EGEMS (Wash DC) 2014; 2:1110
16. Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, Elkind MS, George MG, Hamdan AD, Higashida RT, Hoh BL, Janis LS, Kase CS, Kleindorfer DO, Lee JM, Moseley ME, Peterson ED, Turan TN, Valderrama AL, Vinters HV; American Heart Association Stroke Council, Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular and Stroke Nursing; Council on Epidemiology and Prevention; Council on Peripheral Vascular Disease; Council on Nutrition, Physical Activity and Metabolism: An updated definition of stroke for the 21st century: A statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2013; 44:2064–89
17. Shahi A, Chen AF, Tan TL, Maltenfort MG, Kucukdurmaz F, Parvizi J: The incidence and economic burden of in-hospital venous thromboembolism in the United States. J Arthroplasty 2017; 32:1063–6
18. Poeran J, Rasul R, Suzuki S, Danninger T, Mazumdar M, Opperer M, Boettner F, Memtsoudis SG: 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
19. Jerath A, Yang QJ, Pang KS, Looby N, Reyes-Garces N, Vasiljevic T, Bojko B, Pawliszyn J, Wijeysundera D, Beattie WS, Yau TM, Wąsowicz M: Tranexamic acid dosing for cardiac surgical patients with chronic renal dysfunction: A new dosing regimen. Anesth Analg 2018; 127:1323–32
20. Hourlier H, Fennema P: Single tranexamic acid dose to reduce perioperative morbidity in primary total hip replacement: A randomised clinical trial. Hip Int 2014; 24:63–8
21. Taam J, Yang QJ, Pang KS, Karanicolas P, Choi S, Wasowicz M, Jerath A: Current evidence and future directions of tranexamic acid use, efficacy, and dosing for major surgical procedures. J Cardiothorac Vasc Anesth 2020; 34:782–90
22. Porter SB, White LJ, Osagiede O, Robards CB, Spaulding AC: Tranexamic acid administration is not associated with an increase in complications in high-risk patients undergoing primary total knee or total hip arthroplasty: A retrospective case-control study of 38,220 patients. J Arthroplasty 2020; 35:45–51.e3
23. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, Saunders LD, Beck CA, Feasby TE, Ghali WA: Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care 2005; 43:1130–9
24. Austin PC: An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res 2011; 46:399–424
25. Witte JS, Greenland S, Kim LL, Arab L: Multilevel modeling in epidemiology with GLIMMIX. Epidemiology 2000; 11:684–8
26. Perneger TV: What's wrong with Bonferroni adjustments. BMJ 1998; 316:1236–8
27. Moran JL, Solomon PJ; ANZICS Centre for Outcome and Resource Evaluation (CORE) of the Australian and New Zealand Intensive Care Society (ANZICS): A review of statistical estimators for risk-adjusted length of stay: Analysis of the Australian and New Zealand Intensive Care Adult Patient Data-Base, 2008–2009. BMC Med Res Methodol 2012; 12:68
28. Rascati KL, Smith MJ, Neilands T: Dealing with skewed data: An example using asthma-related costs of Medicaid clients. Clin Ther 2001; 23:481–98
29. American Academy of Orthopaedic Surgeons: Surgical management of osteoarthritis of the knee: Evidence-based clinical practice guideline. 2016. Available at: https://www.aaos.org/uploadedFiles/PreProduction/Quality/Guidelines_and_Reviews/guidelines/SMOAK%20CPG_4.22.2016.pdf. Accessed November 15, 2017.
30. Franchini M, Mengoli C, Marietta M, Marano G, Vaglio S, Pupella S, Mannucci PM, Liumbruno GM: Safety of intravenous tranexamic acid in patients undergoing major orthopaedic surgery: A meta-analysis of randomised controlled trials. Blood Transfus 2018; 16:36–43

31. Hallstrom B, Singal B, Cowen ME, Roberts KC, Hughes RE: The Michigan experience with safety and effectiveness of tranexamic acid use in hip and knee arthroplasty. J Bone Joint Surg Am 2016; 98:1646–55
32. Fillingham YA, Ramkumar DB, Jevsevar DS, Yates AJ, Shores P, Mullen K, Bini SA, Clarke HD, Schemitsch E, Johnson RL, Memtsoudis SG, Sayeed SA, Sah AP, Della Valle CJ: The safety of tranexamic acid in total joint arthroplasty: A direct meta-analysis. J Arthroplasty 2018; 33:3070–3082.e1
33. Lin Z, Xiaoyi Z: Tranexamic acid-associated seizures: A meta-analysis. Seizure 2016; 36:70–3
34. Whiting DR, Gillette BP, Duncan C, Smith H, Pagnano MW, Sierra RJ: Preliminary results suggest tranexamic acid is safe and effective in arthroplasty patients with severe comorbidities. Clin Orthop Relat Res 2014; 472:66–72
35. Sabbag OD, Abdel MP, Amundson AW, Larson DR, Pagnano MW: Tranexamic acid was safe in arthroplasty patients with a history of venous thromboembolism: A matched outcome study. J Arthroplasty 2017; 32:246–50
36. Kurtz S, Ong K, Lau E, Mowat F, Halpern M: Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. J Bone Joint Surg Am 2007; 89:780–5
37. Houston BL, Uminski K, Mutter T, Rimmer E, Houston DS, Menard CE, Garland A, Ariano R, Tinmouth A, Abou-Setta AM, Rabbani R, Neilson C, Rochwerg B, Turgeon AF, Falk J, Breau RH, Fergusson DA, Zarychanski R: Efficacy and safety of tranexamic acid in major non-cardiac surgeries at high risk for transfusion: A systematic review and meta-analysis. Transfus Med Rev 2020; 34:51–62
38. Shakur H, Roberts I, Bautista R, Caballero J, Coats T, Dewan Y, El-Sayed H, Gogichaishvili T, Gupta S, Herrera J, Hunt B, Iribhogbe P, Izurieta M, Khamis H, Komolafe E, Marrero MA, Mejía-Mantilla J, Miranda J, Morales C, Olaomi O, Olldashi F, Perel P, Peto R, Ramana PV, Ravi RR, Yutthakasemsunt S; CRASH-2 Trial Collaborators: Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): A randomised, placebo-controlled trial. Lancet 2010; 376:23–32
39. Thakur NA, Czerwein JK, Butera JN, Palumbo MA: Perioperative management of chronic anticoagulation in orthopaedic surgery. J Am Acad Orthop Surg 2010; 18:729–38
40. Möhnle P, Snyder-Ramos SA, Miao Y, Kulier A, Böttiger BW, Levin J, Mangano DT; Multicenter Study of Perioperative Ischemia (McSPI) Research Group: Postoperative red blood cell transfusion and morbid outcome in uncomplicated cardiac surgery patients. Intensive Care Med 2011; 37:97–109
41. Goldman LE, Chu PW, Osmond D, Bindman A: The accuracy of present-on-admission reporting in administrative data. Health Serv Res 2011; 46:1946–62