A commentary by Charles Cornell, MD, is linked to the online version of this article.

Tranexamic Acid Was Not Associated with Increased Complications in High-Risk Patients with Intertrochanteric Fracture

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Investigation performed at the Mayo Clinic, Jacksonville, Florida

Background: For elective total joint arthroplasty, tranexamic acid (TXA) is considered safe and efficacious. However, evidence of TXA's safety in high-risk patients undergoing nonelective surgery for hip fracture is sparse. This study aimed to assess whether TXA administration to high-risk patients with an intertrochanteric (IT) hip fracture increased the risk of thromboembolic complications or mortality.

Methods: All patients treated surgically for IT hip fracture between 2015 and 2019 across 4 hospitals of a single hospital system were considered. High- versus low-risk patients and those receiving TXA versus no TXA treatment were identified. Propensity scores adjusted for risk differences between patient groups with TXA and no TXA administration were calculated for (1) high-risk patients (n = 141) and (2) the entire population (n = 316). Postoperative mortality, deep venous thrombosis (DVT), pulmonary embolism (PE), myocardial infarction (MI), and stroke within 90 days of surgery were evaluated.

Results: No association between TXA administration and increased risk of mortality or complications in either group was identified. Specifically, out of 282 matched high-risk patients, no differences in mortality (odds ratio [OR], 0.97 [95% confidence interval (CI), 0.90, 1.05]), DVT (OR, 0.97 [95% CI, 0.93, 1.00]), PE (OR 1.00 [95% CI, 0.95, 1.05]), MI (OR, 1.04 [95% CI, 0.98, 1.10]), or stroke (OR, 1.00 [95% CI, 0.95, 1.05]) were identified.

Conclusions: In our review of propensity-matched high-risk patients undergoing surgical repair for IT fracture, we found that TXA administration compared with no TXA administration was not associated with an increased risk of mortality, DVT, PE, MI, or stroke within 90 days of surgery.

Level of Evidence: Therapeutic Level IV. See Instructions for Authors for a complete description of levels of evidence.

Tranexamic acid (TXA) administration reduces bleeding and the risk of transfusion in patients undergoing lower-extremity total joint arthroplasty (TJA)[1,2]. The use of TXA has been supported by clinical practice guidelines for TJA[3]. However, there is a lack of data concerning the safety of TXA in patients with prior arterial thrombotic or prothrombotic conditions. Previous research has found that high-risk patients receiving TXA for TJA and arthroplasty for femoral neck fracture are not at a greater risk for complications[2,4]. However, those analyses did not include patients with intertrochanteric (IT) fracture.

The efficacy of TXA to reduce blood loss and not increase thromboembolic events in patients with IT fracture has been assessed previously[5-9]. However, those studies did not separately assess patients at high risk for these events, and in fact, this patient population was often excluded. The lack of data regarding TXA use for this patient population is concerning. There is a growing population of high-risk patients receiving TXA during their procedures[10], exacerbated by an aging population with comorbidities who more frequently require anticoagulation[11].

Therefore, with the current study, we aimed to investigate the safety of TXA administration in high-risk patients receiving surgical repair of IT fractures. For this study, safety was assessed by identifying differences in mortality, deep venous thrombosis (DVT), pulmonary embolism (PE), myocardial infarction (MI),

Disclosure: The **Disclosure of Potential Conflicts of Interest** forms are provided with the online version of the article (http://links.lww.com/JBJS/H28).

and stroke within 90 days of surgery between patients who did versus did not receive TXA. We hypothesized that there would not be a difference in those outcomes between high-risk patients who received versus did not receive TXA.

Materials and Methods

After receiving institutional review board approval, we utilized International Classification of Diseases (ICD)-9 and ICD-10 codes to identify patients who underwent surgery for IT fracture between January 1, 2015 and December 31, 2019. Patients were excluded if they were identified to have periprosthetic fractures of the femur, pathologic fractures, or polytrauma. Also excluded were patients <18 years of age, those with a history of ipsilateral hip surgery with hardware, patients with hip fractures treated with percutaneous cannulated screws or femoral neck fractures, or American Society of Anesthesiologists (ASA) class-5 patients. In all, 1,147 patients who underwent surgery for IT fracture were identified (Fig. 1).

As previously defined[2], patients designated as high risk were those who had a history of ≥1 of the following before surgery: DVT, PE, MI, stroke, a prothrombotic condition (Factor V Leiden, protein C deficiency, protein S deficiency, or antiphospholipid antibody syndrome), atrial fibrillation, atrial flutter, a coronary artery bypass graft, or a coronary artery stent. Of the 1,147 total patients, 564 (49%) were designated high-risk.

The primary independent variable for this study was the receipt of TXA during surgery. For all hip fracture patients over the study period who received TXA, the median dose was 2 g of intravenous (IV) TXA administered intraoperatively in 2 divided doses on incision and closure. Control variables were determined a priori[12] on the basis of previous work demonstrating associations with the outcomes of interest[13-17]. The following patient variables were included: age, sex, body mass index (BMI), Charlson Comorbidity Index, ASA class, and preoperative tobacco use. Additionally, patient preoperative hemoglobin level, time between admission and surgery, hospital site (masked as A, B, C, and D), year of surgery, receipt of blood transfusion during surgery or postoperatively, and the type of postoperative anticoagulants provided were collected. Our single health system consists of 3 tertiary care academic medical centers and a network of 16 community hospitals. Postoperative anticoagulants were grouped

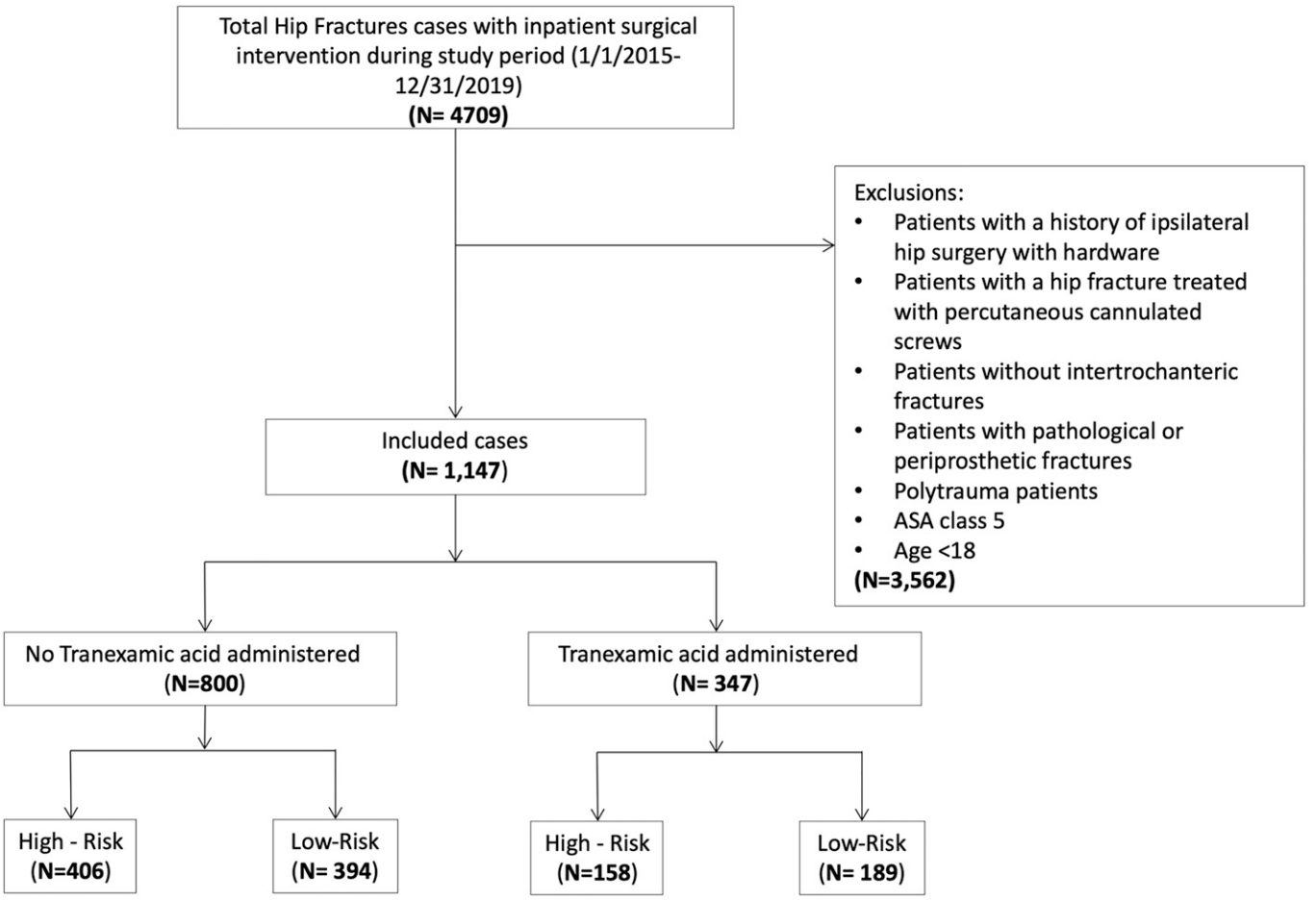

Fig. 1
Flow diagram for study selection.

TABLE I Patient Risk Factors by TXA Administration

	TXA (N = 347)	No TXA (N = 800)	Total (N = 1,147)	P Value
Deep venous thrombosis				0.104
No	335 (96.5%)	754 (94.3%)	1,089 (94.9%)	
Yes	12 (3.5%)	46 (5.8%)	58 (5.1%)	
Pulmonary embolism				0.420
No	324 (93.4%)	736 (92.0%)	1,060 (92.4%)	
Yes	23 (6.6%)	64 (8.0%)	87 (7.6%)	
Myocardial infarction				0.253
No	324 (93.4%)	731 (91.4%)	1,055 (92.0%)	
Yes	23 (6.6%)	69 (8.6%)	92 (8.0%)	
Stroke				0.391
No	281 (81.0%)	630 (78.8%)	911 (79.4%)	
Yes	66 (19.0%)	170 (21.3%)	236 (20.6%)	
Prothrombotic condition				0.075
No	345 (99.4%)	784 (98.0%)	1,129 (98.4%)	
Yes	2 (0.6%)	16 (2.0%)	18 (1.6%)	
Atrial fibrillation				0.510
No	253 (73.0%)	568 (71.0%)	821 (71.6%)	
Yes	94 (27.1%)	232 (29.0%)	326 (28.4%)	
Atrial flutter				0.125
No	327 (94.2%)	733 (91.6%)	1,060 (92.4%)	
Yes	20 (5.8%)	67 (8.4%)	87 (7.6%)	
Coronary artery bypass graft				0.907
No	346 (99.7%)	798 (99.8%)	1,144 (99.7%)	
Yes	1 (0.3%)	2 (0.3%)	3 (0.3%)	
Coronary artery stent				0.002
No	335 (96.5%)	731 (91.4%)	1,066 (93.0%)	
Yes	12 (3.5%)	69 (8.6%)	81 (7.0%)	

into 4 categories: (1) oral, (2) parenteral, (3) antiplatelet, or (4) P2Y12 inhibitors.

With regard to risk factors, there was little difference between the patients who received and those who did not receive TXA. The patients who received TXA were less likely to have a history of a coronary artery stent (3.5% versus 8.6%; p = 0.002). No other differences were noted (Table I).

Patients identified as high-risk are described in Table II. Those receiving TXA were more likely to have received care at site B (21.5% versus 2.2%) and less likely to have received care at site A (1.9% versus 13.5%) (p < 0.001). Additionally, those who received TXA were more likely to have received care in more recent years. Patients identified as low-risk are described in Table III. Among these low-risk patients, those receiving TXA were more likely to have received care at site B (15.3% versus 4.1%) and less likely to have received care at site A (3.2% versus 12.2%) or site D (28.0% versus 40.6%) (p < 0.001). In addition, those who received TXA were more likely to have received care in more recent years, had a slightly higher ASA class, and were more likely to have undergone surgery >48 hours after admission (13.8% versus 5.1%; p = 0.001).

Mortality and 90-Day Medical Complications

Looking specifically at outcomes, among the high-risk patients, there was a smaller proportion who experienced DVT in the TXA group compared with the no-TXA group (0.0% versus 4.2%, respectively; p = 0.009). We noted no other differences between high-risk patients who did or did not receive TXA. In the low-risk cohort, there were no differences noted between the TXA and no-TXA groups in terms of mortality and 90-day medical complications.

Statistical Analysis

Logit models were used to calculate propensity scores for TXA administration (administered versus not administered) for the high-risk cohort and the entire population. Nearest-neighbor matching was used to match patients based on TXA receipt (1:1 matching) with a caliper of 0.06[18-20]. Matching variables included patient age, sex, BMI, ASA class, Charlson Comorbidity Index, tobacco use, receipt of blood transfusion, postoperative anticoagulants, preoperative hemoglobin level, and the time between admission and surgery. The only difference between the 2 cohorts was that a risk category (high

TABLE II High-Risk Patient Characteristics*

	TXA (N = 158)	No TXA (N = 406)	Total (N = 564)	P Value
Mortality within 90 days				0.565
No	138 (87.3%)	347 (85.5%)	485 (86.0%)	
Yes	20 (12.7%)	59 (14.5%)	79 (14.0%)	
DVT within 90 days				0.009
No	158 (100%)	389 (95.8%)	547 (97.0%)	
Yes	0 (0.0%)	17 (4.2%)	17 (3.0%)	
PE within 90 days				0.760
No	153 (96.8%)	391 (96.3%)	544 (96.5%)	
Yes	5 (3.2%)	15 (3.7%)	20 (3.5%)	
MI within 90 days				0.047
No	147 (93.0%)	393 (96.8%)	540 (95.7%)	
Yes	11 (7.0%)	13 (3.2%)	24 (4.3%)	
Stroke within 90 days				0.898
No	151 (95.6%)	389 (95.8%)	540 (95.7%)	
Yes	7 (4.4%)	17 (4.2%)	24 (4.3%)	
Sex				0.129
Male	51 (32.3%)	159 (39.2%)	210 (37.2%)	
Female	107 (67.7%)	247 (60.8%)	354 (62.8%)	
Age at procedure *(yr)*				0.994
Mean (SD)	81.5 (10.0)	81.2 (11.4)	81.3 (11.0)	
Site				<0.001
A	3 (1.9%)	55 (13.5%)	58 (10.3%)	
B	34 (21.5%)	9 (2.2%)	43 (7.6%)	
C	70 (44.3%)	187 (46.1%)	257 (45.6%)	
D	51 (32.3%)	155 (38.2%)	206 (36.5%)	
Year of surgery				<0.001
2015	4 (2.5%)	34 (8.4%)	38 (6.7%)	
2016	20 (12.7%)	125 (30.8%)	145 (25.7%)	
2017	31 (19.6%)	81 (20.0%)	112 (19.9%)	
2018	44 (27.8%)	78 (19.2%)	122 (21.6%)	
2019	59 (37.3%)	88 (21.7%)	147 (26.1%)	
ASA class				0.147
Missing	17 (10.8%)	78 (19.2%)	95 (16.8%)	
1	0 (0.0%)	0 (0.0%)	0 (0.0%)	
2	19 (12.0%)	35 (8.6%)	54 (9.6%)	
2E	0 (0%)	1 (0.2%)	1 (0.2%)	
3	85 (53.8%)	195 (48.0%)	280 (49.6%)	
3E	12 (7.6%)	20 (4.9%)	32 (5.7%)	
4	23 (14.6%)	69 (17.0%)	92 (16.3%)	
4E	2 (1.3%)	8 (2.0%)	10 (1.8%)	
Time interval between admission and surgery				0.900
<24 hr	99 (62.7%)	262 (64.5%)	361 (64.0%)	
24-48 hr	32 (20.3%)	76 (18.7%)	108 (19.1%)	
>48 hr	27 (17.1%)	68 (16.7%)	95 (16.8%)	
Charlson Comorbidity Index				0.137
Mean (SD)	2.6 (2.2)	2.8 (2.1)	2.7 (2.1)	

continued

TABLE II (*continued*)

	TXA (N = 158)	No TXA (N = 406)	Total (N = 564)	P Value
BMI *(kg/m²)*				0.412
Mean (SD)	25.1 (5.8)	25.4 (5.8)	25.4 (5.8)	
Tobacco use				0.886
No	140 (88.6%)	358 (88.2%)	498 (88.3%)	
Yes	18 (11.4%)	48 (11.8%)	66 (11.7%)	
Preop. hemoglobin *(g/dL)*				0.587
Mean (SD)	11.3 (1.7)	11.4 (1.9)	11.4 (1.8)	
Blood products transfused				0.540
No	99 (62.7%)	243 (59.9%)	342 (60.6%)	
Yes	59 (37.3%)	163 (40.1%)	222 (39.4%)	
Postop. oral anticoagulant				0.163
No	108 (68.4%)	252 (62.1%)	360 (63.8%)	
Yes	50 (31.7%)	154 (37.9%)	204 (36.2%)	
Postop. parenteral anticoagulant				0.079
No	46 (29.1%)	150 (37.0%)	196 (34.8%)	
Yes	112 (70.9%)	256 (63.0%)	368 (65.2%)	
Postop. anti-platelet anticoagulant				0.248
No	86 (54.4%)	199 (49.0%)	285 (50.5%)	
Yes	72 (45.6%)	207 (51.0%)	279 (49.5%)	
Postop. P2Y12 inhibitor†				0.897
No	149 (94.3%)	384 (94.6%)	533 (94.5%)	
Yes	9 (5.7%)	22 (5.4%)	31 (5.5%)	

*DVT = deep venous thrombosis, PE = pulmonary embolism, MI = myocardial infarction, SD = standard deviation, ASA = American Society of Anesthesiologists, and BMI = body mass index. †Clopidogrel, prasugrel, ticlopidine, cangrelor, or ticagrelor.

versus low) was included for the entire population cohort. After propensity matching, the standardized mean differences were less than the guideline maximum differences of 25%[19], with 87% in the high-risk group and 100% in the all-patient group demonstrating a standardized mean difference of <10% (see Table IV). Additionally, c-statistics were close to 0.5 (0.65 for the high-risk group and 0.61 for the entire population; see Appendix Supplemental Table 1), indicating successful balance[21]. Differences in the occurrence of mortality, a DVT, PE, MI, or stroke within 90 days of surgery were assessed using the average treatment effect on the treated. Results were reported as adjusted odds ratios (ORs). An OR and 95% confidence interval (CI) exclusive of 1.0 were required for results to be considered significant. Stata/MP 16.1 (StataCorp) was used to conduct the analysis.

Source of Funding
No funding was used for this research.

Results

After matching, no differences were identified for any outcome between those who received versus did not receive TXA in the high-risk group (Fig. 2, Table V). Specifically, there were no differences in mortality (OR, 0.97 [95% CI, 0.90, 1.05]), DVT (OR, 0.97 [95% CI, 0.93, 1.00]), PE (OR, 1.00 [95% CI, 0.95, 1.05]), MI (OR, 1.04 [95% CI, 0.98, 1.10]), or stroke (OR, 1.00 [95% CI, 0.95, 1.05]).

Similarly, for the all-patients cohort, there were no identified differences between those who received versus did not receive TXA (Fig. 2, Table V). Specifically, there were no differences in mortality (OR, 0.97 [95% CI, 0.92, 1.02]), DVT (OR, 0.98 [95% CI, 0.96, 1.01]), PE (OR, 1.00 [95% CI, 0.97, 1.02]), MI (OR, 1.03 [95% CI, 1.00, 1.06]), or stroke (OR, 1.02 [95% CI, 0.98, 1.04]).

Discussion

The results of our study revealed no association between TXA administration and mortality, DVT, PE, MI, or stroke within the high-risk patient cohort (n = 282 matched patients). Additionally, TXA was not associated with differences in mortality or serious postoperative complications within the entire population (n = 632 matched patients). As a result, this study provides support for TXA administration's safety profile for all patients presenting for surgical repair of IT fractures.

Several small randomized controlled trials (77 to 122 patients) investigated the safety of TXA in hip fracture

TABLE III Low-Risk Patient Characteristics*

	TXA (N = 189)	No TXA (N = 394)	Total (N = 583)	P Value
Mortality within 90 days				0.216
No	179 (94.7%)	362 (91.9%)	541 (92.8%)	
Yes	10 (5.3%)	32 (8.1%)	42 (7.2%)	
DVT within 90 days				0.63
No	185 (97.9%)	383 (97.2%)	568 (97.4%)	
Yes	4 (2.1%)	11 (2.8%)	15 (2.6%)	
PE within 90 days				0.827
No	187 (98.9%)	389 (98.7%)	576 (98.8%)	
Yes	2 (1.1%)	5 (1.3%)	7 (1.2%)	
MI within 90 days				0.605
No	185 (97.9%)	388 (98.5%)	573 (98.3%)	
Yes	4 (2.1%)	6 (1.5%)	10 (1.7%)	
Stroke within 90 days				0.231
No	184 (97.4%)	389 (98.7%)	573 (98.3%)	
Yes	5 (2.6%)	5 (1.3%)	10 (1.7%)	
Sex				0.361
Male	52 (27.5%)	123 (31.2%)	175 (30.0%)	
Female	137 (72.5%)	271 (68.8%)	408 (70.0%)	
Age at procedure *(yr)*				0.61
Mean (SD)	74.5 (16.0)	73.8 (16.1)	74.1 (16.1)	
Site				<0.001
A	6 (3.2%)	48 (12.2%)	54 (9.3%)	
B	29 (15.3%)	16 (4.1%)	45 (7.7%)	
C	101 (53.4%)	170 (43.1%)	271 (46.5%)	
D	53 (28.0%)	160 (40.6%)	213 (36.5%)	
Year of surgery				<0.001
2015	4 (2.1%)	43 (10.9%)	47 (8.1%)	
2016	18 (9.5%)	108 (27.4%)	126 (21.6%)	
2017	35 (18.5%)	79 (20.1%)	114 (19.6%)	
2018	57 (30.2%)	94 (23.9%)	151 (25.9%)	
2019	75 (39.7%)	70 (17.8%)	145 (24.9%)	
ASA class				0.012
Missing	10 (5.3%)	62 (15.7%)	72 (12.3%)	
1	2 (1.1%)	13 (3.3%)	15 (2.6%)	
1E	0 (0.0%)	0 (0.0%)	0 (0.0%)	
2	62 (32.8%)	96 (24.4%)	158 (27.1%)	
2E	3 (1.6%)	7 (1.8%)	10 (1.7%)	
3	87 (46.0%)	167 (42.4%)	254 (43.6%)	
3E	11 (5.8%)	18 (4.6%)	29 (5.0%)	
4	12 (6.3%)	27 (6.9%)	39 (6.7%)	
4E	2 (1.1%)	4 (1.0%)	6 (1.0%)	
Time interval between admission and surgery				0.001
<24 hr	114 (60.3%)	244 (61.9%)	358 (61.4%)	
24-48 hr	49 (25.9%)	130 (33.0%)	179 (30.7%)	
>48 hr	26 (13.8%)	20 (5.1%)	46 (7.9%)	
Charlson Comorbidity Index				0.463

continued

TABLE III (*continued*)

	TXA (N = 189)	No TXA (N = 394)	Total (N = 583)	P Value
Mean (SD)	1.31 (1.6)	1.16 (1.5)	1.21 (1.5)	
BMI *(kg/m²)*				0.195
Mean (SD)	26.0 (6.1)	25.6 (6.3)	25.7 (6.2)	
Tobacco use				0.462
No	165 (87.3%)	335 (85.0%)	500 (85.8%)	
Yes	24 (12.7%)	59 (15.0%)	83 (14.2%)	
Preop. hemoglobin *(g/dL)*				0.137
Mean (SD)	11.9 (1.8)	12.0 (1.9)	12.0 (1.8)	
Blood products transfused				0.469
No	143 (75.7%)	287 (72.8%)	430 (73.8%)	
Yes	46 (24.3%)	107 (27.2%)	153 (26.2%)	
Postop. oral anticoagulant				0.568
No	181 (95.8%)	373 (94.7%)	554 (95.0%)	
Yes	8 (4.2%)	21 (5.3%)	29 (5.0%)	
Postop. parenteral anticoagulant				0.251
No	69 (36.5%)	125 (31.7%)	194 (33.3%)	
Yes	120 (63.5%)	269 (68.3%)	389 (66.7%)	
Postop. anti-platelet anticoagulant				0.048
No	90 (47.6%)	222 (56.3%)	312 (53.5%)	
Yes	99 (52.4%)	172 (43.7%)	271 (46.5%)	
Postop. P2Y12 inhibitor†				0.12
No	189 (100.0%)	389 (98.7%)	578 (99.1%)	
Yes	0 (0.0%)	5 (1.3%)	5 (0.9%)	

*DVT = deep venous thrombosis, PE = pulmonary embolism, MI = myocardial infarction, SD = standard deviation, ASA = American Society of Anesthesiologists, and BMI = body mass index. †Clopidogrel, prasugrel, ticlopidine, cangrelor, or ticagrelor.

procedures[6,7,9,22]. However, these previous works either did not focus on or excluded patients at higher risk for thromboembolic complications, including those with a history of DVT, PE, MI, stroke, or a coronary stent[6-8,22]. Thus, the several meta-analyses summarizing the safety of TXA in hip fracture surgeries are limited to existing studies that have not focused on high-risk patients[23,24].

Other prior retrospective work also evaluated the safety of TXA in hip fractures but likewise excluded high-risk patients. For example, in a study using the Premier Healthcare Database, a propensity-matched cohort (1:3) of 9,957 patients, of whom 2,002 were patients with IT fracture, revealed no differences in venous thromboembolism, renal failure, or MI when comparing those receiving TXA and those who did not[25]. While their work provides meaningful evidence toward the safety of TXA, their population did not focus on, nor subcategorize separately, high-risk patients. Furthermore, they did not evaluate outcomes past hospital discharge.

The current study provides evidence from a large single health system concerning TXA safety for high-risk patients with IT fracture. On the basis of the sample size of high-risk patients in this study, we estimate an ability to detect a 0.20 effect size with 90% power. As a result, our findings align with previous research indicating the safety of TXA in patients (high-risk or not) receiving TXA for IT fractures. Importantly, and consistent with practice guidelines for TJA, our practice uses a median dose of 2 g IV[3].

While the current study was focused on safety, it is important to note that multiple previous studies have investigated the efficacy of TXA in patients with hip fracture. For example, in a population of patients with IT fracture undergoing surgical repair, Tian et al. randomized 100 patients to a dose of 10 mg/kg of IV TXA preoperatively and a second dose 5 hours postoperatively versus no TXA[8]. Their results revealed that patients receiving TXA had less total blood loss (182 mL) and were less likely to need a blood transfusion. Again, high-risk patients were excluded from this trial. Similarly, a meta-analysis of IV TXA efficacy in hip fracture surgeries revealed less blood loss (−273 mL; $p < 0.0001$) and a lower risk of blood transfusion (relative risk [RR], 0.66; $p = 0.003$)[26]. Hence, our study's focus was not on the efficacy of TXA administration with respect to transfusion requirements, but on the remaining pertinent clinical questions regarding its safety in this non-elective, highly morbid patient population. Although there

TABLE IV Comparison of Propensity-Score-Matched Vs. Non-Matched Groups for High-Risk and All-Patient Cohorts

	High-Risk							
	Propensity-Score-Matched				Non-Matched			
Variable	TXA (N = 141)	No TXA (N = 141)*	P Value	Standardized Mean Difference *(%)*	TXA (N = 141)	No TXA (N = 328)	P Value	Standardized Mean Difference *(%)*
Age (mean) *(yr)*	81.3	81.5	0.904	1.5	81.5	81.2	0.774	2.8
Female sex	67%	63%	0.455	8.9	68%	61%	0.129	14.4
BMI (mean) *(kg/m²)*	24.9	25.2	0.547	6.6	25.1	25.4	0.566	5.4
ASA (mean)	2.1	2.1	0.683	4.3	2.1	2.2	0.278	11
Charlson Comorbidity Index (mean)	2.4	2.6	0.534	6.9	2.6	2.8	0.277	10.1
Tobacco use	11%	11%	0.85	2.2	11%	12%	0.887	1.3
Blood transfusion	37%	36%	0.902	1.5	37%	36%	0.541	5.7
Postop. parenteral anticoagulation	73%	77%	0.41	9.1	71%	63%	0.08	16.7
Postop. antiplatelet	44%	44%	1	0	46%	51%	0.249	10.8
Postop. P2Y12 inhibitor	6%	5%	0.792	3.1	6%	5%	0.897	1.2
Postop. oral anticoagulation	31%	33%	0.704	4.5	32%	38%	0.164	13.2
Preop. hemoglobin (mean) *(g/dL)*	11.3	11.1	0.284	12.5	11.3	11.4	0.554	5.7
Surgical interval								
<24 hr	63%	60%	0.543	7.4	63%	65%	0.678	3.9
24-48 hr	20%	17%	0.541	7.1	20%	19%	0.678	3.9
>48 hr	17%	23%	0.183	17.0	17%	17%	0.923	0.9
	All							
	Propensity-Score-Matched				Non-Matched			
Variable	TXA (N = 316)	No TXA (N = 316)	P Value	Standardized Mean Difference *(%)*	TXA (N = 316)	No TXA (N = 632)	P Value	Standardized Mean Difference *(%)*
High risk	45%	47%	0.577	4.4	46%	51%	0.98	10.4
Age (mean) *(yr)*	77.7	78.8	0.339	7.9	77.7	77.6	0.92	0.8
Female sex	71%	68%	0.546	4.7	70%	65%	0.91	11.9
BMI (mean) *(kg/m²)*	25.5	25.7	0.787	2.1	25.6	25.5	0.98	1.4
ASA (mean)	1.9	1.9	0.554	4.5	1.9	2.0	1.09	10.6
Charlson Comorbidity Index (mean)	1.8	1.9	0.789	2.1	1.9	2.0	0.97	5.2
Tobacco use	11%	13%	0.469	5.7	12%	13%	0.9	3.8
Blood transfusion	30%	28%	0.6	4.1	30%	34%	0.94	7.5
Postop. parenteral anticoagulation	68%	67%	0.799	2	67%	66%	0.95	2.6
Postop. antiplatelet	48%	48%	0.874	1.3	49%	47%	1	3.8
Postop. P2Y12 inhibitor	3%	4%	0.364	7.4	3%	3%	0.79	4.6
Postop. oral anticoagulation	16%	16%	0.914	0.8	17%	22%	0.93	13.1
Preop. Hemoglobin (mean) *(g/dL)*	11.6	11.6	0.649	3.6	11.6	11.7	0.88	6.2
Surgical interval								
<24 hr	62%	59%	0.417	6.5	61%	63%	1.03	3.8
24-48 hr	22%	26%	0.88	8.1	23%	26%	0.93	5.6
>48 hr	16%	16%	0.913	0.9	15%	11%	1.2	12.7

*Patients missing ASA were removed.

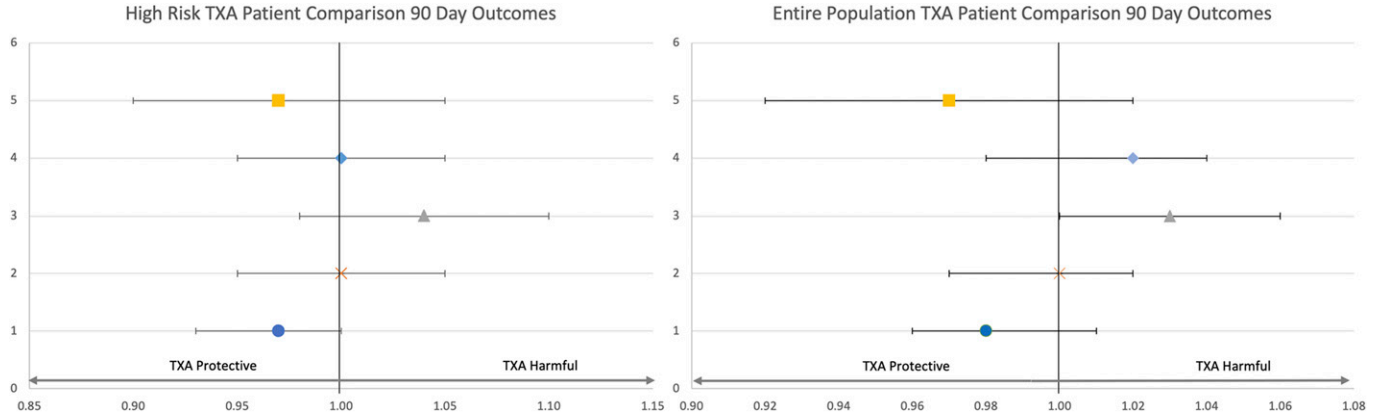

Fig. 2

Forest plots of outcome comparisons for high-risk patients and all patients after propensity-score matching. Yellow square = mortality, blue circle = deep venous thrombosis, orange x = pulmonary embolism, grey triangle = myocardial infarction, and blue diamond = stroke. Whiskers represent the 95% confidence interval. The X axis shows the odds ratio.

was a 3% lower rate of blood transfusion in both the high and low-risk TXA groups compared with the no-TXA group, this difference was not significant.

The current study is not without limitations. First, it relies on accurate coding within the institution's electronic medical record (EMR), which could be inaccurate. While this is a common limitation for large, retrospective studies, it is worth noting the potential for bias[25]. Next, we did not explore the duration or timing of conditions qualifying patients for high-risk status. It is plausible that differences in these characteristics could contribute to outcomes, and they should be evaluated further in future studies. Similarly, we used several conditions aggregated to define high risk. This could potentially mask the associations between specific conditions and outcomes of interest. However, because of the limited sample size, we cannot specifically assess associations at this granular a level. We encourage additional research and the use of larger data sets to evaluate further if any differences in specific high-risk conditions are differentially associated with outcomes. Next, because of the increasing use of TXA in orthopaedic surgery over time, we could not balance our model by surgical year. This limitation has been noted by other authors as well[25]. Furthermore, we were unable to balance the model to include hospital site, and as a result, patient clustering may also bias the results. However, the 4 sites are geographically distant and have separate orthopaedic surgery departments.

In conclusion, in this propensity-matched study of high-risk patients receiving TXA during surgical repair of IT fractures, we found no evidence of increased mortality risk or other serious adverse outcomes. These results held for both the high-risk and entire-population cohorts.

TABLE V Comparison of 90-Day Outcomes for High-Risk Patients and All Patients Receiving TXA Versus No TXA After Propensity-Score Matching

	High-Risk Patients (N = 282)		
90-Day Outcomes	OR*	95% CI	P Value
Mortality	0.97	(0.90, 1.05)	0.493
Deep venous thrombosis	0.97	(0.93, 1.00)	0.039
Pulmonary embolism	1.00	(0.95, 1.05)	0.999
Myocardial infarction	1.04	(0.98, 1.10)	0.240
Stroke	1.00	(0.95, 1.05)	0.999
	All Patients (N = 632)		
90-Day Outcomes	OR*	95% CI	P Value
Mortality	0.97	(0.92, 1.02)	0.200
Deep venous thrombosis	0.98	(0.96, 1.01)	0.166
Pulmonary embolism	1.00	(0.97, 1.02)	0.811
Myocardial infarction	1.03	(1.00, 1.06)	0.073
Stroke	1.02	(0.98, 1.04)	0.857

*Patients receiving TXA vs. no TXA (reference).

Appendix

eA Supporting material provided by the authors is posted with the online version of this article as a data supplement at jbjs.org (http://links.lww.com/JBJS/H29). ■

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References

1. Duncan CM, Gillette BP, Jacob AK, Sierra RJ, Sanchez-Sotelo J, Smith HM. Venous thromboembolism and mortality associated with tranexamic acid use during total hip and knee arthroplasty. J Arthroplasty. 2015 Feb;30(2):272-6.

2. Porter SB, Spaulding AC, Duncan CM, Wilke BK, Pagnano MW, Abdel MP. Tranexamic Acid Was Not Associated with Increased Complications in High-Risk Patients with Hip Fracture Undergoing Arthroplasty. J Bone Joint Surg Am. 2021 Oct 20;103(20):1880-9.

3. 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 in total joint arthroplasty: the endorsed clinical practice guides of 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. Reg Anesth Pain Med. 2019 Jan;44(1):7-11.

4. 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 Jan;35(1):45-51.e3.

5. Jiang W, Shang L. Tranexamic acid can reduce blood loss in patients undergoing intertrochanteric fracture surgery: A meta-analysis. Medicine (Baltimore). 2019 Mar;98(11):e14564.

6. Lei J, Zhang B, Cong Y, Zhuang Y, Wei X, Fu Y, Wei W, Wang P, Wen S, Huang H, Wang H, Han S, Liu S, Zhang K. Tranexamic acid reduces hidden blood loss in the treatment of intertrochanteric fractures with PFNA: a single-center randomized controlled trial. J Orthop Surg Res. 2017 Aug 15;12(1):124.

7. Mohib Y, Rashid RH, Ali M, Zubairi AJ, Umer M. Does tranexamic acid reduce blood transfusion following surgery for inter-trochanteric fracture? A randomized control trial. J Pak Med Assoc. 2015 Nov;65(11)(Suppl 3):S17-20.

8. Tian S, Shen Z, Liu Y, Zhang Y, Peng A. The effect of tranexamic acid on hidden bleeding in older intertrochanteric fracture patients treated with PFNA. Injury. 2018 Mar;49(3):680-4.

9. Zhou XD, Zhang Y, Jiang LF, Zhang JJ, Zhou D, Wu LD, Huang Y, Xu NW. Efficacy and Safety of Tranexamic Acid in Intertrochanteric Fractures: A Single-Blind Randomized Controlled Trial. Orthop Surg. 2019 Aug;11(4):635-42.

10. Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A, Tosteson A. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. J Bone Miner Res. 2007 Mar;22(3):465-75.

11. Brauer CA, Coca-Perraillon M, Cutler DM, Rosen AB. Incidence and mortality of hip fractures in the United States. JAMA. 2009 Oct 14;302(14):1573-9.

12. Samuel M, Batomen B, Rouette J, Kim J, Platt RW, Brophy JM, Kaufman JS. Evaluation of propensity score used in cardiovascular research: a cross-sectional survey and guidance document. BMJ Open. 2020 Aug 26;10(8):e036961-036961.

13. Goltz DE, Ryan SP, Hopkins TJ, Howell CB, Attarian DE, Bolognesi MP, Seyler TM. A Novel Risk Calculator Predicts 90-Day Readmission Following Total Joint Arthroplasty. J Bone Joint Surg Am. 2019 Mar 20;101(6):547-56.

14. Kristiansson J, Hagberg E, Nellgård B. The influence of time-to-surgery on mortality after a hip fracture. Acta Anaesthesiol Scand. 2020 Mar;64(3):347-53.

15. Ravi B, Pincus D, Khan H, Wasserstein D, Jenkinson R, Kreder HJ. Comparing Complications and Costs of Total Hip Arthroplasty and Hemiarthroplasty for Femoral Neck Fractures: A Propensity Score-Matched, Population-Based Study. J Bone Joint Surg Am. 2019 Apr 3;101(7):572-9.

16. 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 Oct 28;11(1):21240.

17. Khazi ZM, An Q, Duchman KR, Westermann RW. Incidence and Risk Factors for Venous Thromboembolism Following Hip Arthroscopy: A Population-Based Study. Arthroscopy. 2019 Aug;35(8):2380-2384.e1.

18. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. Pharm Stat. 2011 Mar-Apr;10(2):150-61.

19. Garrido MM, Kelley AS, Paris J, Roza K, Meier DE, Morrison RS, Aldridge MD. Methods for constructing and assessing propensity scores. Health Serv Res. 2014 Oct;49(5):1701-20.

20. Reeve BB, Smith AW, Arora NK, Hays RD. Reducing bias in cancer research: application of propensity score matching. Health Care Financ Rev. 2008 Summer;29(4):69-80.

21. Granger E, Watkins T, Sergeant JC, Lunt M. A review of the use of propensity score diagnostics in papers published in high-ranking medical journals. BMC Med Res Methodol. 2020 May 27;20(1):132.

22. Zhang S, Xiao C, Yu W, Long N, He F, Cai P, Luo K, Jiang Y. Tranexamic acid safely reduces hidden blood loss in patients undergoing intertrochanteric fracture surgery: a randomized controlled trial. Eur J Trauma Emerg Surg. 2020 May 15.

23. Luo X, Huang H, Tang X. Efficacy and safety of tranexamic acid for reducing blood loss in elderly patients with intertrochanteric fracture treated with intramedullary fixation surgery: A meta-analysis of randomized controlled trials. Acta Orthop Traumatol Turc. 2020 Jan;54(1):4-14.

24. Xing F, Chen W, Long C, Huang F, Wang G, Xiang Z. Postoperative outcomes of tranexamic acid use in geriatric trauma patients treated with proximal femoral intramedullary nails: A systematic review and meta-analysis. Orthop Traumatol Surg Res. 2020 Feb;106(1):117-26.

25. Cheung ZB, Anthony SG, Forsh DA, Podolnick J, Zubizarreta N, Galatz LM, Poeran J. Utilization, effectiveness, and safety of tranexamic acid use in hip fracture surgery: A population-based study. J Orthop. 2020 Jan 28;20:167-72.

26. Qi YM, Wang HP, Li YJ, Ma BB, Xie T, Wang C, Chen H, Rui YF. The efficacy and safety of intravenous tranexamic acid in hip fracture surgery: A systematic review and meta-analysis. J Orthop Translat. 2019 Apr 19;19:1-11.