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A commentary by David C. Ayers, MD, is linked to the online version of this article at jbjs.org.

Perioperative Tranexamic Acid Treatment and Risk of Cardiovascular Events or Death After Total Hip Arthroplasty

A Population-Based Cohort Study from National Danish Databases

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Background: There have been concerns that the antifibrinolytic drug tranexamic acid (TXA) might increase the postoperative risk of cardiovascular events. Our objective was to determine whether perioperative TXA use is associated with cardiovascular events and death within 30 days after primary total hip arthroplasty (THA).

Methods: We conducted a nationwide cohort study of cardiovascular outcomes after perioperative exposure to tranexamic acid during THA. We included 45,290 patients who had a THA in the study period of 2006 to 2013; 38,586 received perioperative TXA, and 6,704 did not. Propensity scores were calculated on the basis of age, sex, income, year of surgery, Elixhauser comorbidity index, and a variety of comorbidities and coprescribed medications. The primary outcome was venous thromboembolism. The secondary outcomes were deep venous thrombosis, pulmonary embolism, myocardial infarction, ischemic stroke, and all-cause mortality. Data were analyzed using Cox regression, either in a multivariable model with inclusion of covariates (full cohorts) or in propensity-score-matched cohorts.

Results: After propensity score matching, all prognostic covariates balanced well. In the matched cohort, TXA use was not found to significantly increase the risk of venous thromboembolism (hazard ratio [HR] = 1.18; 95% confidence interval [CI] = 0.83 to 1.68), deep vein thrombosis (HR = 1.15; CI = 0.78 to 1.68), pulmonary embolism (HR = 1.50; CI = 0.60 to 3.78), myocardial infarction (HR = 0.83; CI = 0.46 to 1.50), ischemic stroke (HR = 0.89; CI = 0.39 to 2.01), or all-cause mortality (HR = 0.73; CI = 0.41 to 1.28). Similar results were found in the multivariable Cox regression analyses.

Conclusions: Our data do not support a detrimental effect of TXA on the risk of cardiovascular events or death following THA.

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

Total hip arthroplasty (THA) is an effective surgical treatment for severe hip osteoarthritis. The rate of THA has increased during the years and is expected to rise further as a result of changes in demographics and indications[1,2]. In the U.S., the annual number of primary THA procedures is expected to increase 174% by 2030 compared with 2005[3]. Although THA is a common procedure, perioperative blood loss remains a concern and blood transfusion following THA is associated with a worse prognosis with respect to death and pneumonia[4]. The antifibrinolytic drug tranexamic acid (TXA) has been shown to reduce blood loss in several orthopaedic procedures such as THA and total knee replacement (TKA), and both topical[5] and intravenous administrations have proven to be effective[6-8]. TXA is a synthetic lysine analog that reduces fibrinolysis by reversibly and competitively binding to the lysine-binding sites of plasminogen[9]. Given the pharmacological action of TXA, there are concerns about the

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routine use of TXA in THA and the risk of inducing a hypercoagulatory state with an increased risk of venous thromboembolism (either deep venous thrombosis or pulmonary embolism) and possibly other cardiovascular outcomes such as myocardial infarction or ischemic stroke[10,11]. However, we are not aware of any study that has shown perioperative TXA to be associated with an increased risk of thromboembolic events[12,13].

The aim of this study was to estimate the 30-day risk of venous thromboembolism (primary outcome) and deep venous thrombosis, pulmonary embolism, myocardial infarction, ischemic stroke, and all-cause mortality (secondary outcomes) in relation to perioperative treatment with TXA following primary THA.

Materials and Methods

This study was designed as a register-based cohort study performed by linkage of several Danish databases with complete or nearly complete national coverage. We identified patients who had undergone primary THA for the treatment of idiopathic osteoarthritis in the period from 2006 to 2013. Our main analysis was Cox regression performed on the unmatched cohorts of patients exposed to TXA and those not exposed to TXA, and we calculated the hazard ratios (HRs) for the chosen outcomes occurring within 30 days after the primary THA. Because of issues of small-number bias[14], we could only control for age, sex, and the Elixhauser comorbidity index in the multivariable analysis. A secondary analysis based on propensity score matching was performed to adjust for a large number of potential confounders.

Data Sources

All Danes are issued a unique 10-digit number allowing unambiguous linkage at the individual level among all government registers. The Danish Civil Registration System (CRS) contains data on vital status (including date of birth and death) and migrations[15]. We used these data to exclude subjects with a limited look-back period (<2 years) before THA.

The Danish Hip Arthroplasty Register (DHR) registers all hip arthroplasties performed in Denmark, in both public and private hospitals, and includes diagnosis, type of implant, perioperative procedures, postoperative complications, and medications including perioperative TXA. Data are registered by the surgeon, and 129,970 primary THAs have been registered in the period of 1995 to 2013, with a completeness of 97.8% for primary THA in 2015[1,16]. The data quality was validated in 2004, with the positive predictive value of a diagnosis of osteoarthritis of 84%[17]. All study subjects were identified from this register.

The Danish National Patient Register (NPR) registers all hospitalizations, outpatient visits, and discharge diagnoses in Denmark. All non-psychiatric hospitalizations since 1977 and all outpatient visits since 1995 have been recorded. Since 1994, all discharge diagnoses have been coded according to the International Classification of Diseases-10 (ICD-10)[18]. The data from the NPR were used to generate the Elixhauser comorbidity indexes.

The Danish National Database of Prescriptions (DNPR) contains data on all prescriptions filled by pharmacies in Denmark since 1995. The data include the World Health

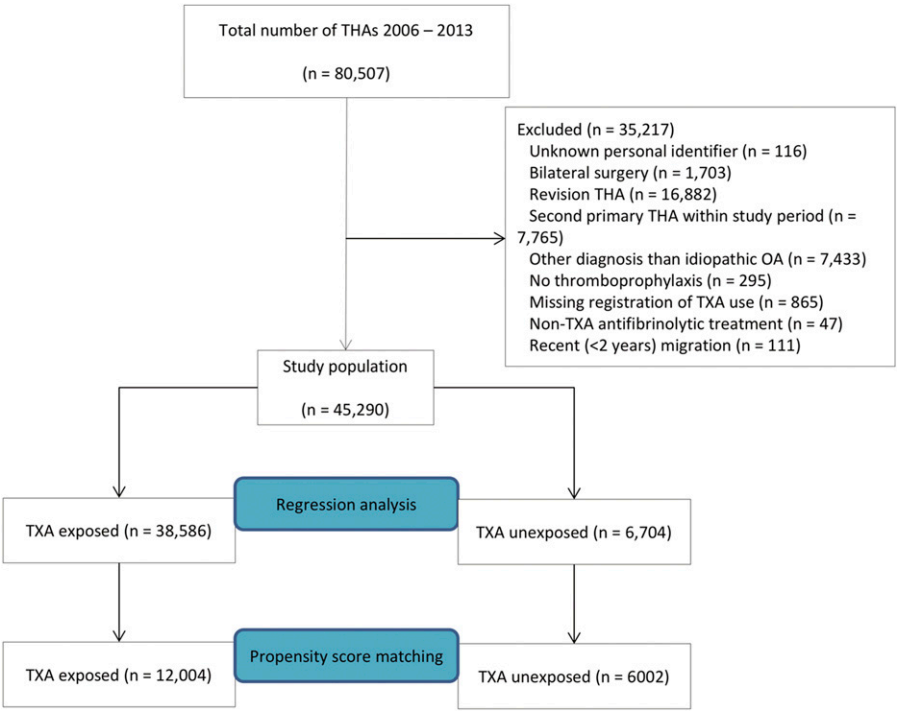

Fig. 1

Flowchart of the study population. A total of 80,507 THAs were performed between 2006 and 2013. After application of exclusion criteria, 45,290 primary THAs in 45,290 individuals with idiopathic osteoarthritis (OA) were included in this study; 38,586 patients were given TXA during THA and 6,704 were not. A 2:1 propensity score matching resulted in a cohort of 12,004 TXA-exposed and 6,002 TXA-unexposed patients.

TABLE I Characteristics of Patients Exposed and Not Exposed to TXA During THA Included in Unmatched and Propensity-Score-Matched Cohorts

	Unmatched Cohort			Propensity-Score-Matched Cohort		
Characteristics	TXA-Exposed (N = 38,586) *(no. [%]*)*	TXA-Unexposed (N = 6,704) *(no. [%]*)*	SMD	TXA-Exposed (N = 12,004) *(no. [%]*)*	TXA-Unexposed (N = 6,002) *(no. [%]*)*	SMD
Median age (interquartile range) *(yr)*	70 (63-76)	72 (65-78)	0.2172	72 (65-78)	72 (65-78)	0.0146
Male sex	16,896 (43.8%)	3,077 (45.9%)	0.0425	5,340 (44.5%)	2,670 (44.5%)	0.0000
Year of surgery						
2006-2007	8,333 (21.6%)	2,185 (32.6%)	0.2604	3,445 (28.7%)	1,917 (31.9%)	0.0709
2008-2009	10,091 (26.2%)	1,614 (24.1%)	0.0474	3,405 (28.4%)	1,472 (24.5%)	0.0864
2010-2011	10,303 (26.7%)	1,529 (22.8%)	0.0886	2,990 (24.9%)	1,415 (23.6%)	0.0310
2012-2013	9,859 (25.6%)	1,376 (20.5%)	0.1164	2,164 (18.0%)	1,198 (20.0%)	0.0496
Diagnoses prior to index date						
Arterial thrombosis	2,527 (6.5%)	928 (13.8%)	0.2748	1,118 (9.3%)	598 (10.0%)	0.0221
Myocardial infarction	1,345 (3.5%)	492 (7.3%)	0.1953	579 (4.8%)	308 (5.1%)	0.0142
Ischemic stroke	1,282 (3.3%)	483 (7.2%)	0.2006	563 (4.7%)	300 (5.0%)	0.0144
Venous thromboembolism	1,176 (3.0%)	313 (4.7%)	0.0909	463 (3.9%)	245 (4.1%)	0.0116
Deep venous thrombosis	332 (0.9%)	118 (1.8%)	0.0907	135 (1.1%)	72 (1.2%)	0.0070
Pulmonary embolism	931 (2.4%)	226 (3.4%)	0.0607	359 (3.0%)	189 (3.1%)	0.0092
Diabetes type 1	704 (1.8%)	176 (2.6%)	0.0580	296 (2.5%)	144 (2.4%)	0.0043
Diabetes type 2	2,020 (5.2%)	493 (7.4%)	0.0926	823 (6.9%)	419 (7.0%)	0.0049
Rheumatic arthritis	741 (1.9%)	135 (2.0%)	0.0068	246 (2.0%)	122 (2.0%)	0.0012
COPD	1,662 (4.3%)	430 (6.4%)	0.1004	666 (5.5%)	335 (5.6%)	0.0015
Kidney failure	357 (0.9%)	125 (1.9%)	0.0915	148 (1.2%)	81 (1.3%)	0.0104
Cancer	4,032 (10.4%)	736 (11.0%)	0.0172	1,326 (11.0%)	656 (10.9%)	0.0037
Thrombophilia	29 (0.1%)	6 (0.1%)	0.0052	7 (0.1%)	5 (0.1%)	0.0097
Hypertension	8,454 (21.9%)	2,152 (32.1%)	0.2406	3,506 (29.2%)	1,738 (29.0%)	0.0055
Atrial fibrillation	2,453 (6.4%)	771 (11.5%)	0.2000	1,043 (8.7%)	527 (8.8%)	0.0032
Congestive heart failure	1,320 (3.4%)	454 (6.8%)	0.1727	565 (4.7%)	298 (5.0%)	0.0121
Elixhauser comorbidity index						
Median (interquartile range)	0 (0-3)	0 (0-4)	0.2141	0 (0-4)	0 (0-4)	0.0064
<0	2,012 (5.2%)	379 (5.7%)	0.0196	614 (5.1%)	354 (5.9%)	0.0347
0	25,207 (65.3%)	3,713 (55.4%)	0.2069	7,165 (59.7%)	3,495 (58.2%)	0.0297
1-4	5,251 (13.6%)	978 (14.6%)	0.0284	1,753 (14.6%)	897 (14.9%)	0.0096
≥5	6,116 (15.9%)	1,634 (24.4%)	0.2263	2,472 (20.6%)	1,256 (20.9%)	0.0082
Prescription drugs†						
HRT	3,572 (9.3%)	513 (7.7%)	0.0560	941 (7.8%)	473 (7.9%)	0.0015
Warfarin	1,433 (3.7%)	550 (8.2%)	0.2194	641 (5.3%)	330 (5.5%)	0.0070
Aspirin	7,056 (18.3%)	1,902 (28.4%)	0.2532	3,195 (26.6%)	1,553 (25.9%)	0.0168
Statin	9,074 (23.5%)	2,093 (31.2%)	0.1787	3,448 (28.7%)	1,737 (28.9%)	0.0048
Antihypertensive	17,900 (46.4%)	3,578 (53.4%)	0.1398	6,254 (52.1%)	3,134 (52.2%)	0.0023
ACE inhibitor	5,626 (14.6%)	1,236 (18.4%)	0.1076	2,020 (16.8%)	1,037 (17.3%)	0.0120
Platelet inhibitor	7,670 (19.9%)	2,100 (31.3%)	0.2783	3,458 (28.8%)	1,708 (28.5%)	0.0077
Urate lowering drug	877 (2.3%)	181 (2.7%)	0.0283	286 (2.4%)	154 (2.6%)	0.0119
Metformin	1,840 (4.8%)	378 (5.6%)	0.0403	673 (5.6%)	337 (5.6%)	0.0004
NSAID	16,604 (43.0%)	2,592 (38.7%)	0.0884	4,879 (40.6%)	2,390 (39.8%)	0.0168
SSRI	2,235 (5.8%)	460 (6.9%)	0.0452	783 (6.5%)	395 (6.6%)	0.0024
Income quartile						
1	9,075 (23.5%)	1,805 (26.9%)	0.0797	3,288 (27.4%)	1,626 (27.1%)	0.0067

continued

TABLE I (*continued*)

Characteristics	Unmatched Cohort			Propensity-Score-Matched Cohort		
	TXA-Exposed (N = 38,586) *(no. [%]*)*	TXA-Unexposed (N = 6,704) *(no. [%]*)*	SMD	TXA-Exposed (N = 12,004) *(no. [%]*)*	TXA-Unexposed (N = 6,002) *(no. [%]*)*	SMD
2	9,210 (23.9%)	1,904 (28.4%)	0.1053	3,349 (27.9%)	1,678 (28.0%)	0.0013
3	9,404 (24.4%)	1,544 (23.0%)	0.0313	2,838 (23.6%)	1,416 (23.6%)	0.0012
4	10,884 (28.2%)	1,450 (21.6%)	0.1478	2,527 (21.1%)	1,282 (21.4%)	0.0075
Unknown	13 (0.0%)	N < 5	0.0107	N < 5	—	0.0158

*Unless otherwise indicated. †HRT = hormone replacement therapy, ACE = angiotensin converting enzyme, NSAID = nonsteroidal anti-inflammatory drug, and SSRI = selective serotonin reuptake inhibitor.

Organization (WHO)-defined Anatomical Therapeutic Chemical (ATC) code[19], dosage, and amount as well as the date that the drug was dispensed[20]. We used this register to identify covariates defined by drug use.

Statistics Denmark[21] registers of income and socioeconomic status contain data on gross earnings and employment status (employee, pensioner, etc.) as well as different measures of income. These data were used for descriptive purposes, as well as for propensity matching according to income quartiles, as a crude proxy for socioeconomic status. To prevent retiree status and the concomitant drop in income from misdirecting our income quartiles as a measure of health behavior, the study population was divided into retirees and non-retirees and then the income quartiles were established for both populations. Retiree and non-retiree quartiles were then combined.

Linkage between databases was performed by Statistics Denmark, which received a copy of the DHR database. By using the CPR (Danish personal identification) number, unambiguous linkage at the person level for all included databases was possible. An anonymized data set containing the linked data was constructed by Statistics Denmark and used in the analyses.

According to Danish law, register-based studies do not require approval by an ethics committee[22]. Approval by the Danish Data Protection Agency was obtained (Reg-93-2015).

Cohort

Figure 1 shows a flowchart of the cohorts included in this study. In the DHR, we identified all persons who received a THA (revision or primary) between 2006 and 2013. Only a person's first entry with a unilateral THA in the DHR was included to ensure independence between observations. To limit variability and therefore the potential for confounding, only persons with idiopathic osteoarthritis (accounting for 79% of all primary THAs[23]) as the indication for THA were included. We excluded patients who did not receive standard thromboprophylaxis as they might be outliers with respect to the outcomes. Those registered as "unknown" with respect to TXA and those registered with non-TXA prophylaxis against bleeding were also excluded. Finally, persons who had immigrated to Denmark <2 years prior to the THA were excluded because of a lack of data on comorbidities.

The index date was defined as the date of surgery. Follow-up began on the index date and lasted until the occurrence of an outcome—revision surgery, THA in the contralateral hip, emigration from Demark, or 30 days, whichever came first. We chose 30 days of follow-up because TXA is rapidly excreted[9], and we considered outcomes after 30 days to be unlikely to be related to TXA exposure.

Data on preexisting comorbidities from 1995 to 2014 were obtained from the NPR.

Using the Elixhauser disease categories as defined by Quan et al. in 2005[24], we calculated the Elixhauser comorbidity index as described by van Walraven et al. in 2009[25]. The Elixhauser comorbidity index was chosen because it provides a better prediction of in-hospital mortality after orthopaedic surgery than the Charlson comorbidity index[26].

Outcomes

Our primary outcome was venous thromboembolism, defined as a composite of the ICD-10 codes for the secondary outcomes of deep venous thrombosis (ICD-10 I801-I809) and

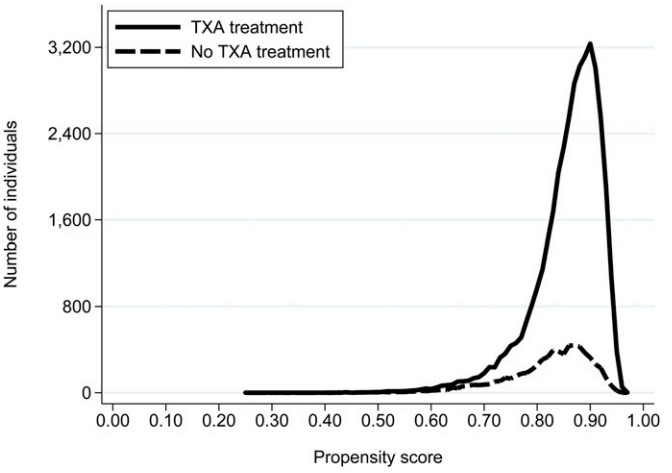

Fig. 2

Graph of the propensity scores for the individuals treated (solid line) and not treated (dotted line) with TXA in this study.

TABLE II Thirty-Day Risk of Venous Thromboembolism, Arterial Thrombosis, and Death from All Causes in Unmatched Cohort According to TXA Exposure During Primary THA

	TXA-Exposed (N = 38,586)		TXA-Unexposed (N = 6,704)		HR* (95% CI)	
Outcome	Events *(no.)*	Risk *(%)*	Events *(no.)*	Risk *(%)*	Crude	Adjusted†
Venous thromboembolism	288	0.75	49	0.73	1.02 (0.75-1.38)	1.07 (0.79-1.46)
Deep venous thrombosis	234	0.61	43	0.64	0.94 (0.68-1.31)	0.99 (0.72-1.38)
Pulmonary embolism	56	0.15	6	0.09	1.59 (0.69-3.70)	1.73 (0.74-4.03)
Arterial thrombosis	118	0.31	38	0.57	0.51 (0.35-0.73)	0.64 (0.44-0.93)
Myocardial infarction	75	0.19	24	0.36	0.51 (0.32-0.80)	0.66 (0.41-1.05)
Ischemic stroke	44	0.11	14	0.21	0.52 (0.28-0.95)	0.64 (0.35-1.17)
Death from all causes	77	0.20	31	0.46	0.45 (0.29-0.69)	0.61 (0.39-0.94)

*TXA-unexposed group set as reference. †Adjusted for age, sex, and Elixhauser comorbidity index.

pulmonary embolism (ICD-10 I26). The other secondary outcomes were arterial thrombosis, defined as a composite of the codes for myocardial infarction (ICD-10 I21) and ischemic stroke (ICD-10 I63-64), and death from all causes. All outcome data were drawn from the NPR or, in the case of death, from the CRS.

Analysis

Our main analysis was Cox regression, and we calculated 30-day cumulative risks and HRs with 95% confidence intervals (CIs) for the unmatched cohorts of TXA-exposed and TXA-unexposed patients. As mentioned, because of the issue of small-number bias we could only control for age, sex, and the Elixhauser comorbidity index in the unmatched analyses.

To address the large number of potential confounders (Table I), we performed propensity score matching of TXA-exposed patients to TXA-unexposed patients (Fig. 2). Propensity score matching was used to balance known covariates in the study, which included a large number of covariates and relatively few outcomes, to reduce small-sample bias, which may occur in a conventional regression analysis[27]. The included covariates are shown in Table I. Propensity scores were calculated using logistic regression to estimate the probability of a person receiving TXA and then matching TXA-exposed persons with TXA-unexposed persons who had similar propensity scores. The matching technique was a sequential, balanced nearest-neighbor approach[28] without replacement, applying a caliper of 0.01 on the probability scale. Trimming was performed at the upper and lower 2.5 percentiles on the probability scale for TXA-exposed and TXA-unexposed patients, respectively. Covariate balance was evaluated by calculating the standardized difference of means (SMD)[29].

As the TXA-exposed cases (n = 38,586) outnumbered the TXA-unexposed cases (n = 6,704), we performed a 2:1 matching of TXA-exposed cases to TXA-unexposed cases. A subgroup analysis was performed in which we stratified according to sex, age, Elixhauser category, and previous cardiovascular events. We also performed sensitivity analyses in which patients with a history of different cardiovascular events were removed to test whether this would affect the estimated HRs.

All analyses were performed with Stata version IC 14.2 (StataCorp).

TABLE III Thirty-Day Risk of Venous Thromboembolism, Arterial Thrombosis, and Death from All Causes in Propensity-Score-Matched Cohort According to TXA Exposure During Primary THA

	TXA-Exposed (N = 12,004)		TXA-Unexposed (N = 6,002)		
Outcome	Events *(no.)*	Risk *(%)*	Events *(no.)*	Risk *(%)*	HR* (95% CI)
Venous thromboembolism	104	0.87	44	0.73	1.18 (0.83-1.68)
Deep venous thrombosis	87	0.72	38	0.63	1.15 (0.78-1.68)
Pulmonary embolism	18	0.15	6	0.10	1.50 (0.60-3.78)
Arterial thrombosis	48	0.40	27	0.45	0.85 (0.53-1.37)
Myocardial infarction	32	0.27	18	0.30	0.83 (0.46-1.50)
Ischemic stroke	16	0.13	9	0.15	0.89 (0.39-2.01)
Death from all causes	29	0.24	20	0.33	0.73 (0.41-1.28)

*TXA-unexposed group set as reference.

TABLE IV Subgroup Analysis of 30-Day Risk of Venous Thromboembolism Following Primary THA in Propensity-Score-Matched Cohort

	TXA-Exposed (N = 12,004)			TXA-Unexposed (N = 6,002)			
Subgroup	Persons *(no.)*	Events *(no.)*	Risk *(%)*	Persons *(no.)*	Events *(no.)*	Risk *(%)*	HR* (95% CI)
All	12,004	104	0.87	6,002	44	0.73	1.18 (0.83-1.68)
Sex							
Male	5,340	50	0.94	2,670	21	0.79	1.19 (0.72-1.98)
Female	6,664	54	0.81	3,332	23	0.69	1.18 (0.72-1.92)
Age							
51-70 yr	5,234	42	0.80	2,607	17	0.65	1.23 (0.70-2.17)
>70 yr	6,546	60	0.92	3,260	26	0.80	1.15 (0.73-1.82)
Elixhauser comorbidity index							
0	7,165	61	0.85	3,495	21	0.60	1.42 (0.86-2.33)
1-4	1,753	23	1.31	897	10	1.11	1.18 (0.56-2.48)
≥5	472	16	0.65	1,256	11	0.88	0.74 (0.34-1.60)
Previous arterial thrombosis	1,539	26	1.69	821	8	0.97	1.75 (0.79-3.86)

*TXA-unexposed group set as reference.

Results

As shown in Figure 1, 45,290 persons fulfilled the inclusion criteria; 38,586 had been exposed to TXA, and 6,704 had not. These persons were included in our main analysis.

Baseline covariates differed between the unmatched cohorts, with TXA-exposed individuals being younger than those not treated with TXA (median age, 70 and 72 years, respectively) and less likely to have had a myocardial infarction or an ischemic stroke or to have a history of chronic obstructive pulmonary disorder (COPD), hypertension, atrial fibrillation, or congestive heart failure (Table I). TXA-exposed patients had fewer comorbidities. The Elixhauser comorbidity index was ≥5 for 15.9% of the TXA-exposed patients compared with 24.4% of the TXA-unexposed patients.

Propensity score matching was possible for 6,002 TXA-unexposed persons, who were matched 1:2 to 12,004 TXA-exposed persons. Baseline covariates were generally well balanced in the matched cohorts, with a median age of 72 years and a 45% prevalence of males in the both the TXA-exposed and the TXA-unexposed group. While there is no established consensus for a cutoff above which SMDs denote residual imbalance between covariates, a value of 0.1 has been suggested[30]. For the covariates included in our propensity score matching, SMDs ranged between 0.0000 and 0.0864.

Cardiovascular Events

The unmatched analysis of our primary outcome (Table II) showed no significantly increased 30-day risk of venous thromboembolism between TXA-exposed and TXA-unexposed patients (0.75% and 0.73%, respectively), with crude and adjusted HRs of 1.02 (CI = 0.75 to 1.38) and 1.07 (CI = 0.79 to 1.46), respectively. However, this analysis did show that TXA exposure was associated with a significantly reduced risk of arterial thrombosis (HR = 0.64; CI = 0.44 to 0.93) and all-cause mortality (HR = 0.61; CI = 0.39 to 0.94). The propensity-score-matched analysis (Table III) yielded an HR of 1.18 (CI = 0.83 to 1.68) for venous thromboembolism. No increased risk of the secondary outcomes (deep venous thrombosis, pulmonary embolism, myocardial infarction, ischemic stroke, or all-cause mortality) was identified.

Subgroup Analysis

In our stratified analysis (Table IV), TXA was not associated with an increased risk of venous thromboembolism in any of the examined subgroups based on age, sex, Elixhauser categories, or a previous diagnosis of arterial thrombosis (myocardial infarction or ischemic stroke). Stratifying by a previous diagnosis of venous thromboembolism was performed, but the numbers were too low for meaningful calculation. We also excluded those with a history of cardiovascular events as a sensitivity analysis, and this exclusion did not affect the HRs (data not shown).

Discussion

We did not find an association between TXA and an increased risk of venous thromboembolism, any other cardiovascular outcomes, or all-cause mortality within 30 days after primary THA. This was consistently found in all examined subgroups.

Prior research has established that THA is associated with an increased risk of venous thromboembolism in the postoperative period, with the 30-day cumulative risk estimated at 0.9% despite routine thromboprophylaxis[31]. There have therefore been concerns that routine administration of an antifibrinolytic drug to patients undergoing THA might increase the risk of thromboembolic events.

In 2014, Poeran et al. reported that TXA was not associated with an increased risk of thromboembolic events in a retrospective analysis of the records on 872,416 patients treated with THA or TKA at 510 U.S. hospitals, with 20,051 of those patients exposed to TXA[32]. A propensity-score-matched analysis was included, but the follow-up period was limited to the postoperative hospital stay of a few days. In our analysis, the cumulative risk of both venous thromboembolism and deep venous thrombosis rose during the entire 30-day period of observation, with only a few of the venous thromboembolism events occurring within the first 5 days after surgery (data not shown). Only including the period of the in-hospital stay thus severely underestimates the risk of complications and may dilute the relative-risk measures.

Among the strengths of this study is that it is, to our knowledge, the largest linkage study using nationwide databases to address the putative association between perioperative TXA treatment and postoperative cardiovascular events and death from all causes among patients treated with THA. We employed unambiguous linkage on the person level and used databases with complete or nearly complete national coverage. We were able to account for all hospital admissions and prescriptions within the study period. We included both specific risk factors for cardiovascular outcomes and the Elixhauser comorbidity index. The positive validity of the outcomes drawn from the NPR is generally high, with the diagnosis of venous thromboembolism made on hospital wards found, by Severinsen et al. in 2010, to have a positive predictive value of 75.0%[33]. The diagnosis of ischemic stroke was validated in 2007 by Krarup et al., who found a positive predictive value of 97%[34]. The diagnosis of myocardial infarction has been found to have a positive predictive value of 99% (CI = 94% to 100%)[35]. To our knowledge, there is no validation study for the TXA variable in the DHR and no standard against which to measure it.

Propensity score matching was employed as a secondary analysis to ensure balance between covariates, and this was achieved according to the SMDs. While our main analysis showed that TXA exposure was associated with a reduced risk of arterial thrombosis and all-cause mortality, this association was not found in our propensity-score-matched analysis. As the unmatched cohorts differed with respect to the prevalence of cardiovascular risk factors, such as previous arterial thrombosis, we concluded that the observed protective effect of TXA was due to confounding. Our study findings are comparable with those of Poeran et al. in 2014[32], Zhou et al. in 2013[36], and Wei and Liu in 2015[37], while being based on full national coverage and a complete 30-day follow-up.

The limitations of our study include a lack of information on body mass index, smoking, and alcohol use, which are all risk factors for the outcomes under study. Smoking was partially controlled for by including COPD among our covariates, while alcohol-abuse-related diagnoses are included as an Elixhauser disease category. Although we cannot exclude some residual confounding by lifestyle factors, we believe these limitations to be of minor importance. While we would have liked to have stratified on the basis of previous cardiac procedures such as insertion of arterial stents, our study did not have the statistical strength for us to do so. Stratification according to the use of arterial stents in particular would present difficulties due to the number of different implants, time since surgery, number of stents, etc. Another limitation of the study is that the dosage of TXA is not registered in the DHR, but we assume that local guidelines for the use of TXA were followed. Topical TXA was not used in Denmark in the study period; thus, the vast majority of TXA-exposed patients are assumed to have been given 10 to 15 mg of TXA/kg body weight intravenously, with a maximum of 1 to 1.5 g, according to the Danish Orthopaedic Society's Reference Program[38] as well as local hospital guidelines[39,40].

Our outcome of ischemic stroke is a composite of the ICD-10 codes for ischemic and unspecified stroke. As approximately 60% of patients registered as having had an unspecified stroke did in fact have an ischemic stroke, with only 5% having intracranial hemorrhage[34], the diagnoses were combined under the term *ischemic stroke*. The positive predictive value for a diagnosis of deep venous thrombosis is 75%; however, we have no reason to believe that the validity of the deep venous thrombosis diagnosis would depend on whether the patient was given TXA.

It is possible that health-care providers would be more likely to suspect deep venous thrombosis in a patient treated with TXA, thus leading to an increase in the measured venous thromboembolism risk following TXA exposure, but that would bias the HR upward. As we found a null result, we can still conclude that TXA is safe with respect to venous thromboembolism.

In conclusion, our data do not support a detrimental effect of TXA on the risk of cardiovascular events or death following THA. The reduced blood loss and the reduced risk of blood transfusions and related complications can be expected to reduce both the individual risk to the patient and the societal cost of THA. ■

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