BRIEF REPORT

OPEN

Tranexamic Acid in Upper Gastrointestinal Bleeding is Associated With Venous and Arterial Thromboembolic Events

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OBJECTIVES: To determine the risk difference of arterial and venous thromboembolic events between patients with upper gastrointestinal bleeding (UGIB) who received and did not receive tranexamic acid.

DESIGN: Retrospective cohort study.

SETTING: The TriNetX Analytics (Cambridge, MA) Research Network, a deidentified mixed electronic health record and claims-derived database with over 110 million patients, primarily located in the United States.

PATIENTS: A total of 2,016,763 patients diagnosed with hematemesis or melena between October 31, 2003, and October 31, 2023.

INTERVENTIONS: Receipt of tranexamic acid within 7 days of a UGIB diagnosis.

MEASUREMENTS AND MAIN RESULTS: We measured the incidence of thromboembolic events, both venous (deep venous thrombosis [DVT] and pulmonary embolism [PE]) and arterial (cerebrovascular accident [CVA] and myocardial infarction [MI]), within either 7 days of tranexamic acid (for recipients) or 7 days of UGIB diagnosis (for nonrecipients). Subsequently, we developed similar subcohorts using propensity score matching (PSM) for demographic and comorbidity data and reexamined the incidence of thromboembolic events, both before and after excluding any patients with any prior episodes of the outcomes. In all analyses, tranexamic acid recipients experienced significantly more adverse thromboembolic outcomes, with the post-PSM cohorts' risk difference generating an odds ratio of 1.4 for MI (95% CI, 1.2–1.7), 1.6 in CVA (95% CI, 1.3–1.9), 1.8 in PE (95% CI, 1.5–2.3), and 2.1 in DVT (95% CI, 1.8–2.5); all *p* values of less than 0.001.

CONCLUSIONS: Leveraging data from a large, multi-institutional database, we identified a correlation between tranexamic acid use in patients with UGIB and the occurrence of both venous and arterial thromboembolic events. Although the former is well-attested in the literature, the latter finding is more novel, underscoring the need for further prospective research to better characterize the risk-benefit profile of tranexamic acid in the management of gastrointestinal bleeding.

KEYWORDS: deep vein thrombosis; gastrointestinal bleed; myocardial infarction; pulmonary embolism; stroke; tranexamic acid

Upper gastrointestinal bleeding (UGIB) is a common condition that may be life-threatening (1). Tranexamic acid is an antifibrinolytic therapy that has been shown to improve outcomes in trauma and postpartum hemorrhage, but evidence for its use in gastrointestinal bleeding is conflicting (2–6). There is also a discrepancy among clinical trials regarding the association or nonassociation of tranexamic acid with thromboembolic events, particularly venous thromboembolic disease (VTE). We sought to compare the incidence of both venous and arterial thromboembolic events between UGIB patients

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who received tranexamic acid with those who did not. We used a very large, multicenter, predominantly U.S. cohort to test the hypothesis that tranexamic acid recipients would have higher rates of both forms of thromboembolic events, even after accounting for any demographic and clinical dissimilarities between the two groups.

MATERIALS AND METHODS

We queried the TriNetX Analytics (Cambridge, MA) platform's Research Network, a federated database containing the deidentified, mixed electronic health record (EHR) and claims-derived data of over 110 million patients from 80 healthcare organizations in 5 countries, predominantly the United States, from which all 50 states are represented (7). We used the *International Classification of Diseases*, Tenth Revision, Clinical Modification diagnostic codes for hematemesis (K92.0) and melena (K92.1) to identify patients with first instances of UGIB between October 31, 2003, and October 31, 2023, and then derived a cohort that received tranexamic acid (as determined by Logical Observation Identifiers Names and Codes coding) within the week preceding or succeeding this diagnosis. We then derived a nontranexamic acid UGIB cohort that never received tranexamic acid at any time point. Subsequently, we obtained data on the comorbidities of each generated cohort, including demographic and medical antecedent data (namely, age at index, sex, race, preexisting hypertension, arrhythmia, heart failure, dyslipidemia, type 2 diabetes mellitus, cirrhosis, chronic obstructive pulmonary disease, acute and chronic kidney disease, coagulopathy, cancer, and tobacco and alcohol use disorders). We generated propensity score-matched (PSM) cohorts to account for any significant dissimilarities we observed between tranexamic acid recipients and nonrecipients using an in-platform 1:1 "greedy" nearest-neighbor matching algorithm with a caliper distance of 0.1 pooled SDs of the logit of the propensity score (such that patients with very different propensity scores were not matched). We then examined the incidence of a priori-established thromboembolic outcomes comprising cerebrovascular accident (CVA), myocardial infarction (MI), deep venous thrombosis (DVT), and pulmonary embolism (PE) at either up to 7 days from tranexamic acid coding (in the tranexamic acid-receiving cohort) or up to 7 days from UGIB diagnosis (among nonrecipients) in three sets of cohorts: the starting cohorts that met inclusion criteria, PSM-matched cohorts, and PSM-matched cohorts that excluded patients with any prior instance of the predetermined thromboembolic outcomes (i.e., examining only de novo outcomes). Using in-platform logistic regression, we then determined the association of tranexamic acid receipt circa UGIB diagnosis with all outcomes, through which odds ratios (ORs) with 95% CIs were derived. In accordance with our local institutional review board (IRB) determination, this study did not require IRB oversight (November 20, 2023).

RESULTS

Of the 113,796,889 patients in the database, 2,016,763 (1.8%) were diagnosed with UGIB in the study time period, with 1,965,474 of these (97.4%) patients located in the U.S. 9,644 (0.5%) of UGIB patients received tranexamic acid within 1 week of the date of diagnosis. 1,940,058 (96.2%) of UGIB patients never received tranexamic acid at any time point preceding or succeeding the index event, forming the nontranexamic acid starting cohort. Patient demographic and comorbidity data of tranexamic acid recipients and nonrecipients are summarized in **Table 1**. Patients who received tranexamic acid in the starting cohort had different demographic and comorbidity characteristics, having a higher prevalence of all preexisting comorbidities assessed. Following the use of PSM to generate like cohorts, significant differences between tranexamic acid-receiving and tranexamic acid-naive groups were negligible with a standardized mean difference below 0.1 among all matched covariates. Outcomes across all cohorts, including the starting cohorts, the post-PSM cohorts, and post-PSM de novo cohorts, are summarized in **Table 2**. Before PSM, the tranexamic acid cohort carried a significantly higher absolute risk difference (ARD) for all thromboembolic outcomes assessed (CVA, MI, DVT, and PE). This significance was retained across all four outcomes following the generation of PSM cohorts. These associations persisted in patients who had previously been diagnosed with any of the outcomes and were excluded from analysis.

Before PSM, the outcome ARDs between tranexamic acid recipients and nonrecipients ranged

TABLE 1.
Patient Characteristics

Variable (*International Classification of Diseases*, Tenth Revision, Clinical Modification)	Starting Cohorts		Propensity Score-Matched Cohorts	
	UGIB (+) Tranexamic Acid (*n* = 9,644)	UGIB (–) Tranexamic Acid (*n* = 1,940,058)	UGIB (+) Tranexamic Acid (*n* = 9,644)	UGIB (–) Tranexamic Acid (*n* = 9,644)
Age at index	56.1 ± 22.5	47.5 ± 24.2	56.1 ± 22.5	56.6 ± 22.4
Caucasian	57.7	68.3	57.7	55.9
Female	46.5	50.9	46.5	45.9
Hypertension (I10–I16)	48.9	35.6	48.9	50.5
Cancer (C00–D49)	32.2	25.0	32.2	32.9
Dyslipidemia (E78)	32.9	28.5	32.9	33.7
Acute kidney failure/chronic kidney disease (N17–N19)	31.7	17.2	31.7	32.0
Type 2 diabetes mellitus (E11)	26.7	17.5	26.7	27.0
Heart failure (I50)	19.9	8.9	19.9	19.9
Tobacco use (Z72.0)	13.5	8.2	13.5	13.4
Atrial fibrillation/flutter (I48)	14.5	7.7	14.5	14.9
Chronic obstructive pulmonary disease (J44)	10.8	7.5	10.8	11.2
Coagulopathy (D68.9)	13.2	2.9	13.2	12.4
Alcohol disorder (F10)	15.6	7.2	15.6	14.8
Cirrhosis (K74)	6.9	3.0	6.9	6.2

UGIB = upper gastrointestinal bleeding.
Categorical variable prevalence is represented by rounded percentages, whereas the continuous variable (age at index) is represented by mean ± SD. All standardized mean differences postpropensity score matching were below 0.1, indicating negligible differences between matched cohorts.

between 1.5% in the case of PE (OR 2.6; 95% CI, 2.3–3.0), through 2.0% each in the case of MI (OR 2.5; 95% CI, 2.2–2.8) and CVA (OR 2.4; 95% CI, 2.2–2.7), and 4.3% in DVT (OR 3.5; 95% CI, 3.2–3.8); all p values were less than 0.001. Following PSM, ARDs and their respective ORs were reduced across all outcomes and ranged from 1% in MI (OR 1.4; 95% CI, 1.2–1.7), through 1.1% in PE (OR 1.8; 95% CI, 1.5–2.3), 1.3% in CVA (OR 1.6; 95% CI, 1.3–1.9), and 3.1% in DVT (OR 2.1; 95% CI, 1.8–2.5); all p values were less than 0.001. After excluding patients from each outcome analysis who had ever received a diagnosis of that given outcome before the index event, ARDs and ORs were as follows: 0.4% in MI (OR 1.9; 95% CI, 1.3–2.7; $p = 0.001$), 0.5% in CVA (OR 2.4; 95% CI, 1.5–3.6; $p < 0.001$), 0.7% in PE (OR 4.0; 95% CI, 2.5–6.5; $p < 0.001$), and 1.6% in DVT (OR 2.8; 95% CI, 2.1–3.6).

DISCUSSION

We found a significant association between the administration of tranexamic acid in UGIB patients and the development of VTE, echoing the existing literature; however, we also identified a significant association between tranexamic acid use and arterial thromboembolic events. With our largely U.S. cohort of close to 10,000 tranexamic acid recipients with UGIB, which we compared initially to the overall UGIB dataset population but subsequently contrasted against a narrowed and similar PSM nontranexamic acid cohort, we found tranexamic acid was more strongly associated with VTE

TABLE 2.
Patient Outcomes

Outcome Variables	Tranexamic Acid	Nontranexamic Acid	Absolute Risk Difference (95% CI)	*p*	OR (95% CI)
Starting cohorts					
n	9,644	1,940,058			
CVA (%)	341 (3.5)	28,554 (1.5)	0.020 (0.017–0.024)	< 0.001	2.4 (2.2–2.7)
MI (%)	322 (3.3)	26,161 (1.3)	0.020 (0.016–0.023)	< 0.001	2.5 (2.2–2.8)
DVT (%)	589 (6.0)	34,766 (1.8)	0.043 (0.038–0.047)	< 0.001	3.5 (3.2–3.8)
PE (%)	243 (2.5)	18,567 (1.0)	0.015 (0.012–0.018)	< 0.001	2.6 (2.3–3.0)
Post-PSM cohorts					
n	9,644	9,644			
CVA (%)	340 (3.5)	219 (2.3)	0.013 (0.008–0.017)	< 0.001	1.6 (1.3–1.9)
MI (%)	322 (3.3)	225 (2.3)	0.010 (0.005–0.015)	< 0.001	1.4 (1.2–1.7)
DVT (%)	588 (6.1)	285 (3.0)	0.031 (0.026–0.037)	< 0.001	2.1 (1.8–2.5)
PE (%)	243 (2.5)	133 (1.4)	0.011 (0.008–0.015)	< 0.001	1.8 (1.5–2.3)
Post-PSM cohorts, de novo outcomes					
n[a]	9,644	9,644			
CVA (%)[a]	67 (0.9)	31 (0.4)	0.005 (0.003–0.007)	< 0.001	2.4 (1.5–3.6)
MI (%)[a]	76 (1.0)	44 (0.5)	0.004 (0.002–0.007)	0.001	1.9 (1.3–2.7)
DVT (%)[a]	193 (2.5)	77 (0.9)	0.016 (0.012–0.020)	< 0.001	2.8 (2.1–3.6)
PE (%)[a]	84 (1.0)	22 (0.2)	0.007 (0.005–0.010)	< 0.001	4.0 (2.5–6.5)

CVA = cerebrovascular accident (*International Classification of Diseases*, Tenth Revision, Clinical Modification code I63), DVT = deep venous thrombosis (I83), MI = myocardial infarction (I21), OR = odds ratio, PSM = propensity score-matched.
[a]In the third analysis, all patients who had experienced a particular outcome event at any time point preceding the index event (receipt of tranexamic acid or upper gastrointestinal bleeding diagnosis, depending on cohort) were excluded from the analysis, leaving only patients whose outcome diagnosis was their first ever diagnosis of this event (de novo). This was an additional analysis conducted after the second ("post-PSM cohorts"), which made no such exclusion.

than arterial events, with venous events ranging from twice to four times as likely in this group. Meanwhile, excess arterial events were less pronounced but still significantly greater in the tranexamic acid cohorts. Recently a large, international randomized controlled trial (the Hemorhage ALleviation with Tranexamic acid—Intestinal system [HALT-IT] trial) found that tranexamic acid was associated with an excess risk of VTE in patients with acute gastrointestinal bleeding, but did not see a statistical difference in arterial thrombotic events, which it defined as rates of CVA and MI (8). The weight of HALT-IT cannot be understated: in two systematic reviews and meta-analyses that included this trial, its approximately 6000 tranexamic acid recipients outnumber the combined weight of all other included trials (4, 6). Consequently, these meta-analyses found statistically significant excess rates of VTE, whereas three that did not include HALT-IT found no association between tranexamic acid and any form of thromboembolic event (2, 3, 5). However, rates of arterial thromboembolic events (CVA and MI) were very low across all study populations included in these meta-analyses, and no significant risk excess was observed. The burden of comorbidities in our cohort, which had a prevalence of cancer several times that of the HALT-IT trial, as well as of other disease states, may partially explain the disparity in arterial thromboembolic outcomes.

Our study faced several important limitations which should be taken into consideration in the

interpretation of these findings. We used retrospective, EHR-derived data in our analysis, and thus had no control over which patients were allocated to receive tranexamic acid and which were not. As such, we did not have access to the complete medical records of the cohort patients, including laboratory data that may be relevant (such as thromboelastographic parameters) or individual prothrombotic or antithrombotic medication regimens. Changes in patterns in the administration of tranexamic acid over time, its dosing, and formulation, were beyond the scope of our analysis. Neither were we able to make a granular assessment of acute illness severity (such as transfusion requirements) and could only generate parameters for analysis using standardized terminology and coding for diagnoses and observations with deidentified patient records. The latter limitation is in place due to applicable U.S. laws and regulations—it is only through the TriNetX database's adherence to these restrictions that we were able to derive a tranexamic acid cohort approximately 50% larger than that of the HALT-IT trial. This resulting sample size may have contributed to detecting a significant arterial thromboembolic event burden in addition to the already-described venous burden.

CONCLUSIONS

In this study, we leveraged data from a large, multi-institutional database and identified a correlation between the use of tranexamic acid and the occurrence of both venous and arterial thromboembolic events in individuals being managed for UGIB. This association persisted despite a rigorous process of propensity matching to generate like cohorts. These findings, aligning with prior research, emphasize a heightened incidence of DVT and PE, but also reveal a substantial association with CVA and MI, a relationship less documented in the literature. Although our study's scale and findings are noteworthy, the constraints inherent to the use of a federated database and retrospective analysis must be recognized. Our results underline the need for further prospective research to better characterize the thromboembolic risks of tranexamic acid use.

Tranexamic acid is not labeled by the Food and Drug Administration for use in gastrointestinal bleeding.

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