# Tranexamic acid in severe trauma patients managed in a mature trauma care system

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**BACKGROUND:** Tranexamic acid (TXA) use in severe trauma remains controversial notably because of concerns of the applicability of the CRASH-2 study findings in mature trauma systems. The aim of our study was to evaluate the outcomes of TXA administration in severely injured trauma patients managed in a mature trauma care system.

**METHODS:** We performed a retrospective study of data prospectively collected in the TraumaBase registry (a regional registry collecting the prehospital and hospital data of trauma patients admitted in six Level I trauma centers in Paris Area, France). In hospital mortality was compared between patients having received TXA or not in the early phase of resuscitation among those presenting an unstable hemodynamic state. Propensity score for TXA administration was calculated and results were adjusted for this score. Hemodynamic instability was defined by the need of packed red blood cells (pRBC) transfusion and/or vasopressor administration in the emergency room (ER).

**RESULTS:** Among patients meeting inclusion criteria (n = 1,476), the propensity score could be calculated in 797, and survival analysis could be achieved in 684 of 797. Four hundred seventy (59%) received TXA, and 327 (41%) did not. The overall hospital mortality rate was 25.7%. There was no effect of TXA use in the whole population but mortality was lowered by the use of TXA in patients requiring pRBC transfusion in the ER (hazard ratio, 0.3; 95% confidence interval, 0.3–0.6).

**CONCLUSION:** The use of TXA in the management of severely injured trauma patients, in a mature trauma care system, was not associated with reduction in the hospital mortality. An independent association with a better survival was found in a selected population of patients requiring pRBC transfusion in the ER. (*J Trauma Acute Care Surg.* 2018;84: S54–S62. 

**LEVEL OF EVIDENCE:** Therapeutic study, level III.

**KEY WORDS:** Tranexamic acid; multiple trauma; hemorrhage; trauma centers.

Trauma is the leading cause of death for people younger than 46 years.[1] One fourth of these deaths could be preventable,[1] with hemorrhage remaining the leading cause of these preventable deaths.[2] Tranexamic acid (TXA) is a synthetic lysine analog which can inhibit fibrinolysis by blocking the binding of plasminogen to fibrin, preventing localization of plasmin to degrade fibrin.[3] Its sparing effect on blood loss and blood products requirement has been thoroughly demonstrated in a wide range of medical and surgical settings.[4]

In the trauma setting, its use is mainly supported by the results of the CRASH-2 study, which has shown a survival benefit with its early empiric use.[5,6] The generalizability of these results to mature trauma systems has been challenged[7] since the majority of patients in CRASH-2 were treated in undeveloped trauma systems. Nevertheless, TXA has been widely adopted in trauma care, including in France. Since then, several studies have tried to assess the actual impact of the use TXA in mature trauma systems. Its use was associated with a deleterious effect in three US studies[8–10] and with a survival benefit in two European studies[11,12] and a Japanese one.[13] To bring further evidence to the debate, we evaluated the outcomes of TXA administration in severely injured trauma patients managed in the French trauma care system.

Our goal was to determine if an early empiric use of TXA for patients at risk of major bleeding could improve their outcome. Using a propensity score analysis performed on a prospectively acquired regional registry database, we tested the hypothesis that the empiric use of TXA reduced mortality in severely injured trauma patients who received clinical interventions associated with hemorrhage management (transfusion and vasopressor support).

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## MATERIALS AND METHODS

### Data Source

This retrospective observational cohort study was conducted from May 2011 to December 2015 in six French academic trauma centers that are staffed with a full range of specialists who are available 24 hours a day. These centers provide the highest level of care for trauma patients and correspond to the comprehensive service (i.e., Level I) described by the American College of Surgeons, and are the primary resources for critically injured adults in the "Ile de France" area, which includes the Paris metropolitan area, where 12 million people live. The TraumaBase is a regional registry collecting the prehospital and hospital data of trauma patients admitted to these six academic trauma centers. This registry was created in May 2011 and has received the approval of the Advisory Committee for the Treatment of Research Information in the field of Health (*Comité consultatif pour le traitement de l'information en matière de recherche dans le domaine de la santé*) and the National Commission on Informatics and Liberties (*Commission nationale de l'informatique et des libertés*: authorization 911461).

### Inclusion Criteria

Adult (>16 years of age) trauma patients admitted directly to one of the six trauma centers before December 31, 2015, were eligible for the analysis. Patients were included if they had (1) presented a major hemorrhage (defined by the need of four or more packed red blood cells [pRBC] in the first 6 hours following the trauma), or (2) received at least one pRBC in the emergency room (ER), or (3) received vasopressors either in the prehospital setting or in the ER. These inclusion criteria were chosen to be comparable to those of the CRASH-2 study (adult patients with hemorrhage, identified by systolic blood pressure <90 mm Hg and or heart rate >110 beats per minute, or thought to be at risk for hemorrhage), but were refined to select for a population that was likely to have experienced truly significant hemorrhage that led to clinical interventions centered on hemorrhage management (transfusion and vasopressor support). Early vasopressor support was included because its use is recommended in the French and European guidelines[14,15] and to reduce as much as possible the noninclusion of hemorrhaging patients since a recent French study in the same setting has shown that one fourth of trauma patients receiving more than four pRBC in the first 6 hours following hospital admission were not transfused in the ER.[16] The threshold of four pRBC in the first 6 hours used in our database to define major hemorrhage was based on the work of Stanworth et al.[17] who later validated its clinical relevance.[18] The inclusion criteria of the transfusion of at least one unit of RBCs in the ER was chosen because it has proved to be relevant in the PROPPR and PROMMTT studies[19,20] and to not miss the early deaths (ie: before having the opportunity to receive six pRBCs).

### Data Collection

Collected data were divided into five categories. "Epidemiologic items" included age, sex, body mass index, type of trauma, prehospital triage elements. "Prehospital items" included Glasgow Coma Scale (GCS) score, clinical neurologic impairment (prehospital presence of mydriasis), lowest arterial systolic and diastolic pressures, maximal heart rate, arterial systolic and diastolic pressures, and heart rate at prehospital team arrival, prehospital fluid replacement with either crystalloids or colloids, initial hemoglobin level, hemoglobin level at arrival in the ER, vasopressor requirement, lowest pulse oxygen saturation and initiation of prehospital invasive ventilation. "Arrival hospital items" included GCS, heart rate, systolic and diastolic arterial pressures, pulse oxygen saturation, temperature at admission, ultrasound and radiologic assessments, laboratory parameters (blood count, coagulation, and chemistry), transfusion requirements in the first 6 hours and 24 hours, vasopressor requirement, TXA administration. Tranexamic acid administration was defined as use in the prehospital setting or in the ER, meaning an early administration. "Outcome items" included mortality, time to death, intensive care unit-free days to day 28, total blood product requirements, hospital-free days to day 90. "Score items" included Simplified Acute Physiology Score II, Sepsis-related Organ Failure Assessment (24 hours), Injury Severity Score (ISS).

### Endpoints

Analysis was performed on the whole population and compared trauma patients having received TXA or not. Tranexamic acid administration was defined as use in the prehospital setting or in the ER, meaning an early administration. The primary endpoint was hospital mortality.

### Statistical Analysis

Data are presented as mean (SD) for continuous variables or median (first to third quartiles) and in number and percentage (n, %) for incidence rate. Continuous variables were compared using the unpaired *t* test or Wilcoxon test for non-normally distributed variables, and dichotomous data with the $\chi^2$ or Fisher's exact test.

Because data were previously acquired and TXA was not randomly used, it was necessary to estimate a propensity score to assess the probability of receiving TXA. The score was calculated for each patient, using a logistic regression with administration of TXA as dependent variable in regard of the following criteria: hospital of admission, mechanism of injury, age, sex, body weight, previous antiplatelet or anticoagulant treatment, time between accident and hospital, volume of crystalloid or colloid infused during the prehospital phase, prehospital vasopressor requirement, prehospital invasive ventilation, initial GCS, admission temperature, initial point-of-care hemoglobin level. Area under curve of the model was calculated (with its 95% confidence interval [CI]) to assess the postestimation of the model.

Mortality among the two groups was compared by survival analysis with the Cox model, with inverse probability of treatment weighting using the calculated propensity score. First, a univariate regression was applied to find all factors associated with death. Then, a multivariate regression (stepwise backward method) was applied to compare mortality in groups TXA and No TXA adjusted on all others factor associated with death in univariate analysis with $p < 0.25$. All one-level interactions were tested. When an interaction was identified a new term was created (product of the interacting variables). Then this term was included in the survival analysis. Cox model adequacy was evaluated graphically using Cox-Snell residuals.

Adjusted survival curves were developed using Kaplan-Meier method and compared by log rank test.

All tests were two-tailed and significance level was set at $p$ less than 0.05. Statistical analysis was performed using the Stata 12.0 software, (StataCorp LP, College Station, TX).

## RESULTS

A total of 6,994 patients were included in the Traumabase registry before December 31, 2015. Of these 6,994 patients, 1,476 (21%) met the inclusion criteria. After exclusion of patients with missing data, propensity score was calculated for 797 patients and survival analysis could be performed in 684 patients. The flowchart is displayed in Figure 1.

Patients were predominantly young men; their median age was 42 (19) years. Most of them suffered road accident (57%), whereas penetrating injuries accounted for less than 10% of the traumas (gunshot wounds and stab wounds represented 4% and 6% of the injuries). Patients presented with severe injuries; their median ISS was 29 (17–38). Forty-four percent of them received prehospital vasopressor infusion and 65% required prehospital invasive ventilation. Among the 797 patients for whom the propensity score could be calculated, 470 (59%) received TXA and 327 (41%) did not. Moreover, 389 (49%) patients did not receive any pRBC during their management. Most of these patients suffered a traumatic brain injury (TBI) with a GCS score less than 13 for 211 (54%) of 389 and less than 8 for 149 (38%) of 389 patients. Mechanical ventilation and sedation were used during the prehospital phase for 258 (66.3%) of 389 patients which explains the use of vasopressor to maintain a target blood pressure. Overall hospital mortality was assessed in 782 patients and death occurred in 201 (26%). Table 1 summarizes the baseline characteristics of these patients.

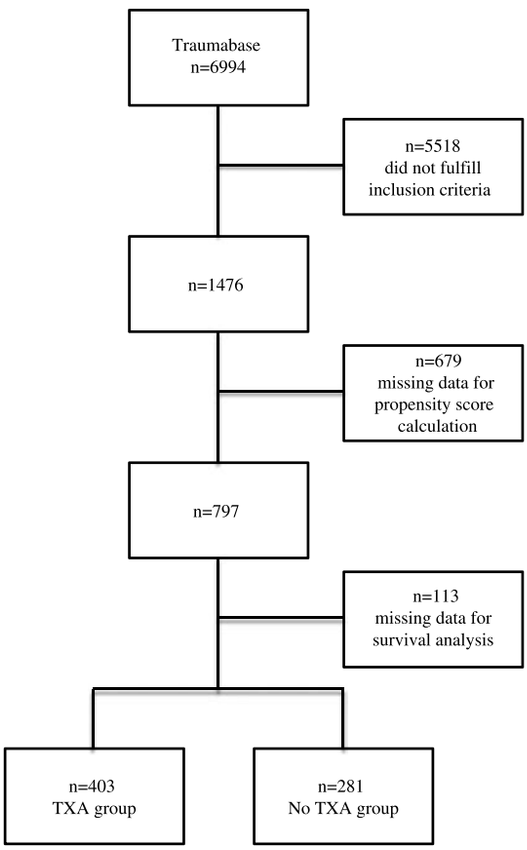


**Figure 1.** Flowchart diagram.

Tranexamic acid use differed by center, mechanisms, time between accident and hospital, initial point-of-care hemoglobin level and total volume (crystalloid and colloid) infused. After propensity score weighting, the TXA groups were well balanced in all the characteristics used for the propensity score calculation (Table 2). Area under curve of the model was 0.76 (95% CI, 0.73–0.79). Baseline characteristics (weighted by the inverse of the propensity score) of the population used for the survival analysis are displayed in supplemental Table 1 (see Table, Supplemental Digital Content 1, http://links.lww.com/TA/B98).

After univariate analysis weighted by inverse of the propensity score, TXA use was not associated with in-hospital mortality. Hazard ratios for in-hospital mortality, after univariate analysis adjusted for the propensity score are displayed in Table 3.

Multivariate regression identified the following predictive factors for in-hospital mortality (Fig. 2): age ≥ 60 years, anticoagulant or antiplatelet treatment, initial mydriasis, severe hypotension, hypoxemia (defined by a pulse oxygen saturation lower than 90%), severe hypothermia (≤34°C), thrombocytopenia less than 150,000/mm$^3$, prothrombin rate less than 50%, initial GCS score less than 8. An interaction was revealed between TXA and pRBC transfusion in the ER ($p < 0.001$), and a new term was created. This term was included in the survival analysis showing that the adjusted mortality rate in patients receiving pRBC in the ER was lower in patients receiving TXA (hazard ratio [HR], 0.3; 95% CI, 0.3–0.6), whereas it did not significantly differ in patients who did not receive pRBC transfusion in the ER (HR, 1.2; 95% CI, 0.8–2.6). The Kaplan Meier survival curves of patients without pRBC transfusion or with pRBC transfusion in the ER are displayed in Figure 3.

## DISCUSSION

The results of our study, conducted on a prospectively collected cohort of severely injured trauma patients managed in a mature trauma care system, showed no effect from use of TXA in the early management of trauma in a population at risk of bleeding. On the other hand, in our analysis, we retrieved an interaction between mortality, immediate pRBC transfusion, and TXA, suggesting that severely injured patients requiring immediate pRBC transfusion (in the ER) benefited from an early TXA administration, exhibiting better survival rates than the transfused patients who did not receive TXA. Moreover, for patients who did not require pRBC transfusion, the administration of TXA was not associated with a higher in-hospital mortality. We tested the robustness of our results, by a sensitivity analysis focused on various end points (see Table, Supplemental Digital Content 2, http://links.lww.com/TA/B99). The direction of our results did not vary according to the judgment criteria.

Our results are in accordance with those of the CRASH-2 study which had included patients in countries with variable standards of care.[5] This is significant because concerns have

**TABLE 1.** Baseline Characteristics of Patients with Propensity Score Calculation (n = 797)

| | N = 797 | |
|---|---|---|
| Age, y | 42 | (19) |
| <60 | 655 | (82.2%) |
| ≥60 | 142 | (17.2%) |
| Male | 583 | (73.1%) |
| Mechanisms of injury | | |
| Road accident | 458 | (57.5%) |
| Gunshot wound | 31 | (3.9%) |
| Stab wound | 48 | (6%) |
| Fall | 232 | (29.1%) |
| Other | 9 (5.7) | (3.5%) |
| Anticoagulant, antiplatelet drug | | |
| No | 736 | (92.3%) |
| Yes | 61 | (7.7%) |
| Prehospital catecholamine | | |
| No | 445 | (55.8%) |
| Yes | 352 | (44.2%) |
| Prehospital invasive ventilation | | |
| No | 281 | (35.3%) |
| Yes | 516 | (64.7%) |
| Time between accident and hospital, min | 50 | (25–54) |
| Initial GCS | | |
| <8 | 271 | (34%) |
| [8–12] | 117 | (14.7%) |
| >12 | 409 | (51.3%) |
| Prehospital i.v. fluids, mL | | |
| <750 | 192 | (24.1%) |
| [750–1,500] | 400 | (50.2%) |
| >1,500 | 205 | (25.7%) |
| Initial point of care hemoglobin level (n = 789), g/dL | | |
| <10 | 302 | (38.3%) |
| [10–13] | 347 | (44%) |
| ≥13 | 140 | (17.7%) |
| Temperature at admission, °C | 35.7 | (34.8–36.4) |
| ≤34 | 129 | (16.2%) |
| >34 | 668 | (83.8%) |
| ISS | | |
| <16 | 143 | (17.9%) |
| [16–30] | 322 | (40.4%) |
| >30 | 332 | (41.7%) |
| ICU length of stay (n = 789), d | 10 | (3–23) |
| pRBC transfusion in ER | | |
| No | 389 | (48.8%) |
| Yes | 408 | (51.1%) |
| Early TXA administration | | |
| No | 327 | (41%) |
| Yes | 470 | (59%) |
| Death (n = 782) | | |
| No | 581 | (74.3%) |
| Yes | 201 | (25.7%) |

Data are presented in mean (SD), median (first to third quartiles) or n (%). i.v.: intravenous; ICU, Intensive care unit.

been raised regarding the CRASH-2 randomization principle,[21] mostly focusing on the fact that the trial included patients in areas with a lack of modern trauma system, or a lack of laboratories to diagnose coagulopathy. Moreover, the small number of penetrating trauma included and the fact that only half of patients required blood product transfusion fueled the debate.[22] The Military Application of Tranexamic Acid in Trauma Emergency Resuscitation study assessed TXA use in wartime trauma patients.[22] Findings supported the possible extension of CRASH-2 results to a population of severe war casualties and suggested that the beneficial effect of TXA use was prominent in the patients with the most severe injury score but a recent analysis of the Joint Trauma System failed to find this reduction in mortality with the use of TXA in the war casualties.[23]

In the civilian setting, four retrospective studies of trauma patients regardless their coagulation status are available for consideration. The first is a small retrospective study comparing 150 trauma patients needing an emergency transfusion and/or surgery treated with TXA and 150 control patients matched using a propensity score. This study did not observe a mortality benefit in patients treated with TXA at physician discretion.[10] Surprisingly, the control group had a lower transfusion rate and a lower ISS, suggesting that the propensity score failed to thoroughly describe the severity of trauma. In addition, no multivariate analysis was performed.

The second study included 160 severely injured civilian trauma patients (ISS > 15) receiving TXA and 225 patients who did not. Despite higher severity scores in patients receiving TXA, no significant difference could be determined with regard to mortality (8% in each group). However, subgroup analysis demonstrated a reduction in mortality [odds ratio, 0.16 (0.03–0.86)] among patients with shock receiving TXA.[11]

The third study was an analysis of a German hospital trauma registry linked to a prehospital trauma registry allowing assessment of the impact of prehospital use of TXA in 5,765 patients documented in both databases. Among them, 258 had received TXA before ER arrival and could be matched through a propensity score with 258 patients having not received TXA. Tranexamic acid administration was associated with a lower early mortality (6, 12, and 24 hours after admission) but not with late mortality (30 days and in-hospital mortality).[12] The last study included 796 severely injured adult patients (>16 years old with an ISS > 15) in 15 hospital in Japan and, using a propensity matching score, concluded to a lower 28-day mortality with the use of TXA.[13]

Besides these studies on severe trauma patients regardless of their coagulation status assessed on laboratory tests, some authors have evaluated the impact of the use of TXA according to the fibrinolysis status assessed on thromboelastography. Harvin et al.,[8] on 1,032 severe trauma patients presenting with hyperfibrinolysis, found no impact of the TXA use on in-hospital survival rate. Furthermore, selecting severely adult trauma patients (NISS > 15), Moore et al.[9] analyzed the impact of the use of TXA according to the type of fibrinolysis measured on an early sample. Their results suggest the need for targeted use of this product due to a possible deleterious effect on patients with a "physiological" fibrinolysis profile.

All these studies were performed in mature trauma systems, but except for the study by Valle et al.,[10] none of the

**TABLE 2.** Baseline Characteristics of Patients Receiving or not TXA, Before and After Weighting by the Inverse of Propensity Score (N = 797)

| | Unweighted | | | Weighted | | |
|---|---|---|---|---|---|---|
| | TXA | No TXA | | TXA | No TXA | |
| | n = 470 | n = 327 | | n = 470 | n = 327 | |
| | (%) | (%) | *p* | (%) | (%) | *p* |
| Sex | | | 0.15 | | | 0.9 |
| Male | 71.3 | 75.8 | | 73.6 | 73.1 | |
| Female | 28.7 | 24.2 | | 26.4 | 26.9 | |
| Center | | | <0.0001 | | | 0.99 |
| a | 28.6 | 30.6 | | 34.1 | 35.8 | |
| b | 16.4 | 36.1 | | 25.9 | 26 | |
| c | 5.4 | 4.6 | | 4.6 | 4.2 | |
| d | 6.2 | 5.4 | | 3.9 | 3.5 | |
| e | 2.8 | 0.6 | | 1.6 | 1.1 | |
| f | 40.5 | 22.7 | | 30.0 | 29.3 | |
| Mechanisms | | | 0.002 | | | 0.98 |
| Road accident | 53.8 | 62.7 | | 57.1 | 57.1 | |
| Gunshot wound | 5.3 | 1.8 | | 3.9 | 4.5 | |
| Stab wound | 7.0 | 4.6 | | 5.9 | 5.4 | |
| Fall | 31.5 | 25.7 | | 28.5 | 29.1 | |
| Other | 2.3 | 5.2 | | 4.6 | 3.8 | |
| Prehospital catecholamine | | | 0.52 | | | 0.76 |
| No | 54.9 | 57.2 | | 55.0 | 56.1 | |
| Yes | 45.1 | 42.8 | | 45.0 | 43.8 | |
| Prehospital invasive ventilation | | | 0.52 | | | 0.65 |
| No | 36.2 | 33.9 | | 33.8 | 35.6 | |
| Yes | 63.8 | 66.1 | | 66.2 | 64.3 | |
| | Mean (SD) | Mean (SD) | *p* | Mean (SD) | Mean (SD) | *p* |
| Weight, kg | 74.9 (13.8) | 75.6 (14.8) | 0.47 | 74.8 (14.6) | 74.3 (19.1) | 0.68 |
| Time between accident and hospital, min | 82.1 (37.3) | 91.6 (40.7) | <0.001 | 86.0 (41.8) | 85.8 (42.5) | 0.95 |
| Total volume (crystalloid and colloid) infused, mL | 1,401.2 (806.9) | 1,117.0 (706.4) | <0.0001 | 1,288.2 (780.6) | 1,277.6 (980.9) | 0.87 |
| Initial point of care hemoglobin, g/dL | 12.4 (2.3) | 13.4 (2.0) | <0.00001 | 12.8 (2.3) | 12.8 (2.8) | 0.85 |

civilian studies were designed to select a population clearly suffering a life-threatening hemorrhage. For that reason, we chose inclusion criteria with the aim to include such patients but we also aimed to include patients at risk of major bleeding to assess the empiric use of TXA. Thus, the use of vasopressor support to identify patients at risk of major bleeding led us to include 389 (48.8%) of 797 patients who were not transfused in our population. This proportion is comparable to the one observed in CRASH-2.[5] Nonetheless, our population of interest involved severely injured trauma patients as assessed by the 82.9% of patients with an ISS greater than 15. This resulted in a mortality rate of 25.7%—higher than the 15.3% observed in CRASH-2 and consistent with the data in studies of bleeding patients (22% mortality in Military Application of Tranexamic Acid in Trauma Emergency Resuscitation, 21% in PROMMTT and 24% in PROPPR). Our results are also consistent with previous data showing a survival benefit with TXA use for the most severely bleeding patients. In our study, the beneficial effect of TXA was achieved for patients requiring pRBC transfusion in the ER, whereas survival of patients who did not require pRBC transfusion did not improve.

Our inclusion criteria led us to include patients with severe TBI requiring vasopressors to achieve an adequate cerebral perfusion pressure, and the majority of the nontransfused patients of our cohort were suffering from severe TBI. Overall, 156 (22.8%) patients presented with initial mydriasis and initial GCS score was lower than 8 in 229 (33.5%) patients. This proportion of patients is twice that observed in CRASH-2.[5] This issue of case mix is probably the cause of the strong interaction between the pRBC requirement in the ER and the effect of TXA on mortality. It suggests that the empiric use of TXA in severe trauma patients may be useful in case of hemorrhage and may not increase mortality in the absence of hemorrhage. This point is relevant in clinical practice, for patients presenting both hemorrhage and TBI for whom the beneficial effect of the TXA on hemorrhage would not be offset by an adverse effect on TBI. For instance, in the PROMMTT study which was selected for severely bleeding patients, TBI represented 38% of all causes of death.[19]

Our study has several limitations. First, the study design was not a randomized clinical trial and was based on a retrospective analysis of a prospectively collected database. This does not allow us to conclude a formal causal link. To minimize

**TABLE 3.** Risks Factors for Mortality; Univariate Analysis Weighted by the Inverse of the Propensity Score (N = 684)

| | Death | | | | |
|---|---|---|---|---|---|
| | Yes | No | | | |
| | N = 159 | N = 525 | Univariate Analysis | | |
| | (%) | (%) | HR* | 95% CI | *p* |
| Age, y | | | | | <0.001 |
| <60 | 108 (67.9) | 458 (87.2) | 1.0 | — | |
| ≥60 | 51 (32.1) | 67 (12.8) | 2.4 | 1.6–3.5 | |
| Anticoagulant, antiplatelet drug | | | | | 0.01 |
| No | 137 (86.2) | 500 (95.2) | 1.0 | — | |
| Yes | 22 (13.8) | 25 (4.8) | 1.9 | 1.1–3.2 | |
| Mydriasis | | | | | <0.001 |
| No | 71 (44.7) | 457 (87.0) | 1.0 | — | |
| Yes | 88 (55.3) | 68 (13.0) | 4.9 | 3.5–6.9 | |
| Prehospital systolic blood pressure, mm Hg | | | | | <0.001 |
| <70 | 72 (45.3) | 71 (13.5) | 3.4 | 2.2–5.4 | |
| 70–90 | 32 (20.1) | 162 (30.9) | 0.7 | 0.4–1.3 | |
| 90–110 | 26 (16.4) | 162 (30.9) | 0.7 | 0.4–1.2 | |
| ≥110 | 29 (18.2) | 130 (24.8) | 1.0 | — | |
| Prehospital i.v. Fluids, mL | | | | | 0.17 |
| <750 | 37 (23.3) | 126 (24.0) | 1.0 | — | |
| 750–1,500 | 75 (47.2) | 270 (51.4) | 0.9 | 0.6–1.4 | |
| >1,500 | 47 (29.6) | 129 (24.6) | 1.3 | 0.8–2.1 | |
| $SpO_2$ (%) | | | | | <0.001 |
| ≤90 | 27 (17.0) | 32 (6.1) | 3.0 | 1.8–5.0 | |
| >90 | 132 (83.0) | 493 (93.9) | 1.0 | — | |
| Temperature at admission, °C | | | | | <0.001 |
| ≤34 | 57 (35.8) | 48 (9.1) | 4.1 | 2.9–5.8 | |
| >34 | 102 (64.2) | 477 (90.9) | 1.0 | — | |
| Lactate at admission, mmol/L | | | | | <0.001 |
| <2.3 | 38 (23.9) | 187 (35.6) | 1.0 | — | |
| 2.3–4.5 | 45 (28.3) | 221 (42.1) | 0.8 | 0.5–1.3 | |
| ≥4.5 | 76 (47.8) | 117 (22.3) | 2.5 | 1.6–3.8 | |
| Hemoglobin at admission, g/dL | | | | | <0.001 |
| <10 | 85 (53.5) | 170 (32.4) | 1.6 | 1.0–2.6 | |
| 10–13 | 48 (30.2) | 257 (49.0) | 0.7 | 0.4–1.2 | |
| ≥13 | 26 (16.4) | 98 (18.7) | 1.0 | — | |
| Platelet count at admission, /$mm^3$ | | | | | <0.001 |
| <150,000 | 67 (42.1) | 95 (18.1) | 2.6 | 1.8–3.8 | |
| ≥150,000 | 92 (57.9) | 430 (81.9) | 1.0 | — | |
| Prothrombin ratio, % | | | | | <0.001 |
| <50 | 91 (57.2) | 112 (21.3) | 3.9 | 2.5–6.2 | |
| 50–70 | 42 (26.4) | 216 (41.1) | 1.2 | 0.7–2.1 | |
| ≥70 | 26 (16.4) | 197 (37.5) | 1.0 | — | |
| Fibrinogen at admission, g/L | | | | | <0.001 |
| <1 | 51 (32.1) | 40 (7.6) | 3.9 | 2.5–6.1 | |
| 1–2 | 61 (38.4) | 269 (51.2) | 1.0 | 0.6–1.5 | |
| ≥2 | 47 (29.6) | 216 (41.1) | 1.0 | — | |
| Major hemorrhage | | | | | 0.98 |
| Yes | 65 (40.9) | 231 (44.0) | 1.0 | 0.7–1.4 | |
| No | 94 (59.1) | 294 (56.0) | 1.0 | — | |

*Continued next page*

**TABLE 3.** *(Continued)*

| | Death | | | | |
|---|---|---|---|---|---|
| | Yes | No | | | |
| | N = 159 | N = 525 | Univariate Analysis | | |
| | (%) | (%) | HR* | 95% CI | *p* |
| Initial GCS | | | | | <0.001 |
| <8 | 116 (73.0) | 113 (21.5) | 6.0 | 3.7–9.7 | |
| 8–12 | 11 (6.9) | 90 (17.1) | 1.3 | 0.6–2.8 | |
| >12 | 32 (20.1) | 322 (61.3) | 1.0 | — | |
| ISS | | | | | <0.001 |
| <16 | 9 (5.7) | 108 (20.6) | 1.0 | — | |
| 16–30 | 45 (28.3) | 233 (44.4) | 1.7 | 0.7–4.0 | |
| >30 | 105 (66.0) | 184 (35.0) | 3.9 | 1.8–8.2 | |
| Without pRBC | | | | | 0.68 |
| TXA | 27 (36.0) | 98 (36.2) | 0.9 | 0.5–1.5 | |
| No TXA | 48 (64.0) | 173 (63.8) | 1.0 | — | |
| With pRBC | | | | | 0.37 |
| TXA | 67 (79.8) | 211 (83.1) | 0.8 | 0.4–1.4 | |
| No TXA | 17 (20.2) | 43 (16.9) | 1.0 | — | |

*HR—weighted by the inverse of the propensity score.

the impact biases inherent in an analysis of retrospective data, we conducted a survival analysis weighted on the inverse of a propensity score. Instead of using a matched score method, we retained an inverse of a propensity score calculation to maximize the sample size. Another limitation of our study that is common in database studies is that incomplete data led us to exclude more than a half of the patients who fulfilled the inclusion criteria. Despite that, our study remains the largest

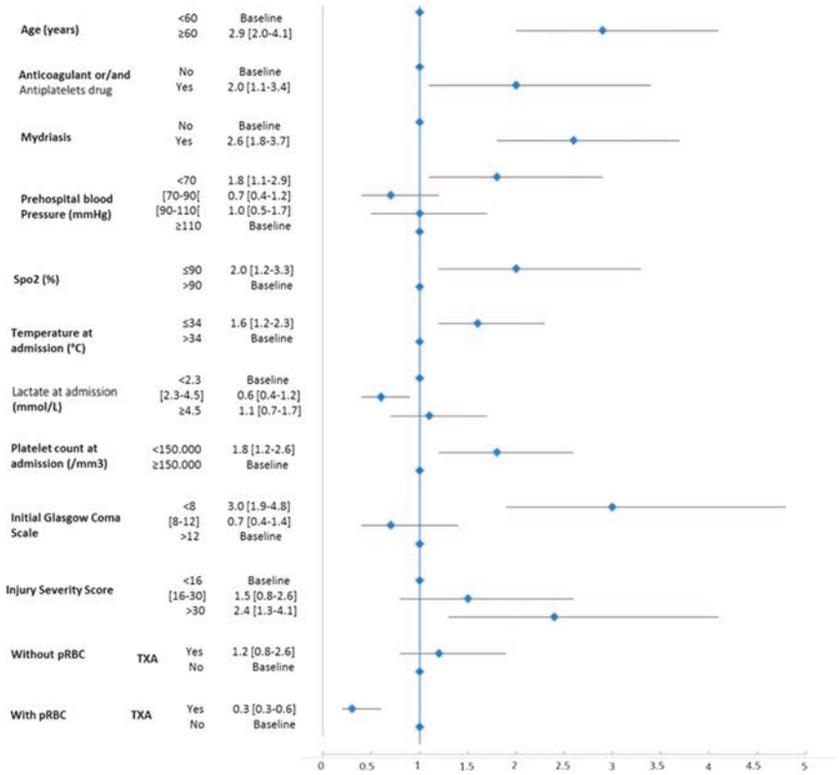


**Figure 2.** Risk factors for mortality; survival multivariate analysis weighted by the inverse of the propensity score (n = 684).

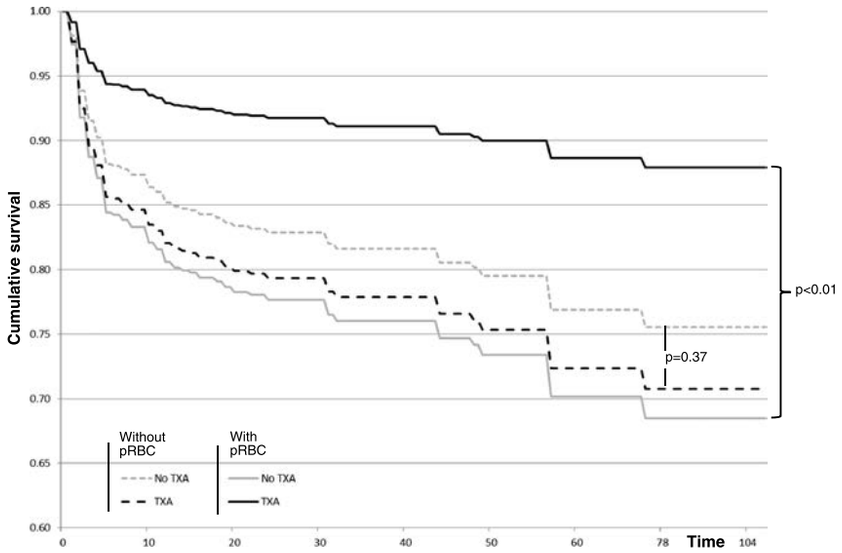


**Figure 3.** Kaplan-Meier survival curves of patients receiving or not pRBC in ER (Log rank test) (n = 684). Time is expressed in days.

retrospective study conducted on the use of TXA use in a mature civilian trauma care system and provides useful information for design of future clinical trials. Another limitation is due to the database architecture. Unfortunately, the Traumabase register did not allow us to evaluate the safety of TXA use in terms of major thromboembolic events. First of all, we were unable to assess the presence of contraindications to TXA use in patients who received (or did not receive) TXA. Moreover, the registry did not systematically include major thromboembolic event occurrence such as deep venous thrombosis or pulmonary embolism. Similarly, TXA dosage regimens were not recorded. We were only able to report the use of TXA in early management, in the prehospital setting or in the ER, without any more information about dosages and duration of administration. Knowing that the median time between injury and hospital admission was 50 minutes with an interquartile range of 25 minutes to 74 minutes and 20 minutes with an interquartile range of 15 minutes to 30 minutes for the time spent in the ER, we can only speculate that use of TXA was in accordance with the current guidelines.[15] The last limitation is that we cannot draw definitive conclusions concerning the safety of the use of TXA for the nonbleeding patients since we are not sure to not be underpowered. This issue is likely to be solved by the ongoing Clinical Randomisation of an Antifibrinolytic in Significant Head Injury study who plan to enroll 13,000 adults with TBI[24] and the Patch study who plan to enroll a thousand patients at risk for traumatic coagulopathy.[25]

## CONCLUSION

The use of TXA in the management of severely injured trauma patients, in a mature trauma care system, was not associated with reductions in the hospital mortality. An independent association with a better survival was found in a selected population of patients requiring pRBC transfusion in the ER. Our study was not able to demonstrate any association with mortality for patients who received TXA but not pRBC transfusion, but cannot exclude that such an effect may be retrieved with a larger cohort. Our study supports early use of TXA in selected patients requiring emergency transfusion, while empiric use had no overall benefit in reduction of mortality.

### AUTHORSHIP

M.B., P.A., F.S., A.H., A.F., N.I., J.T., and S.A. contributed to design the study and collect data. J.T. performed the statistical analysis. M.B., S.A., and A.C. wrote the draft of the article. All authors read and accepted the final version of the article.

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