BJA

British Journal of Anaesthesia, xxx (xxx): xxx (xxxx)

doi: 10.1016/j.bja.2022.03.032
Advance Access Publication Date: xxx
Clinical Investigation

CLINICAL INVESTIGATION

Use of tranexamic acid in major trauma: a sex-disaggregated analysis of the Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage (CRASH-2 and CRASH-3) trials and UK trauma registry (Trauma and Audit Research Network) data

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Abstract

Background: Women are less likely than men to receive some emergency treatments. This study examines whether the effect of tranexamic acid (TXA) on mortality in trauma patients varies by sex and whether the receipt of TXA by trauma patients varies by sex.

Methods: First, we conducted a sex-disaggregated analysis of data from the Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage (CRASH)-2 and CRASH-3 trials. We used interaction tests to determine whether the treatment effect varied by sex. Second, we examined data from the Trauma and Audit Research Network (TARN) to explore sex differences in the receipt of TXA. We used logistic regression models to estimate the odds ratio for receipt of TXA in females compared with males. Results are reported as *n* (%), risk ratios (RR), and odds ratios (OR) with 95% confidence intervals.

Results: Overall, 20 211 polytrauma patients (CRASH-2) and 12 737 patients with traumatic brain injuries (CRASH-3) were included in our analysis. TXA reduced the risk of death in females (RR=0.69 [0.52–0.91]) and in males (RR=0.80 [0.71–0.90]) with no significant heterogeneity by sex (P=0.34). We examined TARN data for 216 364 patients aged ≥16 yr with an Injury Severity Score ≥9 with 98 879 (46%) females and 117 485 (54%) males. TXA was received by 7198 (7.3% [7.1–7.4%]) of the females and 19 697 (16.8% [16.6–17.0%]) of the males (OR=0.39 [0.38–0.40]). The sex difference in the receipt of TXA increased with increasing age.

Conclusions: Administration of TXA to patients with bleeding trauma reduces mortality to a similar extent in women and men, but women are substantially less likely to be treated with TXA.

Keywords: haemorrhage; injuries; multiple trauma; tranexamic acid; transfusion; trauma

Editor's key points

- There is emerging evidence of inequalities in healthcare provision between men and women.
- This analysis of data from published trials and a national trauma registry suggests potentially important differences in the use of tranexamic acid between men and women which may affect patient outcomes.

Received: 11 January 2022; **Accepted:** 28 March 2022

- Further research is needed to explore sex-based inequalities in healthcare. Clinical trials of new treatments should be designed and reported to inform clinicians about this issue.

There are important differences in the health status of women and men.[1] These differences may be attributable to biological sex or to the social construct of gender. Owing to sex differences in physiology and in the pharmacokinetics and pharmacodynamics of drug treatments, there is the potential for sex differences in treatment effects.[2] Gender can also affect health status by influencing who receives treatment and the timing and type of treatment offered.[2] For example, women with chest pain are less likely than men to receive aspirin and defibrillation when it is indicated.[3] Analysis of data from the Resuscitation Outcomes Consortium registry found that 39% of women with out-of-hospital cardiac arrest received bystander cardiopulmonary resuscitation (CPR) compared with 45% of men, and men were 23% more likely to survive.[4]

Each year, worldwide, more than 4 million people die from injury.[5] Most injury deaths are from exsanguination or traumatic brain injury (TBI).[6] The Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage (CRASH-2; n=20 211 patients) and CRASH-3 (n=12 737 patients) trials showed that timely treatment with the antifibrinolytic drug tranexamic acid (TXA) reduces deaths on the day of the injury in polytrauma patients and in patients with isolated TBI by about 20%.[7–9] Although there are no strong biological reasons to expect sex differences in the effect of TXA in trauma patients, animal studies have raised the possibility of sex differences in the effect of plasmin on the blood–brain barrier.[10] To date, there have been no sex-disaggregated analyses of the data from the CRASH trials. In this pre-specified analysis, we report sex-disaggregated analyses of the CRASH-2 and CRASH-3 trials.

Tranexamic acid is the only drug proven to reduce deaths after traumatic injury; it is therefore important to examine whether there are sex or gender differences in the use of TXA. Women with trauma receive lower prioritisation than their male counterparts and are less likely to be taken to a major trauma centre.[11 12] In the second part of this pre-specified analysis, we examine sex differences in receipt of TXA by patients with major trauma in the UK, using data from the Trauma and Audit Research Network (TARN) registry.

Methods

Patient inclusion is summarised in Fig 1. Firstly, we conducted a sex-based subgroup analyses of data from the CRASH-2 and CRASH-3 randomised trials. We examined the data from both

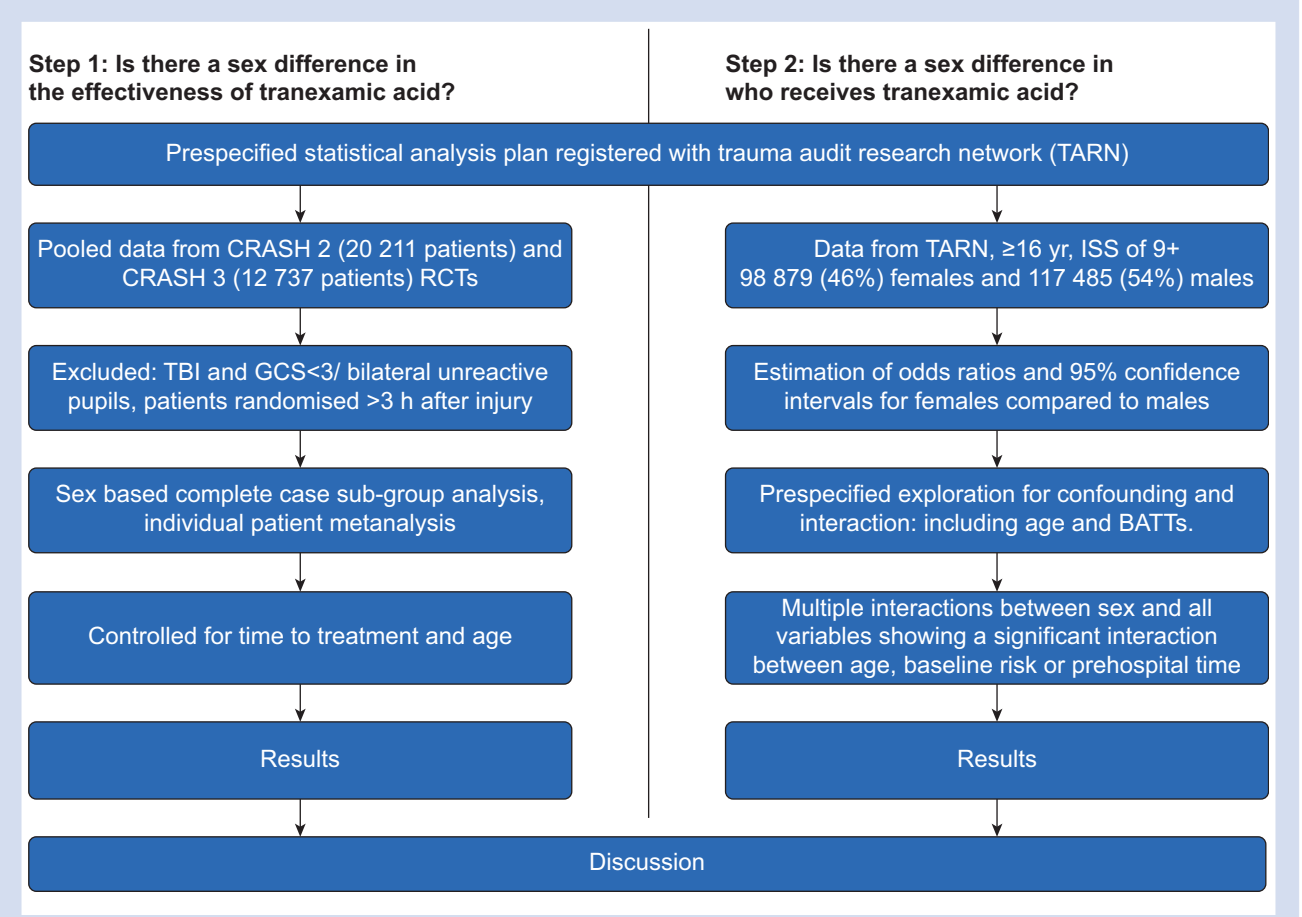

Fig 1. Explanation of Step 1 and Step 2 including data sources and planned analysis. BATT, Bleeding Audit for Trauma and Triage; CRASH, Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage; GCS, Glasgow Coma Scale; TBI, traumatic brain injury.

trials separately and also when combined in an individual patient data (IPD) meta-analysis. Patients in the CRASH-2 and CRASH-3 trials received the same dose of TXA and within the same time since injury (3 h). Combining the data from the CRASH-2 and CRASH-3 trials provides a large population of patients with major trauma. We examined the effect of TXA on death from any cause within 24 h of injury in patients treated within 3 h of injury stratified by sex. The CRASH-2 trial randomly allocated 20 211 trauma patients with, or at risk of significant bleeding within 8 h of injury to either TXA (loading dose of 1 g over 10 min than infusion of 1 g over 8 h) or placebo in 274 hospitals in 40 countries. The CRASH-3 trial randomly allocated 12 737 patients with TBI to either TXA or placebo in 175 hospitals in 29 countries. Eligible patients were adults with TBI with a Glasgow Coma Scale (GCS) score <13 or any intracranial bleeding on a CT scan. Patients with TBI who have a GCS score of 3 or bilateral unreactive pupils at baseline have a very poor prognosis regardless of treatment; these patients were excluded as pre-specified in the CRASH-3 trial statistical analysis plan. Patients randomised more than 3 h after injury in both trials were also excluded as the explanatory analysis of the CRASH-2 trial showed that TXA has no beneficial effect beyond this time.

The CRASH-2 and CRASH-3 trials reported in June 2010 and October 2019, respectively. We examined the receipt of TXA treatment by females and males with major trauma using data from the UK TARN registry for England and Wales from January 1, 2017 to December 31, 2020. The TARN registry includes patients of all ages who sustain injury resulting in hospital admission for longer than 3 days, critical care admission, transfer to a tertiary or specialist centre, or death within 30 days of hospital arrival. Isolated femoral neck or single pubic ramus fracture in patients >65 yr and simple isolated injuries are excluded. The TARN registry records patient sex but not gender. We selected injured patients aged ≥16 yr with an Injury Severity Score (ISS) of 9 or more. This population represents a major trauma population at risk of haemorrhagic death with at least one serious injury. As demonstrated previously, all these patients have the potential to benefit from TXA treatment.[13] In the TARN cohort analysis, sex was the exposure of interest and receipt of TXA treatment was the outcome. We pre-specified age, prehospital time (999 first call to hospital arrival), and baseline risk of death as a result of bleeding as potential confounders or effect modifiers. Baseline risk was estimated using a validated prognostic model and clinical score (Bleeding Audit and Triage Trauma Score [BATT] score) that predicts death caused by bleeding by assigning a composite score based on mechanism of injury, age, systolic blood pressure, GCS, ventilatory frequency, and heart rate.[14] This score was developed within an international trauma cohort including a trauma registry and a trial recruiting in 40 countries.[14] The BATT score was externally validated in the TARN registry.[15] The score includes variables used for initial assessment (vital signs, level of consciousness, mechanism of injury, and age) that are available at the scene of injury. Although the predominant injury mechanisms are different in women and men, we did not control for mechanism of injury as it is already included in the BATT score and this could lead to over-adjustment bias (Supplementary Appendix 1).

Statistical analyses

Data on death were available for 99.6% of the patients included in the CRASH-2 trial and 99.2% of the patients included in the CRASH-3 trial. Because missing data were minimal in the CRASH-2 and CRASH-3 trials, we conducted a complete-case analysis on intention-to-treat basis. As the first step of an IPD meta-analysis, we tested the homogeneity of the treatment effect by trial using interaction tests. Time to treatment and age could confound the effect of sex on treatment effectiveness, so we controlled for these variables. To control for possible confounding by the baseline risk of death within 24 h, we used a Poisson regression model with robust variance to estimate adjusted treatment effects by sex. We used interaction tests to see whether the effect of the treatment differs by sex. Because there was no biological reason to expect that the effect of TXA would vary by sex, we pre-specified that unless there was strong evidence against the null hypothesis of homogeneity of effects (i.e. $P<0.001$), the overall relative risk would be considered the most reliable guide to the approximate treatment effect in both females and males.

To examine sex differences in the receipt of TXA, we estimated odds ratios and 95% confidence intervals (95% CI) for TXA treatment in females compared with males. To explore potential confounding and interaction, we used logistic regression including the potential confounders detailed in our pre-specified statistical analysis plan. We estimated odds ratios for TXA treatment in females compared with males stratified by age (16–29, 30–49, 50–64, 65–74, 75–84, 85 yr and older) and baseline risk of death as a result of bleeding (BATT score low, intermediate, high, and very high risk). We tested the homogeneity of the association with sex across categories using a χ^2 test. We ran logistic regression models to explore potential interactions. We performed separate models to explore interaction individually before combining significant interactions in a final model. We explored interaction between pre-specified variables: sex and baseline risk (model 1); sex and age (model 2); sex and prehospital time (model 3); multiple interactions between sex and all variables showing a significant interaction between age, baseline risk, or prehospital time (model 4); and a model including any significant simple or multiple interactions (model 5). All equations are detailed in Supplement 1. For continuous variables, we assessed graphically the linearity of the relationship between TXA administration and potential confounders and interactions. We included quadratic and cubic terms in the regression equation for all continuous variables that showed a non-linear relationship. Logistic regression equations are shown in the Supplementary material. We plotted odds ratios for TXA treatment in females compared with males on significant interaction variables. We pre-specified that we would use the BATT score to predict the baseline risk of death as a result of bleeding for purposes of adjustment and for exploring effect modification. The BATT score has the advantage of including several of the main confounders in one variable and provides an accurate estimate of the risk of death from bleeding.

Although there are sex differences in injury mechanisms, we did not control for injury mechanism in our analysis as this would lead to over-adjustment bias. For people with the same risk of death from bleeding, mechanism of injury should not influence the receipt of TXA treatment. However, we did conduct analysis to explore the interaction between sex, mechanism of injury, and ISS. Apart from models with prehospital time and baseline risk from the TARN registry, we conducted complete case analyses. Missing values for prehospital physiological variables and prehospital time in the TARN data represent 20–31% of patients in the TARN registry. We reported missing values in the results and used multiple

imputation with chained equation to estimate missing values for prehospital systolic blood pressure, heart rate, GCS, ventilatory frequency, and prehospital time. We imputed five datasets of 77 394 patients. We assumed that values were missing at random. For models including prehospital time and baseline risk, we present analysis with imputed data because complete case analysis would have been biased toward the null.[16]

In the Supplementary material, we present analysis for interaction between sex and baseline risk for sensitivity analysis. All analyses were done in STATA (version 16.0; Stata Corp., College Station, TX, USA). The methods and analysis described above were pre-specified and registered with TARN before data acquisition.[17] In addition, we performed analysis stratified by mechanism of injury to explore possible gender bias. We also examined TXA treatment by severity of injury with the ISS available at hospital discharge. Details of these analysis can be found in the accompanying supplemental file. Patients and the public were involved in the design or delivery of the CRASH-2 and CRASH-3 trials, and we sought the opinions of the advocacy group GENDRO on our analysis plan.

Results

A total of 13 530 patients in CRASH-2 trial and 7694 patients in CRASH-3 trial fulfilled the inclusion criteria. Table 1 summarises the baseline characteristics of the CRASH-2 and CRASH-3 trial participants. The females (median age, 39 yr [26–55]) were older than the males (31 yr [24–45]). Females and males received TXA or placebo in the same proportion. There was no significant heterogeneity in the effect of TXA treatment by trial (P=0.76). Figure 2 shows the effect of TXA on death from any cause within 24 h of injury, stratified by sex. Eighty (4.3%) females in the TXA arm and 110 (6.2%) females in the placebo arm died within 24 h (risk ratio [RR]=0.69; 95% CI, 0.52–0.91). Four hundred and forty (5.2%) males in the TXA arm and 550 (6.5%) males in the placebo arm died within 24 h (RR=0.80; 95% CI, 0.71–0.90). In unadjusted analyses, TXA reduced the risk of death by 20–30% in females and males with no significant heterogeneity (heterogeneity P-value, P=0.34). The pooled RR adjusted for baseline risk of death from bleeding was similar in males (RR=0.75; 95% CI, 0.66–0.86) and females (RR=0.68; 95% CI, 0.51–0.91) with no significant heterogeneity (P=0.57).

Table 2 shows the characteristics of the TARN patients included in the analysis. Among the 216 364 injured patients, there were 98 879 (46%) females and 117 485 (54%) males. Females were less likely to have high-energy trauma such as road traffic injury or a high fall. Females (mean age, 73 yr) were older than males (mean age, 59 yr). Most injured patients (156 465, 72%) had low and intermediate baseline risk of death as a result of bleeding (BATT score from 2 to 7). On average, females had a lower risk of death as a result of bleeding than males (BATT score ≥8, n=2415 [2.4%] in females and n=5368 [4.5%] in males). The mean prehospital time was longer for females (126 min) than for males (106 min).

Tranexamic acid was received by 7198 (7.3%; 95% CI, 7.1–7.4%) of females and by 19 697 (16.8%; 16.6–17.0%) of males. The odds ratio for the receipt of TXA in females compared with males was 0.39 (95% CI, 0.38–0.40). Females were less likely than males to receive TXA in both the prehospital and hospital settings. The odds ratio for prehospital TXA treatment in females compared with males was 0.35 (95% CI, 0.33–0.36). Figure 3 shows the receipt of TXA in females compared with males by baseline risk of death caused by bleeding adjusted by prehospital time. Females were less likely to be treated with TXA in all risk categories. The disparity increased as the risk of death caused by bleeding decreased. Logistic regression modelling (model 1) found a highly significant interaction between sex

Table 1 Characteristics of CRASH-2 and CRASH-3 trials patients by sex. CRASH, Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage; IQR, inter-quartile range; SD, standard deviation.

	All (n=21 121)	Females (n=3737)	Males (n=17 485)	P-value
Age, mean (SD), yr	37 (16)	42 (19)	36 (15)	<0.01
Age, median [IQR], yr	32 [24–45]	39 [26–55]	31 [24–45]	<0.01
<25	5622 (27)	741 (20)	4881 (28)	<0.01
25–44	9630 (45)	1475 (39)	8153 (47)	
45–64	4228 (20)	936 (25)	3292 (19)	
≥65	1743 (8)	585 (16)	1158 (7)	
Unknown	1 (0)	0 (0)	1 (0)	
Systolic blood pressure, mean (SD)	107 (32)	108 (33)	107 (32)	0.136
<90 mm Hg, n (%)	4795 (23)	851 (23)	3944 (23)	0.251
Unknown	23 (0)	8 (0)	15 (0)	
Glasgow Coma Scale				
3–8	4154 (20)	617 (16)	3537 (20)	<0.01
9–12	4838 (23)	919 (25)	3918 (23)	
13–15	12 164 (57)	2175 (58)	9988 (57)	
Unknown	68 (0)	26 (1)	42 (0)	
Time since injury, n (%)				
0–1 h	8960 (42)	1464 (39)	7496 (43)	<0.01
2–3 h	12 262 (58)	2273 (61)	9989 (43)	
Unknown	0 (0)	0 (0)	0 (0)	
Tranexamic acid	10 710 (50)	1905 (51)	8804 (50)	0.786
CRASH-2	6801 (50)	1151 (52)	5650 (50)	0.245
CRASH-3	3909 (51)	751 (50)	3154 (51)	0.513
Placebo	10 514 (50)	1832 (49)	8681 (50)	0.786
CRASH-2	6729 (50)	1081 (48)	5647 (50)	0.245
CRASH-3	3785 (49)	754 (50)	3034 (49)	0.513

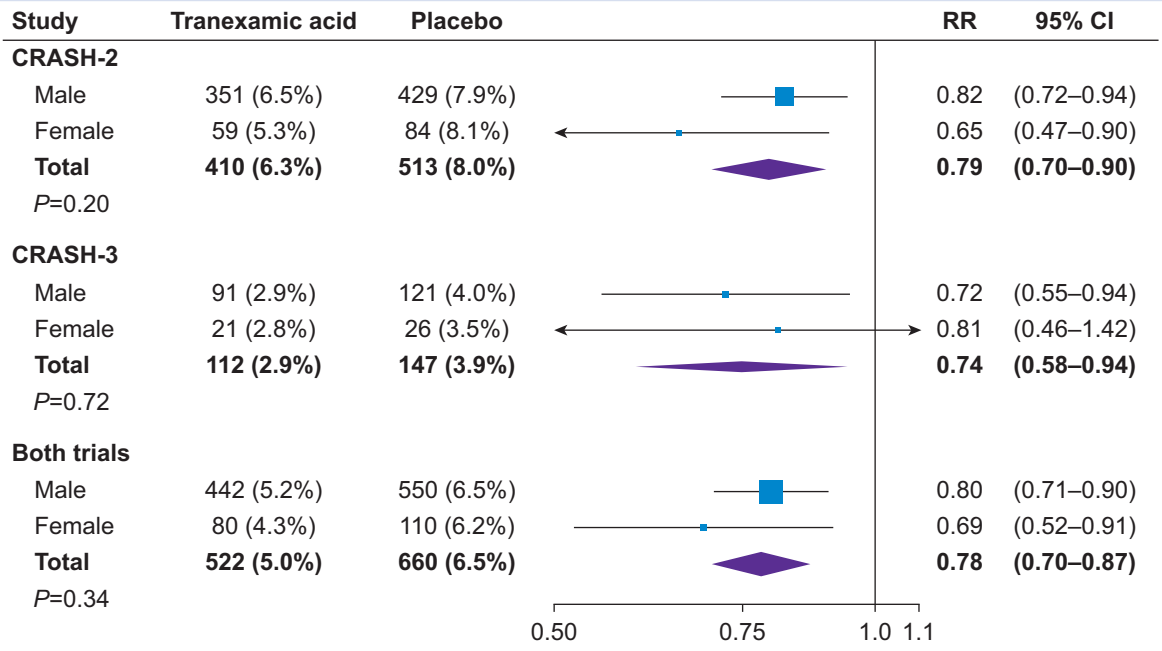

Fig 2. Forest plot demonstrating the effect of tranexamic acid treatment on relative risk (RR) of death from any cause within 24 h of injury, stratified by sex in the CRASH-2, CRASH-3 trials and both trials pooled. CRASH, Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage; CI, confidence interval.

Table 2 Characteristics of Trauma and Audit Research Network patients by sex. *Time from call to 999 to ambulance arrival. †Time from first call to 999 to arrival at hospital. AIS, Abbreviated Injury Scale; BATT, Bleeding Audit for Trauma and Triage; GCS, Glasgow Coma Scale; ISS, Injury Severity Score; SD, standard deviation.

	All (*n*=216 364)	Missing (%)	Females (*n*=98 879)	Males (*n*=117 485)	*P*-value
Age		0			
Mean age (SD), yr	65 (22)		73 (18)	59 (22)	<0.001
Mechanism of injury		0			
Traffic incident	38 585 (17.8)		9467 (9.6)	29 118 (24.8)	<0.001
Fall more than 2 m	21 380 (9.9)		7387 (7.5)	13 993 (11.9)	
Fall less than 2 m	137 991 (63.8)		78 995 (79.9)	58 996 (50.2)	
Shooting	467 (0.2)		21 (0.02)	446 (0.4)	
Stabbing	5017 (2.3)		475 (0.5)	4542 (3.9)	
Blows	8623 (4.0)		1389 (1.4)	7234 (6.2)	
Others	4301 (2.0)		1145 (1.2)	3156 (2.7)	
Penetrating injury	6002 (2.8)	0	673 (0.7)	5329 (4.5)	<0.001
Prehospital SBP <100 mm Hg	10 561 (6.7)	28	4115 (5.6)	6446 (7.9)	<0.001
Prehospital heart rate >100 beats min^{-1}	35 085 (22.0)	26	15 244 (20.2)	19 841 (23.5)	<0.001
Prehospital GCS		26			
GCS ≤8	10 752 (6.7)		3125 (4.2)	7627 (9.0)	<0.001
GCS 9–12	7016 (4.4)		2622 (3.5)	4394 (5.2)	
GCS ≥13	142 644 (88.9)		69 449 (92.4)	73 195 (85.9)	
Mean ISS (SD)	16 (9)	0	14 (8)	17 (9)	<0.001
ISS 9–15	118 769 (54.9)		62 102 (62.8)	56 667 (48.2)	<0.001
ISS 16–24	52 436 (24.2)		21 735 (22.0)	30 701 (26.1)	
ISS 25–34	37 333 (17.3)		12 905 (13.0)	24 428 (20.8)	
ISS ≥35	7816 (3.6)		2131 (2.2)	5685 (4.8)	
AIS head ≥3, *n* (%)	69 880 (32.3)		27 088 (27.4)	42 792 (36.4)	<0.001
BATT score (baseline risk)		36			
Very low risk (BATT 0–1)	31 181 (22.4)		15 160 (22.9)	16 021 (22.0)	<0.001
Low risk (BATT 2–4)	89 510 (64.4)		44 091 (66.6)	45 419 (62.4)	
Intermediate risk (BATT 5–7)	13 371 (9.6)		5348 (8.1)	8023 (11.0)	
High risk (BATT 8–11)	3830 (2.8)		1285 (1.9)	2545 (3.5)	
Very high risk (BATT ≥12)	1078 (0.8)		317 (0.5)	761 (1.1)	
Mean response time* (min)	40 (52)	31	46 (58)	33 (46)	<0.001
Mean prehospital time† (min)	115 (62)	29	126 (66)	106 (57)	<0.001

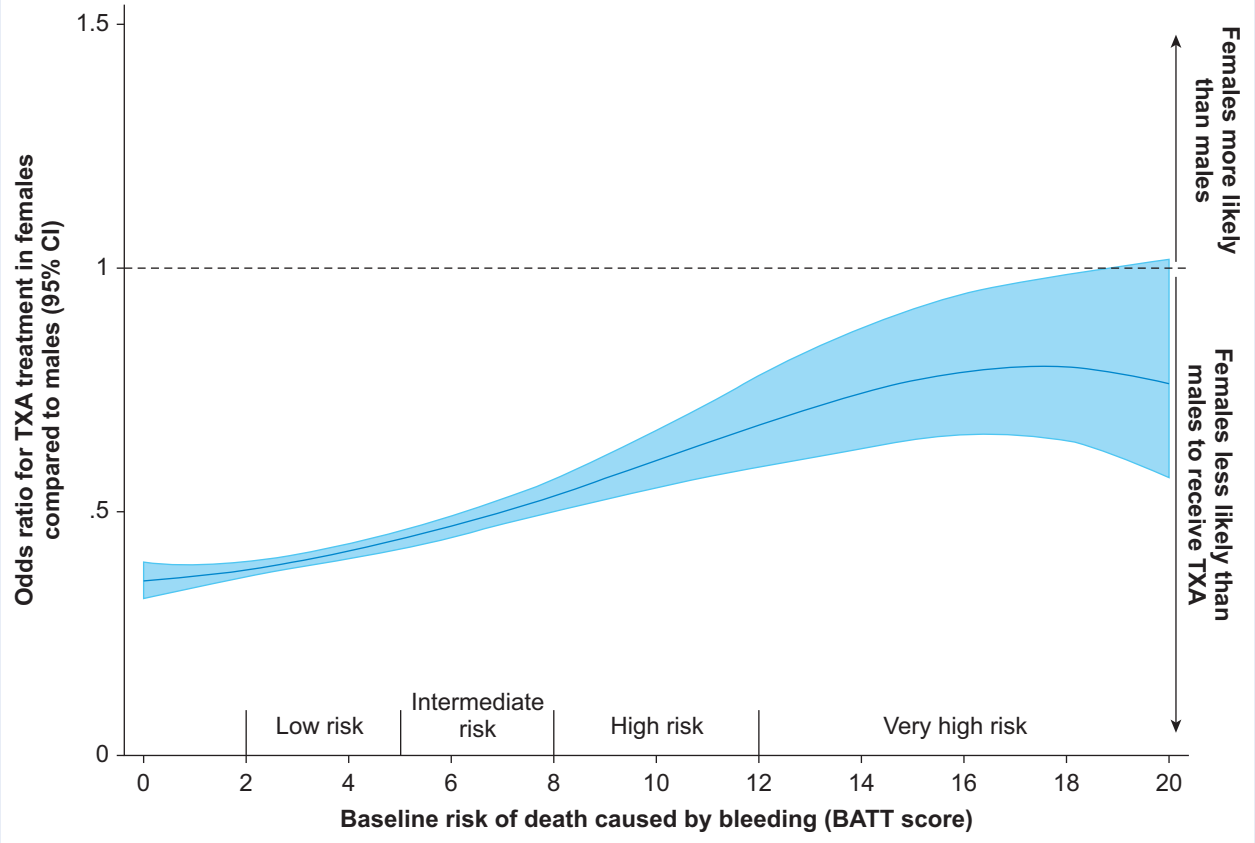

Fig 3. Receipt of tranexamic acid (TXA) treatment in females compared with males by baseline risk of death caused by bleeding adjusted by prehospital time. BATT, Bleeding Audit for Trauma and Triage.

and baseline risk of death caused by bleeding (P<0.001) (Supplement 2). The odds ratio for receipt of TXA in females compared with males was 0.56 (95% CI, 0.53–60) in patients at high baseline risk and 0.73 (95% CI, 0.63–0.83) in patients at very high baseline risk.

Additional figures are available in the Supplementary material. When we compared TXA treatment in females and males stratified by age, females were less likely than males to receive TXA in all age groups. There was a statistically significant interaction between sex and age (P<0.001, model 2 in Supplement 2). The sex difference in the receipt of TXA increased with increasing age. When we stratified receipt of TXA by ISS, females were less likely than males to receive TXA in all ISS categories. The sex difference in the receipt of TXA decreased as the severity of injury increased. The odds ratio for receipt TXA in females compared with males in ISS of 25 and above was 0.71 (95% CI, 0.64–0.79). There was no significant interaction between sex and prehospital time (model 3). There were no significant multiple interactions (model 4). The final model presents significant interaction between sex and baseline risk, sex and age, and adjusted on prehospital time (Supplement 2). All regression models are presented in the Supplementary file (Supplement 2). Additional analyses stratifying by mechanism of injury and ISS showed that females received TXA less often than males for all injury mechanisms except for motor vehicle crashes (Supplementary files 8 and 9).

Discussion

Tranexamic acid reduces trauma deaths to a similar extent in women and men, but women are less likely to be treated. Women are treated less frequently than men regardless of their risk of death from bleeding (BATT score) or the severity of their injuries. When women and men with the same mechanism of injury and ISS are compared, women are again treated less frequently than men. The survival benefit from TXA treatment does not vary by mechanism of injury or baseline risk of death caused by bleeding, but earlier treatment is substantially more effective.[13 18] The disparity in treatment between women and men was seen in all age groups but was greatest in older women and in women at lower risk.

Our analyses have important strengths. Sub-group analyses are often underpowered, but with more than 30 000 randomised participants the chances of missing a clinically relevant sex difference in the effect of TXA are reduced. The CRASH-2 and CRASH-3 trials were large trials with strengths and weakness as previously described.[7 8] They had good allocation concealment, rigorous blinding, and minimal loss to follow-up. The TARN registry is a well-designed inception cohort starting at the point of injury, collecting data until hospital discharge or death. We pre-specified that risk of death as a result of bleeding, age, and prehospital time were potential confounders or effect modifiers for TXA treatment, and we used regression methods to control for pre-specified confounders

and to examine interaction. Our prognostic model for death caused by bleeding was externally validated in this population and has good accuracy and discrimination. The strengths and weaknesses of the BATT score are discussed in the external validation study.[15] The TARN registry had missing values for prehospital physiological variables, for time of injury, and for receipt of TXA. For this reason, we imputed missing values, assuming that they were missing at random. Although imputation is superior to complete case analysis when variables are missing value at random, if not missing at random, our regression analysis might have been biased.[16] Owing to the large size of the TARN registry, our estimates are precise.

The possible limitations of our analysis are reliance on multiple imputation for missing TARN data, particularly for the time of ambulance and hospital arrival. Like all registry and database studies, we rely on accurate data capture and transcription. We rely on the BATT score to estimate the risk of death from bleeding. The BATT score was developed in an international cohort and was independent of the TARN registry. It was, however, validated using the TARN dataset in a separate study. Although the BATT score is a new prognostic score which is not currently used in routine clinical practice, the evidence on its accuracy is reassuring. Although the CRASH-3 trial was ongoing during the time window of our TARN data analysis, there was clear evidence from the CRASH-2 trial about the benefits of TXA in trauma patients, and so this would not have influenced the sex-based comparison in use.

Women are less likely to receive TXA in every stratum of risk of death as a result of bleeding. Although fall injuries are more common in women and road traffic injuries are more common in men, women and men with the same risk of death caused by bleeding have the same potential for benefit from treatment. We have previously shown that the mortality benefit from TXA treatment does not vary by mechanism of injury, and so sex differences in injury mechanism do not justify differences in TXA treatment.[18] Injured women are older than injured men, and the risk of death caused by bleeding increases with age.

Women were less likely than men to receive TXA treatment in every age category. Some of the sex disparity in TXA treatment may be attributable to the failure of clinicians to fully appreciate the impact of age on bleeding risk.[19] Although we have shown large sex differences in TXA treatment, we can only speculate about the causes of this disparity or why it is so large. Paramedics are responsible for acute prehospital assessment of trauma patients in the UK.[20] Paramedics rely on patient group directions (PGD) as the legal framework through which they administer TXA.[21] These PGD guide the use of TXA by providing legally binding inclusion and exclusion criteria for giving TXA.[22] Such PGD are often directed towards the treatment of severe haemorrhage and as such many trauma patients who do not meet the specific PGD criteria will not be treated. For example, the current PGD template recommends TXA use in trauma patients with signs of actual or suspected severe haemorrhage as demonstrated by a systolic blood pressure <90 mm Hg or absent radial pulse or a heart rate >110 beats min^{-1}. The focus on patients with signs of severe haemorrhage is inappropriate and excludes many patients with the potential to benefit from TXA. The CRASH-2 trial included trauma patients with, or at risk of, significant bleeding. This trial included thousands of patients with an SBP >90 mm Hg and a heart rate <110 beats min^{-1}. TXA safely reduced mortality in both severely and non-severely injured patients. As most trauma patients do not have hypotension and tachycardia at presentation, limiting TXA use to patients with signs of severe haemorrhage denies thousands of patients the potential to benefit from TXA, and it is likely that those excluded are disproportionately women. The explanation for the differences in other environments may include trauma stereotypes in medical education, differing presentations of trauma, and unconscious bias.

Gender disparities and inequalities in healthcare access, practice, and research are increasingly acknowledged but overall remain unaddressed.[23] Gender can impact on equitable health outcomes through its interaction with other determinants of health (such as social and economic factors), protective or harmful health behaviours, or the healthcare system's direct response to the gender of patients.[24] There are gender differences in the receipt of other emergency treatments. Women with chest pain are less likely to receive aspirin and nitroglycerine and are less likely to be conveyed to hospital by an ambulance using lights and sirens.[3] Women are less likely to be resuscitated for out of hospital cardiac arrest.[3 25] Injured women are less likely to receive opioid analgesia.[26] Women and older patients are less likely to be transferred to a major trauma centre and less likely to receive whole-body CT in the setting of major trauma.[27 28]

We have shown that administration of tranexamic acid to bleeding trauma patients reduced mortality to a similar extent in women and men, but women were substantially less likely to be treated. At the intersection of sex and older age, the disparities are particularly marked. Efforts to reduce the sex disparities in tranexamic acid treatment are needed. Interventions to reduce gender disparities in clinical practice are effective and as such should be applied here.[29] Standardising clinical practice through decision support tools (such as the BATT score) without reliance on the clinical gestalt may improve care.[15] In UK prehospital care, ensuring that PGD reflect the scope of delivery supported by the evidence base and enabling use of tranexamic acid outside of patient group directions through Schedule 16 and 17 classification may result in more equitable delivery.[21] Future research should examine why women less frequently received treatment and study the effectiveness of interventions to improve equity in trauma care.

Authors' contributions

Study concept and planning: TN, FA, IR, with contributions from LW, FL.
Statistical analysis: FA, AB.
Data visualisation: FA.
Writing of the original draft of the manuscript: IR, TN, FA.
All authors contributed to, reviewed and approved the final manuscript.

Funding

Open access publication charges were funded by the London School of Hygiene and Tropical Medicine.

Declarations of interest

None of the authors have any conflicts of interest to declare.

Acknowledgements

The team thanks TARN for its support, particularly Professor Fiona Lecky and the TARN Research committee for their

contributions and feedback. We are indebted to Shirin Heidari, founder of GENDRO (advancing sex and gender equity in research) for her valuable guidance and feedback. Our thanks go to the CTU team at the LSHTM for the provision of the CRASH-2 and CRASH-3 data for analysis.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2022.03.032.

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Handling editor: Rupert Pearse