Title Page

Nationwide analysis of pre-hospital tranexamic acid for trauma demonstrates systematic bias in adherence to treatment guidelines: a retrospective cohort study

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Abstract

Background

Prehospital (PH) tranexamic acid (TXA) improves survival from trauma haemorrhage. Injury mechanism, physiology and sex demographics vary with patient age. We hypothesised that these factors influence TXA guideline compliance and examined national trends in PH use to identify any systematic biases in bleeding management.

Materials & Methods

UK Trauma Audit & Research Network data for TXA eligible patients admitted to Major Trauma Centres were divided into cohorts: 2013-2015 (n=32,072) and 2017-2019 (n=14,974). Patients were stratified by PH, Emergency Department (ED) or no TXA use. Logistic regression models explored interaction between PH variables and TXA administration. Results are presented as Odds Ratios (OR) with 95% Confidence Intervals (CI).

Results

PH TXA use increased from eight percent to 27% over time ($p<0.001$). Only three percent of eligible patients who fell <2m received PH TXA vs. 63% with penetrating injuries ($p<0.001$). Older patients eligible for pre-hospital TXA were less likely to receive it compared to younger patients (≥65 years old: 590 [13%] vs <65 years old: 3361 [33%], $p<0.001$). There was significant interaction between age and sex with fewer older women receiving PH TXA. In shocked patients, one third of females compared to a fifth of men did not receive TXA ($p<0.001$). There was a decrease in pre-hospital TXA use as age increased ($p<0.001$)

Conclusions

Despite a three-fold increase in use, treatment guidance for PH TXA is not universally applied. Older people, women and patients with low energy injury mechanisms appear to be systematically under-treated. Training and education for pre-hospital providers should address these potential treatment biases.

250 words

Key words: Haemorrhage, injury, major trauma, older patient, pre-hospital TXA, sex.

Introduction:

Haemorrhage after major injury accounts for 40% of overall trauma mortality [1–3]. Patients with major bleeding die early with almost three quarters of bleeding trauma patients dying within the first six hours of injury, either pre-hospital or upon arrival at hospital [4]. Acute Traumatic Coagulopathy occurs within minutes after injury, exacerbates bleeding and is associated with worse clinical outcomes after major trauma [5,6]. Hyperfibrinolysis is a key component of post traumatic coagulopathy [5] and can be effectively treated with pharmacological interventions such as the antifibrinolytic drug, Tranexamic Acid (TXA) [7]. Currently TXA is the only medication available for the treatment of haemorrhage, that in clinical trials has been found to reduce mortality when administered in pre-hospital care [8,9] or in the early phase of in-hospital trauma resuscitation [10]. It is therefore considered a vital component of trauma care for bleeding patients in both civilian and military settings, and as such is included on the WHO list of essential medications [11]. However, recent reports have suggested even in mature trauma systems it is not universally provided to all patients at risk of haemorrhage [12,13].

A meta-analysis of the CRASH-2 & WOMAN trials of TXA for trauma and post-partum haemorrhage respectively, reported a 10% reduction in survival benefit for every 15-minute delay in treatment [14]. Similarly, in secondary analysis of the Study of Tranexamic Acid During Air Medical and Ground Prehospital Transport (STAAMP) trial, only when TXA was administered within one hour of injury, or to shocked patients, was there a reduction in 30-day mortality [9]. Following publication of the CRASH-2 trial in 2010 [10], the administration of pre-hospital TXA was approved in the UK by the Joint Royal Colleges Ambulance Liaison Committee (JRCALC) in 2012 [15] and similarly, the American College of Surgeon now endorse the pre-hospital administration of TXA [16]. However, many trauma patients fail to receive TXA early after injury, with an apparent sex disparity in use evident in both pre-hospital care and the Emergency Department (ED) from a recent study of the national trauma system of England and Wales [12]. Mechanism of injury and patient demographics change with increasing age [17] and decisions whether or not to administer TXA at scene may be consciously or unconsciously influenced by certain patient factors [18].

The pre-hospital phase of care is an opportunity to deliver time critical interventions for haemorrhage, but it is unknown which clinical factors (patient and injury) at scene influence clinician decision-making to administer TXA. Hence, it is important to characterize the missed opportunities

for a clinically effective pharmacological intervention, in order to target education and training programme for prehospital care providers. The overall objective of this study was to evaluate the real-world use of pre-hospital TXA across a national trauma system in patients who survive to reach hospital. Firstly, we wished to determine whether the introduction of national guidance led to an improvement in delivery of pre-hospital TXA, and assess any guideline implementation effect. Second, in a contemporary cohort we aimed to quantify the delays to administration and characterise the injury, demographic and physiologic phenotypes of patients who received (and did not receive) pre-hospital TXA in the context of national treatment guidelines. Finally, we specifically examined the patient subgroups most likely to derive benefit from early TXA treatment (e.g. evidence of active haemorrhage and requiring blood transfusion) to determine any clinical characteristics or patient cohorts which have lower rates of pre-hospital TXA administration. We hypothesized that it is possible to identify patients who fail to receive pre-hospital TXA using demographic or clinical parameters available at scene, which may offer a potential opportunity to target improvements in the pre-hospital care of bleeding trauma patients.

Materials & Methods:

We retrospectively analysed data from the UK Trauma Audit and Research Network (TARN) submitted by all 27 Major Trauma Centres in England & Wales over seven years, between January 2013 and December 2019.

Study population:

TARN submissions are mandatory for all major trauma centres in England and Wales with data quality assured and validated against Hospital Episode Statistic data. It collects data on trauma patients admitted for three or more days to hospital or require critical care admission. Deaths at scene are excluded from the registry as are single system frailty fractures. TXA was introduced for pre-hospital administration by paramedics in 2012 after approval by JRCALC. Indications for TXA administration in trauma patients are: suspected or active blood loss, administration blood component transfusion and/or presence of any sign of shock (Systolic Blood Pressure (SBP) ≤90mmHg or Heart Rate (HR) ≥110 b/m). UK Best Practice Tariff incentivizes clinicians to administer TXA within one hour from injury [19] with compliance monitored via TARN. Dosing guidance was standardised according to the CRASH-2 trial protocol [10] with a 1g intravenous bolus administered

followed by a 1g intravenous infusion (in-hospital). For the purpose of this study, all patients eligible for TXA administration were defined using the following TARN criteria: haemorrhage control operation (Supplemental Table 1) and/or blood component transfusion within 24 hours of injury. Location of TXA use (pre-hospital care or within the Emergency Department) was recorded by administering clinicians. Paediatric patients (<16 years), pregnant women, and patients who were transferred to a Major Trauma Centre from another hospital or suffered burns on more than five percent of the total body surface area were excluded. Regarding Ethics approval, TARN has Health Research Authority approval (Patient Information Advisory Group, Section 251) for research on the anonymized data it holds from NHS Trusts. The study was reported following the STROCSS guidelines [20].

Data collection:

All data was provided by TARN and included demographics, injury patterns, vital parameters (pre-hospital and ED), time intervals (time to TXA and time to arrival), mode of arrival, TXA administration and location. Outcomes included red blood cell (RBC) administration within 24 hours, mortality at 24 hours and at 28-days. Patients were divided into two study time periods (2013-15 vs 2017-19), to examine the early vs. late phases of JRCALC pre-hospital TXA guidance implementation. In each time period, patients were categorized into administration groups: pre-hospital (PH) TXA, ED TXA, and No TXA. Sub-group analysis for patients most likely to benefit from TXA e.g. shocked and/or received one or more units of RBCs transfusion was pre-defined.

Statistical analysis:

Data analysis was performed using IBM SPSS v25 and Graph Pad Prism v8. According to Kolmogorov–Smirnov tests continuous data was non-parametric and therefore compared with Mann-Whitney U tests and reported as median and inter-quartile range (IQR). Categorical variables were compared using Chi-squared tests and reported as frequencies and percentages. Chi-squared for trend tests were reported when comparing the negative trend of PH TXA among age and shock categories. Shock was defined as pre-hospital systolic blood pressure (SBP) ≤90mmHg and/or pre-hospital heart rate (HR) ≥110 /min prior to any interventions.

To explore the relationship between age, sex and pre-hospital TXA use, the odds for PH TXA administration in male and female subgroups were calculated. The Odds Ratio (OR) between sexes

was derived for ages covering the full range of the cohort (20, 40, 60, 80 and 100 years; supplemental Table 2). A p value <0.05 was considered statistically significant.

Multivariable logistic regression analysis was conducted to examine the association between PH TXA administration and clinically relevant variables available at within pre-hospital care: patient age and sex, mechanism of injury, PH SBP, PH Glasgow coma score (GCS) and PH clinician (air ambulance doctor or land ambulance paramedic). Variables with a p value <0.10 in univariate analysis were entered into the final multivariable models. Model fit was assessed using Hosmer Lemeshow test. Results are presented as OR with 95% Confidence Intervals (CI).

Results:

Overall, 51,310 TARN patients who were eligible for TXA were included in the study. These were subdivided into two equal time periods to quantify the TXA guideline implementation effect following changes to treatment guidelines: January 2013 to December 2015 (n=32,072) and January 2017 to December 2019 (n=14,974). There was a threefold increase in PH TXA administration during the study period from eight percent (2013-15) to 27% (2017-19), (p<0.001). Across the time periods, PH TXA use was more likely to be in younger, male patients (Table 1). In both study periods, less than five percent of patients who sustained falls <2m received PH TXA, whereas administration in penetrating injuries rates rose from 14% to 26% (Table 1). Pre-hospital times and injury severity were broadly similar between the early and later cohorts (Table 1), although the proportion of shocked patients decreased from 55% to 45% (p<0.001). Time from injury to TXA administration reduced from 51 (35 – 70) minutes in 2013-15 to 43 (31 – 61) minutes in 2017-19, (p<0.001).

To examine contemporary practice, we focused the investigation on the more recent cohort (2017 – 2019) to identify individual factors associated with TXA administration. The use of pre-hospital TXA varied according to the mechanism of injury, with sex differences observed in penetrating trauma (male: 921 [29%] vs. female: 102 [12%], p<0.001) and a similar trend in falls <2m (male: 84 [3%]; female: 63 [7%]) p=0.083 (Figure 1A). TXA treatment was associated with high energy mechanisms, and almost three quarters of patients with penetrating injury received TXA, with 63% administered in pre-hospital care (Figure 1B). However only three percent of patients who fell <2m and were eligible for TXA received it in pre-hospital care, and of these only 17% of patients received TXA at any time point (Figure 1B). When examining the effect of sex on mechanism of injury, more females

received pre-hospital TXA after penetrating trauma or road traffic collisions compared to men (Figure 1C). In contrast, females were less likely to receive it if they had sustained injury by any other mechanism.

Older patients eligible for pre-hospital TXA were less likely to receive it compared to younger patients (≥65 years old: 590 [13%] vs <65 years old: 3361 [33%], p<0.001) (Figure 1D). In both male and female patients, pre-hospital TXA treatment was significantly lower with advancing age, but more pronounced in older females (Figure 1E). In patients aged 45 years or more who were eligible for TXA, between 15 to 40% fewer women received pre-hospital TXA compared to men (Figure 1E), and by 80 years of age, females were half as likely to receive it (OR: 0.524, [95% CI 0.305-0.899]) (Figure 1E). Patients with severe (AIS 3+) limb or head injury had the lowest proportion of pre-hospital TXA administration, 28% and 31% respectively (Figure 1F) and less than 50% of patients with these injuries received TXA in any setting. In multivariable analysis, sex was not associated with pre-hospital TXA use (OR 1.168 [95% CI: 0.980 – 1.393] p=0.08) whereas younger age and low pre-hospital SBP were strongly predictive of TXA administration (Age OR 0.981 [95% CI: 0.978 – 0.984], p<0.001; SBP: OR 0.992 [95% CI: 0.990 – 0.994], p<0.001) (Table 2).

Shocked patients were twice as likely to receive pre-hospital TXA than non-shocked patients (54% vs 24%, p<0.001) (Table 3). In the shocked cohort, one third of females compared to a fifth of men did not receive TXA (p<0.001, Figure 2A). Only 11% of patients who were shocked after a fall of less than 2 metres received PH TXA, whereas this rose to 65% in penetrating injury with shock (p <0.001, Figure 2B). There was a step-wise decrease in pre-hospital TXA use as age increased (p<0.001, Figure 2C) and this trend persisted in older patients with clinical evidence of major haemorrhage and the need for a blood transfusion (p<0.001, Figure 2D).

Overall time to TXA dosing reduced after implementation of the treatment guidelines but only 49% of patients eligible for TXA received it within one hour of injury (Table 1). Time from injury to TXA dosing was faster in shocked patients (51 [34 – 89] minutes) compared to the non-shocked (72 [42 – 133] minutes), p<0.001. Three-quarters of shocked patients received the drug in pre-hospital care (Table 3, Supplemental Figure 1A and 1B). Time of TXA dosing in pre-hospital care or the ED was fastest for shocked patients with penetrating injuries whereas patients with shock following a fall <2m experienced the longest delays to treatment (Supplemental Figure 1C and 1D). Time to pre-

hospital TXA treatment for shocked patients who had fallen <2m was on average 59 minutes compared to 45 minutes for other blunt mechanisms of injury (p<0.001) (Supplemental Figure 1C). Similarly, TXA administration in the ED was one and half times longer for low level falls for patients with shock compared to other blunt injuries (212 minutes vs. 125 minutes, p <0.001) (Supplemental Figure 1D).

Discussion:

In this longitudinal study of all major trauma patients admitted to hospital, within a national trauma system, we examined the clinical characteristics and patient physiology associated with the pre-hospital use of TXA following implementation of trauma haemorrhage treatment guidelines. Overall, pre-hospital TXA treatment increased threefold from the period after publication of the CRASH-2 trial and adoption of TXA into UK ambulance service protocols and National Institute for Health and Care Excellence (NICE) guidelines [10,21–23]. In England and Wales between 2017 and 2019 we found only half of TXA eligible patients (according to TARN criteria) were treated, of which 60% was given in pre-hospital and less than half were dosed within one hour of injury. Pre-hospital TXA use was independently associated with younger patients, penetrating injury, shock, low GCS and the presence of a HEMS team on scene. Whilst we confirmed similar sex inequities in TXA use, with elderly women far less likely to receive TXA in prehospital care [12], we further identified gross treatment disparities in other patient groups. TXA treatment was significantly less common in older patients, those who had sustained low energy falls or patients without clinical evidence of haemorrhagic shock. Real world practice has identified a large cohort of patients that would benefit from early (pre-hospital) TXA administration, whom currently do not receive it despite national guidelines for haemorrhage management [15,21], and should be the focus of education programmes to improve treatment compliance and patient outcomes.

Identification of bleeding in older patients with injury is confounded by an altered physiological response to blood loss [24] and polypharmacy [25]. More recently we have shown the coagulation response to injury of older patients differs to younger patients [26], and may in part explain the increased incidence of major haemorrhage previously reported in this subgroup [27]. A recent systematic review argues that older major trauma patients are at risk of under triage in pre-hospital care and Major Trauma Centres, which may result in less intervention and active management [28]. Our study provides further evidence to support this observation in older patients, and/or those who

have fallen less than 2 metres, who are far less likely to receive TXA despite clinical evidence of shock. Moreover, we show the pre-hospital TXA treatment is not only dependent on age, but that with increasing age women are less likely than men to receive it. This supports the finding of Nutbeam et al., confirming the presence of a sex bias in the treatment of patients in prehospital care despite clinical evidence of shock [12], with the use of TXA unequally distributed amongst patients based on sex, mechanism of injury and age. Importantly the missed therapeutic opportunity, and care inequity, persisted throughout ED admission with many patients in these subgroups failing to receive TXA at any time point.

Major haemorrhage guidelines for pre-hospital care, NICE guidelines for hospital practice and TARN criteria for recording eligibility for TXA are all biased towards the more extreme clinical signs of bleeding, e.g. cardiovascular shock, and/or receipt of a blood transfusion being the key indicators for administration. There is however evidence that a more liberal use of TXA for any trauma patient at risk of bleeding confers survival advantage [29]. This study highlights a clear gap between the real world use of TXA and existing TXA guidelines for managing trauma haemorrhage of any severity. The Bleeding Audit Triage Trauma [30,31] is a validated score for predicting death from bleeding, and a published Bayesian model for predicting TIC [32,33], blood transfusion and mortality, are two examples of simplified decision support tools. Both are suitable for use by PH care practitioners, which if rolled out widely, in conjunction with focused education on patient groups at risk of under-treatment, have the potential to improve compliance of early TXA administration to injured patients at risk of bleeding. Specifically, the Bleeding Audit Triage Tool has an age component which if applied at scene may increase treatment in older patients. Generally, paramedics and trauma teams in ED need greater awareness and training around patient groups we have identified in this study that are far less likely to receive TXA. There is an unexplained clinical bias to selectively administer TXA to younger patients, injured males, and/or those with more violent or higher energy mechanisms of injury and should be urgently addressed to ensure equity of care. Further work should examine decision-making and clinician behaviours around administration of TXA, or the unconscious decision to withhold life-saving treatment for bleeding in trauma.

The study has a number of limitations. First, not all ambulances or fast response vehicles that arrive on scene have a paramedic e.g. technician only crews and therefore are unable to administer TXA. The TARN dataset does not provide this level of information and is a likely confounder in the rate of pre-hospital TXA use for patients with low energy mechanisms e.g. falls <2m who more likely to

receive a lower triage category to which non-paramedic crews will be dispatched. Any confounding however cannot explain the similar trends observed in ED TXA use. Second, we are unable to determine from the retrospective dataset the decision-making process, or rationale of paramedics and physicians at the ED trauma call. In particular, we cannot say *why* practitioners deviated from national guidelines for the treatment of major haemorrhage with TXA, or *why* it was selectively applied to particular patient cohorts. Behavioural studies of clinicians are required to further examine and understand subjective decision making of PH care providers and how these are influenced by patient and injury factors. Relevant contraindications to TXA use in trauma are thromboembolic disease and a history of convulsions, neither of which are easily discernible during the clinical examination or patient history, and therefore we consider the risk of bias from an active clinical choice to withhold treatment based on these factors to be low. TARN does now collect information on patient comorbidities but these were not available in our dataset and medication history is not reported therefore we are unable to determine the impact of these factors on the treatment compliance. Third, similarly from the dataset it was possible to understand the impact of dynamic physiology on treatment decisions as TARN only collects the first set of prehospital observations. If the first set of vital signs are not complete or not available, then ED observations are permissible which may not represent the clinical status during which decisions to administer pre-hospital TXA were made by the clinician. Fourth, TARN recording of TXA administration does not describe which prehospital provider administered the medication e.g. first paramedic on scene or a prehospital doctor, only that a HEMS service was present. Fifth, national guidance for TXA dosing was to follow the CRASH-2 trial protocol (1g bolus then 1g infusion) but we were unable to explore different doses that may have been given, intentionally or in error, within the context of this study due to the available data. Sixth, TARN excludes prehospital deaths and at present there is no national repository of medical records for this patient cohort who die before reaching hospital. Seventh, we were not able to look at clinical outcomes as TARN does not capture all deaths in patients who may have received TXA e.g. pre-hospital deaths and other important outcomes e.g. venous thromboembolism are not mandatory fields for reporting. Finally, TXA eligibility according to TARN best practice tariff was modified over the duration of study towards a more liberal approach over time and it was not possible to specifically determine the impact of these changes although NICE and JRCALC guidelines have remained constant.

In summary, since adoption of TXA into hospital and pre-hospital national guidelines there has been a three-fold increase in use for injured patients. Time to treatment has reduced although significant numbers of patients continue to receive TXA late, or not at all. Practice guidelines for the use of TXA

are not universally applied across the spectrum of older trauma patients, those with low energy mechanism of injury, and non-shocked cohort significantly less likely to receive it. Our data suggests that pre-hospital ambulance crews may not associate this type of patient as one at risk of haemorrhage. Paramedics all carry TXA and are often the first on scene of an incident, therefore need greater awareness of the patient subgroups identified in this study who are less likely to treated pre-hospital, given it is one of the few interventions in their kit that is proven to improve survival from bleeding. Physician led teams had improved compliance with TXA treatment guidelines suggesting that targeted education for ambulance crews may be of importance in achieving widespread implementation. An alternative mode of delivery e.g. intramuscular has been evaluated in small studies for bleeding patients [34] and in mild traumatic brain injury is under evaluated in the CRASH-4 clinical trial (NCT04521881). This method of dosing may improve compliance for those bleeding patients in which TXA treatment is not currently possible due to inability to secure venous access by paramedics, or providers at scene that do not have the necessary skill set to administer intravenous medication. Key performance indicators for pre-hospital practitioners, training and a greater understanding of early decision making are needed to address the barriers to universal early TXA for all injured patients with bleeding.

Provenance and peer review:

Not commissioned, no funding. Externally peer-reviewed

Figure legends

Figure 1

*Figure 1A: Frequency of PH TXA use across mechanism of injury according to patient sex; *signifies p value <0.001. 1B: Percentage patients eligible to receive TXA in mechanism of injury group; *signifies p value <0.001 when comparing PH TXA in penetrating vs other types of mechanism of injury. 1C: percentage of PH TXA use across mechanism of injury according to patient sex; *signifies p value <0.001. 1D: Percentage patients eligible to receive TXA in age groups; *signifies p value <0.001 when measuring the negative trend of PH TXA with age increased. 1E: Odds of PH TXA for males and females were reported for value of age between 20, 40, 60, 80 and 100 years. 1F: Percentage of PH TXA use across injury groups.*

Figure 2

*Figure 2. TXA use in eligible patients (percentage values all figure). 2A: TXA administration in all eligible patients separated by shock status and sex; *signifies p value <0.001 when comparing PH TXA in shocked (male vs female) & non-shocked (male vs female). 2B: TXA administration in all shocked eligible patients in*

*mechanism of injury groups; *signifies p value <0.001 when comparing PH TXA in penetrating vs other types of mechanism of injury. 2C: TXA administration in all shocked eligible patients in age groups; *signifies p value <0.001 when measuring the negative trend of PH TXA with age increased. 2D: TXA administration in all shocked eligible patients having received RBC transfusion in age groups. *signifies p value <0.001 when measuring the negative trend of PH TXA with age increased.*

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Figure 1:

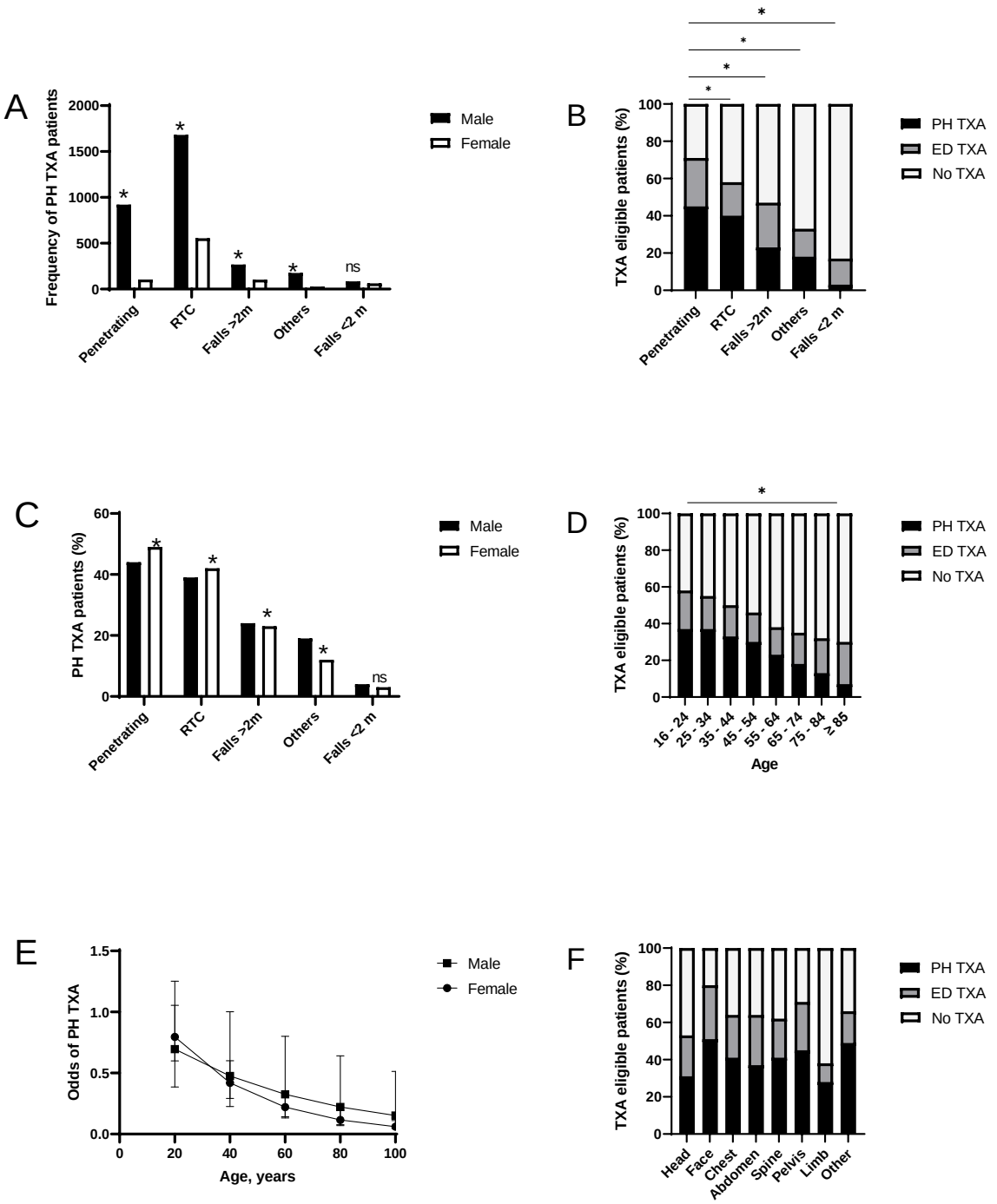

*Figure 1A: Frequency of PH TXA use across mechanism of injury according to patient sex; *signifies p value <0.001. 1B: Percentage patients eligible to receive TXA in mechanism of injury group; *signifies p value <0.001 when comparing PH TXA in penetrating vs other types of mechanism of injury. 1C: percentage of PH TXA use across mechanism of injury according to patient sex; *signifies p value <0.001. 1D: Percentage patients eligible to receive TXA in age groups; *signifies p value <0.001 when measuring the negative trend of PH TXA with age increased. 1E: Odds of PH TXA for males and females were reported for value of age between 20, 40, 60, 80 and 100 years. 1F: Percentage of PH TXA use across injury groups.*

Figure 2:

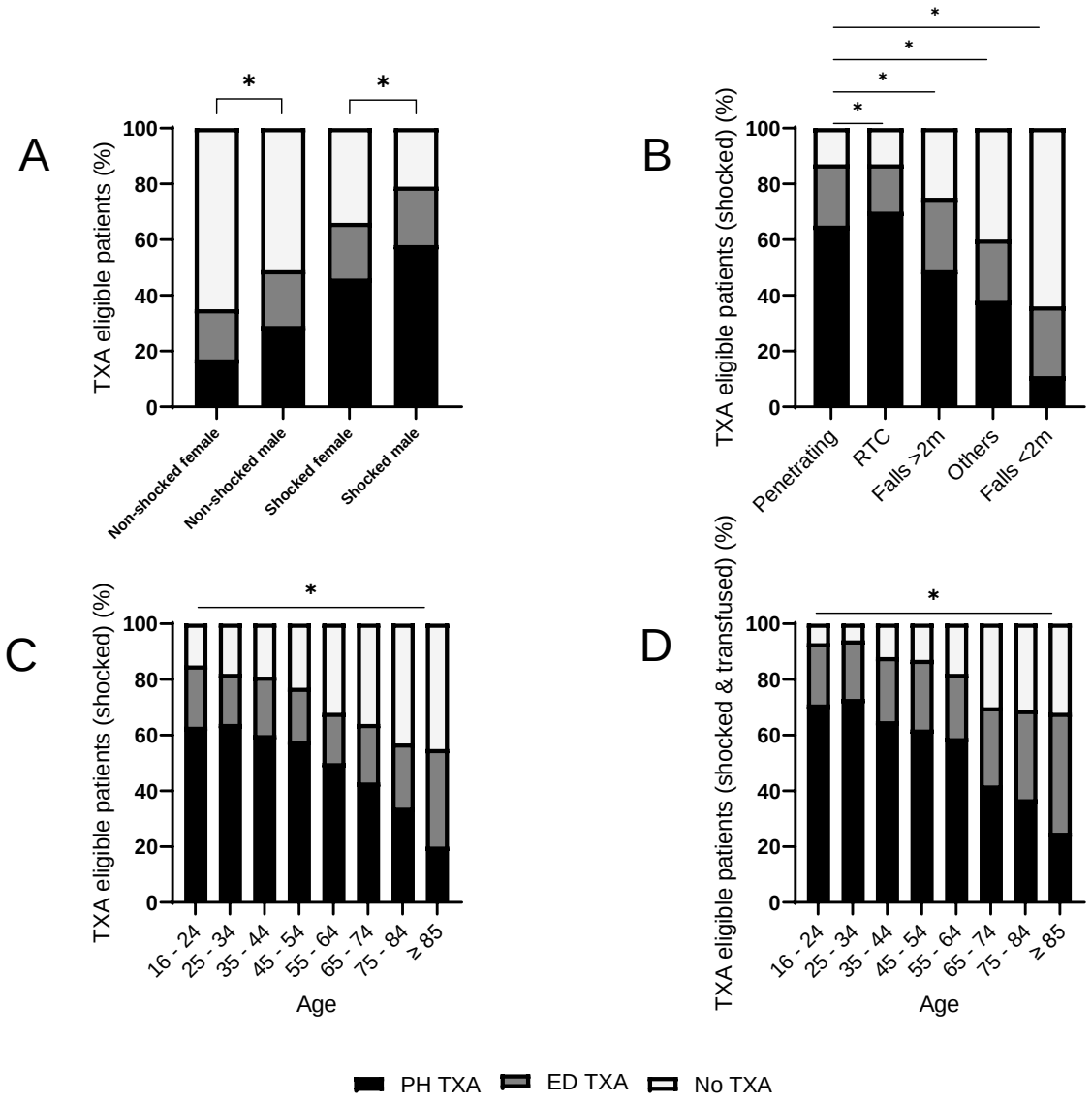

*Figure 2. TXA use in eligible patients (percentage values all figure). 2A: TXA administration in all eligible patients separated by shock status and sex; *signifies p value <0.001 when comparing PH TXA in shocked (male vs female) & non-shocked (male vs female). 2B: TXA administration in all shocked eligible patients in mechanism of injury groups; *signifies p value <0.001 when comparing PH TXA in penetrating vs other types of mechanism of injury. 2C: TXA administration in all shocked eligible patients in age groups; *signifies p value <0.001 when measuring the negative trend of PH TXA with age increased. 2D: TXA administration in all shocked eligible patients having received RBC transfusion in age groups. *signifies p value <0.001 when measuring the negative trend of PH TXA with age increased.*

Table 1: Patient and injury characteristics

	2013-15 PH TXA n=2411	2017-19 PH TXA n=3979	p value	2013-15 ED TXA n=2899	2017-19 ED TXA n=2737	p value	2013-15 No TXA n=26762	2017-19 No TXA n=8258	p value
Age+	38 (25 – 54)	39 (26 – 56)	0.010	40 (26 – 59)	49 (29 – 72)	<0.001	59 (42 – 78)	56 (35 – 74)	<0.001
Male	1850 (77)	3129 (79)	0.075	2195 (76)	2008 (73)	0.043	13823 (52)	5421 (66)	<0.001
Female	561 (23)	850 (21)	<0.001	704 (24)	729 (27)	<0.001	12939 (48)	2837 (44)	<0.001
MOI:			<0.001			<0.001			<0.001
Penetrating	347 (14)	1025 (26)		492 (17)	600 (22)		683 (3)	676 (8)	
Fall <2 m	62 (3)	147 (4)		224 (8)	568 (21)		15463 (58)	3587 (43)	
Fall >2 m	218 (9)	370 (9)		490 (17)	371 (14)		2736 (10)	844 (10)	
RTC	1651 (69)	2235 (56)		1524 (53)	1018 (37)		6408 (24)	2376 (29)	
Others	133 (6)	202 (5)		169 (6)	180 (7)		1472 (6)	775 (9)	
ISS+	22 (11 – 34)	25 (13 – 38)	<0.001	22 (13 – 34)	21 (11 – 30)	0.016	9 (9 – 10)	10 (9 – 20)	<0.001
AIS Head ≥ 3	590 (25)	1052 (26)	0.081	728 (25)	755 (28)	0.035	1762 (7)	1586 (19)	<0.001
PH SBP <90 mmHg	449 (22)	849 (25)	0.012	323 (16)	289 (15)	0.223	593 (3)	266 (7)	<0.001
PH HR ≥110 /m	763 (34)	1399 (38)	0.005	620 (28)	529 (25)	0.027	1835 (10)	659 (14)	<0.001
GCS < 8	455 (19)	806 (21)	0.137	434 (15)	344 (13)	0.012	503 (2)	390 (5)	<0.001
Mode of arrival:			<0.001			<0.001			<0.001
Ambulance	1417 (59)	2526 (64)		2052 (71)	2072 (76)		18902 (71)	5755 (70)	
HEMS	990 (41)	1086 (36)		416 (14)	376 (14)		965 (4)	524 (6)	
Other	4 (0)	371 (1)		431 (15)	289 (11)		6895 (26)	1979 (24)	
Time from injury to admission (minutes) +	95 (74 – 95)	89 (67 – 114)	<0.001	81 (59 – 111)	87 (62 – 122)	<0.001	101 (75 – 143)	115 (79 – 222)	<0.001
Time from injury to TXA (minutes) +	51 (35 – 70)	43 (31 – 61)	<0.001	125 (85 – 184)	141 (95 – 248)	<0.001	-	-	-

Data presented as + median (IQR), otherwise n (%). TXA: Tranexamic Acid; MOI: mechanism of injury; RTC: Road Traffic Collision; ISS: Injury Severity Score; AIS: Abbreviated Injury Scale; PH SBP: pre-hospital systolic blood pressure; PH HR: pre-hospital heart rate; GCS: Glasgow Coma Scale; HEMS: Helicopter Emergency Medical Services.

Table 2: Pre-hospital factors associated with TXA administration

	Unadjusted OR (95% CI)	p value	Adjusted OR (95% CI)	p value
Age	0.982 (0.980 – 0.984)	**0.000**	0.981 (0.978 – 0.984)	**0.000**
Male sex	1.336 (1.193 – 1.497)	**0.000**	1.168 (0.980 – 1.393)	0.083
Blunt injury	1.789 (1.704 – 1.885)	**0.000**	1.601 (1.496 – 1.728)	**0.000**
PH SBP	0.991 (0.989 – 0.993)	**0.000**	0.992 (0.990 – 0.994)	**0.000**
PH GCS	0.946 (0.934 – 0.957)	**0.000**	0.955 (0.938 – 0.973)	**0.000**
Air ambulance	0.997 (0.997 – 0.998)	**0.000**	4.180 (3.357 – 5.204)	**0.000**

OR: Odds Ratio; CI: Confidence Intervals; PH: Pre-hospital; SBP: Systolic Blood Pressure; GCS: Glasgow Coma Scale. Hosmer Lemeshow goodness of fit: X^2: 51.198, p value <0.001.

Table 3: Patient and injury characteristics in shock and transfusion cohorts, 2017-2019

	All patients 14974	Non-shocked n=6816	Shocked n=3523	p value	Shocked + no RBCs n=2371	Shocked + RBCs n=1150	p value
Age+	70 (103 – 50)	54 (34 – 73)	43 (27 – 61)	<0.001	43 (28 – 60)	43 (27 – 63)	0.742
Male	10558 (71)	4630 (68)	2606 (74)	<0.001	1762 (74)	842 (73)	0.487
Female	4416 (29)	2186 (32)	917 (26)	<0.001	609 (26)	308 (27)	<0.001
MOI:				<0.001			0.419
Penetrating	2301 (15)	832 (12)	798 (23)		530 (22)	268 (23)	
Fall <2 m	4302 (27)	2324 (34)	598 (17)		414 (18)	184 (16)	
Fall >2 m	1585 (11)	713 (11)	382 (11)		250 (11)	132 (12)	
RTC	5629 (38)	2508 (37)	1512 (43)		1011 (43)	500 (44)	
Others	1157 (8)	439 (6)	233 (7)		166 (7)	66 (6)	
ISS+	26 (16 – 75)	16 (9 – 25)	22 (10 – 36)	<0.001	22 (10 – 35)	24 (13 – 36)	0.123
AIS Head ≥ 3	3393 (23)	1632 (24)	1026 (29)	<0.001	694 (29)	331 (29)	0.765
PH SBP <90 mmHg	1404 (9)	0 (0)	1404 (43)	<0.001	882 (40)	522 (50)	<0.001
PH HR ≥110 b/m	2587 (17)	0 (0)	2587 (74)	<0.001	1806 (77)	779 (87)	<0.001
GCS < 8	1540 (11)	459 (7)	676 (19)	<0.001	413 (18)	263 (23)	<0.001
Mode of arrival:				<0.001			0.058
Ambulance	10343 (69)	5734 (84)	2615 (74)		1786 (75)	827 (72)	
HEMS	2330 (16)	1066 (15)	902 (27)		580 (25)	322 (28)	
Others	2301 (15)	16 (0)	6 (0)		5 (0)	1 (0)	
Time from injury to admission (minutes) +	143 (99 – 1434)	97 (73 – 128)	87 (64 – 116)	<0.001	88 (64 – 117)	85 (65 – 113)	0.182
Time from injury to TXA (minutes) +	124 (61 – 1406)	72 (42 – 133)	51 (34 – 89)	<0.001	50 (33 – 85)	52 (35 – 93)	0.065
PH TXA	3979 (27)	1643 (24)	1918 (54)	<0.001	1230 (52)	687 (60)	<0.001

Data presented as +median (IQR), otherwise n (%). RBCs: Red Blood Cells; MOI: mechanism of injury; ISS: Injury Severity Score; AIS: Abbreviated Injury Scale; PH SBP: pre-hospital systolic blood pressure; PH HR: pre-hospital heart rate; GCS: Glasgow Coma Scale; HEMS: Helicopter Emergency Medical Services; PH TXA: pre-hospital Tranexamic Acid

Supplemental Table 1: List of haemorrhage control operation and interventions used to identify submissions

Operations:	**Interventions:**
Abdominal Packing	Direct Compression
Amputation of Upper/Lower Limb	Embolisation
Aortic Repair	
BOAST 4 – External fixation – Circular frame	
BOAST 4 – External fixation – Monolateral (Non-circular) frame	
BOAST 4 – Internal fixation: Nail	
BOAST 4 – Internal fixation: Other	
BOAST 4 – Internal fixation: Plate	
BOAST 4 – POP	
Bowel operations (specified)	
Caesarian Delivery	
Cholecystectomy	
Diaphragm repair	
Embolisation (interventional radiology)	
Excision of Pancreas	
External Fixation Pelvis	
Extracorporeal Circulation (incl. ECMO)	
Fixation of Acetabulum	
Fixation of Pelvic Ring	
Heart Bypass	
Heart Surgery	
Hemicolectomy/Colectomy	
Ileectomy	
Laparoscopy	
Laparotomy	
Limb perfusion	
Nephrectomy	
Packing of Nose	
Pericardiocentesis	
Pneumonectomy	
REBOA, abdominal	
REBOA, thoracic	

Rectal operation	
Repair Colon laceration	
Repair Kidney laceration	
Repair Liver laceration	
Repair mesentery of colon	
Repair mesentery of small bowel	
Repair Oesophagus	
Repair of Artery	
Repair of chest wall	
Repair of Duodenum	
Repair of Ileum	
Repair of Jejunum	
Repair of lung	
Repair of Stomach	
Repair of Vein	
Repair Rupture to Bladder	
Repair Spleen	
Resection Liver	
Rib fracture fixation	
Splenectomy	
Sternum fixation	
Thoracotomy	
Tracheostomy	

Supplemental Table 2: Logistic regression analysis of age and sex for patients receiving PH TXA comprising the interaction between the two independent variables.

	β	(95% CI)	Odds Ratio	(95% CI)	p
Intercept	0.410	(0.206; 0.614)	1.507	(1.229; 1.848)	<0.001
Age	-0.032	(-0.036; -0.028)	0.969	(0.965; 0.972)	<0.001
sex, male	-0.393	(-0.620; -0.166)	0.675	(0.538; 0.847)	<0.001
Age*sex	0.013	(0.009; 0.017)	1.013	(1.009; 1.017)	<0.001

Supplemental figure:

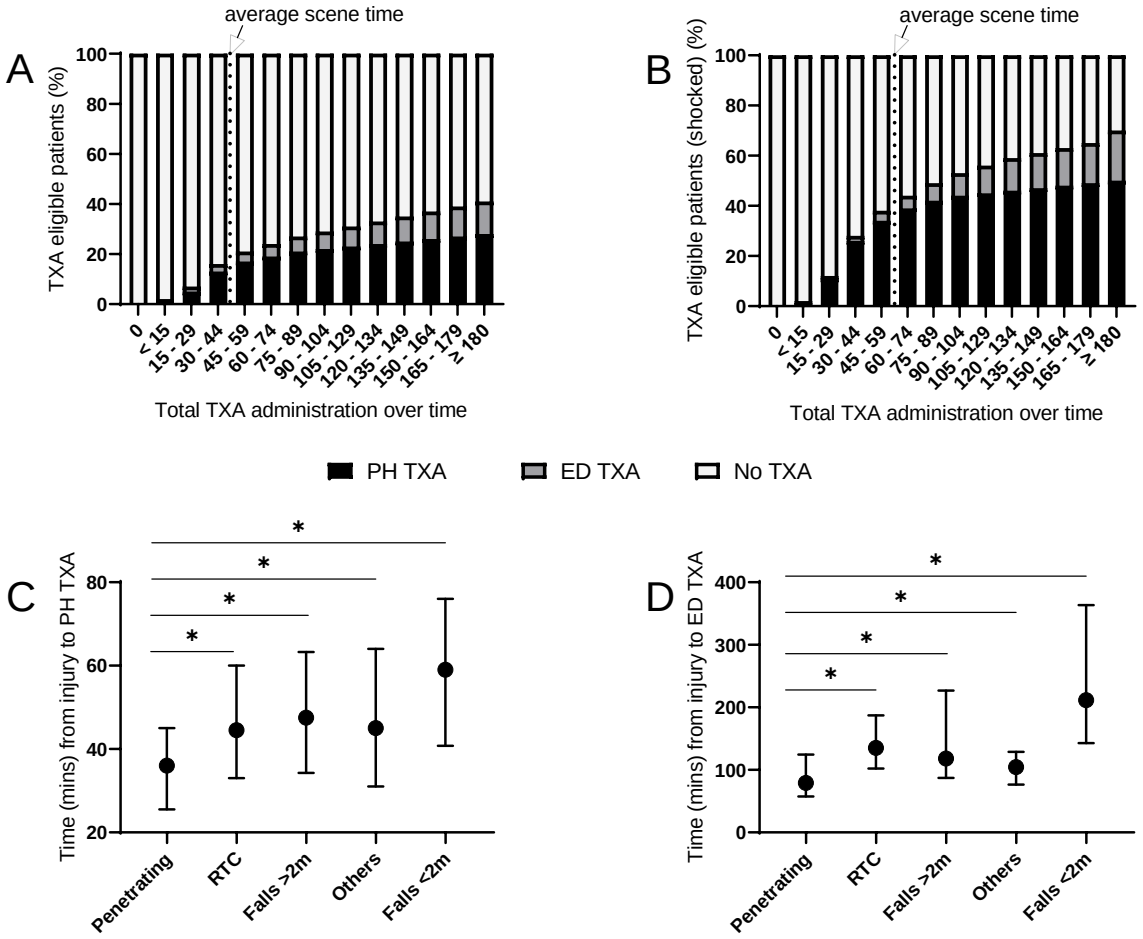

*Figure 1A: Cumulative TXA use in 15-minute windows for TXA eligible patients from 2017 to 2019; 1B: Cumulative TXA use in 15-minute windows for TXA eligible shocked patients from 2017 to 2019; 1C: Time from injury to PH TXA administration stratified by mechanism of injury in shocked & RBC transfusion patients. 1D: Time from injury to ED TXA administration stratified by mechanism of injury in shocked & RBC transfusion patients. *signifies p value <0.001 when comparing time from injury to TXA in penetrating vs other types of mechanism of injury.*