National Institute for Health and Care Excellence

Draft

Head Injury: assessment and early management (update)

[A] Evidence review for tranexamic acid

NICE guideline <number>

Evidence reviews underpinning recommendations x to y and research recommendations in the NICE guideline

September 2022

Draft for Consultation

These evidence reviews were developed by the Guideline Development Team NGC

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1. Contents

1. Tranexamic acid

1.1. Review question

What is the clinical and cost effectiveness of tranexamic acid (TXA) for managing suspected or confirmed isolated traumatic intracranial bleeding pre-hospital and in hospital?

1.1.1. Introduction

Head injuries may cause bleeding within the intracranial cavity, manifesting for example as extradural or subdural haematomas. This bleeding causes increased intracranial pressure, with secondary brain injury occurring due to pressure effects. In some patients this bleeding continues, leading to a more severe brain injury profile. Being able to arrest this bleeding prior to neurosurgery may therefore result in better outcomes for patients, provided the method of doing so is safe. Tranexamic acid is a haemostatic agent which is widely used in major trauma, in which it has been shown to result in better outcomes for adult patients. Patients with head injuries may currently receive tranexamic acid if their injury pattern includes other body parts, but the role for giving tranexamic acid to patients with a head injury alone has not previously been evaluated in NICE guidance. If evidence exists to support the use of tranexamic acid for isolated head injury, as well as for major trauma, guidance may result in earlier use leading to patient benefit.

1.1.2. Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	Inclusion: All adults and children (including infants under 1 year) with suspected or confirmed isolated traumatic intracranial bleeding Stratified by: Age • Adults (aged ≥16 years) • Children (aged ≥1 to <16 years) • Infants (aged <1 year) Severity of TBI/Degree of consciousness- defined according to the Glasgow Coma Scale score • Mild traumatic brain injury (TBI)- GCS 13-15 • Moderate traumatic brain injury (TBI)- GCS 9-12 • Severe traumatic brain injury (TBI)- GCS 3-8 Data with different categories of GCS will be included but downgraded for indirectness Timing of TXA • <3 hours of injury • >3 hours of injury
Intervention	Tranexamic acid (TXA)
Comparison	Usual care/Control (to include placebo or study arm receiving no TXA)
Outcomes	• All-cause mortality at 30 days.

	• Mortality from head injury/TBI at 30 days. • Length of hospital stay • Surgical intervention • Objective measures of disability (including (Extended) Glasgow Outcome Scale, King's Outcome Scale for Childhood Head Injury and Cerebral Performance Category scale, Rivermead Post-Concussion Syndrome Questionnaire, Disability Rating Scale). • Serious adverse event • Post-concussion syndrome • Concussion/mild TBI • Quality of life (validated quality of life scores only).
Study design	• Systematic reviews of RCTs • RCTs • If no RCT evidence is available, non-randomised studies will be considered if they adjust for key confounders, starting with prospective cohort studies Published NMAs and IPDs will be considered for inclusion. Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available.

1.1.3. Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.4. Effectiveness evidence

1.1.4.1. Included studies

Two studies (4 papers) [1, 2, 8, 13] were included in the review; these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3).

Evidence was stratified based on setting (pre-hospital or hospital); timing of administration of TXA (> 3 hours of injury or > 3 hours of injury) and severity of injury (mild/moderate/severe TBI based on GCS score).

Population

Both studies were in adults. There was no evidence was available for children and infants. One study (Rowell 2020) included people aged 15 years or older with moderate or severe blunt or penetrating TBI (with GCS score of 12 or less).

CRASH-3 trial adults with TBI who were within 3 h of injury, had a GCSs core of 12 or lower or any intracranial bleeding on CT scan, and no major extracranial bleeding.

Severity of injury (based on GCS score)

Rowell 2020 included people with mild, moderate to severe TBI (GCS 12 or less) **(**mild: 4%, moderate: 39%, severe: 57%).

CRASH-3 trial included people with mild, moderate and severe TBI **(**mild: 28%, moderate:33%, severe: 38%, unknown: 1%). The trial classified severity of head injury based on baseline GCS score–mild to moderate (GCS 9‑15) and severe (GCS 3‑8)–and by pupil reactivity. This classification of severity was different to as stated in our protocol: mild GCS 13-15; moderate 9-12; severe GCS 3-8. The study reported data for combined severity (mild, moderate and severe) for some outcomes and separately for mild-moderate and severe TBI for some.

Setting and intervention

Rowell 2020 compared tranexamic acid (TXA) with placebo in an out-of-hospital setting, and CRASH-3 trial 2019 compared TXA with placebo in a hospital setting.

Timing of TXA administration

In Rowell 2020 the median estimated time from injury to out-of-hospital TXA administration ranged from 40 to 43 minutes. In this study participants were eligible only if the study drug could be administered within 2 hours of injury. This study was analysed in the strata TXA administration <3 hours of injury.

CRASH-3 trial included people within 8 hours of injury in the early phase and within 3 hours of injury in the later phase of the trial, where available data was analysed separately for TXA administration <3 hours and > 3 hours after injury.

TXA dose

Rowell 2020 included 2 does of TXA in a pre-hospital setting. Group 1: 1-g IV tranexamic acid bolus in the out- of-hospital setting followed by a 1-g tranexamic acid IV infusion initiated upon hospital arrival and infused over 8 hours (bolus maintenance group), and Group 2: 2-g IV tranexamic acid bolus in the out-of-hospital setting followed by a placebo infusion (bolus only group)

CRASH-3 trial included a loading dose of 1 g of TXA infused over 10 min, started immediately after randomisation, followed by an intravenous infusion of 1 g over 8 hours.

Randomisation of participants

In Rowell 2020 randomisation was done pre-CT.

In the CRASH -3 trial protocol patients with GCS 13-15 (mild) were randomised post CT, but the protocol was that patients with GCS 3-12 (moderate and severe) were to be randomised prior to CT. Protocol was not adhered to in the majority of patients with GCS 3-12 due to diagnostic uncertainty particularly in intoxicated patients, particularly in high income countries (HICs) with easy access to CT. The results of a published in GCS 3-12 suggest that only 35% of GCS 3-12 patients were randomised prior to CT. There was lack of clarity about protocol violations in GCS 3-12 with regards to relationship of randomisation to CT.

Outcomes

There was no evidence available for the outcomes: quality of life, post-concussion syndrome and concussion. Gaps in evidence particularly data separately for timing of injury, severities, and country income status.

See also the study selection flow chart in Appendix C, study evidence tables in Appendix D, forest plots in Appendix E and GRADE tables in Appendix F.

Request for additional data:

Authors of the key paper CRASH-3 trial were contacted for additional data on outcomes by TBI (traumatic brain injury) severity grouping (GCS 3-8, GCS 9-12, GCS 13-15) to allow for stratification as per the protocol. Additional data was not shared by the authors.

1.1.4.2. Excluded studies

See the excluded studies list in Appendix J.

1.1.5. Summary of studies included in the effectiveness evidence

Table 2: Summary of studies included in the evidence review

TXA in pre-hospital setting - adults

Study	Intervention and comparison	Population	Outcomes	Comments
Rowell 2020 [8] Multi-centre RCT USA and Canada Setting: out-of-hospital setting by paramedics treatment	**Tranexamic acid** <u>Bolus maintenance group</u> (N=312) 1-gram IV TXA bolus in the prehospital setting followed by a 1-gram IV maintenance infusion initiated on hospital arrival and infused over 8 hours. <u>Bolus only group (N=345)</u> 2g IV tranexamic acid bolus in the out-of-hospital setting followed by a placebo infusion	Patients aged age ≥ 15yrs with blunt and penetrating traumatic mechanism with a Glasgow Coma Scale (GCS) score of 3 to 12, at least 1 reactive pupil, and systolic blood pressure of at least 90 mm Hg prior to randomisation. Patients were eligible only if an intravenous (IV) catheter was in place, the study drug could be administered	All-cause mortality at 28 days All-cause mortality at 6 months Hospital-free days (included any day from hospital admission through day 28 that the participant was alive and out of the hospital) Degree of disability - Glasgow Outcome Scale-	Randomisation pre-CT Timing: treatment initiated within 2 hours of TBI GCS: Mild: 4% Moderate: 39% Severe: 57% High income economy based on World Bank income group Follow-up: mortality- at 28 days

Study	Intervention and comparison	Population	Outcomes	Comments
	Placebo N=309 Placebo IV bolus in the prehospital setting followed by a placebo maintenance infusion initiated on hospital arrival and infused over 8 hours.	within 2 hours of injury, and the predefined emergency medical services (EMS) transport destination was a participating trauma centre. Participants with both blunt and penetrating injuries were enrolled in this trial to reflect military and civilian populations. Only 3% of participants experienced penetrating injury, so the results may not be generalisable to patients with penetrating TBI. The target population for the trial was patients aged 15 years or older with moderate or severe blunt or penetrating TBI,	Extended (GOS-E) Score >4 (at discharge and 6 months after injury). The GOS-E subdivides the categories of severe and moderate disability and good recovery using a scale of 1 to 8, where 1 indicates death; 2, vegetative state; 3, lower severe disability; 4, upper severe disability; 5, lower moderate disability; 6, upper moderate disability; 7, lower good recovery; and 8, upper good recovery. The measure was dichotomised into unfavourable (1-4) and favourable (5-8) outcomes for this trial. Neuro surgical intervention (include craniotomy, craniectomy, and placement of a neuromonitoring or drainage device. The follow-up period for interventions continued through hospital discharge or 28 days, whichever occurred first) Adverse events: pulmonary embolism (PE), deep vein	All other outcomes at 6 months Strata: TXA <3 hours of injury Limitations reported in the study: Because the GCS has limited ability to discriminate between ICH and other central nervous system depressed states (eg, intoxication, sedation, shock), a fairly low percentage of patients with intra cranial haemorrhage (ICH) were enrolled in this trial which may have diluted treatment differences. 20% of participants enrolled in the trial had a GCS score of 13 or higher on admission, potentially contributing further to an overall low injury severity. The median estimated time from injury to out-of-hospital TXA administration ranged from 40 to 43 minutes across groups, and the bolus completion percentage ranged from 93% to 95%. The median time from out-of-hospital bolus completion to start of the in-hospital infusion ranged from 86 to 94 minutes, and the in-hospital dose

Study	Intervention and comparison	Population	Outcomes	Comments
			thrombosis (DVT), stroke, myocardial infarction (MI)	completion percentage ranged from 69% to 77%. Strata: TXA> 3 hours of injury

1

2 **TXA in hospital setting – adults**

Study	Intervention and comparison	Population	Outcomes	Comments
CRASH-3 2019, Brenner, 2020, Williams 2020 [1, 2, 13] Multi-centre RCT Setting: 175 hospitals in 29 countries.	**Tranexamic acid** N=6406 (All patients- < 3 hours and ≥3 hours of injury) N= 4649 (randomly assigned within 3 hours of injury) Patients allocated to receive a loading dose of 1 g of tranexamic acid infused over 10 min, started immediately after randomisation, followed by an intravenous infusion of 1 g over 8 h. **Placebo** N=6331 (All patients- < 3 hours and ≥3 hours of injury) N=4553 (randomly assigned within 3 hours of injury) Patients allocated to receive placebo, matching the dosing regimen of the TXA study group, and starting immediately after randomisation.	Adults with TBI who were within 3 h of injury, had a Glasgow Coma Scale (GCS) score of 12 or lower or any intracranial bleeding on CT scan, and no major extracranial bleeding were eligible.	TBI related mortality within 28 days of injury Disability rating scale score Adverse events: all vascular occlusive events, pulmonary embolism (PE), deep vein thrombosis (DVT), Stroke Myocardial infarction (MI) [available separately for < 3 hours and > 3 hours of injury] Brenner 2020 (post-hoc analysis data): - all-cause mortality within 24 hours of injury, after 24 hours and at 28 days stratified by severity and country income level in patients randomised within 3 hours of injury, excluding those with a GCS score of 3 or bilateral unreactive pupils -vascular occlusive events (fatal and non-fatal) at 28 days	Randomisation post-CT scan Timing: <8 hours/ <3 hours of injury The time window for eligibility was originally within 8 hours of injury. However, on Sept 6, 2016, in response to evidence external to the trial indicating that tranexamic acid is unlikely to be effective when initiated beyond 3 hours of injury, the trial steering committee amended the protocol to limit recruitment to within 3 hours of injury and the primary endpoint was changed to head injury death in hospital within 28 days of injury for patients treated within 3 hours of injury. GCS: Mild: 28% Moderate: 33% Severe: 38% Unknown: 1%

Study	Intervention and comparison	Population	Outcomes	Comments
			in all patients, stratified by severity and country income level Williams 2020: TBI mortality according country income level	Follow-up: within 28 days of injury. Study does not report number of participants in each group after excluding people with GCS< 3 or bilateral unreactive pupils. International including lower, middle and high income countries. 175 hospitals in 29 countries Strata: TXA < 3 hours of injury, TXA > 3 hours of injury, TXA > 3 hours and <3 hours of injury.

See Appendix D for full evidence tables.

1.1.6. Summary of the effectiveness evidence

PRE- HOSPITAL SETTING

Table 3: Clinical evidence summary: TXA vs Placebo (adults) in pre-hospital setting

TXA < 3 hours of injury- Mixed GCS (mild, moderate and severe TBI) [out-of-hospital tranexamic acid (1 g) bolus and in-hospital tranexamic acid (1 g) 8-hour infusion]

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with TXA
All-cause mortality (at 28 days)	570 (1 RCT) Rowell 2020[e]	⊕◯◯◯ Very low[a,b]	RR 1.06 (0.75 to 1.50)	175 per 1,000	11 more per 1,000 (44 fewer to 88 more)
All-cause mortality at 6 months	534 (1 RCT) Rowell 2020[e]	⊕◯◯◯ Very low[a,b]	RR 1.06 (0.76 to 1.48)	199 per 1,000	12 more per 1,000 (48 fewer to 95 more)
Length of hospital stay (hospital free days at 28-days)[c]	621 (1 RCT) Rowell 2020[e]	⊕⊕⊕◯ Moderate[a]	-	The mean length of hospital stay (hospital free days at 28-days) was 13.6 days	MD 0 (1.68 lower to 1.68 higher)
Neurosurgical intervention (at 28 days) [d]	621 (1 RCT) Rowell 2020[e]	⊕⊕◯◯ Low[a,b]	RR 1.14 (0.82 to 1.58)	175 per 1,000	24 more per 1,000 (31 fewer to 101 more)
Degree of disability: favourable outcome at discharge (GOS-E >4) [moderate disability or good recovery])	586 (1 RCT) Rowell 2020[e]	⊕⊕◯◯ Low[a,b]	RR 1.04 (0.83 to 1.31)	329 per 1,000	13 more per 1,000 (56 fewer to 102 more)
Degree of disability: favourable outcome at 6 months (GOS-E >4) [moderate disability or good recovery])	534 (1 RCT) Rowell 2020[e]	⊕⊕⊕◯ Moderate[a]	RR 0.97 (0.85 to 1.12)	599 per 1,000	18 fewer per 1,000 (90 fewer to 72 more)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with TXA
Adverse events: myocardial infarction (MI) (at 28 days)	621 (1 RCT) Rowell 2020[e]	⊕◯◯◯ Very low[a,b]	RR 2.97 (0.31 to 28.41)	3 per 1,000	6 more per 1,000 (2 fewer to 89 more)
Adverse events: Pulmonary embolism (at 28 days)	621 (1 RCT) Rowell 2020[e]	⊕◯◯◯ Very low[a,b]	RR 0.59 (0.14 to 2.47)	16 per 1,000	7 fewer per 1,000 (14 fewer to 24 more)
Adverse events: Deep vein thrombosis (DVT) (at 28 days)	621 (1 RCT) Rowell 2020[e]	⊕⊕◯◯ Low[a,b]	RR 0.33 (0.09 to 1.21)	29 per 1,000	20 fewer per 1,000 (27 fewer to 6 more)
Adverse events: Thrombotic stroke (at 28 days)	621 (1 RCT) Rowell 2020[e]	⊕⊕◯◯ Low[a,b]	RR 0.30 (0.08 to 1.07)	32 per 1,000	23 fewer per 1,000 (30 fewer to 2 more)

a. Downgraded by 1 increment for indirectness. Mixed severity based on GCS. Mild: 4%, moderate: 39%, severe: 57%.

b. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group for continuous outcomes. MID for hospital free days at 28 days is 5.35).

c. Hospital-free days include any day from hospital admission through day 28 that the participant was alive and out of the hospital. Some participants, primarily those who withdrew before discharge, are missing this measure (20 in the bolus maintenance group and 14 in the placebo group).

d. Neurosurgical interventions include craniotomy, craniectomy, and placement of a neuromonitoring or drainage device.

e. The median estimated time from injury to out-of-hospital TXA administration ranged from 40 to 43 minutes. Participants were eligible only if the study drug could be administered within 2 hours of injury. This study was analysed in the strata TXA administration <3 hours of injury.

Table 4: Clinical evidence summary: TXA vs Placebo (adults) in pre-hospital setting

TXA < 3 hours of injury- Mixed GCS (mild, moderate and severe TBI) [out-of-hospital tranexamic acid (2 g) bolus and in-hospital placebo 8-hour infusion]Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with TXA
All-cause mortality (at 28 days)	603 (1 RCT) Rowell 2020[e]	⊕⊕◯◯ Low[a,b]	RR 0.72 (0.49 to 1.05)	175 per 1,000	49 fewer per 1,000 (89 fewer to 9 more)

TXA < 3 hours of injury- Mixed GCS (mild, moderate and severe TBI) [out-of-hospital tranexamic acid (2 g) bolus and in-hospital placebo 8-hour infusion]Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with TXA
All- cause mortality at 6 months	561 (1 RCT) Rowell 2020 [e]	⊕⊕◯◯ Low[a,b]	RR 0.80 (0.56 to 1.15)	199 per 1,000	40 fewer per 1,000 (87 fewer to 30 more)
Length of hospital stay (hospital free days at 28-days)[c]	654 (1 RCT) Rowell 2020 [e]	⊕⊕⊕◯ Moderate [a]	-	The mean length of hospital stay (hospital free days at 28-days) was 13.6 days	MD 0.5 higher (1.12 lower to 2.12 higher)
Neurosurgical intervention (at 28 days)[d]	654 (1 RCT) Rowell 2020 [e]	⊕⊕◯◯ Low[a,b]	RR 1.24 (0.91 to 1.70)	175 per 1,000	42 more per 1,000 (16 fewer to 122 more)
Degree of disability: favourable outcome at discharge (GOS-E >4) [moderate disability or good recovery])	621 (1 RCT) Rowell 2020 [e]	⊕⊕◯◯ Low[a,b]	RR 0.93 (0.74 to 1.18)	329 per 1,000	23 fewer per 1,000 (85 fewer to 59 more)
Degree of disability: favourable outcome at 6 months (GOS-E >4) [moderate disability or good recovery])	561 (1 RCT) Rowell 2020 [e]	⊕⊕⊕◯ Moderate [a]	RR 1.03 (0.90 to 1.17)	599 per 1,000	18 more per 1,000 (60 fewer to 102 more)
Adverse events: myocardial infarction (MI) (at 28 days)	654 (1 RCT) Rowell 2020 [e]	⊕◯◯◯ Very low[a,b]	RR 1.79 (0.16 to 19.66)	3 per 1,000	3 more per 1,000 (3 fewer to 60 more)
Adverse events: Pulmonary embolism (at 28 days)	654 (1 RCT) Rowell 2020 [e]	⊕◯◯◯ Very low[a,b]	RR 1.07 (0.33 to 3.49)	16 per 1,000	1 more per 1,000 (11 fewer to 40 more)

TXA < 3 hours of injury- Mixed GCS (mild, moderate and severe TBI) [out-of-hospital tranexamic acid (2 g) bolus and in-hospital placebo 8-hour infusion]Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with TXA
Adverse events: Deep vein thrombosis (DVT) (at 28 days)	654 (1 RCT) Rowell 2020 [e]	⊕◯◯◯ Very low[a,b]	RR 1.00 (0.41 to 2.42)	29 per 1,000	0 fewer per 1,000 (17 fewer to 41 more)
Adverse events: Thrombotic stroke (at 28 days)	654 (1 RCT) Rowell 2020 [e]	⊕◯◯◯ Very low[a,b]	RR 1.16 (0.52 to 2.62)	32 per 1,000	5 more per 1,000 (16 fewer to 52 more)

a. Downgraded by 1 increment for indirectness. Mixed severity based on GCS. Mild: 4%, moderate: 39%, severe: 57%.

b. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group for continuous outcomes. MID for hospital free days at 28 days is 5.35).

c. Hospital-free days include any day from hospital admission through day 28 that the participant was alive and out of the hospital. Some participants, primarily those who withdrew before discharge, are missing this measure (14 in the bolus only group, and 14 in the placebo group).

d. Neurosurgical interventions include craniotomy, craniectomy, and placement of a neuromonitoring or drainage device.

e. The median estimated time from injury to out-of-hospital TXA administration ranged from 40 to 43 minutes. Participants were eligible only if the study drug could be administered within 2 hours of injury. This study was analysed in the strata TXA administration <3 hours of injury.

1 **HOSPITAL SETTING**

2 **Table 5:Clinical evidence summary: TXA vs Placebo (adults) in hospital setting**

3 **TXA < 3 hours of injury- Mixed GCS (mild, moderate and severe TBI)**

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with TXA
TBI related mortality (overall) at 28 days	9127 (1 RCT) CRASH-3 2019	⊕⊕⊕◯ Moderate [a]	RR 0.94 (0.86 to 1.02)	198 per 1,000	12 fewer per 1,000 (28 fewer to 4 more)
TBI related mortality at 28 days - pupil reactivity (both react)	7548 (1 RCT) CRASH-3 2019	⊕⊕◯◯ Low[a,b]	RR 0.87 (0.77 to 0.98)	132 per 1,000	17 fewer per 1,000 (30 fewer to 3 fewer)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with TXA
TBI related mortality at 28 days - pupil reactivity (any non-reactive)	1579 (1 RCT) CRASH-3 2019	⊕⊕⊕◯ Moderate [a]	RR 1.03 (0.94 to 1.13)	508 per 1,000	15 more per 1,000 (30 fewer to 66 more)
All vascular occlusive events (all severities) 28 days	9127 (1 RCT) CRASH-3 2019	⊕⊕◯◯ Low[a,b]	RR 1.13 (0.80 to 1.59)	13 per 1,000	2 more per 1,000 (3 fewer to 8 more)
Adverse events: deep vein thrombosis (DVT) 28 days	9127 (1 RCT) CRASH-3 2019	⊕◯◯◯ Very low[a,b]	RR 1.22 (0.57 to 2.61)	3 per 1,000	1 more per 1,000 (1 fewer to 4 more)
Adverse events: stroke 28 days	9127 (1 RCT) CRASH-3 2019	⊕◯◯◯ Very low[a,b]	RR 1.23 (0.71 to 2.13)	5 per 1,000	1 more per 1,000 (1 fewer to 6 more)
Adverse events: Pulmonary embolism 28 days	9127 (1 RCT) CRASH-3 2019	⊕◯◯◯ Very low[a,b]	RR 0.98 (0.51 to 1.88)	4 per 1,000	0 fewer per 1,000 (2 fewer to 4 more)
Adverse events: myocardial infarction (MI) 28 days	9127 (1 RCT) CRASH-3 2019	⊕◯◯◯ Very low[a,b]	RR 0.73 (0.31 to 1.74)	3 per 1,000	1 fewer per 1,000 (2 fewer to 2 more)
Disability Rating Scale score (lower score means less disabled) 28 days	9127 (1 RCT) CRASH-3 2019	⊕⊕⊕◯ Moderate [a]	-	The mean disability Rating Scale score (lower score means less disabled) was 5.03	MD 0.04 lower (0.35 lower to 0.27 higher)

a. Downgraded by 1 increment for indirectness. Mixed severity based on GCS.

b. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group for continuous outcomes. MID for disability rating scale score is 3.8)

Table 6:Clinical evidence summary: TXA vs placebo (adults) in hospital setting

TXA < 3 hours of injury - Excluding those with a GCS score of 3 or bilateral unreactive pupils mixed GCS (mild, moderate and severe TBI)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with TXA
All-cause mortality within 24 hours of injury (All participants)	(1 RCT) Brenner 2020	⊕◯◯◯ Very low[a,b,c]	RR 0.74 (0.59 to 0.94)	See comment[d]	See comment[d]
All-cause mortality within 24 hours of injury – low and middle income countries (LMIC)	(1 RCT) Brenner 2020	⊕◯◯◯ Very low[a,b,c]	RR 0.75 (0.58 to 0.97)	See comment[d]	See comment[d]
All-cause mortality within 24 hours of injury – high income countries (HIC)	(1 RCT) Brenner 2020	⊕◯◯◯ Very low[a,b,c]	RR 0.65 (0.33 to 1.27)	See comment[d]	See comment[d]
All-cause mortality after 24 hours of injury (All participants)	(1 RCT) Brenner 2020	⊕◯◯◯ Very low[a,b,c]	RR 0.98 (0.77 to 1.24)	See comment[d]	See comment[d]
All-cause mortality after 24 hours of injury – low and middle income countries (LMIC)	(1 RCT) Brenner 2020	⊕⊕◯◯ Low[a,b]	RR 1.01 (0.88 to 1.16)	See comment[d]	See comment[d]
All-cause mortality after 24 hours of injury – high income countries (HIC)	(1 RCT) Brenner 2020	⊕◯◯◯ Very low[a,b,c]	RR 0.86 (0.63 to 1.18)	See comment[d]	See comment[d]
All-cause mortality at 28 days of injury (all participants)	(1 RCT) Brenner 2020	⊕⊕⊕◯ Moderate[b]	RR 0.93 (0.85 to 1.03)	See comment[d]	See comment[d]
All-cause mortality at 28 days of injury – low and middle income countries (LMIC)	(1 RCT) Brenner 2020	⊕⊕◯◯ Low[a,b]	RR 0.95 (0.85 to 1.07)	See comment[d]	See comment[d]
All-cause mortality at 28 days of injury – high income countries (HIC)	(1 RCT) Brenner 2020	⊕◯◯◯ Very low[a,b,c]	RR 0.82 (0.62 to 1.08)	See comment[d]	See comment[d]

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias. Exclusion of those with a GCS score of 3 or bilateral unreactive pupils post-randomisation.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with TXA
b. Downgraded by 1 increment for indirectness. Mixed severity based on GCS. c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group for continuous outcomes). d. GIV analysis used as only RR reported in the paper. Total number of participants in each group not available. Unable to calculate absolute risk.					

Table 7:Clinical evidence summary: TXA vs Placebo (adults) in hospital setting

TXA < 3 hours of injury - mild and moderate TBI (GCS 9-15)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with TXA
TBI mortality at 28 days -mild and moderate (GCS 9-15)	5615 (1 RCT) CRASH-3 2019	⨁⨁◯◯ Low[a,b]	RR 0.78 (0.64 to 0.95)	75 per 1,000	16 fewer per 1,000 (27 fewer to 4 fewer)
a. Downgraded by 1 increment for indirectness. Mixed severity based on GCS. b. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes)					

Table 8:Clinical evidence summary: TXA vs placebo (adults) in hospital setting

TXA < 3 hours of injury- Excluding those with bilateral unreactive pupils - mild and moderate TBI (GCS 9‑15)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with TXA
All-cause mortality within 24 hours of injury – mild/moderate TBI	(1 RCT) Brenner 2020	⨁◯◯◯ Very low[a,b,c]	RR 0.66 (0.41 to 1.08)	See comment[d]	See comment[d]
All-cause mortality after 24 hours of injury – mild/moderate TBI	(1 RCT) Brenner 2020	⨁◯◯◯ Very low[a,b,c]	RR 0.85 (0.70 to 1.04)	See comment[d]	See comment[d]
All-cause mortality at 28 days of injury – mild/moderate TBI	(1 RCT) Brenner 2020	⨁◯◯◯ Very low[a,b,c]	RR 0.82 (0.69 to 0.98)	See comment[d]	See comment[d]

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with TXA
a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias. Exclusion of those with a GCS score of 3 or bilateral unreactive pupils post-randomisation. b. Downgraded by 1 increment for indirectness. Mixed severity based on GCS. c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group for continuous outcomes). d. GIV analysis used as only RR reported in the paper. Total number of participants in each group not available. Unable to calculate absolute risk.					

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2 **Table 9:Clinical evidence summary: TXA vs Placebo (adults) in hospital setting**

3 **TXA < 3 hours of injury – severe TBI (GCS 3-8)**

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with TXA
TBI mortality at 28 days - severe (GCS 3-8)	3449 (1 RCT) CRASH-3 2019	⊕⊕⊕⊕ High	RR 0.99 (0.91 to 1.07)	401 per 1,000	4 fewer per 1,000 (36 fewer to 28 more)
TBI mortality at 28 days in severe TBI in high income countries (HIC)	(1 RCT) Williams 2020	⊕⊕⊕◯ Moderate [a]	RR 0.90 (0.75 to 1.09)	See comment [b]	See comment [b]
TBI mortality at 28 days in severe TBI in low and middle income (LMIC) countries	(1 RCT) Williams 2020	⊕⊕⊕⊕ High	RR 1.03 (0.95 to 1.11)	See comment [b]	See comment [b]
a. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group for continuous outcomes) b. GIV analysis used as only RR reported in the paper. No of events and number of participants in each group not available from the paper. Unable to calculate absolute risk.					

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Table 10:Clinical evidence summary: TXA vs placebo (adults) in hospital setting

TXA < 3 hours of injury- Excluding those with a GCS score of 3 or bilateral unreactive pupils – severe TBI (GCS 3‑8)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with TXA
All-cause mortality within 24 hours of injury – severe TBI	(1 RCT) Brenner 2020	⊕⊕◯◯ Low[a,b]	RR 0.76 (0.59 to 0.98)	See comment[c]	See comment[c]
All-cause mortality after 24 hours of injury – severe TBI	(1 RCT) Brenner 2020	⊕⊕⊕◯ Moderate[a]	RR 1.05 (0.92 to 1.21)	See comment[c]	See comment[c]
All-cause mortality at 28 days of injury – severe TBI	(1 RCT) Brenner 2020	⊕⊕⊕◯ Moderate[a]	RR 0.98 (0.87 to 1.10)	See comment[c]	See comment[c]
TBI mortality 28 days in severe TBI in low and middle income (LMIC) countries (excluding those patients with a GCS score of 3 or bilateral unreactive pupils)	(1 RCT) Williams 2020	⊕⊕⊕◯ Moderate[a]	RR 1.01 (0.88 to 1.16)	See comment[c]	See comment[c]
TBI mortality 28 days in severe TBI in high income countries (HIC) (excluding with a GCS score of 3 or bilateral unreactive pupils)	(1 RCT) Williams 2020	⊕⊕◯◯ Low[a,b]	RR 0.62 (0.40 to 0.95)	See comment[c]	See comment[c]

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias. Exclusion of those with a GCS score of 3 or bilateral unreactive pupils post-randomisation.

b. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group for continuous outcomes).

c. GIV analysis used as only RR reported in the paper. Total number of participants in each group not available. Unable to calculate absolute risk.

Table 11:Clinical evidence summary: TXA vs Placebo (adults) in hospital setting

TXA >3 hours of injury- mixed GCS (mild, moderate and severe TBI)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with TXA
All vascular occlusive events 28 days	3512 (1 RCT) CRASH-3 2019	⨁⨁◯◯ Low[a,b]	RR 0.77 (0.49 to 1.21)	24 per 1,000	5 fewer per 1,000 (12 fewer to 5 more)
Adverse events: deep vein thrombosis (DVT) 28 days	3512 (1 RCT) CRASH-3 2019	⨁◯◯◯ Very low[a,b]	RR 1.01 (0.25 to 4.04)	2 per 1,000	0 fewer per 1,000 (2 fewer to 7 more)
Adverse events: Stroke 28 days	3512 (1 RCT) CRASH-3 2019	⨁◯◯◯ Very low[a,b]	RR 0.90 (0.47 to 1.74)	11 per 1,000	1 fewer per 1,000 (6 fewer to 8 more)
Adverse events: Pulmonary embolism (PE) 28 days	3512 (1 RCT) CRASH-3 2019	⨁⨁◯◯ Low[a,b]	RR 0.43 (0.17 to 1.13)	8 per 1,000	5 fewer per 1,000 (7 fewer to 1 more)
Myocardial infarction (MI) 28 days	3512 (1 RCT) CRASH-3 2019	⨁◯◯◯ Very low[a,b]	RR 1.14 (0.44 to 2.94)	5 per 1,000	1 more per 1,000 (3 fewer to 9 more)
Disability Rating Scale score (lower score means less disabled) 28 days	3512 (1 RCT) CRASH-3 2019	⨁⨁⨁◯ Moderate[a]	-	The mean disability Rating Scale score (lower score means less disabled) was 5.03	MD 0.5 lower (0.98 lower to 0.02 lower)

a. Downgraded by 1 increment for indirectness. Mixed severity based on GCS.

b. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group for continuous outcomes. MID for disability rating scale score is 3.8)

Table 12:Clinical evidence summary: TXA vs placebo (adults) in hospital setting

Including all participants (TXA < 3 hours and >3 hours of injury)- mixed GCS (mild, moderate and severe TBI)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with TXA
non-head injury deaths 28 days	12639 (1 RCT) CRASH-3 2019	⊕◯◯◯ Very low[a,b]	RR 1.20 (0.93 to 1.57)	16 per 1,000	3 more per 1,000 (1 fewer to 9 more)
Any adverse event 28 days	12639 (1 RCT)	⊕◯◯◯ Very low[a,b]	RR 1.16 (0.95 to 1.43)	27 per 1,000	4 more per 1,000 (1 fewer to 12 more)
All vascular occlusive events (fata and non fatal) 28 days	12639 (1 RCT) CRASH-3 2019	⊕◯◯◯ Very low[a,b]	RR 0.98 (0.74 to 1.28)	16 per 1,000	0 fewer per 1,000 (4 fewer to 5 more)
Adverse events: pulmonary embolism (PE) 28 days	12639 (1 RCT) CRASH-3 2019	⊕◯◯◯ Very low[a,b]	RR 0.74 (0.44 to 1.26)	5 per 1,000	1 fewer per 1,000 (3 fewer to 1 more)
Adverse events: deep vein thrombosis (DVT) 28 days	12639 (1 RCT) CRASH-3 2019	⊕◯◯◯ Very low[a,b]	RR 1.17 (0.60 to 2.28)	3 per 1,000	0 fewer per 1,000 (1 fewer to 3 more)
Adverse events: stroke 28 days	12639 (1 RCT) CRASH-3 2019	⊕◯◯◯ Very low[a,b]	RR 1.08 (0.71 to 1.64)	7 per 1,000	1 more per 1,000 (2 fewer to 4 more)
Adverse events: myocardial infarction (MI) 28 days	12639 (1 RCT) CRASH-3 2019	⊕⊕◯◯ Low[a]	not estimable	3 per 1,000	3 fewer per 1,000 (3 fewer to 3 fewer)
All vascular occlusive events(fatal and non-fatal) in LMIC 28 days	8705 (1 RCT) Brenner 2020	⊕◯◯◯ Very low[a,b]	RR 1.41 (0.92 to 2.17)	8 per 1,000	3 more per 1,000 (1 fewer to 9 more)
All vascular occlusive events (fatal and non-fatal) in HIC 28 days	3934 (1 RCT) Brenner 2020	⊕◯◯◯ Very low[a,b]	RR 0.75 (0.52 to 1.07)	34 per 1,000	9 fewer per 1,000 (16 fewer to 2 more)

a. Downgraded by 2 increments for indirectness. Mixed severity based on GCS. Includes both TXA < 3 hours and > 3 hours of injury.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with TXA
b. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group for continuous outcomes).					

Table 13:Clinical evidence summary: TXA vs placebo (adults) in hospital setting including all participants (TXA< 3 hours and > 3 hours of injury)- mild and moderate TBI (GCS 9-15)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with TXA
vascular occlusive events (fatal and non-fatal) in mild/moderate 28 days	8063 (1 RCT) Brenner 2020	⨁◯◯◯ Very low[a,b]	RR 0.78 (0.52 to 1.16)	13 per 1,000	3 fewer per 1,000 (6 fewer to 2 more)
a. Downgraded by 2 increments for indirectness. Mixed severity based on GCS. Includes both TXA < 3 hours and > 3 hours of injury b. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group for continuous outcomes).					

Table 14:Clinical evidence summary: TXA vs placebo (adults) in hospital setting Including all participants (TXA < 3 hours and > 3 hours of injury)- severe TBI (GCS 3-8)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with TXA
vascular occlusive events (fatal and non-fatal) in severe 28 days	4511 (1 RCT) Brenner 2020	⨁⨁◯◯ Low[a,b]	RR 1.19 (0.82 to 1.73)	22 per 1,000	4 more per 1,000 (4 fewer to 16 more)
a. Downgraded by 1 increment for indirectness. Includes both TXA < 3 hours and > 3 hours of injury b. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group for continuous outcomes).					

See Appendix F for full GRADE tables.

1.1.7. Economic evidence

1.1.7.1. Included studies

Two health economic studies (in three papers) were included in this review.[7, 12, 13] These are summarised in the health economic evidence profile below (**Table 15**) and the health economic evidence table in Appendix H.

1.1.7.2. Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in 0.

1.1.8. Summary of included economic evidence

Table 15: Health economic evidence profile: Tranexamic acid plus standard care versus standard care

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Williams 2020[7, 12, 13] UK	Partially applicable[(a)]	Potentially serious limitations[(b)]	Probabilistic model based on within-RCT analysis (CRASH-3) **Subgroup A (base case):** Mild to moderate (GCS 9+) **Subgroup B:** Severe (GCS<9) **Subgroup C:** Severe but excluding those with GCS score of 3 or bilateral unreactive pupils Time horizon: Lifetime Setting: Hospital	**Subgroup A:** £759[(c)] **Subgroup B:** Not reported **Subgroup C:** Not reported	**Subgroup A:** 0.18 QALYs **Subgroup B:** Not reported **Subgroup C:** Not reported	**Subgroup A:** £4,288 per QALY gained **Subgroup B:** £18,519 per QALY gained **Subgroup C:** £18,672 per QALY gained	**Subgroup A:** Probability TXA cost effective (£20K/30K threshold): 99%/99% **Subgroup B:** Probability TXA cost effective (£20K/30K threshold): 62%/86% **Subgroup C:** Probability TXA cost effective (£20K/30K threshold): 65%/98% **Subgroup A** One-way sensitivity analyses were performed with respect to assumptions about utilities, monitoring costs, hospital stay, head injury risk ratio / timing of administration, discount rate, time horizon and excess mortality. Results were most sensitive when arm-specific utilities were estimated: the ICER increased to £14,465 per QALY gained.
Williams 2022[12] UK	Directly applicable	Potentially serious limitations[(d)]	Probabilistic Markov model Population: people aged 80 years with mild TBI	£96.69[(e)]	0.0198 QALYs	£4,858 per QALY gained	Sensitivity analysis showed that results were robust to changes in utility and relative risk of neurosurgery. A mean reduction of greater than 0.02 days hospital stay (mean length of 4 days) led

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
			Time horizon: 20 years (lifetime) Setting: Pre-hospital				to TXA no longer being cost-effective at £20k/QALY gained. An analysis of covariance (ANCOVA) showed that most of the variability in incremental costs and incremental QALYs was due to uncertainty in two parameters: the outcomes following mild TBI and the TXA mortality risk ratio. The EVPI at the £20k/QALY gained threshold was £22.4 million for the whole population (£37.06 per individual).

Abbreviations: ANCOVA= analysis of covariance; DRS=Disability Rating Scale; EVPI= expected value of perfect information; GCS=Glasgow Coma Score, ICER= incremental cost-effectiveness ratio; QALY= quality-adjusted life years; RCT= randomised controlled trial; TBI= traumatic brain injury; TXA=tranexamic acid

(a) People with mild severity and intracranial bleeding were combined with people with moderate severity. This group included patients from both low- and high-income countries. Some patients randomised more than 3 hours after head injury. Utility scores were based on the UK Time-trade-off tariff of the EQ-5D-3L, but they were not measured directly. They were mapped from Glasgow Outcome Score, which was assigned through clinical judgement based on DRS score. Otherwise, the study matched the NICE reference case and review protocol.

(b) Treatment effects were from a single trial rather than a systematic review, but it is the key trial in the hospital setting. Mortality was only followed up for 28 days. Quality of life was not measured in the trial, was derived using expert opinion, was assumed to be the same in both arms (in the base case) and was assumed to be constant over time. Although the results were robust to one-way sensitivity analyses, if both length of stay and DRS had been arm-specific then it is quite likely that the ICER would have been well over £20,000 per QALY.

(c) 2018 UK pounds. Cost components incorporated: Intervention costs, monitoring costs in added years of life (primary care visits, outpatient visits, formal carer time, and rehabilitation) and length of stay (in sensitivity analysis only).

(d) Treatment effects were from a single trial in a broader population and not in a pre-hospital setting. The treatment effect might be overestimated since it was based on a population of patients in hospital with an intracranial haematoma. Quality of life was not measured in the trial, was derived using expert opinion, was assumed to be the same in both arms (in the base case) and was assumed to be constant over time. The mean length of hospital stay was taken from an Australian setting. The GOS outcomes used in the model upon which utility scores were based upon were taken from patients of all ages.

(e) 2020 UK pounds. Cost components incorporated: Intervention costs, adverse event costs, hospital-related costs, monitoring costs

1.1.9. Economic analysis

1.1.10. CRASH-3 economic evaluation

In the absence of additional data that the committee had requested from the CRASH-3 trial, it was not feasible to complete an original model for TXA in a hospital population. However, the results of the published economic have been adjusted by the technical team to account for key omissions from the base case analysis - Table 16. The results were most sensitive to the introduction of differential utility between arms. When all 3 adjustments were made the cost per QALY gained exceeded £20,000 per QALY.

Table 16: CRASH-3 economic evaluation adjustments (Mild TBI with intracranial haematoma on CT and Moderate TBI combined)

	Cost (£)	QALYs	Cost per QALY (£)	Method
Base case				These results reported in Table 2 of Williams 2020
Placebo	55,110	12.10		
TXA	55,869	12.28		
TXA vs Placebo	759	0.18	4,288	
LOS Sensitivity analysis				Placebo arm from Base case. TXA QALYs from base case. Cost per QALY from Tornado diagram (Figure 3 Williams 2020). Then estimated the cost difference as the cost per QALY multiplied by the QALY difference.
Placebo	55,110	12.10		
TXA	56,084	12.28		
TXA vs Placebo	973	0.18	5,500	
Utility Sensitivity analysis				Placebo arm from Base case. TXA cost from base case. Cost per QALY from Tornado diagram (Figure 3 Williams 2020). Then estimated the QALY difference as the cost difference divided by the cost per QALY.
Placebo	55,110	12.10		
TXA	55,869	12.15		
TXA vs Placebo	759	0.052	14,500	
Non-TBI mortality Sensitivity analysis				Results from base case analysis and then reduced both the QALYs and costs in the TXA arm by 0.19% (29/2844 minus 23/2766 derived from Brennan 2020 supplementary Tables 1 and 3 mild/moderate cohort <3 hours from randomisation.)
Placebo	55,110	12.10		
TXA	55,764	12.25		
TXA vs Placebo	654	0.154	4,249	
All three adjustments				Costs from LOS Sensitivity analysis and QALYs from Utility Sensitivity analysis and then reduced both the QALYs and costs in the TXA arm by the 0.19%
Placebo	55,110	12.10		
TXA	55,978	12.13		

	Cost (£)	QALYs	Cost per QALY (£)	Method
TXA vs Placebo	868	0.029	29,427	

1.1.11. Original economic evaluation of tranexamic acid in a pre-hospital setting

A cost-utility analysis was undertaken based upon the randomised controlled study: The Prehospital TXA for TBI trial (Rowell 2020[8]). The following comparators were included in the analysis:

1. Tranexamic acid – 2g intravenous bolus in the out of hospital setting (Rowell 2020 n=345)
2. No tranexamic acid (based on the placebo group of Rowell 2020 n=309)

The population in the trial was people aged ≥15 with blunt and penetrating traumatic mechanism with a GCS score of 3 to 12, at least 1 reactive pupil, and systolic blood pressure of at least 90 mm Hg prior to randomisation.

Details of this analysis can be found in the separate Economic Analysis report. A bespoke analysis was conducted by the trial team so that the guideline team could conduct separate analyses for moderate TBI and severe TBI - Table 17. The results of the economic evaluation are presented in Table 18.

Table 17: Glasgow Outcome Scale at 6 months from Rowell 2020

	TXA		No TXA	
Health state	**Number of people**	**Proportion**	**Number of people**	**Proportion**
Moderate TBI				
Good recovery	99	62%	65	57%
Moderate disability	22	14%	20	18%
Severe disability	27	17%	17	15%
Vegetative state	0	0%	0	0%
Dead	11	7%	13	11%
Severe TBI				
Good recovery	66	38%	76	41%

	TXA		No TXA	
Health state	Number of people	Proportion	Number of people	Proportion
Moderate disability	32	18%	23	12%
Severe disability	41	23%	38	20%
Vegetative state	1	1%	3	2%
Dead	37	21%	46	25%

Table 18: Base case and sensitivity analyses (deterministic)

	Moderate TBI			Severe TBI		
	Mean cost difference (TXA – No TXA)	Mean QALY difference (TXA – No TXA)	Cost per QALY gained	Mean cost difference (TXA – No TXA)	Mean QALY difference (TXA – No TXA)	Cost per QALY gained
Base case (probabilistic)	£4,720	0.54	£8,805	£7,109	0.32	£22,310
Base case (deterministic)	£4,771	0.52	£9,102	£7,161	0.32	£22,256
Utilities						
Utility for vegetative state (VS) equals zero	£4,771	0.52	£9,110	£7,161	0.31	£22,797
Alternative values for utility (Smits 2010) and VS utility same as the base case value	£4,771	0.53	£8,990	£7,161	0.06	£112,978
Alternative values for utility (Smits 2010) and VS utility equals zero	£4,771	0.53	£8,997	£7,161	0.06	£128,444
Resource use and cost						
Halving the time to administer TXA	£4,768	0.52	£9,096	£7,158	0.32	£22,247
Extra day in ICU in TXA arm by	£3,217	0.52	£6,138	£8,840	0.32	£27,473
Double the impact on surgery rate	£5,128	0.52	£9,783	£7,518	0.32	£23,365
Excluding post-discharge costs	£1,705	0.52	£3,253	£1,705	0.32	£5,300

	Moderate TBI			Severe TBI		
	Mean cost difference (TXA – No TXA)	**Mean QALY difference (TXA – No TXA)**	**Cost per QALY gained**	**Mean cost difference (TXA – No TXA)**	**Mean QALY difference (TXA – No TXA)**	**Cost per QALY gained**
Treatment effects (GOS≥4)						
Odds ratio of 1.24 (with the ratio of good recovery and moderate disability the same as the base case)	£1,980	0.66	£3,000	£2,930	0.64	£4,569
Odds ratio of 1.24 (with no adjustment to good recovery)	£2,609	0.62	£4,187	£4,009	0.57	£6,996
Odds ratio of 1.32 (with the ratio of good recovery and moderate disability the same as the base case)	£158	0.75	£211	£908	0.79	£1,143
Odds ratio of 1.32 (with no adjustment to good recovery)	£1,198	0.69	£1,742	£2,503	0.69	£3,610
Other						
SMR of 2.2 applied to mortality after year 13	£4,483	0.49	£9,133	£6,630	0.30	£22,165
Five-year time horizon	£2,026	0.15	£13,361	£1,781	0.08	£22,084

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1.1.12. Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness.

Resource	Unit costs	Dose per patient	Cost per patient	Source
Tranexamic acid solution 500mg/5ml ampoule	£1.50	1g loading dose over 10 minutes followed by 1g infusion over 8 hours Or 2g bolus over 20 minutes	£6.00	Drug tariff, BNF (Last accessed 31st August 2022)

1.1.13. Evidence statements

1.1.13.1. Economic

- One cost–utility analysis found that in adults with traumatic brain injury (without significant extracranial bleeding) treated within 3 hours of their injury, tranexamic acid plus standard care was cost effective compared to standard care alone in three different subgroups:
  - Mild TBI with intracranial haematoma or moderate TBI (GCS 9+), (ICERs: £4,288 per QALY gained).
  - Severe TBI (GCS <9), (ICERs: £18,519 per QALY gained).
  - Severe TBI but excluding those with GC*S* score of 3 or bilateral reactive pupils (ICERs: £18,672 per QALY gained).

  * Adjustments by the guideline technical team suggested that the cost per QALY gained could be as high as £29,000.
  - This analysis was assessed as partially applicable with potentially serious limitations.
- Another cost–utility analysis found that in older adults with mild traumatic brain injury, tranexamic acid plus standard care was cost effective compared to standard care alone (ICER: £4,858 per QALY gained). This analysis was assessed as directly applicable with potentially serious limitations.
- An original cost-utility analysis found that tranexamic acid for people with a moderate TBI is cost effective compared to no tranexamic acid (£8,800 per QALY gained). This study was assessed as directly applicable with minor limitations.

  An original cost-utility analysis modelling for a severe TBI population found that tranexamic acid for people with a severe TBI was not cost effective compared to no tranexamic acid (£22,300 per QALY gained) at NICE's £20,000 threshold but is cost effective at NICE's £30,000 threshold. This study was assessed as directly applicable with potentially serious limitations due to the sensitivity of results.

1.1.14. The committee's discussion and interpretation of the evidence

1.1.14.1. The outcomes that matter most

The committee considered all outcomes as equally important for decision making and therefore have all been rated as critical: all-cause mortality at 30 days, mortality from head injury/TBI at 30 days, length of hospital stay, surgical intervention, objective measures of disability, serious adverse event, post-concussion syndrome, concussion/mild TBI and quality of life.

Evidence was available for all outcomes except for quality of life, post-concussion syndrome and concussion.

1.1.14.2. The quality of the evidence

Evidence from 2 randomised controlled trials was identified in this review. Both studies were in adults when there was no suspicion of extracranial bleeding. There was no evidence available for children and infants.

Evidence in the review was stratified based on setting (pre-hospital/out of hospital or hospital); timing of administration of TXA (> 3 hours of injury, > 3 hours of injury and combined < 3 hours and > 3 hours of injury) and severity of injury (mild/moderate/severe- based on GCS).

One study was in pre-hospital/out of hospital and the other in a hospital setting.

Pre-hospital setting

In the study in pre-hospital/out of hospital setting the median estimated time from injury to out-of-hospital TXA administration ranged from 40 to 43 minutes. Participants were eligible only if the study drug could be administered within 2 hours of injury. The study was analysed in the strata TXA administration < 3 hours injury and it included a mixed severity population (mild, moderate and severe TBI), however majority of the population in this study were with moderate and severe TBI. Data was not reported separately for different severities hence outcomes were downgraded for indirectness. This study included 2 does of TXA, 1-g IV tranexamic acid bolus in the out- of-hospital setting followed by a 1-g tranexamic acid IV infusion initiated upon hospital arrival and infused over 8 hours (bolus maintenance group), and 2-g IV tranexamic acid bolus in the out-of-hospital setting followed by a placebo infusion (bolus only group). Data was analysed separately for the 2 TXA doses. Randomisation was done pre-CT for all people.

In the pre-hospital/out of hospital setting, evidence was available for all outcomes except for TBI related mortality, quality of life, post-concussion syndrome and concussion.

Hospital setting

The study in the hospital setting was an international multi-centre RCT which included a mixed severity population (mild: GCS 13-15, moderate: GCS 9-12 and severe TBI: GCS 3-8). Data was not reported separately for mild, moderate and severe TBI as per protocol. Data was available for mixed severity population or as combined mild-moderate TBI (GCS 9-15) and severe population (GCS 3-8) separately. Most patients with isolated intracranial injury/isolated head injury presenting to NHS emergency departments are with mild TBI (GCS 13-15) and the lack of data separately for this population was noted and committee took this into account while interpreting the evidence.

Where data was not reported separately based on severity, outcomes were downgraded for indirectness.

This study included people within 8 hours of injury in the early phase and within 3 hours of injury in the later phase of the trial, hence data was analysed separately for TXA administration <3 hours and > 3 hours after injury and combined TXA > 3 hours and < 3 hours of injury. Data was downgraded for indirectness for outcomes reporting TXA > 3 hours and < 3 hours of injury. The study included a loading dose of 1 g of TXA infused over 10 min, started immediately after randomisation, followed by an intravenous infusion of 1 g over 8 hours.

In the study protocol, patients with mild TBI (GCS 13-15) were to be randomised post CT and patients with moderate and severe TBI (GCS 3-12) were to be randomised prior to CT. However, protocol was not adhered to in the majority of people with moderate and severe TBI due to diagnostic uncertainty particularly in intoxicated patients, mainly in high income countries (HICs) with easy access to CT. The committee noted the lack of clarity with regard to protocol violations and took this into account while interpreting the evidence.

In the hospital setting, evidence was only available for all-cause mortality, TBI related mortality, serious adverse events, and disability rating scale score. No evidence was available for quality of life, post-concussion syndrome/concussion, neurosurgical intervention and length of hospital.

The committee noted gaps in evidence in TXA in hospital setting particularly data separately based on timings of injury (example data not available for all-cause mortality, disability rating scale score not available for TXA< 3 hours of injury), severities (example disability rating scale score and serious adverse events not available for mild/moderate and severe TBI separately), and country income status (example TBI related mortality not available separately for mild/moderate population in low and middle income countries). Additional data was requested from the trial authors but were not made available.

Overall

The assessment of clinical benefit, harm, or no benefit or harm was based on the point estimate of absolute effect. For mortality any reduction represented a clinical benefit. For adverse events 20 events or more per 1000 (2%) represented clinical harm. For neurosurgical interventions 50 events less or more per 1000 (5%) was considered to be a clinically important difference. For continuous outcomes (disability rating scale scores and hospital free days at 28 days) if the mean difference was greater than the minimally important difference (MID) then it was considered to be clinically important.

Absolute effects could not be calculated for some outcomes as raw data was not available. For these outcomes' relative risk (RR) was reported from the papers. The committee used default MIDs (0.5 to 1.25) as a guide to assess clinical importance for these outcomes. The committee also took into account economic evaluation available for these outcomes for decision making.

The quality of the evidence ranged from moderate to very low. The main reasons for downgrading were indirectness, imprecision and risk of bias. Studies were not sufficiently powered, which increased the uncertainty around the point estimates. Studies were downgraded for indirectness if data was not reported separately for different severities (mild, moderate and severe) or combined different timings of injury (TXA < 3 hours and > 3 hours of injury). Some outcomes from a secondary publication of the study in hospital setting were downgraded for risk of bias, as they excluded people with a GCS score of 3 or bilateral unreactive pupils post-randomisation. The committee took into account the quality of the evidence, including the uncertainty in their interpretation of the evidence.

1.1.14.3. Benefits and harms

Pre-hospital setting - TXA vs Placebo (adults) -TXA < 3 hours of injury -Mixed GCS (mild, moderate and severe TBI)

Out-of-hospital tranexamic acid (1 g) bolus and in-hospital tranexamic acid (1 g) 8-hour infusion

The evidence suggested there was increased all-cause mortality at 28 days and 6 months with TXA compared to placebo, but there was uncertainty around the evidence There was no clinically important difference between TXA and placebo for hospital free days at 28 days, degree of disability at discharge and 6 months (GOS-E >4), serious adverse events (myocardial infarction, pulmonary embolism, deep vein thrombosis and stroke). There were more neurosurgical interventions in TXA group, but this was not found to be clinically important. The committee noted that more neurosurgical interventions is not necessarily a negative outcome as this would mean increased access to an intervention that could improve outcomes/survival in those with isolated head injury. The committee acknowledged that some uncertainty existed across the effect sizes seen within the evidence.

The evidence was mainly in people with moderate and severe TBI, there was only a very small proportion of people with mild TBI.

The committee discussed potential reasons for increased all-cause mortality with 1g TXA bolus and 1 g infusion dose. The average half-life of TXA is two hours following intravenous administration hence any delay in the administration of 2nd dose TXA in the hospital could reduce the effectiveness of first dose of 1g TXA leading to increased mortality.

Out-of-hospital tranexamic acid (2 g) bolus and in-hospital placebo 8-hour infusion

The evidence suggested there was reduced all-cause mortality at 28 days and 6 months with TXA compared to placebo, but there was uncertainty around the evidence. There was no clinically important difference between TXA and placebo for hospital free days at 28 days, degree of disability at discharge and 6 months (GOS-E >4), serious adverse events (myocardial infarction, pulmonary embolism, deep vein thrombosis and stroke). There were more neurosurgical interventions in TXA group, but this was not found to be clinically important. The committee noted that more neurosurgical interventions is not necessarily a negative outcome as this would mean increased access to an intervention that could improve outcomes/survival in those with isolated head injury. The committee acknowledged that some uncertainty existed across the effect sizes seen within the evidence.

Summary for pre-hospital/out of hospital TXA administration

In current practice some people with suspected isolated head injury are administered TXA in a pre-hospital/out of hospital setting. There is variation in TXA dosing regimens.

From the evidence, dosing protocol of a single TXA 2g bolus was found to be effective in reducing in all-cause mortality at 28 days and 6 months in a pre-hospital/out of setting.

The committee acknowledged that some uncertainty existed across the effect sizes seen within the evidence, with some confidence intervals crossing the MID thresholds or line of no effect. The committee considered that despite the uncertainty around the effect estimates, benefit of 2g TXA for reducing all-cause mortality with no evidence of negative effects when compared to placebo to justify a recommendation.

Hospital setting

TXA vs placebo-1 g of TXA infused over 10 min, started immediately after randomisation, followed by an intravenous infusion of 1 g over 8 hours.

TXA < 3 hours of injury [mixed severity (mild moderate and severe), mild-moderate TBI and severe TBI]

Mixed severity

The evidence suggested that there was reduced TBI related mortality at 28 days for TXA compared to placebo in people with mixed severity (mild, moderate and severe). There was reduced TBI related mortality at 28 days for TXA compared to placebo in people with reactive pupils (both react) at 28 days whereas there was increased TBI mortality in people with any un-reactive pupils. People with un-reactive pupils are considered have a very poor prognosis. There was no clinically important difference between TXA and placebo for serious adverse events (myocardial infarction, pulmonary embolism, deep vein thrombosis and stroke) and disability rating scale score in this population. The committee acknowledged that some uncertainty existed across the effect sizes seen within the evidence.

Mild- Moderate TBI

The evidence suggested that there was reduced TBI related mortality at 28 days for TXA compared to placebo in people with mild-moderate TBI, but there was uncertainty around the evidence.

Severe TBI

The evidence suggested that there was reduced TBI related mortality at 28 days for TXA compared to placebo in people with severe TBI. Evidence suggested reduced TBI related mortality at 28 days in severe TBI in high income countries however there was no difference for the above outcome in low- and middle-income countries.

Summary for hospital setting

The committee acknowledged that some uncertainty existed across the effect sizes seen within the evidence, with some confidence intervals crossing the MID thresholds or line of no effect. The committee took into account the quality of the evidence, including the uncertainty in their interpretation of the evidence.

There was no evidence for each severity separately, but evidence was available for combined mild-moderate TBI (GCS 9-15) and severe TBI (GCS 3-8). Hence it was not clear which group (mild or moderate) benefited from TXA administration. Given the lack of evidence and clarity of evidence in people with mild TBI (GCS 13-15) the committee did not make a recommendation for this group. They decided to make a research recommendation for people with high risk mild TBI to help inform future guidelines.

Overall summary

Based on the evidence reviewed for TXA < 3 hours in hospital setting and extrapolation of evidence for TXA in pre-hospital setting, the committee agreed to make a recommendation to consider TXA administration for moderate TBI and severe TBI within 2 hours of injury before imaging. Evidence for TXA <3 hours in hospital setting suggested benefit of TXA for reducing TBI mortality at 28 days particularly for moderate and severe TBI. Evidence for TXA in pre-hospital setting suggested benefit of 2g TXA for reducing all-cause mortality (at 28 days and 6 months) with no evidence of negative effects. Majority of this population were moderate or severe TBI. The committee considered that despite the uncertainty around the effect estimates, benefit of TXA for reducing all-cause mortality and TBI mortality when compared to placebo and very few adverse events in either arm to justify a recommendation. The committee recommended a dosing regimen of 2g intravenous bolus injection of TXA (TXA dose used in evidence for pre-hospital setting) instead of 1g bolus pre-hospital followed by an intravenous infusion over 8 hours in hospital (TXA dose used in the evidence for hospital setting), as this dose was found to be safe and effective.

TXA < 3 hours of injury - Excluding those with a GCS score of 3 or bilateral unreactive pupils

[mixed severity (mild moderate and severe), mild-moderate TBI and severe TBI]

Absolute effects were not available for any of the outcomes for this group. Relative risks were used to assess clinical importance for all the outcomes.

Mixed severity

The evidence suggested that there was reduced all-cause mortality within 24 hours of injury for all participants and in both in low-middle income and high-income countries.

There was reduced all-cause mortality after 24 hours of injury in high income countries (HIC).

There was reduced all-cause mortality at 28 days of injury in all participants, and in both low- and middle-income countries (LMIC) and HIC. There was no difference between TXA and placebo for all-cause mortality after 24 hours of injury in all participants and in low- and middle-income countries (LMIC). The committee acknowledged that some uncertainty existed across the effect sizes seen within the evidence.

Mild-moderate TBI

The evidence suggested that there was reduced all-cause mortality within 24 hours for all participants, all-cause mortality after 24 hours of injury in all participants and all-cause mortality at 28 days of injury in all participants. The committee acknowledged that some uncertainty existed across the effect sizes seen within the evidence.

Severe TBI

The evidence suggested that there was reduced all-cause mortality within 24 hours in all participants. There was no difference between TXA and placebo for all-cause mortality after 24 hours of injury in all participants and all-cause mortality at 28 days of injury in all participants.

There was a large benefit for TXA compared to placebo for TBI related mortality in high income countries however this difference was not observed in low- and middle-income countries. The committee discussed that this difference could be attributed to delay in transfer to hospital/administration of TXA in low- and middle-income countries. There was no evidence available for any other outcomes.

There was uncertainty across the effect sizes, with some confidence intervals crossing the MID thresholds or line of no effect. The committee took into account the quality of the evidence, including the uncertainty in their interpretation of the evidence.

Because of a lack of sufficient evidence, the committee did not make any recommendations for this group. However, the committee did not make a research recommendation for this group this as they did not consider it to be a priority for research recommendation.

TXA > 3 hours of injury [mixed severity (mild moderate and severe)]

Evidence for people with mixed severity (mild, moderate and severe) suggested that there was no clinically important difference between TXA and placebo for all vascular occlusive events, myocardial infarction, deep vein thrombosis, pulmonary embolism and stroke and disability rating scale score. There was no evidence available for all-cause mortality or TBI related mortality. The committee acknowledged that some uncertainty existed across the effect sizes seen within the evidence.

The committee from their knowledge and experience noted that benefit of TXA > 3 hours of injury is very low. Based on this and the evidence the committee agreed not to make any recommendation or research recommendation for this group. The committee did not make a not use TXA>3 hours recommendation because people have operative indications which would benefit from TXA.

TXA < 3 hours and >3 hours of injury [mixed severity (mild moderate and severe), mild-moderate TBI and severe TBI]

Mixed severity

Evidence suggested that there was increased non-head injury deaths with TXA in people with mixed severity (mild, moderate and severe TBI). There was no clinically important difference between TXA and placebo for all vascular occlusive events (in all participants, low-middle income and high-income countries), myocardial infarction, deep vein thrombosis, pulmonary embolism and stroke in the mixed severity population. The committee acknowledged that some uncertainty existed across the effect sizes seen within the evidence.

The committee discussed non-head injury deaths could be related to either severity of injury (moderate and severe injury), timing of administration of TXA (TXA administered after 3 hours) or due to adverse effects of TXA.

Mild- Moderate TBI

There was also no clinically important difference between TXA and placebo for all vascular occlusive events in mild-moderate TBI, but there was uncertainty around the evidence.

Severe TBI

There was also no clinically important difference between TXA and placebo for all vascular occlusive events in severe TBI, but there was uncertainty around the evidence.

The committee agreed there is insufficient evidence to make a recommendation particularly for TXA > 3 hours of injury.

Infants and children

There was no evidence for TXA in infants and children.

Current practice is variable. TXA is not routinely administered but there is growing practice for TXA administration in infants and children with isolated head injury.

The committee's experience is that adverse effects of TXA are very rare in children. Seizures and thromboembolic events are reported in children; however, they are found to occur at a lower rate than adults.

TXA dose is variable in clinical practice. TXA dose of 15 mg/kg is used in infants and children with extra cranial injuries however this dose is not widely used in infants and children with isolated head injury.

Due to lack of evidence for TXA in children, the committee made its recommendation through extrapolation of the evidence identified in adults and consensus based on expertise and knowledge in this area. Evidence in adults in a pre-hospital setting suggested benefit of 2g TXA for reducing all-cause mortality (at 28 days and 6 months) with no evidence of negative effects. Hence the committee considered to recommend the equivalent of 2g adult TXA dose for infants and children with a range of 15-30mg/kg. The committee discussed that adult dose of TXA 2g would equate to 30mg/kg in children, considering average adult weight as 70 kg. This upper limit is to avoid exceeding the equivalent adult 2g TXA dose.

The committee did not make a research recommendation as it not feasible to conduct trials in this group, as only a small proportion of children have intracranial injury with adverse outcomes (around 500 children per year in the UK).

The committee are aware of an ongoing TXA trial in children younger than 18 years with haemorrhagic injuries to the torso and/or brain to evaluate the efficacy of TXA (TIC-TOC-Traumatic Injury Clinical Trial Evaluating Tranexamic Acid in Children). The trial compares 2 doses of TXA (15 mg/kg and 30 mg/kg) with placebo. The feasibility trial did not meet the inclusion criteria for this review as it included a mixed population (isolated brain injury and isolated torso injury) with only sixteen participants with isolated brain injury.

Older/frail adults who have suffered a fall

Older adults who have suffered a fall was a sub-group considered in the review. There was no evidence available for this group. Although this population was not excluded, they are generally not eligible for the trials as it requires them to have CT scan within 3 hours of injury. The committee from their prior knowledge of research [11] noted that this group generally comprise people living alone at home, and it would not be possible for them to be in the ED and have CT scan within 3 hours. Mechanism of injury and frequency of anti-coagulation medication is also different in this population. The committee were uncertain if the evidence in adults could be extrapolated to this group hence, they did not make any specific recommendations for older adults.

The committee did not make a research recommendation because it was aware of a large ongoing CRASH-4 trial (Anti-fibrinolytic in Symptomatic Mild Head Injury in Older Adults) which addresses this population. The CRASH-4 trial aims to assess the effects of early intramuscular TXA on intracranial haemorrhage, disability, death, and dementia in older adults with symptomatic mild head injury. This could allow evidence-based recommendations to be made in future guideline updates.

1.1.14.4. Cost effectiveness and resource use

Resource use

Tranexamic acid has a low acquisition cost and is a one-off intervention. Its use results in additional downstream costs for the treatment of complications, such as thromboembolic events, and for the treatment, rehabilitation, and care for those people whose lives were saved.

For major trauma (including head injury combined with other trauma), tranexamic acid is routinely given, usually pre-hospital. However, for isolated head injury, tranexamic acid is administered only in some places. The cost impact of tranexamic for isolated head injury in terms of the drug itself would be small but the impact on hospital stay and rehabilitation might be more significant.

The committee discussed the use of a 2g bolus instead of 1g bolus pre-hospital followed by an intravenous infusion over 8 hours in hospital. If safe and effective, this would allow patients to be discharged earlier, freeing up a trolley in the emergency department to be used by another patient.

Published cost-effectiveness evidence

An economic evaluation was identified that was conducted as part of the CRASH-3 trial where adults received tranexamic acid in the emergency department.

A published economic focused on the group that were either:

- Moderate TBI severity (GCS 9-12)
- Mild TBI severity (GCS 13-15) with a bleed on CT scan.

The study combined mild with moderate TBI severity, so it was not clear in which group treatment was most effective and cost effective. The study found tranexamic acid to be highly cost effective in this population but there were several potentially serious limitations. In the base case analysis, the main benefits of tranexamic acid were accounted for but not the complications:

a. It was assumed that there was no difference in length of stay
b. It was assumed that there was no difference in quality of life
c. It was also assumed that there was no difference in non-TBI mortality, whereas there was a trend towards increased non-TBI deaths (mainly stroke and MI) in the tranexamic arm of CRASH-3.

The first was captured by sensitivity analyses in the published paper. In a supplementary table of one of the CRASH-3 papers there was an absolute increase of non-TBI deaths 0.19% in the mild/moderate severity group, although this included patients from low as well as high income countries. Adjustments were made by the guideline technical team to the results of the economic evaluation accounting for all 3 of these limitations. Incorporating length of stay and non-TBI mortality made little difference to the cost per QALY gained (about £5,000). Adjusting for differences in disease severity is harder because it is not known how long any difference will persist. When the mapped differential utility (of just 0.01) was assumed to persist over the lifetime the cost per QALY increased to around £29,000. The

committee decided that it was not possible to make conclusions about the cost effectiveness of TXA from this study and that it was important that mild TBI and moderate TBI populations are analysed separately.

In addition to the main analysis, the CRASH-3 economic evaluation reported sensitivity analyses for the severe TBI group. This was about £18,000 per QALY (or £20,000 per QALY after adjusting for difference in length of stay and non-TBI mortality). It is not known if disability levels were better or worse with tranexamic acid for this sub-population.

A second paper by the same team modelled the cost effectiveness of TXA in older people with mild TBI. TXA was found to be cost effective, but this was extrapolating evidence of mortality reduction from a population with mild TBI and an intracranial haematoma on CT scan to the population of older people pre-hospital. This would almost certainly over-estimate the all-cause mortality reduction, since the target population has a lower risk of TBI mortality but would still be exposed to the risks associated with TXA. The authors reasonably concluded that the cost-effectiveness is uncertain for this group due to the uncertain mortality effect.

Original economic modelling

The committee decided to develop an original cost-utility analysis based on the Prehospital TXA for TBI trial, for the following reasons:

a) tranexamic acid was administered in a pre-hospital setting in the trial, which is consistent with current practice for major trauma;
b) the trial population is mainly people with moderate or severe TBI;
c) the study reported all-cause mortality and disability levels at 6 months (compared with 28 days in CRASH-3) and mean length of hospital stay.

A bespoke analysis was conducted for the guideline by the trial team that stratified the 6-month GOSE by TBI severity. Survival beyond 6 months was estimated from a UK cohort, which again was stratified by TBI severity. In the absence of transition data, it was assumed that a patient's GOS state would remain unchanged over their lifetime.

Economic modelling was also conducted around the use of TXA in a pre-hospital setting for people who have mild TBI but who would qualify for urgent CT scanning. For this analysis, benefits were estimated for the subgroup with an intracranial haematoma. The proportion of patients with an intracranial haematoma was assumed to be 10% based on expert opinion.

Adults - Mild traumatic brain injury

The driver of the benefit in the CRASH-3 economic evaluation for mild and moderate severity was the difference in TBI deaths but given that there were few TBI deaths specifically in the mild severity subgroup, the applicability of these results to people with mild severity head injury is questionable.

Modelling conducted for this guideline suggested that TXA might be cost effective for people with mild TBI, especially in the subgroup of people who are GCS 13-14 but this was using an indirect estimate of effectiveness (See Economic Analysis report). Similarly, a published model suggested that TXA might be cost effective for older people with mild TBI but this was dependent on the size of the effect on all-cause mortality, which is uncertain.

Without direct evidence of effectiveness specifically in the mild severity group, and aware that there are risks, the committee did not recommend tranexamic acid in this group. However, given the modelling results for mild TBI (based on expert opinion) and the cost effectiveness of TXA in the moderate TBI group (see below), the committee made a research recommendation for those patients who have mild TBI but who are at relatively high risk of having an intracranial bleed.

Adults – Moderate traumatic brain injury

The guideline model found tranexamic acid to be highly cost effective for the moderate TBI group - £8,800 per QALY in the base case analysis. This was robust to all sensitivity analyses. Therefore, the committee recommended the early use of TXA in this group. However, they did not make it a strong recommendation because the evidence was from a single trial, which showed no significant difference in its primary outcome.

Adults – Severe traumatic brain injury

In the base case of the guideline model, tranexamic acid cost about £22,300 per QALY gained in the severe TBI group. Being over £20,000 per QALY the cost effectiveness would seem borderline. There were sensitivity analyses where the cost per QALY gained was even higher:

- When alternative (lower) utility values for disability were used, TXA cost £112,000 per QALY. The moderate and severe TBI groups saw similar absolute reductions in mortality at 6 months but only in the severe TBI group this was offset by an increase in severe disability. However, there were reasons to conclude that the base case utility values were much more robust, being based on the UK tariff of the EQ-5D-3L and in a much larger population.
- Length of stay was available for the trial population as a whole and not separately for severe TBI. The committee pondered what if the increased time in ICU was all attributable to the severe TBI patients and none of it to the moderate TBI patients. When the increase in ICU stay was doubled from 1 day to 2 days, TXA cost £27,500 per QALY. However, this was considered unlikely, as the absolute improvement in survival in the trial was the same for the moderate and severe TBI strata.

There were also reasons to believe that the cost per QALY was over-estimated:

- Due to lack of data, the model assumed that people stay in the same GOS state over their lifetime, whereas it is likely that some people will continue to improve beyond 6-months. This means that the QALYs would have been under-estimated.
- Within each TBI severity group the baseline TBI severity was substantially poorer in the 2g bolus arm than in the placebo arm of the trial. When a sensitivity analysis was conducted using the adjusted odds ratio for GOSE>4 from the trial the cost per QALY gained reduced to as low as £1,100. The adjusted odds ratio was not applied in the base case analysis, since it was not specific to the moderate TBI or severe TBI strata but was calculated for the trial as a whole. Hence this sensitivity analysis is not necessarily better than the base case analysis, but it does hint that the effectiveness in the model might have been under-estimated.

The committee decided that it was likely that TXA is cost effective for people with severe TBI.

Children

There was no evidence for children. The committee considered the benefits, risks and costs for children with moderate or severe head injury would be similar to those of adults.

1.1.14.5. Other factors the committee took into account

It was noted that the TXA considered within this review does not have a UK marketing authorisation for isolated head injury and are used off license.

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Appendices

Appendix A – Review protocols

Review protocol for tranexamic acid (TXA)

ID	Field	Content
0.	PROSPERO registration number	273433
1.	Review title	Tranexamic acid (TXA)
2.	Review question	What is the clinical and cost effectiveness of tranexamic acid for suspected or confirmed isolated traumatic intracranial bleeding pre-hospital and in hospital?
3.	Objective	To determine the clinical and cost-effectiveness of tranexamic acid for managing suspected or confirmed isolated traumatic intracranial bleeding pre-hospital and in hospital.
4.	Searches	The following databases (from inception) will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by:

		English language studies Human studies Letters and comments are excluded Other searches: Inclusion lists of systematic reviews will be checked by the reviewers The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).
5.	Condition or domain being studied	Head Injury
6.	Population	Inclusion: All adults and children (including infants under 1 year) with suspected or confirmed isolated traumatic intracranial bleeding Stratified by: Age • Adults (aged ≥16 years) • Children (aged ≥1 to <16 years) • infants (aged <1 year)

		Severity of traumatic brain injury (TBI)/Degree of consciousness based on GCS (Glasgow Coma Scale) • Mild GCS 13-15 • Moderate 9-12 • Severe GCS 3-8 Data with different categories of GCS will be included but downgraded for indirectness Timing of TXA • <3 hours of injury • >3 hours of injury Exclusion: Adults and children (including infants under 1 year) with superficial injuries to the eye or face without suspected or confirmed head or brain injury. Adults and children with head injury (including infants under 1 year) and significant extracranial bleeding. To note whether within trials randomisation occurred prior to or after CT.
7.	Intervention	• Tranexamic acid (TXA)
8.	Comparator	• Control (to include placebo or study arm receiving no TXA)
9.	Types of study to be included	• Systematic reviews of RCTs

		• RCTs • If no RCT evidence is available for any of the identified strata, non-randomised studies will be considered for those strata if they adjust for key confounders, starting with prospective cohort studies Published IPDs will be considered for inclusion. Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available. Confounding factor: • Age
10.	Other exclusion criteria	Non-English language studies. Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available.
11.	Context	TXA has been shown to reduce surgical bleeding and decreases mortality in patients with traumatic extracranial bleeding. Intracranial bleeding is common after head injury and can cause brain herniation and death. TXA can be administered within the pre-hospital and hospital setting in people who have experienced an isolated head injury to manage intracranial bleed in a bid to reduce morbidity and mortality.
12.	Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making and therefore have all been rated as critical: • Mortality from head injury/TBI at ≤30 days. • All-cause mortality at ≤30 days. • Objective measures of disability (including (Extended) Glasgow Outcome Scale, King's Outcome Scale for Childhood Head Injury and Cerebral Performance Category scale, Rivermead Post-Concussion Syndrome Questionnaire, Disability rating scale). • Quality of life (validated quality of life scores only). • Length of hospital stay.

		• Serious adverse event • Surgical intervention • Post-concussion syndrome • Concussion/mild TBI Outcomes will be grouped at <30 days, 30 days-6 months, 6-12 months, and at yearly time-points thereafter.
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. Or use following text if using EPPI: All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. This review will make use of the priority screening functionality within the EPPI-reviewer software. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately

		• a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary. Study investigators may be contacted for missing data where time and resources allow.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual For Intervention reviews • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0) • Non randomised study, including cohort studies: Cochrane ROBINS-I
16.	Strategy for data synthesis	• Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). Fixed-effects (Mantel-Haenszel) techniques will be used to calculate risk ratios for the binary outcomes where possible. Continuous outcomes will be analysed using an inverse variance method for pooling weighted mean differences. • Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects. • GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements

		(risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. • The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ • Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. • If data is available according to country income status, a sensitivity analysis will be performed to review the impact of country income on outcome. A sensitivity analysis excluding data from low/middle income countries will be performed to review if data from only high-income countries is significantly different from the estimates from the pooled datasets.	
17.	Analysis of sub-groups	Subgroups that will be investigated if heterogeneity is present: Older adults • older/frail adults who have suffered a fall	
18.	Type and method of review	☒	Intervention
		☐	Diagnostic
		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery

<table>
<tr><td></td><td></td><td>☐</td><td colspan="3">Other (please specify)</td></tr>
<tr><td>19.</td><td>Language</td><td colspan="4">English</td></tr>
<tr><td>20.</td><td>Country</td><td colspan="4">England</td></tr>
<tr><td>21.</td><td>Anticipated or actual start date</td><td colspan="4">[For the purposes of PROSPERO, the date of commencement for the systematic review can be defined as any point after completion of a protocol but before formal screening of the identified studies against the eligibility criteria begins.

A protocol can be deemed complete after sign-off by the NICE team with responsibility for quality assurance.]</td></tr>
<tr><td>22.</td><td>Anticipated completion date</td><td colspan="4">[Give the date by which the guideline is expected to be published. This field may be edited at any time. All edits will appear in the record audit trail. A brief explanation of the reason for changes should be given in the Revision Notes facility.]</td></tr>
<tr><td rowspan="7">23.</td><td rowspan="7">Stage of review at time of this submission</td><td>Review stage</td><td>Started</td><td>Completed</td></tr>
<tr><td>Preliminary searches</td><td>☐</td><td>☐</td></tr>
<tr><td>Piloting of the study selection process</td><td>☐</td><td>☐</td></tr>
<tr><td>Formal screening of search results against eligibility criteria</td><td>☐</td><td>☐</td></tr>
<tr><td>Data extraction</td><td>☐</td><td>☐</td></tr>
<tr><td>Risk of bias (quality) assessment</td><td>☐</td><td>☐</td></tr>
<tr><td>Data analysis</td><td>☐</td><td>☐</td></tr>
</table>

24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail [Guideline email]@nice.org.uk [Developer to check with Guideline Coordinator for email address] 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and [National Guideline Alliance / National Guideline Centre / NICE Guideline Updates Team / NICE Public Health Guideline Development Team] [Note it is essential to use the template text here and one of the centre options to enable PROSPERO to recognise this as a NICE protocol]
25.	Review team members	[Give the title, first name, last name and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong.] From the National Guideline Centre: [Guideline lead] [Senior systematic reviewer] Systematic reviewer [Health economist] [Information specialist] [Others]
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.

27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: [NICE guideline webpage].
29.	Other registration details	[Give the name of any organisation where the systematic review title or protocol is registered (such as with The Campbell Collaboration, or The Joanna Briggs Institute) together with any unique identification number assigned. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.]
30.	Reference/URL for published protocol	[Give the citation and link for the published protocol, if there is one.]
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE. [Add in any additional agree dissemination plans.]
32.	Keywords	[Give words or phrases that best describe the review.]

33.	Details of existing review of same topic by same authors	[Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible. NOTE: most NICE reviews will not constitute an update in PROSPERO language. To be an update it needs to be the same review question/search/methodology. If anything has changed it is a new review]	
34.	Current review status	☐	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information	[Provide any other information the review team feel is relevant to the registration of the review.]	
36.	Details of final publication	www.nice.org.uk	

1 Health economic review protocol

2 Table 19: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.

Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below. The search covered all years
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2006, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published in 2006 or later that were included in the previous guidelines will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[6] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:*

	• UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2006 or later (including any such studies included in the previous guidelines) but that depend on unit costs and resource data entirely or predominantly from before 2006 will be rated as 'Not applicable'. • Studies published before 2006 (including any such studies included in the previous guidelines) will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

1

Appendix B – Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[6]

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies as these concepts may not be indexed or described in the title or abstract and are therefore difficult to retrieve.

Table 20: Database parameters, filters and limits applied

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 22 June 2022	Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	1974 – 22 June 2022	Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
The Cochrane Library (Wiley)	Cochrane Reviews to 2022 Issue 6 of 12 CENTRAL to 2022 Issue 6 of 12	

Medline (Ovid) search terms

1.	craniocerebral trauma/ or exp brain injuries/ or coma, post-head injury/ or exp head injuries, closed/ or head injuries, penetrating/ or exp intracranial hemorrhage, traumatic/ or exp skull fractures/
2.	((skull or cranial) adj3 fracture*).ti,ab.
3.	((head or brain or craniocerebral or cranial or cerebral or skull) adj4 (injur* or trauma*)).ti,ab.
4.	(trauma* and ((subdural or intracranial) adj2 (h?ematoma* or h?emorrhage* or bleed*))).ti,ab.
5.	or/1-4
6.	letter/
7.	editorial/
8.	news/
9.	exp historical article/
10.	Anecdotes as Topic/
11.	comment/
12.	case report/

13.	(letter or comment*).ti.
14.	or/6-13
15.	randomized controlled trial/ or random*.ti,ab.
16.	14 not 15
17.	animals/ not humans/
18.	exp Animals, Laboratory/
19.	exp Animal Experimentation/
20.	exp Models, Animal/
21.	exp Rodentia/
22.	(rat or rats or mouse or mice or rodent*).ti.
23.	or/16-22
24.	5 not 23
25.	limit 24 to English language
26.	Tranexamic Acid/
27.	(tranexamic or txa or cyklokapron).ti,ab.
28.	or/26-27
29.	25 and 28

13 **Embase (Ovid) search terms**

1.	head injury/
2.	exp brain injury/
3.	skull injury/ or exp skull fracture/
4.	((head or brain or craniocerebral or cranial or cerebral or skull) adj4 (injur* or trauma*)).ti,ab.
5.	((skull or cranial) adj3 fracture*).ti,ab.
6.	(trauma* and ((subdural or intracranial) adj2 (h?ematoma* or h?emorrhage* or bleed*))).ti,ab.
7.	or/1-6
8.	letter.pt. or letter/
9.	note.pt.
10.	editorial.pt.
11.	(conference abstract or conference paper).pt.
12.	case report/ or case study/
13.	(letter or comment*).ti.
14.	or/8-13
15.	randomized controlled trial/ or random*.ti,ab.
16.	14 not 15
17.	animal/ not human/
18.	nonhuman/
19.	exp Animal Experiment/
20.	exp Experimental Animal/
21.	animal model/
22.	exp Rodent/
23.	(rat or rats or mouse or mice or rodent*).ti.
24.	or/16-23

25.	7 not 24
26.	limit 25 to English language
27.	tranexamic acid/
28.	(tranexamic or txa or cyklokapron).ti,ab.
29.	1197-18-8.rn.
30.	or/27-29
31.	26 and 30

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Craniocerebral Trauma] this term only
#2.	MeSH descriptor: [Brain Injuries] explode all trees
#3.	MeSH descriptor: [Coma, Post-Head Injury] this term only
#4.	MeSH descriptor: [Head Injuries, Closed] explode all trees
#5.	MeSH descriptor: [Head Injuries, Penetrating] this term only
#6.	MeSH descriptor: [Intracranial Hemorrhage, Traumatic] explode all trees
#7.	MeSH descriptor: [Skull Fractures] explode all trees
#8.	((skull or cranial) near/3 fracture*):ti,ab
#9.	((head or brain or craniocerebral or cranial or skull) near/3 (injur* or trauma*)):ti,ab
#10.	(trauma* and ((subdural or intracranial) near/2 (h?ematoma* or h?emorrhage* or bleed*))):ti,ab
#11.	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
#12.	MeSH descriptor: [Tranexamic Acid] this term only
#13.	(tranexamic or txa or cyklokapron):ti,ab
#14.	#12 or #13
#15.	#11 AND #14

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting searches using terms for a broad Head Injury population. The following databases were searched: NHS Economic Evaluation Database (NHS EED - this ceased to be updated after 31st March 2015), Health Technology Assessment database (HTA - this ceased to be updated from 31st March 2018) and The International Network of Agencies for Health Technology Assessment (INAHTA). Searches for recent evidence were run on Medline and Embase from 2014 onwards for health economics, and all years for quality-of-life studies.

Table 20: Database parameters, filters and limits applied

Database	Dates searched	Search filters and limits applied
Medline (OVID)	Health Economics 1 January 2014 – 22 June 2022	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
	Quality of Life 1946 – 22 June 2022	

Database	Dates searched	Search filters and limits applied
Embase (OVID)	Health Economics 1 January 2014 – 22 June 2022	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
	Quality of Life 1974 – 22 June 2022	
NHS Economic Evaluation Database (NHS EED) (Centre for Research and Dissemination - CRD)	Inception –31st March 2015	
Health Technology Assessment Database (HTA) (Centre for Research and Dissemination – CRD)	Inception – 31st March 2018	
The International Network of Agencies for Health Technology Assessment (INAHTA)	Inception – 22 June 2022	English language

24 **Medline (Ovid) search terms**

1.	craniocerebral trauma/ or exp brain injuries/ or coma, post-head injury/ or exp head injuries, closed/ or head injuries, penetrating/ or exp intracranial hemorrhage, traumatic/ or exp skull fractures/
2.	((skull or cranial) adj3 fracture*).ti,ab.
3.	((head or brain or craniocerebral or intracranial or cranial or skull) adj3 (injur* or trauma*)).ti,ab.
4.	(trauma* and ((subdural or intracranial or brain) adj2 (h?ematoma* or h?emorrhage* or bleed*))).ti,ab.
5.	or/1-4
6.	letter/
7.	editorial/
8.	news/
9.	exp historical article/
10.	Anecdotes as Topic/
11.	comment/
12.	case report/
13.	(letter or comment*).ti.
14.	or/6-13
15.	randomized controlled trial/ or random*.ti,ab.
16.	14 not 15
17.	animals/ not humans/
18.	exp Animals, Laboratory/
19.	exp Animal Experimentation/

20.	exp Models, Animal/
21.	exp Rodentia/
22.	(rat or rats or mouse or mice or rodent*).ti.
23.	or/16-22
24.	5 not 23
25.	limit 24 to English language
26.	economics/
27.	value of life/
28.	exp "costs and cost analysis"/
29.	exp Economics, Hospital/
30.	exp Economics, medical/
31.	Economics, nursing/
32.	economics, pharmaceutical/
33.	exp "Fees and Charges"/
34.	exp budgets/
35.	budget*.ti,ab.
36.	cost*.ti.
37.	(economic* or pharmaco?economic*).ti.
38.	(price* or pricing*).ti,ab.
39.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
40.	(financ* or fee or fees).ti,ab.
41.	(value adj2 (money or monetary)).ti,ab.
42.	or/26-41
43.	quality-adjusted life years/
44.	sickness impact profile/
45.	(quality adj2 (wellbeing or well being)).ti,ab.
46.	sickness impact profile.ti,ab.
47.	disability adjusted life.ti,ab.
48.	(qal* or qtime* or qwb* or daly*).ti,ab.
49.	(euroqol* or eq5d* or eq 5*).ti,ab.
50.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
51.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
52.	(hui or hui1 or hui2 or hui3).ti,ab.
53.	(health* year* equivalent* or hye or hyes).ti,ab.
54.	discrete choice*.ti,ab.
55.	rosser.ti,ab.
56.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
57.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
58.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.

59.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
60.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
61.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
62.	or/43-61
63.	25 and (42 or 62)

25 **Embase (Ovid) search terms**

1.	head injury/
2.	exp brain injury/
3.	skull injury/ or exp skull fracture/
4.	((head or brain or craniocerebral or intracranial or cranial or skull) adj3 (injur* or trauma*)).ti,ab.
5.	((skull or cranial) adj3 fracture*).ti,ab.
6.	(trauma* and ((subdural or intracranial or brain) adj2 (h?ematoma* or h?emorrhage* or bleed*))).ti,ab.
7.	or/1-6
8.	letter.pt. or letter/
9.	note.pt.
10.	editorial.pt.
11.	(conference abstract or conference paper).pt.
12.	case report/ or case study/
13.	(letter or comment*).ti.
14.	or/8-13
15.	randomized controlled trial/ or random*.ti,ab.
16.	14 not 15
17.	animal/ not human/
18.	nonhuman/
19.	exp Animal Experiment/
20.	exp Experimental Animal/
21.	animal model/
22.	exp Rodent/
23.	(rat or rats or mouse or mice or rodent*).ti.
24.	or/16-23
25.	7 not 24
26.	limit 25 to English language
27.	health economics/
28.	exp economic evaluation/
29.	exp health care cost/
30.	exp fee/
31.	budget/
32.	funding/
33.	budget*.ti,ab.
34.	cost*.ti.

35.	(economic* or pharmaco?economic*).ti.
36.	(price* or pricing*).ti,ab.
37.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
38.	(financ* or fee or fees).ti,ab.
39.	(value adj2 (money or monetary)).ti,ab.
40.	or/27-39
41.	quality-adjusted life years/
42.	"quality of life index"/
43.	short form 12/ or short form 20/ or short form 36/ or short form 8/
44.	sickness impact profile/
45.	(quality adj2 (wellbeing or well being)).ti,ab.
46.	sickness impact profile.ti,ab.
47.	disability adjusted life.ti,ab.
48.	(qal* or qtime* or qwb* or daly*).ti,ab.
49.	(euroqol* or eq5d* or eq 5*).ti,ab.
50.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
51.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
52.	(hui or hui1 or hui2 or hui3).ti,ab.
53.	(health* year* equivalent* or hye or hyes).ti,ab.
54.	discrete choice*.ti,ab.
55.	rosser.ti,ab.
56.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
57.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
58.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
59.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
60.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
61.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
62.	or/41-61
63.	26 and (40 or 62)

26 **NHS EED and HTA (CRD) search terms**

#1.	MeSH DESCRIPTOR Brain Injuries EXPLODE ALL TREES
#2.	MeSH DESCRIPTOR Craniocerebral Trauma
#3.	MeSH DESCRIPTOR Coma, Post-Head Injury
#4.	MeSH DESCRIPTOR Head Injuries, Closed EXPLODE ALL TREES
#5.	MeSH DESCRIPTOR Head Injuries, Penetrating
#6.	MeSH DESCRIPTOR Intracranial Hemorrhage, Traumatic EXPLODE ALL TREES
#7.	MeSH DESCRIPTOR Skull Fractures EXPLODE ALL TREES
#8.	(((skull or cranial) adj3 fracture*))
#9.	(((head or brain or craniocerebral or intracranial or cranial or skull) adj3 (injur* or trauma*)))
#10.	((trauma* and ((subdural or intracranial or brain) adj2 (h?ematoma* or h?emorrhage* or bleed*))))

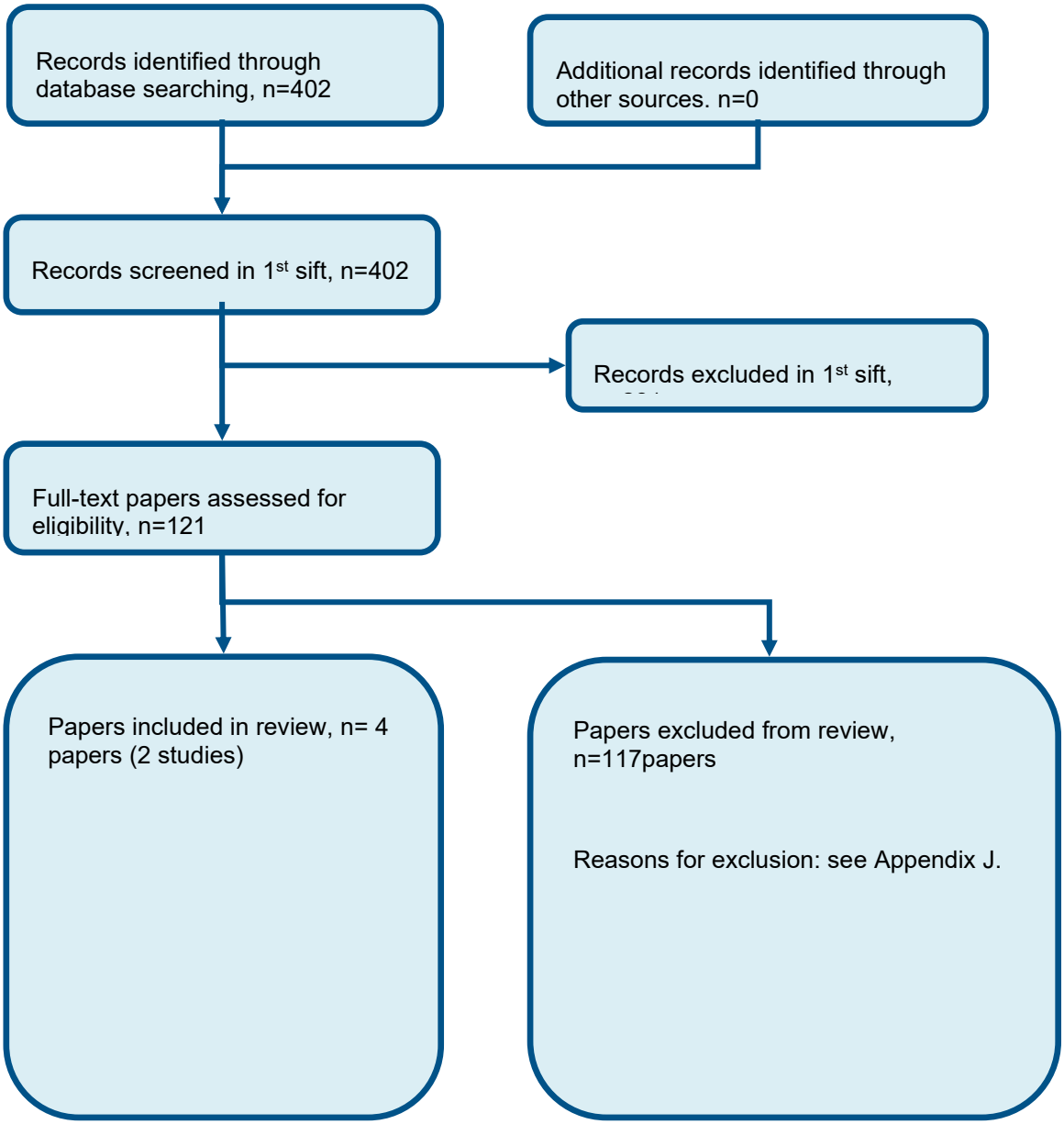
#11.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10

INAHTA search terms

1.	((((trauma* and ((subdural or intracranial or brain) and (haematoma* or hematoma* or haemorrhage* or hemorrhage* or bleed*))))[Title]) AND (((trauma* and ((subdural or intracranial or brain) and (haematoma* or hematoma* or haemorrhage* or hemorrhage* or bleed*))))[Title])) OR ((((skull or cranial) and fracture*))[Title] OR (((skull or cranial) and fracture*))[abs]) OR ((((head or brain or craniocerebral or intracranial or cranial or skull) and (injur* or trauma*)))[Title] OR (((head or brain or craniocerebral or intracranial or cranial or skull) and (injur* or trauma*)))[abs]) OR ("Skull Fractures"[mhe]) OR ("Intracranial Hemorrhage, Traumatic"[mhe]) OR ("Head Injuries, Penetrating"[mh]) OR ("Head Injuries, Closed"[mhe]) OR ("Coma, Post-Head Injury"[mh]) OR ("Brain Injuries"[mhe]) OR ("Craniocerebral Trauma"[mh])

Appendix C – Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of Tranexamic Acid



Appendix D – Effectiveness evidence

CRASH-3 trial, 2019

Bibliographic Reference	CRASH-3 trial, collaborators; Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): a randomised, placebo-controlled trial.; Lancet (London, England); 2019; vol. 394 (no. 10210); 1713-1723 Brenner, Amy, Belli, Antonio, Chaudhri, Rizwana et al. (2020) Understanding the neuroprotective effect of tranexamic acid: an exploratory analysis of the CRASH-3 randomised trial. Critical care (London, England) 24(1): 560 Williams, Jack, Roberts, Ian, Shakur-Still, Haleema et al. (2020) Cost-effectiveness analysis of tranexamic acid for the treatment of traumatic brain injury, based on the results of the CRASH-3 randomised trial: a decision modelling approach. BMJ global health 5(9)

Study details

Secondary publication of another included study- see primary study for details	NR
Other publications associated with this study included in review	NR
Trial name / registration number	CRASH-3

Study location	International, multicentre study. 175 hospitals in 29 countries
Study setting	Emergency care (primary care)
Study dates	July 20th, 2012 to January 31st, 2019 (study protocol amendment made on Sept 6th 2016 - see study population inclusion criteria for details)
Sources of funding	The run-in phase (the first 500 patients) was funded by The JP Moulton Charitable Trust. The main phase was funded jointly by the National Institute for Health Research Health Technology Assessment (NIHR HTA; 14/190/01), and Joint Global Health Trials, Medical Research Council, Department for International Development, Global Challenges Research Fund, and the Welcome Trust (MRM0092111). Paul Atkinson, Saint John Regional Hospital, Canada received a $10 000 CAD grant from the New Brunswick Trauma Program to support the trial in Canada.
Inclusion criteria	Patients with TBI. Adults with TBI who were within 3 h of injury, had a Glasgow Coma Scale (GCS) score of 12 or lower or any intracranial bleeding on CT scan, and no major extracranial bleeding were eligible. The fundamental eligibility criterion was that the responsible clinician was substantially uncertain as to the appropriateness of tranexamic acid treatment. The time window for eligibility was originally within 8 h of injury. However, on Sept 6, 2016, in response to evidence external to the trial indicating that tranexamic acid is unlikely to be effective when initiated beyond 3 h of injury, the trial steering committee amended the protocol to limit recruitment to within 3 h of injury.
Exclusion criteria	NR
Recruitment / selection of participants	Patients recruited through participating hospitals
Intervention(s)	Tranexamic acid. Patients allocated to receive a loading dose of 1 g of tranexamic acid infused over 10 min, started immediately after randomisation, followed by an intravenous infusion of 1 g over 8 hours.
Comparator	Placebo. Patients allocated to receive placebo, matching the dosing regimen of the TXA study group, and starting immediately after randomisation.
Number of participants	12737. 6406 randomised to TXA, 6331 randomised to placebo. 9202 randomised within 3 hours of injury and included in analysis.

Duration of follow-up	28 days
Additional comments	Brenner 2020: data for all-cause mortality within 24 h of injury, after 24 h and at 28 days stratified by severity and country income level in patients randomised within 3 h of injury, excluding those with a GCS score of 3 or bilateral unreactive pupils. Country income level stratification was not pre-specified. Mortality data for Brenner 2020 excluded of those with a GCS score of 3 or bilateral unreactive pupils post-randomisation. High risk of bias.

Study arms

Tranexamic acid (N = 4649)

Patients allocated to receive a loading dose of 1 g of tranexamic acid infused over 10 min, started immediately after randomisation, followed by an intravenous infusion of 1 g over 8 h.

Placebo (N = 4553)

Patients allocated to receive placebo, matching the dosing regimen of the TXA study group, and starting immediately after randomisation.

Characteristics

Study-level characteristics

Characteristic	**Study (N = 9202)**
% Female (%) Nominal	20
Mean age (SD) Mean (SD)	41.8 (19)

Characteristic	Study (N = 9202)
Ethnicity Custom value	NR
Comorbidities Custom value	NR
Timing of TXA administration Custom value	less than 3 hours
Presence/suspicion of extracranial bleeding Custom value	No

Outcomes

Study timepoints

- 28 day

Patients receiving TXA <3 hours from injury

Outcome	Tranexamic acid, 28 day, N = 4613	Placebo, 28 day, N = 4514
TBI related mortality	855	892
Adverse event - Pulmonary embolism (PE)	18	18
Adverse event (DVT)	15	12
Adverse event (stroke)	29	23
Myocardial infarction (MI)	9	12
All vascular occlusive events	69	60

Outcome	Tranexamic acid, 28 day, N = 4613	Placebo, 28 day, N = 4514
Vascular occlusive events (fata and non-fatal) at 28 days (mild/moderate)	41/4066	52/3997
Vascular occlusive events (fata and non-fatal) at 28 days (severe)	60/2264	50/2247
Vascular occlusive events (fata and non-fatal) at 28 days (LMIC)	50/4375	35/4330
Vascular occlusive events (fata and non-fatal) at 28 days (HIC)	51/1984	67/1950
Disability rating scale score	4.99 (7.6)	5.03 (7.6)

Patients randomly assigned within 3 h of injury

Total study population (patients receiving TXA > 3 hours)

Outcome	Tranexamic acid, N = 1746	Placebo, N = 1766
Adverse event - Pulmonary embolism (PE)	6	14
Adverse event (DVT)	4	4
Adverse event (stroke)	17	19
Myocardial infarction (MI)	9	8
All Vascular occlusive events	32	42
Disability rating scale score	4.5 (7)	5 (7.4)

all participants (TXA < 3 hours and >3 hours of injury)

Outcome	Tranexamic acid, N = 6359	Placebo, N = 6280
Non head injury deaths	122	100
Any adverse event	198	168
Adverse event - Pulmonary embolism (PE)	24	32
Adverse event (DVT)	19	16
Adverse event (stroke)	46	42

Outcome	Tranexamic acid, N = 6359	Placebo, N = 6280
Myocardial infarction (MI)	18	20
All Vascular occlusive events	101	102

21 **Outcomes from Brenner 2020 (excluding patients with GCS score of 3 or bilateral unreactive pupils):**

Outcome (total N=7637)	Tranexamic acid, N = NR	Placebo, N =NR
All-cause mortality within 24 hours	112 (2.9%)	147 (3.9%)
All-cause mortality after 24 hours	432 (11.5%)	421 (11.7%)
All-cause mortality after 28 days	544 (14.0%)	568 (15.1%)
All-cause mortality within 24 hours of injury – mild/moderate	25 (0.9%)	37 (1.3%)
All-cause mortality within 24 hours of injury – severe	87(8.5%)	110 (11.3%)
All-cause mortality after 24 hours of injury – mild/moderate	163 (5.8%)	186 (6.9%)
All-cause mortality after 24 hours of injury – severe	269 (28.7%)	235 (27.2%)
All-cause mortality after 28 days of injury – mild/moderate	188 (6.7%)	223 (8.1%)

Outcome (total N=7637)	Tranexamic acid, N = NR	Placebo, N =NR
All-cause mortality after 28 days of injury – severe	356 (34.7%)	345 (35.4%)
All-cause mortality within 24 hours of injury – LMIC	98 (3.3%)	126 (4.4%)
All-cause mortality within 24 hours of injury – HIC	14 (1.5%)	21 (2.4%)
All-cause mortality after 24 hours of injury – LMIC	363 (12.6%)	344 (12.5%)
All-cause mortality after 24 hours of injury – HIC	69 (7.7%)	77 (9.0%)
All-cause mortality after 28 days of injury – LMIC	461 (15.5%)	470 (16.3%)
All-cause mortality after 28 days of injury – HIC	83 (9.2%)	98 (11.1%)

Narrative data (Williams 2020)- No raw data available

TBI mortality (< 3 hours): In high income countries, the head injury death risk ratio was 0.9 (0.74‑ 1.08) for those sustaining a severe TBI, whilst in low- and middle-income countries the risk ratio is 1.03 (0.94-1.12).

A subgroup analysis of patients experiencing severe TBI but excluding those patients with a GCS score of 3 or bilateral unreactive pupils (a sensitivity analysis pre-specified in the trial), the tranexamic acid head injury deaths risk ratio was 0.62 (0.41-0.96) in high income countries, and 1.01 (0.88-1.15) in low- and middle-income countries.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Totalstudypopulation(inc.patientsreceivingTXA<3hours)-TBI related mortality)-NoOfEvents-Tranexamic acid-Placebo-t28

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Totalstudypopulation(inc.patientsreceivingTXA<3hours)-Adverseevent-Pulmonaryembolism(PE)-NoOfEvents-Tranexamic acid-Placebo-t28

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Totalstudypopulation(inc.patientsreceivingTXA<3hours)-Adverseevent(DVT)-NoOfEvents-Tranexamic acid-Placebo-t28

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

34 **Totalstudypopulation(inc.patientsreceivingTXA<3hours)-Adverseevent(stroke)-NoOfEvents-Tranexamic acid-Placebo-t28**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

35

36 **Totalstudypopulation(patients receiving TXA<3hours)-Adverse event- Myocardial infarction- Nominal-Tranexamic acid-Placebo-t28**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

37

38 **PatientsreceivingTXA<3hoursfrominjury-Disability rating scale score -Tranexamic acid-Placebo-t28**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

39

40 **Totalstudypopulation(inc.patientsreceivingTXA<3hours)-Allvascularocclusiveeventsallseverities-Nominal-Tranexamic acid-Placebo-t28**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

41

42 **Totalstudypopulation(inc.patientsreceivingTXA<3hours)-Vascularocclusiveevents(fatal andnon-fatal)at28days(mild/moderate)-Nominal-**
43 **Tranexamic acid-Placebo-t28**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Totalstudypopulation(inc.patientsreceivingTXA<3hours)-Vascularocclusiveevents(fatal andnon-fatal)at28days(severe)-Nominal-Tranexamic acid-Placebo-t28

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Totalstudypopulation(inc.patientsreceivingTXA<3hours)-Vascularocclusiveevents(fatal andnon-fatal)at28days(LMIC)-Nominal-Tranexamic acid-Placebo-t28

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Totalstudypopulation(inc.patientsreceivingTXA<3hours)-Vascularocclusiveevents(fataandnon-fatal)at28days(HIC)-Nominal-Tranexamic acid-Placebo-t28

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Totalstudypopulation(patientsreceivingTXA>3hours)-Adverseevent-Pulmonaryembolism(PE)-Nominal-Tranexamic acid-Placebo-t28

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

51

52 **Totalstudypopulation(patientsreceivingTXA>3hours)-Adverseevent(DVT)-Nominal-Tranexamic acid-Placebo-t28**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

53 **Totalstudypopulation(patientsreceivingTXA>3hours)-Adverseevent(stroke)-Nominal-Tranexamic acid-Placebo-t28**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

54 **Totalstudypopulation(patientsreceivingTXA>3hours)-Adverseevent-Myocardial infarction (MI)- Nominal-Tranexamic acid-Placebo-t28**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

55 **Totalstudypopulation(patientsreceivingTXA>3hours)-Allvascularocclusiveevents-Nominal-Tranexamic acid-Placebo-t28**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

56 **Totalstudypopulation(patients receivingTXA>3hours)-Disability rating scale score-Tranexamic acid-Placebo-t28**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

OutcomesexcludingpatientswithGCSscoreof3orbilateralunreactivepupils):-All-causemortalitywithin24hours-NoOfEvents-Tranexamic acid-Placebo-t28

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

OutcomesexcludingpatientswithGCSscoreof3orbilateralunreactivepupils):-All-causemortalityafter24hours-NoOfEvents-Tranexamic acid-Placebo-t28

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

OutcomesexcludingpatientswithGCSscoreof3orbilateralunreactivepupils):-All-causemortalityafter28days-NoOfEvents-Tranexamic acid-Placebo-t28

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

64

65 **OutcomesexcludingpatientswithGCSscoreof3orbilateralunreactivepupils):-All-causemortalitywithin24hoursofinjury–mild/moderate-**
66 **NoOfEvents-Tranexamic acid-Placebo-t28**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

OutcomesexcludingpatientswithGCSscoreof3orbilateralunreactivepupils):-All-causemortalitywithin24hoursofinjury–severe-NoOfEvents-Tranexamic acid-Placebo-t28

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

OutcomesexcludingpatientswithGCSscoreof3orbilateralunreactivepupils):-All-causemortalityafter24hoursofinjury–mild/moderate-NoOfEvents-Tranexamic acid-Placebo-t28

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

OutcomesexcludingpatientswithGCSscoreof3orbilateralunreactivepupils):-All-causemortalityafter24hoursofinjury–severe-NoOfEvents-Tranexamic acid-Placebo-t28

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

OutcomesexcludingpatientswithGCSscoreof3orbilateralunreactivepupils):-All-causemortalityafter28daysofinjury–mild/moderate-NoOfEvents-Tranexamic acid-Placebo-t28

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

OutcomesexcludingpatientswithGCSscoreof3orbilateralunreactivepupils):-All-causemortalityafter28daysofinjury–severe-NoOfEvents-Tranexamic acid-Placebo-t28

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

78 **OutcomesexcludingpatientswithGCSscoreof3orbilateralunreactivepupils):-All-causemortalitywithin24hoursofinjury–LMIC-NoOfEvents-**
79 **Tranexamic acid-Placebo-t28**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

OutcomesexcludingpatientswithGCSscoreof3orbilateralunreactivepupils):-All-causemortalitywithin24hoursofinjury–HIC-NoOfEvents-Tranexamic acid-Placebo-t28

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

OutcomesexcludingpatientswithGCSscoreof3orbilateralunreactivepupils):-All-causemortalityafter24hoursofinjury–LMIC-NoOfEvents-Tranexamic acid-Placebo-t28

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

OutcomesexcludingpatientswithGCSscoreof3orbilateralunreactivepupils):-All-causemortalityafter24hoursofinjury–HIC-NoOfEvents-Tranexamic acid-Placebo-t28

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

88

89 **OutcomesexcludingpatientswithGCSscoreof3orbilateralunreactivepupils):-All-causemortalityafter28daysofinjury–LMIC-NoOfEvents-**
90 **Tranexamic acid-Placebo-t28**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

OutcomesexcludingpatientswithGCSscoreof3orbilateralunreactivepupils):-All-causemortalityafter28daysofinjury–HIC-NoOfEvents-Tranexamic acid-Placebo-t28

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

93

94 **Rowell, 2020**

Bibliographic Reference	Rowell, Susan E; Meier, Eric N; McKnight, Barbara; Kannas, Delores; May, Susanne; Sheehan, Kellie; Bulger, Eileen M; Idris, Ahamed H; Christenson, Jim; Morrison, Laurie J; Frascone, Ralph J; Bosarge, Patrick L; Colella, M Riccardo; Johannigman, Jay; Cotton, Bryan A; Callum, Jeannie; McMullan, Jason; Dries, David J; Tibbs, Brian; Richmond, Neal J; Weisfeldt, Myron L; Tallon, John M; Garrett, John S; Zielinski, Martin D; Aufderheide, Tom P; Gandhi, Rajesh R; Schlamp, Rob; Robinson, Bryce R H; Jui, Jonathan; Klein, Lauren; Rizoli, Sandro; Gamber, Mark; Fleming, Michael; Hwang, Jun; Vincent, Laura E; Williams, Carolyn; Hendrickson, Audrey; Simonson, Robert; Klotz, Patricia; Sopko, George; Witham, William; Ferrara, Michael; Schreiber, Martin A; Effect of Out-of-Hospital Tranexamic Acid vs Placebo on 6-Month Functional Neurologic Outcomes in Patients With Moderate or Severe Traumatic Brain Injury.; JAMA; 2020; vol. 324 (no. 10); 961-974

95 **Study details**

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	NCT01990768

Study location	The study took place in 12 regions, including 20 trauma centres and 39 emergency medical services (EMS) agencies across the US and Canada
Study setting	out of hospital setting by paramedics
Study dates	Between May 2015 and March 2017 participants were randomised.
Sources of funding	The Resuscitation Outcomes Consortium institutions participating in the trial were supported by a series of cooperative agreements from the National Heart, Lung and Blood Institute administered by the US Army Medical Research & Material Command (W81XWH-13-2-0090), including U01 HL077863 (University of Washington Data Coordinating Center), U01 HL077866 (Medical College of Wisconsin), U01 HL077871 (University of Pittsburgh), U01 HL077873 (Oregon Health and Science University), U01 HL077881 (University of Alabama at Birmingham), and U01 HL077887 (University of Texas Southwestern Medical Center/Dallas).
Inclusion criteria	Patients aged 15 years or older with moderate or severe blunt or penetrating TBI, a Glasgow Coma Scale (GCS) score of 3 to 12, at least 1 reactive pupil, and systolic blood pressure of at least 90 mm Hg prior to randomisation. Emergency medical services (EMS) agencies were provided centralised video and hands-on training to ensure GCS assessment standardisation across sites. It was instructed to obtain the GCS score prior to intubation. Patients were eligible only if an intravenous (IV) catheter was in place, the study drug could be administered within 2 hours of injury, and the predefined EMS transport destination was a participating trauma centre.
Exclusion criteria	Prehospital GCS=3 with no reactive pupil, estimated time from injury to start of study drug bolus dose >2 hours, unknown time of injury, clinical suspicion by EMS of seizure activity, acute MI or stroke or known history, to the extent possible, of seizures, thromboembolic disorders or renal dialysis, CPR by EMS prior to randomisation, burns > 20% total body surface area (TBSA), suspected or known prisoners, suspected or known pregnancy, prehospital TXA or other pro-coagulant drug given prior to randomisation, subjects who have activated the “opt-out” process when required by the local regulatory board
Recruitment / selection of participants	Participants enrolled in the out-of-hospital setting by paramedics
Intervention(s)	<u>TXA- Bolus maintenance group (N=312)</u> 1-g IV tranexamic acid bolus in the out-of-hospital setting followed by a 1-g tranexamic acid IV infusion initiated upon hospital arrival and infused over 8 hours. The out-of-hospital bolus was initiated by EMS prior to arrival and completed

	either out of hospital or in the emergency department. Following completion of the out-of-hospital bolus, the in-hospital infusion was initiated in the emergency department and administered over 8 hours. The bolus maintenance dose was chosen based on the observed decreased mortality in the CRASH-2 trial using this dose and because it is widely considered standard of care in patients with traumatic haemorrhage. <u>TXA- Bolus only group (N=345)</u> 2g IV tranexamic acid bolus in the out-of-hospital setting followed by a placebo infusion. The out-of-hospital bolus was initiated by EMS prior to arrival and completed either out of hospital or in the emergency department. The bolus only dose was chosen as an alternative dosing regimen that could be more feasible in pre-hospital and military settings.
Comparator	Placebo (n=309) IV placebo bolus in the out-of-hospital setting followed by an IV placebo infusion
Number of participants	n = 312- bolus maintenance group; n = 345- bolus only group; and n=309 -placebo group
Duration of follow-up	Mortality at 28 days. All other outcomes at 6 months
Additional comments	Timing: treatment initiated within 2 hours of TBI GCS: Mild: 4% Moderate: 39%

	Severe: 57% The primary outcome was obtained in 819 of the 966 participants (85%) treated with the study drug. The percentage of patients who completed follow-up was higher in the placebo group (87%) than in both the bolus maintenance (84%) and bolus only (83%) groups. The primary reasons for failure to follow-up were participant withdrawal from the study and inability to locate the participant 6 months after injury (Figure 1). Participants lost to follow-up were less severely injured and had better outcomes at discharge than other discharged participants

Study arms

Tranexamic acid -Bolus maintenance group (N = 312)

1-gram IV TXA bolus in the prehospital setting followed by a 1-gram IV maintenance infusion initiated on hospital arrival and infused over 8 hours.

Tranexamic acid- Bolus only group (N=345)

2g IV tranexamic acid bolus in the out-of-hospital setting followed by a placebo infusion.

Placebo (N = 309)

IV bolus in the prehospital setting followed by a placebo maintenance infusion initiated on hospital arrival and infused over 8 hours.

Characteristics

Arm-level characteristics

Characteristic	Tranexamic acid-bolus maintenance (N = 312)	Tranexamic acid-bolus only (N = 345)	Placebo (N = 309)
% Female Custom value	27%	26%	25%
Mean age (SD) Median (IQR)	39 (26 to 57)	40 (26-56)	36 (25 to 55)
Injury type (blunt) Nominal	302	339	294
Injury type (penetrating) Nominal	12	5	16
GCS (mean) Mean (SD)	7.8 (3.3)	7.8 (3.3)	7.6 (3.2)
Time to start of infusion (mins) Median (IQR)	88 (60 to 130)	94 (65-134)	86 (60 to 120)

Outcomes

Study timepoints

- 6 months

Outcome	Tranexamic acid , bolus maintenance N = 312	Tranexamic acid , bolus only N = 345	Placebo, N = 309
All-cause mortality at 28 days Nominal	53/285	40/318	50/285
All-cause mortality at 6 months	55/ 262	46/289	54/ 272
Hospital free days at 28 days Mean (SD)	13.6 (10.7)	14.1 (10.4)	13.6 (10.7)
Any neurosurgical intervention Nominal	62	75	54
Degree of disability: favourable outcome at discharge (GOS-E >4) Nominal	101	101	96
Degree of disability: favourable outcome at 6 months (GOS-E >4) Nominal	153	178	163
Adverse event (DVT) Nominal	3	10	9
Adverse event (PE) Nominal	3	6	5

Outcome	Tranexamic acid , bolus maintenance N = 312	Tranexamic acid , bolus only N = 345	Placebo, N = 309
Adverse event (stroke) Nominal	3	13	10
Adverse event (MI) Nominal	3	2	1

108 **Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT**

109 **Outcomesat6months-Allcausemortalityat28days-Nominal-Tranexamic acid -Placebo-t6**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

110 **Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT**

111 **Outcomesat6months-Allcausemortalityat 6 months-Nominal-Tranexamic acid -Placebo-t6**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

112 **Outcomesat6months-Hospitalfreedaysat28days-MeanSD-Tranexamic acid -Placebo-t6**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

113 **Outcomesat6months-Anyneurosurgicalintervention-Nominal-Tranexamic acid -Placebo-t6**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

114

115 **Outcomesat6months-Degreeofdisability:favourableoutcomeatdischarge(GOS-E>4)-Nominal-Tranexamic acid -Placebo-t6**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

116 **Outcomesat6months-Degreeofdisability:favourableoutcomeat6months(GOS-E>4)-Nominal-Tranexamic acid -Placebo-t6**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

117 **Outcomesat6months-Adverseevent(DVT)-Nominal-Tranexamic acid -Placebo-t6**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

118 **Outcomesat6months-Adverseevent(PE)-Nominal-Tranexamic acid -Placebo-t6**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

119 **Outcomesat6months-Adverseevent(stroke)-Nominal-Tranexamic acid -Placebo-t6**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

120 **Outcomesat6months-Adverseevent(MI)-Nominal-Tranexamic acid -Placebo-t6**

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

121

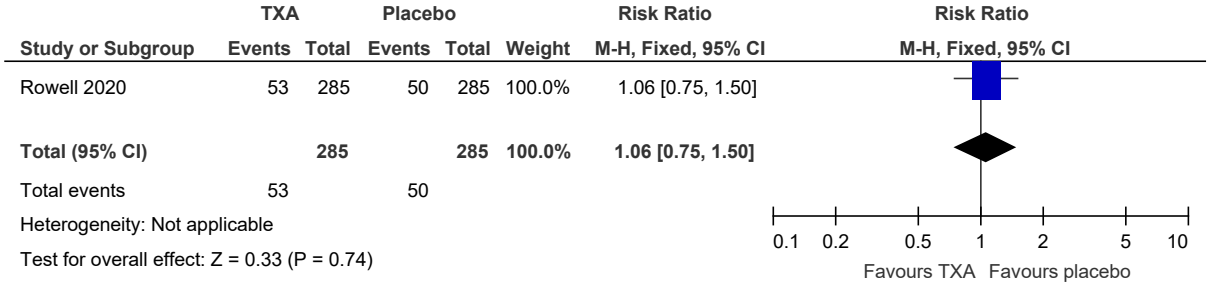
Appendix E – Forest plots

PRE-HOSPITAL SETTING

E.1 TXA vs Placebo (adults)

TXA < 3 hours of injury- Mixed GCS (mild, moderate and severe TBI) [out-of-hospital tranexamic acid (1 g) bolus and in-hospital tranexamic acid (1 g) 8-hour infusion]

Figure 2: All-cause mortality at 28 days



<Insert Note here>

Figure 3: All-cause mortality at 6 months

<Insert Note here>

129

Figure 4: Length of hospital stay (hospital free days at 28-days)

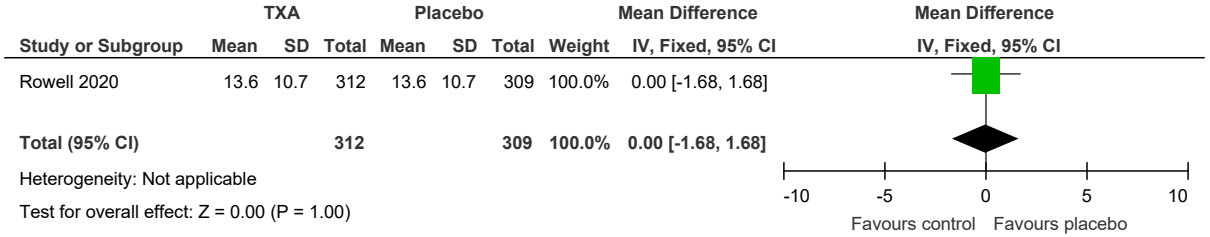


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Figure 5: Neurosurgical intervention (at 28 days)

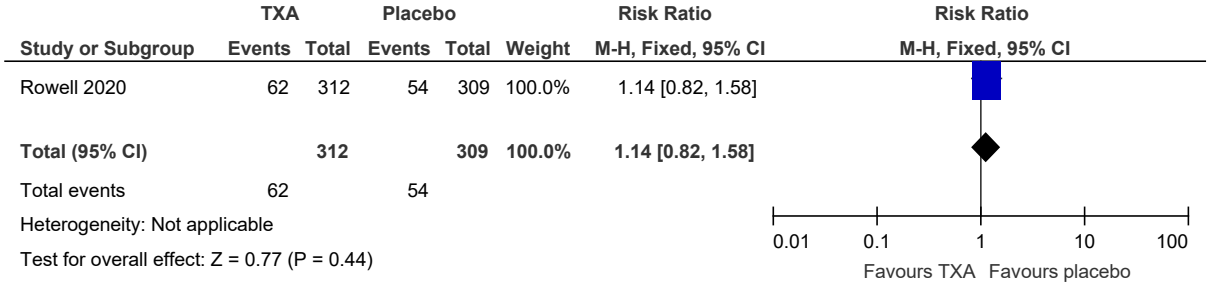

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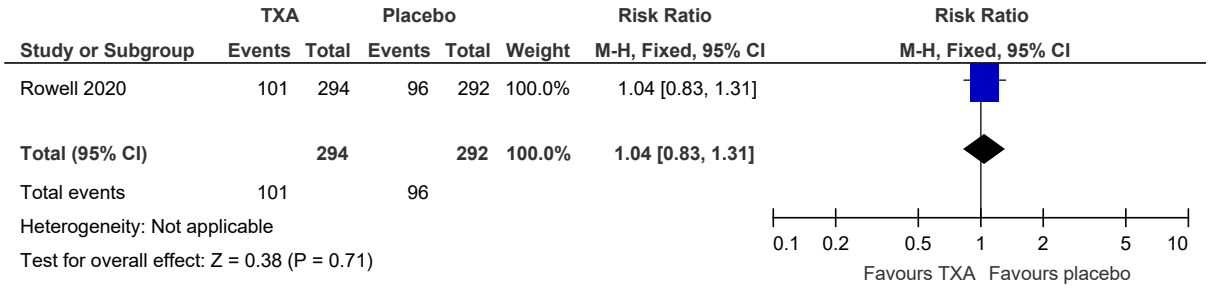
Figure 6: Degree of disability: favourable outcome [moderate disability or good recovery] at discharge (GOS-E >4)



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134

Figure 7: Degree of disability: favourable outcome [moderate disability or good recovery] at 6 months (GOS-E >4)

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136

Figure 8: Adverse events: MI (at 28 days)

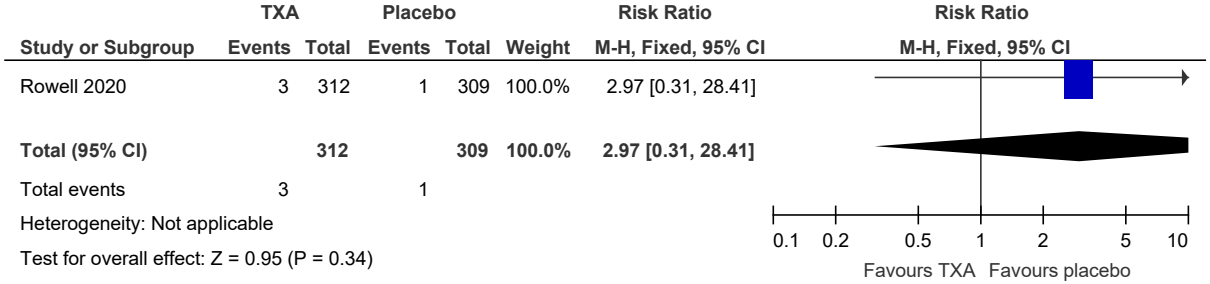

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Figure 9: Adverse events: Pulmonary embolism (at 28 days)

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Figure 10: Adverse events: Deep vein thrombosis (at 28 days)

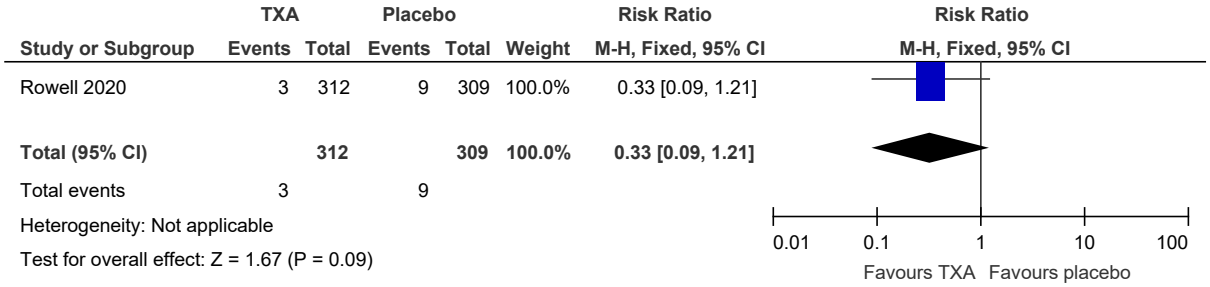

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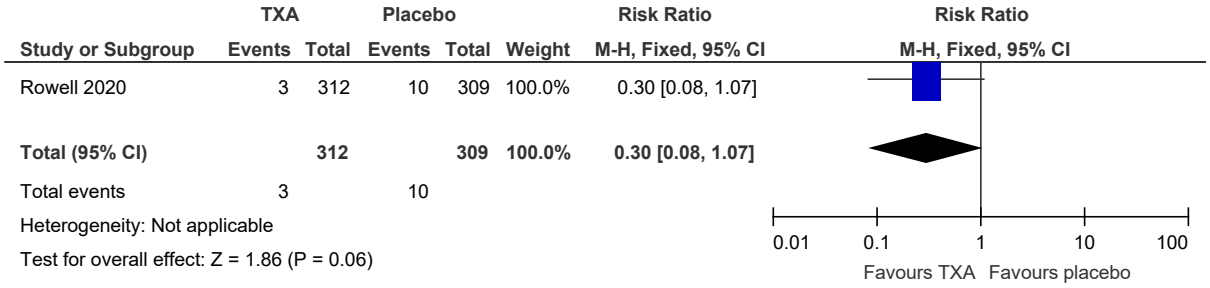
Figure 11: Adverse events: Thrombotic stroke (at 28 days)



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E.2 TXA vs Placebo (adults)

TXA < 3 hours of injury- Mixed GCS (mild, moderate and severe TBI) [out-of-hospital tranexamic acid (2 g) bolus and in-hospital placebo 8-hour infusion]

Figure 12: All-cause mortality at 28 days

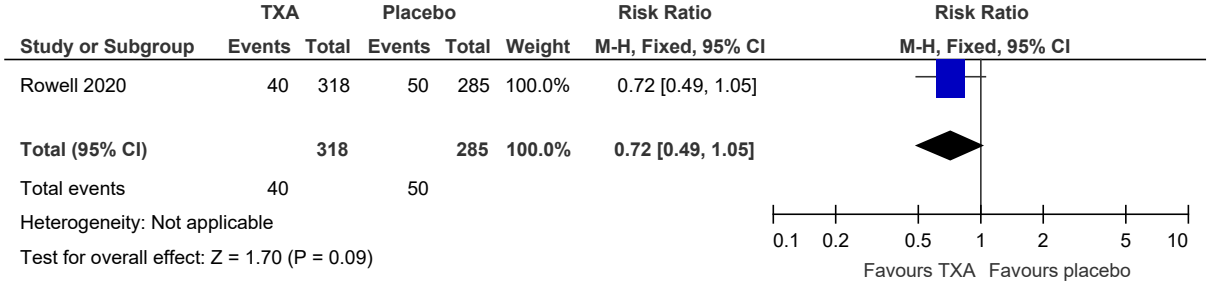

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Figure 13: All-cause mortality at 6 months

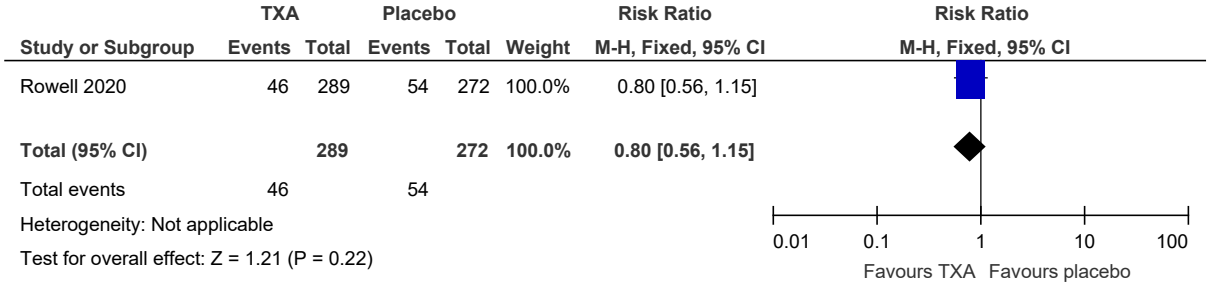

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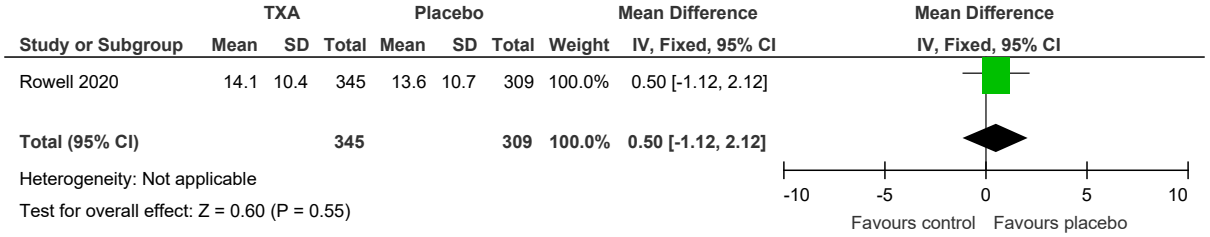
Figure 14: Length of hospital stay (hospital free days at 28-days)



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147

Figure 15: Neurosurgical intervention (at 28 days)

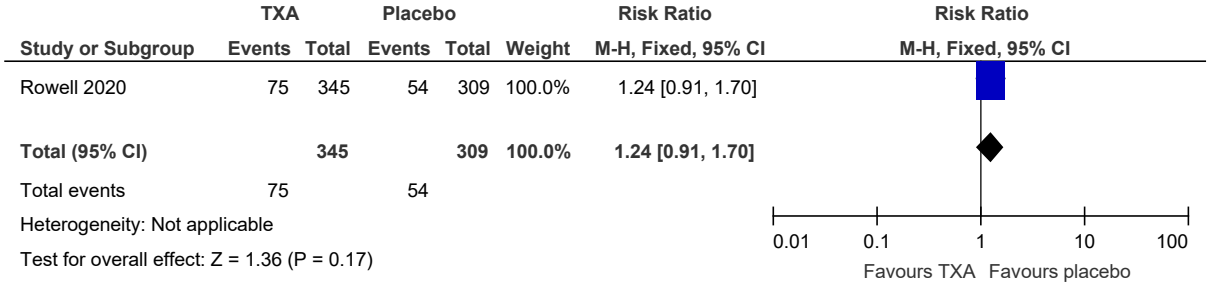

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Figure 16: Degree of disability: favourable outcome [moderate disability or good recovery] at discharge (GOS-E >4)

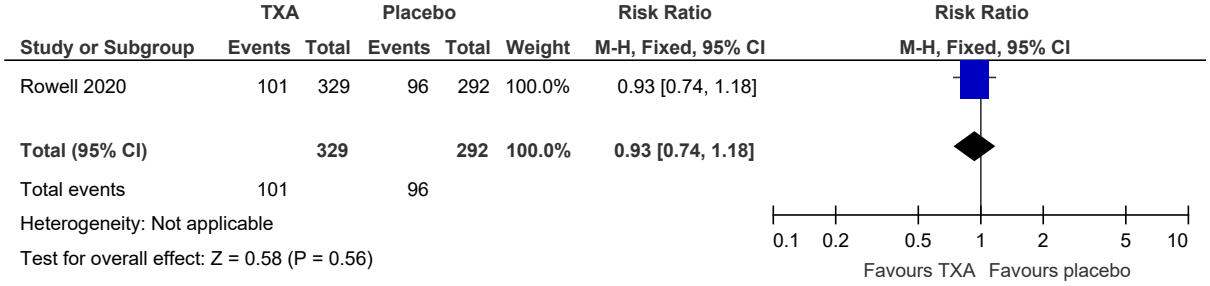

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Figure 17: Degree of disability: favourable outcome [moderate disability or good recovery]) at 6 months (GOS-E >4)

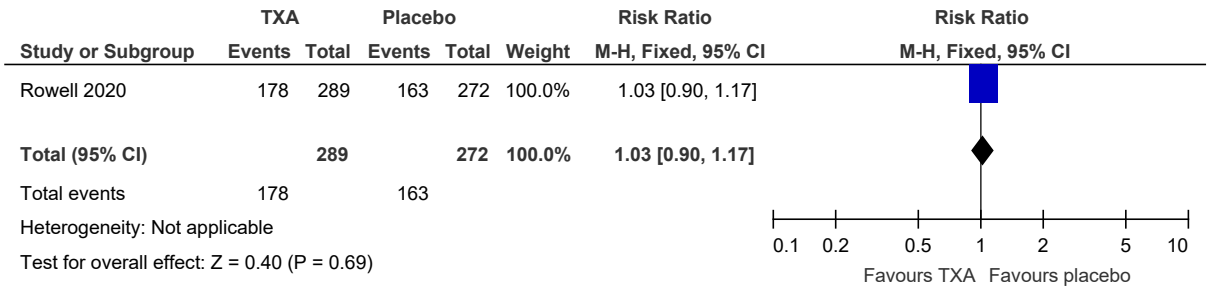

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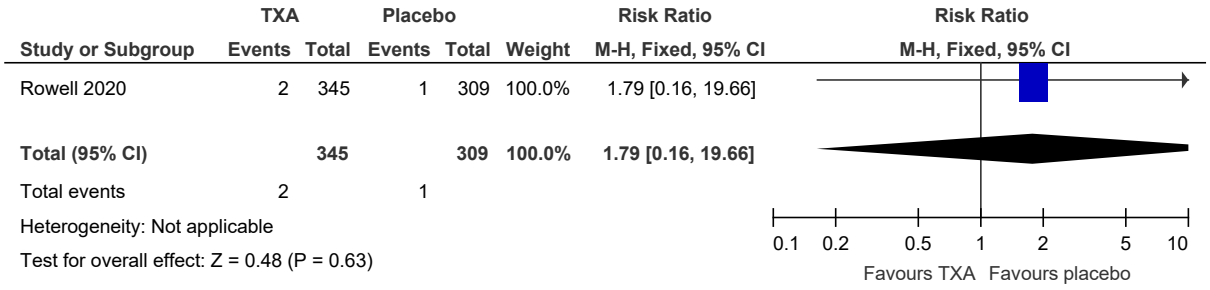
Figure 18: Adverse events: MI (at 28 days)



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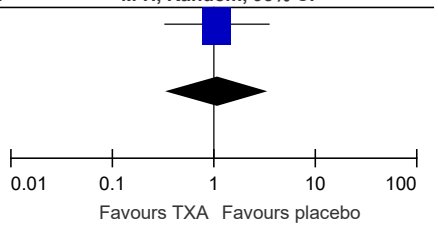
162

Figure 19: Adverse events: Pulmonary embolism (at 28 days)

Study or Subgroup	TXA Events	TXA Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Rowell 2020	6	345	5	309	100.0%	1.07 [0.33, 3.49]
Total (95% CI)		**345**		**309**	**100.0%**	**1.07 [0.33, 3.49]**
Total events	6		5			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.12 (P = 0.90)



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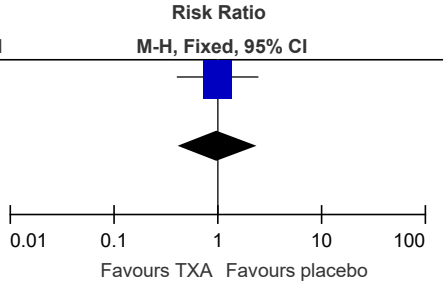
163

Figure 20: Adverse events: Deep vein thrombosis (at 28 days)

Study or Subgroup	TXA Events	TXA Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Rowell 2020	10	345	9	309	100.0%	1.00 [0.41, 2.42]
Total (95% CI)		**345**		**309**	**100.0%**	**1.00 [0.41, 2.42]**
Total events	10		9			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.01 (P = 0.99)



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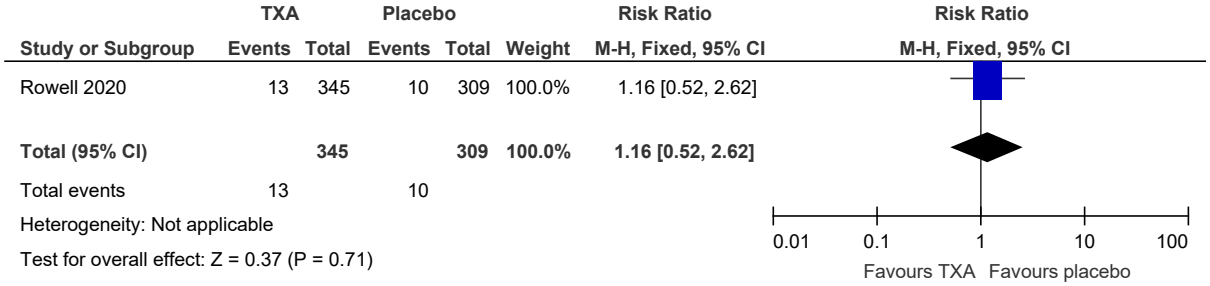
164

Figure 21: Adverse events: Thrombotic stroke (at 28 days)



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HOSPITAL SETTING

E.3 TXA vs Placebo (adults)

TXA < 3 hours of injury- Mixed GCS (mild, moderate and severe TBI)

Figure 22: TBI related mortality (overall)

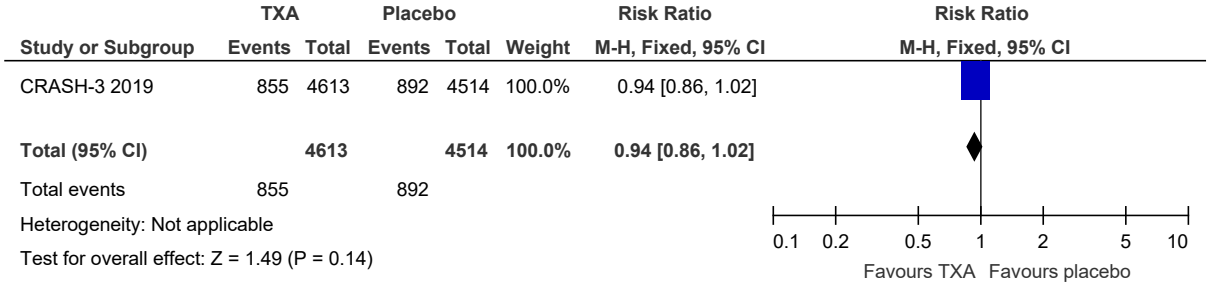

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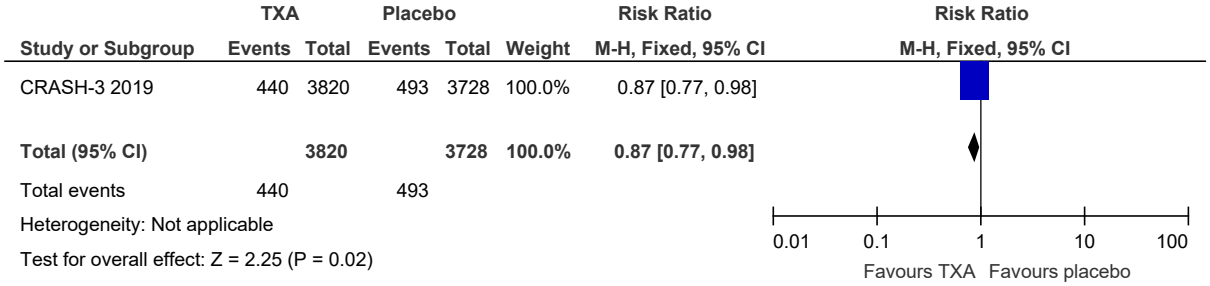
Figure 23: TBI related mortality - pupil reactivity (both react)



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172

Figure 24: TBI related mortality- pupil reactivity (any non-reactive)

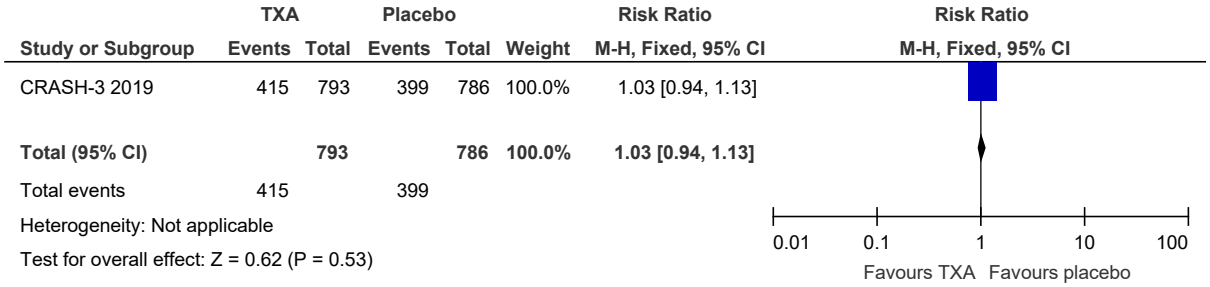

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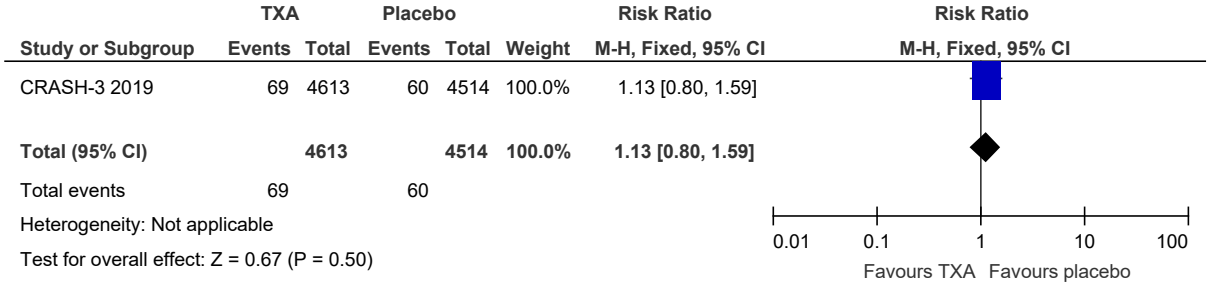
Figure 25: All vascular occlusive events (All severities)



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174

Figure 26: Adverse events: DVT

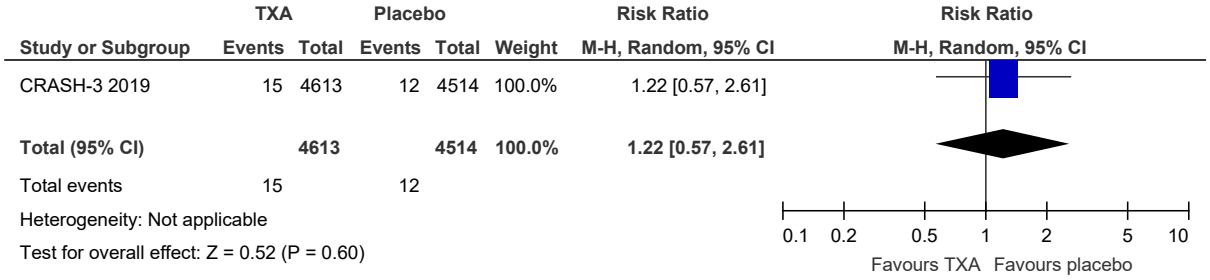

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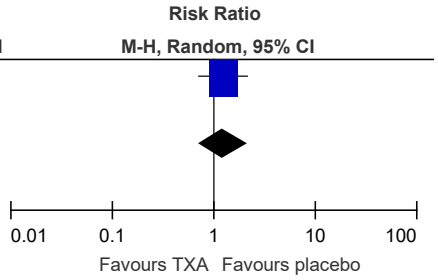
Figure 27: Adverse events: Stroke

Study or Subgroup	TXA Events	TXA Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
CRASH-3 2019	29	4613	23	4514	100.0%	1.23 [0.71, 2.13]
Total (95% CI)		**4613**		**4514**	**100.0%**	**1.23 [0.71, 2.13]**
Total events	29		23			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.75 (P = 0.45)



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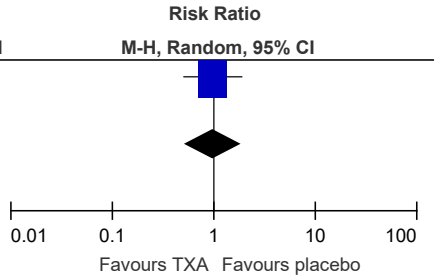
176

Figure 28: Adverse events: Pulmonary embolism

Study or Subgroup	TXA Events	TXA Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
CRASH-3 2019	18	4613	18	4514	100.0%	0.98 [0.51, 1.88]
Total (95% CI)		**4613**		**4514**	**100.0%**	**0.98 [0.51, 1.88]**
Total events	18		18			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.07 (P = 0.95)



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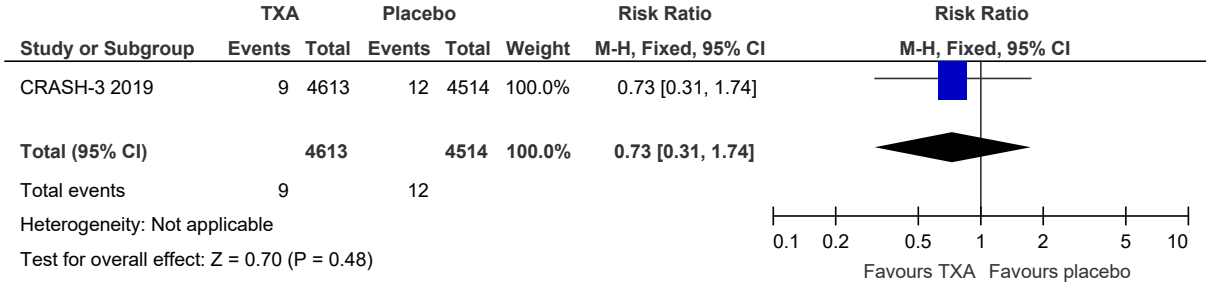
177

Figure 29: Adverse events: MI



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178

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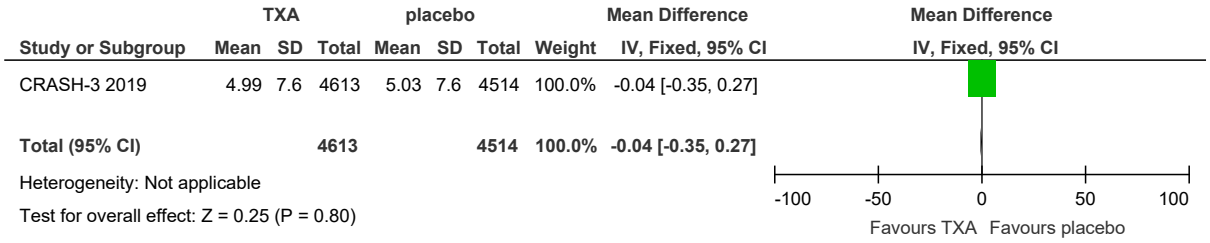
Figure 30: Disability Rating Scale score (lower score means less disabled)



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180

E.4 TXA vs placebo

TXA < 3 hours of injury) - Excluding those with a GCS score of 3 or bilateral unreactive pupils –mixed GCS (mild, moderate and severe TBI)

Figure 31: All-cause mortality within 24 hours of injury (All participants)

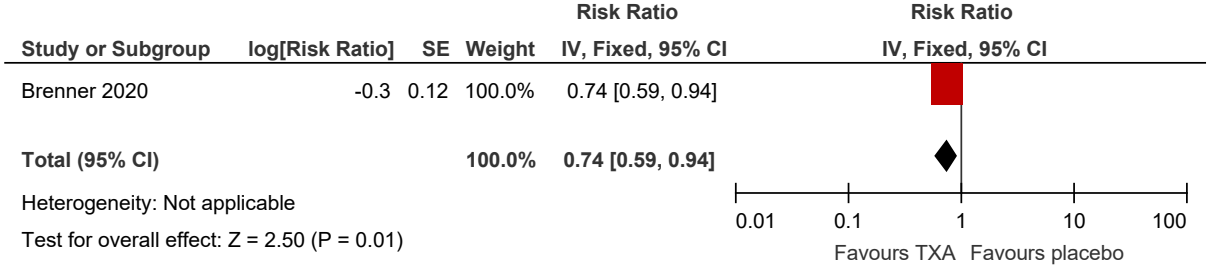

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Figure 32: All-cause mortality within 24 hours of injury – low and middle income countries (LMIC)

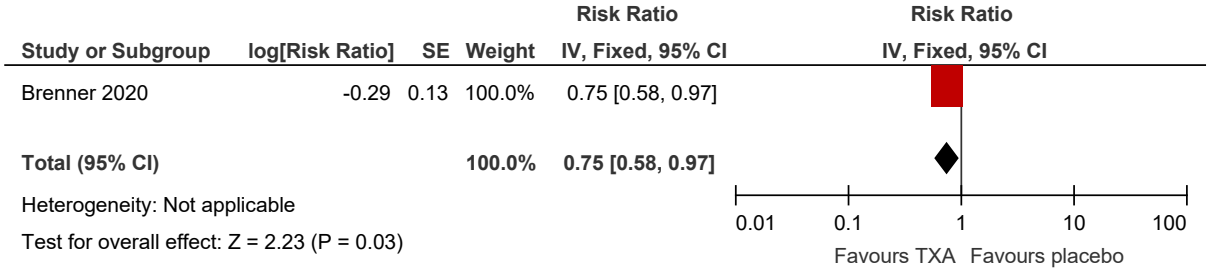

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Figure 33: All-cause mortality within 24 hours of injury – high income countries (HIC)

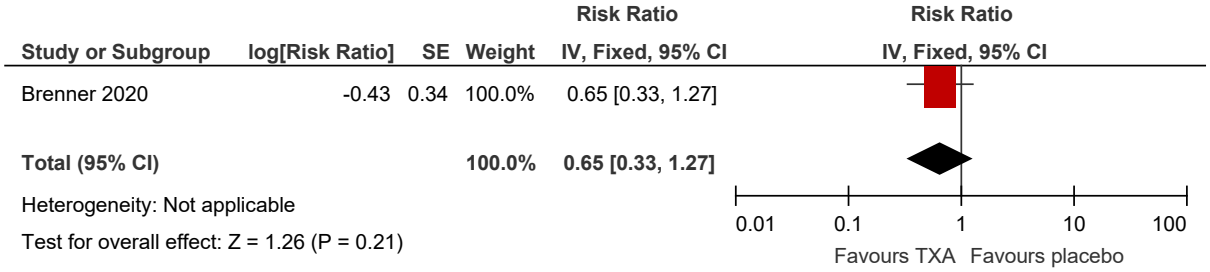

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Figure 34: All-cause mortality after 24 hours of injury (All participants)

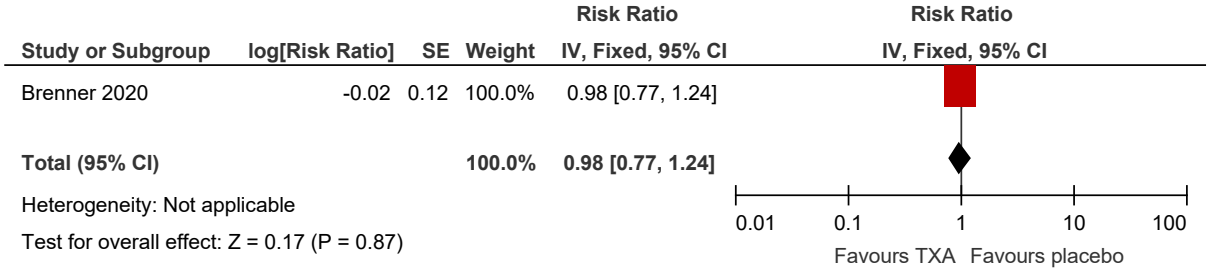

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Figure 35: All-cause mortality after 24 hours of injury – low and middle income countries (LMIC)

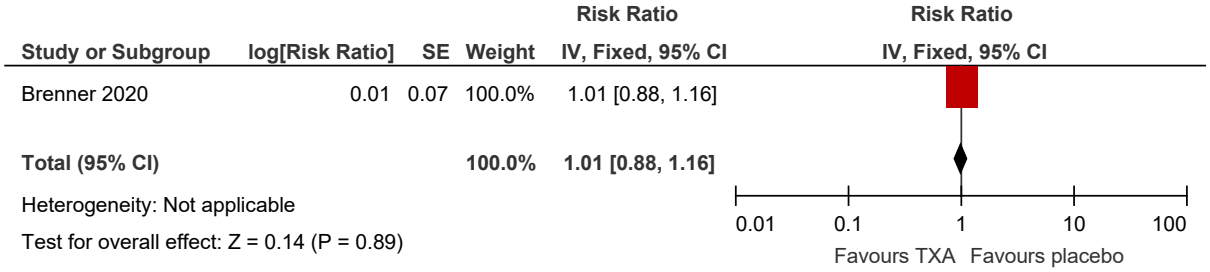

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Figure 36: All-cause mortality after 24 hours of injury – high income countries (HIC)

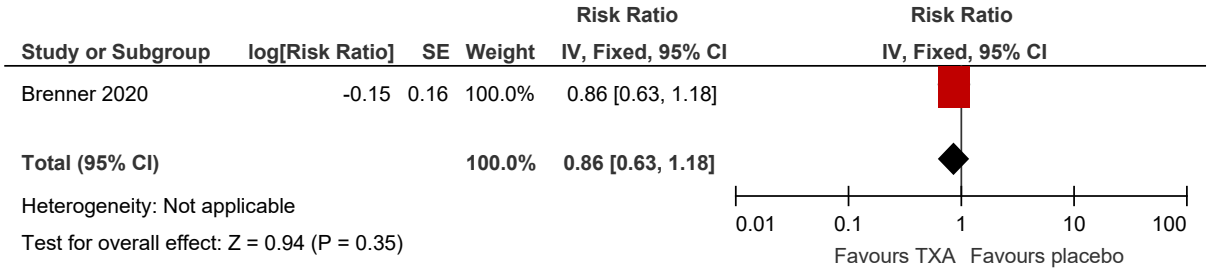

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Figure 37: All-cause mortality at 28 days of injury (All participants)

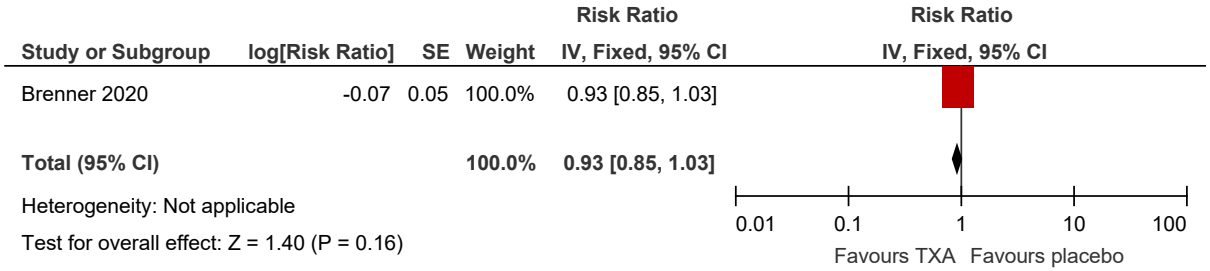

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Figure 38: All-cause mortality at 28 days of injury – low and middle income countries (LMIC)

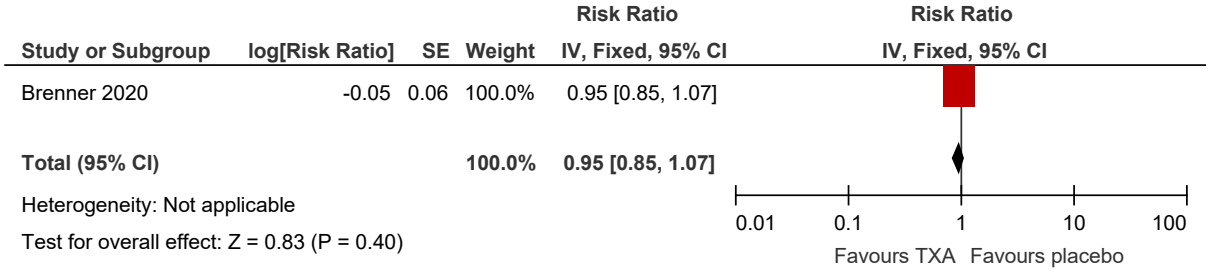

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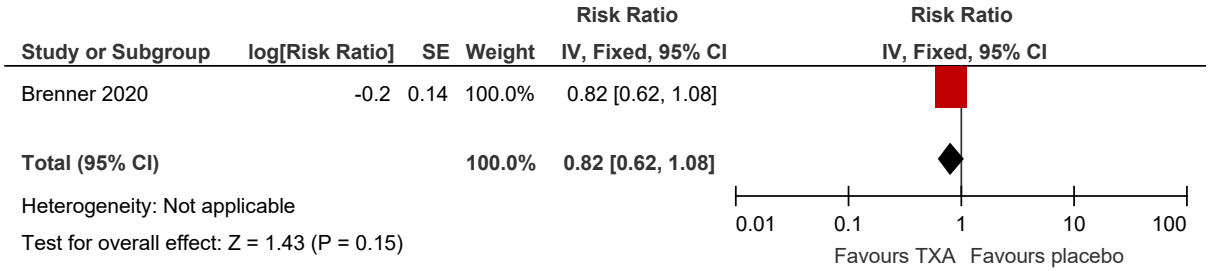
Figure 39: All-cause mortality at 28 days of injury – high income countries (HIC)



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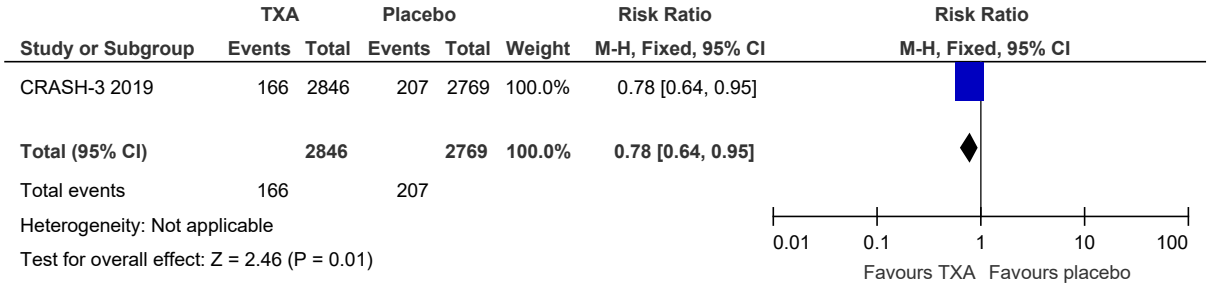
195 E.5 TXA vs Placebo (adults)

196 TXA < 3 hours of injury - mild and moderate TBI (GCS 9-15)

Figure 40: TBI mortality - mild and moderate TBI (GCS 9-15)



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E.6 TXA vs placebo (adults)

TXA < 3 hours of injury) -Excluding those with bilateral unreactive pupils –mild and moderate TBI (GCS 9‑15)

Figure 41: All-cause mortality within 24 hours of injury – mild/moderate

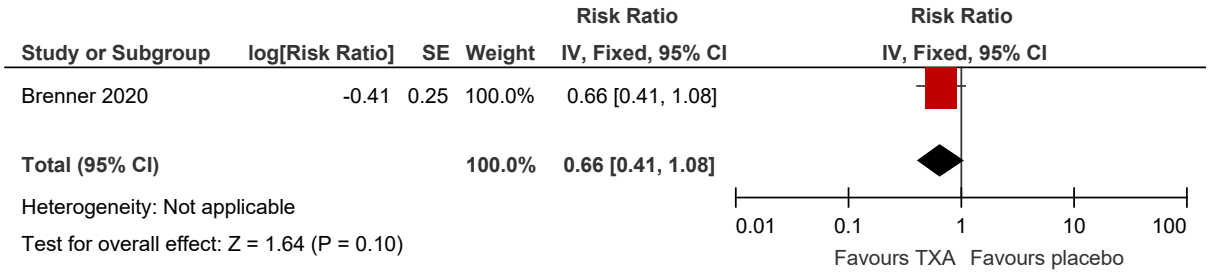

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Figure 42: All-cause mortality after 24 hours of injury – mild/moderate

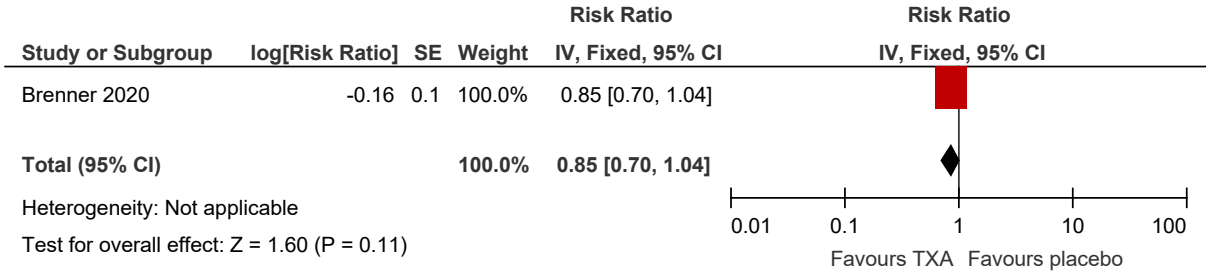

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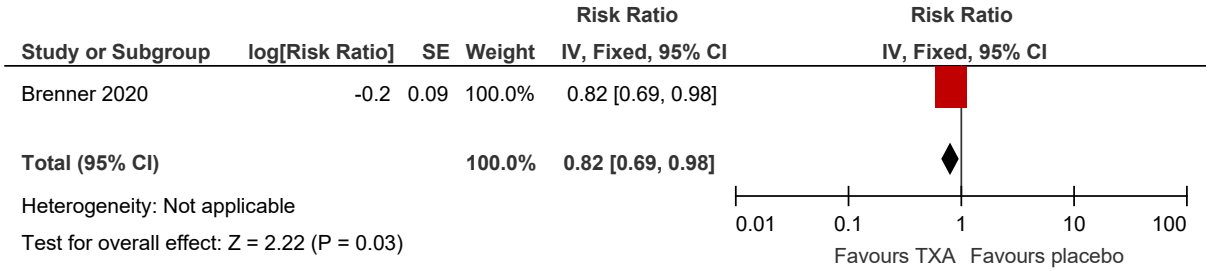
Figure 43: All-cause mortality at 28 days of injury – mild/moderate



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E.7 TXA vs Placebo (adults) TXA < 3 hours of injury – severe TBI (GCS 3-8)

Figure 44: TBI mortality - severe

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Figure 45: TBI mortality in severe TBI in high income countries

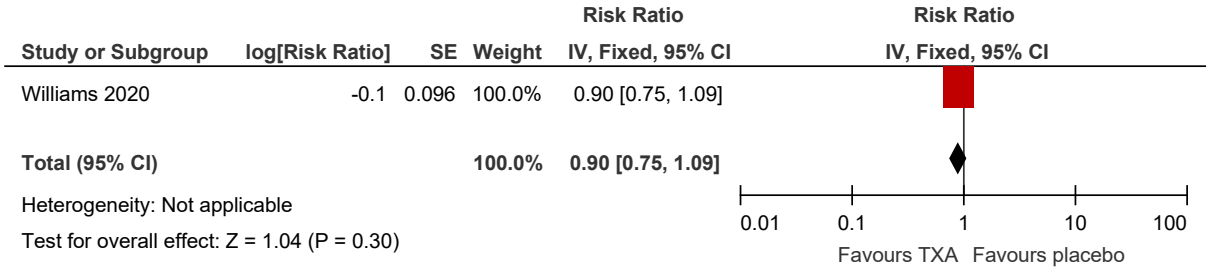

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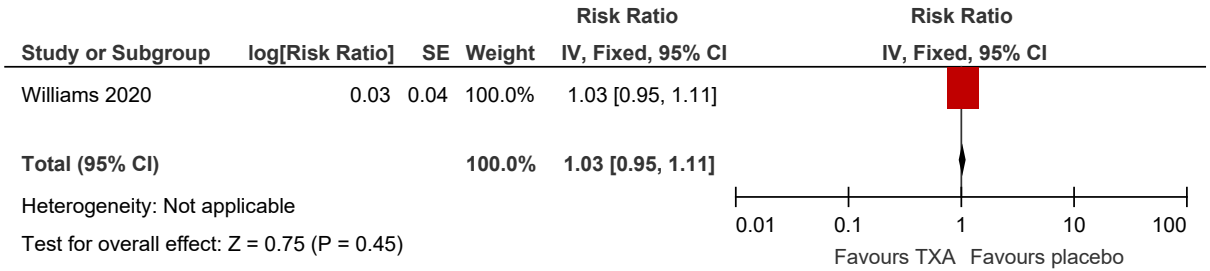
Figure 46: TBI mortality in severe TBI in low and middle income countries



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208

E.8 TXA vs placebo (adults)

TXA < 3 hours of injury- Excluding those with a GCS score of 3 or bilateral unreactive pupils - severe TBI (GCS 3‑8)

Figure 47: All-cause mortality within 24 hours of injury – severe

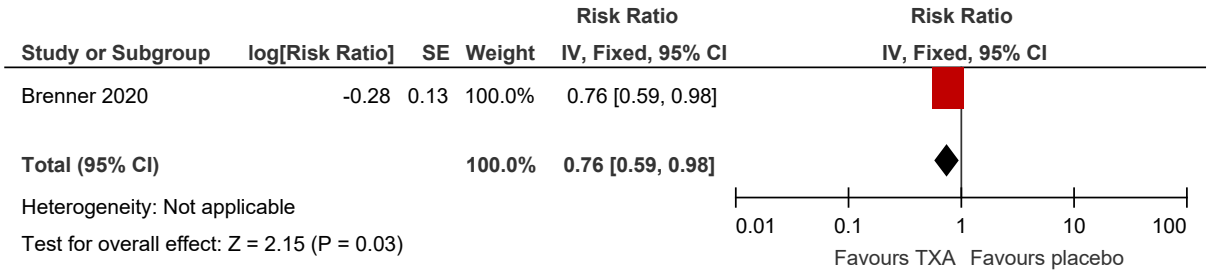

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Figure 48: All-cause mortality after 24 hours of injury – severe

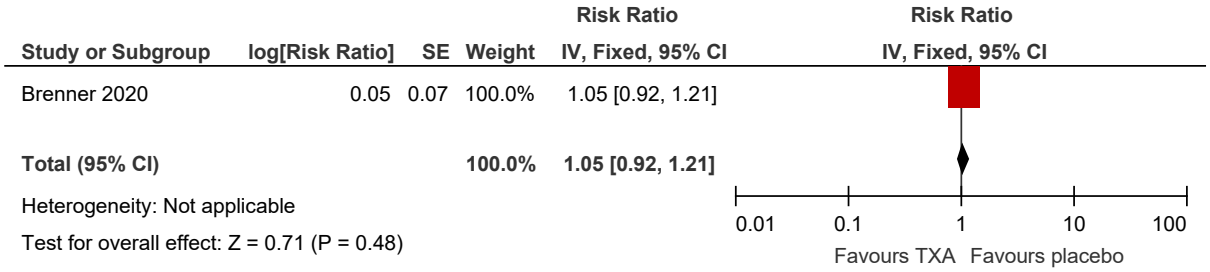


Figure 49: All-cause mortality at 28 days of injury – severe

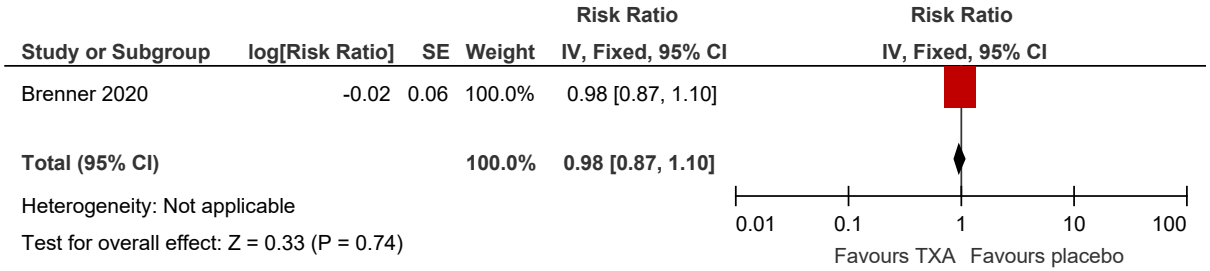
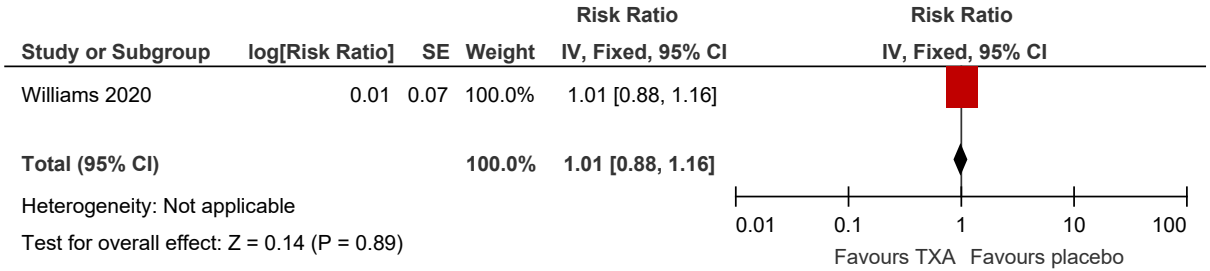
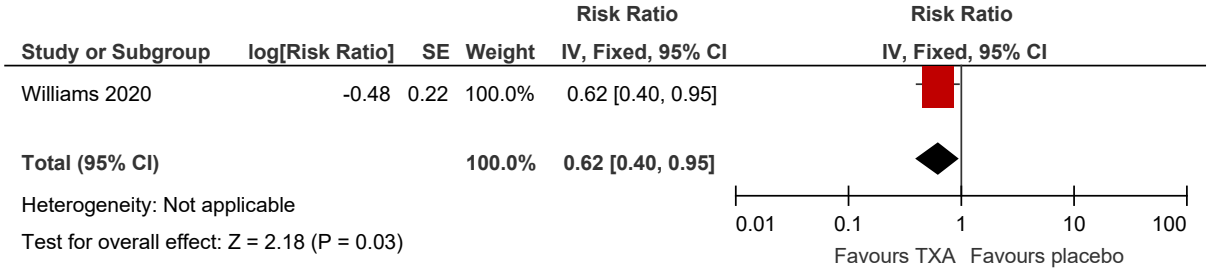


Figure 50: TBI mortality in severe TBI in low- and middle-income countries (excluding with a GCS score of 3 or bilateral unreactive pupils)



214

Figure 51: TBI mortality in severe TBI in high income countries (excluding with a GCS score of 3 or bilateral unreactive pupils)

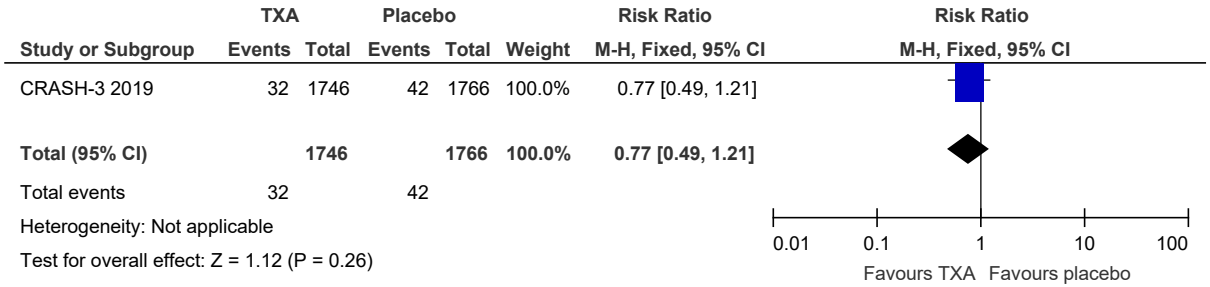


215

E.9 TXA vs Placebo (adults)

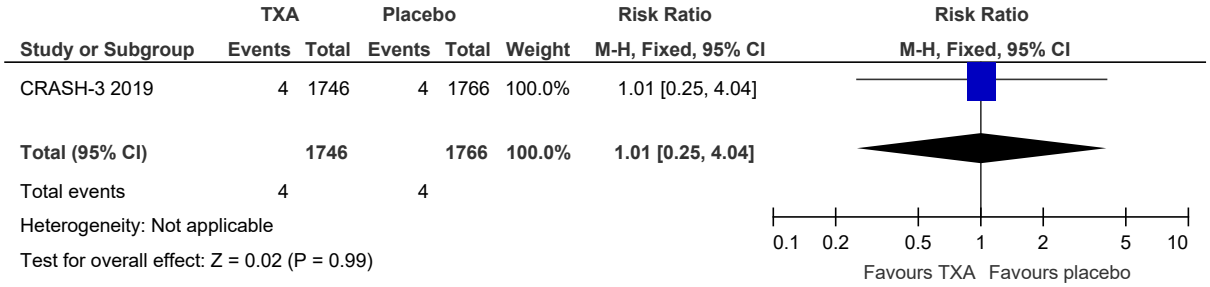
TXA >3 hours of injury- mixed GCS (mild, moderate and severe TBI)

Figure 52: All vascular occlusive events



<Insert Note here>

Figure 53: Adverse events: deep vein thrombosis (DVT)



<Insert Note here>

Figure 54: Adverse events: Stroke

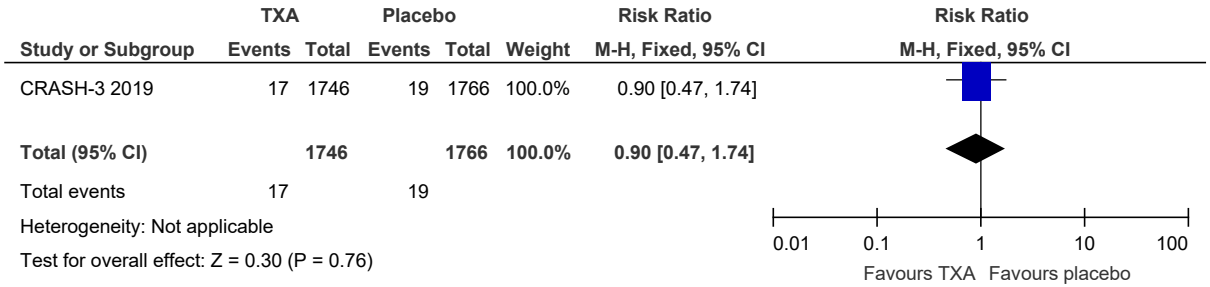


Figure 55: Adverse events: Pulmonary embolism (PE)

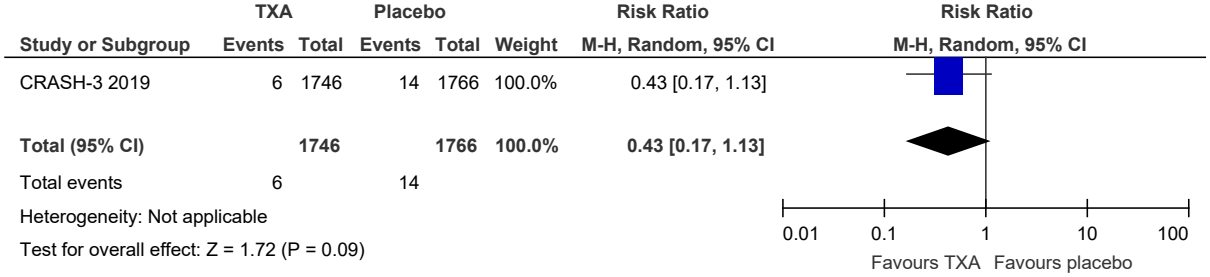
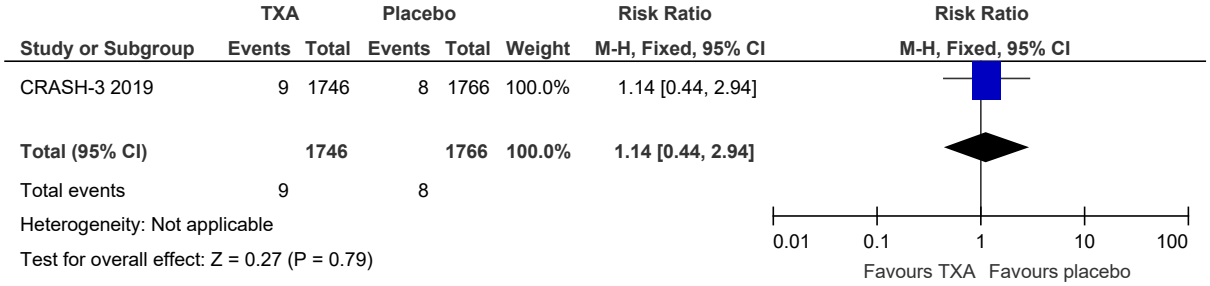
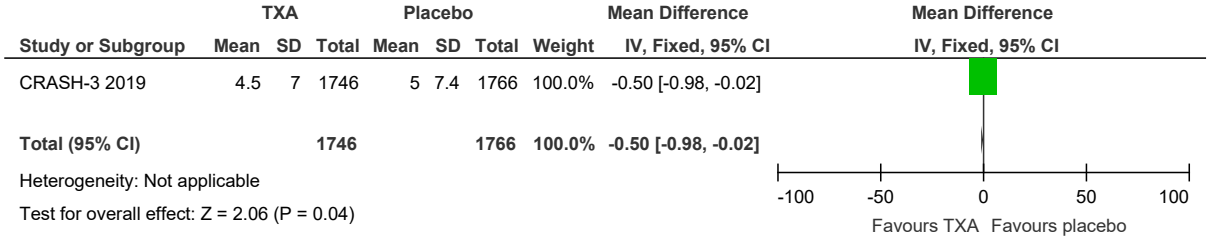


Figure 56: Adverse events : MI



<Insert Note here>

Figure 57: Disability Rating Scale score (lower score means less disabled)



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E.10 TXA vs placebo (adults)

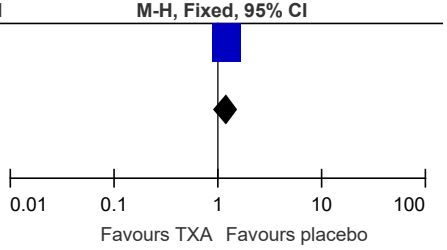
Including all participants (TXA < 3 hours and >3 hours of injury)- mixed GCS (mild, moderate and severe TBI)

Figure 58: non head injury deaths

Study or Subgroup	TXA Events	TXA Total	placebo Events	placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
CRASH-3 2019	122	6359	100	6280	100.0%	1.20 [0.93, 1.57]
Total (95% CI)		**6359**		**6280**	**100.0%**	**1.20 [0.93, 1.57]**
Total events	122		100			

Heterogeneity: Not applicable

Test for overall effect: Z = 1.39 (P = 0.16)



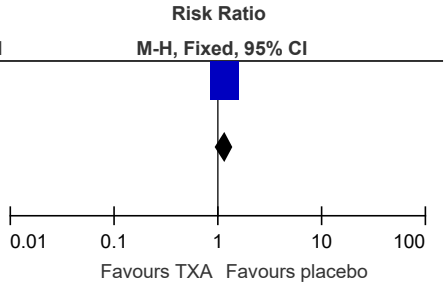
<Insert Note here>

Figure 59: any adverse event

Study or Subgroup	TXA Events	TXA Total	placebo Events	placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
CRASH-3 2019	198	6359	168	6280	100.0%	1.16 [0.95, 1.43]
Total (95% CI)		**6359**		**6280**	**100.0%**	**1.16 [0.95, 1.43]**
Total events	198		168			

Heterogeneity: Not applicable

Test for overall effect: Z = 1.47 (P = 0.14)



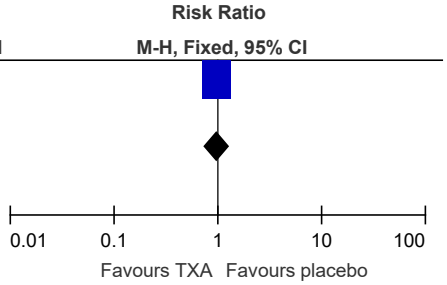
<Insert Note here>

Figure 60: All vascular occlusive events (fatal and non-fatal) at 28 days

Study or Subgroup	TXA Events	TXA Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
CRASH-3 2019	101	6359	102	6280	100.0%	0.98 [0.74, 1.28]
Total (95% CI)		**6359**		**6280**	**100.0%**	**0.98 [0.74, 1.28]**
Total events	101		102			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.16 (P = 0.87)



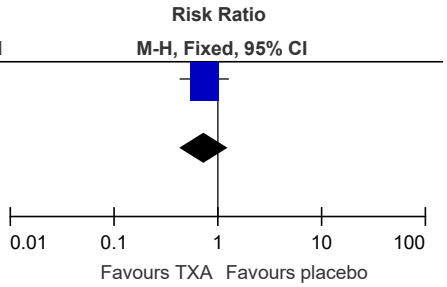
<Insert Note here>

Figure 61: Adverse events: pulmonary embolism

Study or Subgroup	TXA Events	TXA Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
CRASH-3 2019	24	6359	32	6280	100.0%	0.74 [0.44, 1.26]
Total (95% CI)		**6359**		**6280**	**100.0%**	**0.74 [0.44, 1.26]**
Total events	24		32			

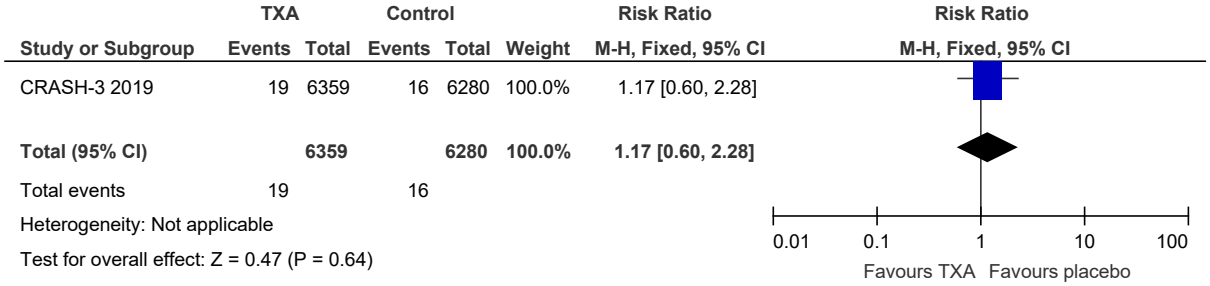
Heterogeneity: Not applicable

Test for overall effect: Z = 1.11 (P = 0.27)



<Insert Note here>

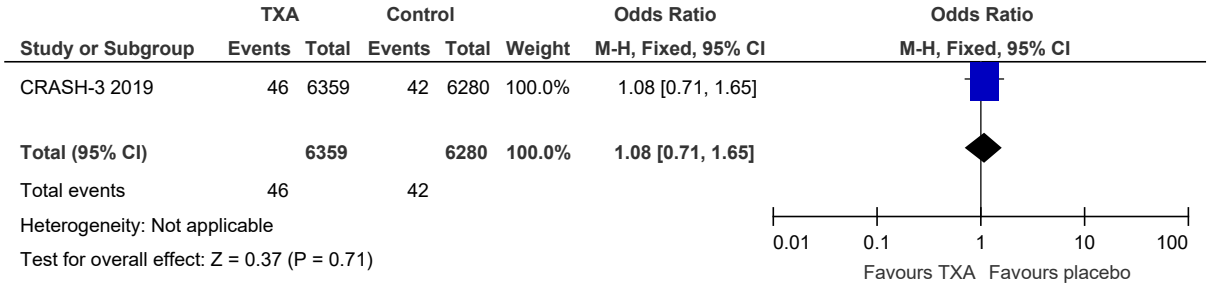
Figure 62: Adverse events: DVT



<Insert Note here>

21

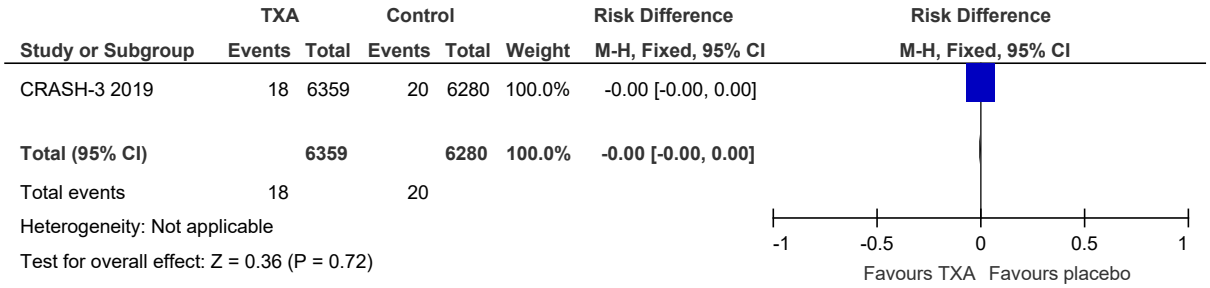
Figure 63: Adverse events: stroke



<Insert Note here>

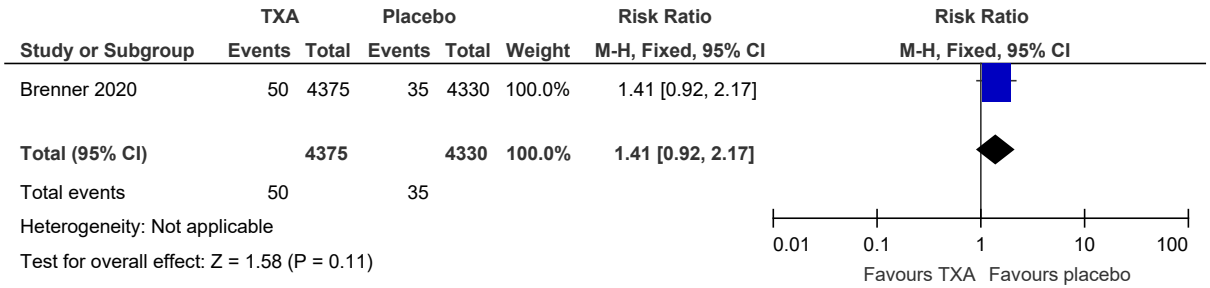
22

Figure 64: Adverse events: MI



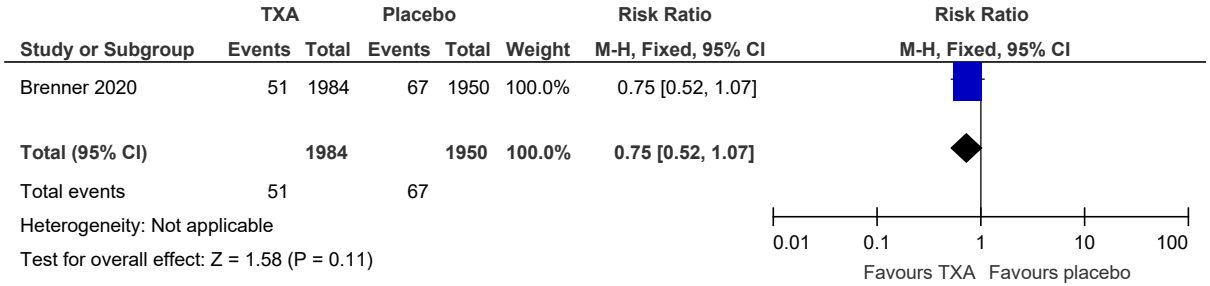
<Insert Note here>

Figure 65: All vascular occlusive events (fatal and non-fatal) at 28 days in low and middle-income countries (LMIC)



<Insert Note here>

Figure 66: All vascular occlusive events (fatal and non-fatal) at 28 days in high income countries (HIC)

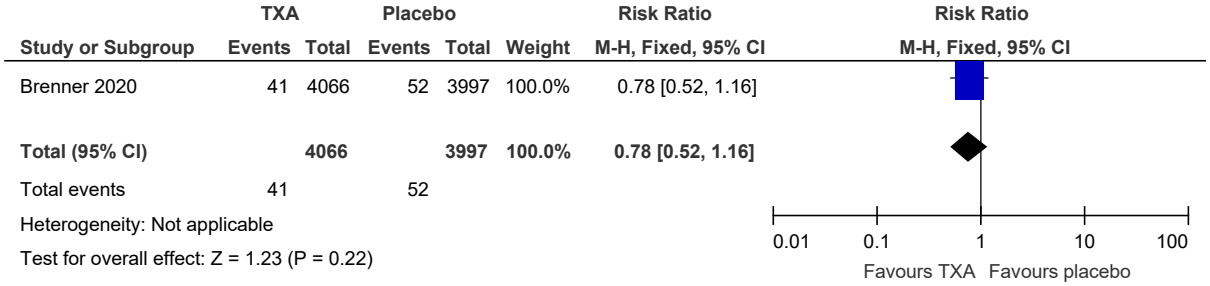


<Insert Note here>

E.11 TXA vs placebo (adults)

Including all participants (TXA< 3 hours and > 3 hours of injury)- mild and moderate TBI (GCS 9‑15)

Figure 67: vascular occlusive events (fatal and non-fatal) at 28 days in mild/moderate

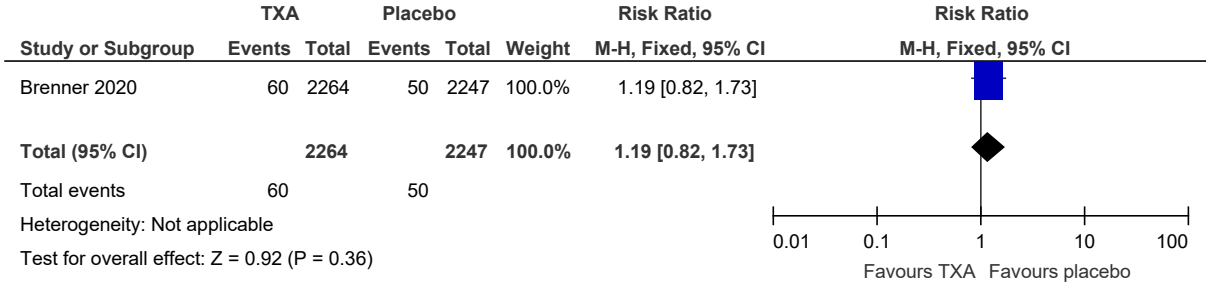


<Insert Note here>

E.12 TXA vs placebo (adults)

Including all participants (TXA < 3 hours and > 3 hours of injury)- severe TBI (GCS 3‑8)

Figure 68: vascular occlusive events (fatal and non-fatal) at 28 days in severe



<Insert Note here>

Appendix F – GRADE tables

PRE-HOSPITAL SETTING

Table 21: Clinical evidence profile: TXA vs Placebo (adults) in pre-hospital setting

TXA < 3 hours of injury- Mixed GCS (mild, moderate and severe TBI) [out-of-hospital tranexamic acid (1 g) bolus and in-hospital tranexamic acid (1 g) 8-hour infusion]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TXA	placebo	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (at 28 days)												
1	randomised trials	not serious	not serious	serious[a]	very serious[b]	none	53/285 (18.6%)	50/285 (17.5%)	**RR 1.06** (0.75 to 1.50)	**11 more per 1,000** (from 44 fewer to 88 more)	⨁◯◯◯ Very low	CRITICAL
All cause mortality at 6 months												
1	randomised trials	not serious	not serious	serious[a]	very serious[b]	none	55/262 (21.0%)	54/272 (19.9%)	**RR 1.06** (0.76 to 1.48)	**12 more per 1,000** (from 48 fewer to 95 more)	⨁◯◯◯ Very low	CRITICAL
Length of hospital stay (hospital free days at 28-days) [c]												
1	randomised trials	not serious	not serious	serious[a]	not serious	none	312	309	-	MD **0** (1.68 lower to 1.68 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Neurosurgical intervention (at 28 days) [d]												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TXA	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	serious[a]	serious[b]	none	62/312 (19.9%)	54/309 (17.5%)	**RR 1.14** (0.82 to 1.58)	**24 more per 1,000** (from 31 fewer to 101 more)	⨁⨁◯◯ Low	CRITICAL
Degree of disability: favourable outcome at discharge (GOS-E >4)												
1	randomised trials	not serious	not serious	serious[a]	serious[b]	none	101/294 (34.4%)	96/292 (32.9%)	**RR 1.04** (0.83 to 1.31)	**13 more per 1,000** (from 56 fewer to 102 more)	⨁⨁◯◯ Low	CRITICAL
Degree of disability: favourable outcome at 6 months (GOS-E >4)												
1	randomised trials	not serious	not serious	serious[a]	not serious	none	153/262 (58.4%)	163/272 (59.9%)	**RR 0.97** (0.85 to 1.12)	**18 fewer per 1,000** (from 90 fewer to 72 more)	⨁⨁⨁◯ Moderate	CRITICAL
Adverse events: MI (at 28 days)												
1	randomised trials	not serious	not serious	serious[a]	very serious[b]	none	3/312 (1.0%)	1/309 (0.3%)	**RR 2.97** (0.31 to 28.41)	**6 more per 1,000** (from 2 fewer to 89 more)	⨁◯◯◯ Very low	CRITICAL
Adverse events: Pulmonary embolism (at 28 days)												
1	randomised trials	not serious	not serious	serious[a]	very serious[b]	none	3/312 (1.0%)	5/309 (1.6%)	**RR 0.59** (0.14 to 2.47)	**7 fewer per 1,000** (from 14 fewer to 24 more)	⨁◯◯◯ Very low	CRITICAL
Adverse events: Deep vein thrombosis (at 28 days)												
1	randomised trials	not serious	not serious	serious[a]	serious[b]	none	3/312 (1.0%)	9/309 (2.9%)	**RR 0.33** (0.09 to 1.21)	**20 fewer per 1,000** (from 27 fewer to 6 more)	⨁⨁◯◯ Low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TXA	placebo	Relative (95% CI)	Absolute (95% CI)		
Adverse events: Thrombotic stroke (at 28 days)												
1	randomised trials	not serious	not serious	serious[a]	serious[b]	none	3/312 (1.0%)	10/309 (3.2%)	**RR 0.30** (0.08 to 1.07)	**23 fewer per 1,000** (from 30 fewer to 2 more)	⨁⨁◯◯ Low	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

a. Downgraded by 1 increment for indirectness. Mixed severity based on GCS. Mild: 4%, moderate: 39%, severe: 57%.

b. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group for continuous outcomes. MID for hospital free days at 28 days is 5.35).

c. Hospital-free days include any day from hospital admission through day 28 that the participant was alive and out of the hospital. Some participants, primarily those who withdrew before discharge, are missing this measure (20 in the bolus maintenance group, and 14 in the placebo group).

d. Neurosurgical interventions include craniotomy, craniectomy, and placement of a neuromonitoring or drainage device.

Table 22: TXA vs Placebo (adults) in pre-hospital setting

TXA < 3 hours of injury- Mixed GCS (mild, moderate and severe TBI) [out-of-hospital tranexamic acid (2 g) bolus and in-hospital placebo 8-hour infusion]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TXA	Placebo	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (at 28 days)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TXA	Placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	serious[a]	serious[b]	none	40/318 (12.6%)	50/285 (17.5%)	**RR 0.72** (0.49 to 1.05)	**49 fewer per 1,000** (from 89 fewer to 9 more)	⨁⨁◯◯ Low	CRITICAL
All cause mortality at 6 months												
1	randomised trials	not serious	not serious	serious[a]	serious[b]	none	46/289 (15.9%)	54/272 (19.9%)	**RR 0.80** (0.56 to 1.15)	**40 fewer per 1,000** (from 87 fewer to 30 more)	⨁⨁◯◯ Low	CRITICAL
Length of hospital stay (hospital free days at 28-days)[c]												
1	randomised trials	not serious	not serious	serious[a]	not serious	none	345	309	-	MD **0.5 higher** (1.12 lower to 2.12 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Neurosurgical intervention (at 28 days)[d]												
1	randomised trials	not serious	not serious	serious[a]	serious[b]	none	75/345 (21.7%)	54/309 (17.5%)	**RR 1.24** (0.91 to 1.70)	**42 more per 1,000** (from 16 fewer to 122 more)	⨁⨁◯◯ Low	CRITICAL
Degree of disability: favourable outcome at discharge (GOS-E >4)												
1	randomised trials	not serious	not serious	serious[a]	serious[b]	none	101/329 (30.7%)	96/292 (32.9%)	**RR 0.93** (0.74 to 1.18)	**23 fewer per 1,000** (from 85 fewer to 59 more)	⨁⨁◯◯ Low	CRITICAL
Degree of disability: favourable outcome at 6 months (GOS-E >4)												
1	randomised trials	not serious	not serious	serious[a]	not serious	none	178/289 (61.6%)	163/272 (59.9%)	**RR 1.03** (0.90 to 1.17)	**18 more per 1,000** (from 60 fewer to 102 more)	⨁⨁⨁◯ Moderate	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TXA	Placebo	Relative (95% CI)	Absolute (95% CI)		
Adverse events: MI (at 28 days)												
1	randomised trials	not serious	not serious	serious[a]	very serious[b]	none	2/345 (0.6%)	1/309 (0.3%)	**RR 1.79** (0.16 to 19.66)	**3 more per 1,000** (from 3 fewer to 60 more)	⨁◯◯◯ Very low	CRITICAL
Adverse events: Pulmonary embolism (at 28 days)												
1	randomised trials	not serious	not serious	serious[a]	very serious[b]	none	6/345 (1.7%)	5/309 (1.6%)	**RR 1.07** (0.33 to 3.49)	**1 more per 1,000** (from 11 fewer to 40 more)	⨁◯◯◯ Very low	CRITICAL
Adverse events: Deep vein thrombosis (at 28 days)												
1	randomised trials	not serious	not serious	serious[a]	very serious[b]	none	10/345 (2.9%)	9/309 (2.9%)	**RR 1.00** (0.41 to 2.42)	**0 fewer per 1,000** (from 17 fewer to 41 more)	⨁◯◯◯ Very low	CRITICAL
Adverse events: Thrombotic stroke (at 28 days)												
1	randomised trials	not serious	not serious	serious[a]	very serious[b]	none	13/345 (3.8%)	10/309 (3.2%)	**RR 1.16** (0.52 to 2.62)	**5 more per 1,000** (from 16 fewer to 52 more)	⨁◯◯◯ Very low	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

a. Downgraded by 1 increment for indirectness. Mixed severity based on GCS. Mild: 4%, moderate: 39%, severe: 57%.

b. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group for continuous outcomes. MID for hospital free days at 28 days is 5.35).

c. Hospital-free days include any day from hospital admission through day 28 that the participant was alive and out of the hospital. Some participants, primarily those who withdrew before discharge, are missing this measure (14 in the bolus only group, and 14 in the placebo group).

d. Neurosurgical interventions include craniotomy, craniectomy, and placement of a neuromonitoring or drainage device.

HOSPITAL SETTING

Table 23: TXA vs Placebo (adults) in hospital setting

TXA < 3 hours of injury- Mixed GCS (mild, moderate and severe TBI)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TXA	placebo	Relative (95% CI)	Absolute (95% CI)		
TBI related mortality (overall)												
1	randomised trials	not serious	not serious	serious[a]	not serious	none	855/4613 (18.5%)	892/4514 (19.8%)	**RR 0.94** (0.86 to 1.02)	**12 fewer per 1,000** (from 28 fewer to 4 more)	⨁⨁⨁◯ Moderate	CRITICAL
TBI related mortality - pupil reactivity (both react)												
1	randomised trials	not serious	not serious	serious[a]	serious[b]	none	440/3820 (11.5%)	493/3728 (13.2%)	**RR 0.87** (0.77 to 0.98)	**17 fewer per 1,000** (from 30 fewer to 3 fewer)	⨁⨁◯◯ Low	CRITICAL
TBI related mortality- pupil reactivity (any non-reactive)												
1	randomised trials	not serious	not serious	serious[a]	not serious	none	415/793 (52.3%)	399/786 (50.8%)	**RR 1.03** (0.94 to 1.13)	**15 more per 1,000** (from 30 fewer to 66 more)	⨁⨁⨁◯ Moderate	CRITICAL
All vascular occlusive events (All severities)												
1	randomised trials	not serious	not serious	serious[a]	serious[b]	none	69/4613 (1.5%)	60/4514 (1.3%)	**RR 1.13** (0.80 to 1.59)	**2 more per 1,000** (from 3 fewer to 8 more)	⨁⨁◯◯ Low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TXA	placebo	Relative (95% CI)	Absolute (95% CI)		
Adverse events: DVT												
1	randomised trials	not serious	not serious	serious[a]	very serious[b]	none	15/4613 (0.3%)	12/4514 (0.3%)	**RR 1.22** (0.57 to 2.61)	**1 more per 1,000** (from 1 fewer to 4 more)	⨁◯◯◯ Very low	CRITICAL
Adverse events: Stroke												
1	randomised trials	not serious	not serious	serious[a]	very serious[b]	none	29/4613 (0.6%)	23/4514 (0.5%)	**RR 1.23** (0.71 to 2.13)	**1 more per 1,000** (from 1 fewer to 6 more)	⨁◯◯◯ Very low	CRITICAL
Adverse events: Pulmonary embolism												
1	randomised trials	not serious	not serious	serious[a]	very serious[b]	none	18/4613 (0.4%)	18/4514 (0.4%)	**RR 0.98** (0.51 to 1.88)	**0 fewer per 1,000** (from 2 fewer to 4 more)	⨁◯◯◯ Very low	CRITICAL
Adverse events: MI												
1	randomised trials	not serious	not serious	serious[a]	very serious[b]	none	9/4613 (0.2%)	12/4514 (0.3%)	**RR 0.73** (0.31 to 1.74)	**1 fewer per 1,000** (from 2 fewer to 2 more)	⨁◯◯◯ Very low	CRITICAL
Disability Rating Scale score (lower score means less disabled)												
1	randomised trials	not serious	not serious	serious[a]	not serious	none	4613	4514	-	MD **0.04 lower** (0.35 lower to 0.27 higher)	⨁⨁⨁◯ Moderate	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

a. Downgraded by 1 increment for indirectness. Mixed severity based on GCS.

b. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group for continuous outcomes. MID for disability rating scale score is 3.8)

Table 24: TXA vs placebo (adults) in hospital setting

TXA < 3 hours of injury- Excluding those with a GCS score of 3 or bilateral unreactive pupils –- mixed GCS (mild, moderate and severe TBI)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TXA	Placebo	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality within 24 hours of injury (All participants)												
1	randomised trials	serious[a]	not serious	serious[b]	serious[c]	none	-/0	-/0	**RR 0.74** (0.59 to 0.94)[d]	-	⨁◯◯◯ Very low	CRITICAL
All-cause mortality within 24 hours of injury – LMIC												
1	randomised trials	serious[a]	not serious	serious[b]	serious[c]	none	-/0	-/0	**RR 0.75** (0.58 to 0.97)[d]	-	⨁◯◯◯ Very low	CRITICAL
All-cause mortality within 24 hours of injury – HIC												
1	randomised trials	serious[a]	not serious	serious[b]	serious[c]	none	-/0	-/0	**RR 0.65** (0.33 to 1.27)[d]	-	⨁◯◯◯ Very low	CRITICAL
All-cause mortality after 24 hours of injury (All participants)												
1	randomised trials	serious[a]	not serious	serious[b]	serious[c]	none	-/0	-/0	**RR 0.98** (0.77 to 1.24)[d]	-	⨁◯◯◯ Very low	CRITICAL
All-cause mortality after 24 hours of injury – LMIC												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TXA	Placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	serious[b]	not serious	none	-/0	-/0	**RR 1.01** (0.88 to 1.16) [d]	-	⨁⨁◯◯ Low	CRITICAL
All-cause mortality after 24 hours of injury – HIC												
1	randomised trials	serious[a]	not serious	serious[b]	serious[c]	none	-/0	-/0	**RR 0.86** (0.63 to 1.18) [d]	-	⨁◯◯◯ Very low	CRITICAL
All-cause mortality at 28 days of injury (All participants)												
1	randomised trials	not serious	not serious	serious[b]	not serious	none	-/0	-/0	**RR 0.93** (0.85 to 1.03) [d]	-	⨁⨁⨁◯ Moderate	CRITICAL
All-cause mortality at 28 days of injury – LMIC												
1	randomised trials	serious[a]	not serious	serious[b]	not serious	none	-/0	-/0	**RR 0.95** (0.85 to 1.07) [d]	-	⨁⨁◯◯ Low	CRITICAL
All-cause mortality at 28 days of injury – HIC												
1	randomised trials	serious[a]	not serious	serious[b]	serious[c]	none	-/0	-/0	**RR 0.82** (0.62 to 1.08) [d]	-	⨁◯◯◯ Very low	CRITICAL

CI: confidence interval; **RR:** risk ratio

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias. Exclusion of those with a GCS score of 3 or bilateral unreactive pupils post-randomisation.

b. Downgraded by 1 increment for indirectness. Mixed severity based on GCS.

c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group for continuous outcomes).

d. GIV analysis used as only RR reported in the paper. Total number of participants in each group not available. Unable to calculate absolute risk

Table 25: TXA vs Placebo (adults) in hospital setting

TXA < 3 hours of injury - mild and moderate TBI (GCS 9-15)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TXA	placebo	Relative (95% CI)	Absolute (95% CI)		
TBI mortality -mild and moderate (GCS 9-15)												
1	randomised trials	not serious	not serious	serious[a]	serious[b]	none	166/2846 (5.8%)	207/2769 (7.5%)	**RR 0.78** (0.64 to 0.95)	**16 fewer per 1,000** (from 27 fewer to 4 fewer)	⨁⨁◯◯ Low	CRITICAL

CI: confidence interval; **RR:** risk ratio

a. Downgraded by 1 increment for indirectness. Mixed severity based on GCS.

b. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes)

Table 26: TXA vs placebo (adults) in hospital setting

TXA < 3 hours of injury- Excluding those with bilateral unreactive pupils- mild and moderate TBI (GCS 9‑15)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TXA	Placebo	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality within 24 hours of injury – mild/moderate TBI												
1	randomised trials	serious[a]	not serious	serious[b]	serious[c]	none	-/0	-/0	**RR 0.66** (0.41 to 1.08)[d]	-	⨁◯◯◯ Very low	CRITICAL
All-cause mortality after 24 hours of injury – mild/moderate TBI												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TXA	Placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	serious[b]	serious[c]	none	-/0	-/0	**RR 0.85** (0.70 to 1.04) [d]	-	⨁◯◯◯ Very low	CRITICAL

All-cause mortality at 28 days of injury – mild/moderate TBI

1	randomised trials	serious[a]	not serious	serious[b]	serious[c]	none	-/0	-/0	**RR 0.82** (0.69 to 0.98)[d]	-	⨁◯◯◯ Very low	CRITICAL

CI: confidence interval; **RR:** risk ratio

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias. Exclusion of those with a GCS score of 3 or bilateral unreactive pupils post-randomisation.

b. Downgraded by 1 increment for indirectness. Mixed severity based on GCS.

c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group for continuous outcomes).

d. GIV analysis used as only RR reported in the paper. Total number of participants in each group not available. Unable to calculate absolute risk.

Table 27: TXA vs Placebo (adults) in hospital setting

TXA < 3 hours of injury – severe TBI (GCS 3-8)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TXA	placebo	Relative (95% CI)	Absolute (95% CI)		
TBI mortality - severe (GCS 3-8)												
1	randomised trials	not serious	not serious	not serious	not serious	none	689/1739 (39.6%)	685/1710 (40.1%)	**RR 0.99** (0.91 to 1.07)	**4 fewer per 1,000** (from 36 fewer to 28 more)	⨁⨁⨁⨁ High	CRITICAL
TBI mortality in severe TBI in high income countries												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	-/0	-/0	**RR 0.90** (0.75 to 1.09)[b]	-	⨁⨁⨁◯ Moderate	CRITICAL
TBI mortality in severe TBI in low and middle income countries												
1	randomised trials	not serious	not serious	not serious	not serious	none	-/0	-/0	**RR 1.03** (0.95 to 1.11)[b]	-	⨁⨁⨁⨁ High	CRITICAL

CI: confidence interval; **RR:** risk ratio

a. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group for continuous outcomes)

b. GIV analysis used as only RR reported in the paper. No of events and number of participants in each group not available from the paper. Unable to calculate absolute risk.

Table 28: TXA vs placebo (adults) in hospital setting

TXA < 3 hours of injury- Excluding those with a GCS score of 3 or bilateral unreactive pupils - severe TBI (GCS 3‑8)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TXA	placebo	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality within 24 hours of injury – severe TBI												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	-/0	-/0	**RR 0.76** (0.59 to 0.98) [c]	-	⨁⨁◯◯ Low	CRITICAL
All-cause mortality after 24 hours of injury – severe TBI												
1	randomised trials	serious[a]	not serious	not serious	not serious	none	-/0	-/0	**RR 1.05** (0.92 to 1.21) [c]	-	⨁⨁⨁◯ Moderate	CRITICAL
All-cause mortality at 28 days of injury – severe TBI												
1	randomised trials	serious[a]	not serious	not serious	not serious	none	-/0	-/0	**RR 0.98** (0.87 to 1.10) [c]	-	⨁⨁⨁◯ Moderate	CRITICAL
TBI mortality in severe TBI in low and middle income countries (excluding those patients with a GCS score of 3 or bilateral unreactive pupils)												
1	randomised trials	serious[a]	not serious	not serious	not serious	none	-/0	-/0	**RR 1.01** (0.88 to 1.16) [c]	-	⨁⨁⨁◯ Moderate	CRITICAL
TBI mortality in severe TBI in high income countries (excluding with a GCS score of 3 or bilateral unreactive pupils)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	-/0	-/0	**RR 0.62** (0.40 to 0.95)[c]	-	⨁⨁◯◯ Low	CRITICAL

CI: confidence interval; **RR:** risk ratio

a. Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias. Exclusion of those with a GCS score of 3 or bilateral unreactive pupils post-randomisation.

b. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group for continuous outcomes).

c. GIV analysis used as only RR reported in the paper. Total number of participants in each group not available. Unable to calculate absolute risk

Table 29: TXA vs Placebo (adults) in hospital setting

TXA >3 hours of injury- mixed GCS (mild, moderate and severe TBI)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TXA	Placebo	Relative (95% CI)	Absolute (95% CI)		
All vascular occlusive events												
1	randomised trials	not serious	not serious	serious[a]	serious[b]	none	32/1746 (1.8%)	42/1766 (2.4%)	**RR 0.77** (0.49 to 1.21)	**5 fewer per 1,000** (from 12 fewer to 5 more)	⨁⨁◯◯ Low	CRITICAL
Adverse events: deep vein thrombosis (DVT)												
1	randomised trials	not serious	not serious	serious[a]	very serious[b]	none	4/1746 (0.2%)	4/1766 (0.2%)	**RR 1.01** (0.25 to 4.04)	**0 fewer per 1,000** (from 2 fewer to 7 more)	⨁◯◯◯ Very low	CRITICAL
Adverse events: Stroke												
1	randomised trials	not serious	not serious	serious[a]	very serious[b]	none	17/1746 (1.0%)	19/1766 (1.1%)	**RR 0.90** (0.47 to 1.74)	**1 fewer per 1,000** (from 6 fewer to 8 more)	⨁◯◯◯ Very low	CRITICAL
Adverse events: Pulmonary embolism (PE)												
1	randomised trials	not serious	not serious	serious[a]	serious[b]	none	6/1746 (0.3%)	14/1766 (0.8%)	**RR 0.43** (0.17 to 1.13)	**5 fewer per 1,000** (from 7 fewer to 1 more)	⨁⨁◯◯ Low	CRITICAL
Myocardial infarction (MI)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TXA	Placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	serious[a]	very serious[b]	none	9/1746 (0.5%)	8/1766 (0.5%)	**RR 1.14** (0.44 to 2.94)	**1 more per 1,000** (from 3 fewer to 9 more)	⨁◯◯◯ Very low	CRITICAL
Disability Rating Scale score (lower score means less disabled)												
1	randomised trials	not serious	not serious	serious[a]	not serious	none	1746	1766	-	MD **0.5 lower** (0.98 lower to 0.02 lower)	⨁⨁⨁◯ Moderate	CRITICAL

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

a. Downgraded by 1 increment for indirectness. Mixed severity based on GCS.

b. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group for continuous outcomes. MID for disability rating scale score is 3.8)

Table 30: TXA vs placebo (adults) in hospital setting

Including all participants (TXA < 3 hours and >3 hours of injury)- mixed GCS (mild, moderate and severe TBI)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TXA	Placebo	Relative (95% CI)	Absolute (95% CI)		
non-head injury deaths												
1	randomised trials	not serious	not serious	very serious[a]	serious[b]	none	122/6359 (1.9%)	100/6280 (1.6%)	**RR 1.20** (0.93 to 1.57)	**3 more per 1,000** (from 1 fewer to 9 more)	⨁◯◯◯ Very low	
Any adverse event												
1	randomised trials	not serious	not serious	very serious[a]	serious[b]	none	198/6359 (3.1%)	168/6280 (2.7%)	**RR 1.16** (0.95 to 1.43)	**4 more per 1,000** (from 1 fewer to 12 more)	⨁◯◯◯ Very low	
All vascular occlusive events (fata and non fatal) at 28 days												
1	randomised trials	not serious	not serious	very serious[a]	very serious[b]	none	101/6359 (1.6%)	102/6280 (1.6%)	**RR 0.98** (0.74 to 1.28)	**0 fewer per 1,000** (from 4 fewer to 5 more)	⨁◯◯◯ Very low	
Adverse events: pulmonary embolism												
1	randomised trials	not serious	not serious	very serious[a]	very serious[b]	none	24/6359 (0.4%)	32/6280 (0.5%)	**RR 0.74** (0.44 to 1.26)	**1 fewer per 1,000** (from 3 fewer to 1 more)	⨁◯◯◯ Very low	
Adverse events: DVT												
1	randomised trials	not serious	not serious	very serious[a]	very serious[b]	none	19/6359 (0.3%)	16/6280 (0.3%)	**RR 1.17** (0.60 to 2.28)	**0 fewer per 1,000** (from 1 fewer to 3 more)	⨁◯◯◯ Very low	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TXA	Placebo	Relative (95% CI)	Absolute (95% CI)		
Adverse events: stroke												
1	randomised trials	not serious	not serious	very serious[a]	very serious[b]	none	46/6359 (0.7%)	42/6280 (0.7%)	**RR 1.08** (0.71 to 1.64)	**1 more per 1,000** (from 2 fewer to 4 more)	⨁◯◯◯ Very low	
Adverse events: MI												
1	randomised trials	not serious	not serious	very serious[a]	not serious	none	18/6359 (0.3%)	20/6280 (0.3%)	not estimable	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ Low	
All vascular occlusive events(fatal and non-fatal) at 28 days in LMIC												
1	randomised trials	not serious	not serious	very serious[a]	serious[b]	none	50/4375 (1.1%)	35/4330 (0.8%)	**RR 1.41** (0.92 to 2.17)	**3 more per 1,000** (from 1 fewer to 9 more)	⨁◯◯◯ Very low	
All vascular occlusive events(fatal and non-fatal) at 28 days in HIC												
1	randomised trials	not serious	not serious	very serious[a]	serious[b]	none	51/1984 (2.6%)	67/1950 (3.4%)	**RR 0.75** (0.52 to 1.07)	**9 fewer per 1,000** (from 16 fewer to 2 more)	⨁◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

a. Downgraded by 2 increments for indirectness. Mixed severity based on GCS. Includes both TXA < 3 hours and > 3 hours of injury.

b. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group for continuous outcomes).

Table 31: TXA vs placebo (adults) in hospital setting

Including all participants (TXA< 3 hours and > 3 hours of injury)- mild and moderate TBI (GCS 9‑15)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TXA	Placebo	Relative (95% CI)	Absolute (95% CI)		
vascular occlusive events(fatal and non-fatal) at 28 days in mild/moderate												
1	randomised trials	not serious	not serious	very serious[a]	serious[b]	none	41/4066 (1.0%)	52/3997 (1.3%)	**RR 0.78** (0.52 to 1.16)	**3 fewer per 1,000** (from 6 fewer to 2 more)	⨁◯◯◯ Very low	CRITICAL

CI: confidence interval; **RR:** risk ratio

a. Downgraded by 2 increments for indirectness. Mixed severity based on GCS. Includes both TXA < 3 hours and > 3 hours of injury

b. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group for continuous outcomes).

Table 32: TXA vs placebo (adults) in hospital setting

Including all participants (TXA < 3 hours and > 3 hours of injury)- severe TBI (GCS 3‑8)

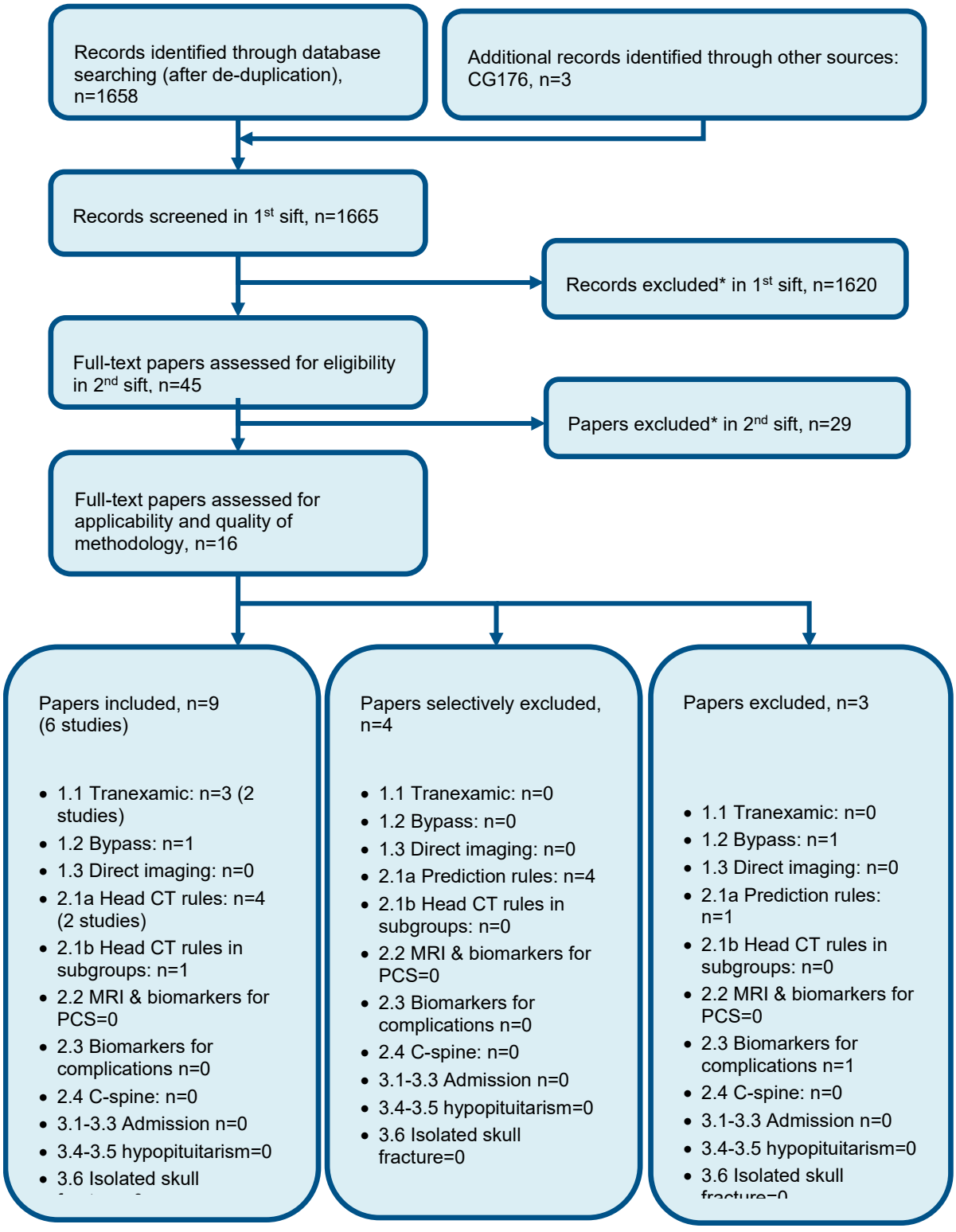
Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TXA	Placebo	Relative (95% CI)	Absolute (95% CI)		
vascular occlusive events(fatal and non-fatal) at 28 days in severe												
1	randomised trials	not serious	not serious	serious[a]	serious[b]	None	60/2264 (2.7%)	50/2247 (2.2%)	**RR 1.19** (0.82 to 1.73)	**4 more per 1,000** (from 4 fewer to 16 more)	⨁⨁◯◯ Low	

CI: confidence interval; **RR:** risk ratio

a. Downgraded by 1 increment for indirectness. Includes both TXA < 3 hours and > 3 hours of injury

b. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group for continuous outcomes).

Appendix G - Economic evidence study selection



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix H – Economic evidence tables

Study	Williams 2020[13] (also reported in Roberts 2021[7])			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Markov model based on randomised placebo-controlled trial: CRASH-3 (n=12,737) **Approach to analysis:** Markov model with states of alive and dead. Daily cycles for first 28 days then yearly. Treatment affects TBI death; no difference in other clinical outcomes **Perspective:** UK NHS **Time horizon:** lifetime **Treatment effect duration:**[(a)] 28 days (mortality) **Discounting:** Costs / Outcomes: 3.5%	**Population:** Adults with traumatic brain injury (without significant extracranial bleeding) treated within 3hours of their injury, with either a GCS score of 12 or lower, or with GCS 13–15 and any intracranial bleeding on their CT scan. **Subgroup A (base case):** Mild to moderate (GCS 9+) Mean age: 42 Male: NR **Subgroup B:** Severe (GCS<9) **Subgroup C:** Severe but excluding those with GCS score of 3 or bilateral unreactive pupils **Intervention 1:** Current care **Intervention 2:** Tranexamic acid and current care. Patients in the trial received a loading dose of 1g of tranexamic acid infused over a 10min period immediately after randomisation, followed by an intravenous infusion of 1g over 8hours	**Total costs (mean per patient)** **Subgroup A:** Intervention 1: £55,110 Intervention 2: £55,869 Incremental (2−1): (95% CI: NR; p=NR) **Subgroup B:** NR **Subgroup C: NR** **Currency & cost year:** 2018 UK pounds **Cost components incorporated:** Intervention cost (tranexamic acid, needle and syringe, saline infusion bag, nurse time). Length of stay (only in a sensitivity analysis because the difference observed in the trial was negligible). Monitoring, i.e. costs in added years of life (primary care visits, outpatient visits, formal carer time and rehabilitation)	**QALYs (mean per patient)** **Subgroup A:** Intervention 1: 12.10 Intervention 2: 12.28 Incremental (2−1): 0.18 (95% CI: NR; p=NR) **Subgroup B:** NR **Subgroup C: NR**	**Intervention 2 versus Intervention 1:** **Subgroup A:** £4,288 per QALY gained (pa) Probability Intervention 2 cost effective (£20K/30K threshold): 99%/99% **Subgroup B:** £18,519 per QALY gained (pa) Probability Intervention 2 cost effective (£20K/30K threshold): 62%/86% **Subgroup C:** £18,672 per QALY gained (pa) Probability Intervention 2 cost effective (£20K/30K threshold): 65%/98% **Analysis of uncertainty (Subgroup A):** One-way sensitivity analyses were performed with respect to assumptions about utilities, monitoring costs, hospital stay, head injury risk ratio / timing of administration, discount rate, time horizon and excess mortality. Results were most sensitive when arm-specific utilities were estimated: the ICER increased to £14,465 per QALY gained.

Data sources
Health outcomes: TBI mortality was the only treatment effect in the model. Both the baseline and the treatment effect were from the CRASH-3 trial – baseline was from the placebo arm high income countries only. Relative treatment effect was from patients from all participating countries. **Quality-of-life weights:** A systematic review and EQ-5D utility mapping study was identified, which reported utility values for patients with TBI, based on their level of disability, as defined by the Glasgow Outcome Scale (GOS). In the absence of GOS outcomes in the CRASH-3 trial, they used the DRS scores of CRASH-3 trial patients to estimate the proportion of patients in each GOS category, using a qualitative estimation involving a clinical expert. In CRASH-3 there was little difference in DRS scores between arms for patients with mild or moderate disease. **Cost sources:** Intervention and hospital stay costs were from standard NHS sources. First year monitoring costs were from a UK costing study. Longer term monitoring costs were from a previous NHS health technology assessment but based on expert opinion.
Comments
Source of funding: JP Moulton Charitable Trust, National Institute for Health Research, Joint Global Health Trials (Medical Research Council, Department for International Development, Wellcome Trust). **Limitations:** Treatment effects were from a single trial rather than a systematic review, but it is the key trial in a hospital population. People with mild severity and intracranial bleeding were combined with people with moderate severity. This group included patients from both low- and high-income countries. Some patients randomised more than 3 hours after head injury. Mortality was only followed up for 28 days. Quality of life was not measured in the trial, was derived using expert opinion, was assumed to be the same in both arms (in the base case) and was assumed to be constant overtime. Although the results were robust to one-way sensitivity analyses, if both length of stay and DRS had been arm-specific then it is quite likely that the cost per QALY gained would have been over £20,000. **Other:** The study also produced results from the perspective of Pakistan, but the assumptions and results have not been described in this review.
Overall applicability:[(b)] Partially applicable **Overall quality:**[(c)] Potentially serious limitations

Abbreviations: 95% CI= 95% confidence interval; CUA= cost–utility analysis; DRS=Disability Rating Scale; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); GCS=Glasgow Coma Scale; GOS=Glasgow Outcome Scale; ICER= incremental cost-effectiveness ratio; NR= not reported; pa= probabilistic analysis; QALYs= quality-adjusted life years; TBI=traumatic brain injury.

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. In this case it was the follow-up in the trial.

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

Study	Williams 2022[12]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost-utility analysis (health outcome: QALYs) **Study design:** Markov model where treatment effect is based on randomised placebo-controlled trial: CRASH-3 (n=12,737) for in-hospital mortality. **Approach to analysis:** Markov model with states of alive and dead. Monthly cycles for the first year, and then yearly thereafter. Treatment affects all-cause mortality; no difference in other clinical outcomes **Perspective:** UK NHS **Time horizon:** 20 years (lifetime) **Discounting:** Costs / Outcomes: 3.5%	**Population:** Older adults with mild traumatic brain injury. Mean age: 80 Male: NR **Intervention 1:** Current care **Intervention 2:** Tranexamic acid and current care.	**Total costs (mean per patient)** Intervention 1: £16,019 Intervention 2: £16,155 Incremental (2−1): £96.69 (95% CI: NR; p=NR) **Currency & cost year:** 2020 UK pounds **Cost components incorporated:** Intervention costs pre-drawn tranexamic acid, needle and syringe, treatment administration time (5 minutes of a paramedic's time). Adverse events costs Weighted average of treatment for pulmonary embolism, deep vein thrombosis, stroke, myocardial infarction, renal failure, sepsis, seizure and GI bleeding Hospital-related costs neurosurgery, hospital stay (per day). Monitoring costs An annual cost dependent on GOS score. A weighted average was used in the study.	**QALYs (mean per patient):** Intervention 1: 3.0656 Intervention 2: 3.0854 Incremental (2−1): 0.0198 (95% CI: NR; p=NR)	**Intervention 2 versus Intervention 1:** £4,858 per QALY gained (pa) Probability Intervention 2 cost effective (£20K/30K threshold):86%/88%[(a)] **Analysis of uncertainty:** Deterministic analysis showed that results were robust to changes in: • tranexamic acid mortality risk ratio from 0.70 in the base case to 0.993 • an incremental utility gain of 0.004 for 1 month • relative risk reduction of neurosurgery of 2.6% An analysis of covariance (ANCOVA) showed that most of the variability in incremental costs and incremental QALYs was due to uncertainty in two parameters: the outcomes following mild TBI and the tranexamic acid mortality risk ratio. The EVPI at the £20k/QALY gained threshold was £22.4 million for the whole population (£37.06 per individual).

Data sources
Health outcomes: All-cause mortality was the only treatment effect in the model. Baseline in-hospital mortality resulting from a head injury was based on a weighted average taken from three studies.[3, 9, 10] The treatment effect during the first 28 days was taken from the CRASH-3 trial for mild TBI patients with intracranial bleeding.[2] Standardised mortality ratios, taken from a case-control study [5], were applied for the period following 28 days to both treatments arms. The percentage of patients undergoing neurosurgery was taken from a systematic review and meta-analysis.[4] **Quality-of-life weights:** A systematic review and EQ-5D utility mapping study was identified, which reported utility values for patients with TBI, based on their level of disability, as defined by the Glasgow Outcome Scale (GOS). These EQ-5D scores were linked to GOS outcomes reported at 6-months post-injury from a Dutch study of patients hospitalised for mild TBI to give an average weighted score. **Cost sources:** Hospital-related costs (including adverse event costs) were taken from NHS reference costs 2017/18. The hourly cost of a paramedic's time was taken from PSSRU 2020. Cost of tranexamic acid solution for injection was taken from the BNF 2019. Cost of needle and syringe was taken from UK-based study published in 2021, which took the lowest cost items from regional suppliers in an unspecified year. The mean length of stay was taken from an Australian study. All costs were inflated, where necessary, to 2020 costs using the NHS inflation index.
Comments
Source of funding: National Institute for Health Research Health Technology Assessment, JP Moulton Charitable Trust, Department of Health and Social Care, Department for International Development, Global Challenges Research Fund, Medical Research Council and Wellcome Trust (Joint Global Health Trials Scheme). **Limitations:** The treatment effect may be overestimated since it came from a population of people who had an intracranial haematoma on CT. The GOS outcomes used in the model to calculate a weighted average utility score were taken from patients of all ages. Treatment effects were from a single trial from a broader population and not in a pre-hospital setting. Quality of life was not measured in the trial, was derived using expert opinion, was assumed to be the same in both arms (in the base case) and was assumed to be constant over time. The mean length of hospital stay was taken from an Australian setting.
Overall applicability:(b) Directly applicable **Overall quality:**(c) Potentially serious limitations

Abbreviations: 95% CI= 95% confidence interval; ANCOVA= analysis of covariance; DRS=Disability Rating Scale; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); EVPI= expected value of perfect information; GI= gastrointestinal; GOS=Glasgow Outcome Scale; ICER= incremental cost-effectiveness ratio; NR= not reported; pa= probabilistic analysis; QALYs= quality-adjusted life years; TBI=traumatic brain injury.

(a) Figure for probability of cost-effectiveness at £30k cost per QALY threshold read from graph

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

Appendix I – Health economic model

See separate report.

4 Appendix J – Excluded studies

5 Clinical studies

6 Table 33: Studies excluded from the clinical review

Study	Code [Reason]
(2020) Neurotraumatology. Tranexamic acid in patients with acute traumatic brain injury: the CRASH-3 trial. Arzneimitteltherapie 38(3): 96-97	- Secondary publication of an included study that does not provide any additional relevant information
(2016) The effect of tranexamic acid on traumatic brain hematomas. Journal of isfahan medical school 34(381): 478-483	- Study does not contain an outcome relevant to this review protocol
Acar, Nurdan; Canakci, Mustafa Emin; Bilge, Ugur (2020) Early and Ultraearly Administration of Tranexamic Acid in Traumatic Brain Injury: Our 8-Year-Long Clinical Experience. Emergency medicine international 2020: 6593172	- Study design not relevant to this review protocol
Ageron, F.-X., Gayet-Ageron, A., Ker, K. et al. (2020) Effect of tranexamic acid by baseline risk of death in acute bleeding patients: a meta-analysis of individual patient-level data from 28 333 patients. British Journal of Anaesthesia 124(6): 676-683	- Population not relevant to this review protocol
Alhelaly, M.M., Soliman, A.M., Khaled, A. et al. (2019) Efficacy of tranexamic acid in traumatic brain injury: Updated systematic review and meta-analysis. Trauma (United Kingdom) 21(3): 167-175	- Systematic review used as source of primary studies
Anderson, Taylor N, Hinson, Holly E, Dewey, Elizabeth N et al. (2020) Early Tranexamic Acid Administration After Traumatic Brain Injury Is Associated With Reduced Syndecan-1 and Angiopoietin-2 in Patients With Traumatic Intracranial Hemorrhage. The Journal of head trauma rehabilitation 35(5): 317-323	- Study does not contain an outcome relevant to this review protocol
Anker-Moller, T., Troldborg, A., Sunde, N. et al. (2017) Evidence for the Use of Tranexamic Acid in Subarachnoid and Subdural Hemorrhage: A Systematic Review. Seminars in Thrombosis and Hemostasis 43(7): 750-758	- Population not relevant to this review protocol

Study	Code [Reason]
Anonymous (2016) Does tranexamic acid improve outcomes in traumatic brain injury?. BMJ (Clinical research ed.) 355: i6418	- Duplicate reference
Anonymous (2013) Trauma and severe bleeding. Tranexamic acid within one hour to reduce mortality. Prescrire international 22(140): 189-90	- Population not relevant to this review protocol
Anonymous. (2020) Erratum: Effect of out-of-hospital tranexamic acid vs placebo on 6-month functional neurologic outcomes in patients with moderate or severe traumatic brain injury (JAMA. (2020) 324: 10 (961-974) DOI: 10.1001/jama.2020.895832897344). JAMA - Journal of the American Medical Association 324(16): 1683	- Duplicate reference
Anonymous. (2016) Correction: Does tranexamic acid improve outcomes in traumatic brain injury? (BMJ (2016) 354 (i4814) DOI: 10.1136/bmj.i4814). BMJ (Online) 355: i6418	- Duplicate reference
Baron, Tanya and Novak, Alex (2020) Tranexamic acid in acute traumatic brain injury. BMJ evidence-based medicine	- Review article but not a systematic review
Blanchard, P.-G., Pare, D., Truchot, J. et al. (2020) Does tranexamic acid reduce traumatic brain injury-related death?. Canadian Journal of Emergency Medicine 22(3): 297-298	- Secondary publication of an included study that does not provide any additional relevant information
Bloom, B. (2020) Tranexamic acid in emergency care. European Journal of Emergency Medicine 27(2): 81-82	- Population not relevant to this review protocol
Boling, Bryan and Moore, Kathryn (2012) Tranexamic acid (TXA) use in trauma. Journal of emergency nursing 38(5): 496-7	- Population not relevant to this review protocol
Bossers, Sebastiaan M, Loer, Stephan A, Bloemers, Frank W et al. (2020) Association Between Prehospital Tranexamic Acid Administration and Outcomes of Severe Traumatic Brain Injury. JAMA neurology	- Study design not relevant to this review protocol
Boudreau, Ryan M, Deshpande, Keshav K, Day, Gregory M et al. (2019) Prehospital Tranexamic Acid Administration During Aeromedical	- Population not relevant to this review protocol

Study	Code [Reason]
Transport After Injury. The Journal of surgical research 233: 132-138	
Bukhari, Nuray Sarmad and Jooma, Rashid (2020) Early tranexamic acid in traumatic brain injury: Evidence for an effective therapy. JPMA. The Journal of the Pakistan Medical Association 70(2 (Suppl 1)): s49-s52	- Literature review
Cap, Andrew P (2019) CRASH-3: a win for patients with traumatic brain injury. Lancet (London, England) 394(10210): 1687-1688	- Review article but not a systematic review
Chakroun-Walha, Olfa, Samet, Amal, Jerbi, Mouna et al. (2019) Benefits of the tranexamic acid in head trauma with no extracranial bleeding: a prospective follow-up of 180 patients. European journal of trauma and emergency surgery : official publication of the European Trauma Society 45(4): 719-726	-Included people with isolated head injury and polytrauma
Chan, David Yuen Chung, Tsang, Anderson Chun On, Li, Lai Fung et al. (2019) Improving Survival with Tranexamic Acid in Cerebral Contusions or Traumatic Subarachnoid Hemorrhage: Univariate and Multivariate Analysis of Independent Factors Associated with Lower Mortality. World neurosurgery 125: e665-e670	- Study design not relevant to this review protocol
Chen, Hongshen and Chen, Muhu (2020) The efficacy of tranexamic acid for brain injury: A meta-analysis of randomized controlled trials. The American journal of emergency medicine 38(2): 364-370	- Population not relevant to this review protocol
Coats, T., Hunt, B., Roberts, I. et al. (2005) Anti-fibrinolytic agents in traumatic haemorrhage: A large scale randomized controlled trial is needed. Pakistan Journal of Medical Sciences 21(1): 10-11	- Population not relevant to this review protocol. CRASH-2 background paper.
Coats, T.J. and Lecky, F.E. (2020) The CRASH3 study: Prehospital TXA for every injured patient?. Emergency Medicine Journal 37(6): 392-394	- Review article but not a systematic review
Coats, Timothy J; Fragoso-Iniguez, Marisol; Roberts, Ian (2019) Implementation of tranexamic acid for bleeding trauma patients: a	- Population not relevant to this review protocol

Study	Code [Reason]
longitudinal and cross-sectional study. Emergency medicine journal : EMJ 36(2): 78-81	
Cook, Rob, Lyon-Maris, Johnny, Martin, Rosie et al. (2020) Tranexamic acid is safe to use following mild-to-moderate traumatic brain injury. BMJ (Clinical research ed.) 368: m514	- Secondary publication of an included study that does not provide any additional relevant information
Cornelius, Brian G, McCarty, Karen, Hylan, Kristi et al. (2018) Tranexamic Acid: Promise or Panacea: The Impact of Air Medical Administration of Tranexamic Acid on Morbidity, Mortality, and Length of Stay. Advanced emergency nursing journal 40(1): 27-35	- Population not relevant to this review protocol
CRASH-2 Collaborators, Intracranial Bleeding Study (2011) Effect of tranexamic acid in traumatic brain injury: a nested randomised, placebo controlled trial (CRASH-2 Intracranial Bleeding Study). BMJ (Clinical research ed.) 343: d3795	- Population not relevant to this review protocol (not isolated TBI)
CRASH-2 trial, collaborators, Shakur, Haleema, Roberts, Ian et al. (2010) Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. Lancet (London, England) 376(9734): 23-32	- Population not relevant to this review protocol
CRASH-3 Intracranial Bleeding Mechanistic Study, Collaborators (2020) Tranexamic acid in traumatic brain injury: an explanatory study nested within the CRASH-3 trial. European journal of trauma and emergency surgery : official publication of the European Trauma Society	- Secondary publication of an included study that does not provide any additional relevant information
Dixon, Alexandra L, McCully, Belinda H, Rick, Elizabeth A et al. (2020) Tranexamic acid administration in the field does not affect admission thromboelastography after traumatic brain injury. The journal of trauma and acute care surgery 89(5): 900-907	- Study does not contain an outcome relevant to this review protocol
Dixon, Alexandra L, McCully, Belinda H, Rick, Elizabeth A et al. (2020) TXA Administration in the Field Does Not Affect Admission TEG after Traumatic Brain Injury. The journal of trauma and acute care surgery	- Study does not contain an outcome relevant to this review protocol

Study	Code [Reason]
Du, Chao-Nan, Liu, Bo-Xue, Ma, Qing-Fang et al. (2020) The effect of tranexamic acid in patients with TBI: a systematic review and meta-analysis of randomized controlled trials. Chinese neurosurgical journal 6: 14	- Systematic review used as source of primary studies
Ebrahimi, Pouya, Mozafari, Javad, Ilkhchi, Reza Bahrami et al. (2019) Intravenous Tranexamic Acid for Subdural and Epidural Intracranial Hemorrhage: Randomized, Double-Blind, Placebo-Controlled Trial. Reviews on recent clinical trials 14(4): 286-291	- Inappropriate population. People with subdural haematoma and epidural haemorrhages too small and specific to be applied to groups in our review.
El-Menyar, A., Ahmed, K., Hakim, S. et al. (2021) Efficacy and safety of the second in-hospital dose of tranexamic acid after receiving the prehospital dose: double-blind randomized controlled clinical trial in a level 1 trauma center. European Journal of Trauma & Emergency Surgery 15: 15	- Population not relevant to this review protocol *All trauma patients*
El-Menyar, Ayman, Sathian, Brijesh, Wahlen, Bianca M et al. (2020) Prehospital administration of tranexamic acid in trauma patients: A 1:1 matched comparative study from a level 1 trauma center. The American journal of emergency medicine 38(2): 266-271	- Population not relevant to this review protocol
Fakharian, Esmaeil; Abedzadeh-Kalahroudi, Masoumeh; Atoof, Fatemeh (2018) Effect of Tranexamic Acid on Prevention of Hemorrhagic Mass Growth in Patients with Traumatic Brain Injury. World neurosurgery 109: e748-e753	Study includes patients with isolated TBI or multiple trauma patients. Does not report number of patients only with isolated TBI
Fernandez, L.M.G.; Ortiz-Velasquez, L.A.; Casas-Arroyave, F.D. (2019) Management and perioperative outcomes of traumatic brain injury: retrospective study. Colombian Journal of Anesthesiology 47(2): 100-106	- Study design not relevant to this review protocol
Gao, Bixi, Xue, Tao, Rong, Xiaoci et al. Tranexamic Acid Inhibits Hematoma Expansion in Intracerebral Hemorrhage and Traumatic Brain Injury. Does Blood Pressure Play a Potential Role? A Meta-Analysis from Randmized Controlled Trials. Journal of stroke and cerebrovascular diseases : the official	- Systematic review used as source of primary studies

Study	Code [Reason]
journal of National Stroke Association 30(1): 105436	
Hamele, Mitchell; Aden, James K; Borgman, Matthew A (2020) Tranexamic acid in pediatric combat trauma requiring massive transfusions and mortality. The journal of trauma and acute care surgery 89(2ssuppl2): 242-s245	- Population not relevant to this review protocol. Inappropriate study design.
Harvey, V.; Perrone, J.; Kim, P. (2014) Does the use of tranexamic acid improve trauma mortality?. Annals of Emergency Medicine 63(4): 460-462	- Population not relevant to this review protocol. Literature review.
Heymann, Eric P (2020) Tranexamic acid in traumatic intracranial bleeding: recognizing the limit of results (of the CRASH-3 trial). European journal of emergency medicine : official journal of the European Society for Emergency Medicine 27(2): 83-84	- Review article but not a systematic review
Hunt, B. (2011) Effects of tranexamic acid on death, vascular occlusive events and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): A randomised, placebo-controlled trial. Transfusion Medicine 21(suppl1): 13	- Population not relevant to this review protocol
Jiao, X., Li, M., Li, L. et al. (2021) Early Tranexamic Acid in Intracerebral Hemorrhage: A Meta-Analysis of Randomized Controlled Trials. Frontiers in neurology [electronic resource]. 12: 721125	- Systematic review- screened for relevant references
Jokar, Abolfazl, Ahmadi, Koorosh, Salehi, Tayyebeh et al. (2017) The effect of tranexamic acid in traumatic brain injury: A randomized controlled trial. Chinese journal of traumatology = Zhonghua chuang shang za zhi 20(1): 49-51	- Study does not contain an outcome relevant to this review protocol
July, Julius and Pranata, Raymond (2020) Tranexamic acid is associated with reduced mortality, hemorrhagic expansion, and vascular occlusive events in traumatic brain injury - meta-analysis of randomized controlled trials. BMC neurology 20(1): 119	- Systematic review used as source of primary studies
Karl, V., Thorn, S., Mathes, T. et al. (2022) Association of Tranexamic Acid Administration With Mortality and Thromboembolic Events in Patients With Traumatic Injury: A Systematic	- Systematic review- screened for relevant references

Study	Code [Reason]
Review and Meta-analysis. JAMA Network Open 5(3): e220625	
Kawada, Tomoyuki (2020) Efficacy of tranexamic acid in patients with traumatic brain injury. EXCLI journal 19: 1547-1548	- Review article but not a systematic review
Ker, K, Roberts, I, Shakur, H et al. (2015) Antifibrinolytic drugs for acute traumatic injury. Cochrane Database of Systematic Reviews	- Population not relevant to this review protocol
Khan, Muhammad, Jehan, Faisal, Bulger, Eileen M et al. (2018) Severely injured trauma patients with admission hyperfibrinolysis: Is there a role of tranexamic acid? Findings from the PROPPR trial. The journal of trauma and acute care surgery 85(5): 851-857	- Population not relevant to this review protocol
Khiabani, K., Ahmadfar, M., Labafchi, A. et al. (2020) Is Preoperative Administration of Tranexamic Acid Effective on Blood Loss Reduction in Mandibular Fracture Surgeries? A Triple-Blind Randomized Clinical Trial. Journal of Oral and Maxillofacial Surgery	- Population not relevant to this review protocol
Kutty, R.K., Leela, S.K., Sreemathyamma, S.B. et al. (2020) The Outcome of Medical Management of Chronic Subdural Hematoma with Tranexamic Acid - A Prospective Observational Study. Journal of Stroke and Cerebrovascular Diseases 29(11): 105273	- Study design not relevant to this review protocol
Lawati, Kumait Al, Sharif, Sameer, Maqbali, Said Al et al. (2020) Efficacy and safety of tranexamic acid in acute traumatic brain injury: a systematic review and meta-analysis of randomized-controlled trials. Intensive care medicine	- Systematic review. Screened for relevant references.
Lei, Jin; Gao, Guo-Yi; Jiang, Ji-Yao (2012) Is management of acute traumatic brain injury effective? A literature review of published Cochrane Systematic Reviews. Chinese journal of traumatology = Zhonghua chuang shang za zhi 15(1): 17-22	- Literature review
Long, Brit and Gottlieb, Michael (2020) Tranexamic Acid for Traumatic Brain Injury. Academic emergency medicine : official journal of the Society for Academic Emergency Medicine	- Review article but not a systematic review

Study	Code [Reason]
Mahmood, Abda, Needham, Kelly, Shakur-Still, Haleema et al. (2020) Effect of tranexamic acid on intracranial haemorrhage and infarction in patients with traumatic brain injury: a pre-planned substudy in a sample of CRASH-3 trial patients. Emergency medicine journal : EMJ	- Secondary publication of an included study that does not provide any additional relevant information
Mahmood, Abda; Roberts, Ian; Shakur, Haleema (2017) A nested mechanistic sub-study into the effect of tranexamic acid versus placebo on intracranial haemorrhage and cerebral ischaemia in isolated traumatic brain injury: study protocol for a randomised controlled trial (CRASH-3 Trial Intracranial Bleeding Mechanistic Sub-Study [CRASH-3 IBMS]). Trials 18(1): 330	- study protocol
Mahmood, Abda, Roberts, Ian, Shakur, Haleema et al. (2016) Does tranexamic acid improve outcomes in traumatic brain injury?. BMJ (Clinical research ed.) 354: i4814	- Review article but not a systematic review
Mansukhani, Raoul, Frimley, Lauren, Shakur-Still, Haleema et al. (2020) Accuracy of time to treatment estimates in the CRASH-3 clinical trial: impact on the trial results. Trials 21(1): 681	- Secondary publication of an included study that does not provide any additional relevant information
Marrero-Miragaya, M., Avila Albuerne, Y., Navarro Rodriguez, Z. et al. (2014) Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant hemorrhage (crash-2): A randomized, placebo-controlled trial. Basic and Clinical Pharmacology and Toxicology 115(suppl1): 69-70	- Population not relevant to this review protocol
Marrero-Miragaya, M.A., Avila Albuerne, Y., Navarro, Z. et al. (2010) Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): A randomised, placebo-controlled trial. VacciMonitor 19(suppl2): 109	- Population not relevant to this review protocol
May S (2019) Prehospital Tranexamic Acid Use for Traumatic Brain Injury (TXA) [trial registry record] .	- Study design not relevant to this review protocol
McCaul, M. and Kredo, T. (2016) Antifibrinolytic drugs for acute traumatic injury. South African Medical Journal 106(8): 777-778	- Population not relevant to this review protocol

Study	Code [Reason]
McCaul, Michael and Kredo, Tamara (2016) Antifibrinolytic drugs for acute traumatic injury. South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde 106(8): 777-8	- Population not relevant to this review protocol
Meade, M.J., Tumati, A., Chantachote, C. et al. Antithrombotic Agent Use in Elderly Patients Sustaining Low-Level Falls. Journal of Surgical Research 258: 216-223	- Population not relevant to this review protocol
Mejia-Mantilla, J.H. (2011) Effect of tranexamic acid in traumatic brain injury: A nested randomized, placebo controlled trial (crash-2 intracranial bleeding study). registration isrctn86750102. Neurocritical Care 15(1suppl1): 19	- Secondary publication CRASH-2. Population not relevant to this review protocol
Mejia-Mantilla, JH (2011) Effect of tranexamic acid in traumatic brain injury: a nested randomized, placebo controlled trial (CRASH-2 intracranial bleeding study). Neurocritical care 1: 19	- Population not relevant to this review protocol
Mitra, B., Bernard, S., Gantner, D. et al. (2021) Protocol for a multicentre prehospital randomised controlled trial investigating tranexamic acid in severe trauma: The PATCH-Trauma trial. BMJ Open 11(3)	- study protocol
Mojallal, Fatemeh, Nikooieh, Mehrnaz, Hajimaghsoudi, Majid et al. (2020) The effect of intravenous tranexamic acid on preventing the progress of cerebral hemorrhage in patients with brain traumatic injuries compared to placebo: A randomized clinical trial. Medical journal of the Islamic Republic of Iran 34: 107	- Population not relevant to this review protocol. Excluded people who needed a craniotomy.
Morte, Douglas, Lammers, Daniel, Bingham, Jason et al. (2019) Tranexamic acid administration following head trauma in a combat setting: Does tranexamic acid result in improved neurologic outcomes?. The journal of trauma and acute care surgery 87(1): 125-129	- Study design not relevant to this review protocol
Mousavinejad, Maryam, Mozafari, Javad, Ilkhchi, Reza Bahrami et al. (2020) Intravenous Tranexamic Acid for Brain Contusion with Intraparenchymal Hemorrhage: Randomized, Double-Blind, Placebo-Controlled Trial. Reviews on recent clinical trials 15(1): 70-75	- no useable outcomes

Study	Code [Reason]
Mozafari, J and Mousavinejad, SM (2016) Evaluation of therapeutic effect of tranexamic acid infusion on reducing blood loss during neurosurgery in traumatic brain injury patients with intraparenchymal hemorrhage.	- study protocol
Napolitano, L.M., Cohen, M.J., Cotton, B.A. et al. (2013) Tranexamic acid in trauma: How should we use it?. Journal of Trauma and Acute Care Surgery 74(6): 1575-1586	- Population not relevant to this review protocol.
Nelson Yap, K B; Albert Wong, S H; Idris, Z (2020) Tranexamic acid in traumatic brain injury. The Medical journal of Malaysia 75(6): 660-665	- Study design not relevant to this review protocol
Nishijima, D.K., Gosdin, M., Naz, H. et al. (2020) Assessment of primary outcome measures for a clinical trial of pediatric hemorrhagic injuries. American Journal of Emergency Medicine	- Population not relevant to this review protocol
Nishijima, D.K., Stanley, R.M., Hewes, H.A. et al. (2020) Enrollment with and without federal exception from informed consent procedures for a pediatric trauma trial. Academic Emergency Medicine 27(supplement1): 166	- Population not relevant to this review protocol
Nishijima, Daniel K, VanBuren, John, Hewes, Hilary A et al. (2018) Traumatic injury clinical trial evaluating tranexamic acid in children (TIC-TOC): study protocol for a pilot randomized controlled trial. Trials 19(1): 593	- Review protocol
Nishijima, D. K., VanBuren, J. M., Linakis, S. W. et al. (2022) Traumatic injury clinical trial evaluating tranexamic acid in children (TIC-TOC): a pilot randomized trial. Academic Emergency Medicine 10: 10	- Population not relevant to this review protocol (mixed population; n=16 with isolated TBI)
Perel, P, Al-Shahi Salman, R, Kawahara, T et al. (2012) CRASH-2 (Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage) intracranial bleeding study: the effect of tranexamic acid in traumatic brain injury--a nested randomised, placebo-controlled trial. Health technology assessment (Winchester, England) 16(13): iii-54	- Population not relevant to this review protocol
Perel, Pablo, Roberts, Ian, Shakur, Haleema et al. (2010) Haemostatic drugs for traumatic brain	- Systematic review- screened for relevant references

Study	Code [Reason]
injury. The Cochrane database of systematic reviews: cd007877	
Rimaitis, M., Bilskiene, D., Tamosuitis, T. et al. (2020) Implementation of thromboelastometry for coagulation management in isolated traumatic brain injury patients undergoing craniotomy. Medical Science Monitor 26: e922879	- Study design not relevant to this review protocol
Roberts, I (2015) Tranexamic acid in trauma: how should we use it?. Journal of thrombosis and haemostasis : JTH 13suppl1: 195-9	- Population not relevant to this review protocol
Roberts, I., Shakur, H., Ker, K. et al. (2011) Antifibrinolytic drugs for acute traumatic injury. Sao Paulo Medical Journal 129(5): 361	- Population not relevant to this review protocol
Roberts, I., Shakur, H., Ker, K. et al. (2011) Antifibrinolytic drugs for acute traumatic injury. Cochrane database of systematic reviews (Online) 1: cd004896	- Duplicate reference. Population not relevant to this review protocol
Roberts, I, Shakur, H, Coats, T et al. (2013) The CRASH-2 trial: a randomised controlled trial and economic evaluation of the effects of tranexamic acid on death, vascular occlusive events and transfusion requirement in bleeding trauma patients. Health technology assessment (Winchester, England) 17(10): 1-79	- Population not relevant to this review protocol
Roberts, Ian, Edwards, Phil, Prieto, David et al. (2017) Tranexamic acid in bleeding trauma patients: an exploration of benefits and harms. Trials 18(1): 48	- Population not relevant to this review protocol
Roberts, Ian, Shakur, Haleema, Ker, Katharine et al. (2011) Antifibrinolytic drugs for acute traumatic injury. The Cochrane database of systematic reviews: cd004896	- Duplicate reference. Population not relevant to this review protocol
Roberts, Ian, Shakur, Haleema, Ker, Katharine et al. (2011) Antifibrinolytic drugs for acute traumatic injury. The Cochrane database of systematic reviews: cd004896	- Duplicate reference. Population not relevant to this review protocol
Roberts, Ian, Shakur, Haleema, Ker, Katherine et al. (2012) Antifibrinolytic drugs for acute traumatic injury. The Cochrane database of systematic reviews 12: cd004896	- Duplicate reference. Population not relevant to this review protocol

Study	Code [Reason]
Roberts, Ian, Shakur, Haleema, Ker, Katherine et al. (2012) Antifibrinolytic drugs for acute traumatic injury. The Cochrane database of systematic reviews 12: cd004896	- Duplicate reference. Population not relevant to this review protocol
Robertsan, I. (2011) Crash-2: Antifibrinolytic treatment in traumatic brain injury. Journal of Neurotrauma 28(5): a33-a34	- Conference abstract
Roberts, I., Shakur-Still, H., Aeron-Thomas, A. et al. (2021) Tranexamic acid to reduce head injury death in people with traumatic brain injury: the CRASH-3 international RCT. Health Technology Assessment (Winchester, England) 25(26): 1-76	- Study already included in the review
Rostami, E; Kongstad, P; Marklund, N (2020) Should all patients with traumatic brain injury receive tranexamic acid?. Lakartidningen 117	- Study not reported in English
Rowell, S., Munar, M., Hwang, J. et al. (2019) Tranexamic acid pharmacokinetics in patients with moderate or severe traumatic brain injury. Journal of Neurotrauma 36(13): a79-a80	- Study design not relevant to this review protocol
Safari, H., Farrahi, P., Rasras, S. et al. (2021) Effect of Intravenous Tranexamic Acid on Intracerebral Brain Hemorrhage in Traumatic Brain Injury. Turkish Neurosurgery 31(2): 223-227	- no useable outcomes
Sanford, Katarina and Garcia, Sarah (2020) Tranexamic acid and traumatic brain injuries. JAAPA : official journal of the American Academy of Physician Assistants 33(12): 53-54	- Review article but not a systematic review
Schreiber, M.A. (2019) Prehospital tranexamic acid improves survival after traumatic brain injury in patients with intracranial hemorrhage. Shock 51(6supplement1): 26	- Conference abstract
Shakur, H (2016) Tranexamic Acid for the treatment of significant traumatic brain injury: an international, randomised, double blind, placebo controlled trial.	- study protocol
Sharma, D. and Vavilala, M.S. (2012) Perioperative Management of Adult Traumatic	- Review article but not a systematic review

Study	Code [Reason]
Brain Injury. Anesthesiology Clinics 30(2): 333-346	
Shiraishi, A, Kushimoto, S, Otomo, Y et al. (2017) Effectiveness of early administration of tranexamic acid in patients with severe trauma. The British journal of surgery 104(6): 710-717	- Population not relevant to this review protocol. Inappropriate study design.
Synnot, A., Bragge, P., Lunny, C. et al. (2018) The currency, completeness and quality of systematic reviews of acute management of moderate to severe traumatic brain injury: A comprehensive evidence map. PLoS ONE 13(6): e0198676	- Review article but not a systematic review
Thurston, Ben, Chowdhury, Sharfuddin, Edu, Sorin et al. (2015) Time since injury is the major factor in preventing tranexamic acid use in the trauma setting: An observational cohort study from a major trauma centre in a middle-income country. South African journal of surgery. Suid-Afrikaanse tydskrif vir chirurgie 53(1): 13-8	- Population not relevant to this review protocol
Trenkler, S, Laincz, A, Valky, J et al. (2011) Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo controlled trial. Anesteziologie a intenzivni medicina 22(2): 103-114	- Population not relevant to this review protocol
Valle, Evan J, Allen, Casey J, Van Haren, Robert M et al. (2014) Do all trauma patients benefit from tranexamic acid?. The journal of trauma and acute care surgery 76(6): 1373-8	- Population not relevant to this review protocol
van Wessem, K. J. P.; Jochems, D.; Leenen, L. P. H. (2021) The effect of prehospital tranexamic acid on outcome in polytrauma patients with associated severe brain injury. European Journal of Trauma & Emergency Surgery 14: 14	- Study design not relevant to this review protocol *Prospective cohort study*
Walker, Patrick F, Bozzay, Joseph D, Johnston, Luke R et al. (2020) Outcomes of tranexamic acid administration in military trauma patients with intracranial hemorrhage: a cohort study. BMC emergency medicine 20(1): 39	- Study design not relevant to this review protocol
Weber, B.J. and Kjelland, C.B. (2012) The use of tranexamic acid for trauma patients?.	- Population not relevant to this review protocol

Study	Code [Reason]
Canadian Journal of Emergency Medicine 14(1): 53-56	
Weng, Shaotao, Wang, Wanqi, Wei, Quantang et al. (2019) Effect of Tranexamic Acid in Patients with Traumatic Brain Injury: A Systematic Review and Meta-Analysis. World neurosurgery 123: 128-135	- Systematic review- screened for relevant references
Williams-Johnson, J A, McDonald, A H, Strachan, G Gordon et al. (2010) Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2) A randomised, placebo-controlled trial. The West Indian medical journal 59(6): 612-24	- Population not relevant to this review protocol
Workewych, A., Callum, J., Saarela, O. et al. (2018) Tranexamic acid in the treatment of residual chronic subdural hematoma: A single-centre, randomized controlled trial (TRACE). Journal of Neurotrauma 35(16): a244-a245	- study protocol
Yokobori, Shoji, Yatabe, Tomoaki, Kondo, Yutaka et al. (2020) Efficacy and safety of tranexamic acid administration in traumatic brain injury patients: a systematic review and meta-analysis. Journal of intensive care 8: 46	- Systematic review- screened for relevant references
Yutthakasemsunt, S., Kittiwattanagul, W., Piyavechvirat, P. et al. (2011) Tranexamic acid for patients with traumatic brain injury: A randomized, double-blinded, placebo-controlled trial. Journal of Neurotrauma 28(6): a55	-Includes people with isolated head injury and polytrauma
Yutthakasemsunt, S., Kittiwattanagul, W., Piyavechvirat, P. et al. (2011) Tranexamic acid in the treatment of traumatic intracranial hemorrhage: A randomized, doubleblinded, placebo-controlled trial. Journal of Neurotrauma 28(5): a4	- Duplicate reference
Yutthakasemsunt, S., Lumbiganon, P., Phuenpathom, N. et al. (2010) Tranexamic acid for preventing progressive intracranial hemorrhage in adults with traumatic brain injury: A preliminary report. Inflammation Research 59(suppl1): 26	- Includes people with isolated head injury and polytrauma
Yutthakasemsunt, S, Kittiwattanagul, W, Piyavechvirat, P et al. (2010) Tranexamic Acid	- Includes people with isolated head injury and polytrauma

Study	Code [Reason]
for preventing progressive intracranial hemorrhage in adults with traumatic brain injury; a preliminary report. National neurotrauma symposium	
Yutthakasemsunt, Surakrant, Kittiwatanagul, Warawut, Piyavechvirat, Parnumas et al. (2013) Tranexamic acid for patients with traumatic brain injury: a randomized, double-blinded, placebo-controlled trial. BMC emergency medicine 13: 20	- Duplicate reference
Zehtabchi, Shahriar, Abdel Baki, Samah G, Falzon, Louise et al. (2014) Tranexamic acid for traumatic brain injury: a systematic review and meta-analysis. The American journal of emergency medicine 32(12): 1503-9	- Systematic review- screened for relevant references

Health Economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2006 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

None.

Appendix K – Research recommendations – full details

K.1 Research recommendation

K.1.1 A.1.2 What is the clinical and cost effectiveness of tranexamic acid (TXA) before imaging in people presenting withing 2 hours of head injury with GCS 13-15 and high risk indications for intracerebral bleeding?

K.1.2 Why this is important

Early tranexamic acid treatment is recommended in this guideline on the basis of current evidence. There is as yet no data for people with mild TBI that shows benefit in this specific group. Gaining such evidence is important as there may be people who may benefit from early TXA treatment, especially those with haemorrhagic lesions. The potential timing of TXA for benefit is likely to be early before a CT scan may have been obtained. This has implications for the potential effectiveness of TXA given the majority of people who sustain a mild TBI will not have haemorrhagic lesions. In addition, the administration of TXA to people with mild TBI potentially has significant resource implications. Research to understand who (including subpopulations e.g. elderly and paediatric populations), when, and how to give TXA in this population is required. The health economic implications should also be addressed.

K.1.3 Rationale for research recommendation

Importance to ‘patients’ or the population	This may provide evidence to change current care by offering TXA as a treatment to people with mild TBI (or a subset of) if proven to improve outcomes. This may improve outcomes and quality of life. Care would be needed to ensure that giving an intervention to people who may not otherwise have one does not "medicalise" them causing worse outcomes.
Relevance to NICE guidance	This question would potentially change guidance in terms of if TXA should be given to those with a mild TBI (GCS >12), and if so when and how.
Relevance to the NHS	Potential impacts on the NHS include on service delivery in prehospital, and emergency department settings.
National priorities	None.
Current evidence base	Two RCTS were included in the review. Rowell 2020 included people with mild, moderate to severe TBI (GCS 12 or less) (mild: 4%, moderate: 39%, severe: 57%). CRASH-3 trial included people with mild, moderate and severe TBI (mild: 28%, moderate:33%, severe: 38%, unknown: 1%). The trial classified severity of head injury based on baseline GCS score—mild to moderate (GCS 9–15) and severe (GCS 3–8)—and by pupil reactivity. This classification of severity was different to as stated in our protocol: mild GCS 13-15; moderate 9-12; severe GCS 3-8. The study reported data for combined severity (mild,

	moderate and severe) for some outcomes and separately for mild-moderate and severe TBI for some. Setting and intervention Rowell 2020 compared tranexamic acid (TXA) with placebo in an out-of-hospital setting, and CRASH-3 trial 2019 compared TXA with placebo in a hospital setting. Timing of TXA administration In Rowell 2020 the median estimated time from injury to out-of-hospital study TXA administration ranged from 40 to 43 minutes. This study was analysed in the strata TXA administration <3 hours of injury. CRASH-3 trial included people within 8 hours of injury in the early phase and within 3 hours of injury in the later phase of the trial, where available data was analysed separately for TXA administration <3 hours and > 3 hours after injury. TXA dose Rowell 2020 included 2 does of TXA in a pre-hospital setting. Group 1: 1-g IV tranexamic acid bolus in the out- of-hospital setting followed by a 1-g tranexamic acid IV infusion initiated upon hospital arrival and infused over 8 hours (bolus maintenance group), and Group 2: 2-g IV tranexamic acid bolus in the out-of-hospital setting followed by a placebo infusion (bolus only group) CRASH-3 trial included a loading dose of 1 g of TXA infused over 10 min, started immediately after randomisation, followed by an intravenous infusion of 1 g over 8 hours.
Equality considerations	In addition to the broader group of patients this research recommendation highlights the need for understanding TXA use in specific subgroups (including but not exclusive to) people < 16 years of age and > 65 years of age.

33

34 ### K.1.4 Modified PICO table

Population	Inclusion: All adults, young people and children (including babies under 1 year) with isolated traumatic intracranial bleeding a suspected or confirmed isolated head injury. Stratified by: Age • Adults (aged ≥16 years) • Children (aged ≥1 to <16 years) • Babies (aged <1 year) GCS 13-15 and high risk indications for intracerebral haemorrhage:

	• Suspected open or depressed skull fracture. • Any sign of basal skull fracture (haemotympanum, 'panda' eyes, cerebrospinal fluid leakage from the ear or nose, Battle's sign). • Post-traumatic seizure. • Focal neurological deficit. • More than 1 episode of vomiting. Exclusion: Adults, young people and children (including babies under 1 year) with superficial injuries to the eye or face without suspected or confirmed head or brain injury. Adults, young people and children with head injury (including babies under 1 year) with and significant extracranial bleeding.
Intervention	Tranexamic acid
Comparison	Control (to include placebo or study arm receiving no TXA)
Outcomes	• Mortality from head injury/TBI at ≤30 days. • All-cause mortality at ≤30 days. • Objective measures of disability (including (Extended) Glasgow Outcome Scale, King's Outcome Scale for Childhood Head Injury and Cerebral Performance Category scale, Rivermead Post-Concussion Syndrome Questionnaire, Disability rating scale). • Quality of life (validated quality of life scores only). • Length of hospital stay. • Serious adverse event • Surgical intervention • Post-concussion syndrome • Concussion/mild TBI Outcomes measured at <30 days, 30 days-6 months, 6-12 months, and at yearly time-points thereafter.
Study design	RCT

Timeframe	Medium term – in time for the next update
Additional information	None

35