



THE UNIVERSITY *of* EDINBURGH

Edinburgh Research Explorer

Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3)

Citation for published version:

The CRASH-3 trial collaborators 2019, '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', *The Lancet*, vol. 394, no. 10210, pp. 1713-1723. [https://doi.org/10.1016/S0140-6736\(19\)32233-0](https://doi.org/10.1016/S0140-6736(19)32233-0)

Digital Object Identifier (DOI):

[10.1016/S0140-6736\(19\)32233-0](https://doi.org/10.1016/S0140-6736(19)32233-0)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Publisher's PDF, also known as Version of record

Published In:

The Lancet

General rights

Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy

The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact openaccess@ed.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.





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

The CRASH-3 trial collaborators*

Summary

Background Tranexamic acid reduces surgical bleeding and decreases mortality in patients with traumatic extracranial bleeding. Intracranial bleeding is common after traumatic brain injury (TBI) and can cause brain herniation and death. We aimed to assess the effects of tranexamic acid in patients with TBI.

Methods This randomised, placebo-controlled trial was done in 175 hospitals in 29 countries. 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 time window for eligibility was originally 8 h but in 2016 the protocol was changed to limit recruitment to patients within 3 h of injury. This change was made blind to the trial data, in response to external evidence suggesting that delayed treatment is unlikely to be effective. We randomly assigned (1:1) patients to receive tranexamic acid (loading dose 1 g over 10 min then infusion of 1 g over 8 h) or matching placebo. Patients were assigned by selecting a numbered treatment pack from a box containing eight packs that were identical apart from the pack number. Patients, caregivers, and those assessing outcomes were masked to allocation. The primary outcome was head injury-related death in hospital within 28 days of injury in patients treated within 3 h of injury. We prespecified a sensitivity analysis that excluded patients with a GCS score of 3 and those with bilateral unreactive pupils at baseline. All analyses were done by intention to treat. This trial was registered with ISRCTN (ISRCTN15088122), ClinicalTrials.gov (NCT01402882), EudraCT (2011-003669-14), and the Pan African Clinical Trial Registry (PACTR20121000441277).

Results Between July 20, 2012, and Jan 31, 2019, we randomly allocated 12 737 patients with TBI to receive tranexamic acid (6406 [50·3%] or placebo [6331 [49·7%], of whom 9202 (72·2%) patients were treated within 3 h of injury. Among patients treated within 3 h of injury, the risk of head injury-related death was 18·5% in the tranexamic acid group versus 19·8% in the placebo group (855 vs 892 events; risk ratio [RR] 0·94 [95% CI 0·86–1·02]). In the prespecified sensitivity analysis that excluded patients with a GCS score of 3 or bilateral unreactive pupils at baseline, the risk of head injury-related death was 12·5% in the tranexamic acid group versus 14·0% in the placebo group (485 vs 525 events; RR 0·89 [95% CI 0·80–1·00]). The risk of head injury-related death reduced with tranexamic acid in patients with mild-to-moderate head injury (RR 0·78 [95% CI 0·64–0·95]) but not in patients with severe head injury (0·99 [95% CI 0·91–1·07]; p value for heterogeneity 0·030). Early treatment was more effective than was later treatment in patients with mild and moderate head injury (p=0·005) but time to treatment had no obvious effect in patients with severe head injury (p=0·73). The risk of vascular occlusive events was similar in the tranexamic acid and placebo groups (RR 0·98 (0·74–1·28)). The risk of seizures was also similar between groups (1·09 [95% CI 0·90–1·33]).

Interpretation Our results show that tranexamic acid is safe in patients with TBI and that treatment within 3 h of injury reduces head injury-related death. Patients should be treated as soon as possible after injury.

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).

Copyright © 2019 The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY 4.0 license.

Introduction

Each year, worldwide, there are more than 60 million new cases of traumatic brain injury (TBI).¹ Road traffic crashes and falls are the main causes and the incidence is increasing.¹ Intracranial bleeding is a common

complication of TBI and increases the risk of death and disability.² Although bleeding can start from the moment of impact, it often continues for several hours after injury.^{3,4} Ongoing intracranial bleeding can lead to raised intracranial pressure, brain herniation, and death.



Lancet 2019; 394: 1713–23

Published Online
October 14, 2019
[https://doi.org/10.1016/S0140-6736\(19\)32233-0](https://doi.org/10.1016/S0140-6736(19)32233-0)

See [Comment](#) page 1687

*Members listed at end of paper

For the Arabic translation of the abstract see [Online for appendix 1](#)

For the Chinese translation of the abstract see [Online for appendix 2](#)

For the French translation of the abstract see [Online for appendix 3](#)

For the Hindi translation of the abstract see [Online for appendix 4](#)

For the Japanese translation of the abstract see [Online for appendix 5](#)

For the Spanish translation of the abstract see [Online for appendix 6](#)

For the Urdu translation of the abstract see [Online for appendix 7](#)

Correspondence to:
Clinical Trials Unit, London
School of Hygiene & Tropical
Medicine, London WC1 E7HT, UK
crash@lshtm.ac.uk

Research in context

Evidence before this study

Evidence from the CRASH-2 trial that administration of tranexamic acid within 3 h of injury reduces death in patients with traumatic extracranial bleeding raised the possibility that tranexamic acid might reduce death from traumatic intracranial bleeding. Intracranial bleeding is common after traumatic brain injury (TBI) and increases head injury-related death and disability. Before the CRASH-3 trial, we made a systematic search for all randomised trials of tranexamic acid in acute traumatic injury. We searched PubMed, Science Citation Index, National Research Register, Zetoc, SIGLE, Global Health, LILACS, Current Controlled Trials, the Cochrane Injuries Group Specialised Register, CENTRAL, MEDLINE, and Embase for all publications until July 15, 2010. Details of our search were published previously. We found two small randomised trials of tranexamic acid in traumatic brain injury with a total of 510 patients. Meta-analysis of the two trials showed a statistically significant reduction in death with tranexamic acid. However, given the small size of the trials, we considered this evidence to be hypothesis generating, requiring confirmation in larger randomised trials.

Added value of this study

Our study found that the risk of death from head injury was reduced in patients treated with tranexamic acid, particularly

when patients who had a Glasgow Coma Scale score of 3 and those with bilateral unreactive pupils at baseline were excluded. We found no evidence of any increase in disability among survivors. The risk of vascular occlusive events was similar in the tranexamic acid and placebo groups.

Implications of all the available evidence

On Aug 30, 2019, an updated search for randomised trials of the early administration of tranexamic acid in patients with traumatic brain injury identified one randomised trial in addition to the CRASH-3 trial. This study was a randomised trial of pre-hospital tranexamic acid in 967 patients with traumatic brain injury. The dose of tranexamic acid was the same as in the CRASH-3 trial and patients with a GCS score of 3 and those with unreactive pupils at baseline were also excluded. When the two trials were pooled, we found a reduction in head injury-related death with tranexamic acid and no evidence of an increased risk in vascular occlusive events or seizures. Combining the results of all available randomised trials shows a reduction in head injury-related death in patients treated with tranexamic acid. Early administration of tranexamic acid should be considered in patients with traumatic brain injury.

Tranexamic acid reduces bleeding by inhibiting the enzymatic breakdown of fibrin blood clots (fibrinolysis). The CRASH-2 trial^{5,6} showed that in patients with trauma with major extracranial bleeding, early administration (within 3 h of injury) of tranexamic acid reduces bleeding deaths by a third. Subsequent analyses showed that even a short delay in treatment reduces the benefit of tranexamic acid administration.⁷ On the basis of these results, tranexamic acid was included in guidelines for the pre-hospital care of patients with trauma, although patients with isolated TBI were specifically excluded. However, increased fibrinolysis, as indicated by increased concentrations of fibrinogen degradation products, is often seen in patients with TBI and predicts intracranial haemorrhage expansion.⁸ Therefore, early administration of tranexamic acid in patients with TBI might prevent or reduce intracranial haemorrhage expansion and thus avert brain herniation and death.

Before the CRASH-3 trial, only two small trials of tranexamic acid in patients with TBI had been done.^{9,10} Meta-analysis of these trials showed a reduction in mortality with tranexamic acid (risk ratio [RR] 0.63 [95% CI 0.40–0.99]) but provided no evidence about the effect of tranexamic acid on disability or adverse events. The CRASH-3 trial aimed to quantify the effects of tranexamic acid on head injury-related death, disability, and adverse events in patients with TBI.¹¹

Methods

Study design and participants

The CRASH-3 trial was an international, multi-centre, randomised, placebo-controlled trial of the effects of tranexamic acid on death and disability in 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,^{6,12,13} the trial steering committee amended the protocol to limit recruitment to within 3 h of injury and the primary endpoint was changed to head injury death in hospital within 28 days of injury for patients treated within 3 h of injury. This change was made without reference to the unblinded trial data. The data monitoring committee was not consulted about the change. The trial was done according to good clinical practice guidelines.

Because of the nature of their injury, most patients with TBI are unable to provide informed consent to participate in a clinical trial. As acknowledged in the Declaration of Helsinki, patients who are incapable of giving consent are

an exception to the general rule of informed consent in clinical trials.¹⁴ In this trial, consent was usually sought from the patient's relative or a legal representative. If no such representative was available, the study proceeded with the agreement of two clinicians. If the patient regained capacity, he or she was told about the trial and written consent was sought to continue participation. If the patient or their representative declined consent, participation stopped. If patients were included in the trial but did not regain capacity, consent was sought from a relative or legal representative. We adhered to the requirements of the local and national ethics committees.

Randomisation and masking

An independent statistician from Sealed Envelope (London, UK) prepared the randomisation codes and gave them to the drug packers so that treatment packs could be prepared. We randomly allocated eligible patients to receive tranexamic acid or matching placebo (0.9% sodium chloride) by intravenous infusion. After baseline information was collected on the entry form, the lowest numbered treatment pack remaining was taken from a box of eight treatment packs. At this point, provided that the ampoules inside the treatment pack were intact, the patient was considered to be randomised. Entry form data were entered into a secure online database by the trial investigators. Participants and study staff (site investigators and trial coordinating centre staff) were masked to allocation. An emergency unblinding service was available for use if the clinician believed that clinical management depended importantly on knowledge of whether the patient received tranexamic acid or placebo. The tranexamic acid was manufactured by Pfizer (Sandwich, UK). The Torbay and South Devon Healthcare NHS Trust (UK) prepared the 0.9% sodium chloride placebo. Ampoules and packaging were identical in appearance. The preparation of the treatment packs was done by Bilcare (Crickhowell, UK), by removal of the manufacturer's label and replacement with the trial label and treatment pack number. Pack label texts were identical for tranexamic acid and placebo. We checked the coding of the blinded ampoules by randomly testing each batch of treatments and doing high performance liquid chromatography to identify the contents.

Procedures

Patients were randomly 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, or matching placebo. Every patient was assigned a uniquely numbered treatment pack, which contained four ampoules of either tranexamic acid (500 mg) or placebo, one 100 mL bag of 0.9% sodium chloride (to use with the loading dose), a syringe and needle, stickers with the trial details and randomisation number (for attaching to infusion bags, forms, and the medical records), and instructions.

We separately provided information for patients and representatives, consent forms, and data collection forms. The stickers, instructions, leaflets, and forms were in local languages. Once randomised, we collected outcome data even if the treatment was not given. Outcome data were collected 28 days after randomisation, at discharge from the randomising hospital, or at death (whichever was first). Because the trial was assessed as low risk (tranexamic acid is widely used and the trial was considered to have a low risk of bias), we used central trial monitoring and central statistical monitoring in conjunction with investigator training, meetings, and written guidance. Trial investigators and their institutions provided direct access to the source data for trial-related monitoring, audits, and regulatory inspections. We planned to monitor approximately 10% of patient records on site. However, after changing the primary outcome we expanded our monitoring plan to include patients enrolled within 3 h of injury who subsequently died. We monitored 2436 (19%) of 12737 patient records onsite or remotely (using videocall or telephone), including 1161 (67%) of the patients who died from head injury (the primary outcome). The team of monitors worked alongside local trial teams to verify data from the source data, including pre-hospital ambulance cards, admission registers, emergency department notes, CT scans, surgery notes, death registers, and death certificates.

Outcomes

The primary outcome was head injury-related death in hospital within 28 days of injury in patients randomly assigned within 3 h of injury. Because most patients with TBI with a GCS score of 3 and those with bilateral unreactive pupils have a very poor prognosis regardless of treatment, their inclusion in the trial might bias any treatment effect towards the null. We therefore prespecified a sensitivity analysis that excluded these patients.¹¹ Cause of death was assessed by the responsible clinician. Secondary outcomes were early head injury-related death (within 24 h after injury), all-cause and cause-specific mortality, disability, vascular occlusive events (myocardial infarction, stroke, deep vein thrombosis, and pulmonary embolism), seizures, complications, neuro-surgery, days in intensive care unit, and adverse events within 28 days of randomisation. A diagnosis of deep vein thrombosis or pulmonary embolism was recorded only if a positive result was found on imaging (eg, ultrasound) or at a post-mortem examination.

We originally estimated that a trial with approximately 10 000 patients would have 90% power (two-sided $\alpha=1\%$) to detect a 15% relative reduction (20–17%) in mortality.¹⁵ However, we changed the primary outcome to head injury-related death in hospital within 28 days of injury in patients randomly assigned within 3 h of injury and limited recruitment to within 3 h of injury. We then increased the sample size to 13 000 to have approximately 10 000 patients treated within 3 h of injury.¹¹

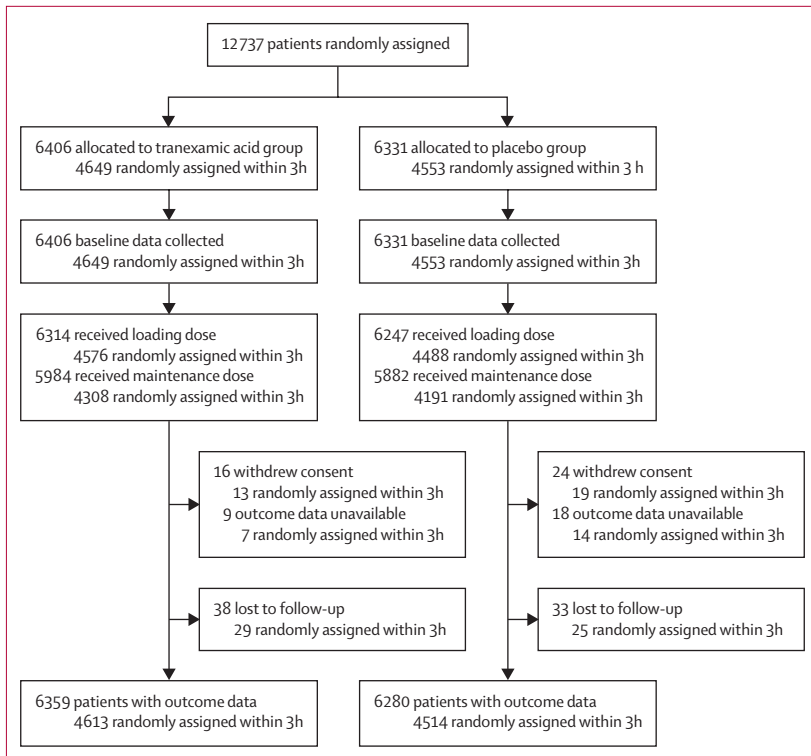


Figure 1: Trial profile

Statistical analysis

We published a statistical analysis plan before unblinding.¹¹ The plan gave our reasons for limiting recruitment to within 3 h of injury and stated that outcomes for patients treated after 3 h of injury would be presented separately. All analyses were on an intention-to-treat basis. For each binary outcome, we calculated RRs and 95% CIs. We did a complete case analysis with no imputation for missing data. The safety of participants was overseen by an independent data monitoring committee, which reviewed four unblinded interim analyses.

We planned to report the effects of tranexamic acid on the primary outcome stratified by three baseline characteristics: severity of head injury, time to treatment, and age. Severity of head injury was assessed using the baseline GCS score—mild to moderate (GCS 9–15) and severe (GCS 3–8)—and by pupil reactivity. We also assessed the effect of severity in a regression analysis that included continuous terms for GCS and its square. We expected that any beneficial effect of tranexamic acid would vary by time to treatment with earlier treatment being most effective. We examined this hypothesis in a subgroup analysis of the effect of tranexamic acid according to the estimated time interval between injury and treatment (≤ 1 , >1 to ≤ 3 , >3 h). We prespecified that this analysis would include patients treated within and beyond 3 h of injury. Because TBI severity, systolic blood pressure, and age could confound the effect of time to

treatment on treatment effectiveness, we planned to control for these variables in a multivariable model. Because fibrinolytic activation after TBI might increase with age, we examined the effect of tranexamic acid on head injury-related death stratified by age: 30 years or younger, 31–60 years, older than 60 years. For subgroup analyses, we report p values for the test for heterogeneity.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between July 20, 2012, and Jan 31, 2019, we recruited patients with TBI from 175 hospitals in 29 countries. We stopped recruiting when the trial treatment expired. We randomly allocated 12737 patients to receive tranexamic acid (6406 [50.3%]) or matching placebo (6331 [49.7%]), of whom 12561 (98.6%) received the first dose of the allocated treatment (figure 1). We enrolled 9202 (72.2%) patients within 3 h of injury. 40 patients withdrew consent after randomisation but 13 of these agreed to outcome data collection or had outcome data collected as part of adverse event reporting. We did not obtain primary outcome data for 75 (0.8%) patients. There were 98 (0.8%) protocol violations. 66 (0.5%) patients did not meet the inclusion criteria (32 had GCS scores >12 and no bleeding on CT scan, 11 had major extracranial bleeding, eight had a time since injury >8 h, six were younger than 16 years, three had non-traumatic bleeding, five had a combination of the above reasons, and one patient received tranexamic acid before randomisation). 32 (0.3%) patients were recruited during a lapse in the annual renewal of ethics committee approval in the UAE. These patients were recruited according to the approved procedure and approval was reissued after the lapse. 13 patients were unmasked to treatment. Baseline characteristics were similar between treatment groups for patients treated within 3 h of injury (table 1) and for those treated after 3 h (appendix 8 p 1). Figure 2 shows the number of deaths due to head injury and all other causes by days since injury in all patients. 2560 deaths occurred and the median time to death was 59 h after injury (IQR 20–151).

Table 2 shows the effect of tranexamic acid on head injury-related death in the 9127 patients randomly assigned within 3 h of injury with outcome data. Among these patients, the risk of head injury-related death was 18.5% in the tranexamic acid group versus 19.8% in the placebo group (855 vs 892 events, RR 0.94 [95% CI 0.86–1.02]). In the prespecified sensitivity analysis that excluded patients with a GCS score of 3 or bilateral unreactive pupils at baseline, the results were 12.5% in the tranexamic acid group versus 14.0% in the placebo group (485 vs 525 events, 0.89 [0.80–1.00]).

See Online for appendix 8

	Tranexamic acid (n=4649)	Placebo (n=4553)
Sex*		
Men	3742 (80%)	3660 (80)
Women	906 (19%)	893 (20)
Age, years		
Mean (SD)	41.7 (19.0)	41.9 (19.0)
<25	1042 (22%)	996 (22%)
25–44	1716 (37%)	1672 (37%)
45–64	1169 (25%)	1184 (26%)
≥65	722 (16%)	701 (15%)
Time since injury, h		
Mean (SD)	1.9 (0.7)	1.9 (0.7)
≤1	877 (19%)	869 (19%)
>1–2	2003 (43%)	1889 (41%)
>2–3	1769 (38%)	1795 (39%)
Systolic blood pressure, mm Hg		
<90	89 (2%)	85 (2%)
90–119	1508 (32%)	1490 (33%)
120–139	1461 (31%)	1504 (33%)
≥140	1576 (34%)	1466 (32%)
Unknown	15 (<1%)	8 (<1%)
Glasgow Coma Scale score		
3	495 (11%)	506 (11%)
4	213 (5%)	213 (5%)
5	163 (4%)	172 (4%)
6	221 (5%)	232 (5%)
7	311 (7%)	294 (6%)
8	354 (8%)	315 (7%)
9	335 (7%)	292 (6%)
10	371 (8%)	364 (8%)
11	375 (8%)	390 (9%)
12	476 (10%)	478 (10%)
13	297 (6%)	312 (7%)
14	526 (11%)	458 (10%)
15	484 (10%)	492 (11%)
Unknown	28 (1%)	35 (1%)
Pupil reaction		
None reacted	425 (9%)	440 (10%)
One reacted	374 (8%)	353 (8%)
Both reacted	3706 (80%)	3636 (80%)
Unable to assess or unknown	144 (3%)	124 (3%)

Data are n (%), unless otherwise indicated. *In the tranexamic acid group, one patient's sex was unknown.

Table 1: Baseline characteristics of patients before randomisation of those randomly assigned within 3 h of injury

We examined the effect of tranexamic acid on head injury-related death stratified by baseline GCS and pupillary reactions (figure 3). We found a reduction in the risk of head injury-related death with tranexamic acid in patients with mild-to-moderate head injury (RR 0.78 [95% CI 0.64–0.95]) but in patients with severe head injury (0.99 [0.91–1.07]) we found no clear evidence of a reduction (p value for heterogeneity 0.030). When

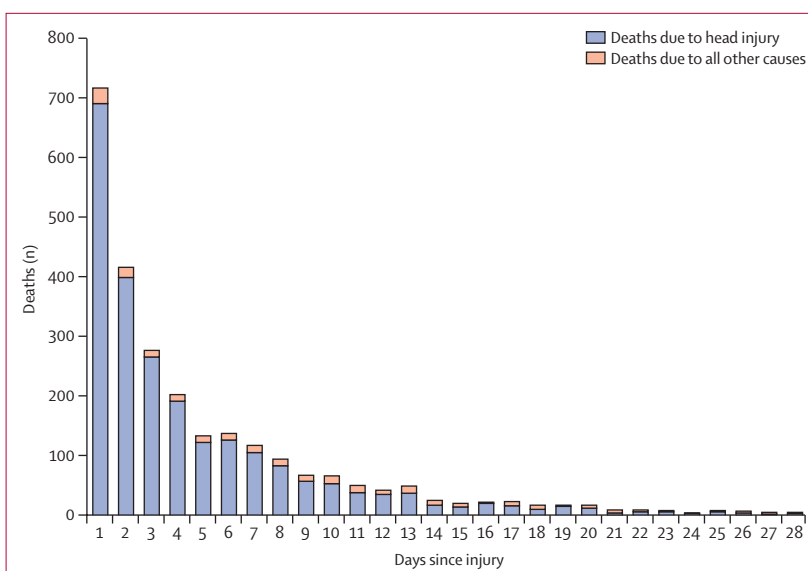


Figure 2: Mortality by days since injury among all patients

	Tranexamic acid	Placebo	Risk ratio (95% CI)
All	855/4613 (18.5%)	892/4514 (19.8%)	0.94 (0.86–1.02)
Excluding patients with GCS score of 3 or bilateral unreactive pupils*	485/3880 (12.5%)	525/3757 (14.0%)	0.89 (0.80–1.00)

GCS=Glasgow Coma Scale. *Prespecified sensitivity analysis.

Table 2: Effect of tranexamic acid on head injury-related death in patients randomly assigned within 3 h of injury

we examined the effect of baseline GCS in a regression analysis we found evidence that tranexamic acid is more effective in less severely injured patients (p=0.007). Among patients with reactive pupils, head injury-related deaths were reduced with tranexamic acid (0.87, [0.77–0.98]).

We examined the effect of tranexamic acid on head injury-related death stratified by time to treatment and recorded no evidence of heterogeneity (p=0.96). The RR of head injury-related death with tranexamic acid was 0.96 (95% CI 0.79–1.17) in patients randomly assigned within 1 h of injury, 0.93 (0.85–1.02) in those randomly assigned within more than 1 h and 3 h or fewer after injury, and 0.94 (0.81–1.09) in those randomly assigned more than 3 h after injury. However, as anticipated in the statistical analysis plan, patients who are treated soon after injury often have more severe head injury and so the effect of time to treatment could be confounded by severity. Figure 4 shows effect of time to treatment on the effect of tranexamic acid in patients with a mild and moderate head injury and in those with severe head injury after adjusting for GCS, systolic blood pressure, and age in a multivariable model including all participants. Early treatment was more effective than later treatment in patients with mild and moderate head injury (p=0.005) but we found no obvious effect of time to treatment

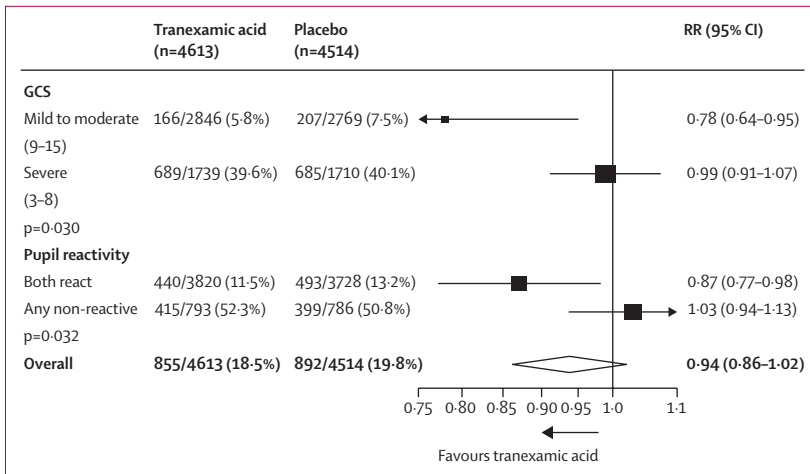


Figure 3: Effect of tranexamic acid on head injury-related death stratified by baseline severity in patients randomised within 3 h of injury

RR=risk ratio. GCS=Glasgow Coma Scale.

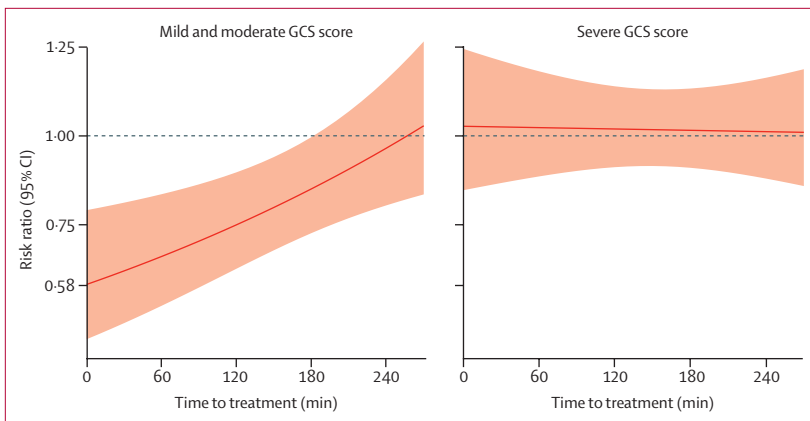


Figure 4: Effect of tranexamic acid on head injury-related death by severity and time to treatment in all patients. The models were adjusted for GCS score, age, and systolic blood pressure. 537 patients with mild and moderate GCS scores (9–15) and 918 patients with severe GCS scores (4–8), excluding those with a GCS score of 3 and those with no reactive pupils, died because of head injury. GCS=Glasgow Coma Scale.

in patients with severe head injury (p=0.73). The effectiveness of tranexamic acid by time to treatment stratified by severity is further shown in the appendix 8 (p 3). We found no evidence of heterogeneity in the effect of tranexamic acid by patient age (p=0.45).

We examined the effect of tranexamic acid on head injury-related death stratified by World Bank income group (high-income vs low-income and middle-income countries). This analysis was not prespecified. Although the reduction in the risk of head injury-related death with tranexamic acid was larger in high-income countries (RR 0.76 [95% CI 0.55–1.04]) than in low-income and middle-income countries (0.92 [0.81–1.04]), we found no statistical evidence of heterogeneity by country income group (p=0.26).

Because early head injury-related deaths are more likely to result from intracranial haemorrhage than are late head injury-related deaths, we examined the effect of tranexamic

acid on head injury-related death within 24 h of injury. The RR of head injury-related death was 0.81 (95% CI 0.69–0.95) within 24 h. When patients with a GCS score of 3 and those with bilateral unreactive pupils at baseline were excluded, the RR was 0.72 (0.56–0.92) within 24 h.

The RR for non-head injury-related deaths was 1.31 (95% CI 0.93–1.85) and 0.96 (0.89–1.04) for all-cause mortality. The results for non-head injury-related deaths broken down by cause are presented in the appendix 8 (p 2).

We assessed the effect of tranexamic acid on disability in survivors by comparing the mean Disability Rating Scale score (lower score means less disabled) between the tranexamic acid and placebo groups. The mean scores were similar between groups for patients treated within 3 h of injury (4.99 [SD 7.6] in the tranexamic acid group vs 5.03 [7.6] in the placebo group) and for those treated after 3 h (4.52 [7.0] in the tranexamic acid group vs 5.00 [7.4] in the placebo group). We also examined the effect of tranexamic acid on disability (table 3) using an outcome measure designed by patient representatives by estimating the RR of being in the most extreme category for six areas of functioning (walking, washing, pain and discomfort, anxiety or depression, agitation or aggression, and fatigue). The prevalence of disability among survivors was similar between groups.

The risk of vascular occlusive events and other complications was similar in the tranexamic acid and placebo groups (table 3). We found no evidence that tranexamic acid increased fatal or non-fatal stroke (RR 1.08 [95% CI 0.71–1.64]). The risk of seizures was similar between groups (1.09 [95% CI 0.90–1.33]). The numbers of other adverse events were similar between groups (appendix 8 p 4).

Discussion

This trial provides evidence that the administration of tranexamic acid to patients with TBI within 3 h of injury reduces head injury-related death, with no evidence of adverse effects or complications. We found a substantial reduction in head injury-related deaths with tranexamic acid in patients with mild and moderate head injuries but no apparent reduction in those with severe head injury. We found no increase in disability among survivors.

Our trial had several strengths but also some limitations. The method of randomisation ensured that participating clinicians had no foreknowledge of the treatment allocation and the use of placebo control ensured that outcome assessments were blind to the intervention. Although the eligibility criteria required the recruiting clinician to be uncertain as to the appropriateness of tranexamic acid treatment, because tranexamic acid is not a recommended treatment for patients with isolated TBI, almost all patients with TBI who met the inclusion criteria were recruited. Baseline prognostic factors were well balanced and because

	<3 h			≥3 h			All		
	Tranexamic acid (n=4613)	Placebo (n=4514)	RR (95% CI)	Tranexamic acid (n=1746)	Placebo (n=1766)	RR (95% CI)	Tranexamic acid (n=6359)	Placebo (n=6280)	RR (95% CI)
Patient-derived disability measures*									
Confined to bed	579 (12.6%)	549 (12.2%)	1.03 (0.93–1.15)	190 (10.9%)	222 (12.6%)	0.87 (0.72–1.04)	769 (12.1%)	771 (12.3%)	0.99 (0.90–1.08)
Unable to wash or dress	580 (12.6%)	583 (12.9%)	0.97 (0.87–1.08)	195 (11.2%)	228 (12.9%)	0.87 (0.72–1.04)	775 (12.2%)	811 (12.9%)	0.94 (0.86–1.03)
Severe pain or discomfort	38 (0.8%)	29 (0.6%)	1.28 (0.79–2.08)	10 (0.6%)	10 (0.6%)	1.01 (0.42–2.42)	48 (0.8%)	39 (0.6%)	1.22 (0.80–1.85)
Severe anxiety or depression	43 (0.9%)	41 (0.9%)	1.03 (0.67–1.57)	19 (1.1%)	20 (1.1%)	0.96 (0.51–1.79)	62 (1.0%)	61 (1.0%)	1.00 (0.71–1.43)
Severe agitation or aggression	53 (1.1%)	53 (1.2%)	0.98 (0.67–1.43)	14 (0.8%)	27 (1.5%)	0.52 (0.28–1.00)	67 (1.1%)	80 (1.3%)	0.83 (0.60–1.14)
Severe fatigue	100 (2.2%)	101 (2.2%)	0.97 (0.74–1.27)	40 (2.3%)	43 (2.4%)	0.94 (0.61–1.44)	140 (2.2%)	144 (2.3%)	0.96 (0.76–1.21)
Complications†									
All vascular occlusive events	69 (1.5%)	60 (1.3%)	1.13 (0.80–1.59)	32 (1.8%)	42 (2.4%)	0.77 (0.49–1.21)	101 (1.6%)	102 (1.6%)	0.98 (0.74–1.28)
Pulmonary embolism	18 (0.4%)	18 (0.4%)	0.98 (0.51–1.88)	6 (0.3%)	14 (0.8%)	0.43 (0.17–1.13)	24 (0.4%)	32 (0.5%)	0.74 (0.44–1.26)
Deep vein thrombosis	15 (0.3%)	12 (0.3%)	1.22 (0.57–2.61)	4 (0.2%)	4 (0.2%)	1.01 (0.25–4.04)	19 (0.3%)	16 (0.3%)	1.17 (0.60–2.28)
Stroke	29 (0.6%)	23 (0.5%)	1.23 (0.71–2.13)	17 (1.0%)	19 (1.1%)	0.90 (0.47–1.74)	46 (0.7%)	42 (0.7%)	1.08 (0.71–1.64)
Myocardial infarction	9 (0.2%)	12 (0.3%)	0.73 (0.31–1.74)	9 (0.5%)	8 (0.5%)	1.14 (0.44–2.94)	18 (0.3%)	20 (0.3%)	0.89 (0.47–1.68)
Renal failure	73 (1.6%)	56 (1.2%)	1.28 (0.90–1.80)	27 (1.5%)	28 (1.6%)	0.98 (0.58–1.65)	100 (1.6%)	84 (1.3%)	1.18 (0.88–1.57)
Sepsis	297 (6.4%)	279 (6.2%)	1.04 (0.89–1.22)	114 (6.5%)	133 (7.5%)	0.87 (0.68–1.10)	411 (6.5%)	412 (6.6%)	0.99 (0.86–1.12)
Seizure	130 (2.8%)	105 (2.3%)	1.21 (0.94–1.56)	76 (4.4%)	81 (4.6%)	0.95 (0.70–1.29)	206 (3.2%)	186 (3.0%)	1.09 (0.90–1.33)
Gastrointestinal bleeding	16 (0.3%)	22 (0.5%)	0.71 (0.37–1.35)	8 (0.5%)	13 (0.7%)	0.62 (0.26–1.50)	24 (0.4%)	35 (0.6%)	0.68 (0.40–1.14)

RR=risk ratio. *Includes survivors only. †Includes fatal and non-fatal events.

Table 3: Effect of tranexamic acid on disability, vascular occlusive events, and other complications in patients randomly assigned within 3 h, patients randomised beyond 3 h, and all patients

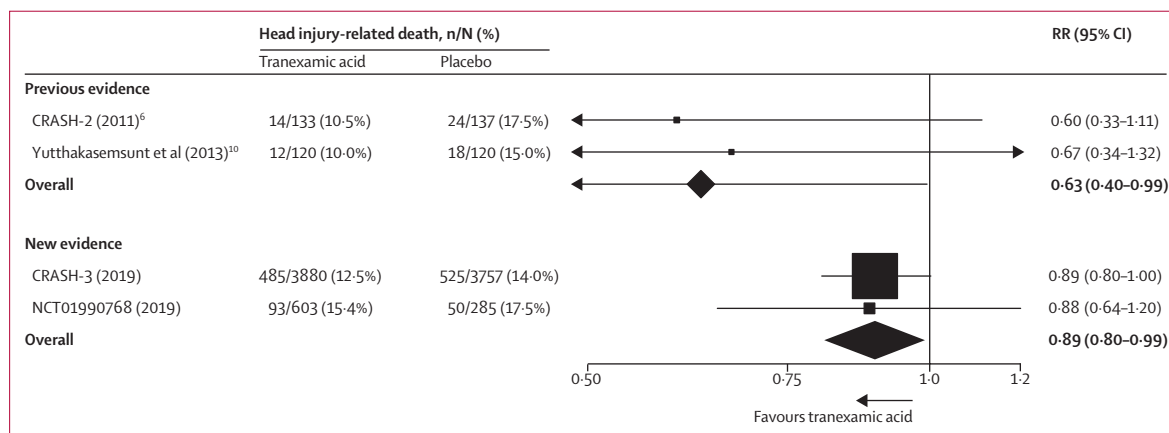


Figure 5: Evidence on the effect of tranexamic acid on head injury-related death
RR=risk ratio.

almost all randomly assigned patients were followed up there was little potential for bias. The analysis was by intention to treat. The primary outcome was head injury-related death as assessed by the responsible clinician. Although some misclassification of cause of death is inevitable, the assessment was made blind to the trial treatment. All-cause mortality combines causes of death that might be affected by tranexamic acid (eg, head injury-related death due to intracranial bleeding) with causes that we do not expect to be affected by tranexamic acid (eg, sepsis) and therefore would be biased towards the null. Although the CRASH-3 trial is one of the largest trials in patients with TBI, the CIs were wide and compatible with a

substantial reduction in head injury-related death and little or no benefit. On the other hand, when set in the context of all the available randomised trials of tranexamic acid in patients with TBI (figure 5), the possibility of no mortality benefit appears remote (NCT01990768).^{9,10} When assessing outcome measures in clinical trials, provided there are few false positives (high specificity), estimates of the RR are unbiased even when sensitivity is imperfect.¹⁶ For this reason, a diagnosis of deep vein thrombosis or pulmonary embolism was recorded only if we found a positive result on imaging (eg, ultrasound) or at post-mortem examination. As a result, although the trial might have underestimated the risk of deep vein thrombosis or

pulmonary embolism, the RR estimates for this outcome should be unbiased.

We anticipated that patients with TBI with a GCS score of 3 and those with bilateral unreactive pupils before treatment would have little potential to benefit from tranexamic acid and that their inclusion in the analysis would bias the treatment effect towards the null. Most patients with bilateral unreactive pupils already have extensive intracranial haemorrhage and brain herniation and so tranexamic acid is unlikely to improve the outcome in these patients. We therefore prespecified a sensitivity analysis that excluded these patients. However, patients with unilateral unreactive pupils were not excluded and because many of these patients have brain herniation their inclusion might also have diluted the treatment effect. Indeed, when patients with a GCS score of 3 and those with unilateral or bilateral unreactive pupils before treatment were excluded in a post-hoc analysis, the treatment effect was noticeably larger.

The effect of tranexamic acid on head injury-related death appears to depend on the time interval between injury and the initiation of the trial treatment and on the severity of TBI. Early treatment of patients with mild (GCS 13–15 and intracranial bleeding on baseline CT scan) and moderate head injury seemed to confer the greatest mortality benefit. This finding is consistent with the hypothesis that tranexamic acid improves outcome by reducing intracranial bleeding. Because haemorrhage expansion occurs in the hours immediately after injury, treatment delay would reduce the potential for tranexamic acid to prevent intracranial bleeding.^{3,4} Patients with severe head injury might have less to gain from tranexamic acid treatment than patients with mild-to-moderate head injury because such patients already have extensive intracranial haemorrhage before treatment or other potentially life-threatening intracranial pathologies that are not affected by tranexamic acid. We anticipated in our statistical analysis plan that the effect of tranexamic acid would be greater for head injury-related deaths occurring in the first few days after injury than for late head injury-related deaths because early head injury-related deaths are more likely due to bleeding. Our data supports this hypothesis, showing a substantial reduction in head injury-related deaths within 24 h of injury. Similar results were obtained in the CRASH-2 trial of tranexamic acid in patients with traumatic extracranial bleeding, in which the effect of tranexamic acid on death from bleeding was greatest on the day of the injury (RR 0.72 [95% CI 0.60–0.86]).¹⁷ However, thereafter the benefit of tranexamic acid in head injury patients was slightly attenuated, probably because patients succumbed to non-bleeding-related pathophysiological mechanisms. This finding might explain why the effect of early tranexamic acid treatment on head injury-related death is slightly smaller than the effect of tranexamic acid on death due to bleeding seen in the CRASH-2 trial.

We found no evidence of any increased risk of adverse events. In particular, the risk of deep vein thrombosis, pulmonary embolism, stroke, and myocardial infarction was similar in the tranexamic acid and placebo groups. This finding is consistent with the results of the CRASH-2 trial, which also found no increased risk of vascular occlusive events with tranexamic acid. Unlike in the CRASH-2 trial, we found no evidence that administration beyond 3 h of injury increased the risk of head injury-related death or any other adverse events. Indeed, given the absence of any adverse effects in this trial, the implications of wrongly concluding that tranexamic acid is ineffective are likely to be far more consequential than are those of wrongly concluding that tranexamic acid is effective.

On the basis of the CRASH-2 trial results, tranexamic acid was included in guidelines for the pre-hospital care of patients with trauma. However, patients with isolated TBI were specifically excluded. The CRASH-3 trial provides evidence that tranexamic acid is safe in patients with TBI and that treatment within 3 h of injury reduces head injury-related deaths.

The CRASH-3 trial collaborators

Writing Committee—Prof Ian Roberts and Prof Haleema Shakur-Still (co-chairs), Amy Aeron-Thomas, Prof Antonio Belli, Amy Brenner, Prof Muhammad Anwar Chaudhry, Prof Rizwana Chaudhri, Sabariah Faizah Bt Jamaluddin, Lauren Frimley, Kiran Javid, Prof Rashid Jooma, Aasia Kayani, Caroline Leech, Prof Khalid Mahmood, Raoul Mansukhani, Julina Md Noor, Jorge Mejia-Mantilla, Phil Moss, Jason Pott, Prof Peter Sandercock, Prof Temitayo Shokunbi, and Liliana Vallecilla. *Trial Steering Committee*—Peter Sandercock (Chair), Henry Benjamin Hartzenberg, Manjul Joshipura (2011–16), Amy Aeron-Thomas (patient representative [trial steering committee]; advocacy and justice manager, RoadPeace), Ian Roberts, Pablo Perel, and Haleema Shakur-Still. *Data Monitoring and Ethics Committee*—Michael J Clarke (chair), Samuel C Ohaegbulam, Anthony Rodgers, and Tony Brady (independent statistician). *Protocol Committee*—Ian Roberts, Haleema Shakur-Still, Yashbir Dewan, Phil Edwards, Edward O Komolafe, Jorge Mejia-Mantilla, and Pablo Perel. *Clinical Trials Unit (CTU)*—Monica Arribas (trial manager and research assistant), Emma Austin (assistant trial manager), Eni Balogun (trial manager), Lin Barneston (data manager 2011–12), Collette Barrow (trial administrator), Danielle Beaumont (senior trial manager and research fellow), Myriam Benyahia (CTU administrator), Amy Brenner (research fellow), Imogen Brooks (trial assistant 2016–18), Madeleine Cargill (data assistant), Laura Carrington (assistant trial administrator), Lisa Cook (assistant trial manager 2011), Beatrice Cornu-Hewitt (trial assistant), Phil Edwards (statistician 2011–16), Lauren Frimley (trial manager and research assistant), Amber Geer (assistant data manager), Daniel Gilbert (data assistant 2012–13), Catherine Gilliam (trial administrator), Julio Gil-Onandia (trial assistant), Daniel Hetherington (trial assistant 2012–13), Courtenay Howe (CTU administrator 2015–17), Carolyn Hughes (data assistant 2016–17), David I'anson (assistant trial manager 2016–17), Rob Jackson (data manager 2012–14), Miland Joshi (statistician 2016–17), Sneha Kansagra (assistant trial manager 2016–18), Taemi Kawahara (senior trial manager 2011–15), Katharine Ker (lecturer), Sergey Kostrov (systems officer), Abda Mahmood (PhD candidate), Raoul Mansukhani (medical statistician), Hakim Miah (IT systems manager), Bernard Ndungu (assistant trial manager 2016–17), Kelly Needham (medical statistician), Cecilia Okusi (data assistant 2014), Aroudra Outtandy (trial assistant 2013–15), Raul Pardinaz-Solis (assistant trial manager 2012–13), Daniel Pearson (data assistant), Tracey Pepple (acting senior data manager), Claude Pisani (assistant trial manager 2013), Jason Pott (lead UK research nurse 2018), David Prieto-Merino

(statistician 2012–15), Danielle Prowse (assistant data manager), Nigel Quashi (data manager 2013–16), Anna Quinn (data assistant 2013–15), Maria Ramos (senior project administrator 2011–15), Mia Reid (clerical assistant 2016–18), Ian Roberts (chief investigator and CTU co-director), Chris Roukas (trial administrator 2013–15), Giulia Scropa (assistant trial manager 2018), Haleema Shakur-Still (project director and CTU co-director), Chelci Squires (trial assistant 2014–16), Jemma Tanner (clinical trials associate 2013–16), Andrew Thayne (data assistant), Lesley Vidaurre (assistant trial manager 2012), and Elizabeth Woods (assistant trial manager 2012–15). *Nigeria Coordinating Team*—Bukola Fawole (coordinating centre director), Olusade Adetayo (assistant trial coordinator), Olujide Okunade (assistant trial coordinator), and Temitayo Shokunbi (clinical lead). *Pakistan Coordinating Team*—Rizwana Chaudhri (coordinating centre director), Kiran Javaid (assistant research coordinator), Rashid Jooma (clinical lead), and Aasia Kayani (research coordinator). *National Coordinators*—Rizwana Chaudhri (Pakistan), Rashid Jooma (Pakistan), Sabariah Faizah Bt Jamaluddin (Malaysia), Julina Md Noor (national coordinators assistant, Malaysia), Tamar Gogichaishvili (Georgia), Maria de los Angeles Munoz-Sanchez (Spain), Bukola Fawole (Nigeria), Temitayo Shokunbi (Nigeria), Jorge Mejia-Mantilla (Colombia), Liliana Vallecilla (Colombia), Fatos Olddashi (Albania), Satish Krishnan (United Arab Emirates), Vincent Djientcheu (Cameroon), Jorge Loria Castellanos (Mexico), Frank Rasulo (Italy), Qadamkhear Hama (Iraq), Yakub Mulla (Zambia), Prof Ioan Stefan Florian (Romania), Juan Tobar (El Salvador), Hussein Khamis (Egypt), Conor Deasy (Ireland), Bobby Wellsh (Papua New Guinea), Jean Williams-Johnson (Jamaica), Susilo Chandra (Indonesia), and Vincent Mutiso (Kenya).

CRASH trial sites and investigators (number of patients randomly assigned)

Pakistan (4567)—Lahore General Hospital Neurosurgery Unit I (1178): Rizwan Butt, Muhammad Hammad Nasir, Salman Ahmad, Farwah Aslam, Khurram Ishaque, Faheem Usmani, Shahrukh Rizvi, Farhad Ali, Omair Sajjad, and Ali Zunair; Jinnah Postgraduate Medical Centre (700): Lal Rehman, Raza Rizvi, Farrukh Javed, Shakeel Ahmed, Asad Abbas, Ali Afzal, and Ali Mikdad; Lahore General Hospital Neurosurgery Unit III (648): Asif Bashir, Anwar Chaudary, Tariq Salahuddin, Bashir Ahemed, Shahrukh Rizvi, Faheem Usmani, and Amir Aziz; Jinnah Hospital Lahore (619): Naveed Ashraf, Shahzad Hussain, Usman Ahmad, Muhammad Asif, Muhammad Adil, and Adeel Rauf; Lahore General Hospital Neurosurgery Unit II (607): Khalid Mahmood, Rizwan Khan, Bilal Ahmad, Umair Afzal, Hassan Raza, and Quratul Ain; DHQ Hospital Narowal (303): Sajjad Yaqoob, Qaiser Waseem, Muffasser Nishat, Suneel Semvel, and Javed Iqbal; Services Hospital Lahore (226) Samra Majeed, Sana Zulfiqar, Madeeha Iqbal, Nazia Majeed, and Manzoor Ahmed; DHQ Rawalpindi (137): Nadeem Akhtar, Mohammad Malik, Yasir Shehzad, and Muhammad Yousaf; DHQ Hospital Khuzdar (65): Abdul Wahid, Abdul Samad, and Saifullah Shah; Lady Reading Hospital (31): Mumtaz Ali and Jehan Zeb; Shifa International Hospital (29): Abdus Salam Khan and Adeela Irfan; Liaquat National Hospital and Medical College (14): Salman Sharif; Liaquat University Hospital (7): Riaz Memon; Aga Khan University Hospital (3): Rashid Jooma. *UK (3143)*—Royal London Hospital (501): Ben Bloom, Tim Harris, Jason Pott, Imogen Skene, Geoffrey Bellhouse, and Olivia Boulton; University Hospital Coventry (312): Caroline Leech, Geraldine Ward, Catherine Jarvis, Carly Swann, and Sathananathan Ratnam; Queen Elizabeth Hospital Birmingham (302): Antonio Belli, Ronald Carrera, Kamal Yakoub, David Davies, and Emma Fellows; St George's Hospital (280): Phil Moss, Heather Jarman, Sarah Rounding, Elizabeth Johnson, and Catherine Loughran; Salford Royal Hospital (176): Fiona Lecky, Kate Clayton, Angiy Michael, and Angela Coumbarides; Southmead Hospital (156): Jason Kendall, Beverley Faulkner, Ruth Worner, and Emma Gendall; King's College Hospital (155): Philip Hopkins, Paul Riozzi, Hannah Cotton, and Raine Astin-Chamberlain; St Mary's Hospital, London (117): Mark Wilson, Jan Bodnar, Rachel Williams, and Alberto Rigoni; Aintree University Hospital (108): Abdo Sattout, John Fletcher, Calum Edge, and Nina Maryanji; Addenbrooke's Hospital (103): Adrian Boyle, Susie Hardwick, Ellen Nichols, and Catherine Hayhurst; Queen's Medical Centre (100): Frank Coffey, Chris Gough, Philip Miller, and Lucy Ryan; John Radcliffe Hospital (76):

Melanie Darwent, Alexis Espinosa, and Sally Beer; Royal Stoke University Hospital (71): Julie Norton, Holly Maguire, and Kay Finney; Derriford Hospital (67): Anthony Kehoe, Rosalyn Squire, and Alison Jeffery; Queen Alexandra Hospital (60): Christiane Vorwerk, Denise Foord, and Eliot Wilkinson; Northern General Hospital (57): Avril Kuhr, Shammi Ramlakhan, and Stuart Reid; Royal Preston Hospital (41): Andy Curran and Sean McMullan; Leeds General Infirmary (39): Tajek Hassan and Stuart Nuttall; Great Western Hospital (32): Stephen Haig and Saif Al-Nahhas; Southampton General Hospital (31): Diederik Bulters and Ardalan Zolnourian; Dorset County Hospital (27): Tamsin Ribbons and Ian Mew; Gloucestershire Royal Hospital (27): Tanya de Weymarn and Victoria Hughes; Royal Liverpool Hospital (21): Jane McVicar; Queen Elizabeth University Hospital (20): Cieran McKiernan; Royal Berkshire Hospital (20): Liza Keating; Poole Hospital (17): Henrik Reschreiter; James Cook University Hospital (16): Judith Wright; Basingstoke and North Hampshire Hospital (13): Louisa Chan; Whiston Hospital (13): Himanshu Kataria; Glasgow Royal Infirmary (12): Alastair Ireland; Manchester Royal Infirmary (12): Richard Body; Royal Alexandra Hospital (12): Alasdair Corfield; Milton Keynes University Hospital (11): Shindo Francis; Hull Royal Infirmary (10): William Townend; Leicester Royal Infirmary (10): Timothy Coats; Musgrove Park Hospital (10): James Gagg; Wexham Park Hospital (10): Sarah Wilson; Royal Sussex County Hospital (8): Rowley Cottingham; Blackpool Victoria Hospital (7): Simon Tucker; Norfolk and Norwich University Hospital (7): Frank Sutherland; North Devon District Hospital (7): Louisa Mitchell; Whipps Cross University Hospital (7): Tim Harris; Whittington Hospital (7): Lucy Parker; Darlington Memorial Hospital (6): Ola Afolabi; Monklands Hospital (6): Fiona Hunter; Royal Cornwall Hospital (6): Mark Jadav; University Hospital of North Tees (6): Kayode Adeboye; Worthing Hospital (5): Mandy Grocutt; Royal Oldham Hospital (4): Gabrielle May; Royal United Hospitals Bath (4): David Watson; Arrows Park Hospital (3): Andrea Wootten; Pinderfields General Hospital (3): Sarah Robertshaw; Birmingham Heartlands Hospital (2): Susan Dorrian; Gwynedd Hospital, Bangor (2): Rob Perry; Newham University Hospital (2): Tim Harris; University Hospital Lewisham (2): Hyun Choi; Western Infirmary (2): Claire McGroarty; Worcestershire Royal Hospital (1): Paul Shone; Yeovil District Hospital (1): David Maritz. *Malaysia (1567)*—Hospital Sungai Buloh (410): Sabariah Jamaluddin, Julina Noor, Norizan Rosli, Leonard Leong Sang Xian and Yong De Jun; Hospital Sultanah Bahiyah (241): Fatahul Mohamed, Cheng Hee Song, Arman Hawari, Leong Yuen Chin, and Hardawani Mohd Hussein; Hospital Sultanah Nur Zahirah (205): Mohd Lotfi, Hafiq Hamid, Nujaimin Udin, Peck Lian, and See Choo; Penang General Hospital (161): Kwanhathai Wong, Fathiyah Gani, Mardhiah Jusoh, and Darrsini Rajakumar; Miri General Hospital (111): Chia Boon Yang, Nur Shahidah Binti Dzulkiilee, Wong Chok Ky, and Muhaamin Azwan Bin Mohd Azman; Hospital Raja Permaisuri Bainun (101): Adi Bin Osman, Azma Haryaty Ahmad, Ramzuzaman Ismail, and Si Qi Lai; Hospital Sultanah Aminah (94): Mohd Amin Bin Mohidin, Norwani Binti Deraman, and Salliza Binti Selamat; Hospital Tuanku Fauziah (72): Ida Abidin, Nurkhairulnizam Halim, and Zuraini Bakar; Hospital Tengku Ampuan Afzan (41): Zainalabidin Mohamed Ismail, Badrul Hisham, and Ruhaida Kamal; Hospital Sultan Abdul Halim (36): Zainal Effendy and Mashitah Ismail; Hospital Seberang Jaya (30): Noor Azleen and Liu Yeo Seng; Universiti Sains Malaysia (26): Kamarul Aryffin Baharuddin and Regunath Kandasamy; Hospital Langkawi (13): Azlan Kamalludin; Hospital Kulim (8): Shamsul Asmee; Hospital Kemaman (7): Mohd Fadzil; Hospital Segamat (6): Ahmad Basitz; Hospital Pakar Sultanah Fatimah (5): Norhaya Abdullah. *Georgia (771)*—High Technology Medical Center, University Clinic (751): Tamar Gogichaishvili, Giorgi Ingorokva, Shota Ingorokva, lamze Agdgomelashvili, Kote Mumladze, Ioseb Maisuradze, and Iulia Kugusheva; Archangel St Michael Multiprofile Clinical Hospital (18): Buba Shalamberidze; City Hospital 1 (2): Gia Tomadze. *Spain (425)*—Hospital Regional Universitario Carlos Haya (102): Juan Fernandez-Ortega, Raimundo Seara-Valero, Guillermo Ibañez-Botella, Victoria Garcia-Martinez; Hospital Alvaro Cunqueiro VIGO (82): Melida Garcia Martul, Santiago Freitas Ramos, Guillermo Lago Preciado; Hospital Universitario Virgen del Rocío (77): Claudio Garcia-Alfaro, Angeles Munoz-Sanchez, Rafael Bellido-Alba;

Hospital General Universitario de Ciudad Real (67): Carmen Corcobado, Ana Bueno, Alfonso Ambros; Complejo Hospitalario de Navarra (44): JuanTihista Jimenez, Jose Roldan Ramirez; Hospital Torrecardenas (21): José Martín; Hospital de Lucus Augusti (13): Laura Inés Rodríguez; Hospital Clinico de Barcelona (9): Jaime Fontanals; Hospital Universitario Puerta del Mar de Cadiz (9): José Manuel Jiménez-Moragas; Hospital General Universitario De Albacete (1): Joaquín Paya Berbegal. *Nigeria* (409)—National Hospital Abuja (64): Olaomi Oluwole, Raji Mahmud, and Nancy Ukwu; Lagos University Teaching Hospital (55): Femi Bankole, Abidemi Oseni, and Barnidele Adebayo; University College Hospital, Ibadan (53): Adefolarin Malomo, Liadi Tiamiyu, and Adefisayo Adekanmbi; Olabisi Onabanjo University Teaching Hospital (38): Lateef Thanni and Ayodeji Olubodun; Federal Medical Centre Abeokuta (36): Fidelis Ojebunu and Michael Uwaezuoke; Obafemi Awolowo University Teaching Hospitals (31): Edward Komolafe and Oluwafemi Owagbemi; Lagos State Accident and Emergency Centre (22): Fatai Ishola; Bowen University Teaching Hospital Ogbomoso (17): Adewumi Durodola; Federal Medical Centre Lokoja (13): Ukpong Udoffa, Federal Medical Centre Bida (12): Adeniran James; Abubakar Tafawa Balewa University Teaching Hospital (11): Azeez Tella; Irrua Specialist Teaching Hospital (9): Andrew Dongo; Federal Medical Centre Umuahia (8): Uchechi Ekpemiro; Nnamdi Azikiwe University Teaching Hospital (8): Stanley Anyanwu; State Hospital, Ijaiye, Abeokuta (8): Nafiu Aigoro; University of Nigeria Teaching Hospital Enugu (7): Wilfred Mezue; Jos University Teaching Hospital (6): Danaan Shilong; University of Benin Teaching Hospital (6): Abiodun Azeez; Federal Medical Centre Ido-Ekiti (2): Olakunle Babalola; Federal Teaching Hospital, Gombe (2): Mohammed Ibrahim; University of Abuja Teaching Hospital (1): Joseph Obande. *Colombia* (335)—Hospital Pablo Tobon Uribe (127), Alfredo Constain Franco, Edwin Vasquez Salazar, Sebastian Betancur Londoño, and Viviana Medina Cardona; Hospital Universitario San Vicente Fundacion (112): Carlos Morales; Santiago Upegui; Santiago Naranjo; July Agudelo; Fundacion Valle del Lili (96): Jorge Mejia-Mantilla, Sandra Carvajal, and Yidhira Fajardo-Gaviria. *Nepal* (255)—Neuro Hospital (103): Yam Roka, Ushma Ghising, Narayani Roka, and Manzil Shrestha; National Institute of Neurological and Allied Sciences (64): Upendra Devkota, Bivek Vaidya, and Pankaj Nepal; Kathmandu Medical College Teaching Hospital (47): Amit Thapa and Bidur KC; Chitwan Medical College Teaching Hospital (24): Ajit Shrestha; Bir Hospital (11): Rajiv Jha; B & B Hospital Ltd. (6): Prabin Shrestha. *Albania* (214)—University Hospital of Trauma (214): Fatos Olldash, Irgen Hodaj, Erion Spaho, Asllan Selaj, and Nirian Bendo. *Japan* (165)—Matsudo City Hospital (64): Tomohisa Shoko, Hideki Endo, and Atsushi Senda; Senshu Trauma and Critical Care Centre (61): Yasushi Hagihara, Takashi Fuse, and Naohisa Masunaga; Tokyo Medical and Dental University (28): Yasuhiro Otomo and Ryuichiro Egashira; Teikyo University Hospital (12): Takahiro Ohnuki. *United Arab Emirates* (126)—Al Qassimi Hospital (126): Satish Krishnan, Alya AlMazmi, Subrata Saha, and Alexander Suvarov. *Myanmar* (121)—1000 Bedded Nay Pyi Taw Hospital (121): Than Latt Aung, Kaung Myat Tun, Tint Tint Khaing, and Thinzar Maw. *Cameroon* (116)—Yaounde Central Hospital (38): Vincent Djentcheu and Orlane Ndome; Hopital General Douala (31): Mireille Mouri and André Mbida; Hopital Laquintinie de Douala (28): Joseph Fondop and N'Diaye; Yaounde General Hospital (19): Mba Sebastien. *Afghanistan* (87)—Nangarhar University Teaching Hospital (87): Abdul Azim, Jan Adil, and Zabiullah Amiry. *Mexico* (79)—Hospital Regional 25 IMSS (24): Jorge Loria-Castellanos; Hospital General Jose G Parres (21): Nancy Guevara Rubio; Hospital General de Uruapan, Pedro Daniel Martinez (11): Patricia Ortega Leon; Hospital General Regional No 1 (10): Francisco Estrada; Hospital General de Zona 197 (8): Erandy Montes de Oca-García; Hospital General Regional Bernardo Sepulveda (3): Hafid Sanchez; Hospital General La Perla (2): Angélica Soria. *Italy* (72)—Azienda Ospedaliera Universitaria Senese (35): Paola Bonucci and Federico Franchi; Fondazione Poliambulanza (19): Alan Girardini; Spedali Civili Di Brescia (18): Frank Rasulo. *Iraq* (55)—Rozhawa Emergency Hospital (51): Qadamkhear Hama, Himdad Hameed, and Muhammad Basim; Rohelat Emergency Hospital (3): Qadamkhear Hama; Par Hospital (1): Qadamkhear Hama. *Cambodia* (45)—World Mate Emergency Hospital (45): Simon Stock and Eap Hourt. *Zambia* (44)—University Teaching Hospital Lusaka (40):

Yakub Mulla and Ali Ilunga; Kitwe Central Hospital (4): Jonathan Mulenga. *Romania* (35)—Timisoara County Hospital (17): Horia Ples; Spitalul Sf Pantelimon Bucharest (11): Adam Danil; Bagdasar-Arseni Emergency Clinical Hospital (5): Mircea Gorgan; Cluj County Emergency Hospital (2): Ioan Florian. *El Salvador* (28)—Hospital Nacional Rosales (28): Juan Tobar, Fernandez. *Egypt* (20)—Mataria Teaching Hospital (20): Hussein Khamis. *Slovenia* (15)—University Medical Centre Ljubljana (15): Dusan Vlahovic. *Ireland* (12)—Cork University Hospital (12): Conor Deasy. *Papua New Guinea* (10)—Port Moresby General Hospital (10): Bobby Wellsh. *Canada* (7)—Saint John Regional Hospital (7): James French. *Jamaica* (7)—Cornwall Regional Hospital (5): Jeffrey East; University Hospital of the West Indies (2): Jean Williams-Johnson. *Indonesia* (6)—Rumah Sakit Sekar Kamulyan (6): Antonius Kurniawan. *Kenya* (1)—Kenyatta National Hospital, University of Nairobi (1): Julius Kiboi.

Declaration of interests

We declare no competing interests.

Data sharing

Following publication of the primary and secondary analyses detailed in this statistical analysis plan, individual de-identified patient data, including a data dictionary, will be made available via our data sharing portal, The Free Bank of Injury and Emergency Research Data (freeBIRD) website indefinitely, which will allow for maximum utilisation of the data to improve patient care and advance medical knowledge. The trial protocol, statistical analysis plan, and trial publications will be freely available online.

Acknowledgments

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 Wellcome Trust (MRM0092111). Paul Atkinson, Saint John Regional Hospital, Canada received a \$10000 CAD grant from the New Brunswick Trauma Program to support the trial in Canada. The study was designed, conducted, analysed, and interpreted by the investigators, entirely independently of all funding sources. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the HTA, NIHR, UK National Health Service, or the UK Department of Health.

References

- Dewan M, Rattani A, Gupta S, et al. Estimating the global incidence of traumatic brain injury. *J Neurosurg* 2018; 1: 1–18.
- Perel P, Roberts I, Bouamra O, Woodford M, Mooney J, Lecky F. Intracranial bleeding in patients with traumatic brain injury: a prognostic study. *BMC Emerg Med* 2009; 9: 15.
- Oertel M, Kelly DF, McArthur D, et al. Progressive hemorrhage after head trauma: predictors and consequences of the evolving injury. *J Neurosurg* 2002; 96: 109–16.
- Narayan RK, Maas AI, Servadei F, Skolnick BE, Tillinger MN, Marshall LF. Progression of traumatic intracerebral hemorrhage: a prospective observational study. *J Neurotrauma* 2008; 25: 629–39.
- The CRASH-2 collaborators. 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* 2010; 376: 23–32.
- The CRASH-2 collaborators. The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. *Lancet* 2011; 377: 1096–101.
- Gayet-Ageron A, Prieto-Merino D, Ker K, Shakur H, Ageron F, Roberts I. Effect of treatment delay on the effectiveness and safety of antifibrinolytics in acute severe haemorrhage: a meta-analysis of individual patient-level data from 40138 bleeding patients. *Lancet* 2018; 391: 125–32.
- Zhang J, He M, Song Y, Xu J. Prognostic role of D-dimer level upon admission in patients with traumatic brain injury. *Medicine* 2018; 97: e11774.

For freeBIRD see <http://freebird.lshmt.ac.uk>

For the trial protocol see <http://www.txcentral.org/>

- 9 Perel P, Al-Shahi Salman R, Kawahara T, Morris Z, Prieto-Merino D. 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 Technol Assess* 2012; **16**: 1–54.
- 10 Yuthakasemsunt S, Kittiwatanagul W, Piyavechvirat P, Thinkamrop B, Phuenpathom N, Lumbiganon P. Tranexamic acid for patients with traumatic brain injury: a randomized, double-blinded, placebo-controlled trial. *BMC Emerg Med* 2013; **13**: 20.
- 11 Roberts I, Belli A, Brenner A et al. Tranexamic acid for significant traumatic brain injury (the CRASH-3 trial): statistical analysis plan for an international, randomised, double-blind, placebo-controlled trial. *Wellcome Open Res* 2018; **3**: 86.
- 12 Hijazi N, Abu Fanne R, Abramovitch R, et al. Endogenous plasminogen activators mediate progressive intracranial hemorrhage after traumatic brain injury. *Blood* 2015; **125**: 2558–67.
- 13 Medcalf RL. The traumatic side of fibrinolysis. *Blood* 2015; **125**: 2457–58.
- 14 World Medical Association. WMA Declaration of Helsinki—ethical principles for medical research involving human subjects. July 9, 2018. <https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects> (accessed July 27, 2019).
- 15 Dewan Y, Komolafe EO, Mejia-Mantilla JH, Perel P, Roberts I, Shakur H. CRASH-3—tranexamic acid for the treatment of significant traumatic brain injury: study protocol for an international randomized, double-blind, placebo-controlled trial. *Trials* 2012; **13**: 87.
- 16 Rogers A, MacMahon S. Systematic underestimation of treatment effects as a result of diagnostic test inaccuracy: implications for the interpretation and design of thromboprophylaxis trials. *Thromb Haemost* 1995; **73**: 167–71.
- 17 Roberts I, Prieto-Merino D, Manno D. Mechanism of action of tranexamic acid in bleeding trauma patients: an exploratory analysis of data from the CRASH-2 trial. *Crit Care* 2014; **18**: 685.