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

*CRASH-2 trial collaborators**

Summary

Background Tranexamic acid can reduce bleeding in patients undergoing elective surgery. We assessed the effects of early administration of a short course of tranexamic acid on death, vascular occlusive events, and the receipt of blood transfusion in trauma patients.

Methods This randomised controlled trial was undertaken in 274 hospitals in 40 countries. 20 211 adult trauma patients with, or at risk of, significant bleeding were randomly assigned within 8 h of injury to either tranexamic acid (loading dose 1 g over 10 min then infusion of 1 g over 8 h) or matching placebo. Randomisation was balanced by centre, with an allocation sequence based on a block size of eight, generated with a computer random number generator. Both participants and study staff (site investigators and trial coordinating centre staff) were masked to treatment allocation. The primary outcome was death in hospital within 4 weeks of injury, and was described with the following categories: bleeding, vascular occlusion (myocardial infarction, stroke and pulmonary embolism), multiorgan failure, head injury, and other. All analyses were by intention to treat. This study is registered as ISRCTN86750102, Clinicaltrials.gov NCT00375258, and South African Clinical Trial Register DOH-27-0607-1919.

Findings 10 096 patients were allocated to tranexamic acid and 10 115 to placebo, of whom 10 060 and 10 067, respectively, were analysed. All-cause mortality was significantly reduced with tranexamic acid (1463 [14·5%] tranexamic acid group *vs* 1613 [16·0%] placebo group; relative risk 0·91, 95% CI 0·85–0·97; p=0·0035). The risk of death due to bleeding was significantly reduced (489 [4·9%] *vs* 574 [5·7%]; relative risk 0·85, 95% CI 0·76–0·96; p=0·0077).

Interpretation Tranexamic acid safely reduced the risk of death in bleeding trauma patients in this study. On the basis of these results, tranexamic acid should be considered for use in bleeding trauma patients.

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Introduction

Injuries are major causes of death worldwide.[1,2] Every year, more than a million people die as a result of road traffic injuries around the world. Road traffic injuries are the ninth leading cause of death globally, and such injuries are predicted to become the third leading cause of death and disability by 2020. About 1·6 million people die as a result of intentional acts of interpersonal, collective, or self-directed violence every year. More than 90% of trauma deaths occur in low-income and middle-income countries.[2] Haemorrhage is responsible for about a third of in-hospital trauma deaths and can also contribute to deaths from multiorgan failure.[3]

The haemostatic system helps to maintain circulation after severe vascular injury, whether traumatic or surgical in origin.[4] Major surgery and trauma trigger similar haemostatic responses, and in both situations severe blood loss presents an extreme challenge to the coagulation system. Part of the response to surgery and trauma is stimulation of clot breakdown (fibrinolysis), which might become pathological (hyper-fibrinolysis) in some cases.[4] Antifibrinolytic agents reduce blood loss in patients with both normal and exaggerated fibrinolytic responses to surgery, and do so without apparently increasing the risk of postoperative complications.[5]

Tranexamic acid is a synthetic derivative of the aminoacid lysine that inhibits fibrinolysis by blocking the lysine binding sites on plasminogen.[6] A systematic review of the randomised trials of tranexamic acid in patients undergoing elective surgery identified 53 studies including 3836 participants.[5] Tranexamic acid reduced the need for blood transfusion by a third (relative risk [RR] 0·61, 95% CI 0·54–0·70), with no significant reduction in mortality (0·61, 0·32–1·12).[5] Because the haemostatic responses to surgery and trauma are similar,[4] tranexamic acid might reduce mortality due to bleeding in trauma patients. However, up until now there have been no randomised trials of this drug in such patients.[7] We assessed the effects of the early administration of a short course of tranexamic acid on death, vascular occlusive events, and the receipt of blood transfusion in trauma patients with or at risk of significant haemorrhage.

Methods

Study design and patients

For the **CRASH-2 trial website** see http://www.crash2.LSHTM.ac.uk

CRASH-2 (Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage 2) is a large placebo-controlled trial of the effects of early administration of a short course of tranexamic acid on death, vascular occlusive events, and the receipt of blood transfusion. The trial was undertaken in 274 hospitals in 40 countries. The first patient was enrolled in May, 2005. The study aims, methods, and protocol have been reported previously. The trial protocol was peer-reviewed and published on *The Lancet* website in 2005.

For the **CRASH-2 protocol** see http://www.thelancet.com/protocol-reviews/05PRT-1

Adult trauma patients with significant haemorrhage (systolic blood pressure <90 mm Hg or heart rate >110 beats per min, or both), or who were considered to be at risk of significant haemorrhage, and who were within 8 h of injury, were eligible for the trial. Patients were included if the responsible doctor was substantially uncertain about whether or not to treat with tranexamic acid (ie, entry was governed by the uncertainty principle).[8] Patients for whom the responsible doctor considered that there was a clear indication for tranexamic acid were not randomly assigned. Similarly, patients for whom there was considered to be a clear contraindication to tranexamic acid treatment were not randomly assigned. However, when the responsible doctor was substantially uncertain as to whether or not to treat with this agent, these patients were eligible for randomisation.

Consent procedures at participating hospitals were established by local regulation and the appropriate ethics committees. Informed consent was obtained from patients if physical and mental capacity allowed. If patients could not give consent, proxy consent was obtained from a relative or representative. If a proxy was unavailable, then if permitted by local regulation, consent was deferred or waived. When consent was deferred or given by a proxy, the patient was informed about the trial as soon as possible and consent obtained for use of the data collected if needed.

Randomisation and masking

After eligibility had been confirmed and the locally approved consent procedures had been completed, patients were randomly assigned. Randomisation was balanced by centre, with an allocation sequence based on a block size of eight, generated with a computer random number generator. In hospitals in which telephone randomisation was not practicable we used a local pack system that selected the lowest numbered treatment pack from a box containing eight numbered packs. Apart from the pack number, the treatment packs were identical. The pack number was recorded on the entry form which was sent to the international trial coordinating centre in London, UK. Hospitals with reliable telephone access used the University of Oxford Clinical Trial Service Unit (CTSU) telephone randomisation service. The randomisation service used a minimisation algorithm balancing for sex, age, time since injury, type of injury (blunt or penetrating), Glasgow Coma Score, systolic blood pressure, respiratory rate, central capillary refill time, and country, taking into account what packs were available at that hospital. Once the treatment pack number was recorded, the patient was included in the trial whether or not the treatment pack was opened or the allocated treatment started. Both participants and study staff (site investigators and trial coordinating centre staff) were masked to treatment allocation.

Tranexamic acid and placebo ampoules were indistinguishable. Tranexamic acid was manufactured by Pharmacia (Pfizer, Sandwich, UK) and placebo by St Mary's Pharmaceutical Unit, Cardiff, UK. The treatment packs were prepared by an independent clinical trial supply company (Bilcare, Crickhowell, UK). Correct blinding and coding of ampoules was assured by independent random testing of each batch by high performance liquid chromatography to confirm the contents. Emergency unblinding was available by telephoning CTSU.

Procedures

Patients were randomly allocated to receive a loading dose of 1 g of tranexamic acid infused over 10 min, followed by an intravenous infusion of 1 g over 8 h, or matching placebo (0·9% saline). 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% saline (for use with the loading dose), a syringe and needle, stickers with the trial details and randomisation number (for attaching to infusion bags, data forms, and patient medical records), and instructions. Each box contained information leaflets for patients and their representatives, consent forms, and data collection forms. The stickers, instructions, leaflets, and forms were in local languages.

Outcome measures and prespecified subgroup analyses

The primary outcome was death in hospital within 4 weeks of injury. Cause of death was described by the following categories: bleeding, vascular occlusion (myocardial infarction, stroke, and pulmonary embolism), multiorgan failure, head injury, and other. Secondary outcomes were vascular occlusive events (myocardial infarction, stroke, pulmonary embolism, and deep vein thrombosis), surgical intervention (neurosurgery, thoracic, abdominal, and pelvic surgery), receipt of blood transfusion, and units of blood products transfused. Dependency was measured at hospital discharge, or on day 28 if still in hospital, with the 5-point Modified Oxford Handicap Scale. The scale was dichotomised into dead or dependent (dead, fully dependent requiring attention day and night, or dependent but not needing constant attention) or independent (some restriction in lifestyle but independent, minor symptoms, or no symptoms).[9] Data for the use of recombinant Factor VIIa and for gastrointestinal bleeding as a complication

were also collected. Because the expected complications of the trial treatment were collected on the outcome form, only adverse events that were serious, unexpected, and suspected to be related to the study treatment were reported separately. Outcomes were recorded if they occurred while the patient was still in hospital for up to 28 days after randomisation. Data were sent to the coordinating centre either electronically (by encrypted electronic data forms which could be sent by email or uploaded to a secure server) or by fax, and were entered onto a central database at the trial coordinating centre in London. We monitored the quality of the trial data using a combination of centralised statistical data checking and site visits at which patient outcome forms were compared with clinical case notes.[10]

We planned to report the effects of treatment on the primary outcome subdivided by four baseline characteristics: (1) estimated hours since injury (<1, 1–3, 3–8 h); (2) systolic blood pressure (≤75, 76–89, ≥90 mm Hg); (3) Glasgow Coma Score (severe 3–8, moderate 9–12, mild 13–15); and (4) type of injury (penetrating only or blunt, which included blunt and penetrating).

Statistical analyses

The statistical analysis plan was sent to all ethics committees and regulatory agencies before unblinding. Because the risk of death might be around 20%, and even a 2% survival difference (corresponding to an RR of death with tranexamic acid of 0·9) would be important, a trial of 20 000 patients was planned, which would then have an 85% chance of achieving a two-sided p value of less than 0·01 and a 95% chance of a two-sided p value of less than 0·05. All analyses were undertaken on an intention-to-treat basis. For each binary outcome, we calculated RRs and 95% CIs, and two-sided p values for statistical significance. The RR gives the number of times more likely (RR >1) or less likely (RR <1) an event is to happen in the tranexamic acid group compared with the placebo group. For analysis of the prespecified subgroups (primary outcome only) we calculated RRs with 99% CIs with two-sided p values. Heterogeneity in treatment effects across subgroups was assessed with χ^2 tests. We prespecified that unless there was strong evidence ($p<0·001$) against homogeneity of effects, the overall RR would be considered the most reliable guide to the approximate RRs in all subgroups. Means and SDs were estimated for count outcomes, and we calculated two-sided p values of the difference in means of logarithms. A complete case analysis, including only cases for which the relevant outcome data were available, was undertaken. There was no imputation for missing data. During the study, unblinded interim analyses were supplied by an independent statistician to the Data Monitoring and Ethics Committee.

This study is registered as ISRCTN86750102, Clinicaltrials.gov NCT00375258, and South African Clinical Trial Register DOH-27-0607-1919.

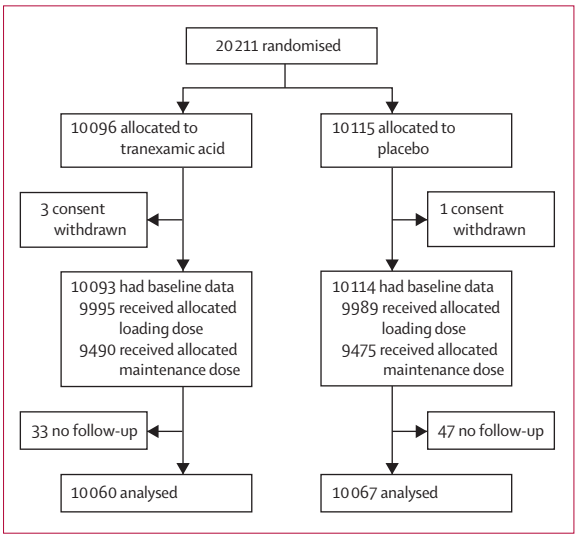

Figure 1: **Trial profile**

Role of the funding source

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

Results

Figure 1 shows the trial profile. 20 211 patients were randomly assigned to tranexamic acid or placebo (figure 1), of whom 20 116 were randomly assigned through the local pack system and 95 through telephone randomisation. The data from four patients were removed from the trial because their consent was withdrawn after randomisation. Five patients enrolled in the study were later found to be younger than 16 years. Age was unknown for four patients. 23 patients were enrolled more than 8 h after their injury. Time of injury was not known for 11 patients. Nine patients had haemorrhage from non-traumatic conditions. Three patients were given a pack that differed from that allocated. The planned consent procedures were not fully followed in 34 patients. The relevant ethics committees were informed and approval for use of data was obtained. All the patients, apart from the four in whom consent was withdrawn, were included in the analysis.

Treatment groups were balanced with respect to all baseline patient characteristics (table 1; the webappendix p 1 shows baseline data of patients with follow-up). Primary outcome data were available for 20 127 (99·6%) randomised patients, 10 060 allocated to tranexamic acid and 10 067 placebo, of whom 19 944 (99·1%) patients were known to have completed the loading dose and 18 965 (94·2%) the 8 h maintenance dose. 3076 (15·3%) patients died, of whom 1086 (35·3%) died on the day of randomisation (figure 2). There were 1063 deaths due to bleeding, of which 637 (59·9%) were on the day of randomisation.

See Online for webappendix

All-cause mortality was significantly reduced with tranexamic acid (table 2). The RR of death with tranexamic acid was 0·91 (95% CI 0·85–0·97, p=0·0035; table 2). The risk of death due to bleeding was significantly reduced (table 2). This effect was also apparent for deaths due to bleeding on the day of randomisation (282 [2·8%] tranexamic acid group *vs* 355 [3·5%] placebo group; RR 0·80, 95% CI 0·68–0·93, p=0·0036). There were 33 (0·3%) deaths in the tranexamic acid group versus 48 (0·5%) in the placebo group from vascular occlusion (table 2), including seven versus 22 deaths from myocardial infarction, eight versus five from stroke, and 18 versus 21 from pulmonary embolism, respectively. Deaths from multiorgan failure, from head injury, or due to other causes did not differ significantly in the tranexamic acid group versus the placebo group (table 2).

Vascular occlusive events (fatal or non-fatal) did not differ significantly, with 168 (1·7%) patients with one or more vascular occlusive events (myocardial infarction, stroke, pulmonary embolism, deep vein thrombosis) in patients allocated to tranexamic acid versus 201 (2·0%) in those allocated to placebo (table 3).

Blood product transfusions were given to 5067 (50·4%) patients allocated to tranexamic acid versus 5160 (51·3%) allocated to placebo (table 3). Those allocated to tranexamic acid and transfused received a mean of 6·06 (SD 9·98) blood units, compared with a mean of 6·29 (10·31) for placebo. 4814 (47·9%) patients in the tranexamic acid group received one or more surgical intervention (neurosurgery, or chest, abdominal, or pelvic surgery) versus 4836 (48·0%) in the placebo group (table 3). Only 17 patients received treatment with recombinant Factor VIIa (13 in the tranexamic acid group *vs* four in the placebo group). 132 patients in each group had gastrointestinal bleeding (p=0·99).

Of patients allocated tranexamic acid, 3453 (34·3%) were classified as dead or dependent at discharge or 28 days compared with 3562 (35·4%) of those allocated to placebo (RR 0·97, 95% CI 0·93–1·00; p=0·12). 1483 (14·7%) patients in the tranexamic acid group had no symptoms at discharge or day 28 versus 1334 (13·3%) in the placebo group (table 3). 1846 (9·2%) patients were still in hospital at 28 days (958 *vs* 888).

We had prespecified that unless there was strong evidence (p<0·001) against homogeneity of effects, the overall RR would be regarded as the most reliable guide as to the approximate RRs in all subgroups. We recorded no such evidence of heterogeneity for any of the prespecified subgroup analyses: systolic blood pressure (heterogeneity p=0·51); Glasgow Coma Score at randomisation (p=0·50); type of injury (p=0·37); or time from injury to randomisation (p=0·11). For the last of these analyses, because of digit preference (the tendency when reporting figures to round to specific digits) the number of patients in the early category (<1 h) was low and the subgroup estimate was imprecise. We therefore (post hoc) defined the early category as those treated less than or equal to 1 h from injury (figure 3).

	Tranexamic acid (n=10 093)	Placebo (n=10 114)
Sex		
Men	8439 (83·6%)	8496 (84·0%)
Women	1654 (16·4%)	1617 (16·0%)
Not known	0	1 (0·01%)
Age (years)		
Mean (SD)	34·6 (14·1)	34·5 (14·4)
<25*	2783 (27·6%)	2855 (28·2%)
25–34	3012 (29·8%)	3081 (30·5%)
35–44	1975 (19·6%)	1841 (18·2%)
>44	2321 (23·0%)	2335 (23·1%)
Not known	2 (0·02%)	2 (0·02%)
Time since injury (h)		
Mean (SD)	2·8 (2·2)	2·9 (2·6)
≤1	3756 (37·2%)	3722 (36·8%)
>1–≤3	3045 (30·2%)	3006 (29·7%)
>3†	3287 (32·6%)	3380 (33·4%)
Not known	5 (0·05%)	6 (0·06%)
Type of injury		
Blunt‡	6812 (67·5%)	6843 (67·7%)
Penetrating	3281 (32·5%)	3271 (32·3%)
Systolic blood pressure (mm Hg)		
≤75	1566 (15·5%)	1608 (15·9%)
76–89	1615 (16·0%)	1697 (16·8%)
≥90	6901 (68·4%)	6791 (67·1%)
Not known	11 (0·11%)	18 (0·18%)
Respiratory rate (per min)		
<10	160 (1·6%)	149 (1·5%)
10–29	8355 (82·8%)	8436 (83·4%)
>29	1491 (14·8%)	1429 (14·1%)
Not known	87 (0·86%)	100 (0·99%)
Central capillary refill time (s)		
≤2	3432 (34·0%)	3406 (33·7%)
3–4	4665 (46·2%)	4722 (46·7%)
>4	1699 (16·8%)	1672 (16·5%)
Not known	297 (2·9%)	314 (3·1%)
Heart rate (beats per min)		
<77	875 (8·7%)	871 (8·6%)
77–91	1727 (17·1%)	1770 (17·5%)
92–107	2556 (25·3%)	2546 (25·2%)
>107	4872 (48·3%)	4853 (48·0%)
Not known	63 (0·62%)	74 (0·73%)
Glasgow Coma Score (total)		
Severe (3–8)	1799 (17·8%)	1839 (18·2%)
Moderate (9–12)	1353 (13·4%)	1351 (13·4%)
Mild (13–15)	6934 (68·7%)	6908 (68·3%)
Not known	7 (0·07%)	16 (0·16%)
Any protocol violation	39 (0·4%)	39 (0·4%)

Data are number (% of group total), unless otherwise indicated. *Includes five patients younger than 16 years. †Includes 23 patients randomly assigned more than 8 h after injury. ‡Includes patients with both blunt and penetrating and those with only blunt injuries.

Table 1: **Baseline data of participants**

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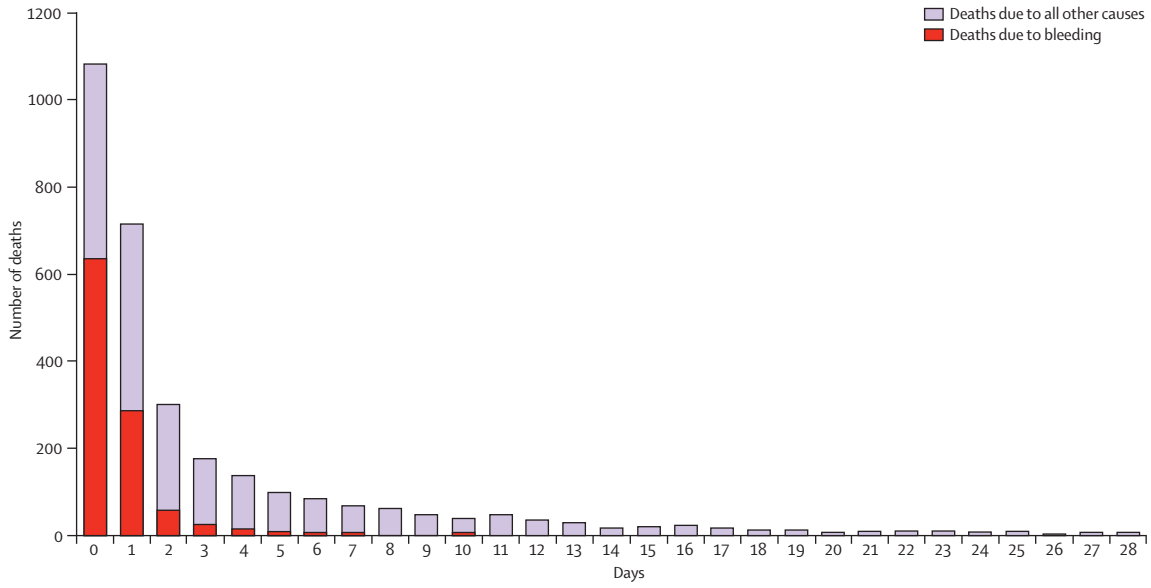

Figure 2: **Mortality by days from randomisation**

	Tranexamic acid (n=10 060)	Placebo (n=10 067)	RR (95% CI)	p value (two-sided)
Any cause of death	1463 (14·5%)	1613 (16·0%)	0·91 (0·85–0·97)	0·0035
Bleeding	489 (4·9%)	574 (5·7%)	0·85 (0·76–0·96)	0·0077
Vascular occlusion*	33 (0·3%)	48 (0·5%)	0·69 (0·44–1·07)	0·096
Multiorgan failure	209 (2·1%)	233 (2·3%)	0·90 (0·75–1·08)	0·25
Head injury	603 (6·0%)	621 (6·2%)	0·97 (0·87–1·08)	0·60
Other causes	129 (1·3%)	137 (1·4%)	0·94 (0·74–1·20)	0·63

Data are number (%), unless otherwise indicated. RR=relative risk. *Includes myocardial infarction, stroke, and pulmonary embolism.

Table 2: **Death by cause**

No emergency unblinding was needed, and there were no adverse events regarded as serious, unexpected, or suspected to be related to the study treatment.

Discussion

The results show that the early administration of tranexamic acid to trauma patients with, or at risk of, significant bleeding reduces the risk of death from haemorrhage with no apparent increase in fatal or non-fatal vascular occlusive events. All-cause mortality was significantly reduced with tranexamic acid.

The trial inclusion criteria were clinical and did not depend on the results of laboratory tests. Patients were enrolled if they were judged to have on-going significant haemorrhage, as evidenced by hypotension or tachycardia, or if they were considered to be at risk of significant haemorrhage—eg, patients with compensated haemorrhage and stable vital signs, or those in whom bleeding might have stopped but who might recommence bleeding following volume resuscitation. The use of clinical inclusion criteria is appropriate in the context of traumatic bleeding in which a range of clinical signs need to be assessed when establishing the presence or absence of haemorrhage, while taking into account remedial measures such as fluid resuscitation. The clinical inclusion criteria, and the large numbers of patients studied in a range of different health-care settings, help these results to be generalised widely.

Our study had strengths and limitations. The randomisation methods ensured that participating clinicians did not have foreknowledge of treatment allocation. Baseline prognostic factors were well balanced. All analyses were on an intention-to-treat basis and, because almost all randomised patients were followed up, there was no need to use imputation methods for missing data.[11] The primary endpoint was all-cause mortality, and the observed reduction in mortality with tranexamic acid was both statistically significant and clinically important. The diagnosis of traumatic haemorrhage can be difficult, and some of the included patients might not have been bleeding at the time of randomisation. This misdiagnosis would have reduced the power of the trial to show an effect of tranexamic acid on mortality from bleeding. Nevertheless, we recorded a significant reduction in death due to bleeding.

	Tranexamic acid (n=10 060)	Placebo (n=10 067)	RR (95% CI)	p value
Vascular occlusive events*				
Any vascular occlusive event	168 (1·7%)	201 (2·0%)	0·84 (0·68–1·02)	0·084
Myocardial infarction	35 (0·3%)	55 (0·5%)	0·64 (0·42–0·97)	0·035
Stroke	57 (0·6%)	66 (0·7%)	0·86 (0·61–1·23)	0·42
Pulmonary embolism	72 (0·7%)	71 (0·7%)	1·01 (0·73–1·41)	0·93
Deep vein thrombosis	40 (0·4%)	41 (0·4%)	0·98 (0·63–1·51)	0·91
Need for transfusion and surgery				
Blood product transfused	5067 (50·4%)	5160 (51·3%)	0·98 (0·96–1·01)	0·21
Any surgery	4814 (47·9%)	4836 (48·0%)	1·00 (0·97–1·03)	0·79
Neurosurgery	1040 (10·3%)	1059 (10·5%)	0·98 (0·91–1·07)	0·67
Chest surgery	1518 (15·1%)	1525 (15·1%)	1·00 (0·93–1·06)	0·91
Abdominal surgery	2487 (24·7%)	2555 (25·4%)	0·97 (0·93–1·02)	0·28
Pelvic surgery	683 (6·8%)	648 (6·4%)	1·05 (0·95–1·17)	0·31
Median (IQR) units of blood product transfused†	3 (2–6)	3 (2–6)	..	0·59‡
Dependency				
No symptoms	1483 (14·7%)	1334 (13·3%)	1·11 (1·04–1·19)	0·0023
Minor symptoms	3054 (30·4%)	3061 (30·4%)	1·00 (0·96–1·04)	0·94
Some restriction	2016 (20·0%)	2069 (20·6%)	0·97 (0·92–1·03)	0·36
Dependent (not requiring constant attention)	1294 (12·9%)	1273 (12·6%)	1·02 (0·95–1·09)	0·63
Fully dependent	696 (6·9%)	676 (6·7%)	1·03 (0·93–1·14)	0·57
Alive (disability status not known)	54 (0·5%)	41 (0·4%)	..	..
Dead	1463 (14·5%)	1613 (16·0%)	0·91 (0·85–0·97)	0·0035

Data are number (%), unless otherwise indicated. Counts are for numbers of patients with at least one such event. RR=relative risk. *Includes both fatal and non-fatal events. †Transfused patients only. ‡Analysis used logarithmic transformation of mean units of blood products transfused.

Table 3: **Vascular occlusive events, need for transfusion and surgery, and level of dependency**

Although we recorded no increased risk of non-fatal vascular occlusive events with tranexamic acid, the precision of the estimates was low and we cannot exclude the possibility of some increase in risk. In the context of outcome assessment in clinical trials, estimates of the RR are unbiased even when the sensitivity of diagnosis is imperfect, provided that there are few false positives (high specificity).[12] Therefore, we sought high specificity in the diagnosis of non-fatal vascular occlusive events and stipulated that occlusive events should be recorded only when there was clear clinical evidence. As a result, we might have under-reported the frequency of these events. However, our estimates of the RR of non-fatal occlusive events should be unbiased.[12]

One weakness of this trial is that it provides limited insight into how tranexamic acid reduces the risk of death in bleeding trauma patients. Early coagulation abnormalities are frequent in severely injured trauma patients and are associated with substantially increased mortality.[13] Recent research showing that hyperfibrinolysis is a common feature of these abnormalities raises the possibility that antifibrinolytic agents such as tranexamic acid might operate via this mechanism.[13] Furthermore, intravenous tranexamic acid administration has an early (within 4 h) antifibrinolytic effect.[14] However, although this mechanism is plausible, because we did not measure fibrinolytic activity in this trial we cannot conclude that this agent acts by reducing fibrinolysis, rather than another mechanism. Further studies are needed into the mechanism of action of tranexamic acid in bleeding trauma patients. Measurement of blood loss is difficult in trauma patients. Much of the bleeding occurs at the scene of the injury and the bleeding that occurs in hospital is often concealed and difficult to quantify, such as, for example, bleeding into the chest, abdomen, pelvis, and soft tissues. However, we did not find any substantial reduction in the receipt of a blood transfusion or the amount of blood transfused in trauma patients. This finding could be an indication of the difficulty of accurate estimation of blood loss in trauma patients when assessing the need for transfusion. Another possible explanation is that after the loading dose, tranexamic acid was infused over 8 h, whereas decisions about transfusion are made soon after admission. Finally, fewer deaths occurred in patients allocated to tranexamic acid than to placebo, and the patients who survived as a result of tranexamic acid administration would have had a greater opportunity to receive a blood transfusion (competing risks).

The tranexamic acid loading dose was given within 8 h of injury, followed by a maintenance infusion over 8 h. We chose the early administration of a short course of tranexamic acid because most deaths from bleeding occur on the day of the injury and we postulated that the drug would act by reducing bleeding. Generally, after the first day, the risk of death from haemorrhage is

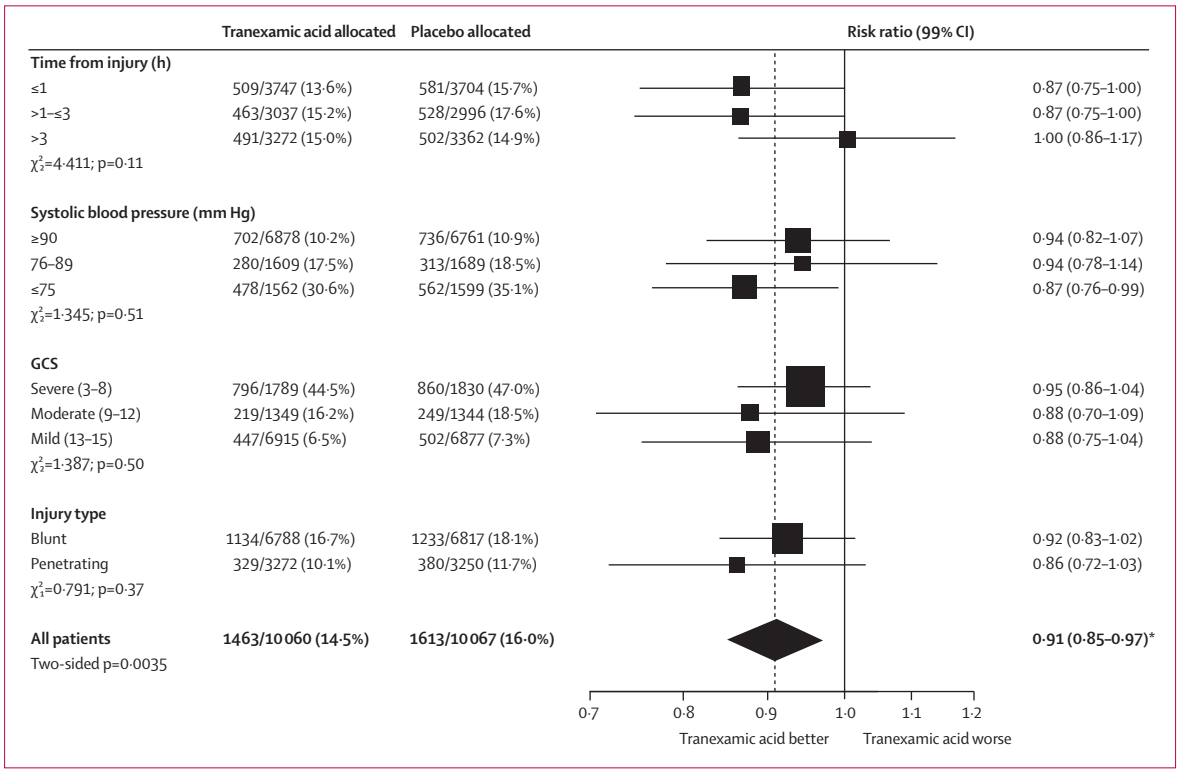

***Figure 3*: All-cause mortality by subgroups**
GCS=Glasgow Coma Score. *95% CI.

reduced but the risk of vascular occlusive events might remain. We therefore selected a regimen that would allow for the effect of tranexamic acid on the early risk of haemorrhage without extending into the period when the risk of vascular occlusive events might be increased by this treatment. The absence of any increase in vascular occlusion with tranexamic acid, whether fatal or non-fatal, provides reassurance that this regimen is safe. Although the effect of this drug on all-cause mortality did not vary substantially according to the time from injury, there was some suggestion that early treatment might be more effective. However, even if this were not the case, the fact that most deaths from haemorrhage occur in the first few hours after injury implies that every effort should be made to treat patients as soon as possible.[15–17]

The dose of tranexamic acid used in this trial was based on studies of this drug in surgical patients in which loading doses range from 2·5 mg/kg to 100 mg/kg, and maintenance doses from 0·25 mg/kg/h to 4 mg/kg/h, delivered over 1–12 h.[5] Findings from studies of the effect of different doses of tranexamic acid on blood loss and blood transfusion showed no significant difference between high and low doses. Studies in cardiac surgery have noted that a 10 mg/kg loading dose of tranexamic acid followed by an infusion of 1 mg/kg/h produces plasma concentrations sufficient to inhibit fibrinolysis, and that a larger dose does not provide any additional haemostatic benefit.[18,19] In emergency situations, the administration of a fixed dose is practicable since determining the weight of a seriously injured patient can be difficult. We therefore selected a fixed dose within the range shown to inhibit fibrinolysis and provide haemostatic benefit that would be efficacious for larger patients (>100 kg) but also safe in smaller patients (<50 kg), to the extent that the dose per kg that smaller patients would receive has been used in surgical trials without adverse effects. The possibility that a higher dose of tranexamic acid would have a greater treatment effect remains open to debate and warrants further study.

The knowledge that tranexamic acid reduces the risk of death from traumatic bleeding raises the possibility that it might also be effective in other situations in which bleeding can be life threatening or disabling. Traumatic brain injury is commonly accompanied by intracranial bleeding, which can develop or worsen after hospital admission. Traumatic intracranial haemorrhage is associated with an increased risk of death and disability, and irrespective of location, haemorrhage size is strongly correlated with outcome.[20–22] If tranexamic acid reduced intracranial bleeding after isolated traumatic brain injury, then patient outcomes might be improved. Studies that assess the effect of tranexamic acid on the extent of intracranial bleeding are needed.

Tranexamic acid might also have a role in bleeding conditions apart from traumatic injury. Post-partum

haemorrhage is a leading cause of maternal mortality, accounting for about 100 000 maternal deaths every year.[23] Although evidence suggests that this drug reduces post-partum bleeding, the quality of the existing trials is poor and none has been large enough to assess the effect of tranexamic acid on endpoints that are important to women.[24] A large trial is being undertaken to assess the effect of tranexamic acid on the risk of death and hysterectomy in women with post-partum haemorrhage.[25]

In conclusion, tranexamic acid could be given in a wide range of health-care settings, and safely reduced the risk of death in bleeding trauma patients in our study. The option to use tranexamic acid should be available to doctors treating trauma patients in all countries, and this drug should be considered for inclusion on the WHO List of Essential Medicines. On the basis of these results, tranexamic acid should be considered for use in bleeding trauma patients.

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Conflicts of interest

Members of the Writing Committee declare that they have no conflicts of interest.

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Antifibrinolytic therapy: new data and new concepts

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Activation of the fibrinolytic system is an integral part of vascular haemostatic mechanisms to maintain vascular patency. The basis of fibrinolysis is the conversion of the inactive substrate plasminogen to plasmin, an enzyme that cleaves fibrin but also has pleiotropic effects.[1,2] Multiple mechanisms are responsible for generating plasmin, including endothelial activation and release of tissue plasminogen activator, and contact activation and kallikrein-mediated plasmin activation.[1–3] Tissue-type and urokinase-type are the two major plasminogen activators expressed in many cell types and tissues.[3] As part of the haemostatic balance, plasmin generation and activity are also modulated by multiple inhibitors that include plasminogen activator inhibitor 1, thrombin-activatable fibrinolysis inhibitor, and α_2-antiplasmin.[1–3] Thus fibrinolysis involves several regulatory mechanisms under physiological conditions.

However, after the extensive tissue injury that occurs with trauma or surgery, the equilibrium is shifted and fibrinolysis that occurs is considered to be an important contributor to bleeding and coagulopathy.[4] In surgical patients, many studies reported the use of antifibrinolytic agents to decrease bleeding and need for allogeneic transfusions.[5,6] The agents most commonly used are the lysine analogues, ε-aminocaproic acid and tranexamic acid, and aprotinin. Lysine analogues interfere with the binding of plasminogen to fibrin, necessary for activating plasmin, whereas aprotinin is a direct plasmin inhibitor. Thus inhibition of fibrinolysis with antifibrinolytics reduces bleeding after tissue injury, as has been extensively studied in surgical patients.

In *The Lancet* today, the CRASH-2 investigators[7] report the use of tranexamic acid in trauma patients with or at risk for substantial bleeding.[7] CRASH-2 evaluated an impressive 20 211 trauma patients randomised and treated within 8 h of injury with either 2 g tranexamic acid (1 g load, then 1 g over 8 h) or placebo. In-hospital mortality within 4 weeks of injury was the primary outcome, while vascular occlusive events, transfusions, or surgical interventions were secondary outcomes. All-cause mortality was 14·5% in the tranexamic acid group (1463/10 060) compared with 16·0% with placebo (1613/10 067; relative risk 0·91, 95% CI 0·85–0·97; p=0·0035). Bleeding-related mortality was also reduced (4·9% *vs* 5·7%, respectively), without an increase in fatal or non-fatal vascular occlusive events. Despite the reduction in mortality, there were no statistically significant differences in transfusion requirements in patients receiving tranexamic acid or placebo.

A crucial aspect of the original idea for the study was to reduce bleeding, an important cause of mortality after trauma, by use of an antifibrinolytic agent. Because tissue injury in trauma and surgery are similar, the investigators hypothesised that tranexamic acid could reduce mortality. Although there were no statistical differences in transfusion between the groups, how inhibition of fibrinolysis might have reduced mortality is important. The study did not show an antifibrinolytic effect on the basis of laboratory values; however, the tranexamic acid dose of 2 g administered over 8 h is sufficient to inhibit fibrinolytic activity.[8] However, there

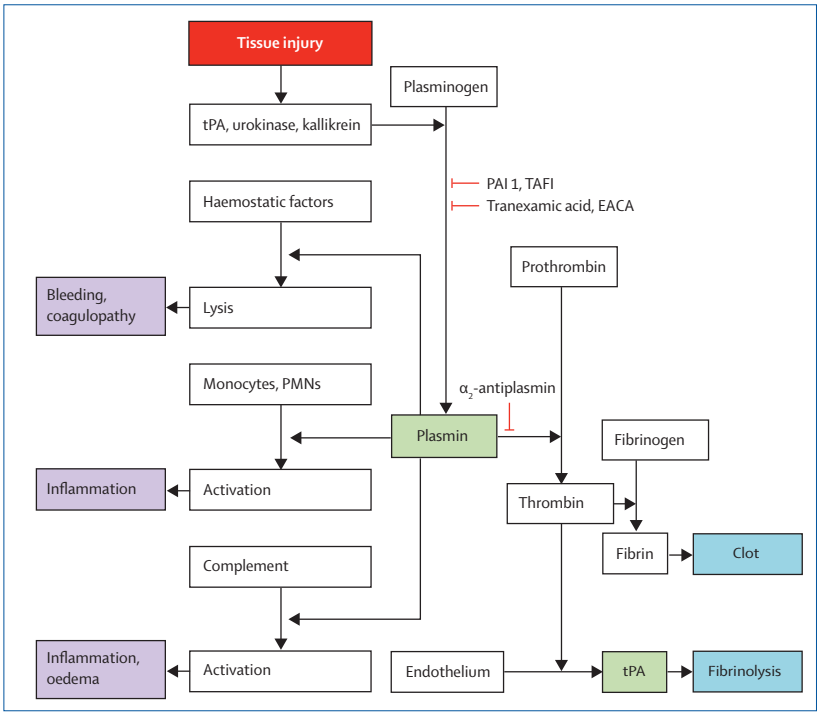

Figure: **Tissue injury and fibrinolysis**
After trauma, tissue injury shifts the complex balance of fibrinolysis to additional plasmin generation, and activation that increases coagulopathy, inflammatory responses, and bleeding. Multiple pathways are responsible for generation of plasmin, including endothelial activation and release of tissue plasminogen activator (tPA), contact activation, and kallikrein-mediated plasmin activation. Plasmin generation and activity are also inhibited by plasminogen activator inhibitor 1 (PAI 1), thrombin-activatable fibrinolysis inhibitor (TAFI), lysine analogues (tranexamic acid and ε-aminocaproic acid [EACA]), and α_2-antiplasmin. Plasmin generation after tissue injury can induce many other responses, including thrombin generation and cleavage of fibrinogen to fibrin. Plasmin also binds and activates monocytes, neutrophils, platelets, and endothelial cells, to increase proinflammatory responses and multiorgan system-failure. Attenuation of these pathophysiological responses with tranexamic acid might provide additional mechanisms to restore haemostatic balance and control of plasmin generation and fibrinolysis, as shown in CRASH–2. PMNs=polymorphonuclear leucocytes.

might be additional beneficial effects to inhibiting plasmin beyond clot lysis.

Plasmin can induce many other responses that contribute to coagulopathy and bleeding, including further activation of thrombin from prothrombin, cleavage of fibrinogen and fibrin to create fibrin(ogeno) lysis, and cleavage of receptors on platelets (including glycoprotein Ib and IIb/IIIa receptors).[1,2,9] In CRASH-2, there were 93 fewer patients receiving blood transfusions in the tranexamic acid group than in the placebo group. Plasmin also produces proinflammatory effects by binding and activating monocytes, neutrophils, platelets, and endothelial cells, and complement-releasing lipid mediators and cytokines, and by inducing proinflammatory genes.[3,10] Thus plasmin exhibits a broad spectrum of proinflammatory responses that could influence pathophysiological responses and multiorgan system-failure that might be attenuated with antifibrinolytic agents. A recent report supports this concept, by reporting that antifibrinolytic therapy can improve mortality in high-risk patients undergoing cardiac surgery.[11]

A note of caution is warranted about tranexamic acid. After cardiac surgery, more cases of postoperative convulsive seizures are being reported, a finding temporally coincident with tranexamic acid doses that are 2–10 fold higher than those used in CRASH-2.[12] A proposed mechanism for seizures is the structural similarity of tranexamic acid to γ-aminobutyric acid as a potential cause of neurotoxicity.

CRASH-2 is an important example of the complex relations between coagulation, fibrinolysis, inflammation, and outcomes after tissue injury.[4] Today's study shows that inhibition of fibrinolysis with tranexamic acid after major trauma is an important mechanism to reduce mortality. The similarities of tissue injury after trauma and surgery create a novel model for antifibrinolytic therapy with tranexamic acid. However, caution is needed before extrapolation of the results of CRASH-2 to other antifibrinolytic agents until they have been studied in a similarly robust manner.

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does a specific middle-age risk factor represent the status of that factor long before and after its measurement? The answer might be less of an issue with BMI than for the intermediate risk factors that might develop. This issue is especially pertinent in children and young adults with high BMI because they are more likely to develop risk factors for cardiovascular disease by middle age than are those with low BMI. Moreover, because the relations between body anthropometry and risk factors for cardiovascular disease were cross-sectional, additional consideration of changes in body size might be relevant for prediction of subsequent risk.

Do the new data from the Emerging Risk Factors Collaboration mean that we should stop measuring BMI? On the contrary, BMI continues to be useful as an indicator of adiposity, despite its obvious and occasional misrepresentation of muscular people and lack of sensitivity to body shape and composition. BMI used with good clinical judgment is highly appropriate in adults because it is so strongly associated with chronic disease risk, although we caution that it is correlated with height in children.[10] Many overweight or obese adolescents, young adults, and middle-aged individuals with few risk factors for cardiovascular disease will develop that risk relatively soon, so BMI should serve as an early warning, both to them and their general practitioners. But identification of which overweight individuals without risk factors for cardiovascular disease will go on to develop those risk factors, and ultimately clinical cardiovascular disease, remains a challenge—here, blood tests continue to be helpful.

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Tranexamic acid for trauma

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See Articles page 1096

After its publication in July, 2010, the CRASH-2 study[1] generated widespread interest in the early administration of the antifibrinolytic agent tranexamic acid to patients with traumatic bleeding. Tranexamic acid is an inexpensive, easily used, and relatively safe drug, and it seemed to have saved lives. However, how it did so was unclear—the blood-transfusion requirements of the tranexamic acid and placebo groups were similar and, survival bias notwithstanding, the mortality benefit might have been attributable to an e ect of tranexamic acid on something other than acute traumatic coagulopathy.[2]

This issue is partly addressed with the publication in The Lancet of a follow-up analysis that used the outcome of death due to bleeding rather than all-cause mortality.[3] The CRASH-2 collaborators[3] report a 32% reduction in death due to bleeding when tranexamic acid is given within 1 h of injury. Although markers of coagulopathy were not measured, the mortality benefit is probably mediated through antifibrinolytic e ects on clot stabilisation.[4] While it will not prevent the massive haemorrhage from disrupted vessels or organs that needs surgical intervention, tranexamic acid appears to improve survival through its e ect on mild to moderate bleeding.

Early administration is necessary, however, and benefit was only seen in CRASH-2 when tranexamic acid was administered within 3 h of injury. Unlike coagulopathy that is secondary to haemodilution, hypothermia, or acidosis, acute traumatic coagulopathy is a hyperacute process in which systemic fibrinolysis releases D-dimers that are detectable within 30 min of injury.[5] While the mechanisms are poorly understood, shock and tissue injury seem to be important initiators.[6] Not all severely injured patients develop acute coagulopathy, but those who do are much more likely to die and to die early.[7] The earlier that tranexamic acid is administered, the more likely it might be to prevent full activation of fibrinolysis. Once fully activated, fibrinolysis has been shown to continue unabated until endogenous antifibrinolytic elements are restored.[8]

Importantly, the CRASH-2 collaborators[3] report increased mortality due to bleeding in patients receiving tranexamic acid when it is given more than 3 h after injury. The cause of these deaths is unclear. Reports exist of prothrombotic e ects of each of the anti-fibrinolytic drugs. Alternatively, it might reflect some factor of the patients who received it late. Whatever the mechanism, the CRASH-2 collaborators[3] have cautioned against the use of tranexamic acid when more than 3 h have expired after injury.

Who, then, should be treated with tranexamic acid? Most of the 274 study sites in CRASH-2 were in low-income and middle-income countries, where other treatments directed at coagulopathy, such as fresh frozen plasma, platelets, and cryoprecipitate, are less available. Although many patients with acute coagulopathy will die before reaching hospital, tranexamic acid is a practical, a ordable, and e ective treatment for bleeding trauma patients in such centres, provided they receive it within 3 h of injury.

Far less clear is the place for tranexamic acid in high income countries where massive transfusion protocols incorporate fresh-frozen plasma that contains all the endogenous antifibrinolytic elements in plasma.[9] Plasma can cause harm as well as benefit, and there is little prospective evidence regarding its e cacy. However, because it is in widespread use, and because late administration of tranexamic acid can be harmful, it is unlikely that many clinicians in major trauma centres will choose tranexamic acid as first-line treatment.

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The best place for tranexamic acid in developed trauma systems might actually be in the prehospital environment. Helicopter and road transport direct to major trauma centres has reduced overall injury mortality, but has extended the time before patients reach hospital.[10] Prehospital administration of blood products, especially plasma, is uncommon in civilian settings, resulting in little directed management of coagulopathy. By contrast, tranexamic acid can be safely stored in vehicles and simply administered. In view of the new findings from CRASH-2, the best outcomes might be achieved with simple measures for haemorrhage control and early inhibition of coagulopathy with tranexamic acid, followed by rapid transport for surgery or angiography and tailored management of coagulopathy in hospital.

CRASH-2 was an extraordinary achievement, with randomisation of more than 20 000 patients in 40 countries. It has established tranexamic acid as an e ective hospital-based treatment for traumatic haemorrhage, provided that the drug is given within 3 h of injury. In trauma systems that have advanced prehospital services and that use other hospital-based treatments for coagulopathy, CRASH-2 raises more questions—and more possibilities—that are worth investigating.

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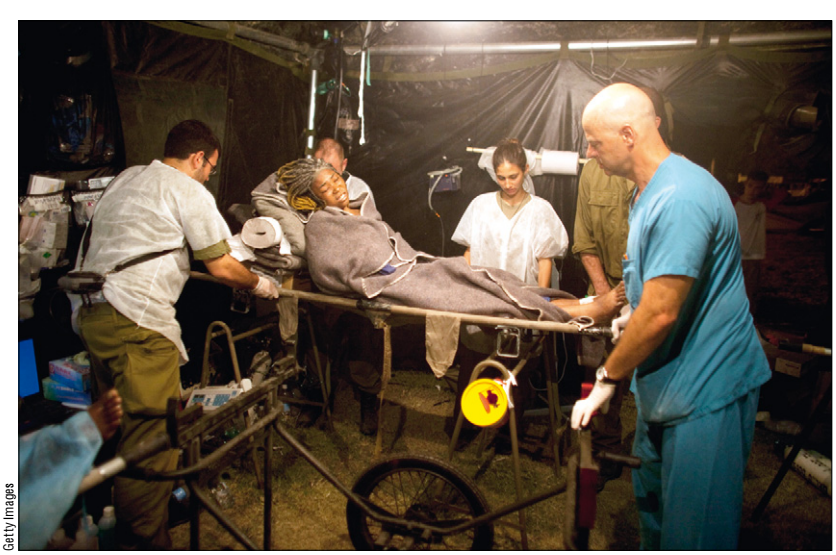
Disasters and a register for foreign medical teams

The tsunami in Asia and earthquakes in Pakistan, Iran, Indonesia, and Haiti at the start of the 21st century, and now the earthquake and tsunami in Japan, have emphasised people's continuing willingness to respond to large-scale disasters overseas. However, these individual acts of altruism are tempered by criticisms about lack of preparedness, coordination, and appropriate skills.[1–3] In the UK, many of these volunteers work in the National Health Service (NHS), and a sudden exodus of highly skilled sta can put considerable strain on their institutions. To address these issues, a formal register of UK surgeons, anaesthetists, emergency physicians and nurses, and other supporting medical, nursing, and paramedical sta has been established.[4]



Getty Images

Patient is transferred out of recovery room the day after surgery at the Israeli army hospital on Jan 19, 2010 in Port-au-Prince, Haiti

The register has been developed with the UK Government's Department of Health and Department for International Development, and with non-governmental organisations including Medical Emergency Relief International (Merlin). Although the idea to create a register has been considered after each major event,[5] only now has su cient momentum been gathered to see its implementation. Governments, non-governmental organisations, and UN agencies can select health-care workers from the register and be assured that they are ready to go and are fit for purpose. The register is supported by the Faculty of Pre-Hospital Care of the Royal College of Surgeons of Edinburgh, the Royal College of Surgeons of England, the UK College of Emergency Medicine, the British Association of Immediate Care Schemes, the British Association of Plastic Reconstructive and Aesthetic Surgeons, the Academy of Medical Royal Colleges in the UK, the UK's Royal College of Nursing, and the British Medical Association. Existing collaboration with other countries will be strengthened.

An important role of the register will be to foster training. The core competencies for deployment to acute surgical emergencies (most noticeably earthquakes) are probably more easily identified and agreed on than are those for longer-term development work. Therefore the register will concentrate its remit on these emergencies. This focus also chimes with WHO's initiative to update its guidelines for the use of foreign field-hospitals. After experts met in Cuba in December, 2010, an ad-hoc working group (chaired by ADR) was formed to explore registration of foreign medical teams, both before and after deployment to sudden-onset disasters.

The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial

The CRASH- collaborators*

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Summary

Background The aim of the CRASH-2 trial was to assess the effects of early administration of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage. Tranexamic acid significantly reduced all-cause mortality. Because tranexamic acid is thought to exert its effect through inhibition of fibrinolysis, we undertook exploratory analyses of its effect on death due to bleeding.

Methods The CRASH-2 trial was undertaken in 274 hospitals in 40 countries. 20 211 adult trauma patients with, or at risk of, significant bleeding were randomly assigned within 8 h of injury to either tranexamic acid (loading dose 1 g over 10 min followed by infusion of 1 g over 8 h) or placebo. Patients were randomly assigned by selection of the lowest numbered treatment pack from a box containing eight numbered packs that were identical apart from the pack number. Both participants and study staff (site investigators and trial coordinating centre staff) were masked to treatment allocation. We examined the effect of tranexamic acid on death due to bleeding according to time to treatment, severity of haemorrhage as assessed by systolic blood pressure, Glasgow coma score (GCS), and type of injury. All analyses were by intention to treat. The trial is registered as ISRCTN86750102, ClinicalTrials.gov NCT00375258, and South African Clinical Trial Register/Department of Health DOH-27-0607-1919.

Findings 10 096 patients were allocated to tranexamic acid and 10 115 to placebo, of whom 10 060 and 10 067, respectively, were analysed. 1063 deaths (35%) were due to bleeding. We recorded strong evidence that the effect of tranexamic acid on death due to bleeding varied according to the time from injury to treatment (test for interaction p<0·0001). Early treatment (≤1 h from injury) significantly reduced the risk of death due to bleeding (198/3747 [5·3%] events in tranexamic acid group *vs* 286/3704 [7·7%] in placebo group; relative risk [RR] 0·68, 95% CI 0·57–0·82; p<0·0001). Treatment given between 1 and 3 h also reduced the risk of death due to bleeding (147/3037 [4·8%] *vs* 184/2996 [6·1%]; RR 0·79, 0·64–0·97; p=0·03). Treatment given after 3 h seemed to increase the risk of death due to bleeding (144/3272 [4·4%] *vs* 103/3362 [3·1%]; RR 1·44, 1·12–1·84; p=0·004). We recorded no evidence that the effect of tranexamic acid on death due to bleeding varied by systolic blood pressure, Glasgow coma score, or type of injury.

Interpretation Tranexamic acid should be given as early as possible to bleeding trauma patients. For trauma patients admitted late after injury, tranexamic acid is less effective and could be harmful.

Funding UK NIHR Health Technology Assessment programme, Pfizer, BUPA Foundation, and J P Moulton Charitable Foundation.

Introduction

The CRASH-2 trial showed that administration of tranexamic acid to adult trauma patients with, or at risk of, significant haemorrhage, within 8 h of injury, significantly reduces all-cause mortality (relative risk [RR] 0·91, 95% CI 0·85–0·97; p=0·0035) with no apparent increase in vascular occlusive events.[1] As a consequence of this trial, tranexamic acid has been incorporated into trauma treatment protocols worldwide.

Results from the CRASH-2 trial raise some important questions. The trial was motivated by the evidence that tranexamic acid reduces bleeding in patients undergoing elective surgery, and the hypothesised mechanism was inhibition of fibrinolysis leading to improved effectiveness of haemostasis.[2] However, no significant difference was recorded in transfusion requirements between the tranexamic acid and placebo groups, and the CRASH-2 trial did not measure the effect of this drug on fibrinolytic assays. Thus an alternative hypothesis is that tranexamic acid might act by reducing the pro-inflammatory effects of plasmin, rather than by improving haemostasis.[3]

There has also been discussion about which trauma patients should be treated with tranexamic acid. The CRASH-2 trial[1] reported the few subgroup analyses that were prespecified in the statistical analysis plan. These analyses assessed the effect of tranexamic acid on the primary endpoint of all-cause mortality, according to time since injury, systolic blood pressure, Glasgow coma score, and type of injury. No strong evidence of

heterogeneity was recorded for any of these analyses, suggesting that tranexamic acid is likely to be equally effective in all the subgroups examined.

The focus on all-cause mortality was appropriate because it is an outcome that matters to patients and one that is not affected by the methodological problem of competing risks.[4] However, the effect of the trial treatment on the biologically relevant outcome could have been diluted by outcomes on which tranexamic acid might have little or no effect. In response to these concerns, we undertook exploratory analyses of the effect of tranexamic acid on mortality due to bleeding. We report the same prespecified subgroup analyses but for the outcome that we hypothesise would be most affected by this drug, specifically mortality due to bleeding.

Methods

Study design and patients

The background to the trial, methods, and baseline characteristics of the randomised patients have been previously reported.[1] Briefly, we randomly allocated 20 211 adult trauma patients with, or at risk of, significant bleeding who were within 8 h of injury to either tranexamic acid (loading dose 1 g over 10 min followed by infusion of 1 g over 8 h) or matching placebo, with 99·6% follow-up. In most hospitals we used a local pack system for randomisation. After eligibility had been confirmed and the locally approved consent procedures had been completed, patients were randomly assigned by selection of the lowest numbered treatment pack from a box containing eight numbered packs. Apart from the pack number, the treatment packs were identical. The pack number was recorded on the entry form, which was sent to the Trial Coordinating Centre in London, UK. Hospitals with telephone access used a telephone randomisation service. Both participants and study staff (site investigators and trial coordinating centre staff) were masked to treatment allocation.

Statistical analysis

The primary outcome was death in hospital within 4 weeks of injury, with cause of death described with the following categories: bleeding, vascular occlusion (myocardial infarction, stroke, and pulmonary embolism), multiorgan failure, head injury, and other.

All analyses were by intention to treat. We examined the effect of the trial treatment on death due to bleeding subdivided by four baseline characteristics: (1) time from injury to treatment (≤1, >1–3, >3 h); (2) severity of haemorrhage as assessed by systolic blood pressure (≤75, 76–89, >89 mm Hg); (3) Glasgow coma score (severe 3–8, moderate 9–12, mild 13–15); and (4) type of injury (penetrating only, blunt plus blunt and penetrating). These were the same subgroup analyses that were reported previously, but for the outcome of death due to bleeding rather than for all-cause mortality.

Heterogeneity in treatment effects across subgroups was assessed by a χ^2 test. We had prespecified that unless there was strong evidence against the null hypothesis of homogeneity of effects (ie, $p<0·001$), the overall RR would be considered the most reliable guide to the approximate RRs in all subgroups. To test the

	N	All causes of death	Bleeding death	Non-bleeding death
Overall	20 127	0·91 (0·85–0·97); p=0·0035	0·85 (0·76–0·96); p=0·0077	0·94 (0·86–1·02); p=0·13
Time to treatment (h)				
≤1	7451	0·87 (0·76–0·97)	0·68 (0·57–0·82)	1·04 (0·89–1·21)
>1–3	6033	0·87 (0·77–0·97)	0·79 (0·64–0·97)	0·91 (0·78–1·05)
>3	6634	1·00 (0·90–1·13)	1·44 (1·12–1·84)	0·89 (0·78–1·02)
^{2} test of homogeneity	..	4·411 (p=0·11)	23·516 (p=0·0000)	2·537 (p=0·28)

Table : **Relative risk (95% CI) of death with tranexamic acid, overall and by time to treatment**

	≤1 h (n=7451)	>1–3 h (n=6033)	>3 h (n=6634)
Age (years)			
Mean (SD)	33·4 (13·9)	35·0 (14·0)	35·5 (14·8)
<25	2283 (30·6%)	1557 (25·8%)	1773 (26·7%)
25–34	2360 (31·7%)	1832 (30·4%)	1882 (28·4%)
35–44	1356 (18·2%)	1177 (19·5%)	1262 (19·0%)
>44	1452 (19·5%)	1467 (24·3%)	1716 (25·9%)
Systolic blood pressure (mm Hg)			
≤75	1380 (18·5%)	1012 (16·8%)	768 (11·6%)
76–89	1203 (16·1%)	1064 (17·6%)	1029 (15·5%)
>89	4857 (65·2%)	3955 (65·6%)	4821 (72·7%)
Heart rate (beats per min)			
<77	681 (9·1%)	450 (7·5%)	603 (9·1%)
77–91	1189 (16·0%)	971 (16·1%)	1326 (20·0%)
92–107	1888 (25·3%)	1562 (25·9%)	1625 (24·5%)
>107	3637 (48·8%)	2990 (49·6%)	3059 (46·1%)
Respiratory rate (breaths per min)			
<10	149 (2·0%)	82 (1·4%)	77 (1·2%)
10–29	6144 (82·5%)	4992 (82·7%)	5590 (84·3%)
>29	1077 (14·5%)	901 (14·9%)	923 (13·9%)
Capillary refill time (s)			
≤2	2450 (32·9%)	2140 (35·5%)	2217 (33·4%)
3–4	3472 (46·6%)	2773 (46·0%)	3110 (46·9%)
>4	1131 (15·2%)	963 (16·0%)	1257 (19·0%)
Glasgow coma score			
Severe (3–8)	1000 (13·4%)	1124 (18·6%)	1494 (22·5%)
Moderate (9–12)	868 (11·7%)	915 (15·2%)	909 (13·7%)
Mild (13–15)	5577 (74·9%)	3994 (66·2%)	4214 (63·5%)
Continents			
Asia	1213 (16·3%)	2475 (41·0%)	3656 (55·1%)
Africa	2490 (33·4%)	1437 (23·8%)	872 (13·1%)
Central and South America	2453 (32·9%)	1456 (24·1%)	1355 (20·4%)
North America, Europe, and Oceania	1295 (17·4 %)	665 (11·0%)	751 (11·3%)

Data are number (%), unless otherwise stated.

Table : **Patient characteristics by time to treatment**

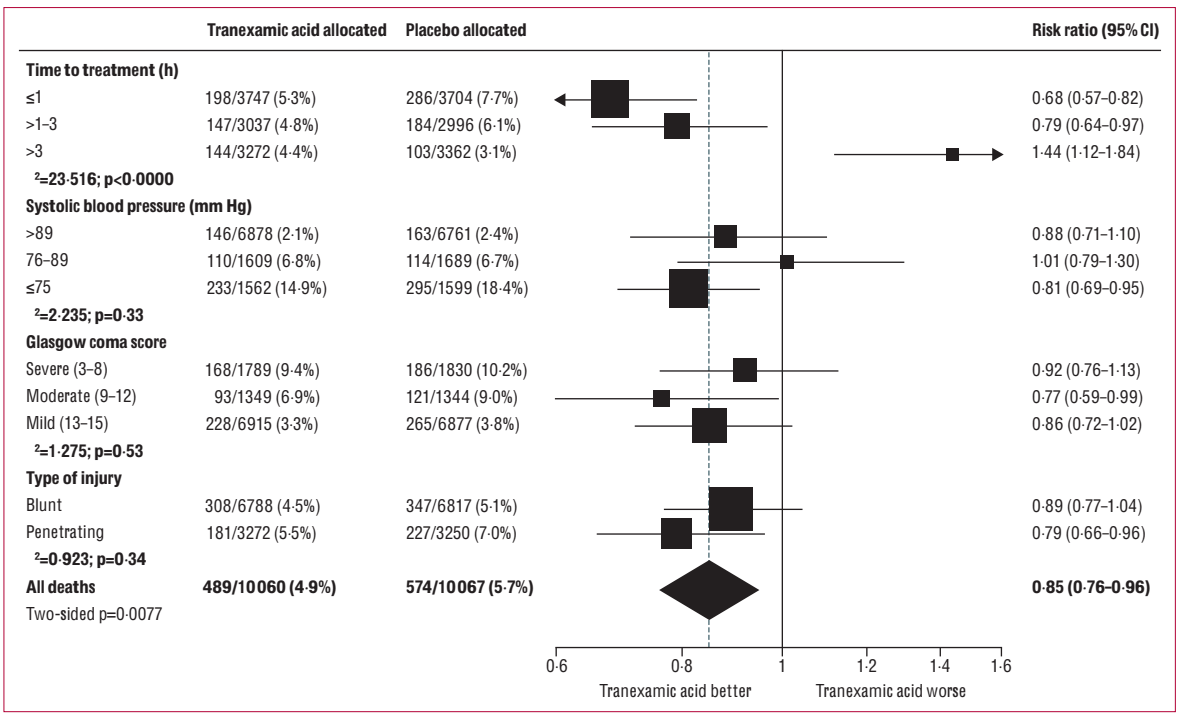

Figure : **Mortality due to bleeding by subgroups**

independence of any observed treatment interactions we ran a logistic model including all possible interactions in the four prespecified baseline characteristics and treatment subgroups.

A logistic regression was estimated with death due to bleeding as the dependent variable and treatment group and time to treatment as explanatory factors. We included an interaction parameter to allow for a proportional change in the odds ratio (OR) as time to treatment increases. ORs and 95% CIs were estimated for different times to treatment. CIs were calculated with a logistic model with time as a continuous term and an interaction term between time and tranexamic acid. We also ran a model with an interaction term for time to treatment squared to allow for a non-constant proportional change in the OR.

The trial is registered as ISRCTN86750102, ClinicalTrials.gov NCT00375258, and South African Clinical Trial Register/Department of Health DOH-27-0607-1919.

Role of the funding source

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

Results

Of the 3076 deaths from all causes, death due to bleeding accounted for 1063 (35%). The risk of death due to bleeding was significantly reduced with tranexamic acid. 489 of 10 060 (4·9%) patients died because of bleeding in the tranexamic acid group versus 574 of 10 067 (5·7%) in the placebo group (RR 0·85, 95% CI 0·76–0·96; p=0·0077). We noted no significant effect on the risk of death for all other (non-bleeding) causes combined (table 1).

Table 2 shows the baseline characteristics of patients according to time to treatment. Figure 1 shows the results of the subgroup analyses for death due to bleeding. Time to treatment was unknown in nine participants. Treatment given 1 h or less from injury significantly reduced the risk of death due to bleeding (198/3747 [5·3%] in tranexamic acid group *vs* 286/3704 [7·7%] in placebo group; RR 0·68, 95% CI 0·57–0·82; p<0·0001). Treatment given between 1 and 3 h also reduced the risk of death due to bleeding (147/3037 [4·8%] *vs* 184/2996 [6·1%]; RR 0·79, 0·64–0·97; p=0·03). Treatment given more than 3 h after injury significantly increased the risk of death due to bleeding (144/3272 [4·4%] *vs* 103/3362 [3·1%]; RR 1·44, 1·12–1·84; p=0·004). We recorded strong evidence that the effect of tranexamic acid on death due to bleeding varied according to time from injury to treatment (p<0·0001). The evidence for interaction remained strong even after adjustment for interactions between the other prespecified baseline characteristics and treatment (p<0·0001; data not shown).

The estimated OR of tranexamic acid on death due to bleeding when given immediately after injury was 0·61

(95% CI 0·50–0·74). We estimated that this OR is multiplied by 1·15 (95% CI 1·08–1·23) for every hour that passes since the injury. Figure 2 shows how the OR and 95% CIs vary with time to treatment. The interaction term for time to treatment squared was not significant (OR=0·99; p=0·38).

We recorded no evidence of heterogeneity for the subgroup analyses according to systolic blood pressure, Glasgow coma score at randomisation, or type of injury (figure 1). We detected no evidence of heterogeneity in the effect of tranexamic acid on the risk of non-bleeding deaths (table 1).

Discussion

The effect of tranexamic acid on death due to bleeding depends on the time between injury and onset of treatment. Early treatment with this drug seems to be much more effective than does late treatment. These results also raise the possibility that late treatment with tranexamic acid might increase the risk of death due to bleeding, although there was no evidence of any increase in all-cause mortality in patients treated after 3 h (table 1). This finding might indicate that patients treated with tranexamic acid beyond 3 h who died from bleeding might otherwise have died from some other non-bleeding cause (competing risks). If late administration does cause harm, this finding would be important since many bleeding trauma patients in low-income and middle-income countries have long prehospital times. Indeed, about a third of trauma patients in the CRASH-2 trial were treated more than 3 h after the injury.

The inclusion criteria in the CRASH-2 trial were entirely clinical, and reflect the situation that doctors are faced with in clinical practice. Patients were enrolled if the treating physician judged them to have ongoing significant haemorrhage, as evidenced by hypotension or tachycardia, or if they were considered to be at risk of significant haemorrhage. Some of the included patients might not have been actively bleeding. Any such misdiagnosis would have reduced the power of the trial to show an effect of tranexamic acid on mortality from bleeding, in which case the large and highly significant reduction in bleeding mortality in patients treated with this drug within 1 h of injury is particularly noteworthy.

Because patients were randomly assigned soon after hospital admission, before the precise anatomical location of bleeding and other injury was known, we were unable to do a stratified analysis based on an anatomical assessment of injury severity. We acknowledge that this omission is a methodological weakness, since such an analysis might provide insight into the mechanism of action of tranexamic acid. However, since this information would not normally be available to treating clinicians, especially in view of the importance of early treatment, the clinical value of a stratified analysis based on anatomical injury severity is small.

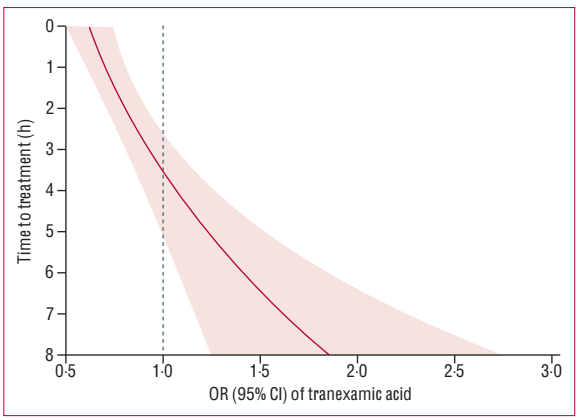

Figure : **Effect of tranexamic acid on death due to bleeding by time to treatment**
Shaded area shows 95% CI. OR=odds ratio.

Data for the time between injury and treatment were available for all but nine trial participants. Because in some cases the injury would not have been witnessed, this interval sometimes had to be estimated and might therefore be inaccurate. However, any inaccuracy would be independent of the trial treatment and therefore should not bias the results. The ascertainment of a death as a bleeding death might also have been inaccurate, but similarly any inaccuracy should be independent of the trial treatment.

In clinical trials, a treatment is not often beneficial in one subgroup but harmful in another (qualitative interaction), and some trialists recommend that qualitative interactions should generally be disbelieved.[5] The results of our analysis of the effect of tranexamic acid on death due to bleeding do, however, satisfy most of the criteria against which the credibility of subgroup results should be judged:[6] time from injury was measured at baseline; the hypothesis that early treatment with tranexamic acid might be more effective was prespecified in the trial protocol; the interaction suggests a very low likelihood that chance explains the findings; the interaction remained significant after controlling for the non-significant interactions between treatment and the other prespecified baseline prognostic factors; the subgroup effect is large; and a biological rationale supports the interaction. Although this clinical trial was not powered to examine subgroup effects, the interaction recorded is large and highly significant.[7]

Nevertheless, we prespecified in our trial protocol that the main subgroup analyses would be undertaken for all-cause mortality, and not for mortality due to bleeding. Even though we postulated that tranexamic acid would act by reducing bleeding, we focused on all-cause mortality because overall survival is most important to patients. However, in view of the significant reduction in all-cause mortality, most of which was attributable to the effect of tranexamic acid on death due to bleeding, and the biological rationale that this drug would act by

Panel: **Research in context**

Systematic review

A 2011 Cochrane systematic review[12] of antifibrinolytic drugs for acute traumatic injury identified two randomised trials of tranexamic acid in bleeding trauma patients, involving 20 451 patients. The review concluded that tranexamic acid safely reduces mortality in bleeding trauma patients without increasing the risk of adverse events.

Interpretation

Our results emphasise the importance of early administration of tranexamic acid and the need for caution in patients presenting several hours after the injury.

improving haemostasis, our analyses, although not prespecified, would seem justified.

Acute severe trauma is associated with increased fibrinolysis that contributes to an early coagulopathy and increased mortality.[8,9] Fibrinolysis can be assessed by measurement of fibrin degradation products, which include small protein fragments called D-dimers. Brohi and colleagues[8] showed that D-dimer concentrations are raised in trauma patients at the time of hospital admission (median prehospital time 28 min), with the highest concentrations measured in the most severely injured patients.[8] Similar results were recorded in a 2009 study from Japan that measured fibrin degradation product and D-dimers in 314 severe trauma patients.[10] If this early increased fibrinolysis exacerbates bleeding and increases the risk of death, then we might expect that an antifibrinolytic drug such as tranexamic acid would be most effective in this period.

Although we had anticipated that early treatment with tranexamic acid might be most effective, the apparent increase in the risk of death due to bleeding in patients treated more than 3 h after the injury is unexpected and cannot readily be explained. It could be a chance finding and there might be no real biological effect. However, patients in the late phase of trauma can develop thrombotic disseminated intravascular coagulation, and antifibrinolytics could be contraindicated in this period.[10,11] Although disseminated intravascular coagulation is characterised by fibrin formation and coagulation, the rapid consumption of coagulation proteins can lead to their exhaustion, resulting in uncontrolled bleeding. The need to avoid giving an antifibrinolytic in this late phase was why we restricted trial inclusion to patients who were within 8 h of injury. The possibility that the change to a prothrombotic state might occur sooner than was previously expected is open to debate and needs further research. We should also bear in mind that patients who arrive at hospital many hours after injury are likely to differ from those who arrive early. For example, there could be an increased prevalence of hypothermia and acidosis. These or other differences could explain the decreased efficacy of tranexamic acid administration when given late.

A 2011 systematic review of randomised controlled trials concluded that tranexamic acid safely reduces mortality in bleeding trauma patients.[12] Our results strongly endorse the importance of early administration of tranexamic acid in bleeding trauma patients and suggest that trauma systems should be configured to facilitate this recommendation (panel). In patients presenting late (several hours after injury) the clinician should be more cautious and make an assessment of the individual benefits and risks of this treatment, since the drug is likely to be much less effective and possibly even harmful. To the extent that our subgroup analyses are consistent with the results of studies showing an early increased fibrinolytic coagulopathy, they support the hypothesis that tranexamic acid acts through the inhibition of fibrinolysis with improved haemostasis.

Future research using the CRASH-2 trial data will develop a prognostic model to predict death due to bleeding.[13] This model will facilitate further analysis of the effect of tranexamic acid according to baseline risk of haemorrhage death.

Contributors

All members of the Writing Committee, apart from AA and GG, attended a 2-day meeting in London, UK, at which the subgroup analyses were presented and discussed and the report was drafted. Both AA and GG contributed to the discussions and drafting by phone and in correspondence.

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Conflicts of interest
Members of the Writing Committee declare that they have no conflicts of interest.

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Neuro Center Gola Ghat: Vinod Tewari; NSCB Medical College: Yad Yadav, Vijay Parihar; BGS Global Hospital: Neelam Venkataramana, Shailesh Rao; Chettinad Hospital and Research Institute: Narayana Reddy; Sir Sayajirao General Hospital and Medical College Baroda: Virsing Hathila; Goyal Hospital and Research Centre Jodhpur: Vithal Das; Krishna Surgical Hospital and Trauma Care Centre: Kantibhai Agaja; Nizam's Institute of Medical Sciences: Aniruddh Purohit; Niramay Hospital: Akilesh Lahari; Apex Hospital Bhopal: Rajesh Bhagchandani; Dr Jeyasekharan Medical Trust: Bala Vidyasagar; Himalayan Institute of Medical Sciences: P K Sachan; Apollo Gleneagles Hospitals: Tanmoy Das; Civil Hospital Gandhinagar:

Sharad Vyas; Sukhdev Raj Soin Hospital: Sujoy Bhattacharjee; Sancheti Institute for Orthopaedics and Rehabilitation: Parag Sancheti; St James Hospital: T Manoj; Al Shifa Hospital: Mubarak Moideen; Anant Institute of Medical Sciences: Kailash Pansey; Vinayaka Mission Hospital: V P Chandrasekaran; Gauhati Medical College and Hospital: Kabul Saikia; Krishna Hospital and Medical Research Centre: Hoshedar Tata; Ruby Hall Clinic: Sanjay Vhora; Shreejee Hospital: Aniket Shah; Nazareth Hospital: Gordon Rangad; Ganga Hospital: S Rajasekaran; Vadamalayan Hospitals: S T Shankarlal; Devadoss Multispeciality Hospital: Sathish Devadoss; KIOT Hospital: M Saleem; Baby Memorial Hospital: Haroon Pillay; Bethany Hospital: Zulfiquer Hazarika; Suretech Hospital and Research Centre: Parikshit Deshmukh; Surya Hospital: S P Murugappan; Apollo Clinic Varanasi: Amit Jaiswal; Fortis Escorts Hospital: Deepak Vangani; Gokul Hospital and Trauma Centre: Prakash Modha; International Hospital Assam: Chawngrolien Chonzik; Lifeline Multispeciality Hospital: Megha Praveen; Meenakshi Mission Hospital and Research Centre: Vijaya Sethurayar; MOSC Medical College Hospital: Sojan Ipe; MS Ramaiah Memorial Hospital: Naresh Shetty; Saykhedkar Hospital and Research Centre: Aniket Shah; Shanti Mukand Hospital: R P Gupta; Shri KM Memorial Jain Heart and General Hospital: Vinod Jain; Usha Hospital: Ketan Shah. *Indonesia* (706)—Soebandi Hospital Jember: Moch Dwikoryanto; Sanglah General Hospital: Nyoman Golden, Kuning Atmadjaya, Ketut Wiargitha, Ketut Sudiasa, Gede Suwedagatha; Saiful Anwar General Hospital: Farhad Bal'afif; Dr Soetomo General Hospital: Vicky Budipramana, Tabrani, Agung Lemuel; Cipto Mangunkusumo Hospital: Susilo Chandra; Muhammadiyah Lamongan Hospital: Faisol Ama. *Iran* (134)—Nemazi Hospital: Ehsan Sherafatkazemzadeh, Ehsan Moradi, Alireza Sheikhi; Erfan Hospital: Ali Ziaee, Ahmad Fanaei; Loqman Medical Center: Esmaeil Hajinasrollah; Imam Hosain Hospital: Kamran Heidari. *Iraq* (392)—Diwaniyah College of Medicine: Bassim Mohammad, Najah Hadi. *Italy* (57)—Spedali Civili di Brescia: Giovanna Perone, Elena de Peri; Azienda Ospedaliera Di Parma: Annalisa Volpi. *Jamaica* (11)—University Hospital of the West Indies: Jean Johnson. *Japan* (9)—Fukuoka University Hospital: Masayoshi Abe. *Kenya* (31)—Kenyatta National Hospital: Vincent Mutiso, Benjamin Okanga; Kapenguria District Hospital: Daniel Ojuka. *Malaysia* (216)—Hospital University Science Malaysia: Baharudin Abdullah, Hishamuddin Rahman, Yazid Noh; Sungai Buloh Hospital: Sabariah Jamaluddin, Hasnah Dawal; University of Malaya Medical Centre: April Roslani, Chee-Wei Law, P Devashanti; Hospital Tengku Ampuan Rahimah: Yusof Wahab, Shanta Velaiutham; Ampang Hospital: Ridzuan Dato. *Mexico* (479)—Hospital General Regional 25: Jorge Loría, Erandy Montes, Eduardo Gómez, Víctor Cazales, Paúl Bautista; Hospital Gustavo Rovirosa: Raúl Bautista, David Ahumada, Edwin Hernández, Germahin Velásquez; Hospital General de Uruapan "Dr Pedro Daniel Martínez": Patricia Ortega, Gabriel Lira, Francisco Estrada; Hospital General Ecatepec Las Américas: Jorge Martínez; Hospital General La Perla: Juan Martínez; Hospital General de Ecatepec "Dr José María Rodríguez": Julio Casasola. *Nigeria* (2053)—National Hospital Abuja: Oluwole Olaomi, Yari Abubakar, Kanati Apollo, Olawale Badejo, Ogemdi Ihekire; University of Benin Teaching Hospital: Pius Iribhogbe, Olugbenga Oludiran, Emmanuel Obeta, Collins Okojie, Ernest Udefiagbon; Obafemi Awolowo University Teaching Hospitals: Edward Komolafe, Patrick Olaleye, Tochukwu Uzochukwu, Uvie Onakpoya; Irrua Specialist Teaching Hospital: Andrew Dongo; Olabisi Onabanjo University Teaching Hospital: Lateef Thanni; University College Hospital Ibadan: Adefemi Afolabi, Titilade Akinola, Adeyinka Ademola, Olusola Akute; Ahmadu Bello University Teaching Hospital: Lawal Khalid, Lawal Abubakar, Muhammad Aminu, Mike Ogirima; Baptist Medical Centre: Ambrose Attansey, Durodola Michael, Olaniran Aremu; University of Ilorin Teaching Hospital: Odebode Olugbenga, Udoffa Ukpong, Yusuf Salman; Enugu State University Teaching Hospital: Nene Obianyo, Chinenye Ani, Roderick Ezeadawi; LAUTECH Teaching Hospital: Oluwadiya Kehinde, Agodirin Olaide; Federal Medical Centre Makurdi: Andrea Jogo, Terna Bitto; Nnamdi Azikiwe University Teaching Hospital: Stanley Anyanwu, Okechukwu Mbonu; Lagos State University Teaching Hospital: Mobolaji Oludara, Michael Somoye; Usmanu Danfodiyo University Teaching Hospital: Bello Shehu, Nasir Ismail; National Orthopaedic Hospital Enugu: Amechi Katchy; University of Calabar Teaching Hospital: Rowland Ndoma-Egba, Ngim Grace-Inah; University of Abuja Teaching Hospital: Zumnan Songden, Abdulrahman Abdulraheem; University of Uyo Teaching Hospital: Akpan Otu, Timothy Nottidge; Federal Medical Centre, Yenagoa: Domingo Inyang, David Idiapho; Seventh Day Adventist Hospital: Herb Giebel; Federal Medical Centre Birnin-Kebbi: Ramatu Hassan; Abia State University Teaching Hospital: Adeyinka Adisa; Wesley Guild Hospital: Akinbolaji Akinkuolie; Federal Medical Centre, Umuahia: Kalu Okam; University of Maiduguri Teaching Hospital: Abubakar Musa; National Orthopaedic Hospital, Igbobi: Ignatius Falope; University of Nigeria Teaching Hospital Enugu: John Eze. *Peru* (452)—Hospital Regional Docente de Trujillo: José Caballero, Wenceslao Azabache, Oscar Salirrosas; Hospital Nacional Hipolito Unanue: Alonso Soto, Elfi Torres, Gloria Ramírez, Mónica Pérez; Clinica Santa Ana: Cesar Malca; Hospital La Caleta: Juan Velez; Hospital Nacional Sergio E Bernales: Raul Yepez; Hospital de Apoyo de Sullana: Hernan Yupanqui; Hospital IV Essalud Huancayo: Pedro Lagos; Hospital Nacional Arzobispo Loayza: Diana Rodriguez; Hospital Municipal Los Olivos: Jorge Flores; Hospital Jose Cayetano Heredia: Anselmo Moya; Hospital Nacional Carlos Alberto Seguin Escobedo: Alejandro Barrionuevo; Hospital Nacional Dos De Mayo: Marco Gonzales-Portillo; Hospital Nacional Cayetano Heredia: Edgar Núñez. *Saudi Arabia* (70)—King Khalid University Hospital: Abdelazeem Eldawlatly, Mohammed Al Naami, Bilal Delvi; King Khalid National Guard Hospital: Walid Alyafi. *Serbia* (1)—Klinicki Centar Srbije: Branko Djurovic. *Singapore* (2)—National Neuroscience Institute: Ivan Ng. *Slovakia* (38)—FNsP Ružinov: Aktham Yaghi; NsP Poprad: Anton Laincz; NsP JA Reiman Hospital: Stefan Trenkler; Faculty Hospital F D Roosevelta: Jozef Valky. *South Africa* (76)—Dr George Mukhari Hospital: Mphako Modiba, Peter Legodi, Thomas Rangaka; George Provincial Hospital: Lee Wallis. *Spain* (23)—Hospital Universitário Virgen del Roció: Ángeles Muñoz; Hospital Ramón y Cajal de Madrid: Ana Serrano; Hospital Universitário Germans Trias i Pujol: Pilar Marcos; Hospital Torrecardenas: Martin Rubi; Hospital Universitário Virgen de la Victoria: Victoria de la Torre. *Sri Lanka* (103)—National Hospital of Sri Lanka: Ranjith Ellawala, Samitha Wijeratna, Lukshrini Gunaratna, Crishantha Wijayanayaka. *Tanzania* (64)—Muhimbili Orthopaedic Institute: Kitugi Nungu, Billy Haonga, Grenda Mtapa. *Thailand* (903)—Khon Kaen Regional Hospital: Surakrant Yutthakasemsunt, Warawut Kittiwattanagul, Parnumas Piyavechvirat, Tawatcahi Impool, Santipong Thummaraj; Pattani Hospital: Rusta Salaeh; Suratthani Hospital: Sakchai Tangchitvittaya; Bhumibol Adulyadej Hospital: Kamol Wattanakrai, Teerasak Jiravongbunrod, Chatchai Soonthornthum; Lampang Hospital: Surasak Meephant; Rayong Hospital: Pusit Subsompon; Roi-Et Hospital: Phaiboon Pensuwan; Phrae Hospital: Wicheanrat Chamnongwit. *Tunisia* (36)—Hospital Habib Thameur: Zouheir Jerbi, Abderraouef Cherif. *UK* (135)—University Hospital of North Staffordshire: Mark Nash; Royal London Hospital: Tim Harris; Leicester Royal Infirmary: Jay Banerjee; Nottingham University Hospitals NHS Trust: Ramzi Freij; Frenchay Hospital: Jason Kendall; Countess of Chester Hospital: Stephen Moore; Hull Royal Infirmary: William Townend; Royal Sussex County Hospital: Rowland Cottingham; Derby Hospitals NHS Trust: Dan Becker; Bedford Hospital NHS Trust: Stuart Lloyd; Royal Liverpool University Hospital: Peter Burdett-Smith; Colchester General Hospital: Kazim Mirza; Royal Lancaster Infirmary: Andrew Webster; Worthing Hospital: Suzanne Brady, Amanda Grocutt; Darent Valley Hospital: John Thurston; Hope Hospital: Fiona Lecky; Northern General Hospital: Steve Goodacre. *Zambia* (62)—University Teaching Hospital, Lusaka: Yakub Mulla, Dennis Sakala; Nchanga North General Hospital: Charles Chengo.