# 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 $\chi^2$ 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.

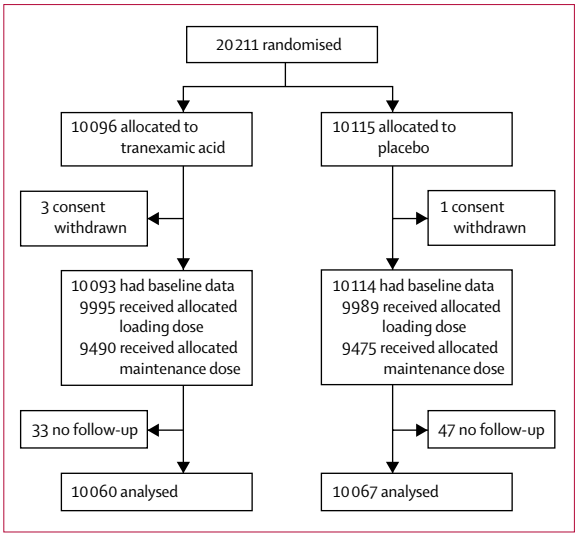


*Figure 1*: **Trial profile**

### 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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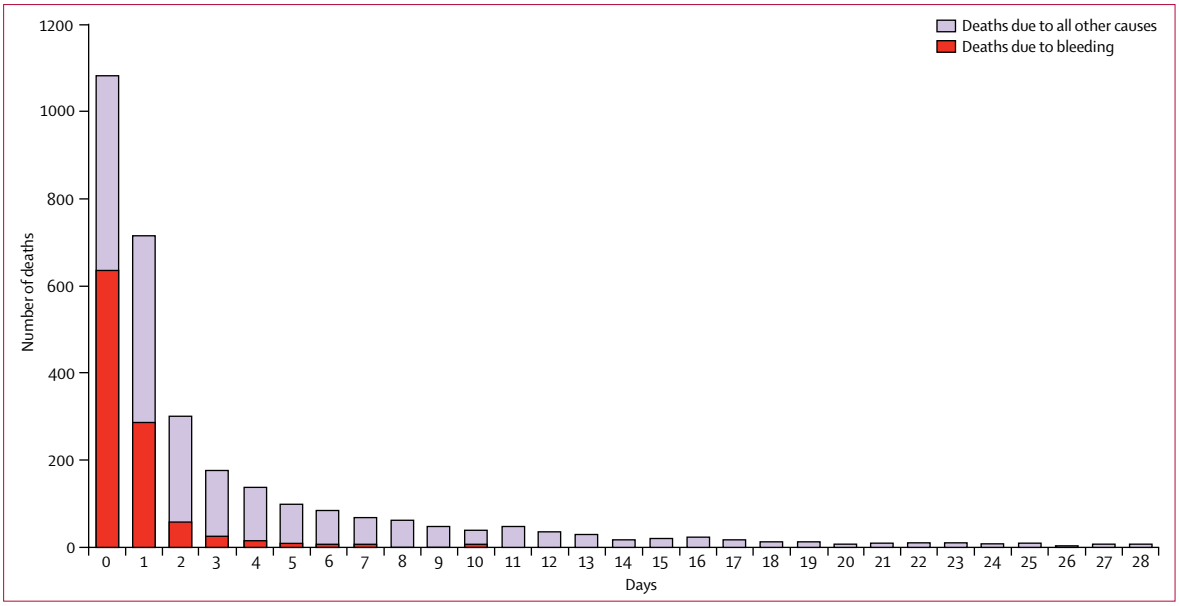


*Figure 2:* **Mortality by days from randomisation**

| | 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

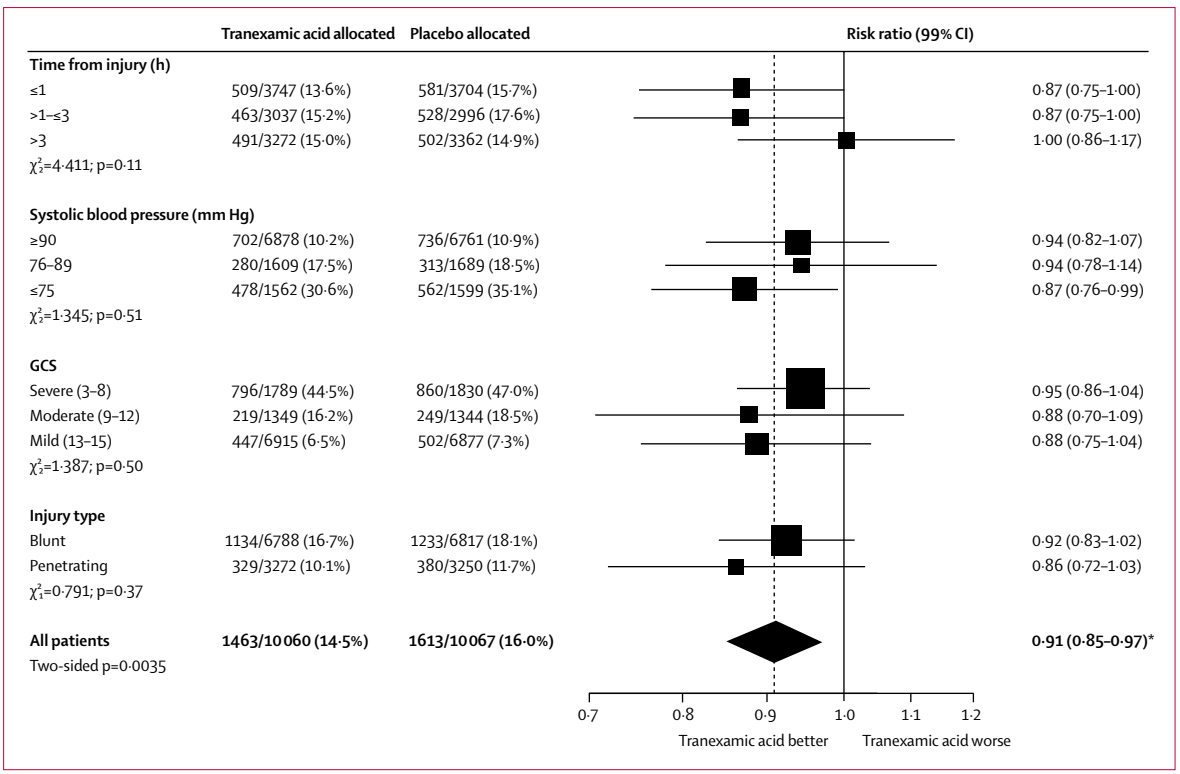


***Figure 3*: All-cause mortality by subgroups**
GCS=Glasgow Coma Score. *95% CI.

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 $\alpha_2$-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

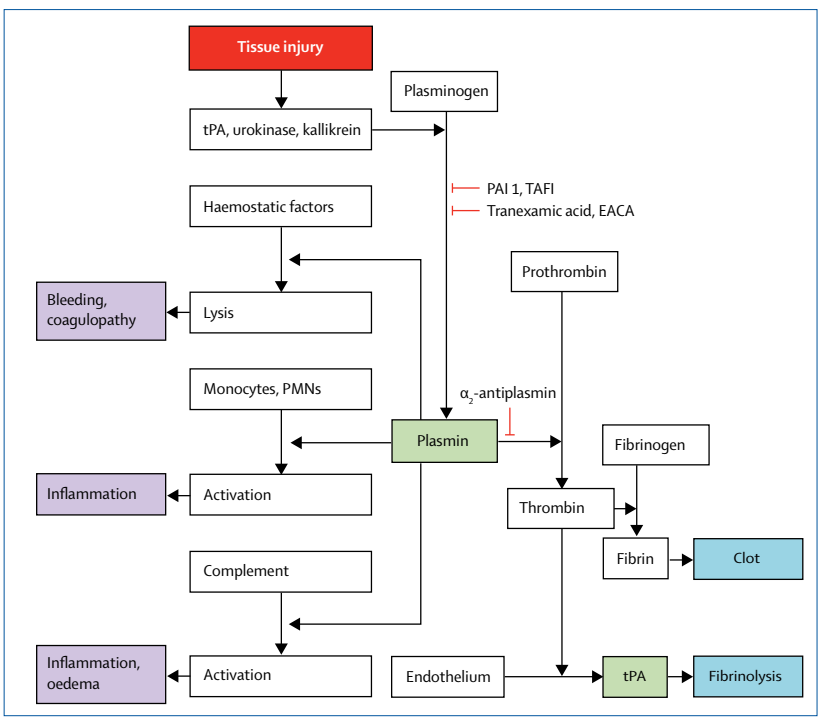


***Figure:*** **Tissue injury and fibrinolysis**
After trauma, tissue injury shifts the complex balance of fibrinolysis to additional plasmin generation, and activation that increases coagulopathy, inflammatory responses, and bleeding. Multiple pathways are responsible for generation of plasmin, including 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 $\alpha_2$-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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