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

The CRASH-2 collaborators*

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.1

There has also been discussion about which trauma patients should be treated with tranexamic acid. The CRASH-2 trial 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. 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.

### Table 1: Relative risk (95% CI) of death with tranexamic acid, overall and by time to treatment

<table>
<thead>
<tr>
<th>Time to treatment (h)</th>
<th>Overall</th>
<th>&lt;1 h (n=7451)</th>
<th>&gt;1–3 h (n=6033)</th>
<th>&gt;3 h (n=6634)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>20,127</td>
<td>1,910 (0.85–0.97)</td>
<td>0.85 (0.76–0.96)</td>
<td>0.94 (0.86–1.02)</td>
</tr>
<tr>
<td>Time to treatment (h)</td>
<td></td>
<td>p=0.0035</td>
<td>p=0.0077</td>
<td>p=0.013</td>
</tr>
<tr>
<td>≤1</td>
<td>7,451</td>
<td>0.87 (0.76–0.97)</td>
<td>0.68 (0.57–0.82)</td>
<td>1.04 (0.89–1.21)</td>
</tr>
<tr>
<td>&gt;1–3</td>
<td>6,033</td>
<td>0.87 (0.77–0.97)</td>
<td>0.79 (0.64–0.97)</td>
<td>0.91 (0.78–1.05)</td>
</tr>
<tr>
<td>&gt;3</td>
<td>6,634</td>
<td>1.00 (0.90–1.13)</td>
<td>1.44 (1.12–1.84)</td>
<td>0.89 (0.78–1.02)</td>
</tr>
</tbody>
</table>

χ² test of homogeneity: 4.411 (p=0.11) 23.516 (p=0.0000) 2.537 (p=0.28)

### Table 2: Patient characteristics by time to treatment

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall</th>
<th>&lt;1 h (n=7451)</th>
<th>&gt;1–3 h (n=6033)</th>
<th>&gt;3 h (n=6634)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) Mean (SD)</td>
<td>35.4 (13.9)</td>
<td>30.0 (14.0)</td>
<td>35.5 (14.8)</td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>2,283</td>
<td>2,180 (18.5)</td>
<td>1,014 (16.8)</td>
<td>768 (11.6)</td>
</tr>
<tr>
<td>25–34</td>
<td>2,360</td>
<td>1,888 (25.3)</td>
<td>1,562 (25.9)</td>
<td>1,625 (24.5)</td>
</tr>
<tr>
<td>35–44</td>
<td>1,356</td>
<td>1,367 (18.2)</td>
<td>1,177 (19.5)</td>
<td>1,262 (19.0)</td>
</tr>
<tr>
<td>≤4</td>
<td>1,452</td>
<td>1,467 (24.3)</td>
<td>1,467 (24.3)</td>
<td>1,716 (25.9)</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;75</td>
<td>1,380</td>
<td>1,380 (18.5)</td>
<td>1,012 (16.8)</td>
<td>768 (11.6)</td>
</tr>
<tr>
<td>76–89</td>
<td>1,203</td>
<td>1,064 (17.6)</td>
<td>1,029 (15.5)</td>
<td>1,029 (15.5)</td>
</tr>
<tr>
<td>&gt;89</td>
<td>4,857</td>
<td>3,955 (65.6)</td>
<td>3,955 (65.6)</td>
<td>4,821 (72.7)</td>
</tr>
<tr>
<td>Heart rate (beats per min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;77</td>
<td>681</td>
<td>450 (7.5%)</td>
<td>602 (9.1%)</td>
<td>602 (9.1%)</td>
</tr>
<tr>
<td>77–91</td>
<td>1,189</td>
<td>971 (16.1%)</td>
<td>1,226 (20.0%)</td>
<td>1,226 (20.0%)</td>
</tr>
<tr>
<td>92–107</td>
<td>1,888</td>
<td>1,562 (25.9)</td>
<td>1,625 (24.5)</td>
<td>1,625 (24.5)</td>
</tr>
<tr>
<td>&gt;107</td>
<td>3,637</td>
<td>2,990 (49.6)</td>
<td>3,059 (46.1)</td>
<td>3,059 (46.1)</td>
</tr>
<tr>
<td>Respiratory rate (breaths per min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>149</td>
<td>82 (1.4%)</td>
<td>77 (1.2%)</td>
<td>77 (1.2%)</td>
</tr>
<tr>
<td>10–29</td>
<td>6,144</td>
<td>4,992 (82.7%)</td>
<td>5,590 (84.3%)</td>
<td>5,590 (84.3%)</td>
</tr>
<tr>
<td>≥29</td>
<td>1,077</td>
<td>903 (14.9%)</td>
<td>923 (13.9%)</td>
<td>923 (13.9%)</td>
</tr>
<tr>
<td>Capillary refill time (s)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2</td>
<td>2,450</td>
<td>2,140 (35.5%)</td>
<td>2,217 (33.4%)</td>
<td>2,217 (33.4%)</td>
</tr>
<tr>
<td>3–4</td>
<td>3,472</td>
<td>2,773 (46.3%)</td>
<td>3,110 (46.9%)</td>
<td>3,110 (46.9%)</td>
</tr>
<tr>
<td>&gt;4</td>
<td>1,131</td>
<td>963 (16.0%)</td>
<td>1,257 (19.0%)</td>
<td>1,257 (19.0%)</td>
</tr>
<tr>
<td>Glasgow coma score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe (3–8)</td>
<td>1,000</td>
<td>1,124 (18.6%)</td>
<td>1,494 (22.5%)</td>
<td>1,494 (22.5%)</td>
</tr>
<tr>
<td>Moderate (9–12)</td>
<td>868</td>
<td>915 (15.2%)</td>
<td>909 (13.7%)</td>
<td>909 (13.7%)</td>
</tr>
<tr>
<td>Mild (13–15)</td>
<td>5,577</td>
<td>3,994 (66.2%)</td>
<td>4,214 (63.5%)</td>
<td>4,214 (63.5%)</td>
</tr>
<tr>
<td>Continents</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asia</td>
<td>1,213</td>
<td>2,475 (41.0%)</td>
<td>3,656 (55.1%)</td>
<td>3,656 (55.1%)</td>
</tr>
<tr>
<td>Africa</td>
<td>2,490</td>
<td>1,437 (23.8%)</td>
<td>872 (13.1%)</td>
<td>872 (13.1%)</td>
</tr>
<tr>
<td>Central and South America</td>
<td>2,453</td>
<td>1,456 (24.1%)</td>
<td>1,355 (20.4%)</td>
<td>1,355 (20.4%)</td>
</tr>
<tr>
<td>North America, Europe, and Oceania</td>
<td>1,295</td>
<td>665 (11.0%)</td>
<td>751 (11.3%)</td>
<td>751 (11.3%)</td>
</tr>
</tbody>
</table>

Data are number (%), unless otherwise stated.

Table 2: Patient characteristics by time to treatment.
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 10060 (4.9%) patients died because of bleeding in the tranexamic acid group versus 574 of 10067 (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
significantly haemorrhage, as evidenced by hypotension or the treating physician judged them to have ongoing faced in clinical practice. Patients were enrolled if entirely clinical, and reflect the situation that doctors are 3 h after the injury.

Patients in the CRASH-2 trial were treated more than prehospital times. Indeed, about a third of trauma income and middle-income countries have long important since many bleeding trauma patients in low-

administration does cause harm, this finding would be non-bleeding cause (competing risks). If late admin-
treatment beyond 3 h who died from 3 h (table 1). This finding might indicate that patients increase in all-cause mortality in patients treated after bleeding, although there was no evidence of any interactions between treatment and 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.

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
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. Fibrinolysis can be assessed by measurement of fibrin degradation products, which include small protein fragments called D-dimers. Brohi and colleagues 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. Similar results were recorded in a 2009 study from Japan that measured fibrin degradation product and D-dimers in 314 severe trauma patients. 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. 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. 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. 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.

CRASH-2 trial coordination
Writing Committee: Ian Roberts (UK) (chair), Haleema Shakur (UK), Adefemi Afolabi (Nigeria), Karim Brohi (UK), Tim Coats (UK), Yashbir Dewan (India), Satoshi Gando (Japan), Gordon Guyatt (Canada), B J Hunt (UK), Carlos Morales (Colombia), Pablo Perel (UK), David Prieto-Merino (UK), Tom Woolley (UK).
National coordinators: Jonathan Dakuko (Ghana), Tamar Gogichaishvili (Georgia), Nyoman Golden (Indonesia), Mario Iurietta (Ecuador), Hussein Khamis (Egypt), Edward Komolafe (Nigeria), Jorge Loria-Castellanos (Mexico), Jorge Mejia-Martilla (Colombia), Jaime Miranda (Peru), Angeles Muñoz (Spain), Vincent Mutiso (Kenya), Patrick Okwen (Cameroon), Zulima Ortiz (Argentina), María Pascual, CENCEC (Cuba), R Ravi (India), April Roslani (Malaysia), Stefan Trenkler (Slovakia), Annalisa Volpi (Italy), Surakranta Yuthakasemsunt (Thailand).
Trial Coordinating Centre team: Ian Roberts (clinical coordinator, chief investigator), Haleema Shakur (trial manager), Pablo Perel (regional coordinator), Lin Barnetson (data manager), Maria Ramos (trial administrator), Lisa Cook (assistant trial manager, regional coordinator from 2007), Taemi Kawahara (assistant trial manager, regional coordinator from 2007), Eni Balogun (regional coordinator from 2006), Matthew Berle (trial assistant from 2007), Collette Barrow (assistant administrator from 2008), Tony Brady (programmer to 2006), Chris Rubery (data assistant from 2009), Jackie Wayte (UK nurse coordinator from 2008), Cynthia To (data assistant 2007–09).
Steering Committee: Ian Franklin (chair), Brigitte Chaudhry, Tim Coats, Charles Deakin, Steve Goodacre, Beverley Hunt, David Meddings, Richard Peto, Ian Roberts, Peter Sandercock.
Management Group: Ian Roberts (chair), Haleema Shakur, Tim Coats, Phil Edwards, Beverley Hunt, Maria Ramos.
Data Monitoring and Ethics Committee: Rory Collins (chair), Adrian Grant, John Myburgh, Alex Baxter (independent statistician).
For the full list of collaborators please see the online version of this Article and Lancet 2010; 376: 23–32.

Panel: Research in context

Systematic review
A 2011 Cochrane systematic review 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.
Conflicts of interest
Members of the Writing Committee declare that they have no conflicts of interest.

Acknowledgments
The London School of Hygiene and Tropical Medicine supported the core trial coordinating staff during the first year of the trial set-up. Funding for the run-in stage was provided by J P Moulton Charitable Foundation and the BUPA Foundation. A grant-in-aid for purchasing the tranexamic acid and placebo was provided by Pfizer. The main phase of this trial was funded by the UK NIHR Health Technology Assessment programme and will be published in full in the Health Technology Assessment journal series. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Department of Health.

References
CRASH-2 trial collaborators by country

Albania (115)—National Trauma Centre Hospital: Fatos Olidashi, Mihal Xergji, Tefik Zhurda, Klotilda Ruçi; Spitali Civil Durres: Arben Banush; Argentina (5)—Hospital Ángel Cruz Padilla: Mario Sardón Traverso, Juan Jiménez; Hospital Regional Rio Grande: Jorge Balbi; Hospital 4 de Junio: Dr Ramon Carrillo: Christian Dellerà; Hospital Castro Rondón: Silvana Sampaio; Hospital San Martin de La Plata: Gustavo Quintana; Hospital Municipal de Agudos: Dr Leonidas Lucero; Gustavo Páteo; Hospital Interciensial General de Agudos: Dr Oscar Alende; Jorge Teves. Australia (17)—Nepean Hospital: Ian Seppelt; Sir Charles Gairdner Hospital: David Mountain; John Hunter Hospital: Zsolt Balogh. Bangladesh (12)—United Hospital Limited: Maniruzzaman. Belgium (5)—Sint-Vincentius Hospital: Patrick Drweu, Robert Buitsaert; Centre Hospitalier Regional de Namur: Guy Mazaric. Cameroon (124)—Tombel District Hospital: Foggas Pascal, Zougno Yvette, Djeuchou Chancelienn; St Theresia’s Catholic Medical Centre: Patrick Okwen; Bamenda Provincial Hospital: Jules Djokam-Liapoe; Bali District Hospital: Ernest Jangwa; Bafut District Hospital: Lawrence Mbusaghov; Fundong District Hospital: Ninifying Fointama; St John of God Medical Centre: Foggas Pascal. Canada (2)—Hamilton General Hospital: Frank Baille. China (51)—Renji Hospital: Ji-yao Jiang, Guo-yi Gao, Yin-hui Bao. Colombuia (294)—University of Antioquia, Hospital San Vicente de Paul: Carlos Salamanca; Hospital San Juan Siera Negra: Camilo Correa; Carolina Gómez; Hospital Universitario San Jose de Popayan: Jorge Herrera, Liliana Caicedo, Alexes Rojas, Henry Pastor, Hugo Miranda; Hospital Pablo Tobon Uribe: Alfredo Constanit, Mayla Zermend, Diego Muñoz, Álvaro Daupte, Edvin Vásquez; Hospital San Arístides del Tintal: Carlos Vélez. Colombia (676)—Medical Trust Hospital: Adan Perez, Carlos Radici; Hospital General Calixto García: Martha Larrea; Hospital Antonio Luaces; Hospital Miguel Enríquez: Thorvald Fortun; La Clínica Universitaria: Eugenio Casola; Hospital Universitario “Arnaldo Milián Castro”: Dr Oscar Alende. Costa Rica (294)—Hospital Universitario de Heredia: María fonseca; Hospital Universitario de Alajuela: Alvaro Mora. Croatia (115)—Clinical Center Zagreb: Vladimir Marohnic; University Hospital Centre: Zvonimir Ajdukovic. Cyprus (115)—Nicosia General Hospital: Eleni Hadjigeorgiou; Limassol General Hospital: Constantinos Papadopoulous; Larnaca General Hospital: Marios Savvides. Czech Republic (159)—Masaryk University Hospital: Miroslav Novotny; Charles University Hospital: Libor Duska. Denmark (115)—Randers University Hospital: Lena Kilde.; Rigshospitalet: Majken Hummel-Jensen. Spain (115)—Hospital Universitario de Salamanca: María Luisa de la Torre; Hospital Universitario de Valladolid: Pedro Martínez. Georgia (115)—Tbilisi State University Clinical Hospital

‘Javakhishvili’: Budu Shalamberidze, Elza Demuria, Nikoloz Rtvilashvili, Gocha Chukhterashvili, David Dostashvili; Tbilisi First Hospital, University Clinic, Neurosurgery Center: Tamar Gogichaishvili, George Ingerokva, David Kazakhvili, Besik Melikidze, Natia Iashvili; Tbilisi City Hospital #1: Gia Tomadze, Manana Chikhhakadze, Leri Khurtsidez, Zviad Lomidze, Diana Dzagania; Tbilisi State Medical University ER Department: Nikoloz Kvakadze, Giorgi Gotsadze, Vakhtung Kainzani; Institute of Critical Care Medicine: Nino Kajaia. Ghana (136)—Korle Bu Teaching Hospital: Jonathan Dakubu, Simon Naaeder, Priscilla Sowah; Nypahinah Government Hospital: Adamu Yusuf, Allahi Ishaq; Sogakope District Hospital: Paul Salasi-Seferu; Methodist Hospital Wench: Ballu Sibu; Effia Nkwanta Regional Hospital: Sampson Sarpom-Pepraah; Saint Theresia’s Hospital: Theodore Boro. India (167)—Medical Trust Hospital Kochi: Kanjithanda Bopaiah, Kishore Shetty, Raja Subhish, Lukenm Mulla, Anand Doshi; Christian Medical College Ludhiana: Yashbir Dewan, Sarvpreet Grewal, Pradip Tripathy, Jacob Mathew, Bharti Gupta; Aditya Neuroscience Centre: Anil Lal, Majule Choudhury; Sri Sai Hospital: Sanjay Gupta, Sweta Gupta, Arun Chug; Care Hospital: Venkataratnam Pamidimutukka, Palaniappan Jagannath, Mohan Maharaj, Ramaraju Vommi, Naresh Gudipati; North Bengal Neuro Research Centre: W H Chhang; Shef VS General Hospital and NHL: Municipal College: Pankti Patel, Niyal Suthar, Deepa Banker, Jyotish Patel, IUT Medical College and General Hospital: Satish Dharap, Ranjeet Kamble, Shradhha Patkar, Sulhil Lohiya; Government Medical College and Associated Hospitals Jammuk: Rakesh Saraf, Dinesh Kumar, Satish Parihar, Rahul Gupta; MKCG Medical College: Lasanand Mangual, Atumumithu, Don Koopeg, Chinmayma Mohapatra; Christian Medical College Hospital Vellore: Suress David, Wesley Rajeelan, Appas; KLE Hospital and Medical Research Centre: Ashok Pangi, Vivek Saraf, Santosh Chikareddy; NKP Salve Institute of Medical Sciences and Lata Mangeshkar Hospital: Sudhish Mankar, Anil Gollaf, Rahul Sakhare, Nitesh Wag; Sanjivani Diagnostics and Hospital: Anil Lal, Dhiman Hazarika; Parkar Hospital: Pratyush Chaudhuri, Jeewan Jyoti Hospital and Research Centre: Prakash Ketan; Manasarovar Hospital: Govindbhau Purohit, Yogesh Purohit, Mandakini Pandya; Postgraduate Institute of Medical Science Rohtak: Rakesh Gupta, Shashi Kiran, Saurabh Wali; Goyal Hospital Jahn: Sonam Goyal, Sidhant Goyal, Satish Goyal; Government Medical College Chandigarh: Sanjay Gupta, Ashok Attiri, Rajveer Sharma; Obari Hospital: Ashok Oberi, Mahesh Oberi, Supriya Oberoi; Rajveer Gandhi Memorial Hospital and Research Centre: Gajendra Kant Tripathi; Calicut Medical College Hospital: Vijayan Pratikkand, Premkumar Karuthillath, Pavithran Vadakkumudi; Krishnamai Medical and Research Foundation’s NIKOP Hospital: Jilindar Pol, Sunita Pol, Manisha Saiete; St Stephen’s Hospital: Subrat Rai, Shashi Tiwari, Neleino Nelly; Government Rajaji Hospital: M Chidambaram; Medical College Trivandum: Viswanathan Kollengode, Sam Thampam, Sanjeevani Hospital; Sunder Rajan, Shuhut Rajan; Kaminiens Hospital: Subodh Raju, Renuka Slaa; Sri Sakthi Hospital: Shubhi Venkatesh Babu, Chellappa Sumathi; Bhattacharya Orthopaedic and Related Research Centre: Pratyush Chatterjee, Alok Agarwal; Sushrut Hospital: Hemant Magar, Meera Magar; All India Institute of Medical Sciences: Manmohan Singh, Deepak Gupta; GM Hospital (P): LTD: Anil Lal; Kalim Halai; Government Medical College and Super specialty Hospital Nagpur: Varsha Sagdeo, Pramod Giri; Government Medical College New Civil Hospital: Nimesh Verma, Ravi Jariwala, Ashish Ghoti; Chikitsa Hospital: Aman Prabhau-Gaonkar, Sagar Utagi; Apollo Health City: Mahesh Joshi, Ruchi Agrawal; Apex Neurotrauma and Superspeciality Hospital: Gopal Sharma, Gurvinder Saini; Neo Center Gola Ghat: Vinod Tewari; NSCB Medical College: Yad Yadav; Vijay Parihar; BGS Global Hospital: Neelam Venkataraman, Shailesh Rao; Chettinad Hospital and Research Institute: Narayana Reddy; Sir Sayajirao General Hospital and Medical College Baroda: Virendra Hathia; Goyal Hospital and Research Centre Jodhpur: Vithal Das; Krishna Surgical Hospital and Trauma Care Centre: Kantiibhi Agaia; Nizam’s Institute of Medical Sciences: Anirudh Purohit; Niramay Hospital: Akipal Lehari; Apex Hospital: Akipal Bhagchandani; Dr Jeyasekharan Medical Trust: Bala Vidyasagar; Himalayan Institute of Medical Sciences: P K Sachan; Apollo Genezrabad: Tannay Das; Civil Hospital Gandhi nagar.
Tranexamic acid for trauma

After its publication in July, 2010, the CRASH-2 study 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 effect 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 collaborators3 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 effects 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 effect 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 markers of 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. 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 collaborators3 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 effects of each of the antifibrinolytic drugs. Alternatively, it might reflect some factor of the patients who received it late. Whatever the mechanism, the CRASH-2 collaborators3 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, affordable, and effective 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 efficacy. 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.

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. 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 effective 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.

We declare that we have no conflicts of interest.

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*Russell L Gruen, Biswadev Mitra
The National Trauma Research Institute (RLG) and Emergency and Trauma Centre (BM), The Alfred Hospital, Monash University, Melbourne, VIC 3004, Australia
r.gruen@alfred.org.au