Critical Review Form
Therapy

Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. Lancet. 2010.

Objectives: **To assess "the effects of the early administration of a short course of tranexamic acid [TXA] on death, vascular occlusive events, and the receipt of blood transfusion in trauma patients with or at risk of significant haemorrhage." (p. 1)**

Methods: **This blinded, randomized, placebo-controlled trial was conducted at 274 hospitals in 40 countries. Adult trauma patients with "significant hemorrhage" were enrolled and randomized to receive either TXA (1 gram over 10 minutes followed by 1 gram over 8 hours) or placebo (0.9% saline). Patients were eligible for enrollment if they had trauma within 8 hours of enrollment, had a systolic blood pressure < 90 mmHg or heart rate > 110 beats per minute, were considered to be at risk for significant hemorrhage, and if the treating physician was uncertain as to whether TXA should be given. Patients in whom the treating physician felt certain that TXA should be given, and those with clear contraindications to TXA, were not eligible for inclusion.**

Group allocation was balanced by center using a randomization block size of 8. The allocation sequence was generated by a computer random number generator. In hospitals with reliable telephone service, the University of Oxford Clinical Trial Service Unit was contacted for treatment pack allocation. In hospitals without reliable telephone service, the lowest numbered treatment pack was selected from a box of 8 numbered packs.

The primary outcome was death within 4 weeks of injury. The cause of death was further subdivided into bleeding, vascular occlusion (MI, stroke, PE), multiorgan failure, head injury, or other. Secondary outcomes included vascular occlusive events (MI, stroke, PE, and DVT), need for surgical intervention, need for blood transfusion, and the number of units of blood products transfused. Functional ability was also recorded at hospital discharge or at day 28 if still hospitalized, using the Modified Oxford Handicap Scale. Data was also collected on the use of recombinant factor VIIa and GI bleeding.

A total of 20207 patients were randomized to either TXA (n = 10093) or placebo (n = 10114). Four patients withdrew consent and were not included in the analysis. Primary outcome data were available for 20127 (99.6%) patients, of whom 10060 were randomized to TXA, while 10067 were randomized to placebo. Of these subjects, 19944 (99.1%) were known to have completed the loading dose, while 18965 (94.2%) completed the 8-hour maintenance dose. Overall, 3076 (15.3%) patients died.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis (answer the questions posed below)?**	
1.	Were patients randomized?	Yes. "Randomisation was balanced by centre, with an allocation sequence based on a block size of eight, generated with a computer random number generator." (p. 2)
2.	Was randomization concealed (blinded)?	Yes. "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...Hospitals with reliable telephone access used the University of Oxford Clinical Trial Service Unit (CTSU) telephone randomisation service..." (p. 2)
3.	Were patients analyzed in the groups to which they were randomized?	Yes. "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." (p. 2) Therefore an intention to treat analysis was used. 4 patients in whom consent was withdrawn were not included in the analysis.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. Patients in the two groups were similar with respect to gender, age, time since injury, type of injury, blood pressure, heart rate, and GCS (Table 1).

<table>
<tr><td></td><td></td><td>Table 1. Demographic data
<table><tr><td></td><td>TXA
(n = 10093)</td><td>Placebo
(n = 10114)</td></tr><tr><td>Sex
• Men
• Women</td><td>
8439 (83.6%)
1654 (16.4%)</td><td>
8496 (84%)
1617 (16.0%)</td></tr><tr><td>Mean age in years (SD)</td><td>34.6 (14.1)</td><td>34.5 (14.4)</td></tr><tr><td>Mean time since injury in hours (SD)</td><td>2.8 (2.2)</td><td>2.9 (2.6)</td></tr><tr><td>Type of injury
• Blunt
• Penetrating</td><td>
6812 (67.5%)
3281 (32.5%)</td><td>
6843 (67.7%)
3271 (32.3%)</td></tr><tr><td>Systolic blood pressure (mmHg)
• ≤ 75
• 76-89
• ≥ 90</td><td>
1566 (15.5%)
1615 (16.0%)
6901 (68.4%)</td><td>
1608 (15.9%)
1697 (16.8%)
6791 (67.1%)</td></tr><tr><td>Heart rate
• < 77
• 77-91
• 92-107
• > 107</td><td>
875 (8.7%)
1727 (17.1%)
2556 (25.3%)
4872 (48.3%)</td><td>
871 (8.6%)
1770 (17.5%)
2546 (25.2%)
4853 (48.0%)</td></tr></table>
The authors do not report other important demographic information, such as base deficits or quantification of the severity and location of injury via Injury Severity Score, Revised Trauma Score, or Abbreviated Injury Scale.</td></tr>
<tr><td>B.</td><td>Did experimental and control groups retain a similar prognosis after the study started (answer the questions posed below)?</td><td></td></tr>
<tr><td>1.</td><td>Were patients aware of group allocation?</td><td>No. This was a blinded, placebo-controlled study. “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).” (p. 2)

"Tranexamic acid and placebo ampoules were indistinguishable." (p. 2)

“Both participants and study staff (site investigators and trial coordinating centre staff) were masked to treatment</td></tr>
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<table>
<tr><td></td><td></td><td>allocation.” (p. 2)</td></tr>
<tr><td>2.</td><td>Were clinicians aware of group allocation?</td><td>No. As noted above, this was a blinded, placebo-controlled study. “Both participants and study staff (site investigators and trial coordinating centre staff) were masked to treatment allocation.” (p. 2)</td></tr>
<tr><td>3.</td><td>Were outcome assessors aware of group allocation?</td><td>No.</td></tr>
<tr><td>4.</td><td>Was follow-up complete?</td><td>Mostly yes. Of 20211 patients randomized, 4 withdrew consent (3 in the TXA group, 1 in the placebo group). A further 80 patients had no follow-up data (33 in the TXA group, 47 in the placebo group. Follow-up data was therefore available for 20127 (99.6%) of the enrolled patients.</td></tr>
<tr><td>II.</td><td>What are the results (answer the questions posed below)?</td><td></td></tr>
<tr><td>1.</td><td>How large was the treatment effect?</td><td>Of 20127 patients with outcome data, 3076 (15.3%) died.

All-cause mortality was reduced with the use of TXA. The relative risk (RR) of death with TXA was 0.91 (95% CI 0.85-0.97, p = 0.0035). The absolute risk reduction (ARR) was 1.5% (95% CI 0.486 -2.474), for a number needed to treat (NNT) of 68 (95% CI 40-206).

The risk of death due to bleeding was significantly reduced with TXA, while the differences in risk of death due to vascular occlusion, multiorgan failure, head injury, and other causes were not statistically significant (Table 2).

Table 2. Death by cause
<table>
<tr><td></td><td>RR (95% CI)</td><td>p-value</td></tr>
<tr><td>Any cause</td><td>0.91 (0.85-0.97)</td><td>0.0035</td></tr>
<tr><td>Bleeding</td><td>0.85 (0.76-0.96)</td><td>0.0077</td></tr>
<tr><td>Vascular occlusion</td><td>0·69 (0·44–1·07)</td><td>0.096</td></tr>
<tr><td>Multiorgan failure</td><td>0.90 (0.75-1.08)</td><td>0.25</td></tr>
<tr><td>Head injury</td><td>0·97 (0·87–1·08)</td><td>0.60</td></tr>
<tr><td>Other</td><td>0.94 (0.74-1.20)</td><td>0.63</td></tr>
</table>

There was no significant difference in the number of vascular occlusive events (fatal and nonfatal), need for surgical intervention, need for blood transfusion, or the number of patients classified as dead or dependent at discharge (Table 3). There was no difference in the median number of units of blood required in the TXA group</td></tr>
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<tr><td></td><td></td><td>compared to the placebo group (3, interquartile range [IQR] 2-6 versus 3, IQR 2-6; p = 0.59).

Table 2. Secondary outcomes<table><tr><td></td><td>RR (95% CI)</td><td>p-value</td></tr><tr><td>Vascular occlusion</td><td>0·84 (0·68–1·02)</td><td>0.084</td></tr><tr><td>Need for transfusion</td><td>0·98 (0·96–1·01)</td><td>0.21</td></tr><tr><td>Any surgery</td><td>1·00 (0·97–1·03)</td><td>0.79</td></tr><tr><td>Dead or dependent</td><td>0.97 (0.93-1.00)</td><td>0.12</td></tr></table></td></tr>
<tr><td>2.</td><td>How precise was the estimate of the treatment effect?</td><td>See above.</td></tr>
<tr><td>III.</td><td>How can I apply the results to patient care (answer the questions posed below)?</td><td></td></tr>
<tr><td>1.</td><td>Were the study patients similar to my patient?</td><td>Not necessarily. Of the total cohort, only 2711 (13.5%) were enrolled in Europe or North America; the vast majority of patients were enrolled in Asia, Africa, and Central or South America. Differences in practice pattern (i.e. more sophisticated resuscitation measures) may have a significant effect on mortality due to bleeding, and may negate the results of the study. The availability of vascular interventional radiology (VIR) alone as a means to stop bleeding following trauma would have significant impact on bleeding and mortality.

Additionally, the exclusion of patients in whom TXA was felt to be clearly indicated would potentially exclude a large number of patients who would benefit from TXA administration. This would reduce the apparent reduction in mortality from its use, making TXA appear less effective. This exclusion comes despite the fact that the efficacy of TXA has not been well established.</td></tr>
<tr><td>2.</td><td>Were all clinically important outcomes considered?</td><td>Yes. The authors considered overall mortality, mortality due to bleeding, need for surgical intervention, need for blood product transfusion, and disability. The authors did not assess the cost of healthcare.</td></tr>
<tr><td>3.</td><td>Are the likely treatment benefits worth the potential harm and costs?</td><td>Uncertain. The exclusion of patients felt to clearly require TXA would bias the results against its use, while the large number of patients in low to middle-income countries could potentially inflate its efficacy. A study conducted in purely</td></tr>
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		high-income countries with similar practice patterns and available resources to ours, including all patients who may benefit from TXA administration may provide a more accurate estimate of effect size.

Limitatons:

1. **The study's inclusion criteria were subjective, including patients "who were considered to be at risk of significant haemorrhage." Additionally, patients with clear indications or contraindications to TXA were not included.**

2. **Only 5% of patients had bleeding as their cause of death, and only ~50% of included patients required blood transfusion. Given the proposed mechanism of action of TXA, this could potentially bias the results against benefit.**

3. **Important demographic information evaluating injury severity was not provided for the groups (base deficits, quantification of the severity and location of injury via Injury Severity Score, Revised Trauma Score, or Abbreviated Injury Scale).**

4. **Despite the proposed mechanism for TXA, its use did not reduce the need for blood transfusion, or the amount of products transfused.**

5. **No patients were enrolled in the US, and only 13.5% were enrolled in Europe or North America (external validity).**

For additional critiques of the CRASH-2 study, see the website and discussion below: http://marylandccproject.org/education/crash2-wrong-review-dr-mark-walsh/

Bottom Line:

In the CRASH-2 trial, administration of TXA to adult trauma patients with, or at risk of, significant hemorrhage, within 8 h of injury, significantly reduced all-cause mortality with a RR of 0·91 (95% CI 0·85–0·97; p=0·0035) with no apparent increase in vascular occlusive events. According to these results, 68 patients would need to be given TXA to prevent one death. The exclusion of patients in whom TXA was felt to be "clearly indicated," the low relative number of patients from North America and Europe, and the low incidence of death due to bleeding make it difficult to interpret the results in the context of our trauma system.