Critical Review Form
Therapy

The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. Lancet. 2011.

Objectives: To assess the effect of tranexamic acid (TXA) on mortality due to bleeding, but performing a subgroup analysis on data from the CRASH-2 trial.

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. A computer random number generator generated the allocation sequence. 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.

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. Overall, there were 3076 (15.3%) deaths, with death due to bleeding accounting for 1063 (35%) cases.

A subgroup analysis was performed to evaluate death due to bleeding subdivided by four baseline characteristics: 1) time from injury (≤1, >1–3, >3 h); 2) severity of hemorrhage determined by systolic blood pressure (SBP) (≤75, 76–89, >89 mmHg); 3) Glasgow Coma Score (GCS) (severe 3-8, moderate 9-12, mild 13-15); and 4) Type of injury (penetrating, blunt or both blunt and penetrating).

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. 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 1. Demographic data

		<table><tr><th></th><th>TXA (n = 10093)</th><th>Placebo (n = 10114)</th></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>
B.	**Did experimental and control groups retain a similar prognosis after the study started (answer the questions posed below)?**	
1.	Were patients aware of group allocation?	No. This was a blinded, placebo-controlled study. Patients were randomly allocated to receive either TXA or a saline infection. Participants and study staff were blinded to treatment allocation.
2.	Were clinicians aware of group allocation?	No. As noted above, this was a blinded, placebo-controlled study.
3.	Were outcome assessors aware of group allocation?	No. As noted above, this was a blinded, placebo-controlled study.
4.	Was follow-up complete?	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.
II.	**What are the**	

<table>
<tr><td></td><td>results (answer the questions posed below)?</td><td></td></tr>
<tr><td>1.</td><td>How large was the treatment effect?</td><td>The risk of death due to bleeding was significantly reduced with TXA: death due to bleeding occurred in 489 of 10060 (4.9%) in the TXA group compared with 574 of 10067 (5.7%) in the placebo group, for a relative risk (RR) of 0.85 (95% CI 0.76-0.96, p = 0.0077).

Treatment within one hour of injury, and 1-3 hours after injury, significantly reduced the risk of death due to bleeding, while treatment more than 3 hours after injury significantly increased the risk of death due to bleeding. Significant reductions in death due to bleeding were also observed for those with a SBP ≤75 mmHg, a GCS of 9-12, and those with penetrating injury (Table 2)

Table 2. Results of subgroup analysis
<table>
<tr><th></th><th>TXA</th><th>Placebo</th><th>RR (95% CI)</th></tr>
<tr><td>Time to treatment (h)
• ≤1
• 1–3
• >3</td><td>
198/3747 (5·3%)
47/3037 (4·8%)
144/3272 (4·4%)</td><td>
286/3704 (7·7%)
184/2996 (6·1%)
103/3362 (3·1%)</td><td>
0·68 (0·57–0·82)
0·79 (0·64–0·97)
1·44 (1·12–1·84)</td></tr>
<tr><td>SBP (mmHg)
• 89
• 76-89
• ≤75</td><td>
146/6878 (2·1%)
110/1609 (6·8%)
233/1562 (14·9%)</td><td>
163/6761 (2·4%)
114/1689 (6·7%)
295/1599 (18·4%)</td><td>
0·88 (0·71–1·10)
1·01 (0·79–1·30)
0·81 (0·69–0·95)</td></tr>
<tr><td>GCS
• Severe (3-8)
• Moderate (9-12)
• Mild (13-15)</td><td>
168/1789 (9·4%)
93/1349 (6·9%)
228/6915 (3·3%)</td><td>
186/1830 (10·2%)
121/1344 (9·0%)
265/6877 (3·8%)</td><td>
0·92 (0·76–1·13)
0·77 (0·59–0·99)
0·86 (0·72–1·02)</td></tr>
<tr><td>Type of injury
• Blunt
• Penetrating</td><td>
308/6788 (4·5%)
181/3272 (5·5%)</td><td>
347/6817 (5·1%)
227/3250 (7·0%)</td><td>
0·89 (0·77–1·04)
0·79 (0·66–0·96)</td></tr>
</table>

The odds ratio (OR) of death due to bleeding with TXA when given early was 0.61 (95% CI 0.50 to 0.74), and is estimated to multiply by 1.15 (95% CI 1.08 to 1.23) for every hour that passes.</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>
</table>

1.	Were the study patients similar to my patient?	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.
2.	Were all clinically important outcomes considered?	Yes. The authors considered overall mortality, mortality due to bleeding, and mortality due to bleeding in several subgroups of the overall cohort, based on time elapsed since injury, GCS, and type of injury.
3.	Are the likely treatment benefits worth the potential harm and costs?	Uncertain. This was a subgroup analysis on a secondary outcome, and could be construed as "data mining" to find significance that could easily be attributed to chance alone. While the results, namely that TXA is more effective when given early after traumatic injury and may be harmful when given later, are thought-provoking and logical, firm conclusions about the timing of administration can not be made based on these results. These results are hypothesis generating, and suggest the need for further research on the timing of TXA administration in severe trauma.

Limitations:

1. **Please see the list of limitations noted for the CRASH-2 trial in the PGY-1 Answer Key.**

2. **This was a subgroup analysis on a secondary outcome of the original CRASH-2 trial. Any statistical significance identified could easily be attributed to chance alone. While thought provoking and hypothesis generating, these results will need to be further validated in a prospective trial.**

Bottom Line:

This subgroup analysis of data from the CRASH-2 trial suggests that the early administration of TXA (< 3 hours) results in a significant reduction in death due to bleeding following severe trauma, while administration beyond 3 hours results in a significant increase in mortality due to bleeding. These results are both logical and

thought provoking, but further investigation will be necessary to validate the results. The additional critiques of the CRASH-2 trial itself further complicate the interpretation of these results in the context of trauma care in large trauma centers in the US.