

# EM Journal Club Eastern Virginia Medical School

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**CITATION:** Shakur H, et al. **Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomized, placebo-controlled trial.** Lancet. 2010 Jul 3; 376: 23-32.

I. WHAT IS BEING STUDIED?	
1. Study Objective	Does tranexamic acid vs NaCl control in trauma patients with shock or high risk of hemorrhage decrease death without increased adverse outcomes such as vasoocclusive events and decrease blood transfusion requirements
2. Study Design	Multi-centered international trial 274 hospitals in 40 countries 'andomized double blind controlled' Tranexamic acid vs NaCl control randomized, 1 mg over 10 min over 8 hrs, 274 hosp 40 countries, physician and pts blinded.
3. Inclusion Criteria	Adults trauma pts. At risk for significant hemorrhage (tachycardia >110 SBP < 90) within 8 hrs from injury, responsible doctor had to be 'uncertain' regarding the use an antifibrinolytic agent in bleeding patient (very unclear how this determination was made)
4. Exclusion Criteria	Children, those with contraindication to TXA, or doctor who is 'certain' regarding appropriate indication for using tranexamic agent in specific patient

5. Interventions Compared	Tranexanic acid vs NaCl (placebo)
6. Outcomes Evaluated	<p><b>Primary</b> -Death at 28 days -&gt; causes – bleeding, vascular occlusion, multigrain failure,</p> <p><b>Secondary</b> - vascular occlusive events (MI, CVA, PE, DVT) surgical intervention, blood transfusions, functional status at 28 days (dependency measured by Modified Oxford Scale)</p> <p>Weakness – no stratification based on injury severity score</p> <p>“Outcomes were recorded if they occurred while the patient was still in the hospital for up to 28 days after randomization”</p>
<b>II. Are the results of the study valid?</b>	
1. Was the assignment of patients randomized?	Unclear– patients apparently underwent a subjective qualification by treating physicians before being placed in a randomization sequence. Treating physicians first determined if patients had definitive indication for TXA or a contradiction. All of these subjects were excluded. Those with indeterminate indications for TXA were randomized. No guidance regarding standardized criteria regarding indications for TXA across study sites. High potential for selection bias.
2. Were all patients who entered the trial properly accounted for and attributed at its conclusions?	Unclear. very little information is provided regarding. It is unclear if patients that were discharged prior to 28 days were followed-up as out patients or if their f/u concluded at the time of D/C. No description regarding the specifics of put-patient f/u were included
3. Was follow-up complete?	Unclear. As stated above, authors claim

	99.6 follow-up but fail to describe exactly how they followed there patients and if they followed them post discharge and if so how did they do it?
4. Were patients, health workers and study personnel “blind” to treatment?	Yes – Once subjects were selected for inclusion (for randomization) by treating physicians. TXA and NS were undistinguishable.
5. Were study groups similar at the start of the trial?	Yes – very similar characteristics as reported by authors.
6. Aside from the experimental intervention, were the groups treated equally	Uncertain. Appears that patients were well matched regarding various interventions however some interventions such as amount of fluid resuscitation between groups was not described.
<b>III. What were the results?</b>	
1. How large was the treatment effect? (difference between treatment and control group).	<p>Risk Reduction Overall Death – TXA vs NaCl ARR 14.5% vs 16% = 1.5% or RR 0.91 (CI 95% .85-97)</p> <p>Risk Reduction Death from bleeding TXA vs NaCl ARR 4.9% vs. 5.7%= 0.8% RR 0.85 (CI 95% 0.76-0.96)</p> <p>Functional Status: Normal at 28 days TXA vs. NaCL ARR 14.7% vs. 13.3% = 1.4% RR 1.10 (CI 95% 1.04-1.19) 149 pts</p> <p><b>No Statistically sig differences</b> in: Blood transfusions; Surgery;Vascular occlusive events;</p>

2. What was the estimated treatment effect at a 95% confidence interval?	Absolute risk reduction of death 1.5% Relative risk reduction of death 9% Number needed to treat 1/ARR = 1/0.015 =66
IV. Will the results help me in caring for my patients? (Applicable?)	
1. Were all clinically important outcomes considered?	Yes – authors appear to have considered most important clinical outcome measures  No mention of following seizures as a complication which is commonly described side effect of TXA use.  No cost analysis was discussed.
2. Are treatment outcomes worth the potential harms?	No statistically significant differences in bad outcomes identified with the use of TXA though seizure frequency was not reported which could have been an important measure considering its description in the literature.

Additional Comments: TXA appears to demonstrate some improvement in death (ARR 1.5%) and bleeding (ARR 0.8%) though marginally so. Statistical significance and narrow CI's are likely a reflection of the sample sizes more than anything else. The authors do not report an NNT, which is curious and unclear as to why it was not included. The NNT is 66, meaning one would have to treat 66 bleeding trauma patients with TXA in order to achieve positive effect in one. In lieu of either a cost analysis or a reporting on the most commonly described side effect of TXA (seizures) it may be difficult to justify routine use of TXA in trauma patients. The lack of an increase in Vascular Occlusive Events with TXA is favorable as these agents have also been associated with stroke and MI as complications. The issues of selection bias persists as the treating physicians needed to decide if the patients were 'eligible for TXA' or had a contraindication either of which have excluded subject from enrollment. The practice of using TXA might be more common in some of the countries that participated however no discussion regarding how those subjects were identified was offered.