

Tranexamic acid treatment for trauma victims

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Abstract

World-wide, traumatic injury is responsible for over 5 million deaths per year, the majority due to exsanguination and head injury. The antifibrinolytic drug tranexamic acid is the only drug proven to reduce deaths after traumatic injury. Several large randomised controlled trials have provided high quality evidence of its effectiveness and safety in trauma patients. Early tranexamic acid reduces deaths on the day of the injury in polytrauma patients and patients with isolated traumatic brain injury by around 20%. Treatment is time critical; for patients to benefit, tranexamic acid must be given as soon as possible after injury. Intramuscular administration is well tolerated and rapidly absorbed, with the potential to reduce time to treatment. Because the proportional reduction in bleeding death with tranexamic acid does not vary by baseline risk, a wide range of trauma patients stand to benefit. There are far more low risk trauma patients than high risk patients, with a substantial proportion of bleeding deaths in the low risk group. As such, treatment should not be limited to patients with severe traumatic haemorrhage. We must give paramedics and physicians the confidence to treat a far wider range of trauma patients whilst emphasizing the importance of early treatment.

Key words: haemorrhage, trauma, traumatic brain injury, tranexamic acid, fibrinolysis

Background

Whilst Japan was struggling to recover from the devastation of world war II, husband and wife researchers, Utako and Shosuke Okamoto, were making medical history.¹ They were searching for a drug that could reduce maternal deaths from post-partum haemorrhage.

Working on blood drawn from their own veins, they identified a powerful inhibitor of blood clot breakdown (fibrinolysis). Initially referred to as AMCHA (aminomethyl cyclohexanecarboxylic acid), the drug is now known as tranexamic acid (TXA). However, the full potential of the Okamoto's discovery would not be recognized for decades. First dentists and then surgeons noted the benefits of TXA treatment. A single dose of TXA, given just before incision, cut surgical bleeding by one third. But it was half a century later - after the CRASH2 (Clinical Randomisation after Significant Haemorrhage) trial randomized over 20,000 bleeding trauma patients to get TXA or placebo - that the world started waking up to the global health importance of TXA.² When given soon after injury, TXA cut bleeding deaths by a third, mostly by reducing deaths on the day of the injury.^{3,4} But questions remained. Could TXA reduce intracranial bleeding and reduce traumatic brain injury (TBI) deaths? To answer this question a second global trial was launched. The CRASH-3 trial recruited over 12,000 patients with isolated TBI and again found that early TXA treatment cut deaths on the day of injury – even in severe TBI.^{5,6} Indeed, the results of the two CRASH trials are almost identical and provide compelling evidence that TXA saves lives after trauma. Importantly, there was no evidence of any increased risk of vascular occlusive events.^{2,5} TXA is the only drug proven to reduce deaths after traumatic injury. Urgent treatment of all trauma patients, ideally at the scene of the injury, would prevent tens of thousands of premature deaths each year world-wide. Nevertheless, ten years after the CRASH-2 trial results were published only a fraction of trauma patients receive TXA.⁷ This article summarises the evidence from randomised trials of TXA in surgery and trauma and asks why it has taken so long for trauma victims to benefit.

Tranexamic acid reduces bleeding in surgery

There have been over one hundred randomized trials of TXA use in surgery. A 2012 systematic review and meta-analysis of 129 trials including 10,488 patients showed that TXA reduced the need for blood transfusion by a third (pooled risk ratio [RR]=0.62, 95% confidence interval [CI] 0.58-0.65).⁸ There were also fewer deaths in TXA-treated patients (RR for death with TXA=0.61, 95% CI 0.38–0.98), although when the analysis was restricted to high quality trials there was more uncertainty about the effects of TXA on mortality (RR=0.67, 95% CI 0.33–1.34). A subsequent meta-analysis, which included data from 104 trials with a total of 8,030 patients, showed that TXA given at the time of surgical incision, reduces bleeding by approximately a third (pooled RR=0.66, 95% CI 0.65–0.67) regardless of the type of surgery and the extent of bleeding.⁹ The proportional reduction in blood loss with TXA was similar regardless of the extent of surgical bleeding. The proportional reduction in blood loss with TXA did not vary substantially by type of surgery or the timing of TXA administration. An examination of the effect of TXA dose on the reduction in bleeding showed that a dose of 1 g is sufficient for most adults with no evidence to support the use of higher doses.⁹

Results from meta-analyses of small trials are prone to selection and other biases and can sometimes be misleading. However, in 2017 the effects of TXA on bleeding in surgical patients was confirmed in a large high-quality randomised trial. The ATACAS (Aspirin and Tranexamic Acid for Coronary Artery Surgery) trial was a multi-centre randomised trial in 4,662 adult patients undergoing elective coronary-artery surgery that compared TXA with matching placebo.¹⁰ TXA use was associated with a significantly lower risk of bleeding post-operatively, a reduced risk of return to theatre for control of bleeding and a highly significant reduction in blood transfusion. TXA was not associated with increased risk of thrombotic adverse effects. A large

randomised trial (10,000 patients) of TXA in non-cardiac surgery, the Perioperative Ischaemic Evaluation-3 (POISE-3) trial is currently recruiting patients.¹¹

Urgent tranexamic acid treatment reduces death due to bleeding in patients with polytrauma

World-wide, traumatic injury is responsible for over 5 million deaths per year.¹² Exsanguination and head injury are responsible for the majority of polytrauma deaths and are the most common cause of early in-hospital death.¹³ Furthermore, haemorrhage is the leading cause of death in military trauma.¹⁴ The evidence that TXA markedly reduces surgical bleeding motivated a large randomised trial of the use of TXA in bleeding trauma patients. The Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage (CRASH-2) trial was a multi-centre international randomised trial of the effect of tranexamic acid on death and vascular occlusive events in bleeding trauma patients.^{2,4} The results were published in 2010. A total of 20,211 adult trauma patients with significant bleeding, who were within 8 h of their injury, were randomly allocated to receive tranexamic acid (TXA, 1 g over 10 min followed by an infusion of 1 g over 8 h) or matching placebo. The primary outcome was death in the hospital within 4 weeks. TXA significantly reduced death due to bleeding (RR = 0.85, 95% CI 0.76–0.96) and all-cause mortality (RR = 0.91, 95% CI 0.85–0.97), with no increase in vascular occlusive events. The reduction in death due to bleeding was greatest when TXA was given within 3 hours of injury, (RR = 0.72, 95% CI 0.63–0.83). Subsequent analyses showed that immediate TXA treatment improves survival by about 70% but thereafter the treatment benefit decreases by 10% for every 15 min of treatment delay until about 3 hours, after which there is little or no benefit.¹⁵ Early administration of TXA reduces mortality primarily by

preventing exsanguination on the day of the injury.³ On the basis of the CRASH-2 trial results, TXA was added to the WHO List of Essential Medicines and included in trauma and haemorrhage protocols around the world.

Tranexamic acid reduces head injury deaths in patients with isolated traumatic brain injury

The CRASH-2 trial included bleeding polytrauma patients, many thousands of whom had TBI, but because all the included patients had significant extracranial bleeding there remained uncertainty about the effects of TXA in patients with isolated TBI. As a result, clinical guidelines on the use of TXA in trauma specified isolated TBI as a contraindication to TXA treatment. The CRASH-3 trial was conducted to resolve this uncertainty. From a pathophysiological perspective there were strong grounds to expect similar results in isolated TBI. Intracranial bleeding is common after TBI and increases the risk of death and disability.¹⁶ Patients with a large intracranial bleed have a worse outcome than those with a small bleed. Importantly, there is evidence that intracranial bleeding continues after hospital admission.¹⁷ Among patients with moderate or severe TBI, intracranial bleeding continues after hospital admission in over 80%.¹⁸ Furthermore, increased fibrinolysis, as indicated by high levels of tissue plasminogen activator (tPA) and fibrin degradation products, is common in isolated TBI and predicts progressive haemorrhage and death.¹⁹

In the CRASH-3 trial, a total of 12,737 patients with isolated TBI were randomly allocated to receive TXA (loading dose 1 g over 10 min followed by infusion of 1 g over 8 h) or matching placebo.⁵ The time window for eligibility was originally 8 h but in 2016 in the light of the results of the CRASH-2 trial and basic research into the timing of post-traumatic fibrinolysis, the protocol was changed to limit recruitment (and the primary analysis) to patients within 3

h of injury. The results were published in 2019.⁵ In patients treated within 3 h of injury, the risk of head injury-related death was 18.5% in the TXA group versus 19.8% in the placebo group (855 vs 892 deaths; RR = 0.94, 95% CI 0.86–1.02). After excluding patients with un-survivable head injuries at baseline (those with a Glasgow Coma Scale (GCS) score of 3 or bilateral unreactive pupils) in a pre-specified sensitivity analysis, the risk of head injury-related death was 12.5% in the TXA group versus 14.0% in the placebo group (485 vs 525 deaths; RR = 0.89, 95% CI 0.80–1.00). The reduction in head injury-related death with TXA was greater in patients with mild-to-moderate head injury (RR = 0.78, 95% CI 0.64–0.95) than in patients with severe head injury (RR = 0.99, 95% CI 0.91–1.07; p-value for heterogeneity 0.030). As in the CRASH-2 trial, the risk of vascular occlusive events was similar in the TXA and placebo groups.

Tranexamic acid reduces death in trauma patients

The CRASH-3 trial used the same dose and duration of TXA as in the CRASH-2 trial and essentially provided data on a group of trauma patients that were underrepresented (patients with isolated TBI) in the CRASH-2 trial. Indeed, as specified in the statistical analysis plan that was prepared and published prior to un-blinding, the CRASH-3 trial should not be considered in isolation but in the wider context of the CRASH-2 trial. When the CRASH-3 trial results are set in the context of the CRASH-2 trial, the results are essentially the same.⁶ Table 1 shows the effects of TXA on all-cause mortality in the CRASH-2 and CRASH-3 trials. The effect of TXA on mortality in patients with isolated TBI and polytrauma patients is almost identical, reducing deaths on the day of the injury by 20% to 25%, with little or no effect on deaths beyond the day of the injury. Because a larger proportion of deaths in patients with isolated TBI occur

after 24 hours (69% in CRASH-3 versus 43% in CRASH-2), and these deaths are unchanged by TXA, the effect on mortality at 28 days is smaller (more diluted) in the CRASH-3 trial, though there is no evidence of statistical heterogeneity (p-value for heterogeneity 0.18).

The CRASH-3 trial manuscript did not present p-values or mention the word 'significant', attempting to avoid the arbitrary dichotomisation of trial results into 'positive' and 'negative' that has been robustly condemned by statisticians. Some commentators nevertheless seized on the p-value for the analysis of head injury death excluding patients with unsurvivable injuries at baseline ($p=0.056$) as if a p value of 0.05 was the celestial threshold between truth and falsehood.²⁰ This is especially disappointing considering that most treatments for TBI are unproven. Indeed, doctors managing TBI patients mostly muddle through using a mix of pathophysiological theory and clinical experience. Large randomised trials like the CRASH trials reduce therapeutic uncertainty. To categorize trial results as positive or negative based on arbitrary statistical rules that were established in the 1920s for use in agricultural experiments, ignoring the totality of the available evidence, is a deplorable waste.

Following publication of the CRASH-3 trial results, results from two small trials of pre-hospital TXA treatment for trauma patients in the USA have become available. Rowell and colleagues conducted a randomised placebo-controlled trial of pre-hospital TXA treatment in 1,063 TBI patients.²¹ The effect of TXA on mortality was similar to that seen in the CRASH-3 trial although with considerably wider confidence intervals due to the smaller sample size (RR=0.88, 95% CI 0.64-1.20). However, when interpreting the results, the authors confused the absence of a statistically significant treatment effect with the absence of an effect stating that "all-cause mortality at 28 days was not different between groups (14% for TXA-treated patients vs 17% for placebo-treated patients)." Their statement illustrates clearly the misuse

of statistical concepts that has so enraged statisticians.²⁰ The STAAMP trial (Study of Tranexamic Acid During Air and Ground Medical Prehospital Transport Trial) is a randomised placebo-controlled trial of 1 g of prehospital TXA given in 903 polytrauma patients during transport to a level 1 trauma centre.²² There were again fewer deaths among TXA-treated patients (8% for TXA-treated patients vs 10% for placebo-treated patients) but the confidence intervals were wide and the difference was not statistically significant at the $p=0.05$ level of significance (RR=0.82, 95% CI 0.54-1.24). However, when set in the context of all the available randomised trial evidence, the two US based trials strengthen the conclusion that TXA treatment reduces mortality in trauma patients (Figure 1).

Tranexamic acid reduces deaths due to bleeding in women with post-partum haemorrhage

There are no hard and fast rules for deciding what evidence is relevant to a particular clinical scenario. Is the evidence that TXA reduces surgical bleeding relevant when considering the role of TXA in trauma patients? This is a matter for judgement. Similarly, how relevant is the evidence on the effect of TXA in women with post-partum haemorrhage? Childbirth is surely traumatic. Many women sustain vaginal lacerations or have an episiotomy and some women have a ruptured uterus. The WOMAN (World Maternal Antifibrinolytic) trial evaluated the effect of TXA in post-partum haemorrhage. A total of 20,060 women with a clinical diagnosis of post-partum haemorrhage were randomly allocated to receive TXA (1 g intravenously followed by a second dose if bleeding continued after 30 min or restarted within 24 h of the first dose) or matched placebo.²³ TXA reduced death due to bleeding (RR=0.81, 95% CI 0.65 - 1.00; $p=0.045$), with no increase in thromboembolic events or complications. Just as in the CRASH-2 trial, the effect on death due to bleeding was greatest when TXA was given within 3

h of childbirth, (RR=0.69, 95% CI 0.52 - 0.91; p=0.008). When given beyond 3 hours of childbirth, there was no reduction in death due to bleeding (RR=1.07, 95% CI 0.76- 1.51; p=0.70). Whilst these results might not be directly generalisable to trauma patients, they are not irrelevant.

Putting it all together – what should we do for trauma victims?

TXA is the only drug proven in randomised trials to reduce mortality in bleeding trauma patients. So how should we use it in practice? First, it needs to be given as soon as possible after injury. To reduce treatment delay, TXA is increasingly given by paramedics at the scene of injury or in the ambulance. Trauma audit data for England and Wales show that when TXA is given by paramedics the median time to treatment is 51 minutes compared to 112 minutes when TXA is given in hospital.⁷ However, world-wide, intravenous (IV) administration is a major obstacle to timely TXA treatment. In high-income countries, paramedics can give an IV injection of TXA at the scene. However, securing IV access can be difficult, particularly in patients trapped in vehicles. Rapid TXA treatment is even more challenging in low- and middle-income countries without formal pre-hospital care systems. In the absence of trained pre-hospital care providers, bystanders or police officers often provide immediate first aid. Patients in low- and middle-income countries might be taken to the nearest small clinic or health centre, often in taxis or private cars and sometimes in basic ambulances, where they receive basic medical care and many unnecessary interventions before transfer to a tertiary hospital. As a result, very few patients get TXA within three hours of injury and hardly any within the first hour. If TXA could be given intramuscularly then trained first responders,

police officers, ambulance drivers could administer it, with important reductions in time to treatment.

A recent prospective, pharmacokinetic study conducted in the emergency departments of two large London trauma centres has shown that intramuscular (IM) TXA is well tolerated and rapidly absorbed in bleeding trauma patients.²⁴ In this study, adult trauma patients who had received an IV 1-gram TXA loading dose, either pre-hospital or in-hospital, were given the second TXA dose by IM injection. The IM dose was given as two 5 mL (0.5 g each) injections into the thigh (rectus femoris or vastus lateralis), gluteal, or deltoid muscles, depending on the clinical situation (e.g. the type of injury). The dose was divided to reduce the volume injected into each muscle. The IM injections were given into non-injured muscles using the Z-track method to reduce TXA leakage. Therapeutic blood concentrations were achieved within 15 minutes of IM injection, with only mild and transient reactions at the injection sites. Blood lactate and clinical signs of shock had no impact on the rate of absorption. These results could have major implications for trauma care, particularly in low- and middle-income countries where IM TXA could greatly expand access to timely treatment.

Another consideration is that TXA should be given to a wide range of trauma patients and its use should not be limited to patients with severe traumatic haemorrhage. The CRASH-2 trial included patients with or at risk of significant haemorrhage and there was a wide range of baseline risk. Some patients had severe trauma with a high risk of death from bleeding whereas others had much less severe injury and a lower risk of bleeding death. However, the proportional reduction in bleeding death with TXA does not vary by baseline risk.²⁵ Timely

TXA treatment reduces the risk of bleeding death by about one third regardless of baseline risk. So, for example, for a patient with severe injury and a 30% risk of bleeding death, TXA treatment would reduce this risk to 20%, a one third proportional reduction. Similarly, in a patient with much less severe injury and a 3% risk of bleeding to death, TXA treatment would reduce this risk to 2%, also a one third reduction. Clearly, severely injured patients have the most to gain from TXA treatment since they have a 10% absolute reduction in the risk of death from bleeding (30% down to 20%) whilst the less severely injured have only a 1% absolute risk reduction (3% down to 2%). However, because there are far more low risk trauma patients than high risk patients, a substantial proportion of bleeding deaths are in low risk patients. If we only treat the severely injured, we will miss an important opportunity to save many lives.

What does this mean for practice? It means that we must give paramedics and physicians the confidence to treat a far wider range of trauma patients whilst emphasising the importance of early treatment. We want to treat patients before their bleeding becomes severe and coagulopathic. All patients with *or at risk of* non-trivial internal or external bleeding should get TXA as soon as possible. All patients with high energy injury mechanisms or penetrating trauma should receive urgent TXA. Because age is a strong risk factor for death from intracranial and extracranial bleeding, older adults (≥ 65 years) with low energy trauma and any abnormal vital signs (blood pressure or rapid pulse) should also be treated urgently. TXA should also be given to patients with TBI. UK ambulance guidelines recommend urgent TXA treatment for patients with “known or suspected head injury with a GCS of 12 or less.” Patients with mild TBI and any evidence of bleeding on CT scan should also be treated. Indeed, the results of the CRASH-3 trial show that early treatment of patients with complicated mild (GCS 13–15 with CT evidence of bleeding) conferred the greatest benefit. However, patients

with mild TBI do not receive pre-hospital TXA and by the time they have had a CT scan, for most patients it will be too late to experience the full benefits of early TXA treatment. Further research is currently underway (the CRASH-4 trial) to assess the effects of early pre-hospital IM TXA treatment on the risk of death, disability and dementia in older adults with mild symptomatic head injury. Research is also needed to define the optimal dose of intramuscular TXA. This might include studies of more concentrated TXA solutions that reduce the volume that has to be injected.

The price of complacency – how many more must die unnecessarily before we act?

Despite one of the most unambiguous findings in trauma care research - a highly significant reduction in mortality with TXA from a large multi-centre randomised placebo-controlled trial - ten years after the publication of the CRASH-2 trial results, only a fraction of trauma patients world-wide receive timely treatment. Even in the UK where the results of the trial have been widely celebrated, trauma audit data for 2017 and 2018 show that only 9% of trauma patients in England and Wales got TXA within 3 h of injury and only 3% got it within an hour.²⁶ This is a tragedy. TXA is the only proven lifesaving drug treatment for traumatic bleeding. So why aren't patients getting it?

There is probably no single cause for this neglect, rather a constellation of causes, although perverse incentives feature strongly. The CRASH-2 trial recruited patients from 274 hospitals in 40 countries and found no evidence that the effect of TXA on death due to bleeding varies by geographical region, yet some researchers question the applicability of the results to their own settings and called for further randomised trials. For example, Gruen et al argued for a new trial of TXA in Australasian trauma patients, stating that many of the patients in CRASH-2 trial were from low- and middle-income countries and 'because substantial differences are

likely between advanced and less developed trauma systems, hypotheses about TXA should be reinvestigated.²⁶ Gruen called for more evidence on the effects of TXA in patients treated to 'modern civilian and military trauma standards.' Although Gruen and colleagues did not explain why the care provided by Australian hospitals can be considered modern (in contrast to that provided by the hospitals participating in the CRASH-2 trial) nor how this modernity would influence the biological effect of TXA treatment, they secured funding for a trial of TXA in Australasian patients. The PATCH study (Pre-hospital Anti-fibrinolytics for Traumatic Coagulopathy and Haemorrhage) is a multi-centre randomised trial of pre-hospital TXA or placebo (the same regimen as the CRASH-2 trial) in bleeding trauma patients and is currently recruiting patients. However, with a planned sample size of 1,300 patients the PATCH trial is seriously underpowered and unlikely to refute the CRASH-2 and CRASH-3 trial conclusions regardless of its results. Nevertheless, provided that the results of these trials are set in the context of all the available evidence from randomised trials then additional evidence is to be welcomed. However, as we have seen, investigators more commonly categorize their results as positive or negative based on whether or not they achieve a p-value less than 0.05 and confuse the absence of evidence with evidence of absence, thus sowing confusion among readers.

TXA is an inexpensive generic drug. In terms of getting research into practice this is an advantage and a disadvantage. The advantage is that TXA use in trauma patients is highly cost-effective even in low- and middle-income settings. The disadvantage is that there is little or no advertising or promotion since profit margins are slim. Pharmaceutical companies spend millions of dollars, often billions, marketing patented drugs. They employ armies of sales representatives, target key opinion leaders to write editorials and speak in conferences, and use the best brains in advertising to sell their drugs. TXA enjoys none of these advantages.

Because it is not in the financial interest of the license holder to seek a license for TXA use in trauma or post-partum haemorrhage, despite free access to the data from the CRASH and WOMAN trials, TXA use for trauma and obstetrics patients is still off-label. Furthermore, trauma disproportionately affects people who are socioeconomically disadvantaged, and there are no well-established patient groups to lobby for effective care. If trauma was a problem that mainly affected wealthy people or if TXA was a patented profitable drug, it seems unlikely we would still be waiting for widespread use of this safe and effective treatment.

Conclusion

TXA safely reduces trauma deaths. However, urgent treatment is critical. Patients should ideally be treated at the scene or in the ambulance. TXA treatment should not be limited to patients with severe traumatic haemorrhage and paramedics should be empowered to treat a far wider range of trauma patients. TXA is well tolerated and rapidly absorbed after intramuscular injection. This could greatly expand access to treatment especially in settings without formal pre-hospital care.

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Tables and figures

Table 1. Effect of early tranexamic acid on all-cause mortality within 24 hours and within 28 days in the CRASH-2 and CRASH-3 trials (excluding patients with GCS 3 or bilateral unreactive pupils at baseline)

	Deaths in TXA group (%)	Deaths in placebo group (%)	Risk ratio (95% CI)
Death within 24 hours			
CRASH-2	6.3	8.0	0.79 (0.70-0.90)
CRASH-3	2.9	3.9	0.74 (0.58-0.94)
Combined	5.0	6.5	0.78 (0.70-0.87)
Death within 28 days			
CRASH-2	12.1	14.3	0.84 (0.77-0.92)
CRASH-3	14.0	15.1	0.93 (0.83-1.03)
Combined	12.8	14.6	0.88 (0.82-0.94)

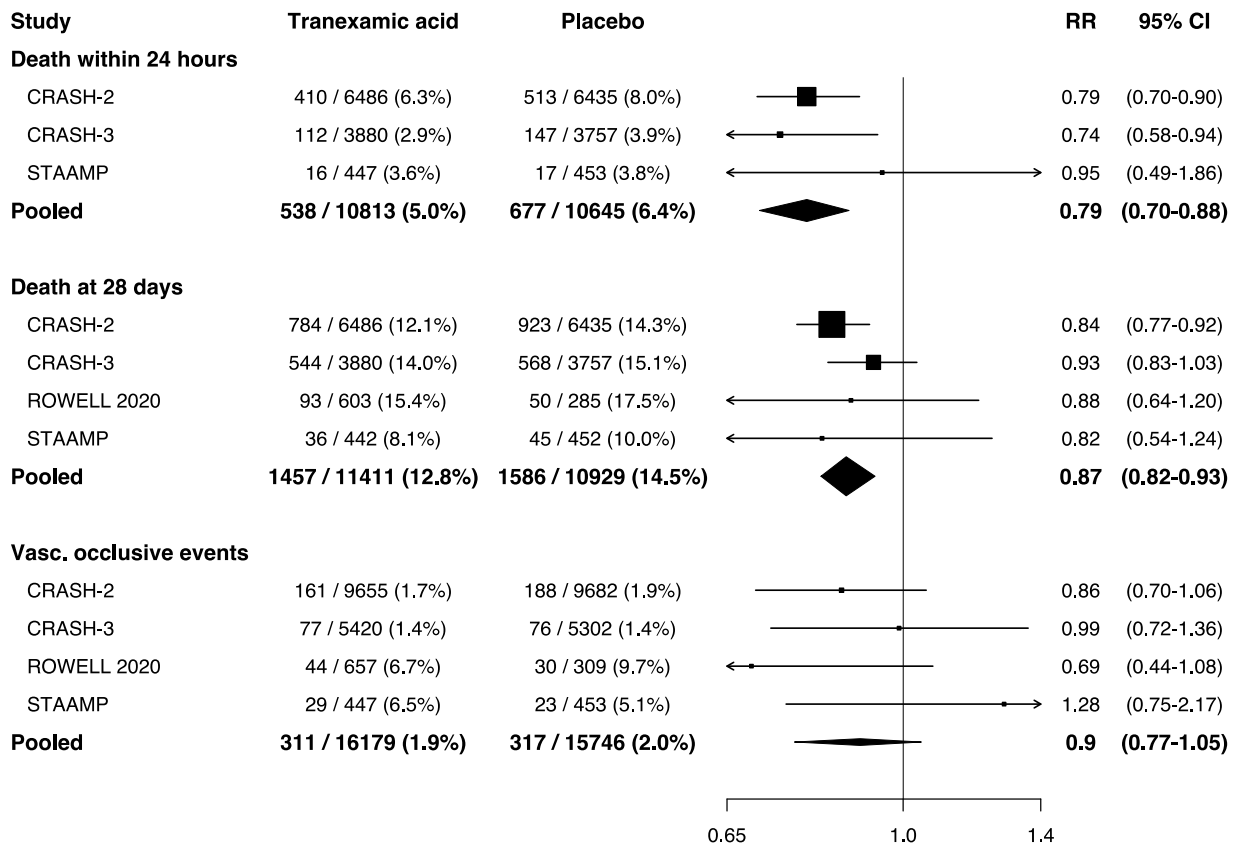


Figure 1. Effect of early tranexamic acid on all-cause mortality at 24 hours and 28 days (trials >500 patients)