Tranexamic Acid in Trauma: does it improve mortality?

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YES, IT DOES

OLD DRUG

NEW STANDARD

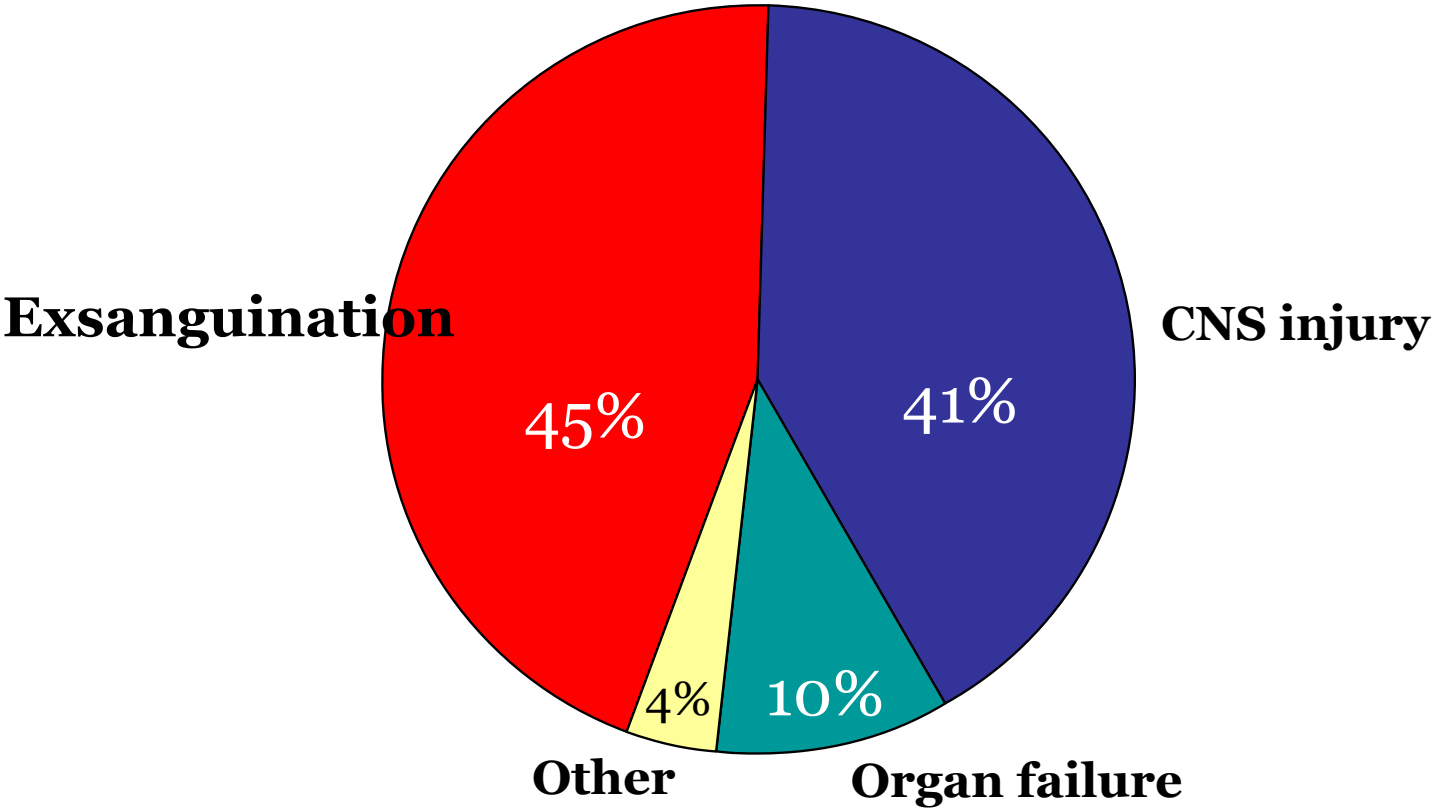
CONTENT

- How it works
- How much it works
- Which population
- Quality of evidences
- Changing daily practice

Global deaths at ages 5-45 years (both sexes)

	Deaths (2000 projected)
HIV/AIDS	2,104,454
Road traffic injury	**657,614**
Tuberculosis	603,522
Self inflicted injury	**431,924**
Violence	**335,202**
War injuries	**167,329**

In-hospital trauma deaths



Sauaia A et al. Epidemiology of trauma deaths: a reassessment. J Trauma 1995;38:185-193

So far

- Perfluorocarbons
- Colloids
- Hypertonics
- Coagulation factors (VIIa)
- Sustained fluid ress
- Devices

Tranexamic Acid (TXA)

What it is

How it works

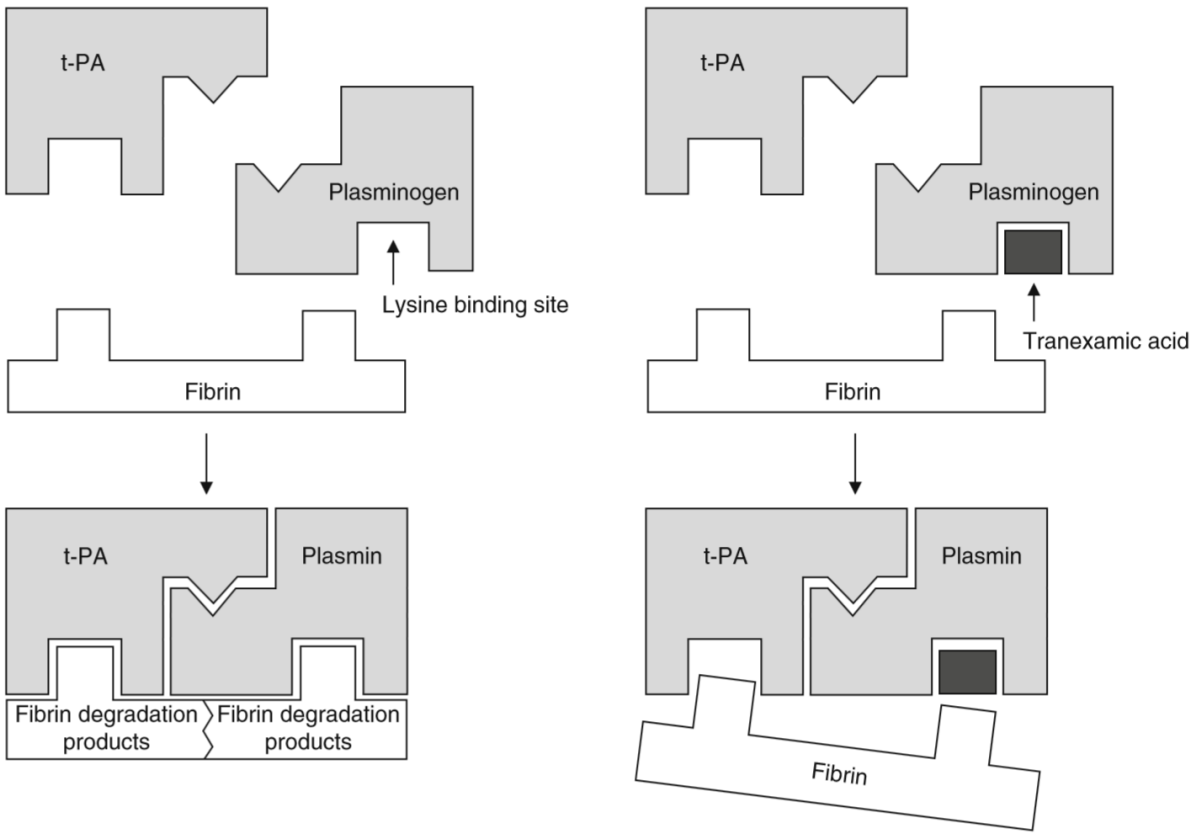


Fig. 2. Antifibrinolytic action of tranexamic acid. Plasminogen normally binds to lysine residues on fibrin and is converted to plasmin in the presence of tissue plasminogen activator; plasmin then digests fibrin. Tranexamic acid reversibly binds to plasminogen at the lysine binding

Antifibrinolytic drugs

- **TXA**; synthetic analog of the amino acid lysine
- **Aprotinin**; monomeric (single-chain) globular polypeptide derived from bovine lung tissue

Antifibrinolytic agents in elective surgery

SYSTEMATIC REVIEWS

APROTININ

61 Randomised controlled trials including 7,027 participants

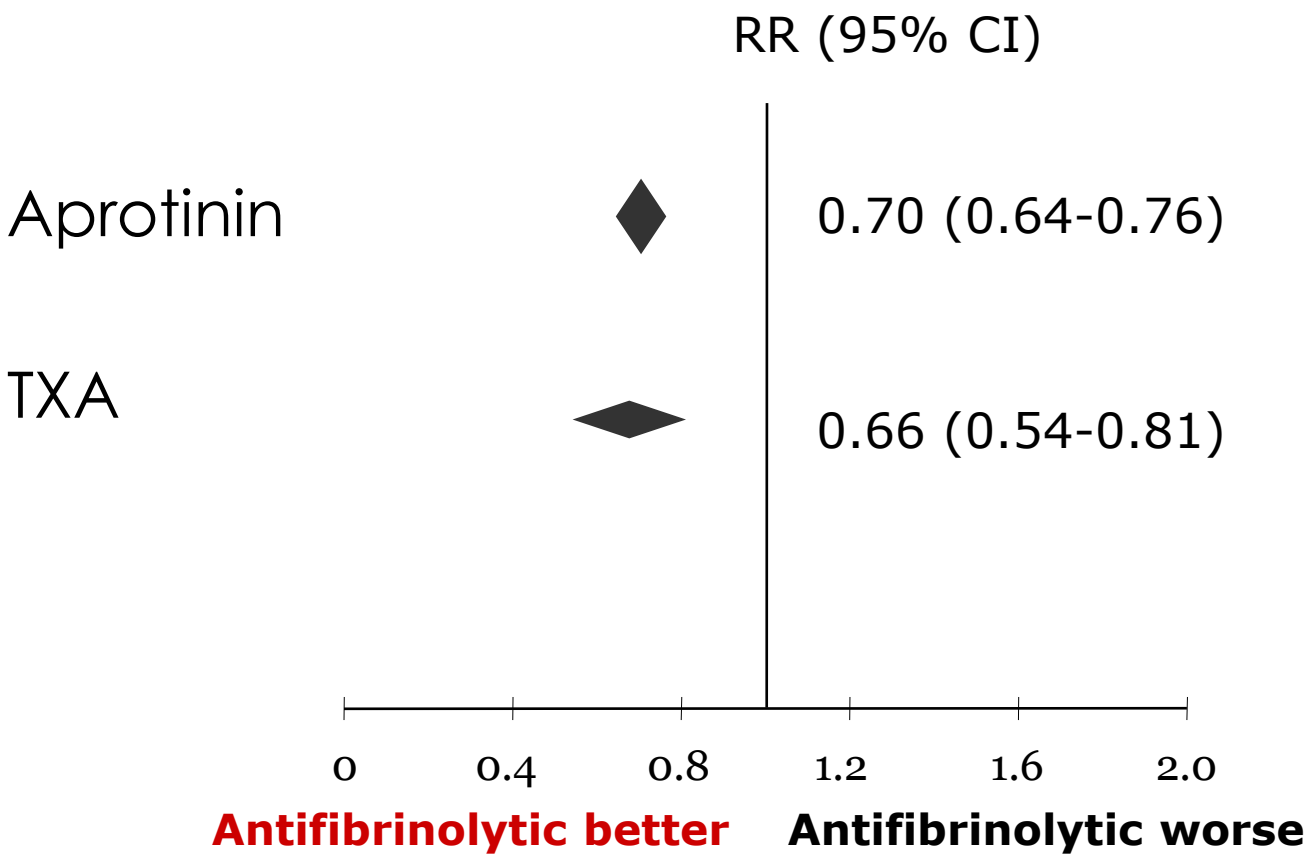
TRANEXAMIC ACID (TXA)

18 Randomised controlled trials including 1342 participants

Henry DA *et al.* Antifibrinolytic use for minimising perioperative allogeneic blood transfusion (Cochrane Review). In: ***The Cochrane Library***, Issue 3, 2004. Chichester, UK: John Wiley & Sons, Ltd

Antifibrinolytic agents in elective surgery

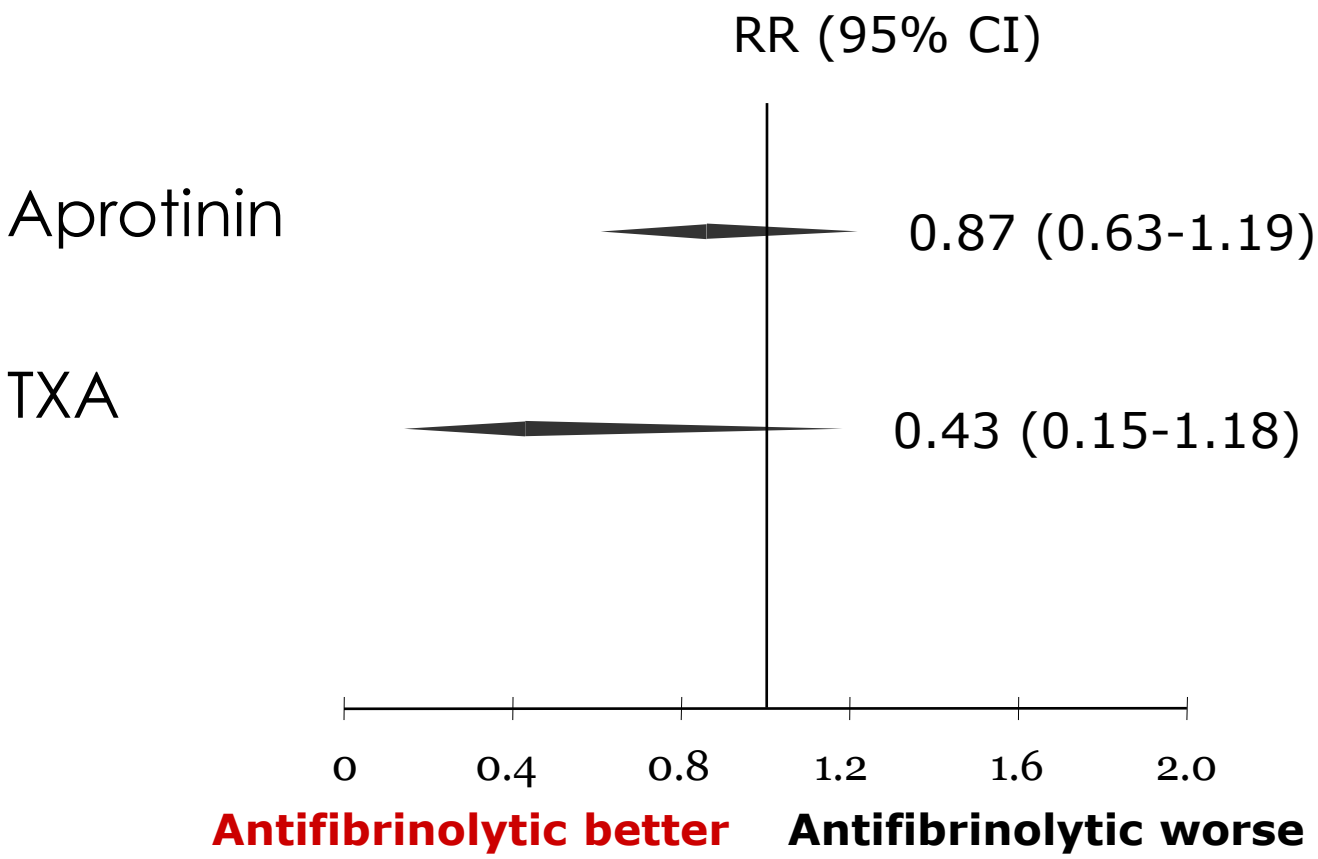
NEED FOR TRANSFUSION



Henry et al

Antifibrinolytic agents in elective surgery

MORTALITY



Henry et al

Tranexamic acid for minimising surgical blood loss

ADVERSE EFFECTS

	RR	95% CI
Non-fatal MI	0.69	0.21 - 2.29
Stroke	2.27	0.65 - 7.99
DVT	0.84	0.30 - 2.30
PE	0.32	0.07 - 1.56
Any thrombosis	0.98	0.49 - 1.94

No evidence of increased adverse effects

Rationale for TXA

- TXA may be as effective as aprotinin*
- **Lower cost** of TXA
- Need for a test dose of aprotinin to assess for potential **allergic reactions** (not practical in emergencies)
- In some settings TXA more acceptable than aprotinin which is derived from **bovine lung**

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

CRASH-2 trial collaborators*

- **Lancet 2010; 376: 23–32** Published Online June 15, 2010 DOI:10.1016/S0140-6736(10)60835-5 See Comment page 3
*Members listed at end of paper Correspondence to: Clinical Trials Unit, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK crash@lshtm.ac.uk

CRASH-2

- **P**atients: Trauma patients with/or at risk of bleeding
- **I**ntervention: TXA
- **C**omparison: Placebo
- **O**utcome: primarily MORTALITY

POTENTIALLY ELIGIBLE

Trauma patients judged to be 16 years or older, with significant haemorrhage (systolic blood pressure less than 90 mmHg and/or heart rate more than 110 beats per minute), or considered to be at risk of significant haemorrhage, within 8 hours of the injury

DOCTOR IS "REASONABLY CERTAIN" THAT ANTI-FIBRINOLYTIC AGENTS ARE INDICATED.

INELIGIBLE
GIVE ANTI-FIBRINOLYTIC AGENTS;
DO NOT RANDOMISE.

DOCTOR IS "REASONABLY CERTAIN" THAT ANTI-FIBRINOLYTIC AGENTS ARE CONTRA-INDICATED.

INELIGIBLE
DON'T GIVE ANTI-FIBRINOLYTIC AGENTS;
DO NOT RANDOMISE.

Doctor is "SUBSTANTIALLY UNCERTAIN" as to the appropriateness of anti-fibrinolytic agents in this patient

TELEPHONE FOR RANDOMISATION OR PAPER RANDOMISE

TRANEXAMIC ACID

PLACEBO

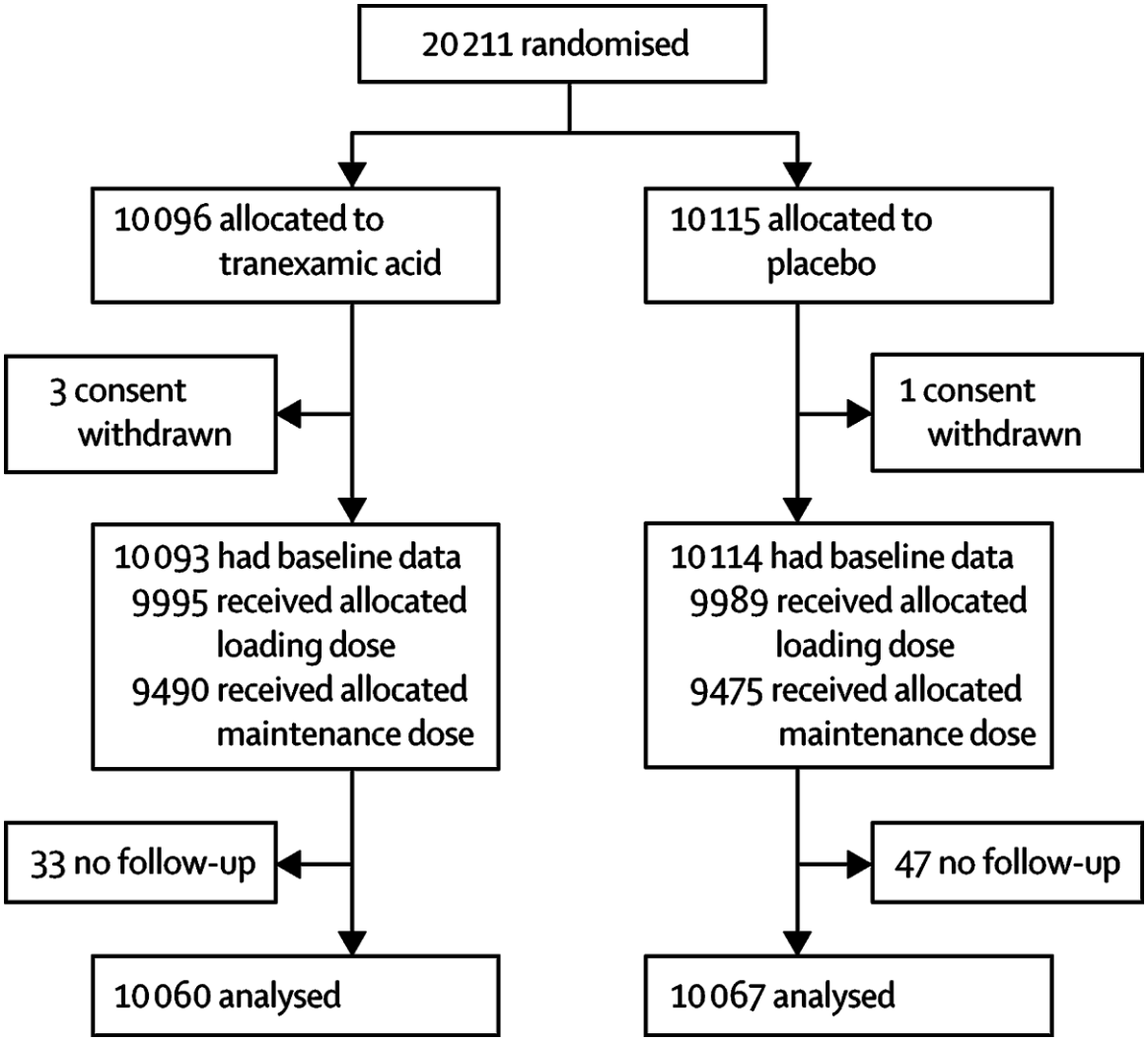
CRASH2

What is meant by ‘risk of significant haemorrhage’

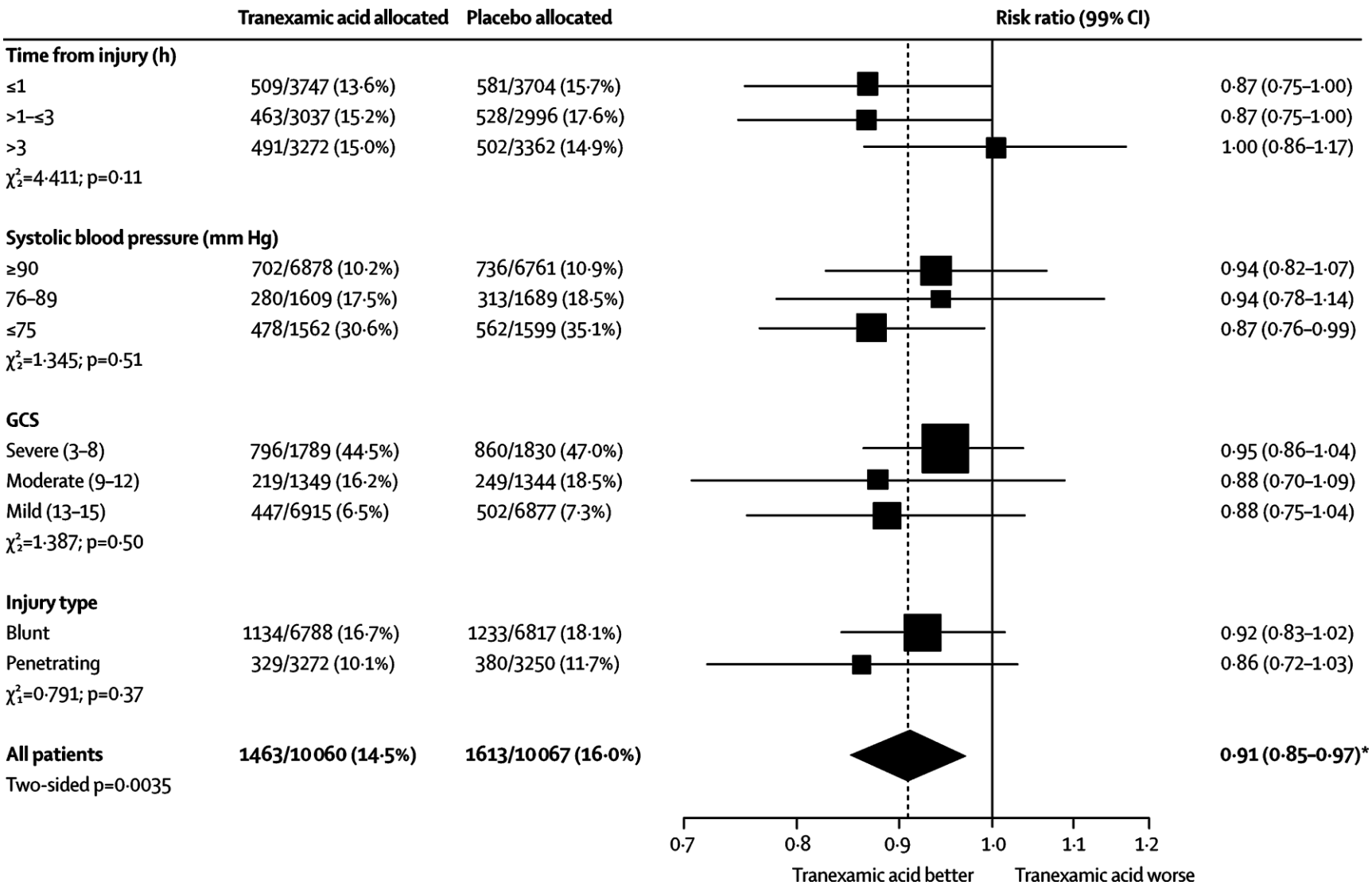
- Patients with major trauma who are likely to need an early blood transfusion in the view of the attending doctor after taking into account mechanism of injury, findings from secondary survey, physiology and response to fluid infusion

CRASH2

Figure 1


20 211 randomised
10 096 allocated to tranexamic acid
10 115 allocated to placebo
3 consent withdrawn
1 consent withdrawn
10 093 had baseline data
9995 received allocated loading dose
9490 received allocated maintenance dose
10 114 had baseline data
9989 received allocated loading dose
9475 received allocated maintenance dose
33 no follow-up
47 no follow-up
10 060 analysed
10 067 analysed

CRASH 2


Tranexamic acid allocated
Placebo allocated
Risk ratio (99% CI)
Time from injury (h)
≤1 509/3747 (13·6%) 581/3704 (15·7%) 0·87 (0·75–1·00)
>1–≤3 463/3037 (15·2%) 528/2996 (17·6%) 0·87 (0·75–1·00)
>3 491/3272 (15·0%) 502/3362 (14·9%) 1·00 (0·86–1·17)
χ^2_2=4·411; p=0·11
Systolic blood pressure (mm Hg)
≥90 702/6878 (10·2%) 736/6761 (10·9%) 0·94 (0·82–1·07)
76–89 280/1609 (17·5%) 313/1689 (18·5%) 0·94 (0·78–1·14)
≤75 478/1562 (30·6%) 562/1599 (35·1%) 0·87 (0·76–0·99)
χ^2_2=1·345; p=0·51
GCS
Severe (3–8) 796/1789 (44·5%) 860/1830 (47·0%) 0·95 (0·86–1·04)
Moderate (9–12) 219/1349 (16·2%) 249/1344 (18·5%) 0·88 (0·70–1·09)
Mild (13–15) 447/6915 (6·5%) 502/6877 (7·3%) 0·88 (0·75–1·04)
χ^2_2=1·387; p=0·50
Injury type
Blunt 1134/6788 (16·7%) 1233/6817 (18·1%) 0·92 (0·83–1·02)
Penetrating 329/3272 (10·1%) 380/3250 (11·7%) 0·86 (0·72–1·03)
χ^2_1=0·791; p=0·37
All patients 1463/10060 (14·5%) 1613/10067 (16·0%) 0·91 (0·85–0·97)*
Two-sided p=0·0035
0·7
0·8
0·9
1·0
1·1
1·2
Tranexamic acid better
Tranexamic acid worse

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 •

Lancet 2011; 377: 1096–101

	N	All causes of death	Bleeding death	Non-bleeding death
Overall	20 127	0·91 (0·85–0·97); p=0·0035	0·85 (0·76–0·96); p=0·0077	0·94 (0·86–1·02); p=0·13
Time to treatment (h)				
≤1	7451	0·87 (0·76–0·97)	0·68 (0·57–0·82)	1·04 (0·89–1·21)
>1–3	6033	0·87 (0·77–0·97)	0·79 (0·64–0·97)	0·91 (0·78–1·05)
>3	6634	1·00 (0·90–1·13)	1·44 (1·12–1·84)	0·89 (0·78–1·02)
χ^2 test of homogeneity	..	4·411 (p=0·11)	23·516 (p=0·0000)	2·537 (p=0·28)

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

Patient group	NNT and ARR
>1 Hour, bleeding death	**41** (ARR: 2,4)
1-3 hour, bleeding death	**76** (ARR:1,3)
All causes death	**66** (ARR:1.5)

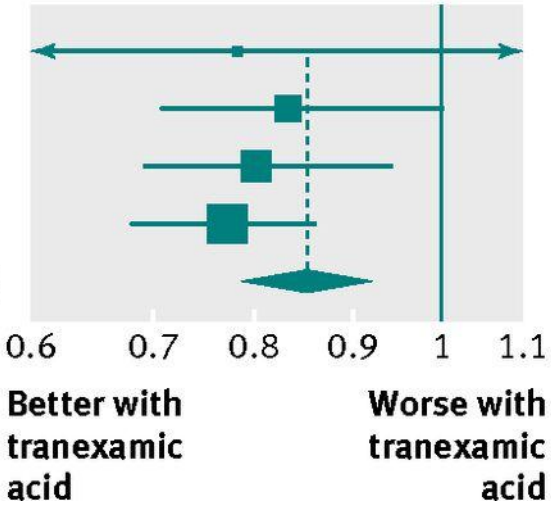
- Tranexamic acid should be given **as early as possible** to bleeding trauma patients.
- For trauma patients seen late after injury **(>3h**), tranexamic acid is less effective and **could be harmful.**

Effect of tranexamic acid on mortality in patients with traumatic bleeding: prespecified analysis of data from randomised controlled trial. Roberts, I; Perel, P; Prieto-Merino, D; et al.

BMJ. 2012 Sep 11; 345: e5839

Fig 1 Deaths from all causes in patients with traumatic bleeding according to treatment with tranexamic acid (P=0.96 for heterogeneity).

Risk of death at baseline	No of patients (%)		Odds ratio (95% CI)	Odds ratio (95% CI)
	Tranexamic acid	Placebo		
<6%	33/2487 (1%)	40/2353 (2%)		0.78 (0.49 to 1.23)
6-20%	223/2682 (8%)	266/2713 (10%)		0.83 (0.70 to 1.00)
21-50%	281/908 (31%)	337/940 (36%)		0.80 (0.69 to 0.94)
>50%	392/607 (65%)	410/583 (70%)		0.77 (0.68 to 0.87)
All	929/6684 (14%)	1053/6589 (16%)		0.85 (0.78 to 0.93)



Ian Roberts et al. BMJ 2012;345:bmj.e5839

Effect of tranexamic acid on mortality in patients with traumatic bleeding: prespecified analysis of data from randomised controlled trial. Roberts, I; Perel, P; Prieto-Merino, D; et al.
BMJ. 2012 Sep 11; 345: e5839

- Tranexamic acid can be administered safely to a wide spectrum of patients with traumatic bleeding and **should not be restricted to the most severely injured**.

NNT values of CRASH-2 study

Patient group	NNT
Crash-2 all patients (n=20,211)	**66** (ARR:1.5)
Crash-2 travmatic bleeding (n=13,373)	**50** (ARR: 2)
Crash-2 travmatic bleeding (DFAC) Risk of Death at baseline > 21%	**20** (ARR:5)

Antifibrinolytic drugs for acute traumatic injury (Systematic Review)

- Cochrane Injuries Group. Publication status and date: January 2015.
- Ker K, Roberts I, Shakur H, Coats TJ. **Antifibrinolytic drugs for acute traumatic injury. Cochrane Database of Systematic Reviews 2015,** Issue 5. Art. No.: CD004896. DOI: 10.1002/14651858.CD004896.pub4.

Ker K, Roberts I,Shakur H, CoatsTJ. **Antifibrinolytic drugs for acute traumatic injury**.
Cochrane Database of Systematic Reviews 2015, Issue 5. Art. No.: CD004896. DOI:

- Selection criteria
- Randomised controlled trials
- Antifibrinolyticagents (aprotinin,tranexamicacid[**TXA**], following acute traumatic injury.

Antifibrinolytic drugs for acute traumatic injury (Systematic Review)

- Main results
- Three trials met the inclusion criteria.
- Two trials (n = 20,451) assessed the effect of **TXA.** The larger of these (**CRASH-2**, n = 20,211) was conducted in 40 countries and included patients with a variety of types of trauma;
- the other (n = 240) restricted itself to those with **traumatic brain injury (TBI) only**.
- One trial (n = 77) assessed **aprotinin** in participants with major bony trauma and shock.

- The pooled data show that antifibrinolytic drugs reduce the risk of death from any cause by 10% (**RR 0.90**, 95% CI 0.85 to 0.96; P = 0.002) **(quality of evidence: high).** This estimate is based primarily on data from **the CRASH-2** trial of TXA, which contributed 99% of the data.

- There is some evidence from pooling data from one study **(n = 240)** and a subset of data from **CRASH-2 (n = 270)** in patients with TBI which suggest that **TXA may reduce mortality** although the estimates are imprecise, the quality **of evidence is low**, and uncertainty remains. Stronger evidence exists for the possibility of **TXA reducing intracranial bleeding** in this population.

CRASH 3 TRIAL (clinicaltrial.gov)

- TXA FOR TBI
- TXA versus PLASEBO

- Will see what happen

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Do I believe that we should use it?

Tranexamic Acid (TXA) versus Tissue Plasminogen Activator (tPA)

• t-PA

• Key paper published in Lancet
• Unblinded trial
• No objective benefit proven,
definite adverse effects observed
• Expensive, huge sales force and campaign
• Mandated by AHA and JC

TXA

• Key paper published in Lancet
• Double blinded, randomized, placebo controlled trial
• Clear, objectively measured benefit without observed adverse effects
• Cheap, generic
• No US mandate

Clopidogrel versus aspirin alone

Clopidogrel

- ARR was 2%
- NNT was 50
- Major bleeding needed intervention 1%
- NNH was 100
- **REAL NNT was 100**

TXA

- ARR: 1,5 % for all pnts
- ARR: 2% travmatic bleeding pnts
- **NNT: 50-66**
- Clear, objectively measured **benefit without observed adverse effects**
- Cheap, generic
- No US mandate

conclusion

- TRAUMA patients with or at risk of bleeding
  - As early as possible after trauma
  - First 1 hour most effective time
  - After third hour could be harmful
  - More effective if patient had traumatic bleeding and/or severe hypotension (>75 mmHg)
  - 1 g in 10 minutes IV
  - 1 g per hour 8 hours infusion