CRASH-2
Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

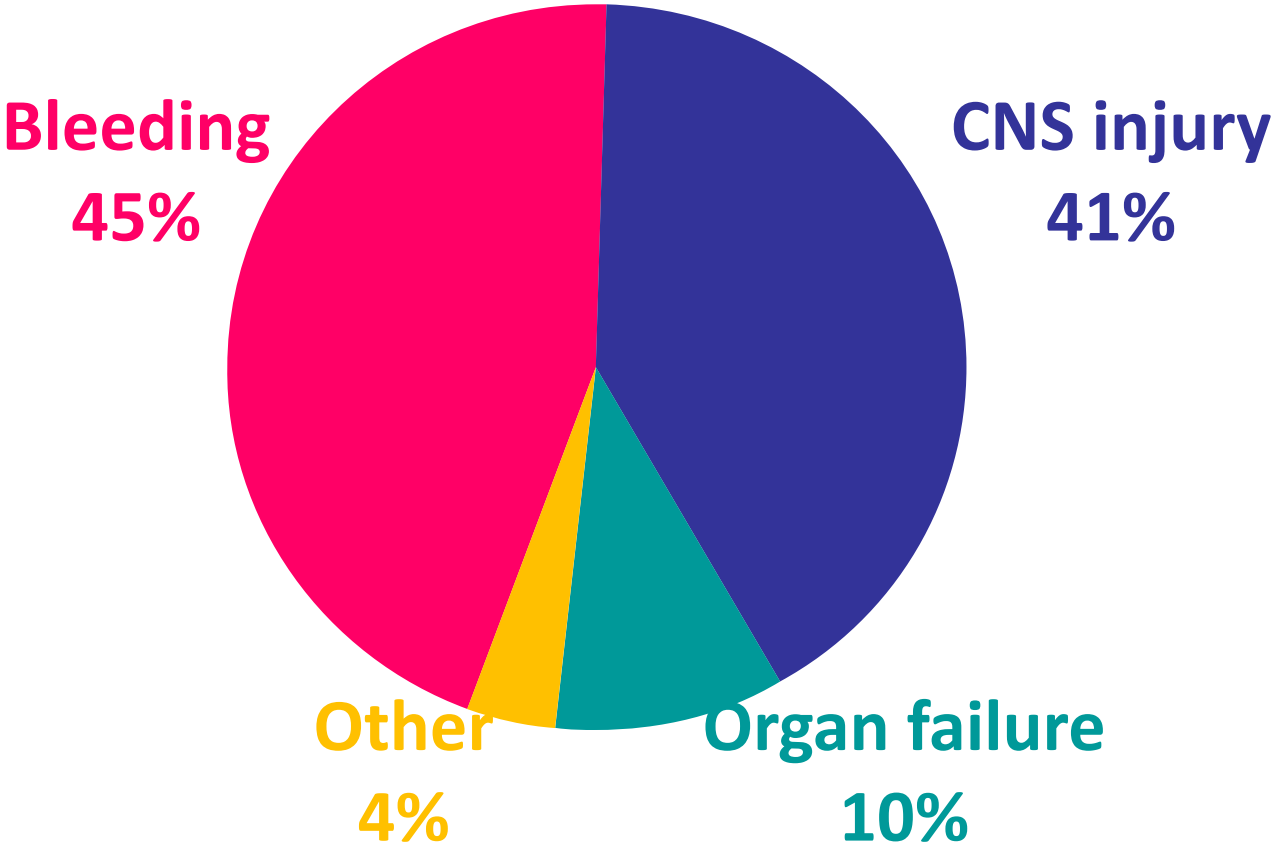
Tranexamic acid safely reduces mortality in bleeding trauma patients

Here we present the evidence

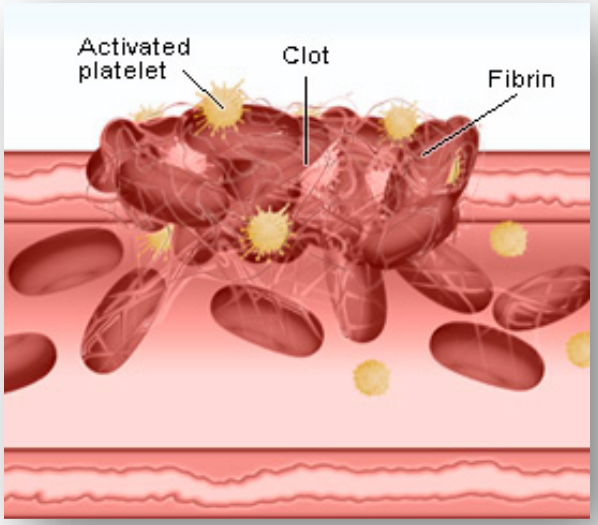
Clinical Trials Unit
London School of Hygiene & Tropical Medicine

Millions bleed to death after trauma each year

There are millions of trauma deaths each year. Many patients survive to reach hospital. This slide shows the causes of in-hospital trauma deaths



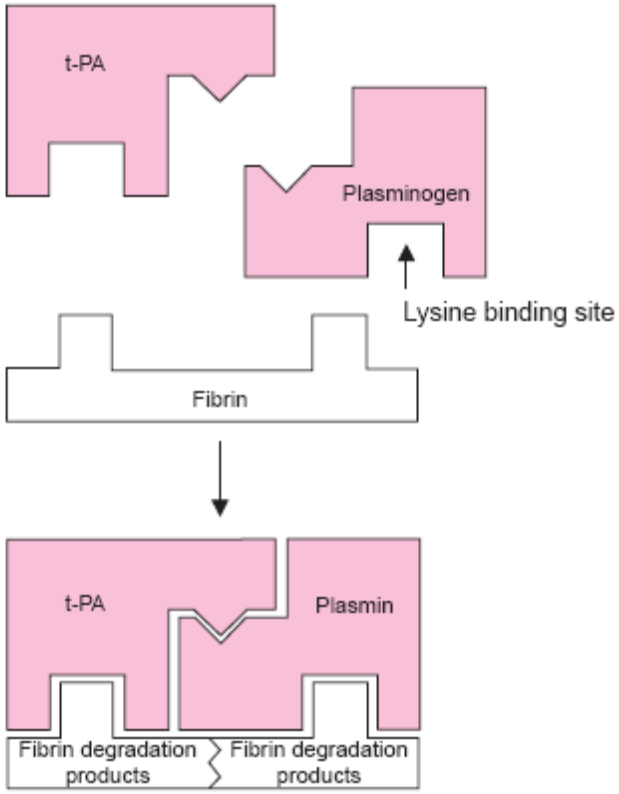
Coagulation and Fibrinolysis



In bleeding trauma patients:

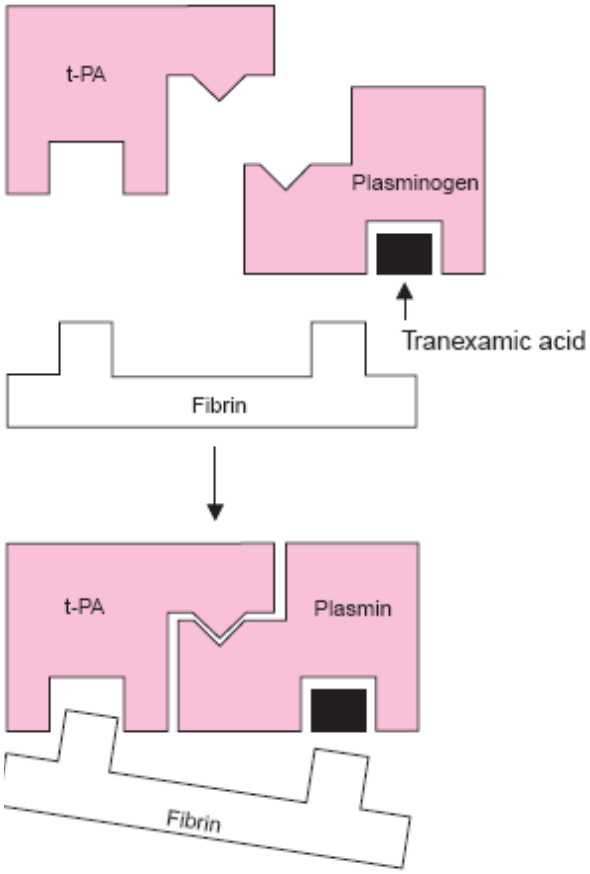
- Coagulation occurs rapidly at the site of damaged blood vessels.
- Fibrinolysis breaks down blood clots.
- In patients with serious bleeding fibrinolysis can make bleeding worse.

Fibrinolysis



- Plasminogen activators from injured blood vessel convert plasminogen to plasmin.
- Plasmin binds to the fibrin blood clot and breaks it down. This is fibrinolysis.

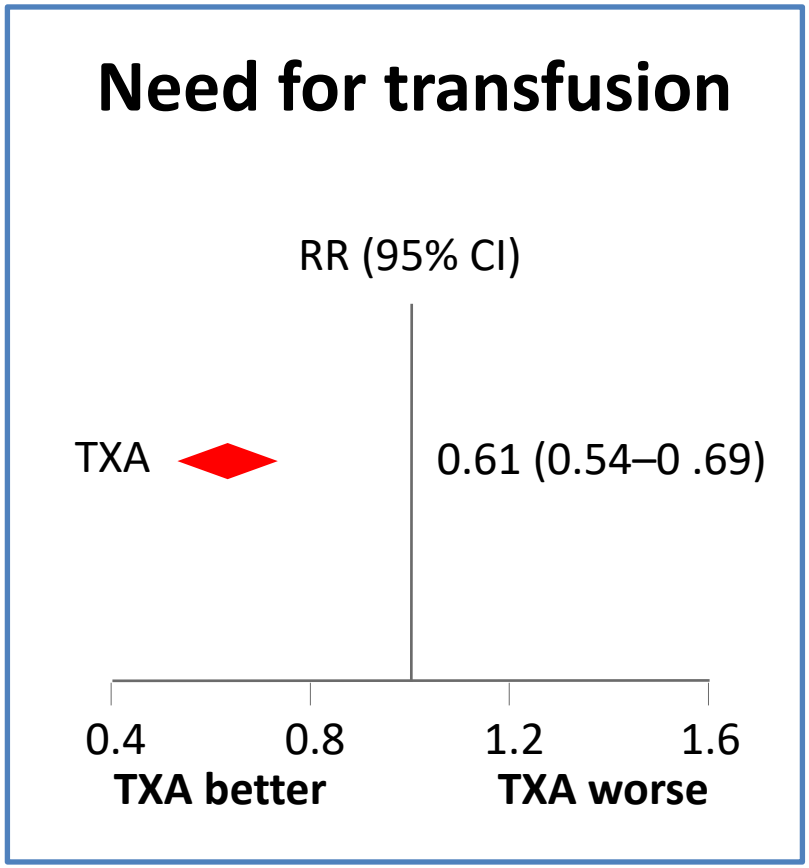
Tranexamic acid reduces fibrinolysis



- Tranexamic acid inhibits plasmin and reduces clot breakdown.

Tranexamic acid reduces surgical bleeding

In surgical patients tranexamic acid (TXA) reduces the need for blood transfusion by about one third.



The CRASH-2 Trial

Tranexamic acid reduces clot breakdown

Tranexamic acid reduces bleeding in surgery

Many trauma patients die from bleeding

To see if tranexamic acid saves lives in bleeding trauma patients we conducted a very large Randomised Controlled Trial called CRASH-2

Methods

- Over 20,000 bleeding trauma patients were randomly allocated to get tranexamic acid or matching placebo
- We included all adult trauma patients who were within 8 hours of their injury, if their doctor thought that they had or could have significant haemorrhage
- We then collected data on death in hospital within 4 weeks of injury and all important side effects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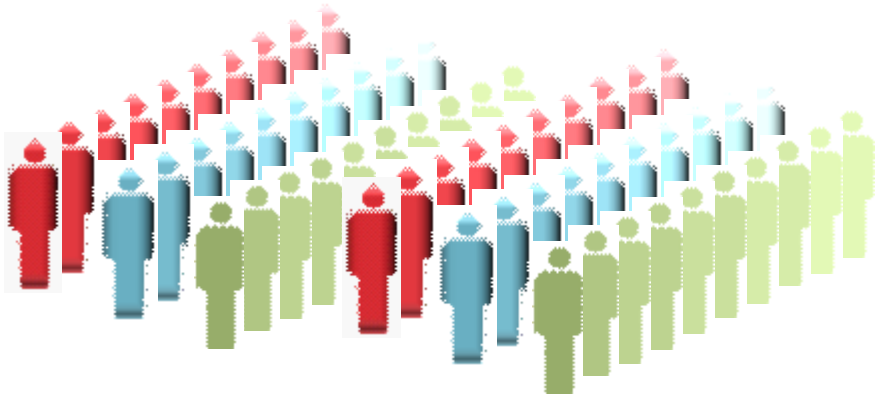
We used this dose of tranexamic acid

Treatment	Tranexamic acid dose
Loading	1 gram over 10 minutes (by slow intravenous injection or an isotonic intravenous infusion)
Maintenance	1 gram over 8 hours (in an isotonic intravenous infusion)

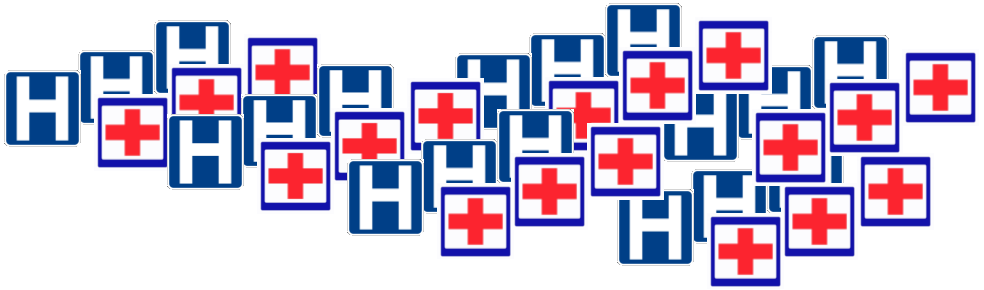
We randomised many trauma patients

Patient enrolment

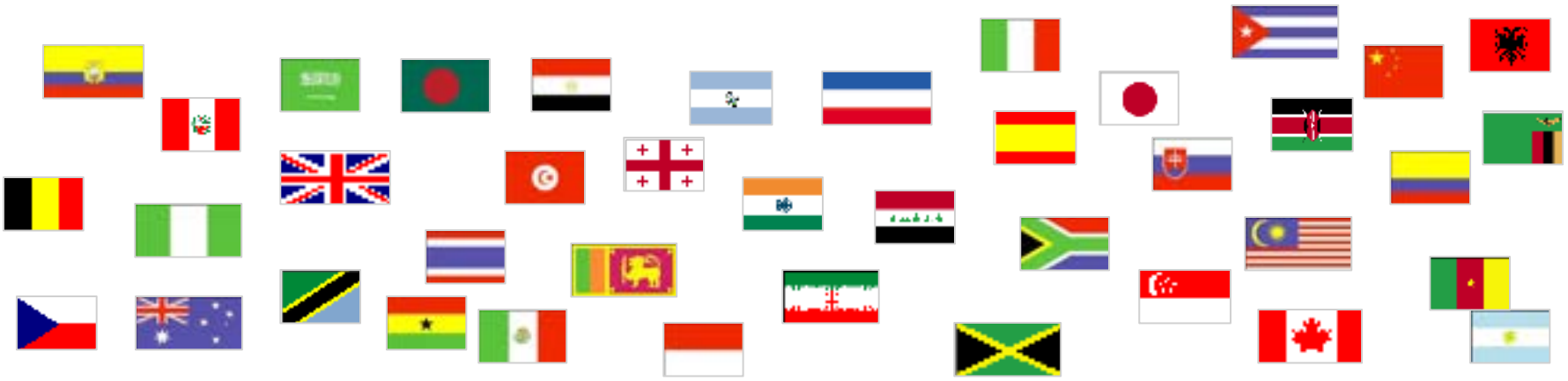


- 20,211 patients

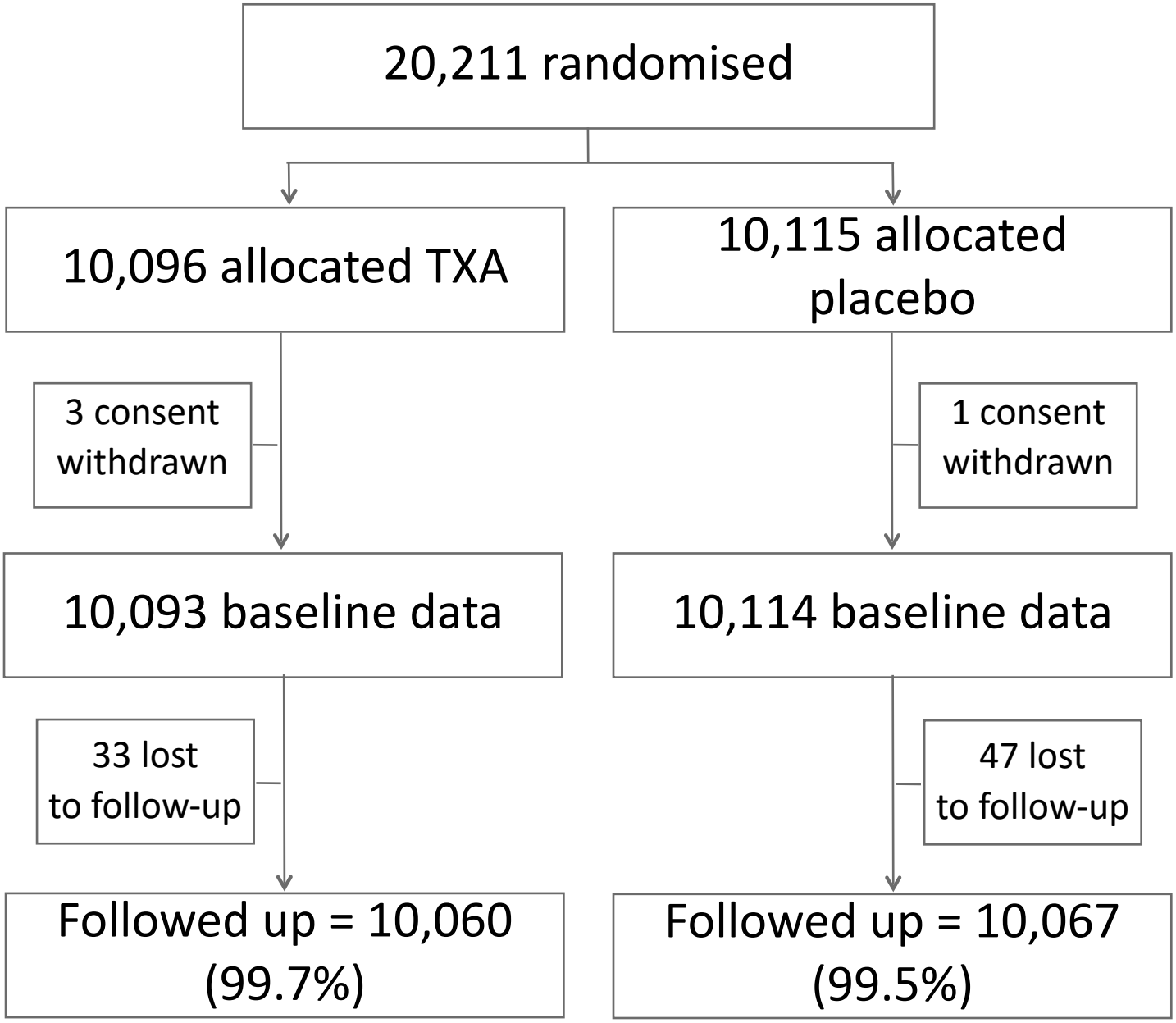
- from 274 hospitals



- in 40 countries



We had excellent follow up



Baseline factors were well balanced

	TXA n (%)	Placebo n (%)
Gender		
Male	8,439 (83.6)	8,496 (84.0)
Female	1,654 (16.4)	1,617 (16.0)
[not known]	0	1
Age (years)		
<25	2,783 (27.6)	2,855 (28.2)
25–34	3,012 (29.8)	3,081 (30.5)
35–44	1,975 (19.6)	1,841 (18.2)
>44	2,321 (23.0)	2,335 (23.1)
[not known]	2	2

Baseline factors were well balanced

	TXA n (%)	Placebo n (%)
Time since injury (hours)		
≤1 hour	3,756 (37.2)	3,722 (36.8)
>1 to ≤3 hours	3,045 (30.2)	3,006 (29.7)
>3 hours	3,006 (29.7)	3,380 (33.4)
[not known]	5	6
Type of injury		
Blunt	6,812 (67.5)	6,843 (67.7)
Penetrating	3,281 (32.5)	3,271 (32.3)

Baseline factors were well balanced

	TXA n (%)	Placebo n (%)
Systolic Blood Pressure (mmHg)		
>89	6,901 (68.4)	6,791 (67.1)
76–89	1,615 (16.0)	1,697 (16.8)
≤75	1,566 (15.5)	1,608 (15.9)
[not known]	11	18
Glasgow Coma Score		
Severe (3–8)	1,799 (17.8)	1,839 (18.2)
Moderate (9–12)	1,353 (13.4)	1,351 (13.4)
Mild (13–15)	6,934 (68.7)	6,908 (68.3)
[not known]	7	16

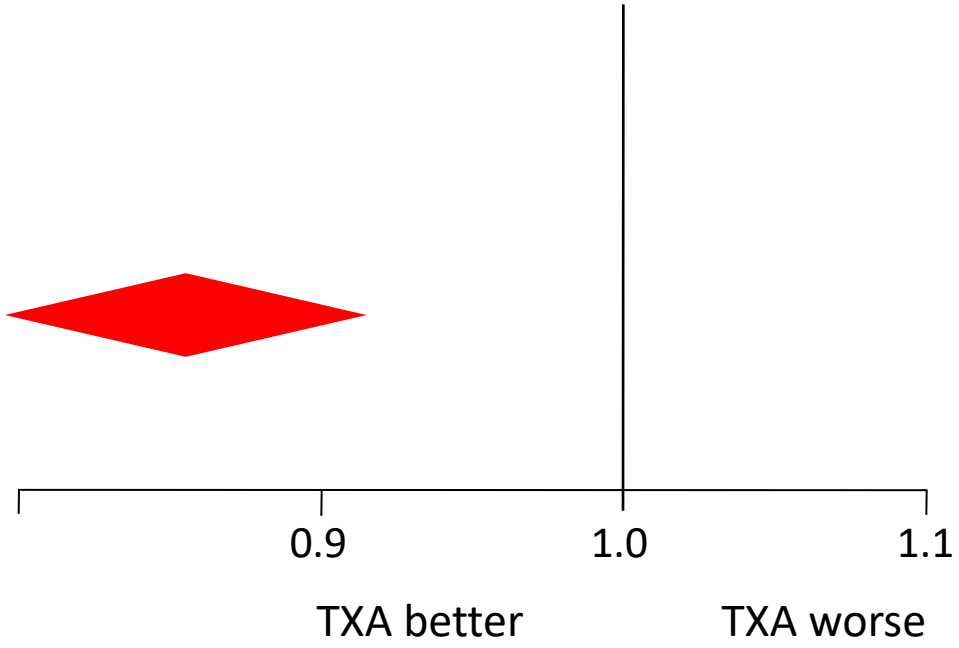
This is what we found

Cause of death	TXA 10,060	Placebo 10,067	Risk of death	P value
Bleeding	489	574	0.85 (0.76–0.96)	0.0077
Thrombosis	33	48	0.69 (0.44–1.07)	0.096
Organ failure	209	233	0.90 (0.75–1.08)	0.25
Head injury	603	621	0.97 (0.87–1.08)	0.60
Other	129	137	0.94 (0.74–1.20)	0.63
Any death	**1463**	**1613**	**0.91 (0.85–0·97)**	**0·0035**

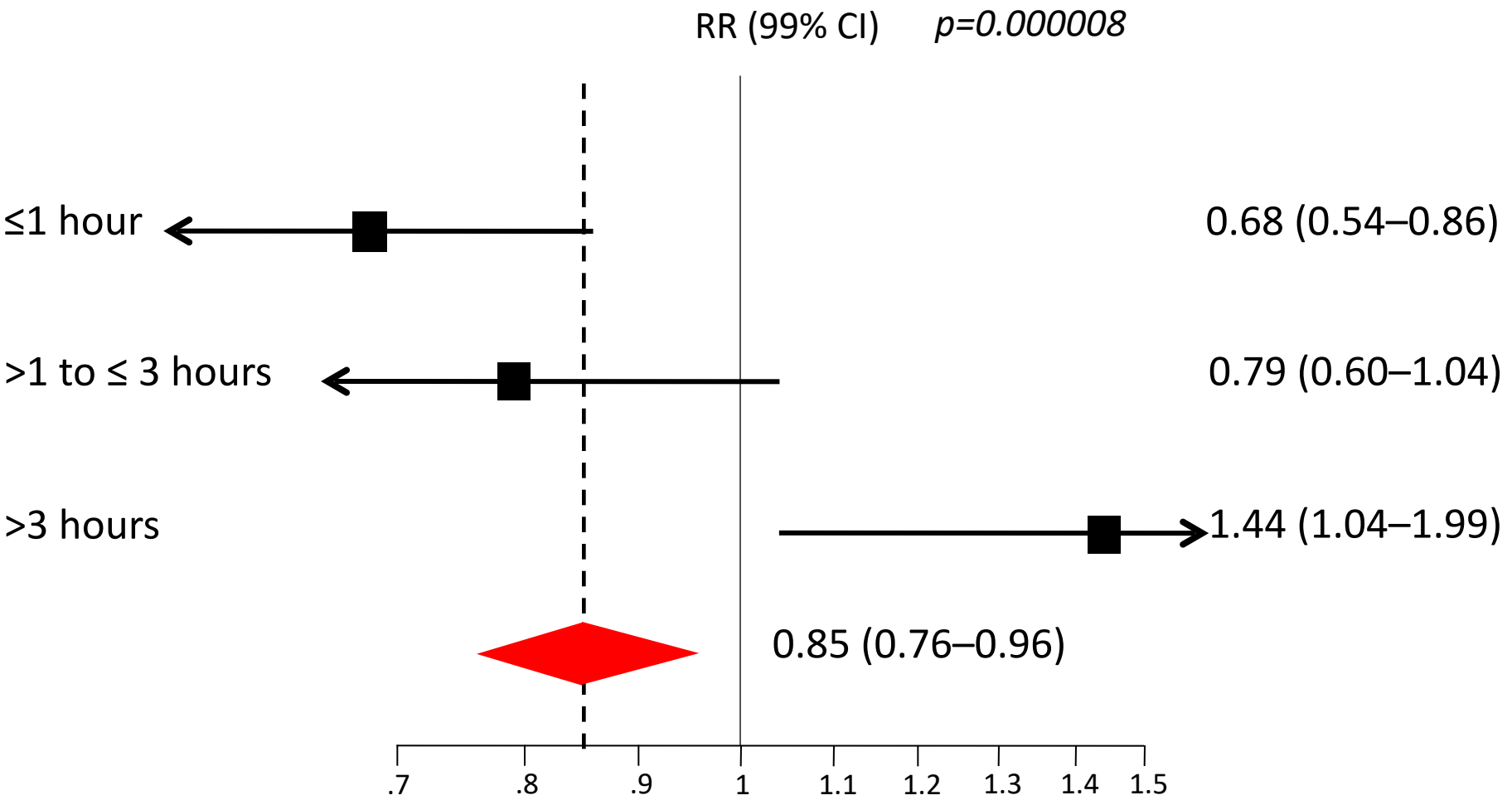
Most of the benefit is for bleeding deaths

TXA (n= 10,060)	Placebo (n= 10,067)	RR (95% CI)
489 (4.9%)	574 (5.7%)	

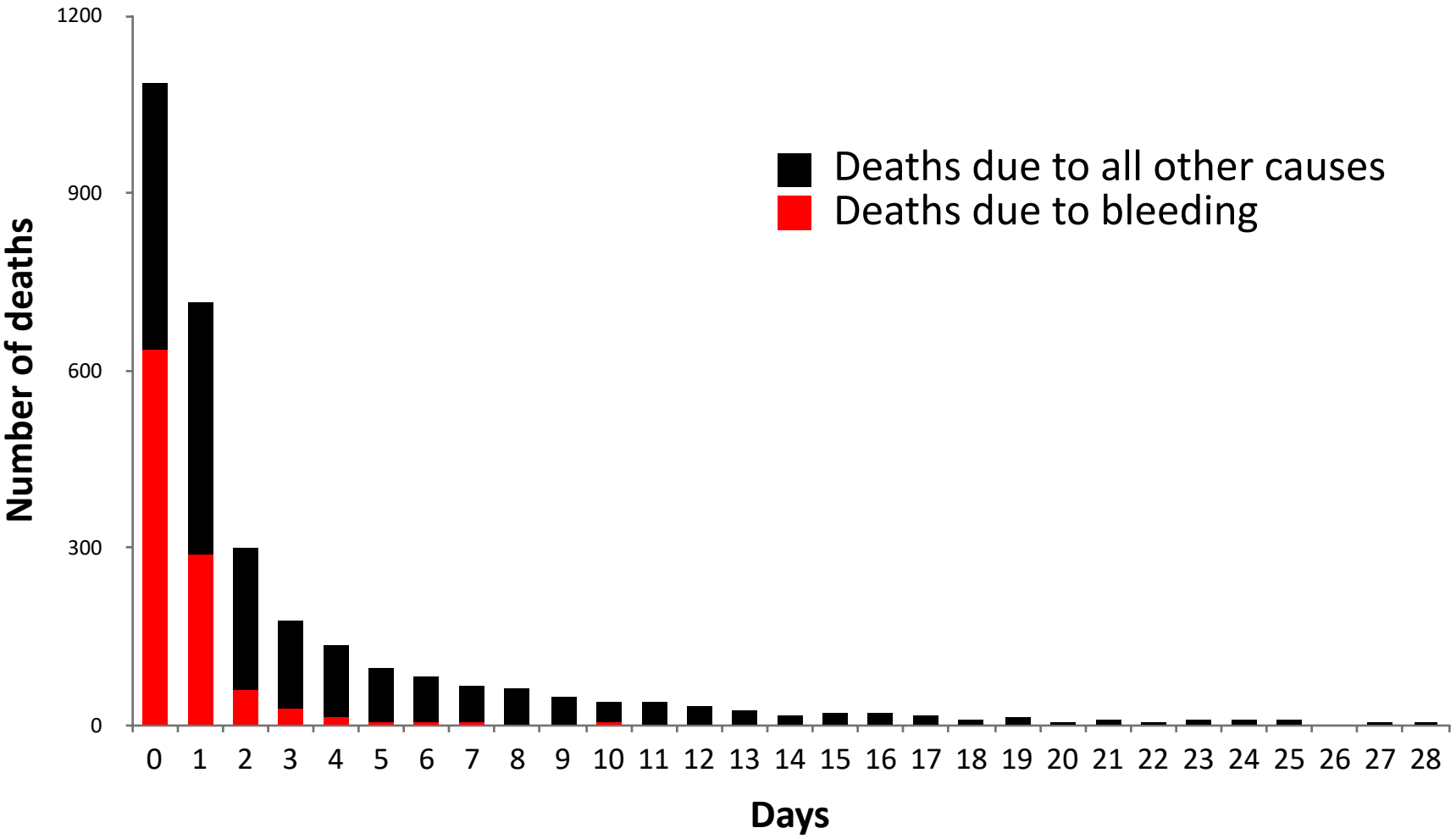
0.85 (0.76–0.96) 2P=0.0077



For bleeding deaths – early treatment is better

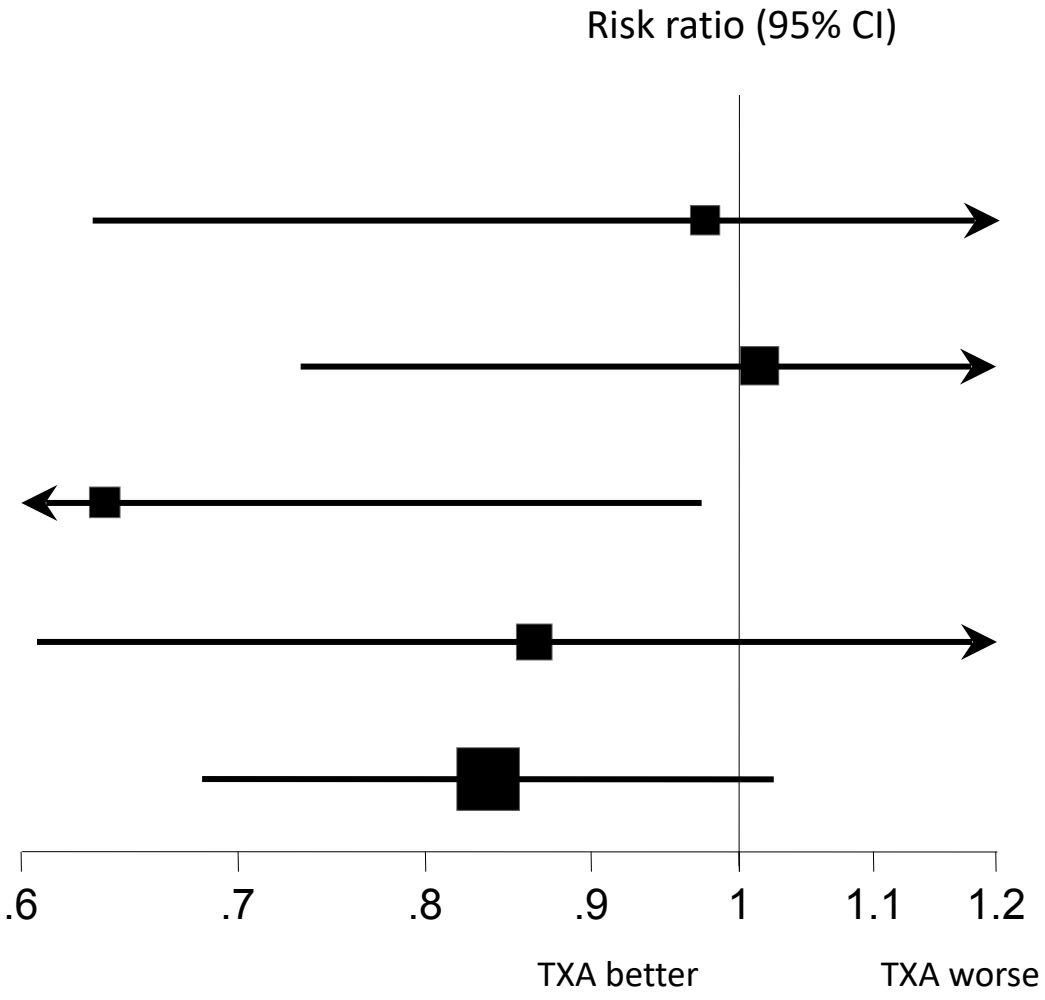


Treatment must be given early because bleeding deaths happen soon after injury



There was no increase in thrombosis

	TXA allocated (10,060)	Placebo allocated (10,067)
DVT	40 (0.40%)	41 (0.41%)
PE	72 (0.69%)	71 (0.70%)
MI	35 (0.35%)	55 (0.52%)
Stroke	57 (0.56%)	66 (0.65%)
Any	168 (1.63%)	201 (1.95%)



Tranexamic acid reduces symptoms

	TXA [n=10060]	Placebo [n=10067]	RR (95% CI)	p-value
No symptoms	1,483 (17.3%)	1,334 (15.8%)	1.11 (1.04 – 1.19)	0.0023
Minor symptoms	3,054 (30.4%)	3,061 (30.4%)	1.00 (0.96 – 1.04)	0.94
Some restriction	2,016 (20.0%)	2,069 (20.6%)	0.97 (0.92 – 1.03)	0.36
Dependent	1,294 (12.9%)	1,273 (12.6%)	1.02 (0.95 – 1.09)	0.63
Fully dependent	696 (6.9%)	676 (6.7%)	1.03 (0.93 – 1.14)	0.57
Dead	1,463 (14.5%)	1,613 (16.0%)	0.91 (0.85 – 0.97)	0.0035

CRASH-2 was conducted on 4 continents and...

was shown to reduce mortality on each!

Tranexamic acid is highly cost effective

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PLoS one

Cost-Effectiveness Analysis of Administering Tranexamic Acid to Bleeding Trauma Patients Using Evidence from the CRASH-2 Trial

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What we concluded

- Tranexamic acid reduces mortality in bleeding trauma patients
- Tranexamic acid does not seem to increase unwanted clotting
- Tranexamic acid needs to be given early – within 3 hours of injury
- Tranexamic acid is not expensive and could save hundreds of thousands of lives each year around the world

Tranexamic acid is now being used

- After the CRASH-2 trial, tranexamic acid was added to the WHO List of Essential Medicines (March 2011)
- The military are using tranexamic acid to treat combat casualties
- Tranexamic acid is being used in hospitals around the world
- Tranexamic acid could be given in ambulances