Tranexamic acid (TXA) safely reduces mortality in bleeding trauma patients

The Evidence Presented

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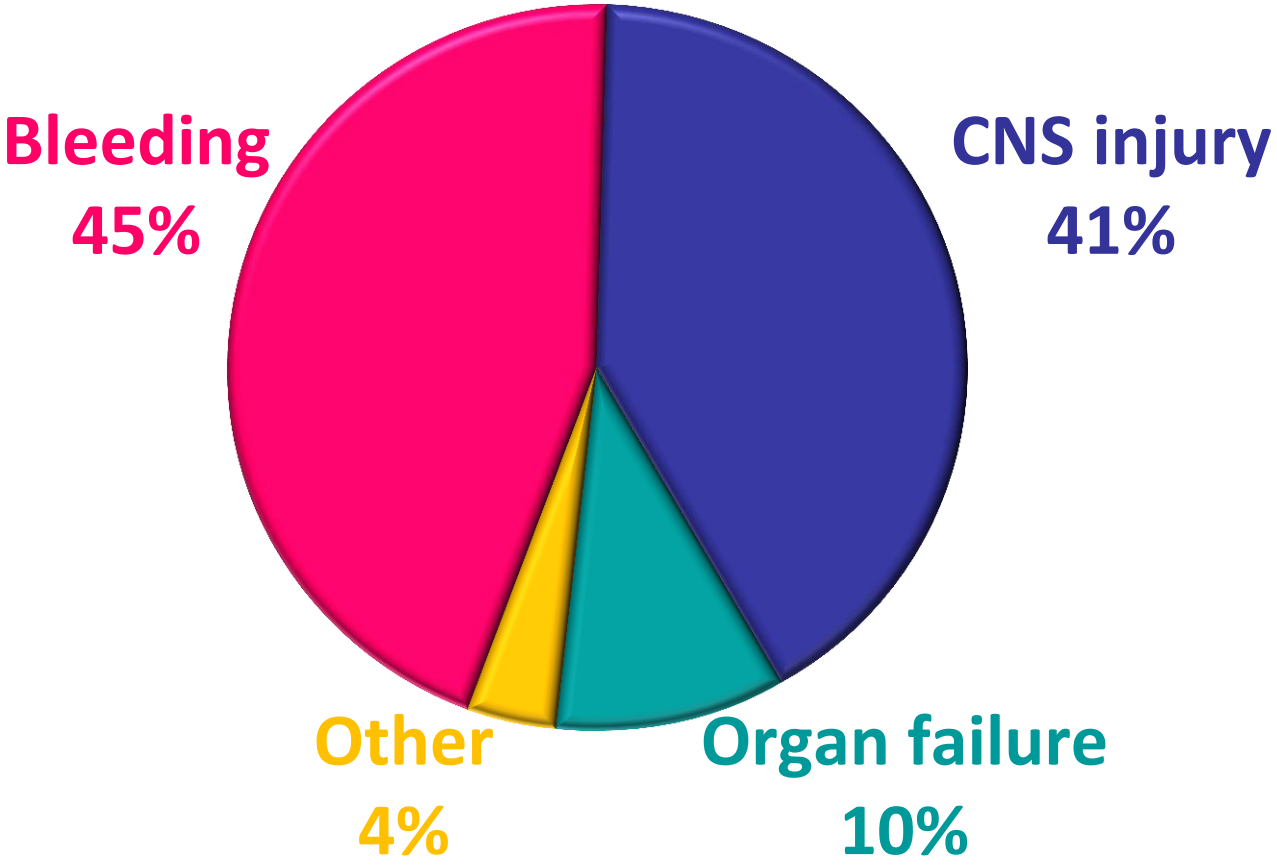
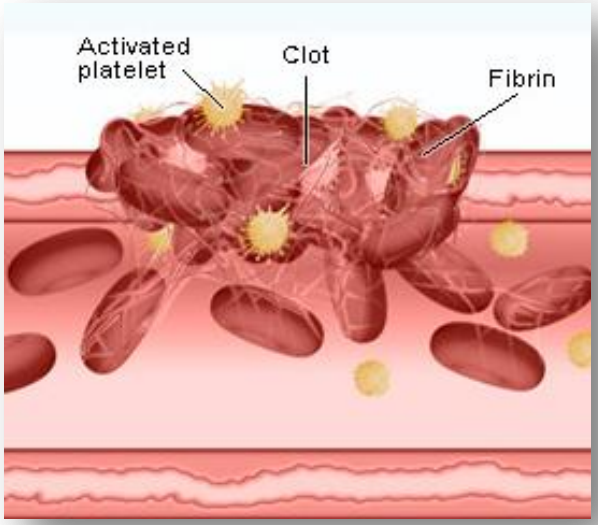
CRASH-2
Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage

Millions bleed to death after trauma each year

Millions die from trauma every year. About half survive to reach hospital. This slide shows the causes of in-hospital trauma deaths



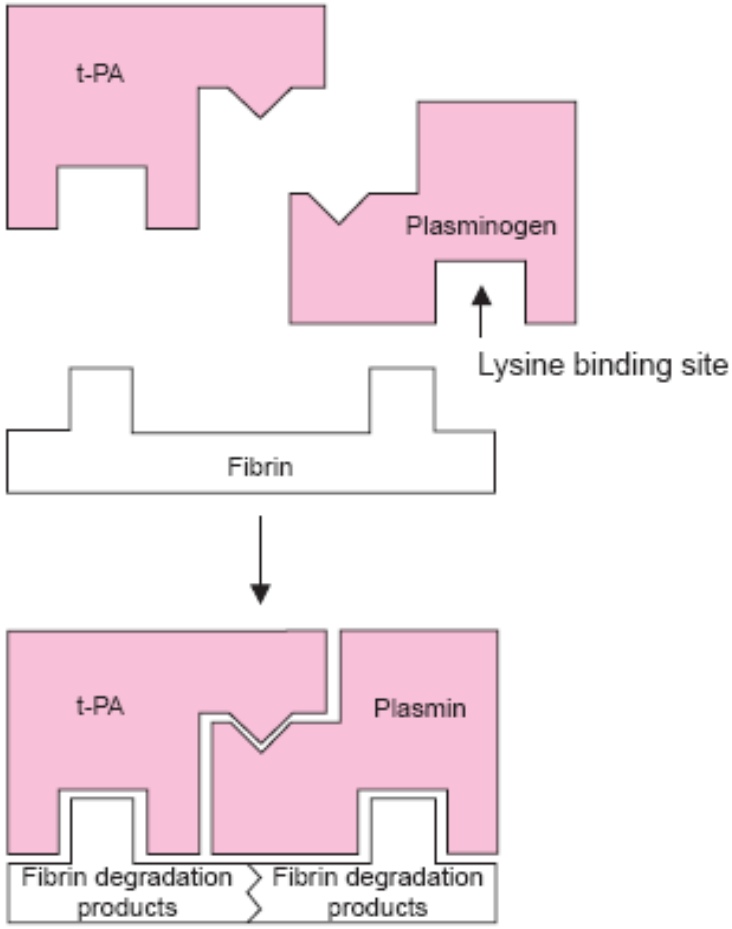
Coagulation and Fibrinolysis



In bleeding trauma patients:

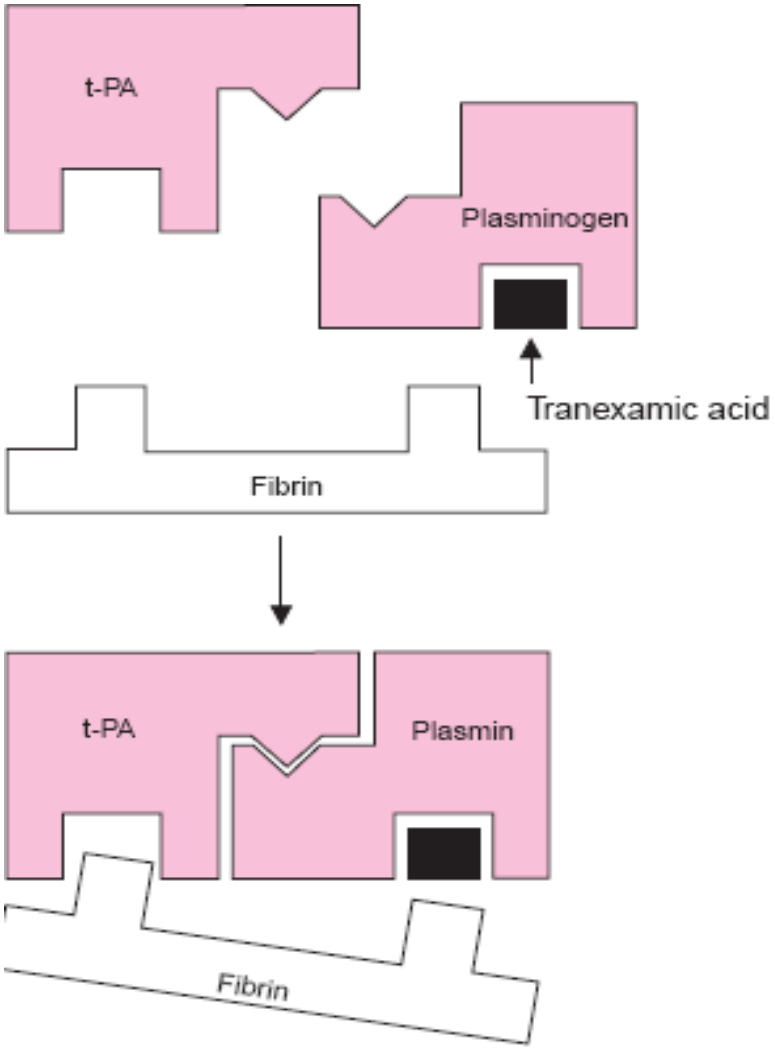
- Coagulation occurs rapidly at the site of injury.
- Fibrinolysis begins immediately to break down blood clots.
- In patients with serious bleeding fibrinolysis can be detrimental and occasionally pathologic in “hyperfibrinolysis”

Fibrinolysis



- Plasminogen activator from injured blood vessels converts plasminogen to plasmin.
- Plasmin binds to the fibrin blood clot and breaks it down. This is fibrinolysis.

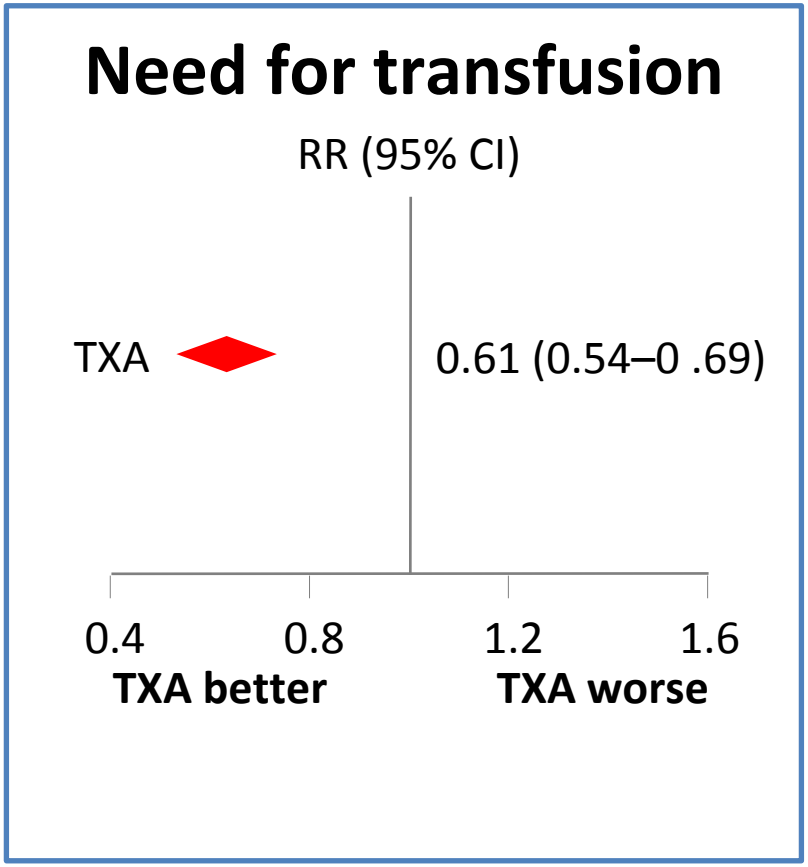
Tranexamic acid reduces fibrinolysis



- Tranexamic acid is a lysine analogue. (similar to aminocaproic acid)
- It binds to the “kringle” domain of plasminogen and inhibits plasminogen’s activation into Plasmin
- and its binding to fibrin – reducing fibrin breakdown

TXA reduces surgical bleeding (BC)

In surgical patients tranexamic acid (TXA) reduces the need for blood transfusion by about one third (prior meta-analysis)



The CRASH-2 Trial - initiated

Tranexamic acid reduces clot breakdown

Tranexamic acid reduces bleeding in surgery

Many trauma patients die from bleeding

Therefore: To see if TXA saves lives in bleeding trauma patients a large Randomized Controlled Trial was conducted in 40 countries - **CRASH-2**

Methods

- Over 20,000 bleeding trauma patients were randomly allocated to get TXA or placebo
- All adult trauma patients who were within 8 hours of their injury were included, if their doctor thought that they had or could have significant haemorrhage
- Data was then collected on in hospital deaths, vascular occlusive crisis, and transfusion, within 4 weeks of injury

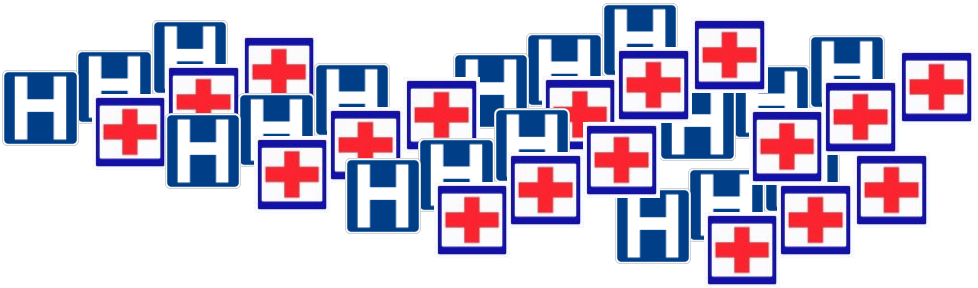
TXA Dosing

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)

They randomised many trauma patients

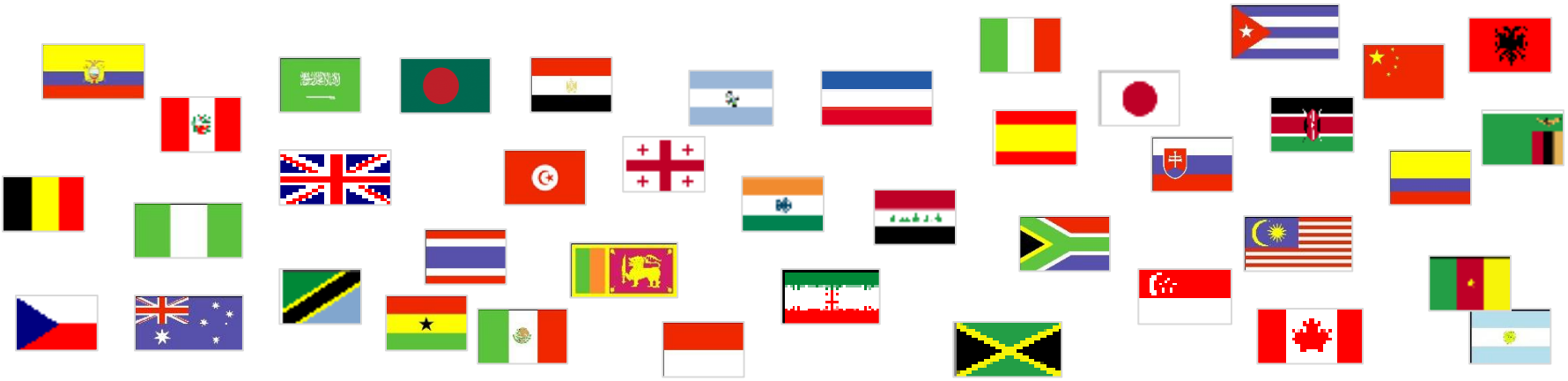
Patient enrolment

- 20,211 patients

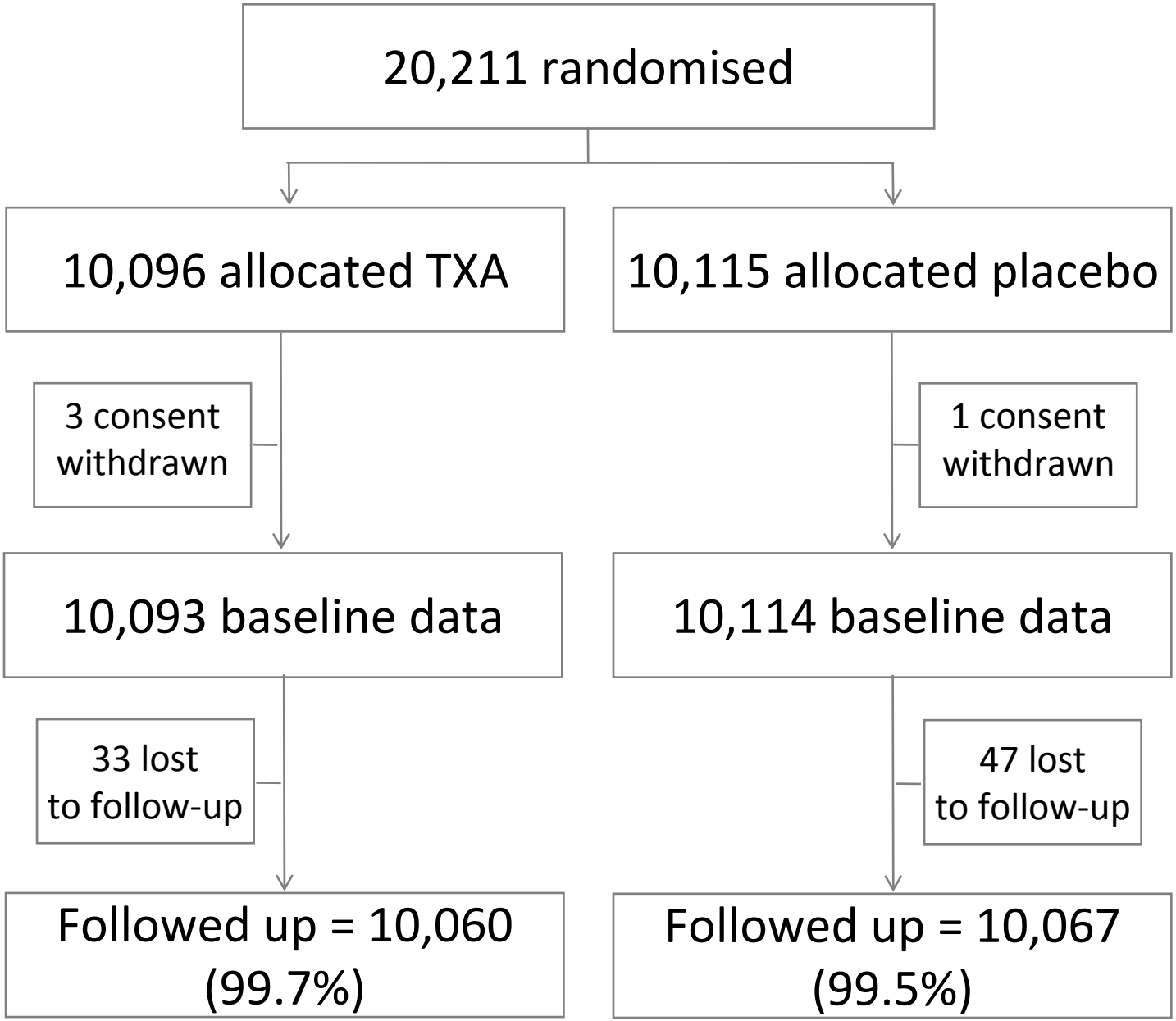


- from 274 hospitals

- in 40 countries



They had excellent follow up



Demographics 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

Trauma 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)

Trauma severity was 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

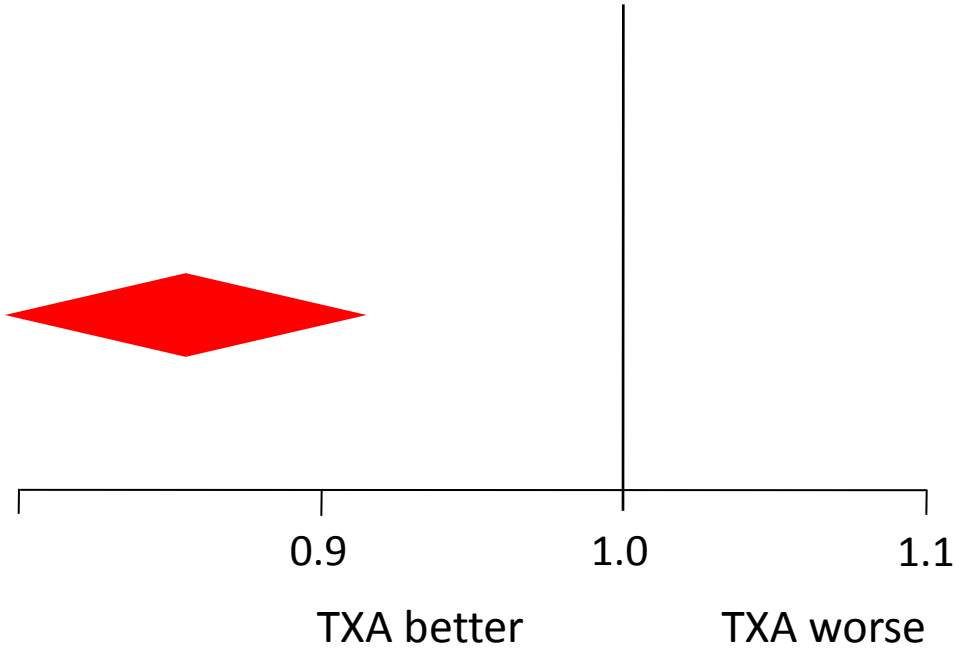
Results

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**

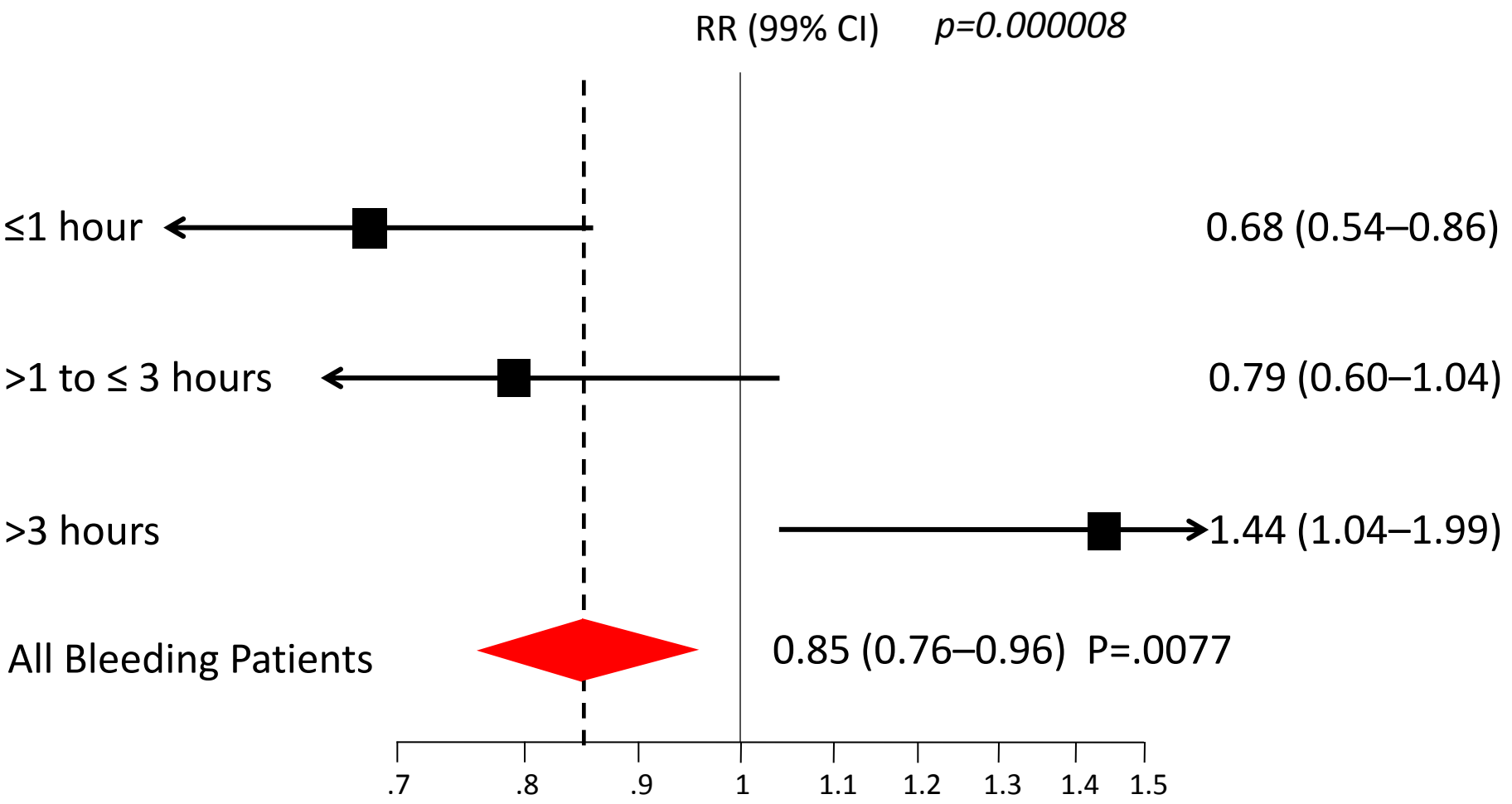
Most of the benefit is for bleeding deaths

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

Risk = 0.85 (0.76–0.96)
2P=0.0077



For bleeding deaths – early treatment is better



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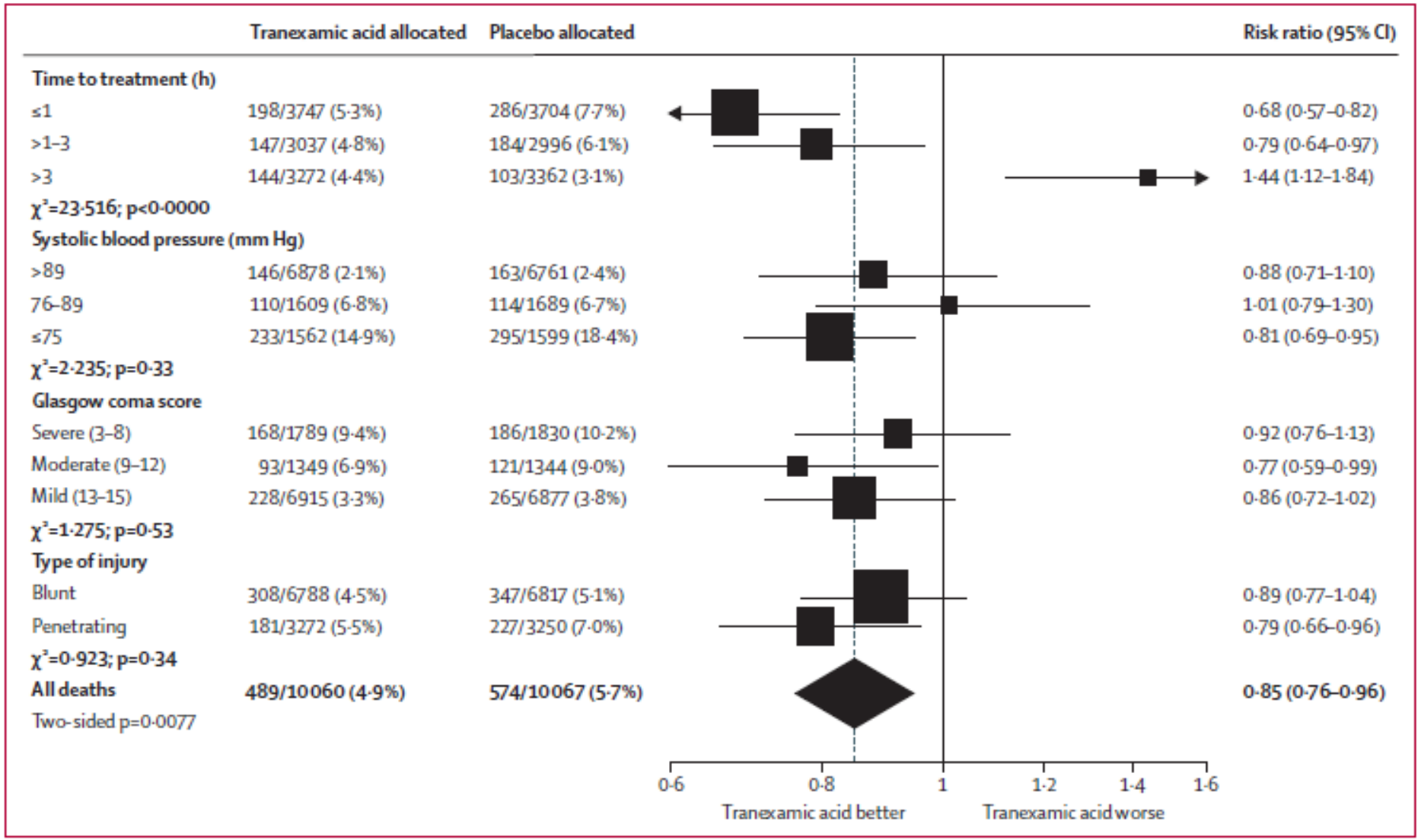
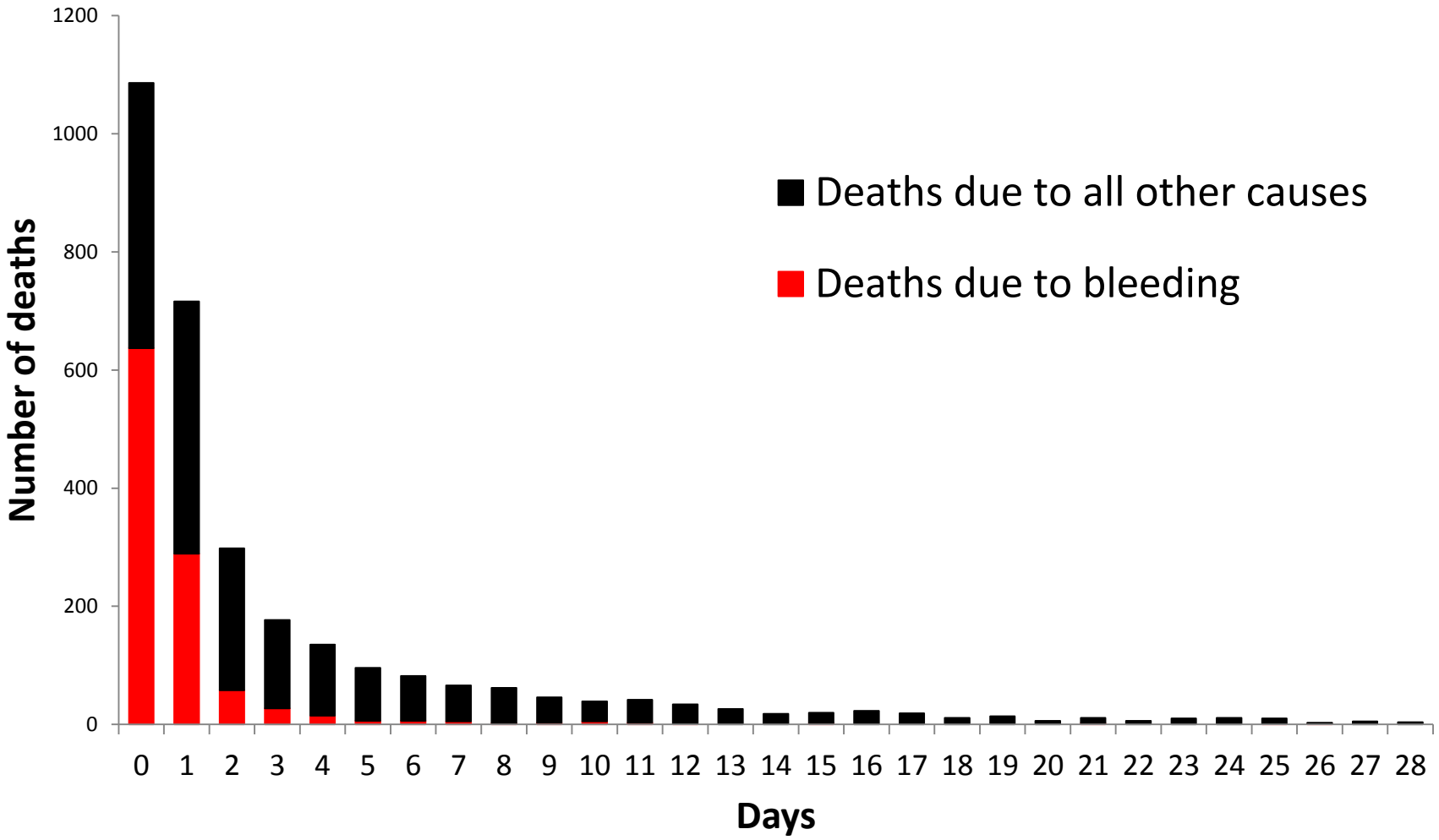


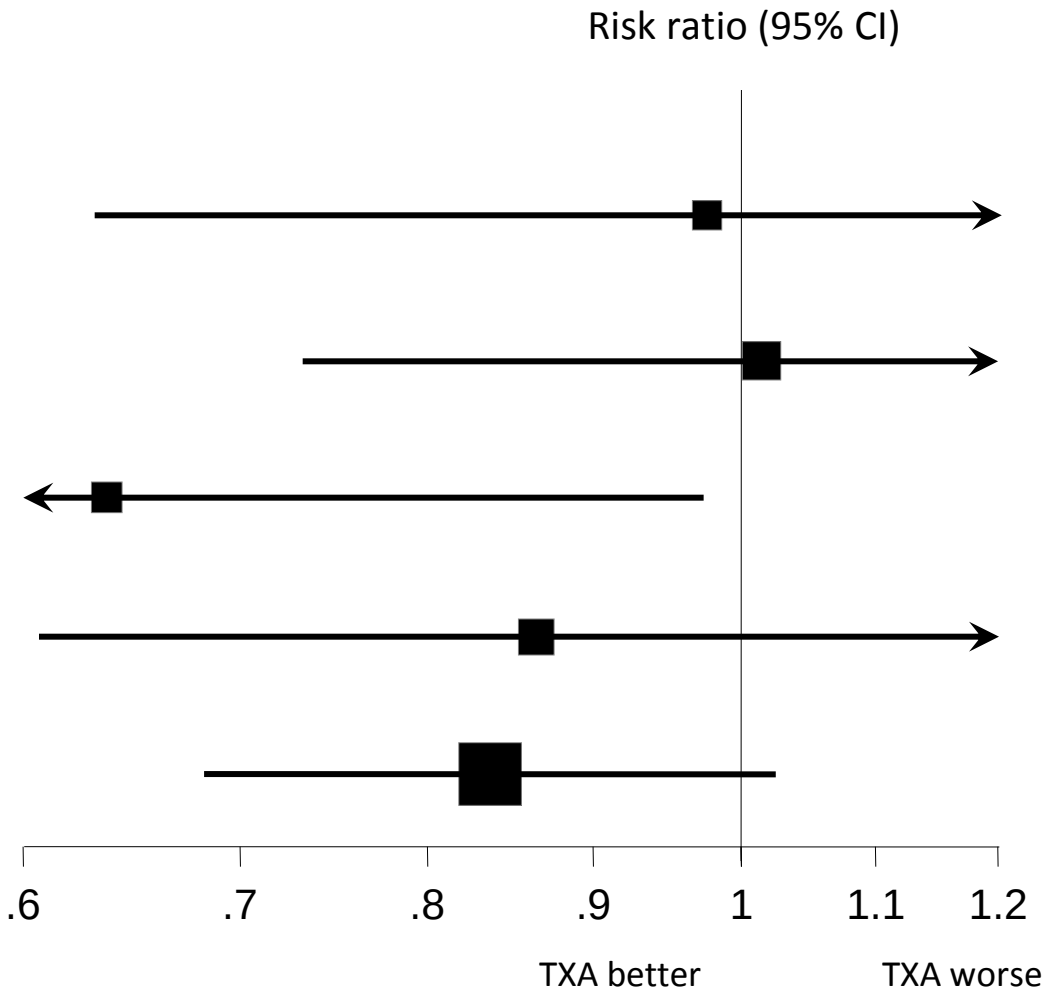
Figure 1: Mortality due to bleeding by subgroups

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

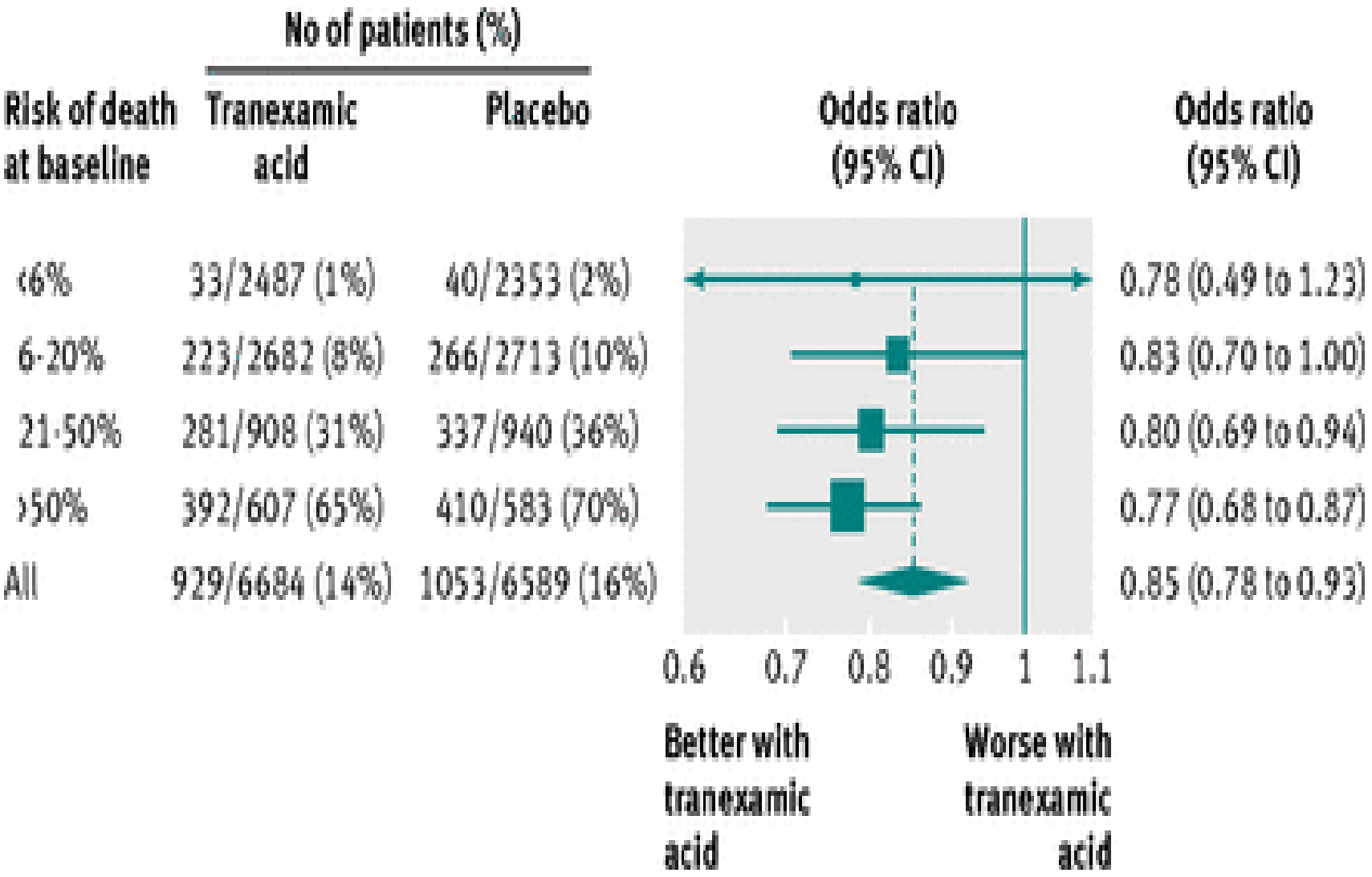


AC: There was no increase in thrombosis

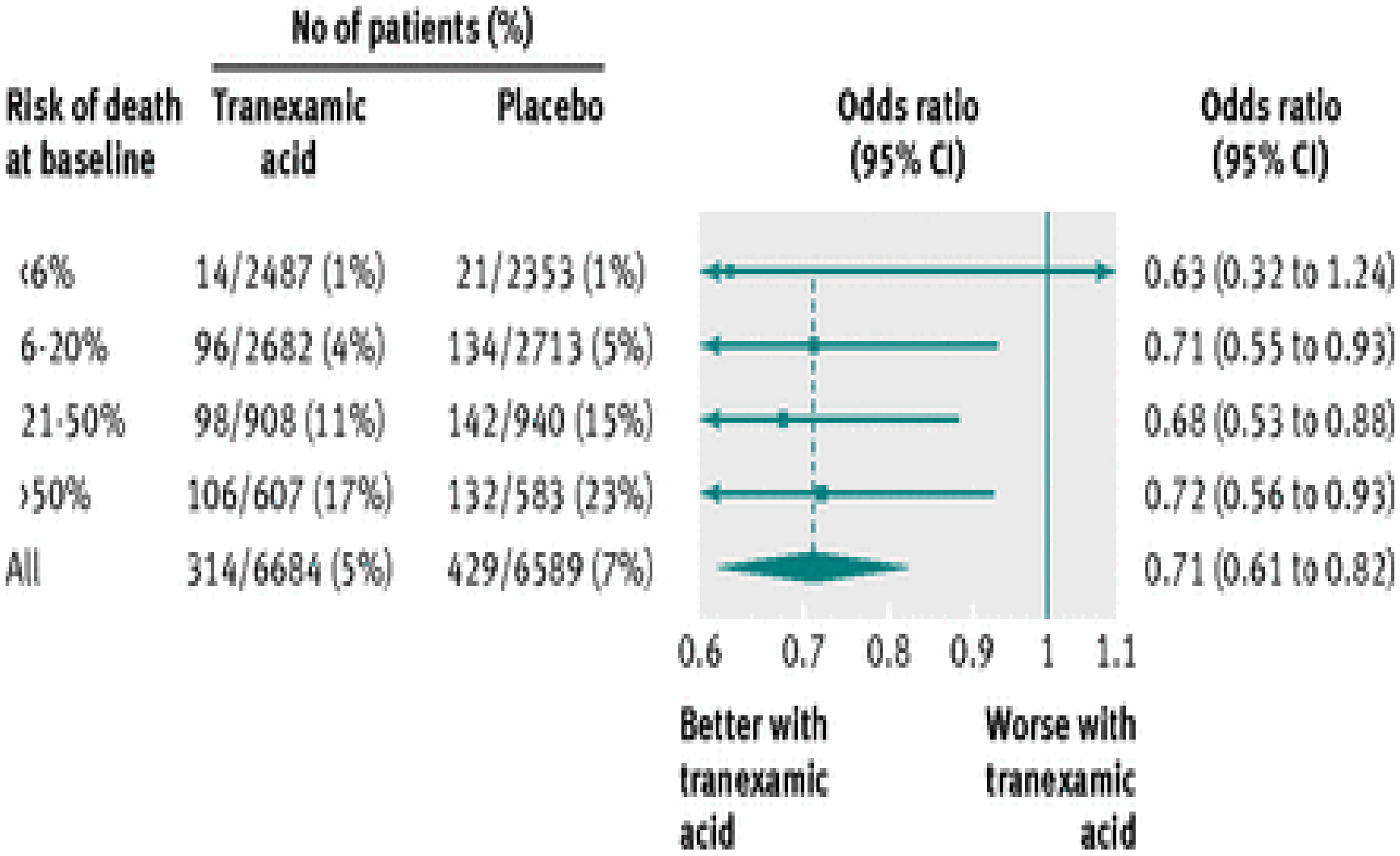
	TXA allocated (10,060)	Placebo allocated (10,067)
DVT	40 (0.40%)	41 (0.41%)
PE	72 (0.69%)	71 (0.70%)
MI	35 (0.35%)	55 (0.52%)
Stroke	57 (0.56%)	66 (0.65%)
Any	168 (1.63%)	201 (1.95%)



AC:TXA post hoc analysis vs standard mortality



TXA post hoc analysis vs standard mortality (specific for bleeding)



TXA in the Military

Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) Study. 293/896 consecutive patients received TXA

RESULTS:

The TXA group had lower unadjusted mortality than the no-TXA group **(17.4% vs 23.9%, respectively; P = .03)** despite being more severely injured (mean Injury Severity Score, 25.2 [16.6] vs 22.5 [18.5], respectively; **P < .001**).

This benefit was greatest in the group that received massive transfusion (**14.4% vs 28.1%, respectively; P = .004**), where TXA was also independently associated with survival (odds ratio = 7.228; 95% CI, 3.016-17.322) and less coagulopathy (P = .003).

Tactical Combat Casualty Care (TCCC):

Tactical Field Care and Tactical Evacuation Care:

(Create #6 Adjunct Medications) BEFORE IV Fluids

• If a casualty is anticipated to need significant blood transfusion (for example: presents with hemorrhagic shock, one or more major amputations, penetrating torso trauma, or evidence of severe bleeding) – Administer 1 gram of tranexamic acid in 100 cc in NS or LR as soon as possible but NOT later than 3 hours after injury.

– Begin second infusion of 1 gm TXA after Hextend or other fluid treatment.

– Move Fluid Resuscitation to a NEW #7

Tranexamic acid is highly cost effective

OPEN ACCESS Freely available online

PLoS one

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

Carla Guerriero[1]*, John Cairns[1], Pablo Perel[2], Haleema Shakur[2], Ian Roberts[2], on behalf of CRASH 2 trial collaborators

1 Department of Health Services Research and Policy, London School of Hygiene and Tropical Medicine, London, United Kingdom, 2 Clinical Trials Unit, London School of Hygiene and Tropical Medicine, London, United Kingdom

Findings: Administering TXA to bleeding trauma patients within three hours of injury saved an estimated 372, 315 and 755 LYs per 1,000 trauma patients in Tanzania, India and the UK respectively. The cost of giving TXA to 1,000 patients was $17,483 in Tanzania, $19,550 in India and $30,830 in the UK. The cost per LY gained of administering TXA is $48, $66 and $64 in Tanzania, India and the UK respectively.

Cost Effective

- WHO rule of thumb: (countries average annual income) X 3
- US = 100K per quality **life year** saved
- TXA: Number needed to treat: < 100
- Cost for 1g bolus PLUS 1g over 8 hours = < $100
- Cost per life saved (worst case): $10,000
  - Cost per life saved if only bolus given: $5000
  - Cost per **life year** saved (assume 20 yrs): $250
  - Cost per **life year** saved if given in the first hour: <$250

Cost Effective

WHICH TREATMENTS ARE THE BEST AND WORST VALUES?

Treatment	Cost to Buy One Quality-Adjusted Life Year (QALY)
GOOD VALUES*	
Beta blockers for high-risk patients after heart attack	Less than $5,000
Combination antiretroviral therapy for HIV/AIDS	$10,000–20,000
Treatment of moderate hypertension	$20,000–50,000
Dialysis for end-stage kidney failure	$50,000–100,000
BAD VALUES	
Lung transplantation	More than $100,000
MRI screening for dementia	More than $500,000
Annual (vs. biennial) Pap smear	$800,000

*Good values in the U.S. are considered to be those with a QALY of $100,000–120,000 or less.

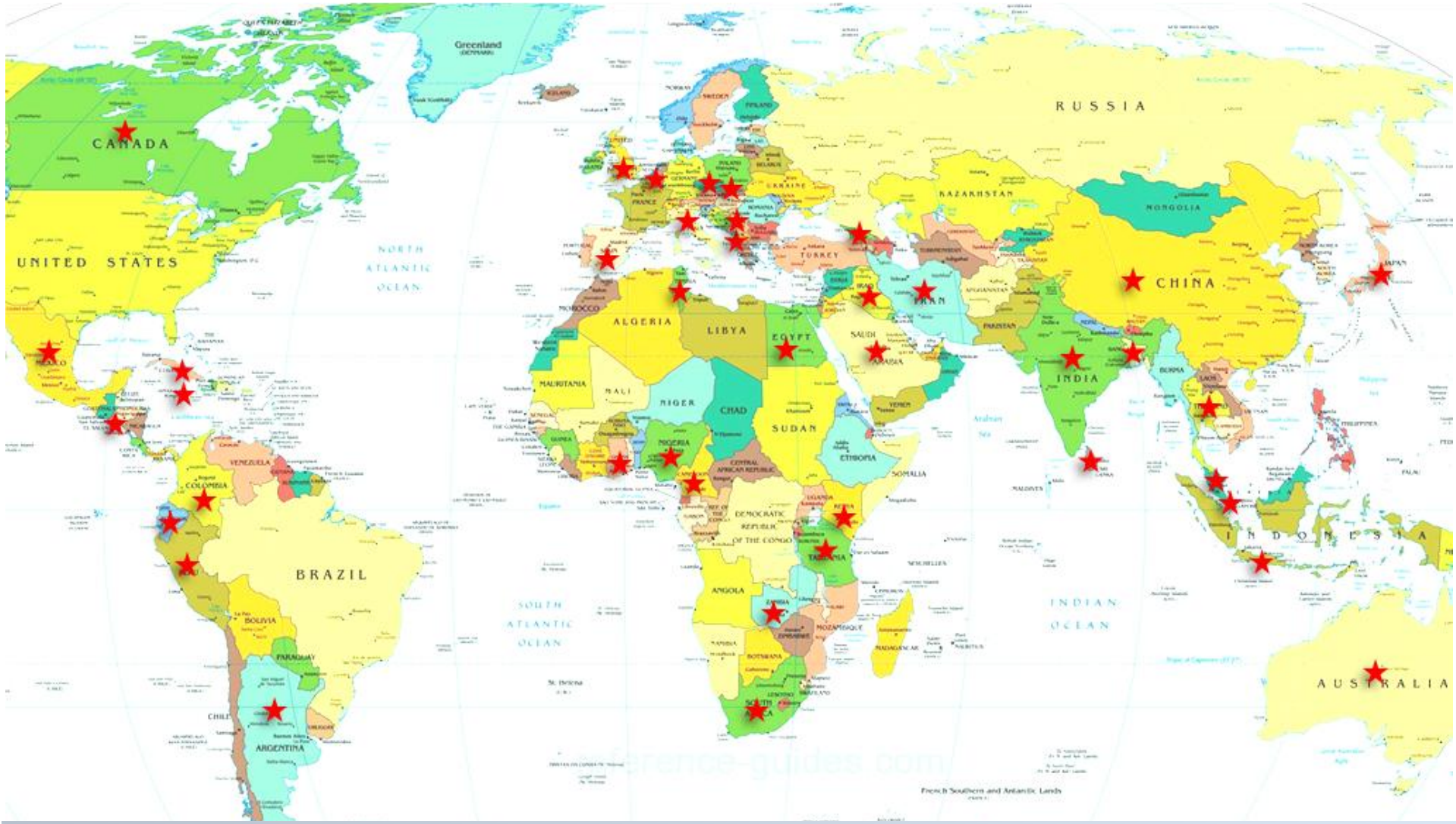
What we concluded

- Tranexamic acid reduces mortality in bleeding trauma patients
- Tranexamic acid did not increase unwanted clotting
- Tranexamic acid needs to be given early – within 3 hours of injury (1 hour is better)
- Tranexamic acid is not expensive and could save hundreds of thousands of lives each year around the world
- Tranexamic acid would likely save 2-3 Californians per day

TXA 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:
  --they consider TXA a class 1a drug – to be given before fluids!
- Tranexamic acid is being used in hospitals around the world
- Tranexamic acid will be given in most UK ambulances within the next year

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



was shown to reduce mortality on each!