Tranexamic acid, civilian trauma and the CRASH-2 trial and Future Trials

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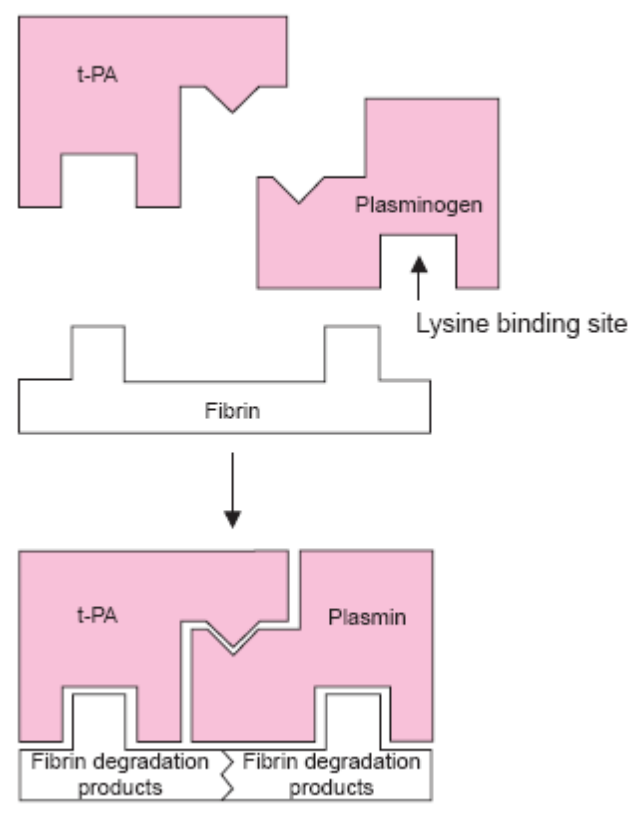
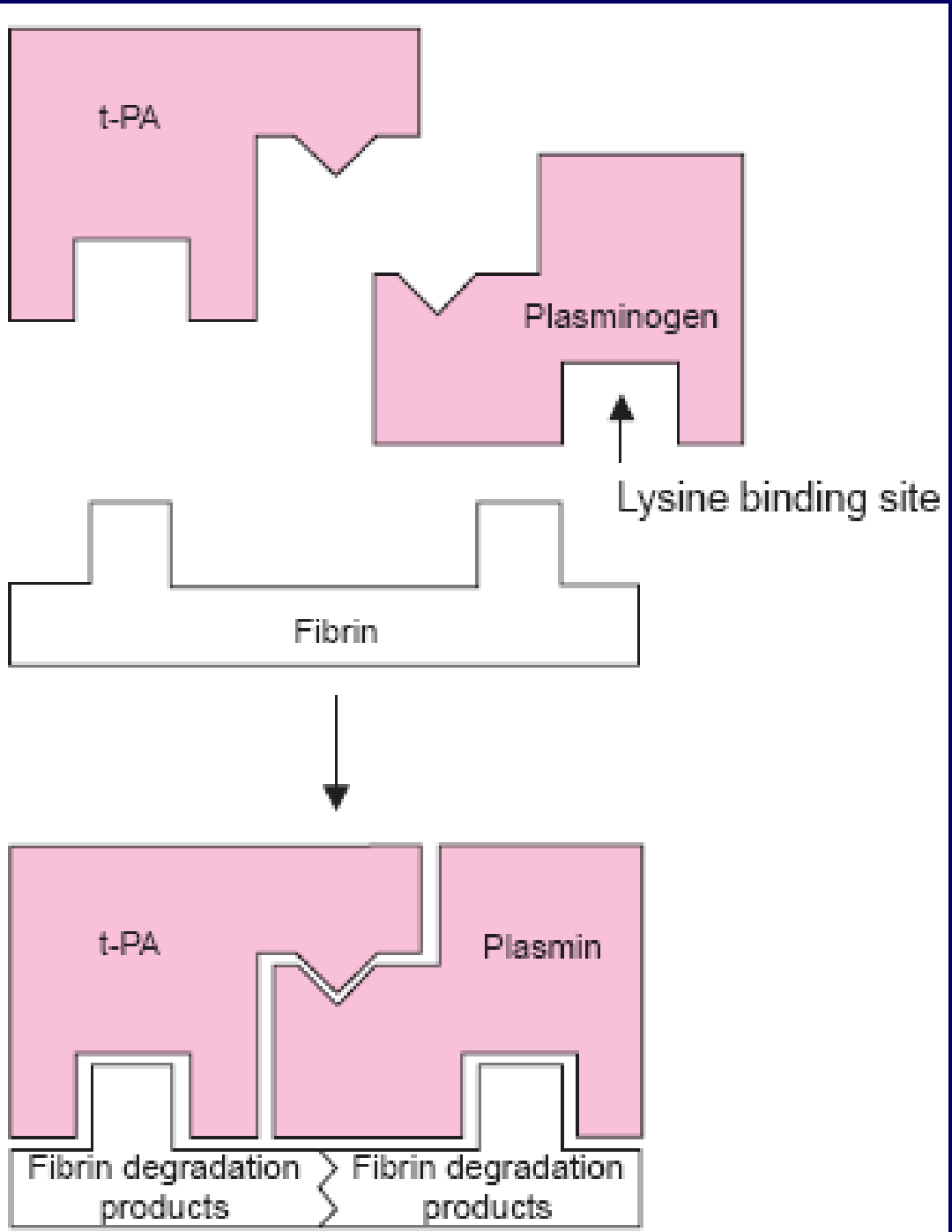
Structure of presentation

- Tranexamic acid and bleeding
- The CRASH-2 trial
- Tranexamic acid in traumatic brain injury
- Future research

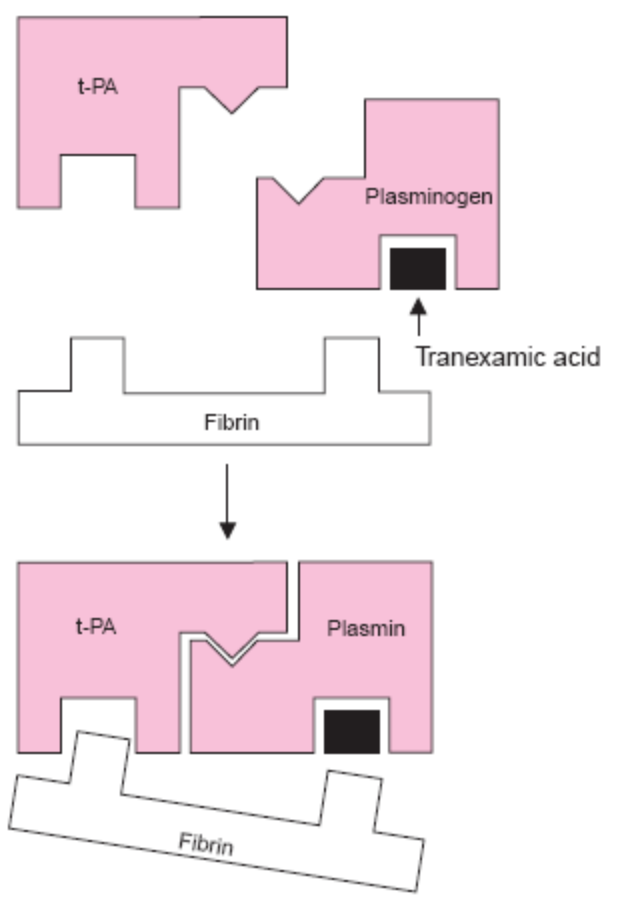
Tranexamic acid and bleeding



- Activators of plasminogen from injured tissue convert it to plasmin.
- Plasmin binds to fibrin via its lysine binding sites to cause fibrinolysis.
- Bleeding and increased fibrinolysis are often found together.


t-PA
Plasminogen
Lysine binding site
Fibrin
t-PA
Plasmin
Fibrin degradation products
Fibrin degradation products

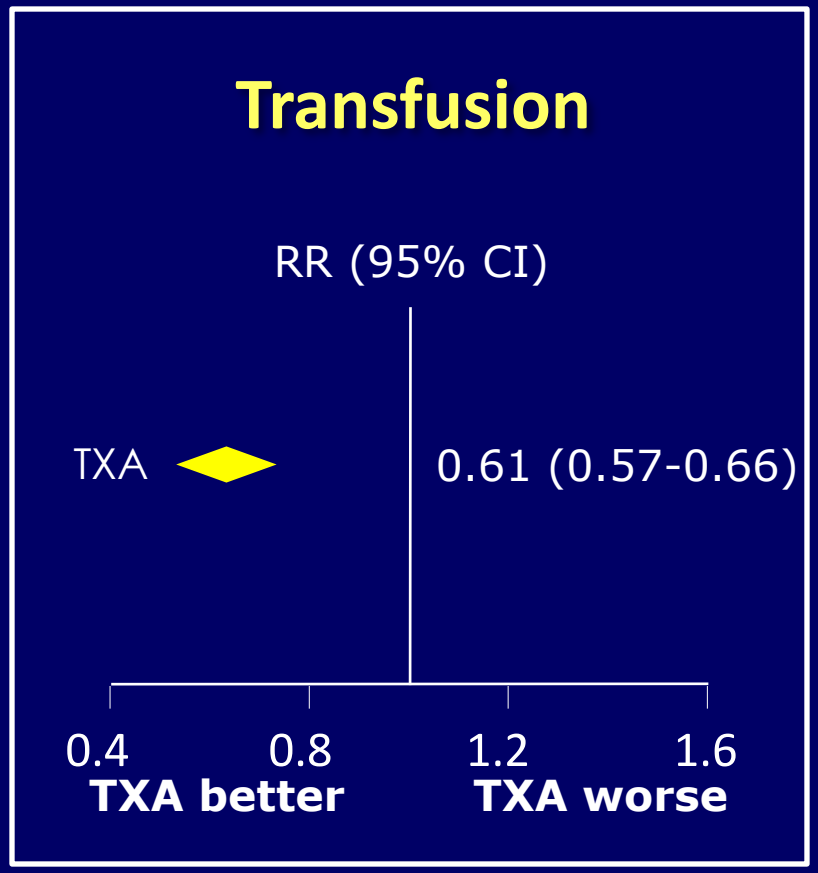
Tranexamic acid and bleeding



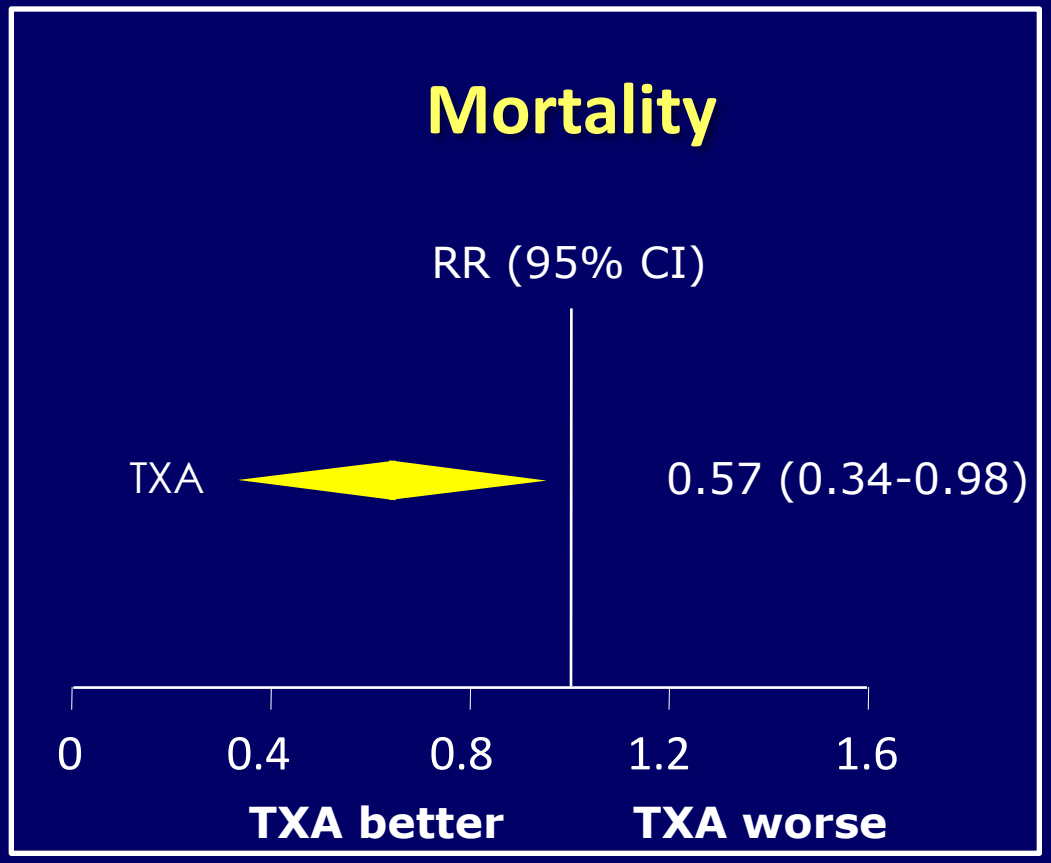
- **Tranexamic Acid (TXA)** is a synthetic derivative of the amino acid lysine.
  - It has a very high affinity for the lysine binding sites of plasminogen.
  - It blocks these sites and prevents binding of plasmin to the fibrin surface, thus exerting its antifibrinolytic effect.

TXA and bleeding

TXA reduces bleeding in surgery (Henry et al, 2011)



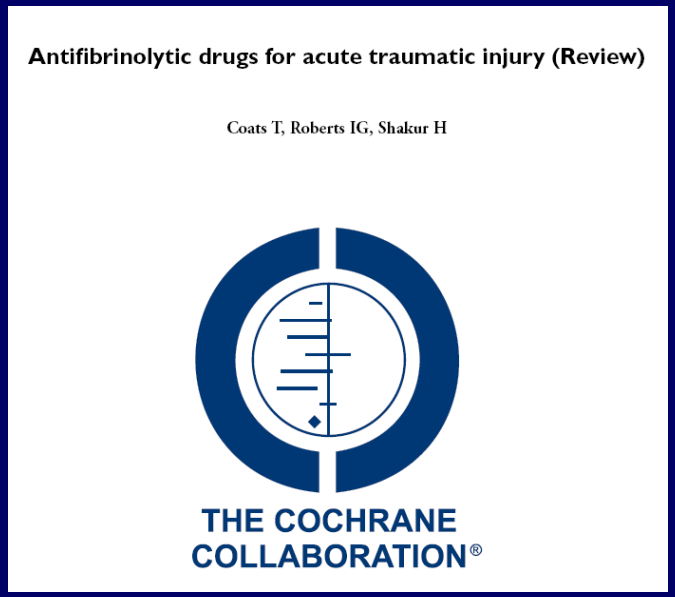
65 trials (4,842 patients)



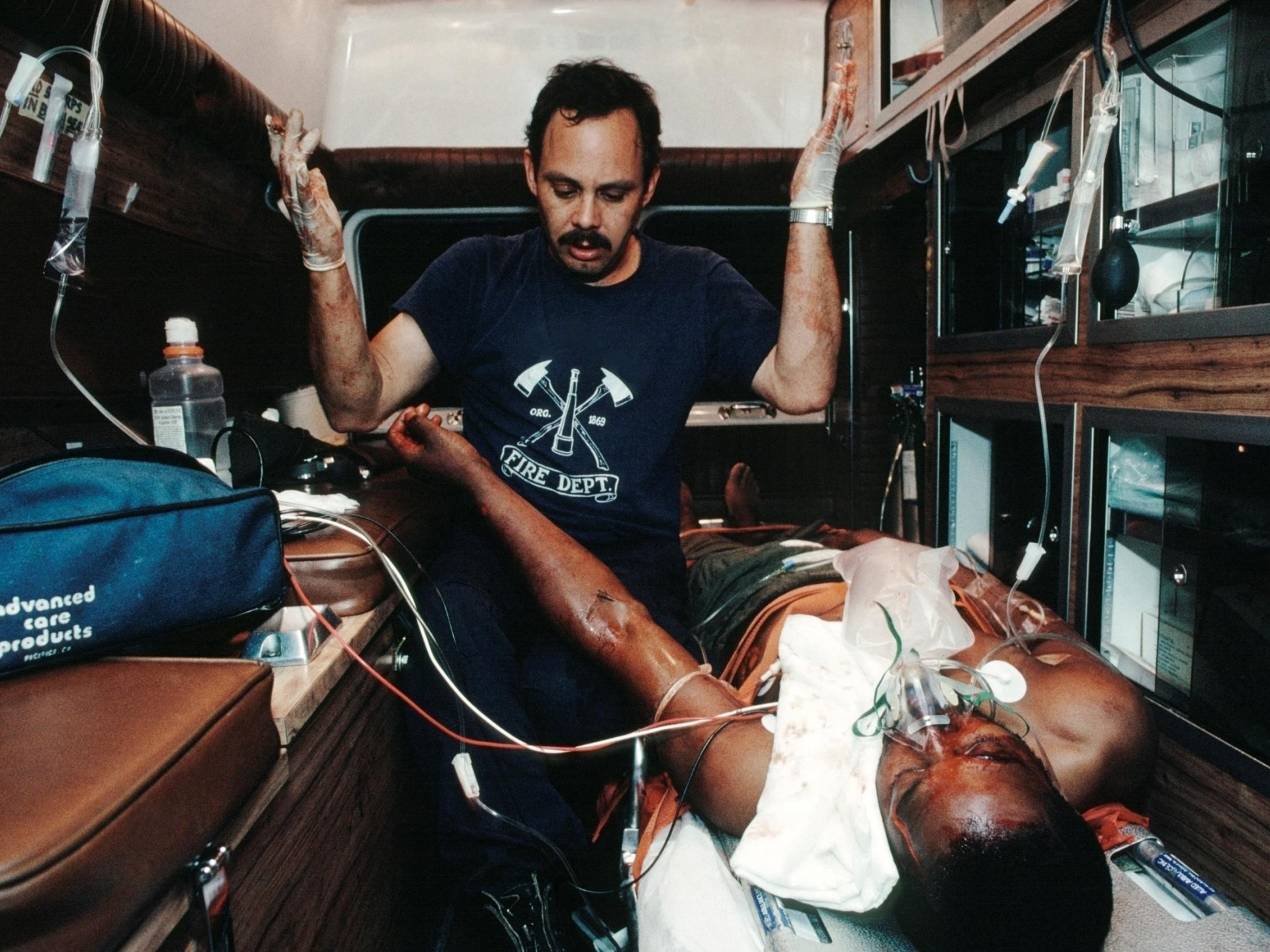
30 trials (2,917 patients)

TXA and bleeding

Does TXA reduce mortality in trauma (Coats, 2004)?



- Insufficient evidence to either support or refute a clinically important treatment effect.
- Further RCTs of tranexamic acid in trauma are needed.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advanced
care
products

The CRASH-2 trial

A randomized, placebo controlled trial among trauma patients with significant hemorrhage, of the effects of tranexamic acid on death and vascular occlusive events

Potentially eligible

Adult trauma patients, within 8 hours injury
with significant hemorrhage or
at risk of significant hemorrhage

Doctor is "certain" that tranexamic acid is indicated

INELIGIBLE

Give tranexamic acid

Doctor is "certain" that tranexamic acid is not indicated

INELIGIBLE

Don't give tranexamic acid

Doctor is "**SUBSTANTIALLY UNCERTAIN**" as to the appropriateness of tranexamic acid in this patient

RANDOMISE

TRANEXAMIC ACID

PLACEBO

Methods

Treatment	Dose (Tranexamic Acid or placebo)
Loading	1 gram /10 minutes (IV infusion)
Maintenance	1 gram /8 hours (IV infusion)

Methods

Primary outcome

Death in hospital within four weeks of injury

Cause of death to be described: bleeding, vascular occlusion (myocardial infarction, stroke and pulmonary embolism combined and separately), multi-organ failure, head injury, other

Methods

Secondary outcomes

- Vascular occlusive events: combined and separately
- Blood products transfusion
- Surgical intervention (head, chest, abdominal, pelvis, bleeding)
- Death or dependency (modified Oxford Handicap Scale)

Methods

Statistical analysis

- Intention-to-treat analysis
- Relative Risks (RR)
- 95% confidence intervals for overall results
- 99% confidence intervals for subgroup results

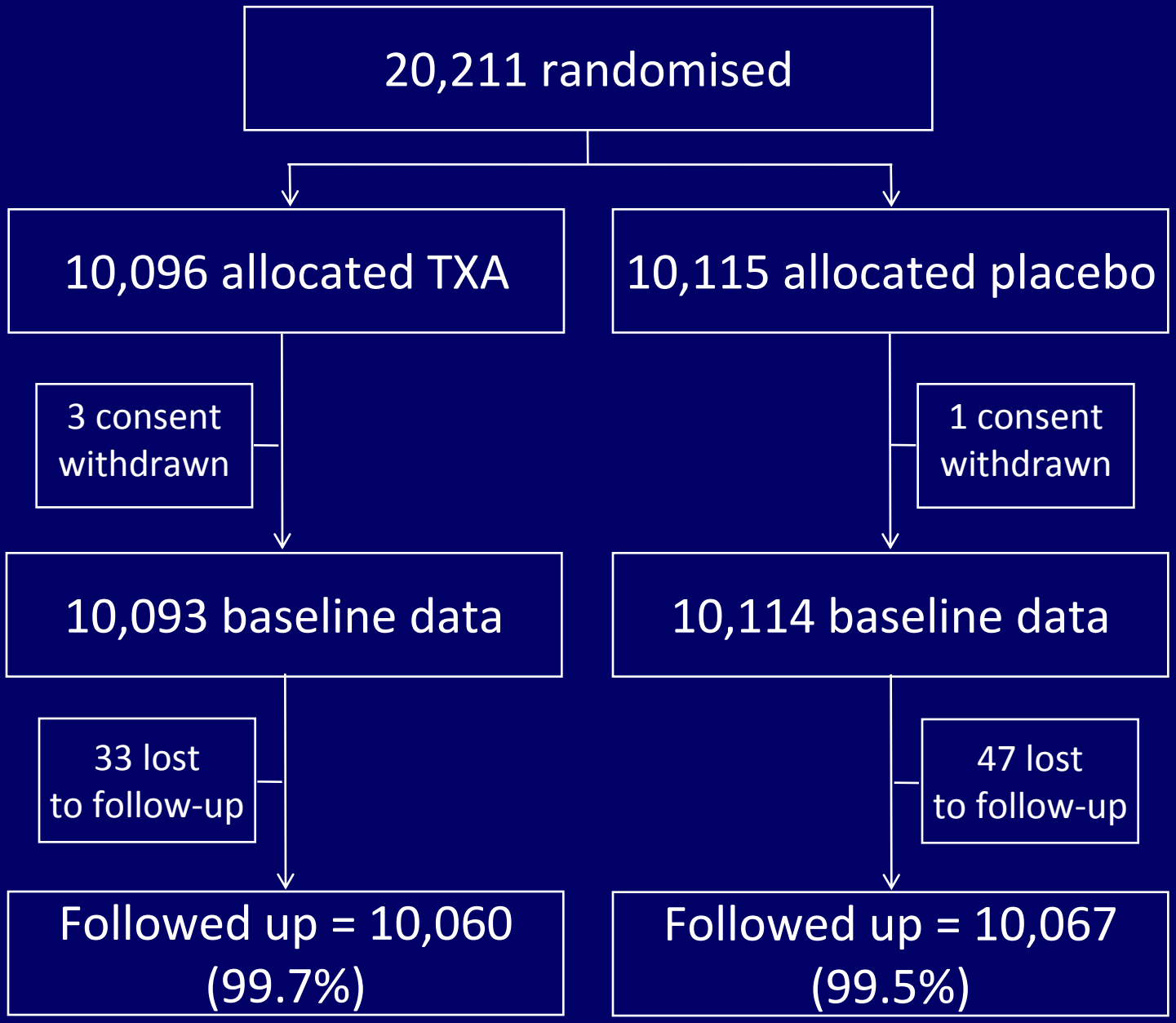
Results

Patient enrolment

20,211 patients

from 274 hospitals in 40 countries

CRASH-2 trial profile



Baseline characteristics

	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 characteristics

	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 characteristics

	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
Respiratory rate (breaths per minute)		
>29	1,491 (14.8)	1,429 (14.1)
10–29	8,355 (82.8)	8,436 (83.4)
<10	160 (1.6)	149 (1.5)
[not known]	87 (0.9)	100 (1.0)

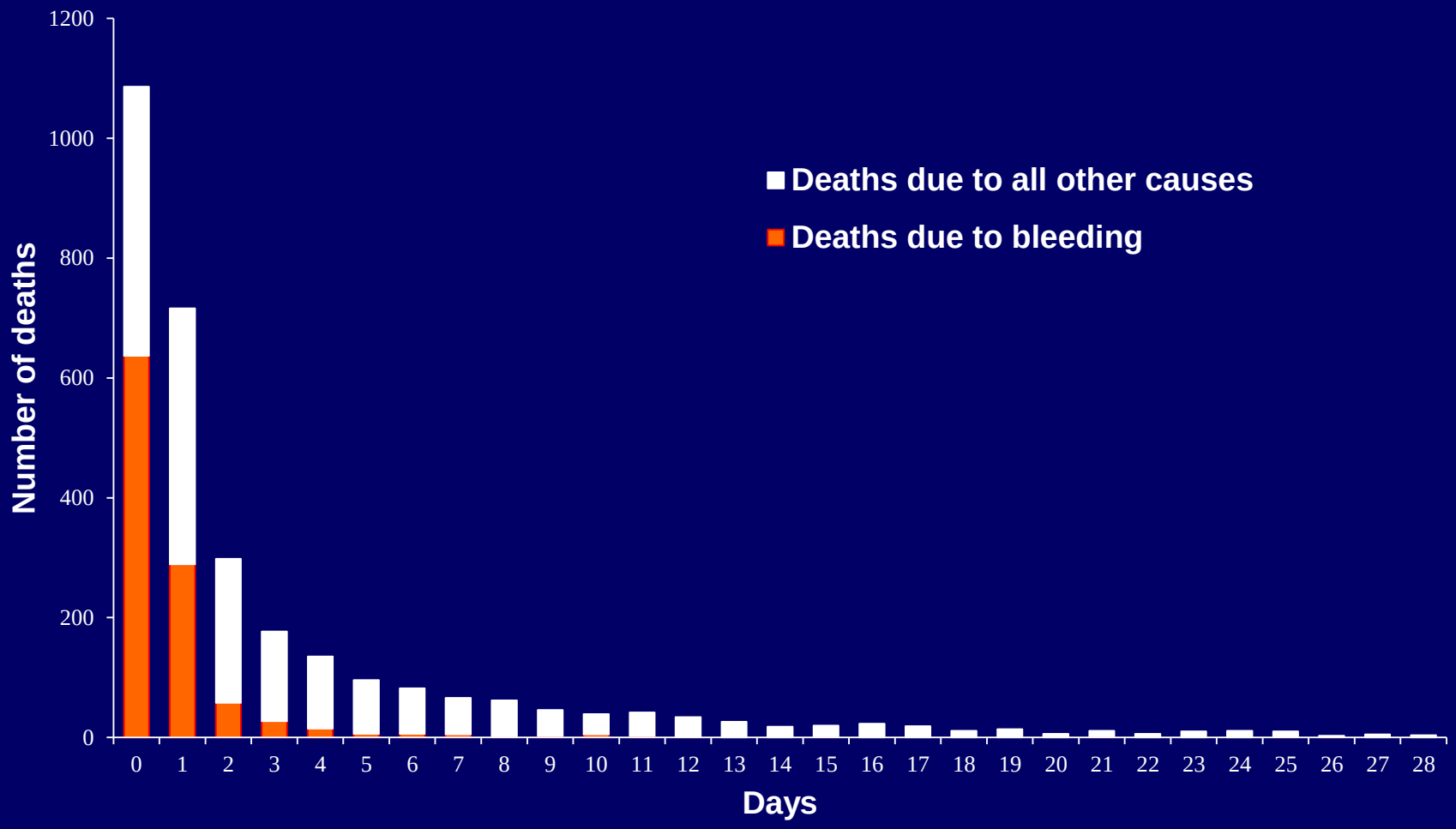
Baseline characteristics

	TXA n (%)	Placebo n (%)
Capillary Refill Time (seconds)		
2 or less	3,432 (34.0)	3,406 (33.7)
3–4	4,665 (46.2)	4,722 (46.7)
>4	1,699 (16.8)	1,672 (16.5)
[not known]	297 (2.9)	314 (3.1)
Heart rate (beats per minute)		
>107	4,872 (48.3)	4,853 (48.0)
92–107	2,556 (25.3)	2,546 (25.2)
77–91	1,727 (17.1)	1,770 (17.5)
<77	875 (8.7)	871 (8.6)
[not known]	63 (0.6)	74 (0.7)

Baseline characteristics

	TXA n (%)	Placebo n (%)
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

Death: When patients die

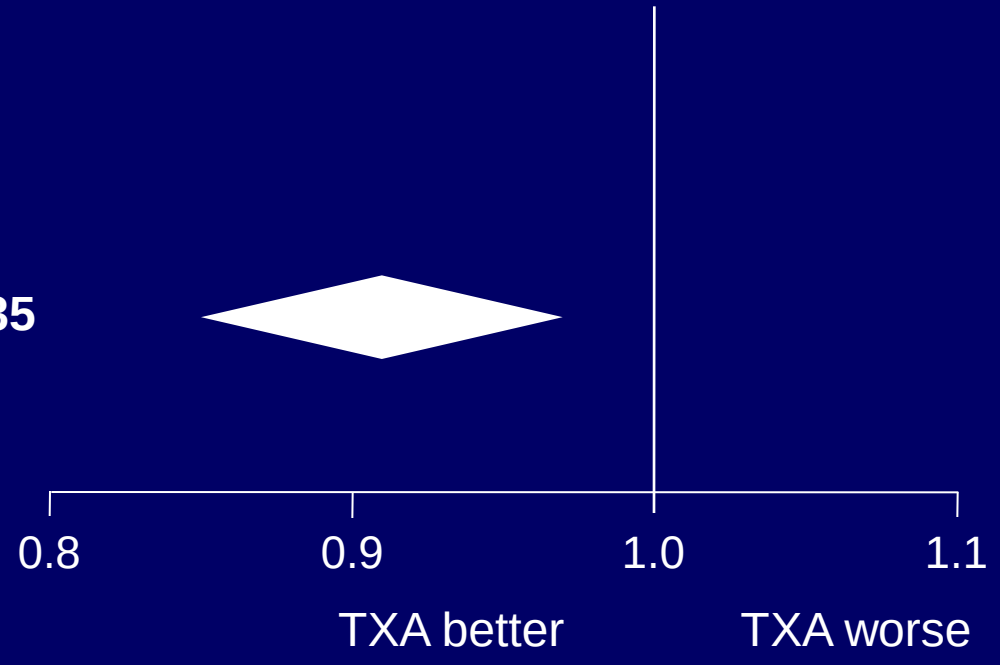


Cause of death

Cause of death	TXA 10,060	Placebo 10,067	RR for death	P value
Bleeding	489	574	0·85 (0·76–0·96)	0·0077
Vascular occlusion	33	48	0·69 (0·44–1·07)	0·096
Multiorgan 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**

Any cause of death

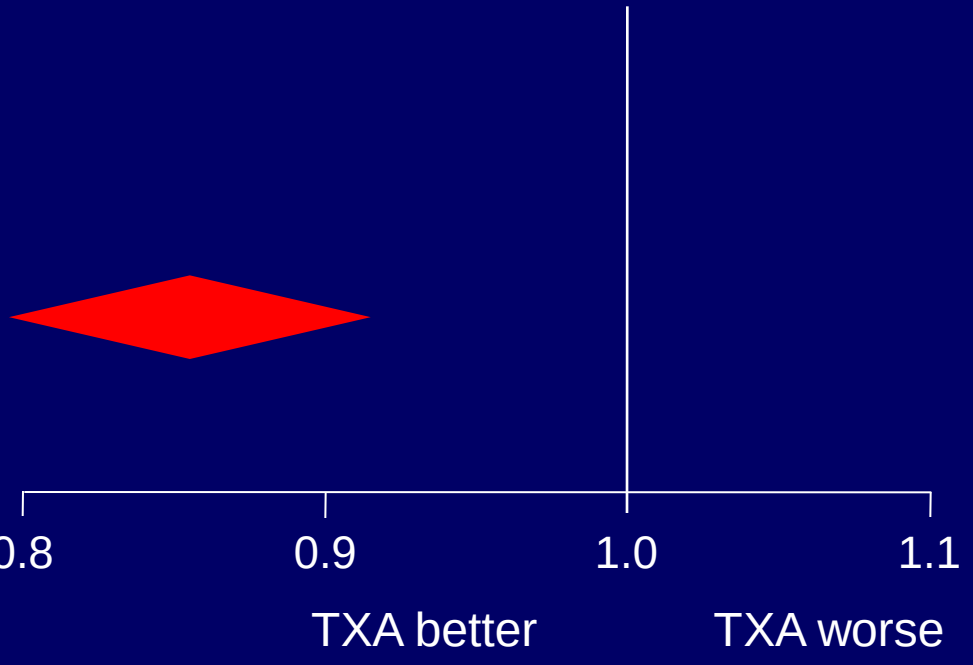
TXA	**Placebo**	RR (95% CI)
(n= 10,060)	**(n= 10,067)**	
1,463 (14.5%)	1,613 (16.0%)	
0.91 (0.85–0.97) 2P=0.0035		



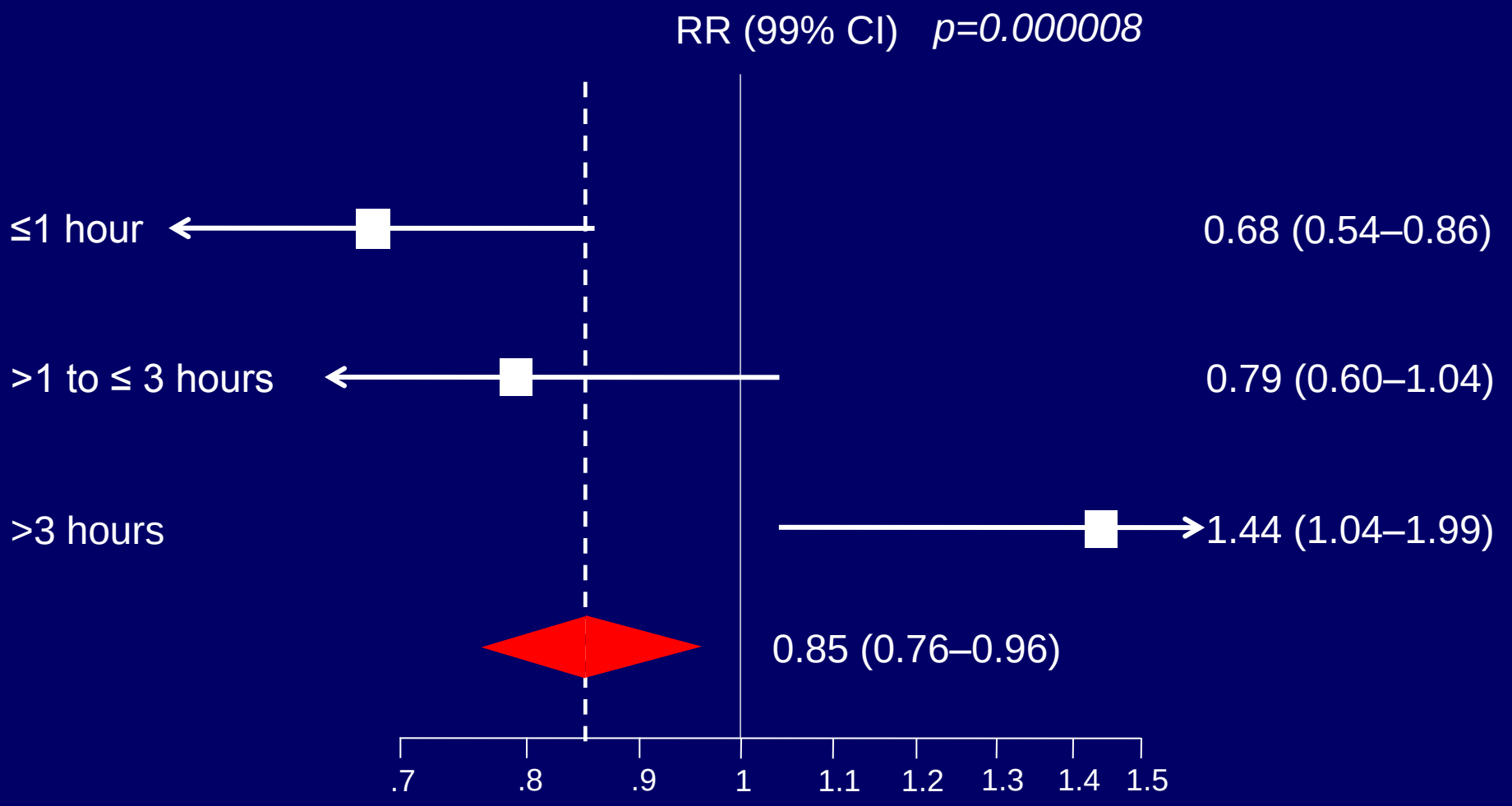
Death due to bleeding

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

0.85 (0.76–0.96) 2P=0.0077



Bleeding death: early treatment is better

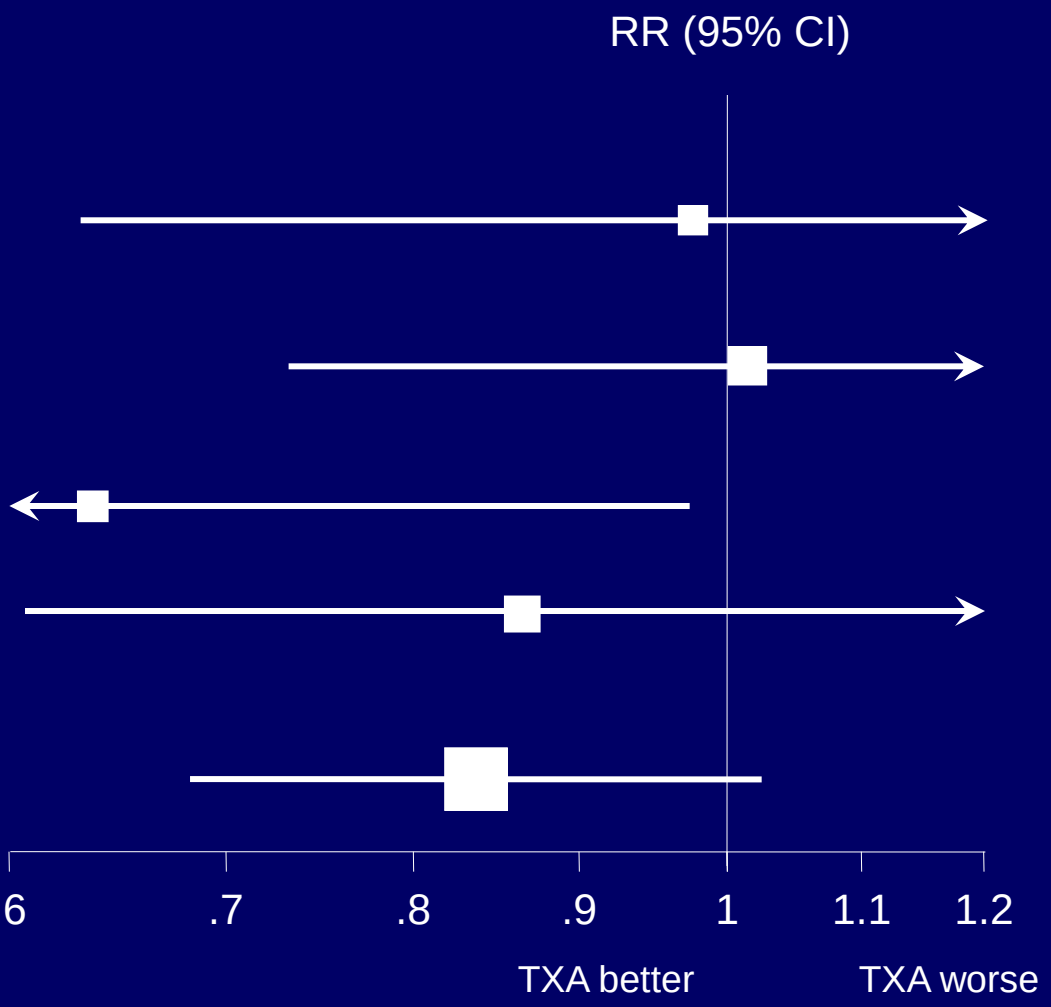


Bleeding death: early treatment is better

	N	All causes of death	Bleeding	Non-bleeding
RR (95%CI)	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
≤1	7 451	0·87 (0·76–0·97)	0·68 (0·57–0·82)	1·04 (0·89–1·21)
≥1–3	6 033	0·87 (0·77–0·97)	0·79 (0·64–0·97)	0·91 (0·78–1·05)
>3	6 634	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)*

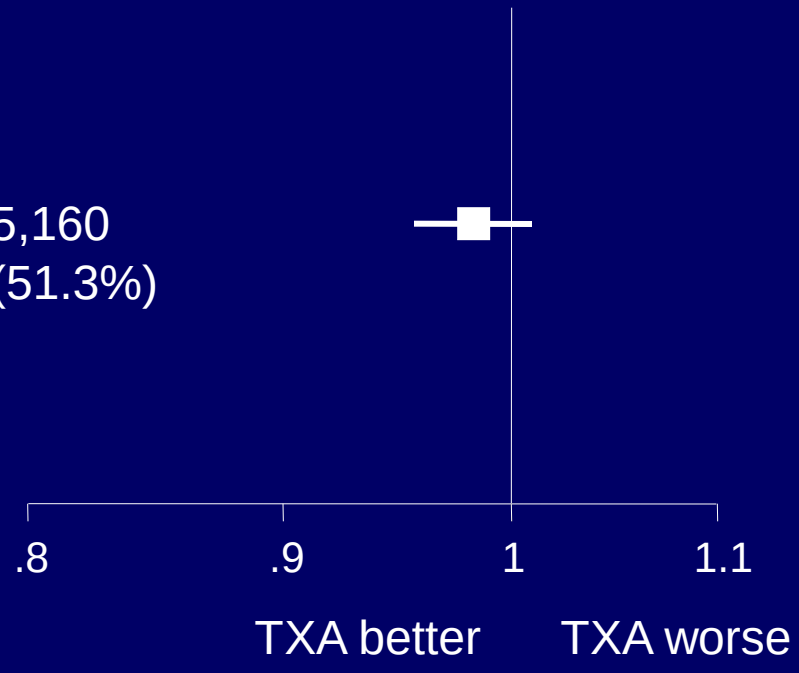
Vascular occlusive events

	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%)



Blood transfusion

	TXA allocated (10,060)	Placebo allocated (10,067)	RR (95% CI)
Blood transfusion	5,067 (50.4%)	5,160 (51.3%)	

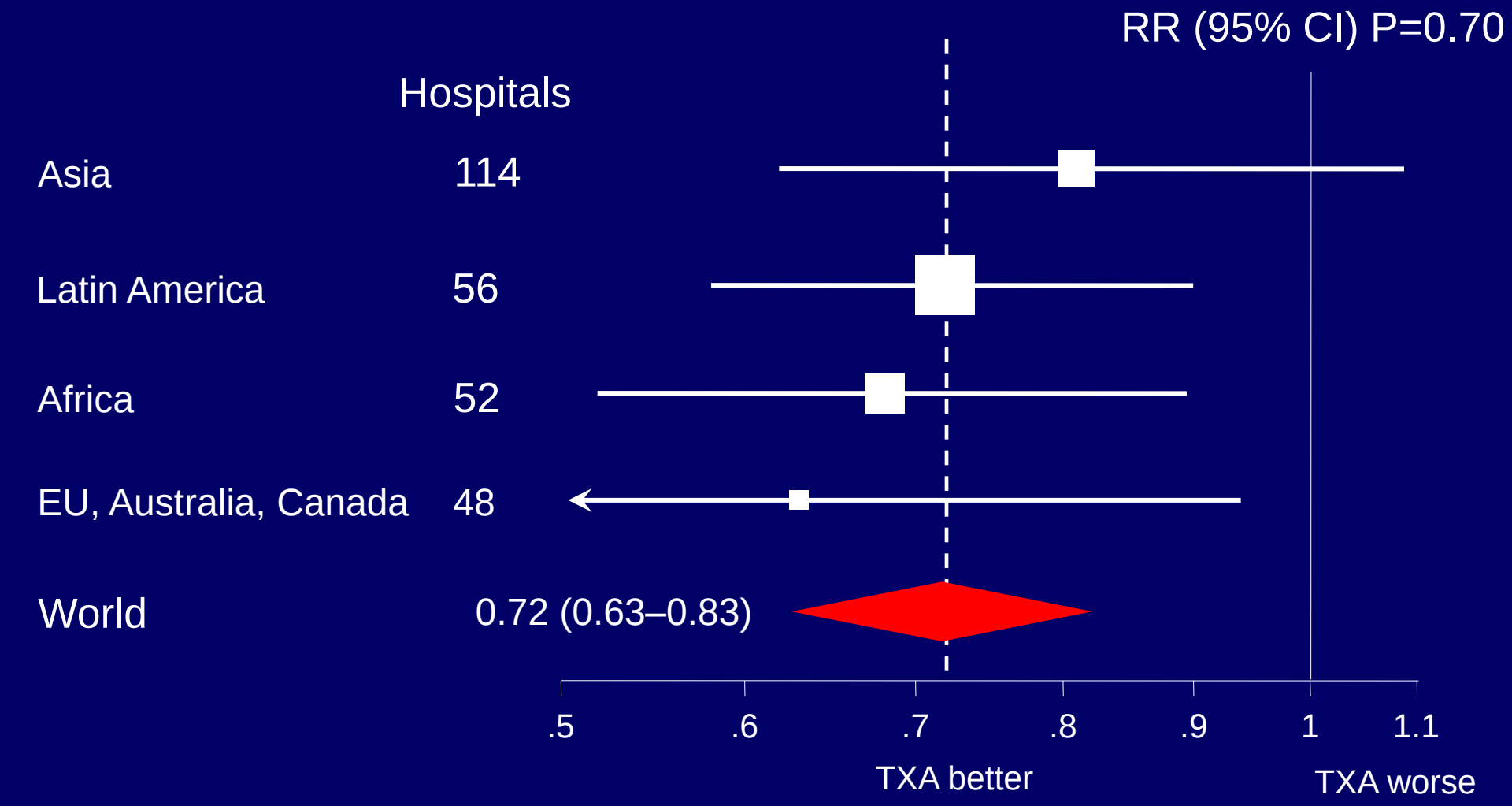


Death and Dependency

	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

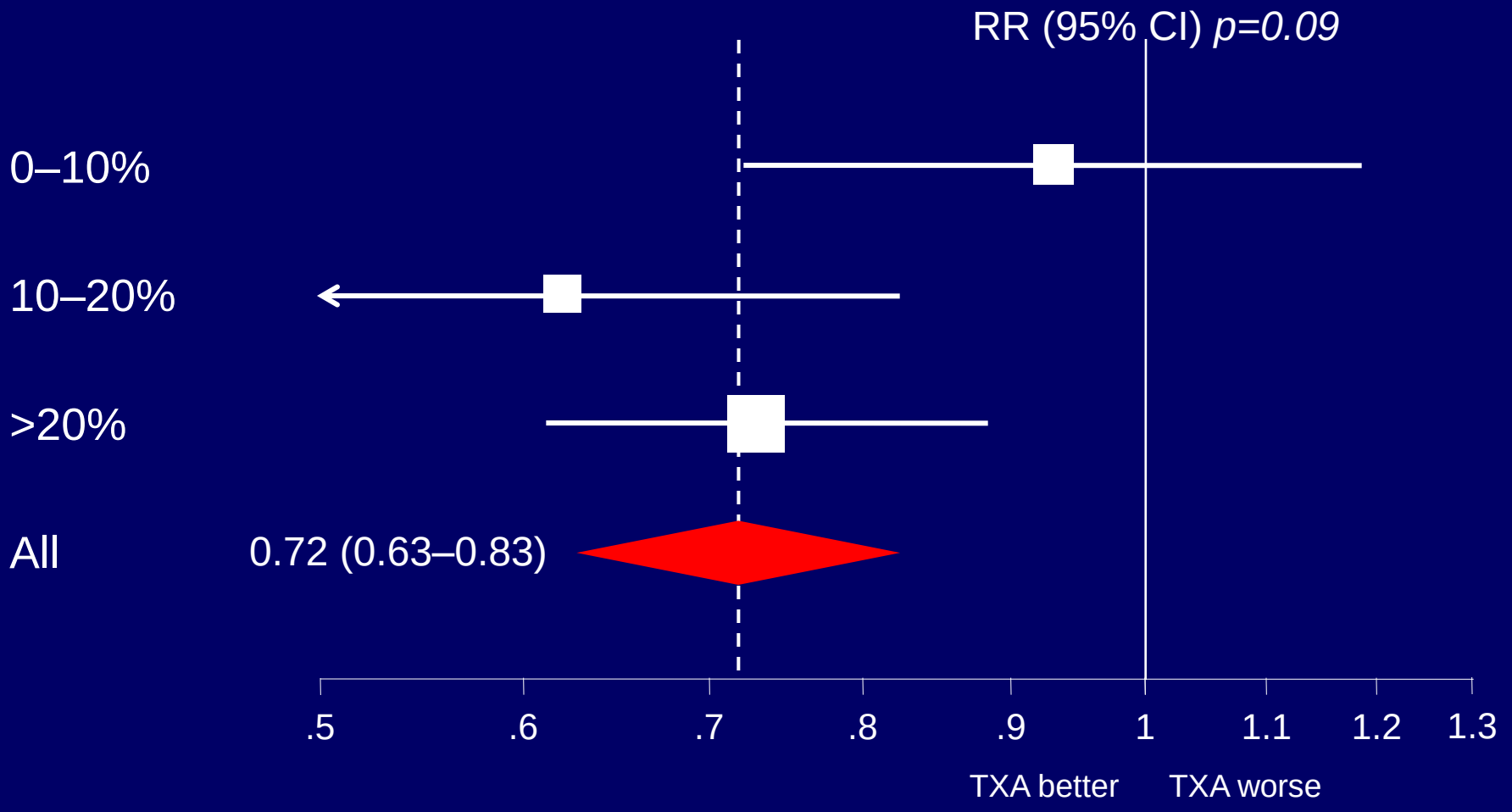
Effect of early TXA on death due to bleeding

(by geographical region)



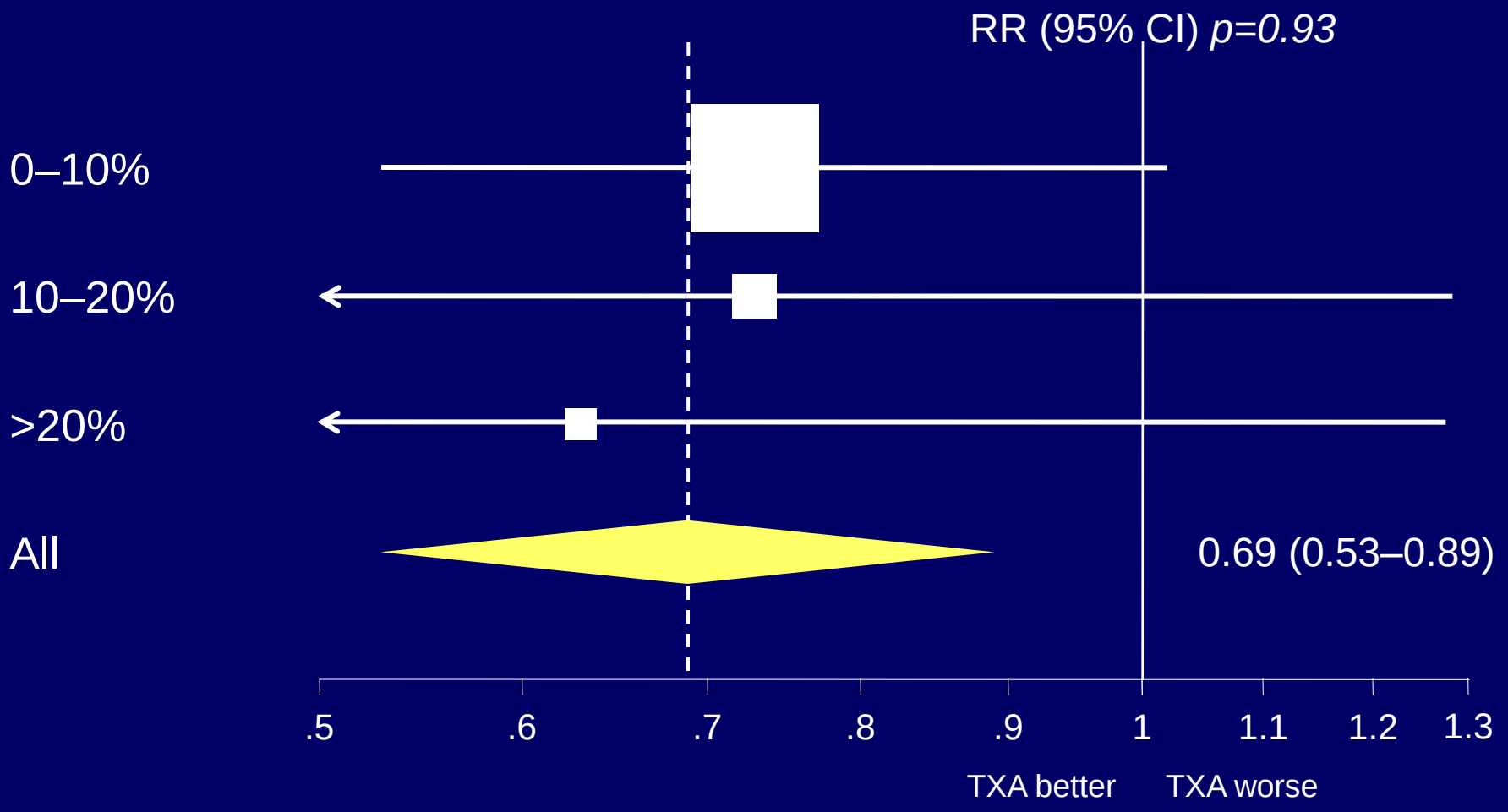
Effect of early TXA on death due to bleeding

(by baseline risk of death)



Effect of early TXA on vascular occlusion

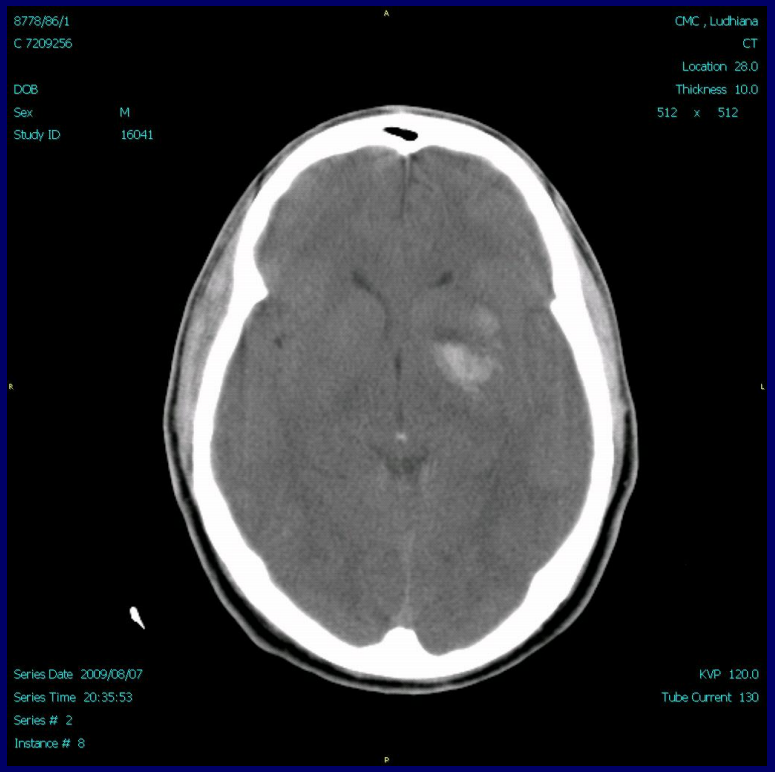
(by baseline risk of death)

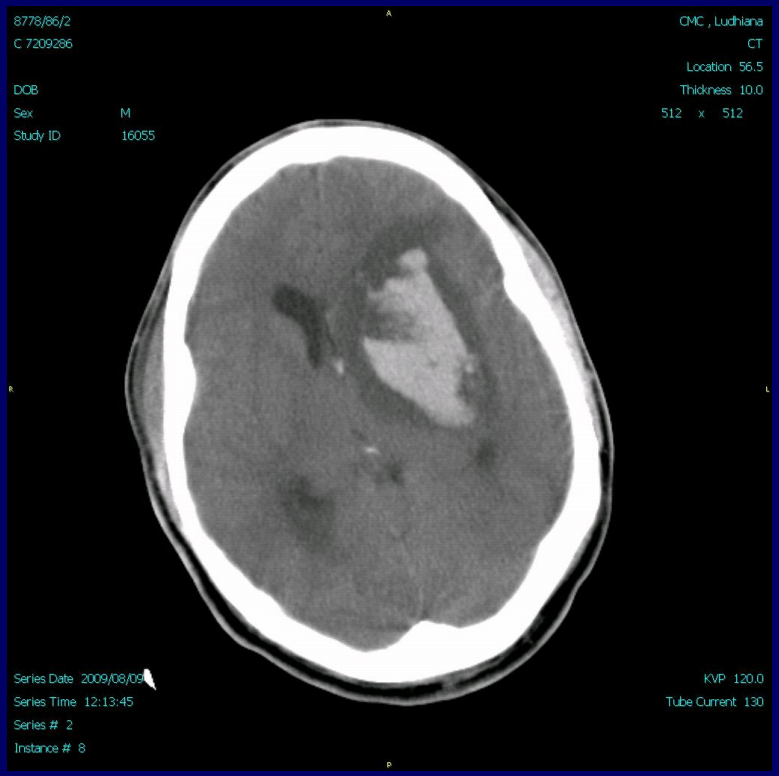


Conclusion

- TXA reduces mortality in bleeding trauma patients
- TXA should be given as soon as possible (<3 hours)
- No increased risk of vascular occlusive events

What is the effect of TXA in TBI?





Methods

Study design

Double blind randomised placebo controlled trial
nested in a subset of CRASH-2 trial participants

Participants

Patients MUST fulfil eligibility criteria for the CRASH-2 trial

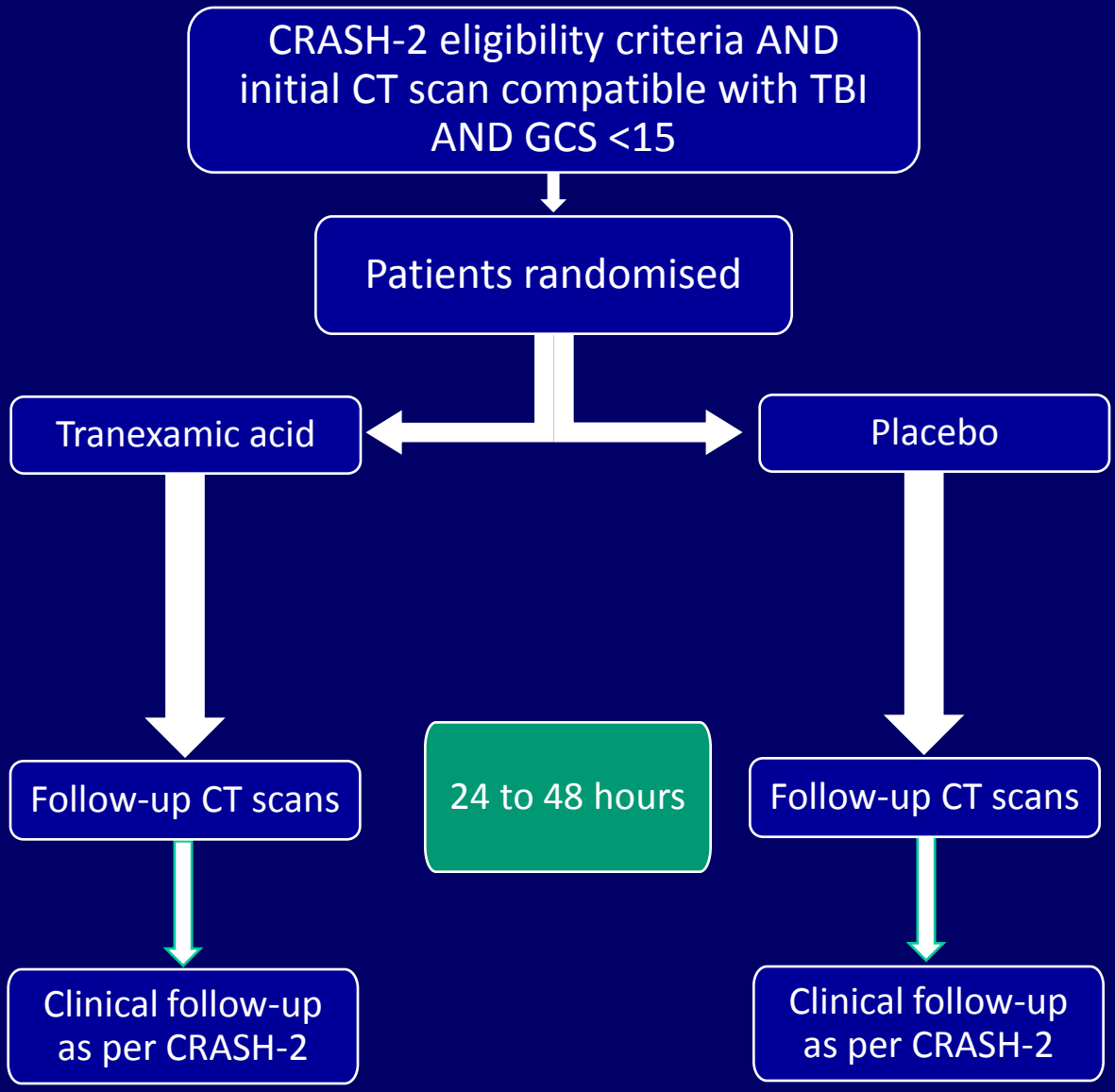
+

CT scan showing intracranial abnormality consistent with traumatic brain injury and GCS <15

Intervention

1 gram of TXA (10 min), 1 gram (eight hours)
or matching placebo (sodium chloride 0·9%)

Flow diagram



Outcomes

CT scan outcomes

Total haematoma growth

Significant haematoma growth
(increase >25% in size)

New intracranial haemorrhage

New focal cerebral ischaemic lesions

Mass effect

Traumatic subarachnoid haemorrhage

Clinical outcomes

Mortality

Need for neurosurgery

Methods

Randomisation was balanced by centre

Treatment allocation was concealed

All analyses were undertaken on an intention to treat basis

Analysis was adjusted for baseline variables
(Initial volume, Time from injury to first and second CT scan Glasgow Coma Score , and Age)

Methods for CT scan reading

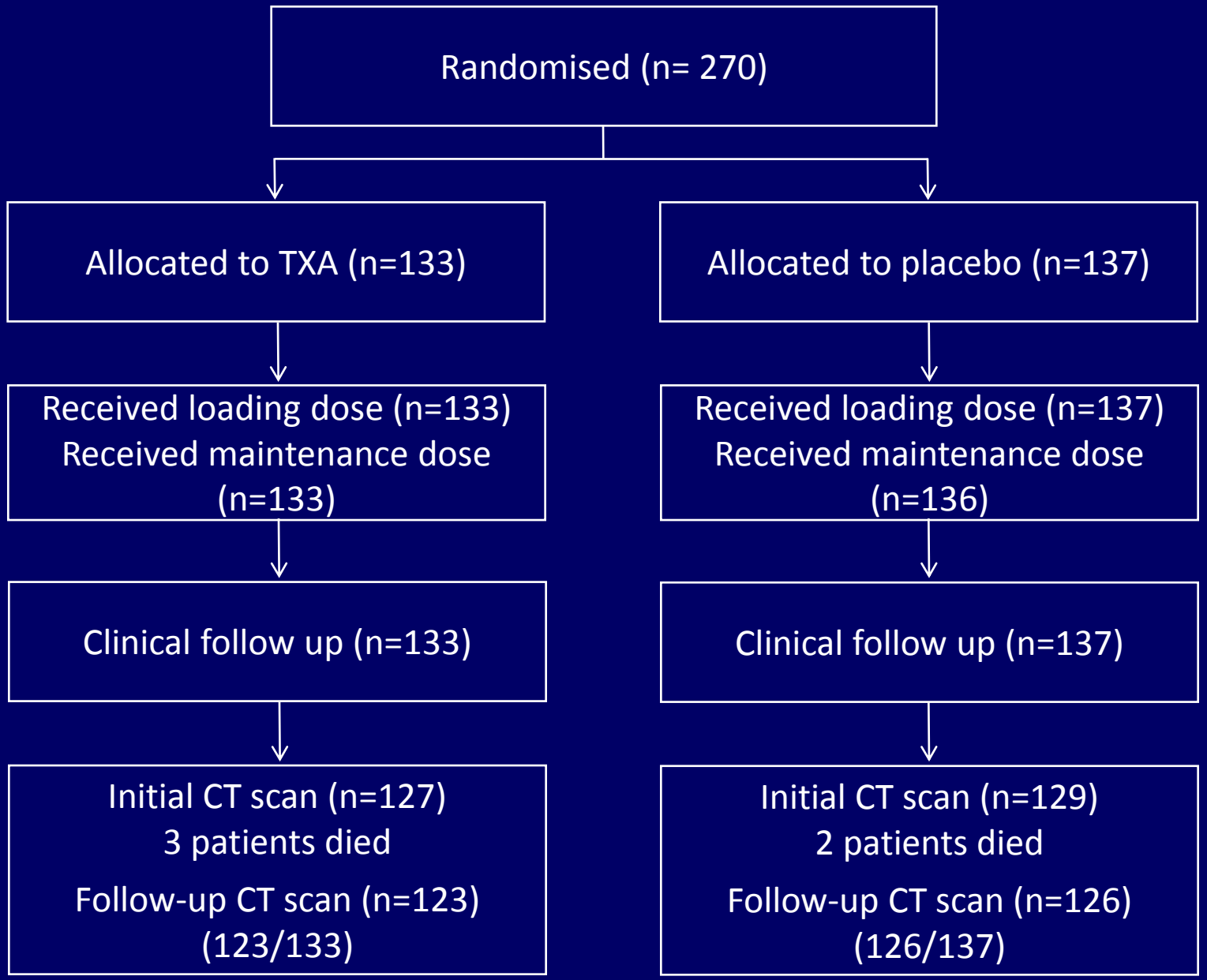
Experienced radiologist

Protocol for CT scan reading using validated methods

Double reading of all the CT scans

Kappa and Intraclass correlation coefficient for reliability

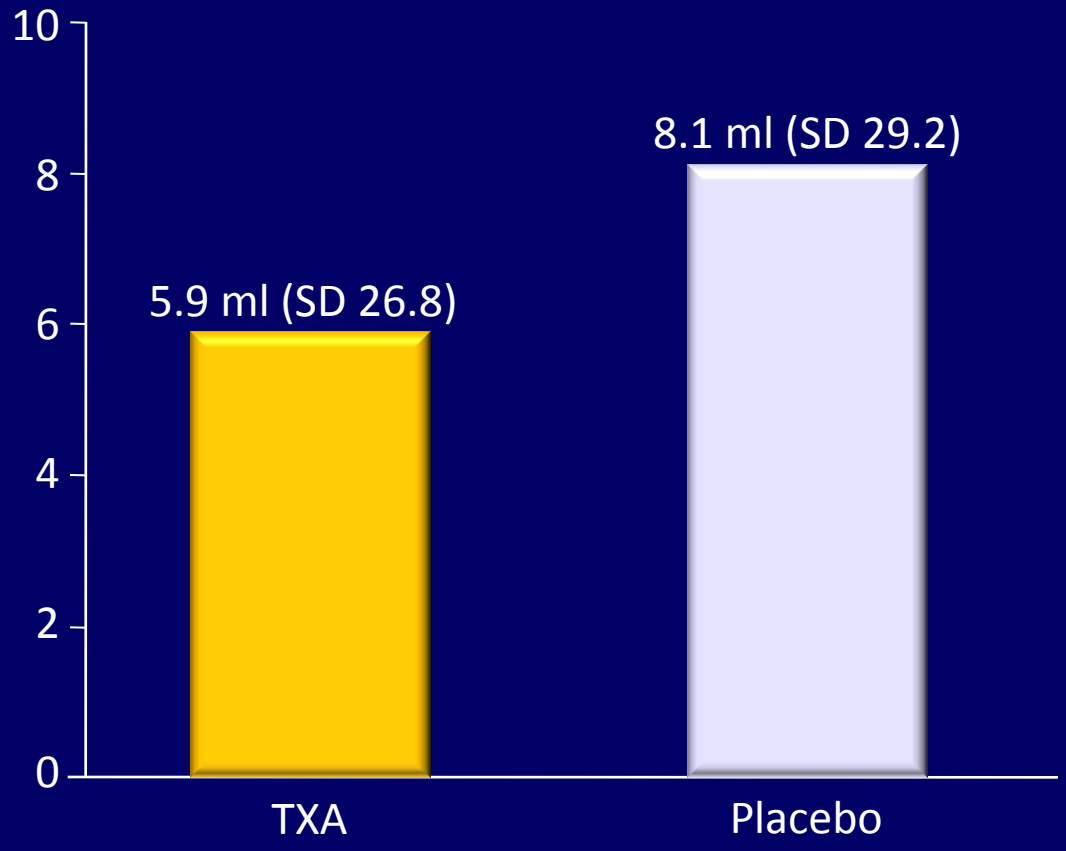
Trial Profile



Patients baseline characteristics

		TXA N=133	Placebo N=137
Sex	Male	111 (84%)	117 (85%)
	Female	22 (16%)	20 (15%)
Age (years)	Mean (SD)	36 (14)	37 (14)
Glasgow Coma Score	Mild [15-13]	63 (47%)	58 (42%)
	Moderate [12-9]	25 (19%)	34 (25%)
	Severe [8-3]	45 (34%)	45(33%)
Systolic blood pressure	<90 mm Hg	9 (7%)	10 (7%)
	90-119 mm Hg	63 (47%)	69 (50%)
	≥120 mm Hg	61 (46%)	58 (43%)

Mean total haemorrhage growth



CT scan outcomes – Haematoma growth (ml)

	Total patients	Unadjusted difference (95% CI)	Adjusted difference ± (95% CI)	P value
All patients	206	-2.1 (-9.8 to 5.6)	-3.79 (-11.5 to 3.9)	0.33
Neurosurgery	46	-6.3 (-35.0 to 22.4)	-15.5 (-46.5 to 15.5)	0.32
No neurosurgery	160	-1.6 (-7.3 to 4.0)	-2.11 (-7.1 to 2.9)	0.40

± Adjusted for age, GCS, size of initial bleeding, time since injury to first CT scan and time since first CT scan to second CT scan

CT scan outcomes

	TXA n (%) n=123	Placebo n (%) n=126	Adjusted ± OR (95% CI)
Significant haematoma growth	44 (36%)	56 (44%)	0.67 (0.40–1.13)
New haemorrhage	13 (11%)	20 (16%)	0.62 (0.28–1.35)
Mass effect findings	58 (47%)	76 (60%)	0.53 (0.23–1.21)
New focal ischaemic regions	6 (5%)	12 (9%)	0.51 (0.18–1.44)

± Adjusted for age, GCS, size of initial bleeding, time since injury to first CT scan and time since first CT scan to second CT scan

Clinical outcomes

	TXA n (%) n=133	Placebo n (%) n=137	Adjusted ± OR (95% CI)
Overall mortality	14 (10%)	24 (17%)	0.47 (0.21–1.04)
Need for neurosurgery	20 (15%)	21 (15%)	0.98 (0.45–1.93)

± *Adjusted for age and GCS*

TXA in isolated TBI trial (Surakrant et al)

240 patients with moderate or severe TBI

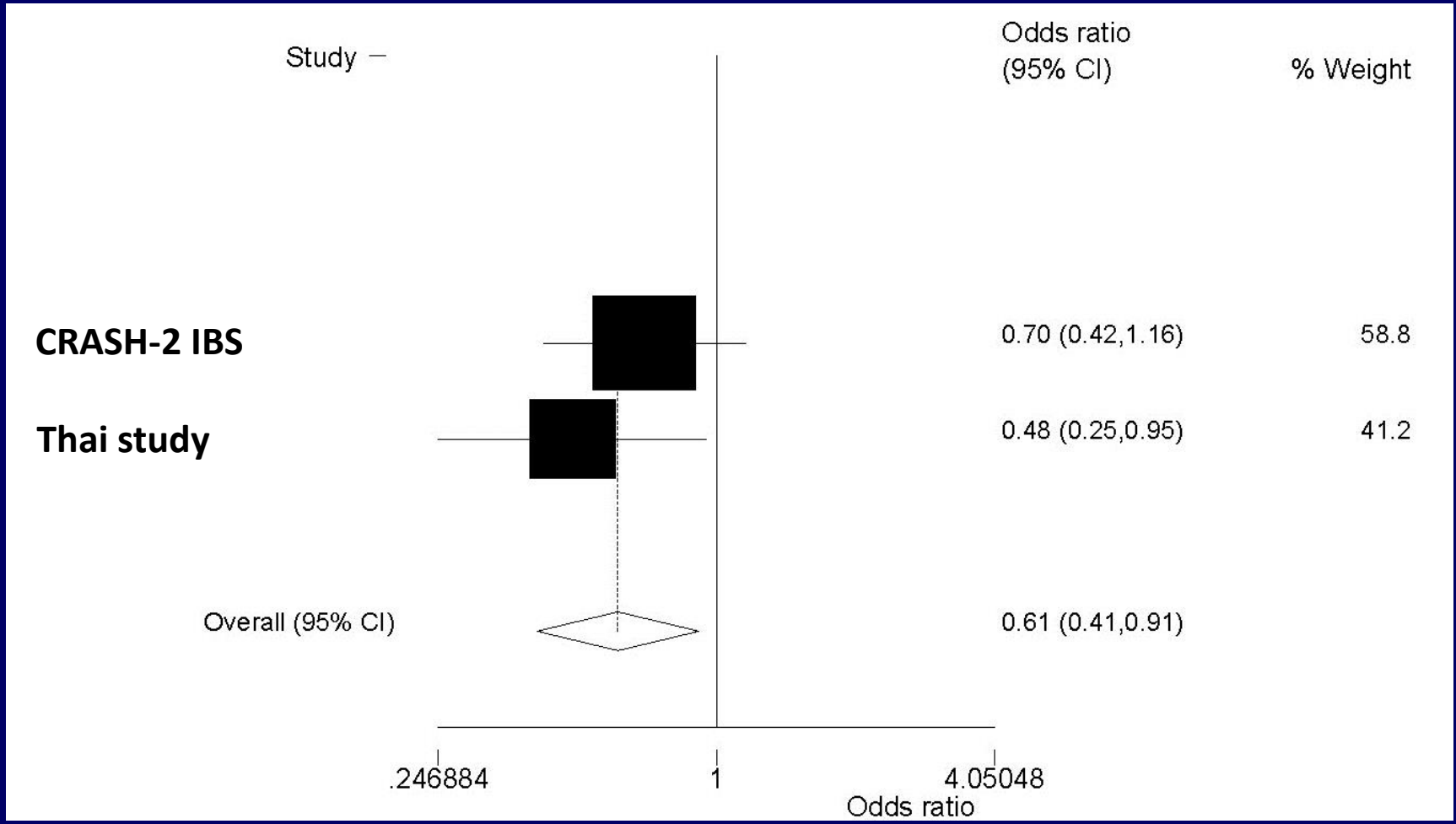
Within 8 hours of injury

Same TXA dose as CRASH-2 trial

Outcomes: Haemorrhage growth and mortality

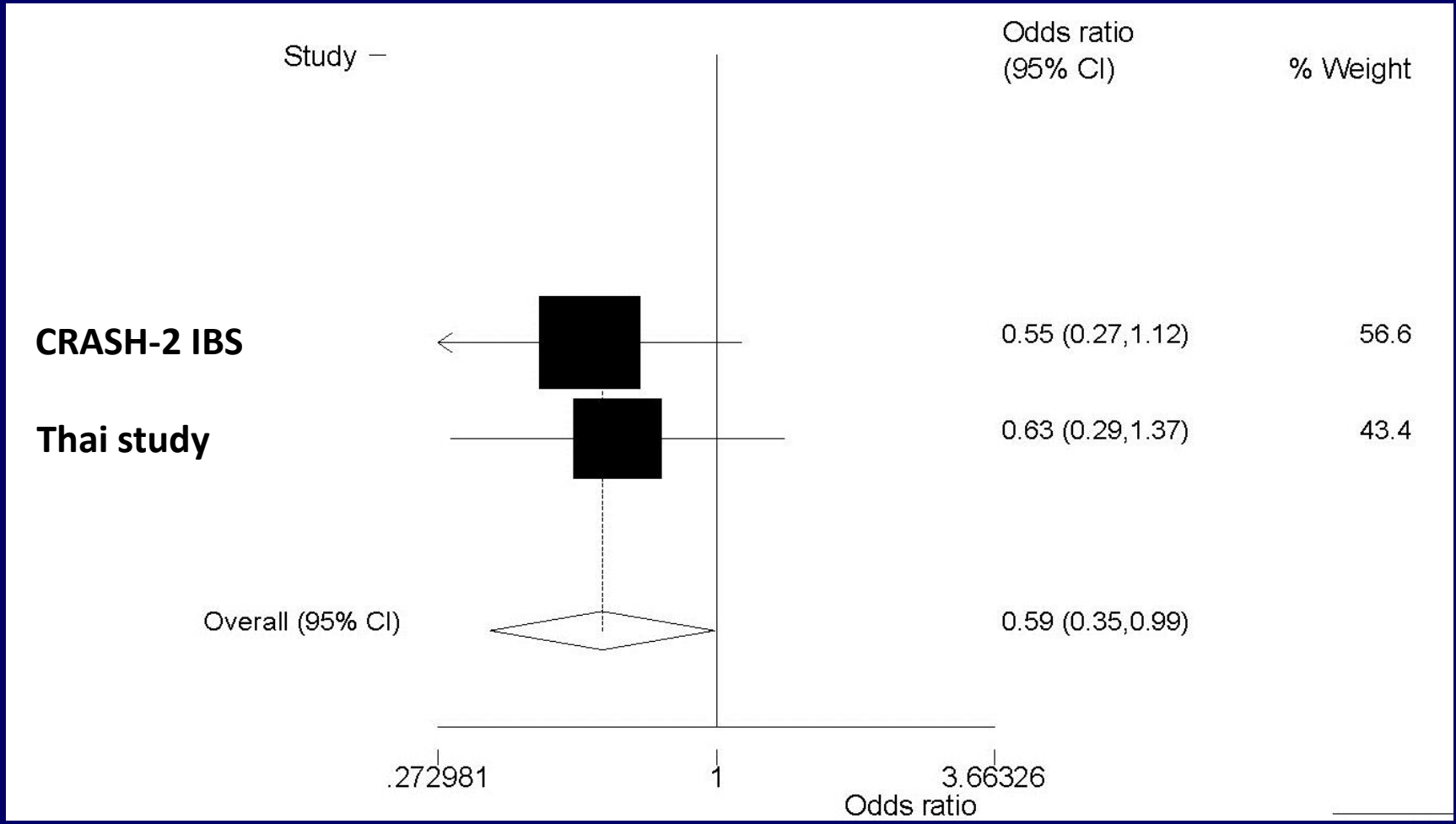
Meta-analysis

Significant Haemorrhage growth



Meta-analysis

Mortality



CRASH-3 Trial

A double blind randomised placebo-controlled trial of the effects of tranexamic acid in patients with traumatic brain Injury

Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) Study

Jonathan J. Morrison, MB ChB, MRCS; Joseph J. Dubose, MD; Todd E. Rasmussen, MD; Mark J. Midwinter, BMedSci, MD, FRCS

Arch Surg. 2012;147(2):113-119.

MATTERS Methods

- Military Application of Tranexamic Acid in Trauma Emergency Resuscitation Study (MATTERs)
- Retrospective observational study: 1 Surgical Hospital in Afghanistan
- Inclusion criteria: combat-related injury and ≥1 unit of RBCs.
- Primary outcomes: 24, 48-hour and in-hospital mortality
- Secondary endpoints:
  - Transfusion requirement
  - Correction of lab measures of coagulopathy
  - Adverse thrombotic events

MATTERS Results

Table 1. Demographic Data, Mechanism of Injury, Injury Severity, Physiology, and Transfusion Requirement for Overall and Massive Transfusion Groups

Variable	Overall (N=896)			Massive Transfusion (n=231)		
	TXA (n=293)	No TXA (n=603)	*P* Value[a]	TXA (n=125)	No TXA (n=196)	*P* Value[a]
Demographic data						
Age, mean (SD), y	24.9 (9.6)	23.1 (10.1)	.12	23.8 (7.7)	22.9 (9.2)	.46
Male, %	97.3	94.2	**.04**	98.4	96.9	.49
Host national, No. (%)	116 (39.6)	261 (43.3)	.29	39 (31.2)	65 (33.2)	.71
NATO military	177 (60.4)	342 (56.7)		86 (68.8)	131 (66.8)	
Mechanism of injury, %						
GSW	25.3	36.7	**<.001**	24.0	32.1	.14
Explosion	74.7	62.4		76.0	66.8	
Injury severity						
ISS, mean (SD)	25.2 (16.6)	22.5 (18.5)	**<.001**	26.1 (17.1)	25.2 (20.5)	.11

MATTERS Results

- In Overall Cohort (896 total consecutive patients)
- TXA patients had increased injury
  - ISS 25.2 vs. 22.5, ($p<0.001$)
  - % GCS < 8
  - % SBP $\leq$ 90 mmHg on admission.
  - Increased RBCs, FFP, platelet, and cryoprecipitate transfusions

MATTERS Results

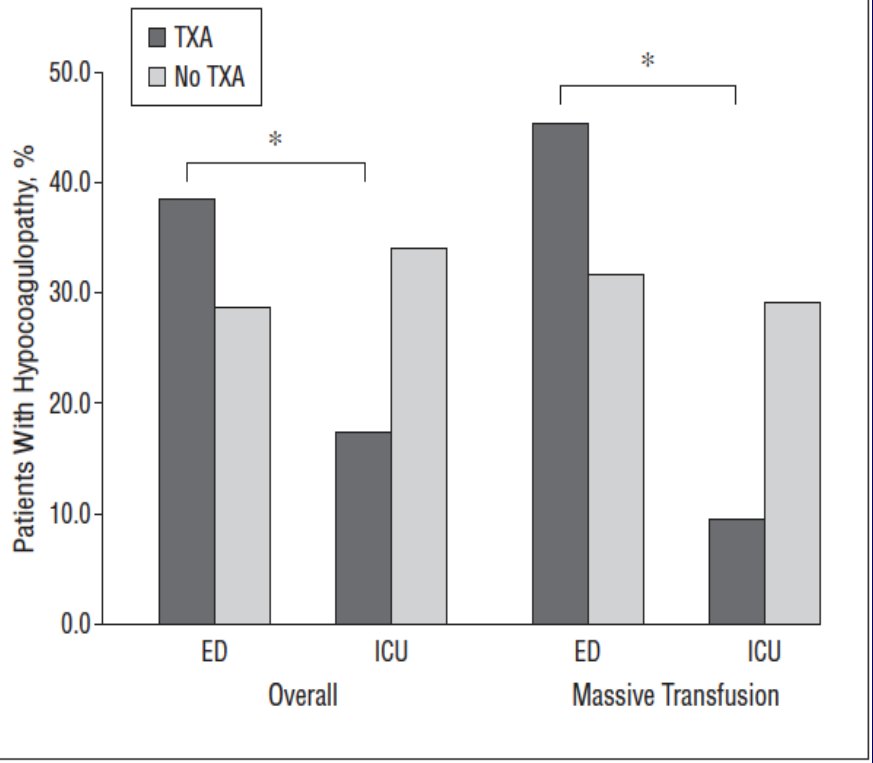


Figure 2. Percentage of patients with hypocoagulopathy on admission to the emergency department (ED) and then the intensive care unit (ICU) following the initial operation. Coagulation data were available for 462 patients in the overall cohort and 155 patients in the groups that received massive transfusion. TXA indicates tranexamic acid. *$P < .05$.

Table 2. All-Cause Mortality of Overall and Massive Transfusion Groups Within 24 Hours, Within 48 Hours, and In-Hospital Mortality

End Point	Total No. of Patients in Follow-up (Mortality, %)		*P* Value[a]
	TXA	No TXA	
Overall			
<24 h	293 (9.6)	603 (12.4)	.20
<48 h	264 (11.3)	507 (18.9)	**.004**
In-hospital mortality[b]	264 (17.4)	603 (23.9)	**.03**
Massive transfusion			
<24 h	125 (9.6)	196 (14.8)	.17
<48 h	112 (10.4)	160 (23.5)	**.003**
In-hospital mortality[c]	125 (14.4)	196 (28.1)	**.004**

MATTERS Results

Table 3. Factors Associated With Survival Following Multivariate Analysis of the Overall Group and the Massive Transfusion Group

Cohort	Odds Ratio (95% CI)[a]	*P* Value[b]
Overall		
GCS score ≤8	0.304 (0.108-0.860)	**.02**
Hypotension	0.303 (0.107-0.855)	**.02**
Coagulopathy at admission	0.291 (0.113-0.749)	**.01**
Massive transfusion		
GCS score ≤8	0.027 (0.008-0.085)	**<.001**
ISS >15	0.359 (0.123-1.053)	.06
TXA	7.228 (3.016-17.322)	**<.001**

MATTERS Results (MT Cohort)

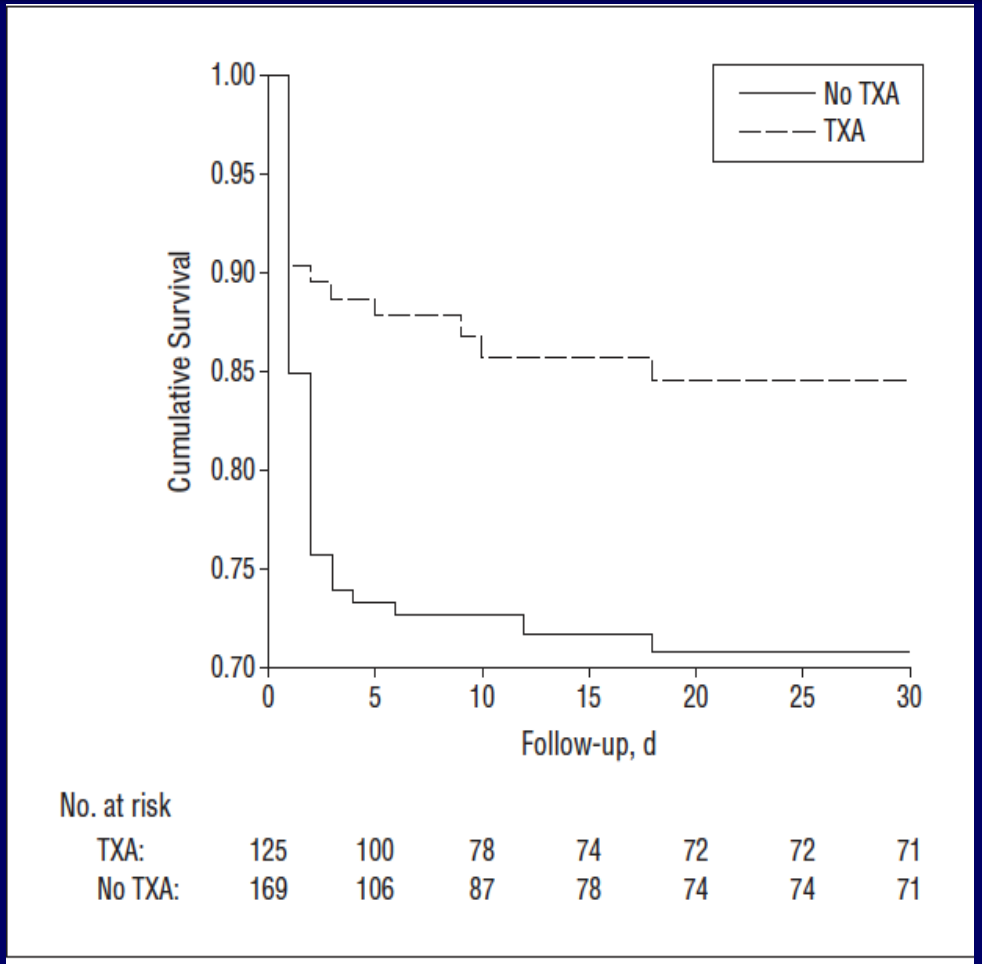


Figure 4. Kaplan-Meier survival curve of the massive transfusion group receiving tranexamic acid (TXA) or no TXA. $P=.004$, Mantel-Cox log-rank test.

MATTERS Secondary Results

- In overall cohort, TXA treated had increased PE and DVT
  - 2.7 vs 0.3 %, (p=0.001)
  - 2.4 vs 0.2 %, (p=0.001)
- Unadjusted outcomes
- TXA group had increased injury
- No prospective screening for these outcomes

Background

- Despite both CRASH-2 trial and MATTERs study indicating TXA use reduced the risk of mortality
- Questions remain regarding
  - Underlying mechanisms of TXA
  - Optimal dosing and pharmacokinetics
  - Safety
  - Outcomes

US Military Funded TXA Mechanisms Study Update

Philip C. Spinella, MD, FCCM
Associate Professor of Pediatrics
Washington University in St Louis

THOR 2014 RDCR Symposium
Solstrand Hotel
10 June 2014

Background

- CRASH-2 and MATTERS studies lead to most massive transfusion protocols to incorporate tranexamic acid
- CRASH-2
  - Reduction in death from hemorrhage
  - When given after 3 hours increased risk of death
- MATTERS
  - Survival benefit – Adjusted analysis
  - Thrombosis risk - unadjusted

Questions

- What are mechanisms?
- What is best dose?
- What are risks?
- Prehospital benefit?
- When is it indicated?
  - Empiric or goal directed
- Traumatic brain injury patients?

Tranexamic Acid Clinical Research

- Program Announcement in 2012
  - U. S. Army Medical Research and Materiel Command (USAMRMC)
  - Telemedicine and Advanced Technology Research Center (TATRC)
  - Combat Casualty Care Joint Program Committee (CCCJPC)
  - Directorate for Combat Casualty Care (CCC)

Priorities

- Prospective clinical studies examining the effects of TXA in the treatment of patients with traumatic hemorrhage (polytrauma and TBI).
- Doses up to the range of those published for trauma are recommended.
- Treatment with TXA should begin within 2 hours of injury.

Priorities

- Use of other pro-hemostatic or antifibrinolytic drugs must be carefully documented and should be included only as part of the current local standard of care.
- Use of fluids and blood products for resuscitation and surgery should also be documented.
- Randomized studies and studies that examine more than one dose-level are preferred.

Expectations

- Provide insight into one or more of the following:
  - Safety
    - Deep vein thrombosis
    - Pulmonary thromboembolism
    - Post-operative seizures
  - Mechanism of action
    - Coagulation function/dysfunction
    - Fibrinolysis, Immune function, etc.
  - Pharmacokinetics and pharmacodynamics in trauma

Funding

- The amount currently available for funding Combat Casualty Care Research Program 2012 for this Priority Area is approximately $12 million over three (3) years.
- This Program Announcement is expected to result in approximately 3-5 investigator initiated awards, depending on the quality and number of applications received.
- **Funding of Applications received in response to this Program Announcement is contingent upon the availability of Federal funds for this program.**

Grants Awarded

- University of Oregon -
  - Marty Schreiber
- University of Pittsburgh -
  - Jason Sperry
- Washington University in St. Louis
  - Phil Spinella and Grant Bochicchio

TXA in TBI

- Study Centers:
  - 10 North American Trauma Centers
- Design: Double Blinded RCT
- Hypothesis:
  - Prehospital administration of **TXA** in patients with moderate to severe **TBI** will increase favorable long-term neurologic outcome compared to placebo

Inclusion Criteria

- Blunt or penetrating traumatic mechanism consistent with traumatic brain injury
- Prehospital Glasgow Coma Score (GCS) score ≤ 12 at any time prior to randomization and administration of sedative and/or paralytic agents
- Prehospital systolic blood pressure (SBP) ≥ 90 mmHg prior to randomization
- Prehospital intravenous (IV) or intraosseous (IO) access
- Estimated Age ≥ 15
- Emergency Medicine System (EMS) transport to a participating trauma center

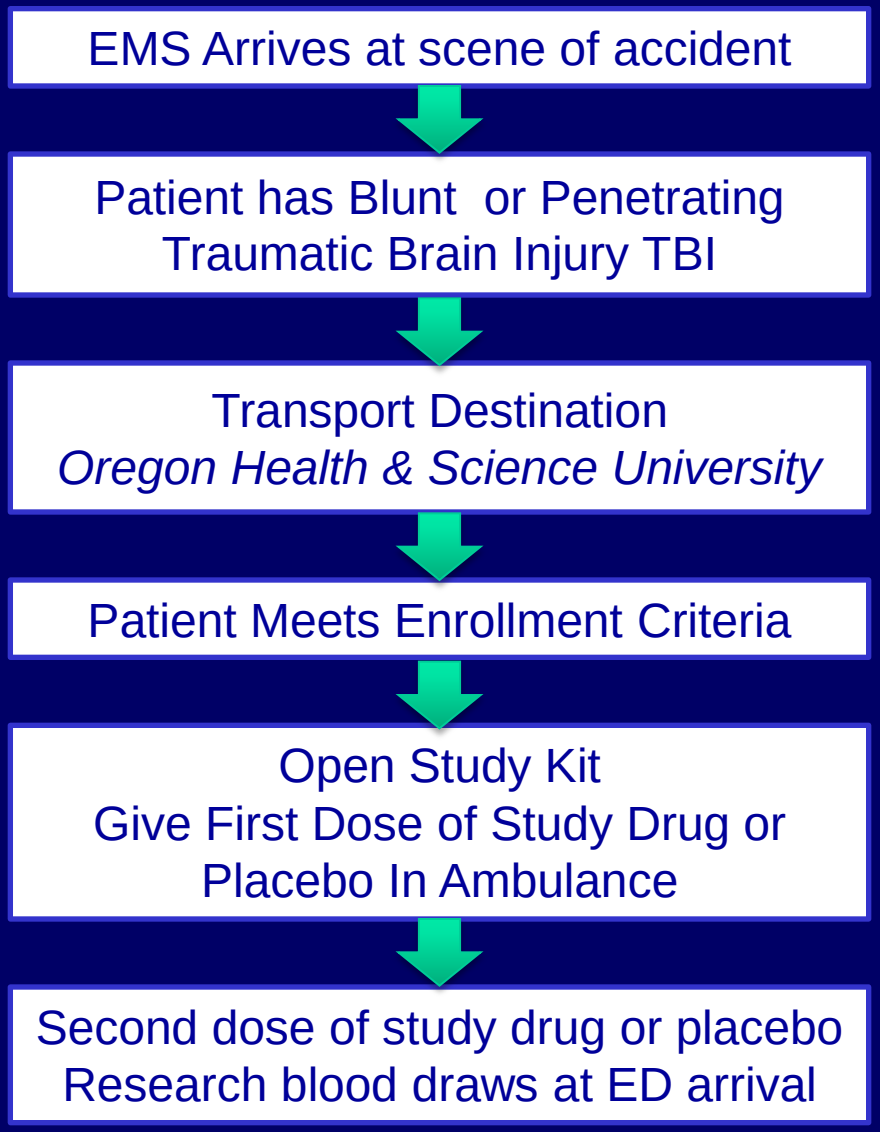
Exclusion Criteria

- Prehospital GCS=3 with no reactive pupil
- Estimated time from injury to hospital arrival > 2 hours
- Unknown time of injury - no known reference times to support estimation
- Clinical suspicion by EMS of seizure activity or known history of seizures, acute myocardial infarction (MI) or stroke
- Cardio-pulmonary resuscitation (CPR) by EMS prior to randomization

Exclusion Criteria

- Burns > 20% total body surface area (TBSA)
- Suspected or known prisoners
- Suspected or known pregnancy
- Prehospital TXA given prior to randomization
- Subjects who have activated the "opt-out" process when required by the local regulatory board

Study enrollment



Study Arms

- Bolus with infusion
  - EMS gives 1 gram TXA IV bolus
  - 1 gram TXA infusion post admission over 8 hrs
- Bolus no infusion
  - EMS gives 2 grams IV bolus
  - Placebo (NS) infusion post admission over 8 hrs
- Placebo
  - EMS gives placebo IV bolus
  - Placebo infusion post admission over 8 hours

TXA in TBI

- Primary Outcome:
  - Glasgow Outcome Scale Extended score (GOS-E)
  - 6 months post-injury
- Secondary Outcomes:
  - Observed volume (absolute and relative) of intracranial hemorrhage (ICH) progression
  - On hospital arrival through 28 days or from hospital admission through the end of the hospital stay, an expected average of 14 days post injury

Secondary Outcomes

- 28 day survival
- Seizure, stroke, MI, DVT, PE frequency during hospitalization
- Vent Free days
- Hematologic parameters
  - Fibrinolysis
  - TEG

TXA in TBI

- Sample Size is 1002 (334 per group),
  - Which will allow for 80% power to detect an 8.1% absolute difference in favorable long-term neurological outcome as determined by the GOS-E 6 months after injury, using a one-sided, level 0.1 test.

Exception to Informed Consent

- Life-threatening situation
- Intervention must be administered before consent is feasible
- No reasonable way to identify prospectively individuals at risk
- Patients have the prospect of benefit from the treatment
- The research could not practically be carried out without the waiver of consent

Study of Tranexamic Acid During Air Medical Prehospital Transport Trial (STAAMP Trial)

- Study Centers:
  - U of Pittsburgh, Utah, Rochester
  - UT San Antonio
- Design: Double Blind RCT
- Hypothesis:
  - Prehospital infusion of tranexamic acid in patients at risk for bleeding will reduce the incidence of 30 day mortality.

Inclusion Criteria

- 18-90 years of age
- Blunt or penetrating injured patients being transported via air medical services from the scene of injury or from referring hospital to a definitive trauma center that is participating in the trial AND
- Within 2 hours of time of injury AND
- Hypotension (Systolic Blood Pressure (SBP) < 90mmHg)
- At scene of injury or during air medical transport

Inclusion Criteria

- Documented at referring hospital prior to air medical transport arrival AND
- Tachycardia (heart rate >110 beats per minute)
- At scene of injury or during air medical transport
- Documented at referring hospital prior to air medical transport arrival Inclusion criteria #3. and #4. not required to be simultaneous

Exclusion Criteria

- Age > 90 or < 18 years of age
- Inability to obtain intravenous access
  - (intraosseous access not sufficient)
- Documented cervical cord injury with motor deficit
- Known prisoner or pregnancy
- Traumatic arrest with > 5 minutes CPR without return of vital signs

Exclusion Criteria

- Penetrating cranial injury
- Traumatic brain injury with brain matter exposed
- Isolated drowning or hanging victims
- Wearing an opt out bracelet.

Study Groups

- TXA, 1 Gram IV given prehospital
- Placebo IV given prehospital
- Sample size of 1000 patients

Outcomes

- Primary Outcome:
  - 30 Day Mortality
- Secondary Outcome Measures:
  - 24 Hour Mortality
  - Acute Lung Injury
  - Multiple Organ
  - Nosocomial Infection
  - 24 Hour Blood Transfusion
  - Hyperfibrinolysis

Tranexamic Acid Mechanisms and Pharmacokinetics In Traumatic Injury (TAMPITI Trial)

- Study Center: Washington University in STL
- Design: Double Blinded RCT
- Hypothesis:
  - We hypothesize that early TXA use in patients with severe traumatic injuries, reduces a pro-inflammatory state.
  - We expect reduced inflammation, and monocyte activation in TXA treated patients compared to placebo.

Secondary Hypothesis

- We hypothesize that the pharmacokinetics of TXA administration are affected by the degree of shock measured by admission base deficit, StO2, presence of acute renal failure, and blood products administered in patients with severe traumatic injury.
- We expect that the degree of shock and blood products transfused will affect TXA pharmacokinetics.

Study groups

- The three treatment arms will be
  - TXA 2 gram IV bolus
    - 50 patients
  - TXA 4 gram IV bolus
    - 50 patients
  - Placebo
    - 50 patients

Primary Outcome

- Change in immune parameters, monocyte function, from time 0 to time 72 hours.

Inclusion Criteria

- Hospitalized patients with traumatic injury who can receive study drug < 2 hours from injury
  - **And**
- Who ordered to receive at least 1 blood product
  - **Or**
- Patients that have been determined by the physician of record to require directly transfer to the operating room from the ED < 2 hours from injury

Exclusion criteria

- Patients < 18 years of age
- Known inherited coagulation disorders
- Known history of thromboembolic events
- Pregnancy and/or lactating, incarceration
- Futile care
- Risk of immune suppression
- Unknown time of injury

Laboratory Parameters

- Cytokines: TNF-α, IL-6, IL-10, and IFN-γ measured at time 0, 6, 24 and 72 hours.
- Flow cytometric analyses on leukocytes measured at time 0, 6, 24 and 72 hours:
  - CD66+/ROS+ to identify activated polymorphonuclear cells
  - CD4+/CD69+ and CD8+/CD69+ to identify activated lymphocytes
  - CD14+/HLA-DR+ to identify activated monocytes
  - CD4+/Foxp3+ to identify T regulatory cells

Pharmacodynamics

- Compare pharmacokinetic data between patients with varying degrees of shock (base deficit and StO2 measures) and adjusting for acute renal failure and total amount of blood products transfused in the first 12 hours of injury.

- Blood samples will be collected in 50 patients within each TXA treatment group at time 0 (before administration of TXA), then at 10 min, 20 min, 40 min, 1 hr 1.5 hr, 2 hr, 3 hr, 4 hr, 6 hr, 8 hr, 10 hr, 12 hr and 24 hr.

Conclusion

- TXA shows promise as a new therapy in Trauma Patients.
- HOWEVER, THERE IS NO FDA INDICATION FOR THE USE IN TRAUMA PATIENTS (ESPECIALLY PRE-HOSPITAL)
- DATA IS COMING……..