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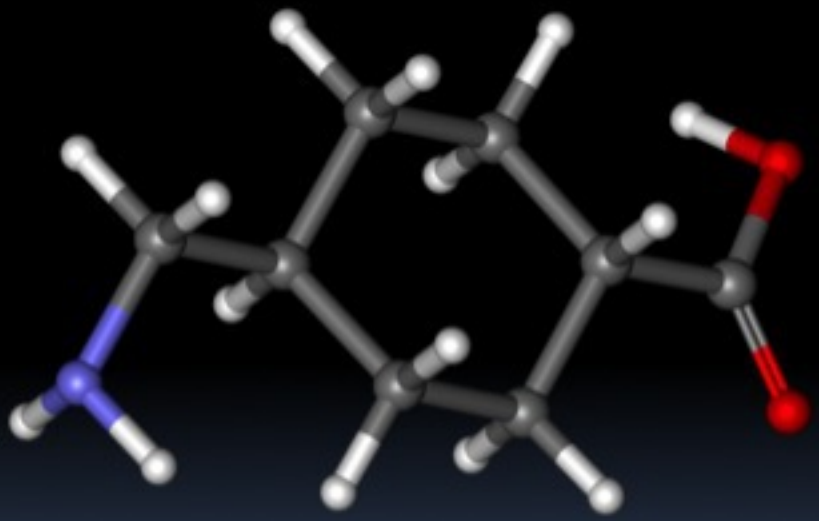
CRASH-2 & TRANEXAMIC ACID: WHERE WE ARE AT IN 2014

Injury Conference Auckland
August 2014

Tranexamic acid

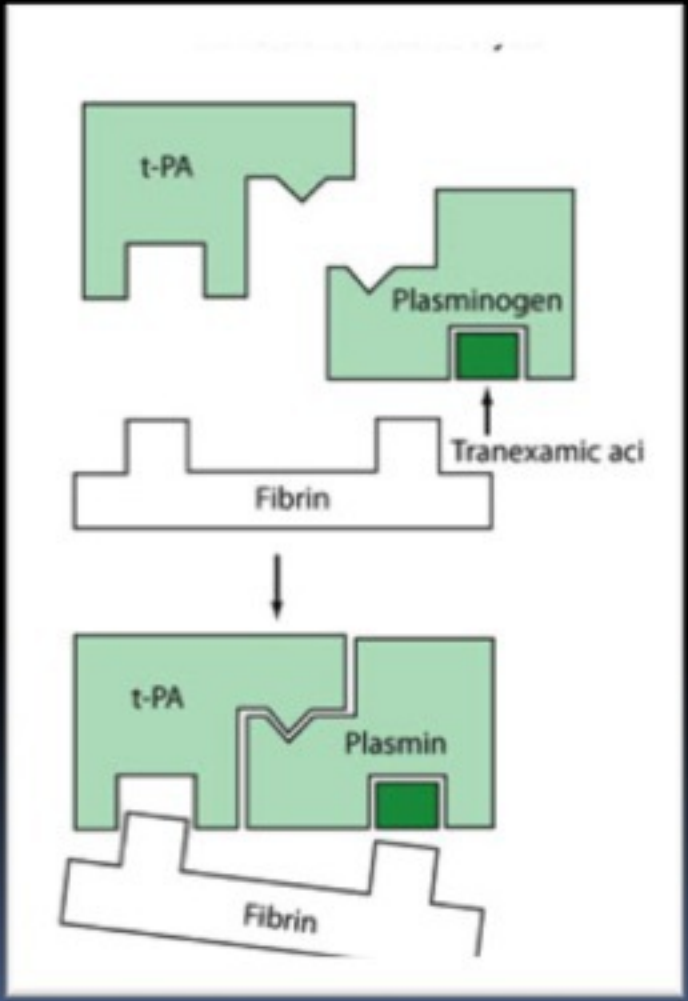
- What
- Why
- When
  - Based not only on CRASH 2

TRANEX



Synthetic analog of aminoacid lysine developed in 1950 by Japanese researchers

TRANEX

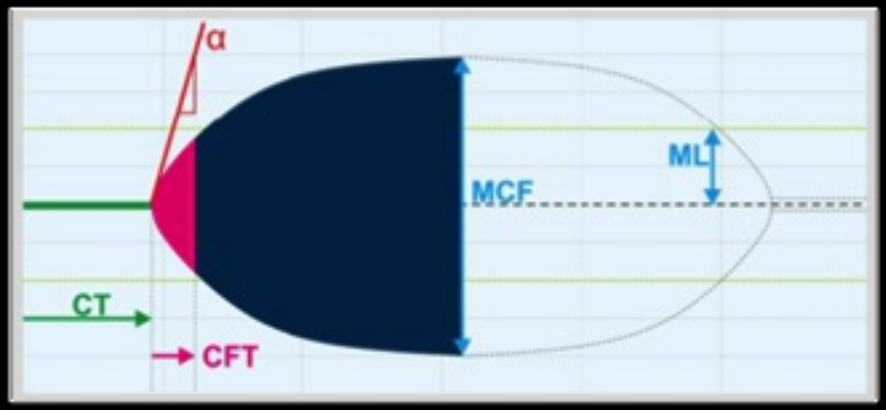


Synthetic analog of aminoacid lysine

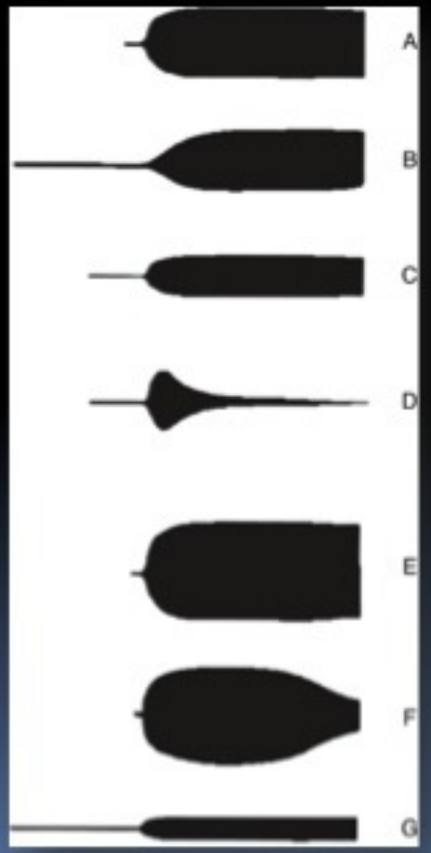
Links and blocks plasminogen

Contrast fibrinolysis and reverse hyperfibrinolysis

Hyperfibrinolysis



MCF: Max clot firmness



Before and after Tranex

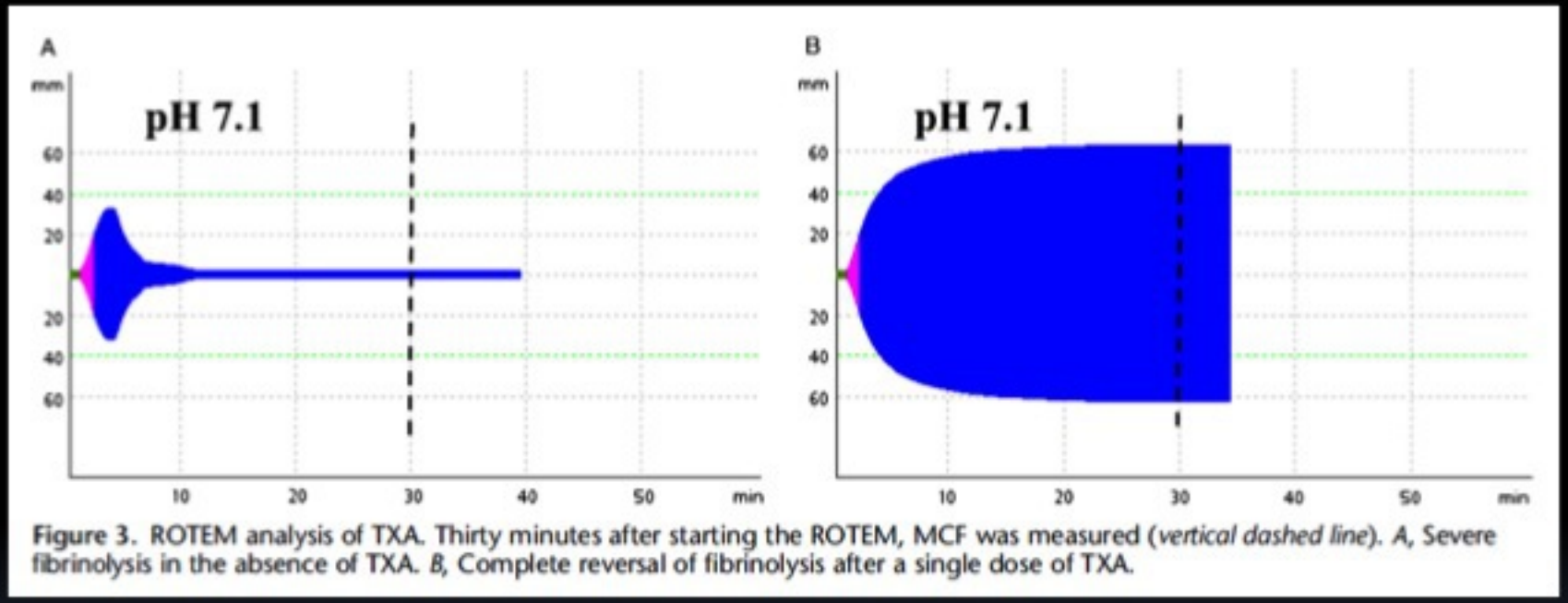
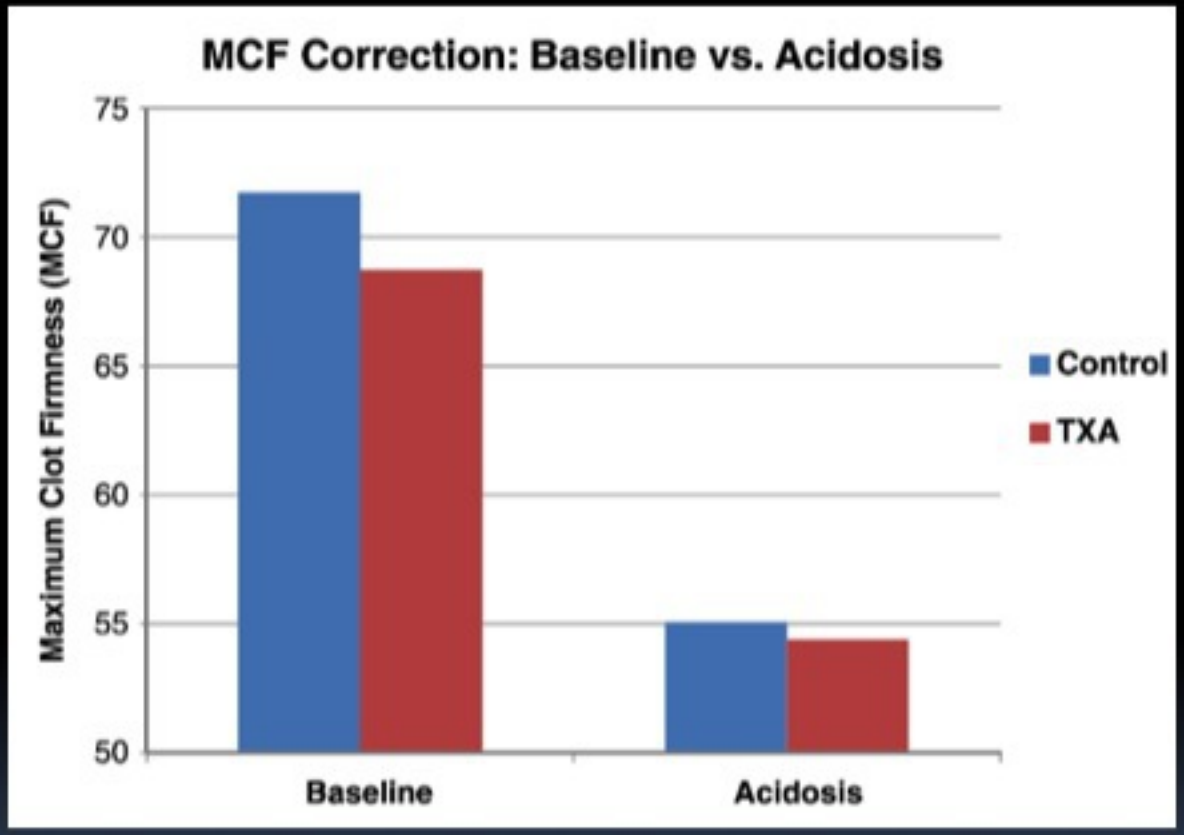


Figure 3. ROTEM analysis of TXA. Thirty minutes after starting the ROTEM, MCF was measured (*vertical dashed line*). *A*, Severe fibrinolysis in the absence of TXA. *B*, Complete reversal of fibrinolysis after a single dose of TXA.

Pig model of haemorrhagic shock and reperfusion

Plasminogen activator (to mimic hyperfibrinolysis)

Porta. J Trauma Acute Care 2013



TXA group: Plasminogen activator (to mimic fibrinolysis) + TXA

Porta. J Trauma Acute Care 2013

Tranex and elective surgery

- Several RCT
  - Liver
  - Gynaecology
  - Obstetrics
  - Cardiac
- Cochrane reviews
- Less need for blood transfusion (RR 0.61)

CRASH-2

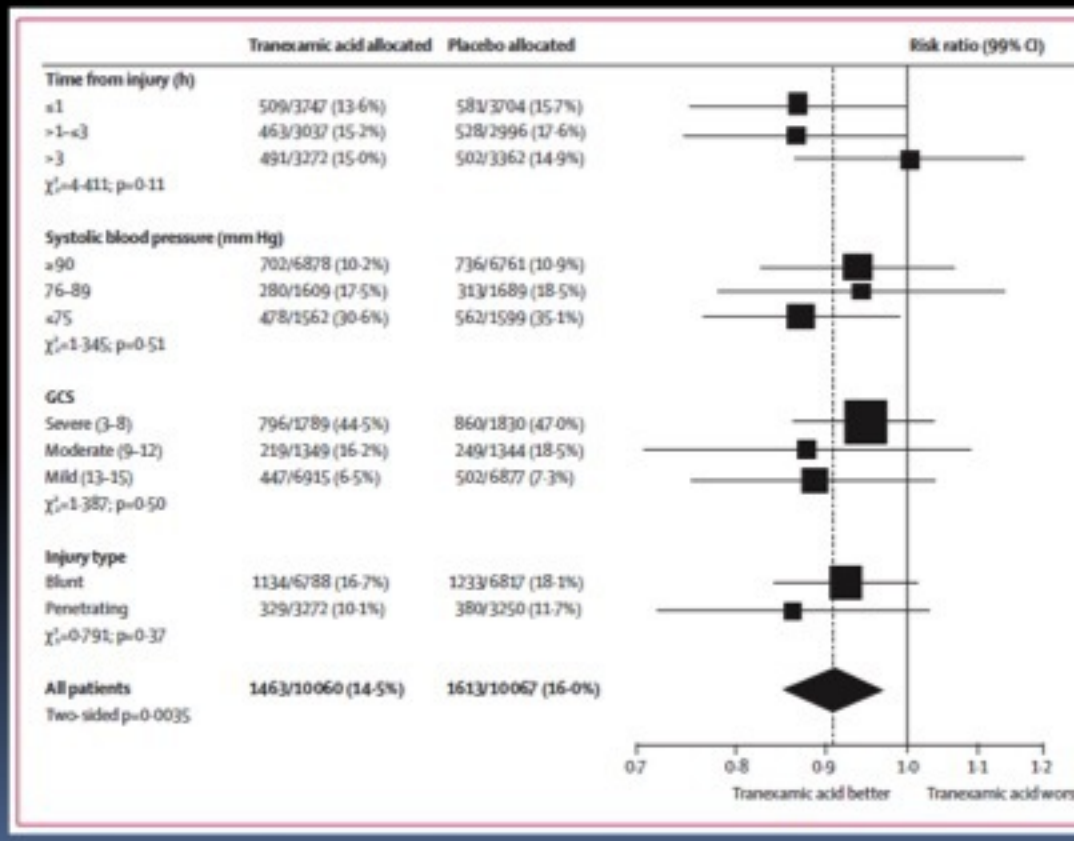
- 274 hospitals
- 40 countries
- Adults
- Trauma patients considered at risk of bleeding randomized within 8 h of injury

- 10 096 tranexamic acid 10 115 placebo
- 3076 (15%) deaths
- 1063 (5%) death from bleeding

Lancet 2010

Offers survival advantage if:

- Penetrating trauma
- Hypotensive
- Not severe TBI
- Administered early



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

Lancet 2010

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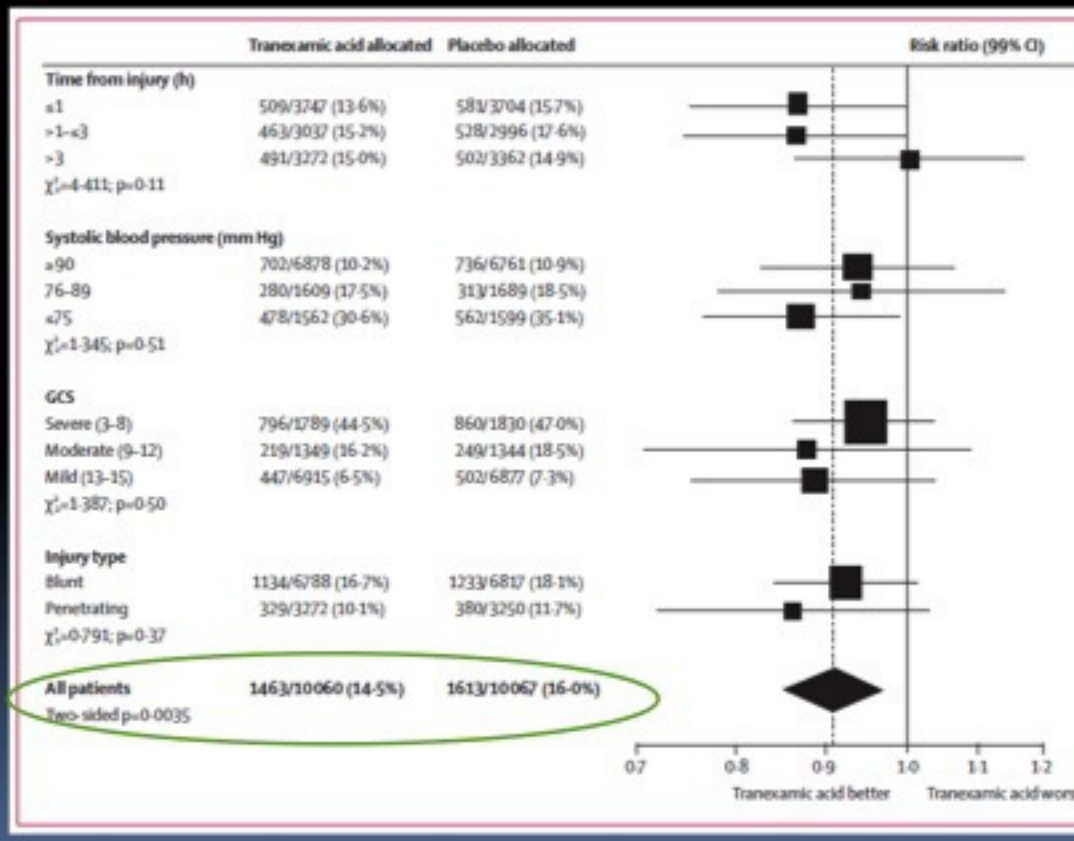

	Tranexamic acid allocated	Placebo allocated	Risk ratio (99% CI)
Time from injury (h)			
≤1	509/3747 (13·6%)	581/3704 (15·7%)	
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0·7 0·8 0·9 1·0 1·1 1·2

Tranexamic acid better | Tranexamic acid wors

Lancet 2010

Causes of death

	Tranexamic acid (n=10 060)	Placebo (n=10 067)	RR (95% CI)	p value (two-sided)
Any cause of death	1463 (14·5%)	1613 (16·0%)	0·91 (0·85–0·97)	0·0035
Bleeding	489 (4·9%)	574 (5·7%)	0·85 (0·76–0·96)	0·0077
Vascular occlusion*	33 (0·3%)	48 (0·5%)	0·69 (0·44–1·07)	0·096
Multiorgan failure	209 (2·1%)	233 (2·3%)	0·90 (0·75–1·08)	0·25
Head injury	603 (6·0%)	621 (6·2%)	0·97 (0·87–1·08)	0·60
Other causes	129 (1·3%)	137 (1·4%)	0·94 (0·74–1·20)	0·63

Data are number (%), unless otherwise indicated. RR=relative risk. *Includes myocardial infarction, stroke, and pulmonary embolism.

Table 2: **Death by cause**

- 150 (1.5%) less patients died
- 85 (1.2%) less patients bled to death

Lancet 2010

Other outcomes:

	Tranexamic acid (n=10 060)	Placebo (n=10 067)	RR (95% CI)	p value
Vascular occlusive events*				
Any vascular occlusive event	168 (1·7%)	201 (2·0%)	0·84 (0·68–1·02)	0·084
Myocardial infarction	35 (0·3%)	55 (0·5%)	0·64 (0·42–0·97)	0·035
Stroke	57 (0·6%)	66 (0·7%)	0·86 (0·61–1·23)	0·42
Pulmonary embolism	72 (0·7%)	71 (0·7%)	1·01 (0·73–1·41)	0·93
Deep vein thrombosis	40 (0·4%)	41 (0·4%)	0·98 (0·63–1·51)	0·91
Need for transfusion and surgery				
Blood product transfused	5067 (50·4%)	5160 (51·3%)	0·98 (0·96–1·01)	0·21
Any surgery	4814 (47·9%)	4836 (48·0%)	1·00 (0·97–1·03)	0·79
Neurosurgery	1040 (10·3%)	1059 (10·5%)	0·98 (0·91–1·07)	0·67
Chest surgery	1518 (15·1%)	1525 (15·1%)	1·00 (0·93–1·06)	0·91
Abdominal surgery	2487 (24·7%)	2555 (25·4%)	0·97 (0·93–1·02)	0·28
Pelvic surgery	683 (6·8%)	648 (6·4%)	1·05 (0·95–1·17)	0·31
Median (IQR) units of blood product transfused†	3 (2–6)	3 (2–6)	..	0·59‡

- Similar transfusions (competing risk)
- Similar surgical requirements
- Similar occlusive events

Exploratory analysis: the bleeders

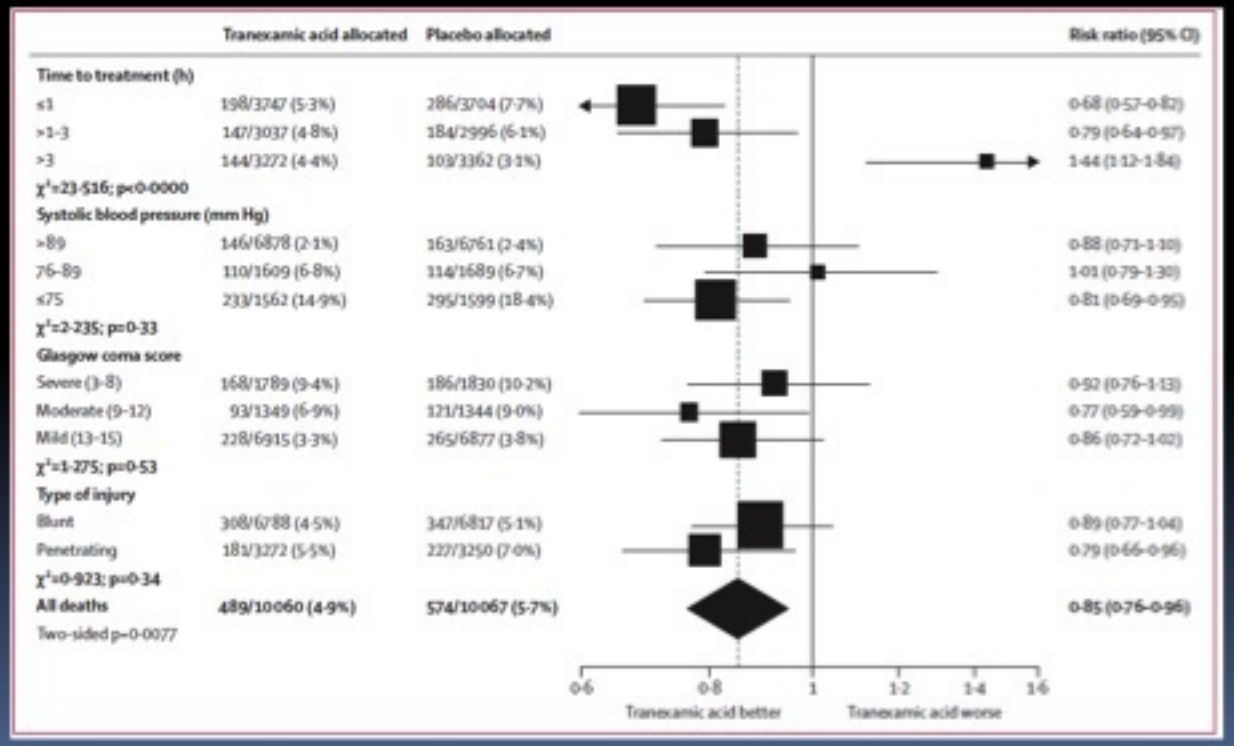
	N	All causes of death	Bleeding death	Non-bleeding death
Overall	20127	0·91 (0·85–0·97); p=0·0035	0·85 (0·76–0·96); p=0·0077	0·94 (0·86–1·02); p=0·13
Time to treatment (h)				
≤1	7451	0·87 (0·76–0·97)	0·68 (0·57–0·82)	1·04 (0·89–1·21)
>1–3	6033	0·87 (0·77–0·97)	0·79 (0·64–0·97)	0·91 (0·78–1·05)
>3	6634	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

Lancet 2011

Exploratory analysis: the bleeders

- Administered early
- Hypotensive
- Penetrating



	Tranexamic acid allocated	Placebo allocated	Risk ratio (95% CI)
Time to treatment (h)			
≤1	198/3747 (5·3%)	286/3704 (7·7%)	0·68 (0·57–0·82)
>1–3	147/3037 (4·8%)	184/2996 (6·1%)	0·79 (0·64–0·97)
>3	144/3272 (4·4%)	103/3362 (3·1%)	1·44 (1·12–1·84)
χ^2=23·516; p<0·0000			
Systolic blood pressure (mm Hg)			
>89	146/6878 (2·1%)	163/6761 (2·4%)	0·88 (0·71–1·10)
76–89	110/1609 (6·8%)	114/1689 (6·7%)	1·01 (0·79–1·30)
≤75	233/1562 (14·9%)	295/1599 (18·4%)	0·81 (0·69–0·95)
χ^2=2·235; p=0·33			
Glasgow coma score			
Severe (3–8)	168/1789 (9·4%)	186/1830 (10·2%)	0·92 (0·76–1·13)
Moderate (9–12)	93/1349 (6·9%)	121/1344 (9·0%)	0·77 (0·59–0·99)
Mild (13–15)	228/6915 (3·3%)	265/6877 (3·8%)	0·86 (0·72–1·02)
χ^2=1·275; p=0·53			
Type of injury			
Blunt	308/6788 (4·5%)	347/6817 (5·1%)	0·89 (0·77–1·04)
Penetrating	181/3272 (5·5%)	227/3250 (7·0%)	0·79 (0·66–0·96)
χ^2=0·923; p=0·34			
All deaths	**489/10060 (4·9%)**	**574/10067 (5·7%)**	**0·85 (0·76–0·96)**
Two-sided p=0·0077			

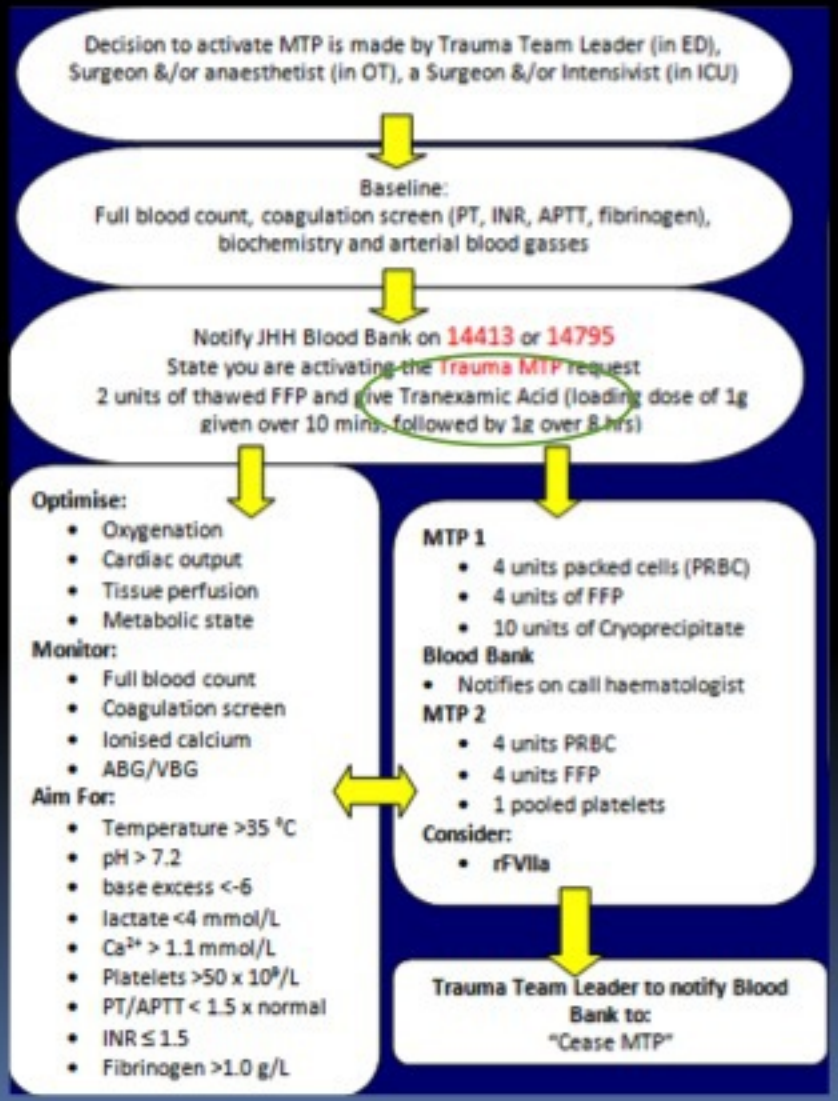
0·6 0·8 1 1·2 1·4 1·6

Tranexamic acid better Tranexamic acid worse

Lancet 2011

Massive Transfusion Protocols

- Included in British and US armed forces guidelines
-



Mind the gap

- <2% pts from developed trauma system
- Different:
  - timing
  - products
  - imaging
  - therapy
- High mortality (16%)
- Age< 40 (20%)

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

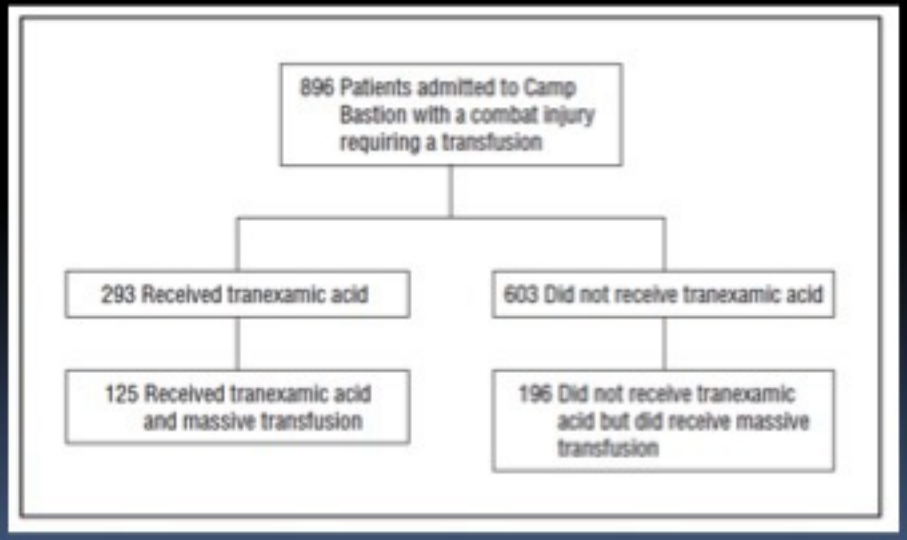
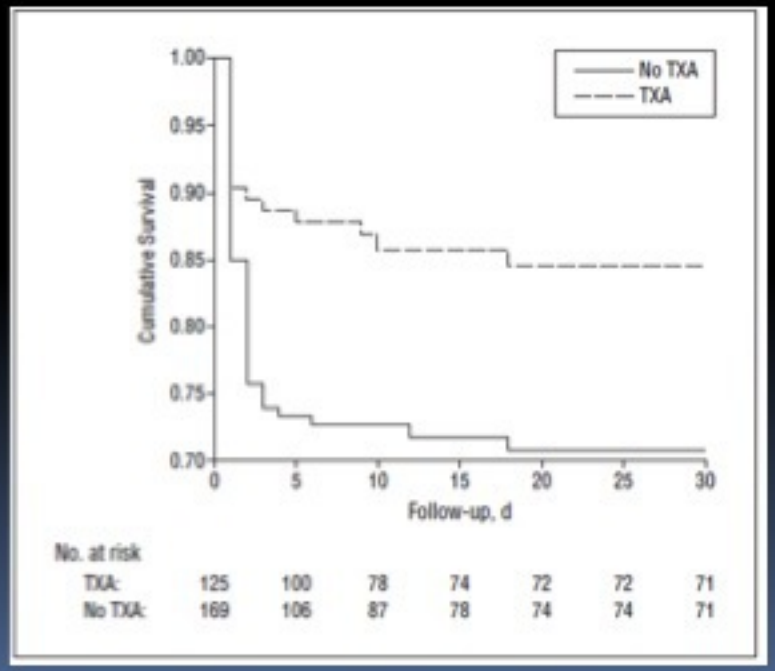


Table 3. Factors Associated With Survival Following Multivariate Analysis of the Overall Group and the Massive Transfusion Group

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

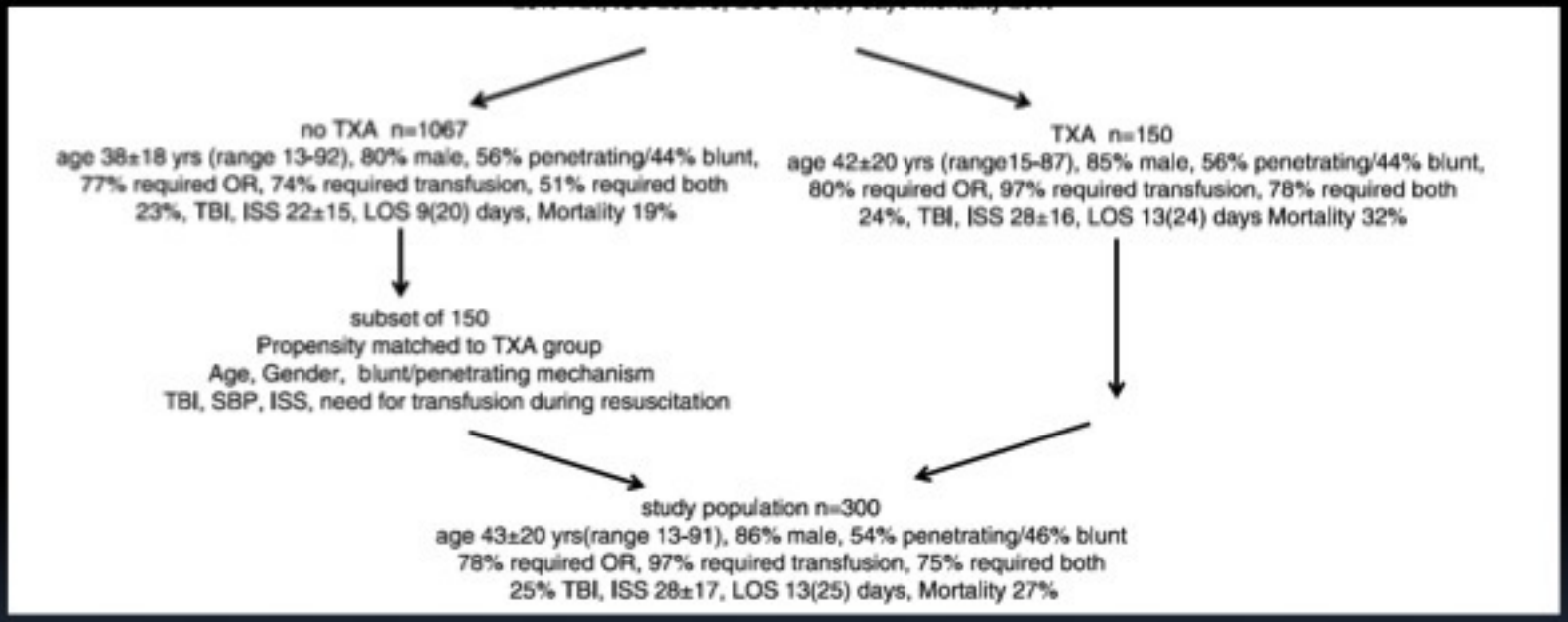
Arch Surg 2012

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



Arch Surg 2012

Do all trauma patients benefit from tranexamic acid?



J Trauma 2014

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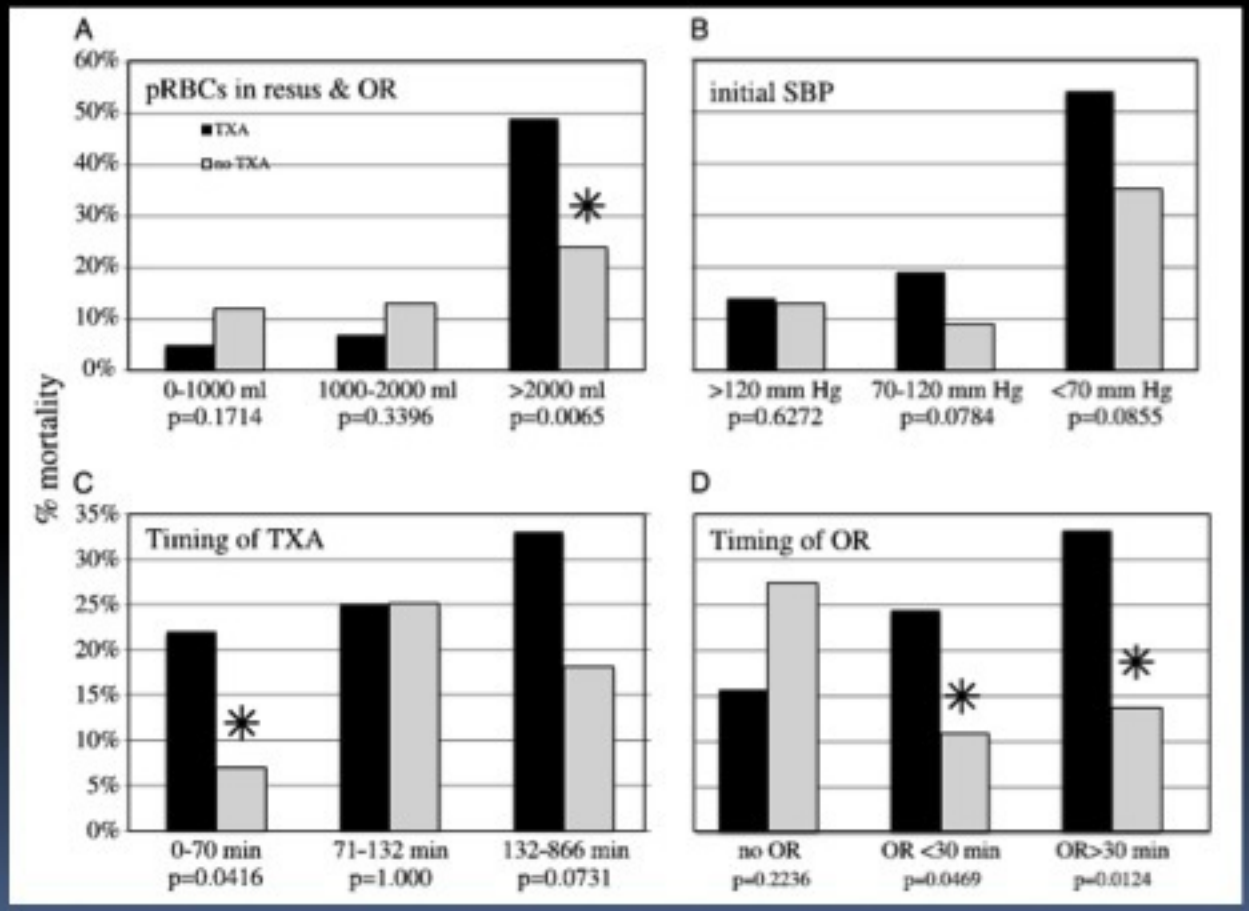
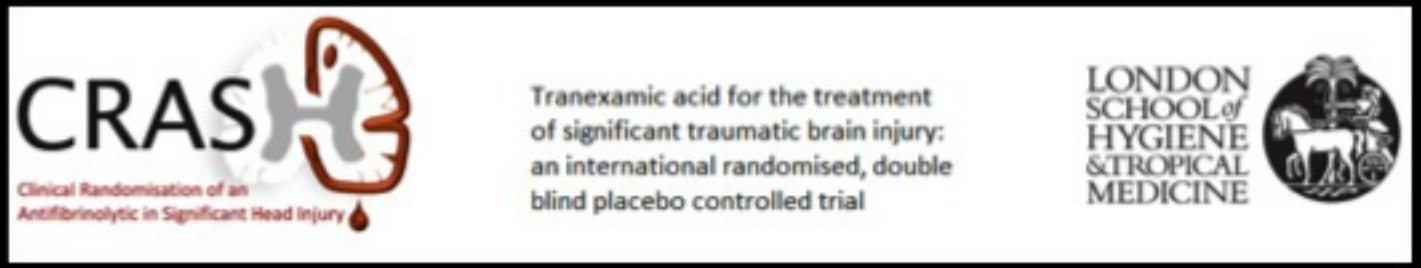


J Trauma 2014

The earlier the better?

- 1184 pts>18
- <3 hrs from injury
- 1g by paramedics
- Australia and New Zealand
- mortality and functional outcome at 6 months
- TEG
- Vascular occlusive complications
- Inflammation

Not yet recruiting



- 10000 pts (>16)
- Inclusion:
  - GCS<12 or intracranial bleed on CT
  - no other sources of bleeding)
  - 8 hrs from trauma
- 1g in 10 min + 1g in 8 hrs

OUTCOME

- Mortality
- Occlusive events
- Interventions
- In hospital disability
- LOS ICU

Recruiting

Summary

- Small benefit, small cost, good safety profile
- More questions than answers from Crash 2
- Feasibility and importance of multicentre studies
- More to come (stay tuned)

Old (and cheap) chicken makes good soup