Too Much To Lose

Pharmacological Management of Major Haemorrhage in Trauma

Dr Jonathan Shelton

Epidemiology of Trauma

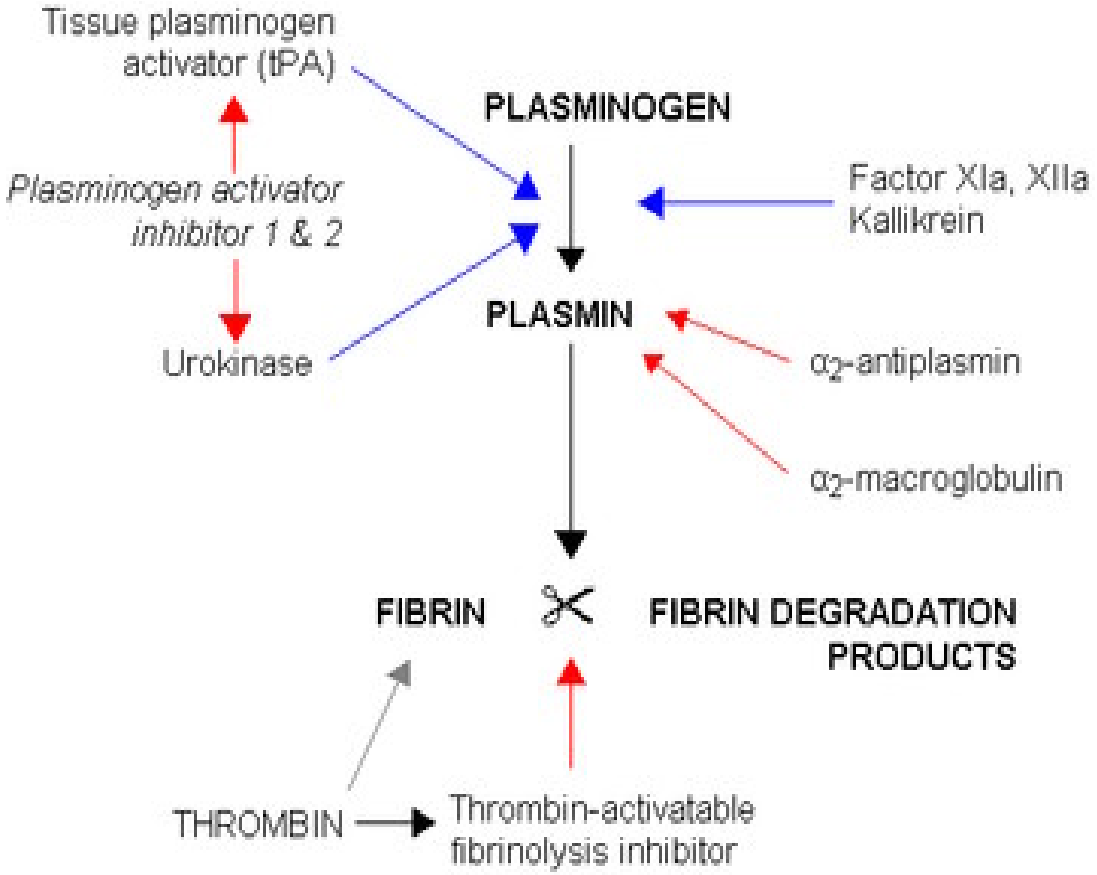
- 5 million deaths per year worldwide
- 90% in low and middle income countries
- 3rd leading cause of death in developed world
- Estimated 20 000 cases of major trauma in England each year
  - 5 400 deaths
- Leading cause of death in those <40yrs

Epidemiology of Trauma

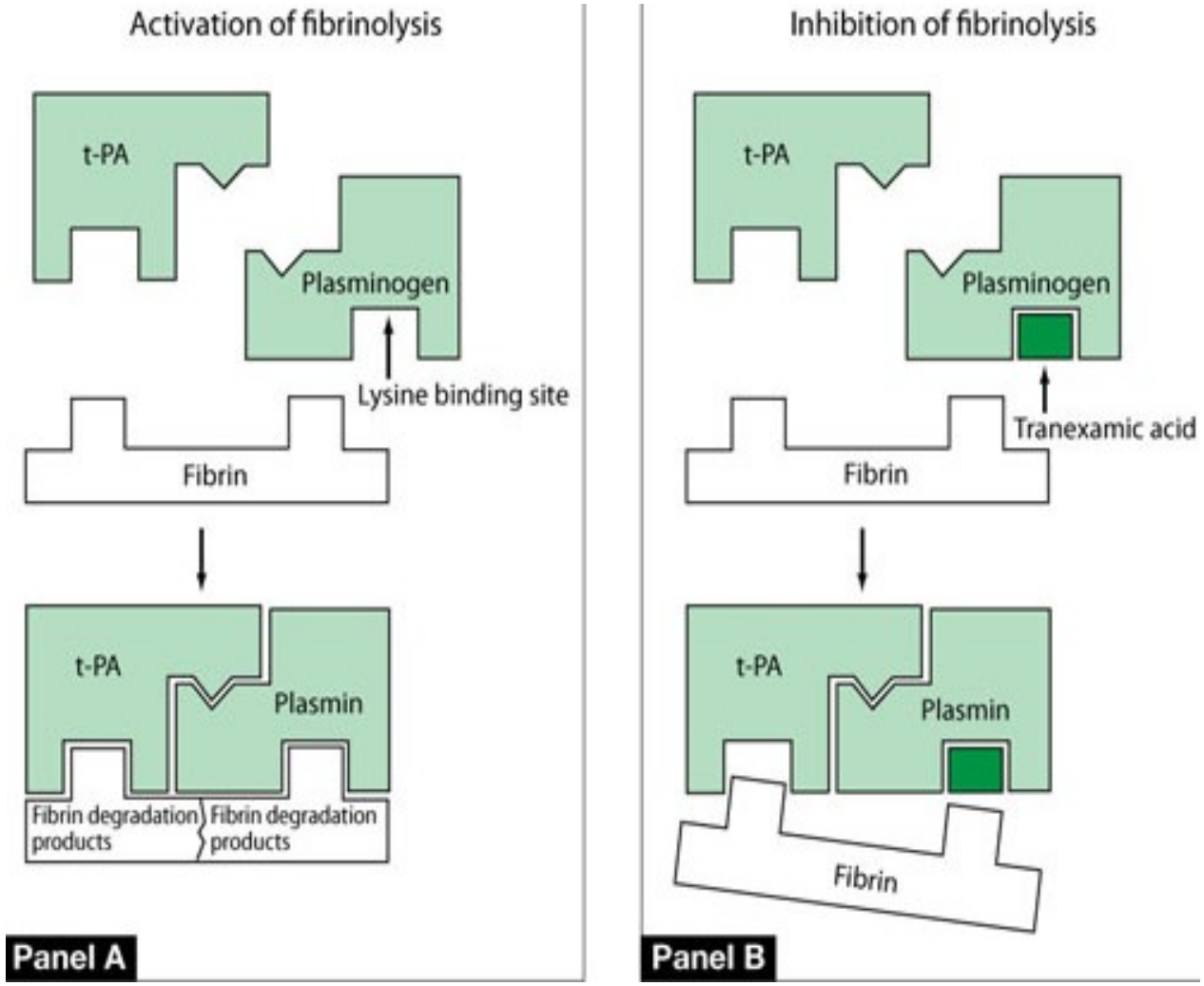
- Massive cost
  - Life years lost
  - Financial
- Cause of death
  - Neurological injury 40-50%
  - Haemorrhage 30-40%
  - Multiorgan failure 20%

Pharmacotherapy

Tranexamic acid



Tranexamic acid



Tranexamic acid

- History
  - 1966
    - First described
  - 1970’s
    - Dental extraction in haemophiliacs
  - 1980’s and 90’s
    - Extended surgical uses

Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion (Review)

Henry DA, Carless PA, Moxey AJ, O'Connell D, Stokes BJ, Fergusson DA, Ker K

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Analysis 2.7. Comparison 2 Tranexamic Acid versus Control (Blood Transfusion & Blood Loss), Outcome 7 Units of Allogeneic Blood Transfused - All Patients.

Review: Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

Comparison: 2 Tranexamic Acid versus Control (Blood Transfusion & Blood Loss)

Outcome: 7 Units of Allogeneic Blood Transfused - All Patients

Study or subgroup	TXA N	TXA Mean(SD)	Control N	Control Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Armellin 2001	143	0.41 (0.93)	140	0.87 (1.3)		-0.46 [-0.72, -0.20]
Blauhut 1994	15	0.8 (1.08)	14	1.57 (1.5)		-0.77 [-1.73, 0.19]
Caglar 2008	50	0.3 (0.8)	50	0.3 (0.7)		0.0 [-0.29, 0.29]
Corbeau 1995	41	0.8 (1.1)	20	1.7 (1.8)		-0.90 [-1.76, -0.04]
Dalmau 2000	42	5.33 (5.77)	40	7.75 (6.3)		-2.42 [-5.04, 0.20]
Diprose 2005	60	0.87 (1.52)	60	1.68 (3.51)		-0.81 [-1.78, 0.16]
Hilpala 1995	15	1.5 (1.3)	13	3.3 (1.8)		-1.80 [-2.98, -0.62]
Hilpala 1997	39	1 (1.2)	38	3.1 (1.6)		-2.10 [-2.73, -1.47]
Horrow 1990	18	0.92 (0.8)	20	0.76 (1.08)		0.16 [-0.44, 0.76]
Jansen 1999	21	0.46 (1.45)	21	2.5 (2.47)		-2.04 [-3.26, -0.82]
Jimenez 2007	24	1.58 (0.49)	26	3.21 (0.55)		-1.63 [-1.92, -1.34]
Katoh 1997	62	1.42 (2.74)	31	3.03 (4.57)		-1.61 [-3.36, 0.14]
Kazemi 2010	32	0.31 (0.64)	32	0.84 (0.9)		-0.53 [-0.91, -0.15]
MacGillivray 2010	40	0.76 (0.75)	20	1.11 (0.97)		-0.35 [-0.83, 0.13]
Maddali 2007	111	2.03 (0.78)	111	3.17 (0.97)		-1.14 [-1.37, -0.91]
Murphy 2006	50	0.38 (0.81)	50	0.34 (0.59)		0.04 [-0.24, 0.32]
Speekenbrink 1995	15	2.87 (1.9)	15	3.13 (3.3)		-0.26 [-2.19, 1.67]
Uozaki 2001	6	4.1 (2.23)	6	9.16 (6.6)		-5.06 [-10.63, 0.51]
Veien 2002	15	0 (0)	15	0.27 (0.7)		0.0 [0.0, 0.0]
Wei 2006	36	1.27 (1.07)	40	1.33 (0)		0.0 [0.0, 0.0]
Wong 2008	73	0.89 (1.8)	74	1.35 (2.16)		-0.46 [-1.10, 0.18]
Yazan 1993	10	7.9 (3.3)	10	12.4 (8)		-4.50 [-9.86, 0.86]
Zabeeda 2002	25	0.52 (0.9)	25	1.68 (1)		-1.16 [-1.69, -0.63]
Total (95% CI)	**943**		**871**			**-0.87 [-1.20, -0.53]**

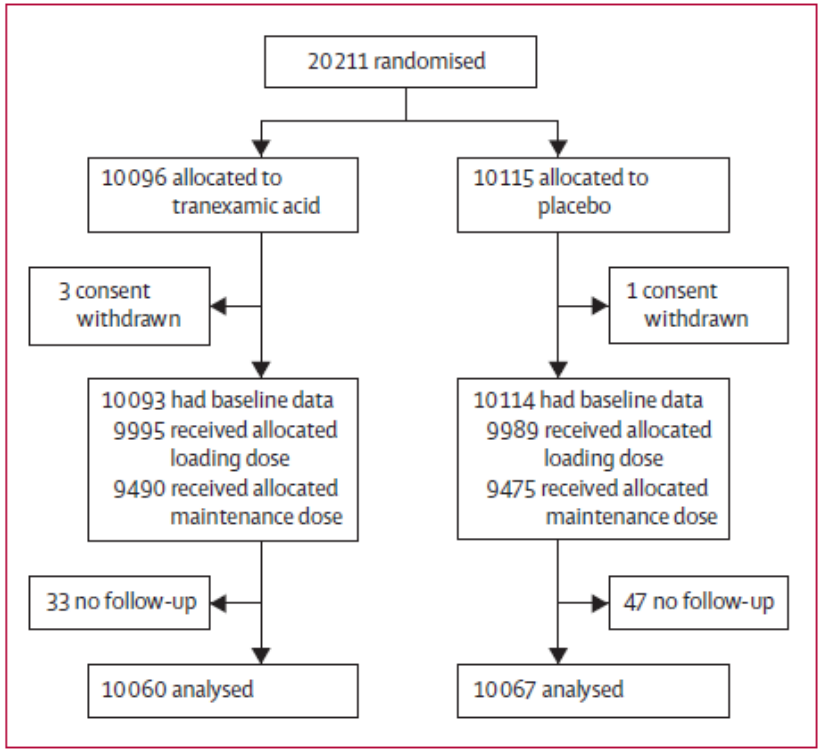
Heterogeneity: $Tau^2 = 0.40$; $Chi^2 = 154.24$, df = 20 ($P<0.00001$); $I^2 = 87\%$

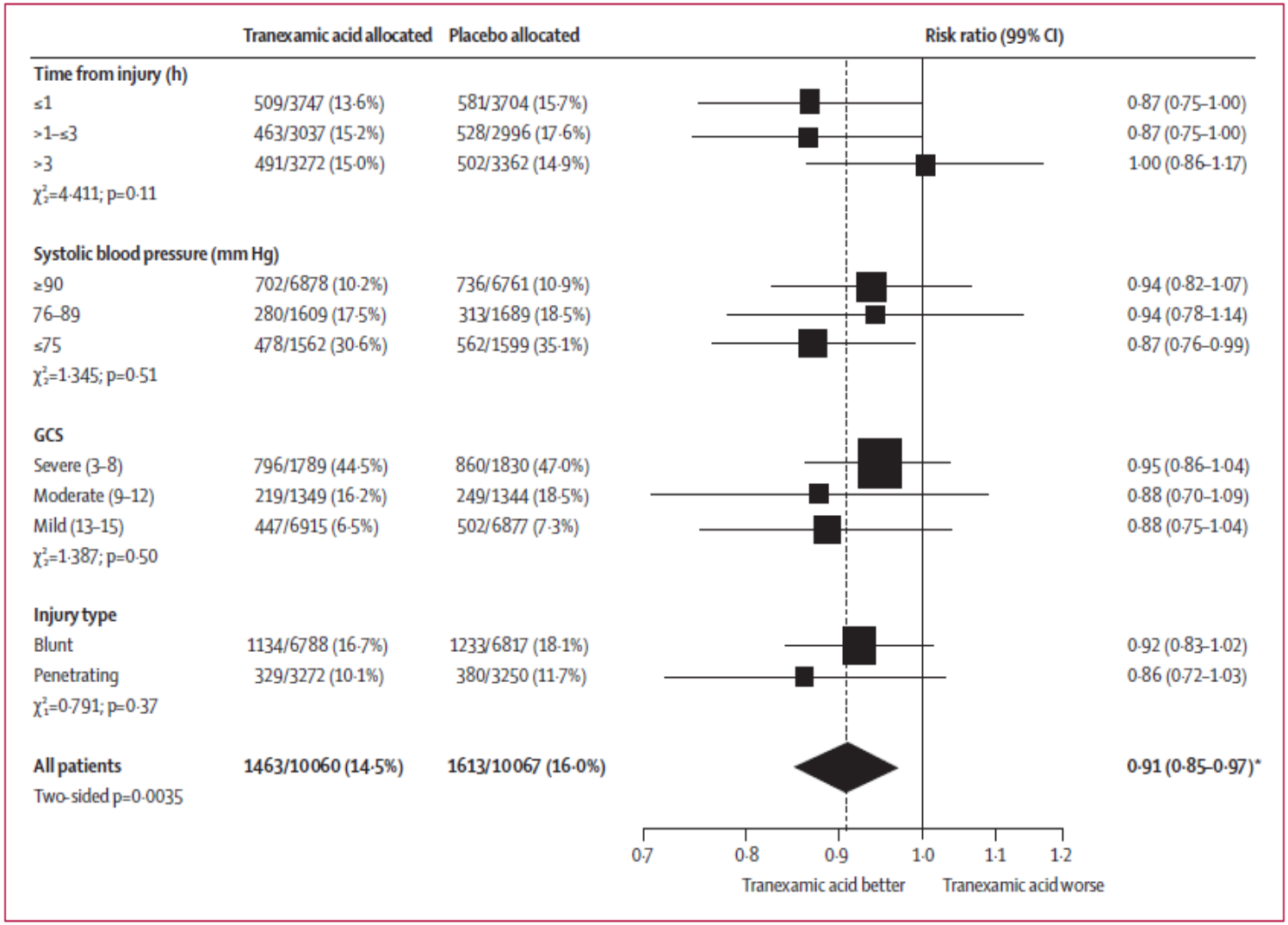
Test for overall effect: $Z = 5.04$ ($P < 0.00001$)

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

www.thelancet.com Published online June 15, 2010

*CRASH-2 trial collaborators**




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

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

*CRASH-2 trial collaborators**

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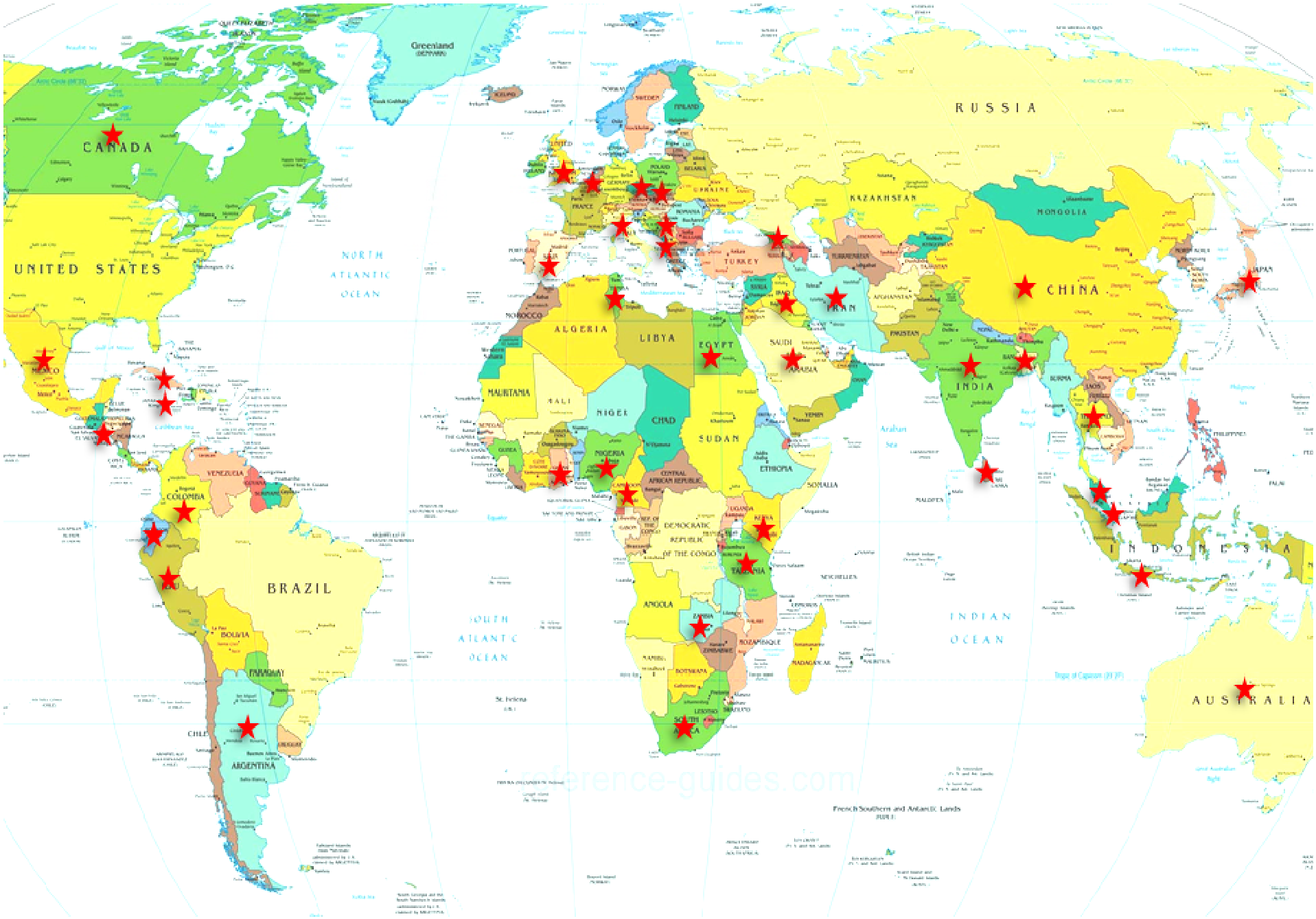
	Tranexamic acid (n=10 060)	Placebo (n=10 067)	RR (95% CI)	p value
Vascular occlusive events*				
Any vascular occlusive event	168 (1·7%)	201 (2·0%)	0·84 (0·68–1·02)	0·084
Myocardial infarction	35 (0·3%)	55 (0·5%)	0·64 (0·42–0·97)	0·035
Stroke	57 (0·6%)	66 (0·7%)	0·86 (0·61–1·23)	0·42
Pulmonary embolism	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

Criticisms

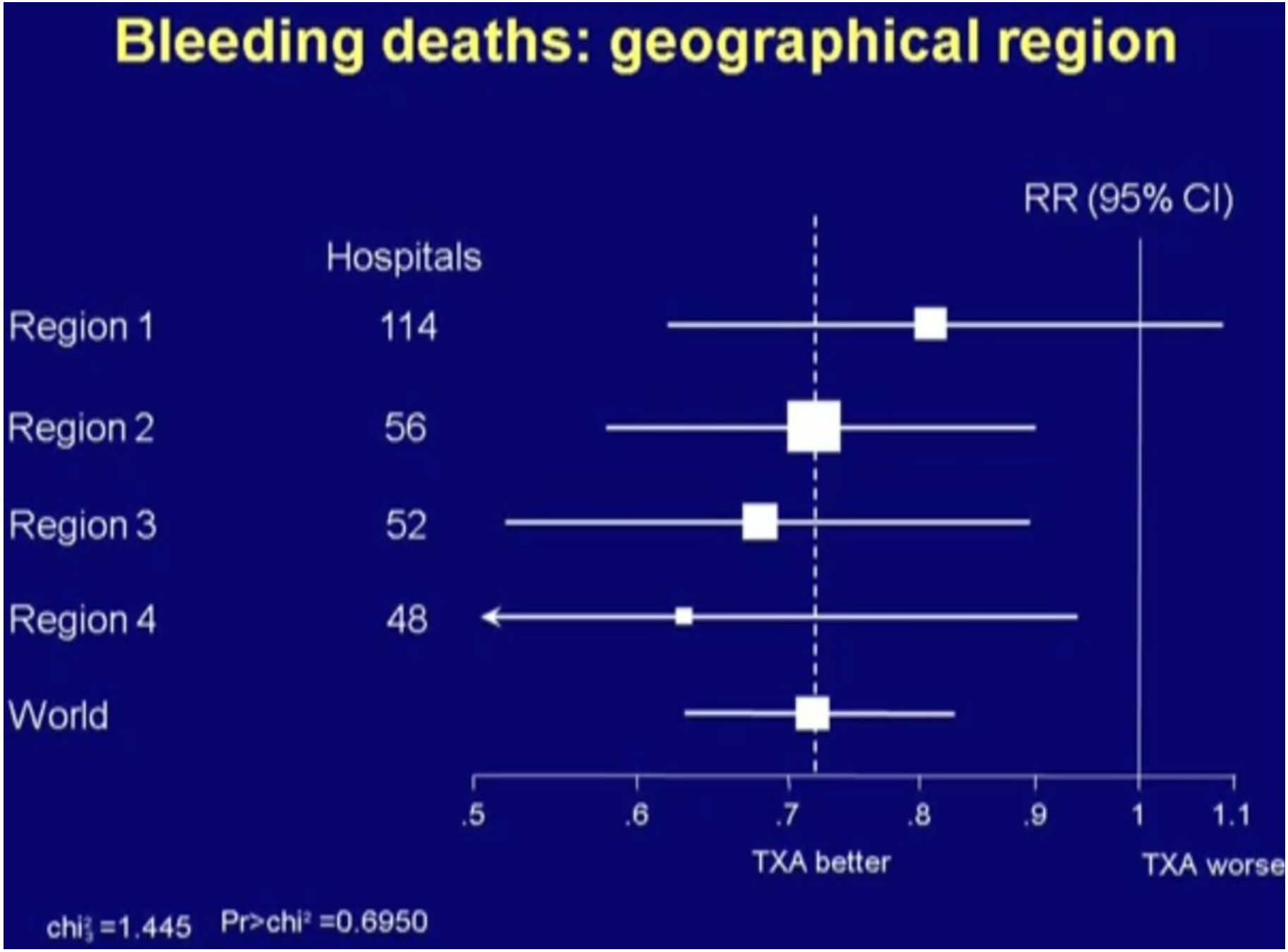
- No documentation of number of patients screened
- No major haemorrhage protocol
  - No documentation of transfusion ratios
- No supporting data to mortality benefit
  - No evidence of hyperfibrinolysis
  - No reduction in number of units transfused
- No injury severity score

Criticisms

- Predominantly in low and middle income countries
  - Pre-hospital care
  - Hospital care
  - Detection of vascular events
- Younger cohort
  - Less comorbidities
  - Less aspirin/warfarin/etc


Greenland
CANADA
UNITED STATES
RUSSIA
NORTH ATLANTIC OCEAN
KAZAKHSTAN
MONGOLIA
CHINA
JAPAN
TURKEY
IRAN
ALGERIA
LIBYA
EGYPT
MOROCCO
INDIA
MAURITANIA
MALI
NIGER
CHAD
SUDAN
NIGERIA
ETHIOPIA
SOMALIA
VENEZUELA
COLOMBIA
BRAZIL
PERU
BOLIVIA
PARAGUAY
CHILE
ARGENTINA
ANGOLA
INDONESIA
SOUTH ATLANTIC OCEAN
INDIAN OCEAN
AUSTRALIA

Bleeding deaths: geographical region

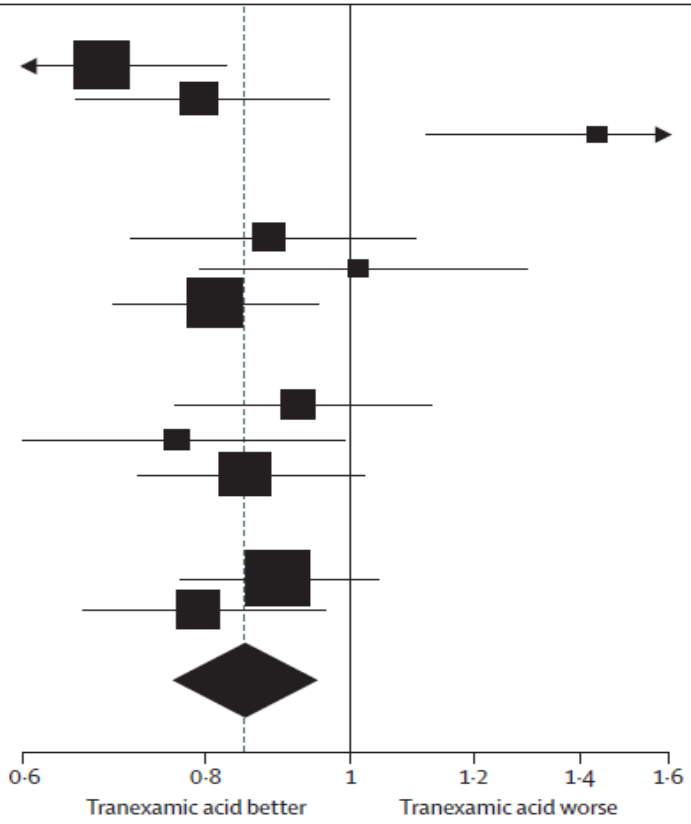


The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial

*The CRASH-2 collaborators**

www.thelancet.com Published online March 24, 2011

	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			



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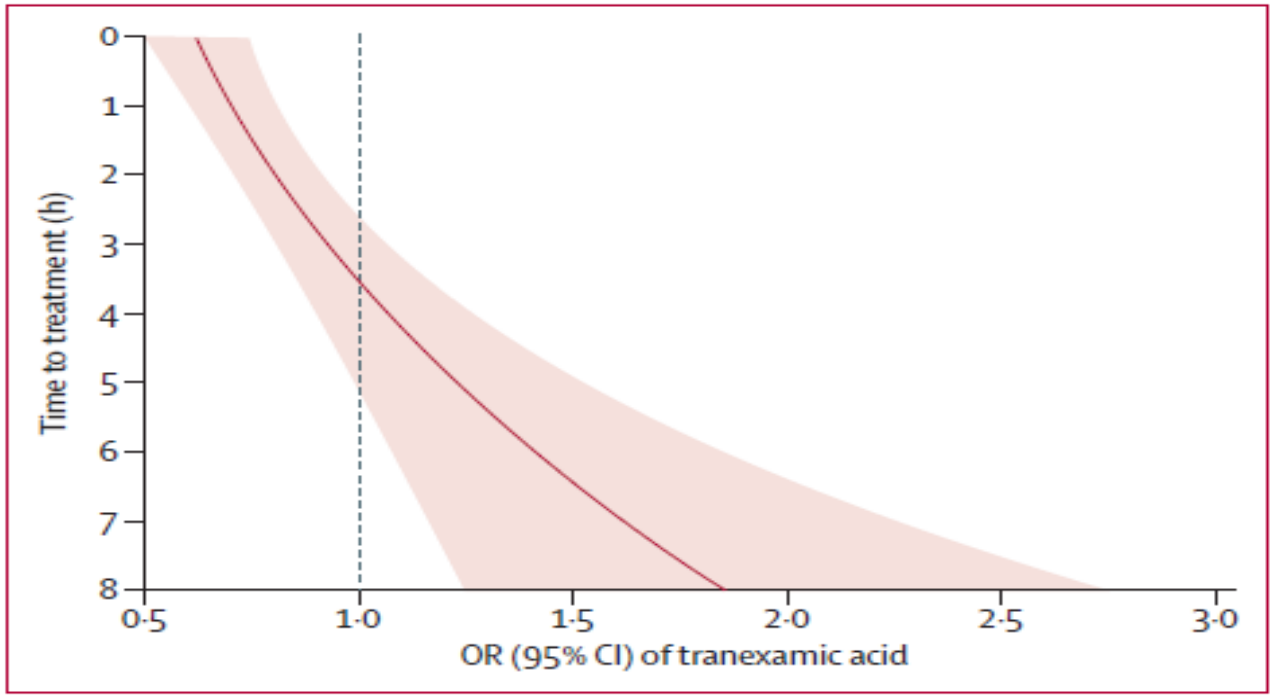
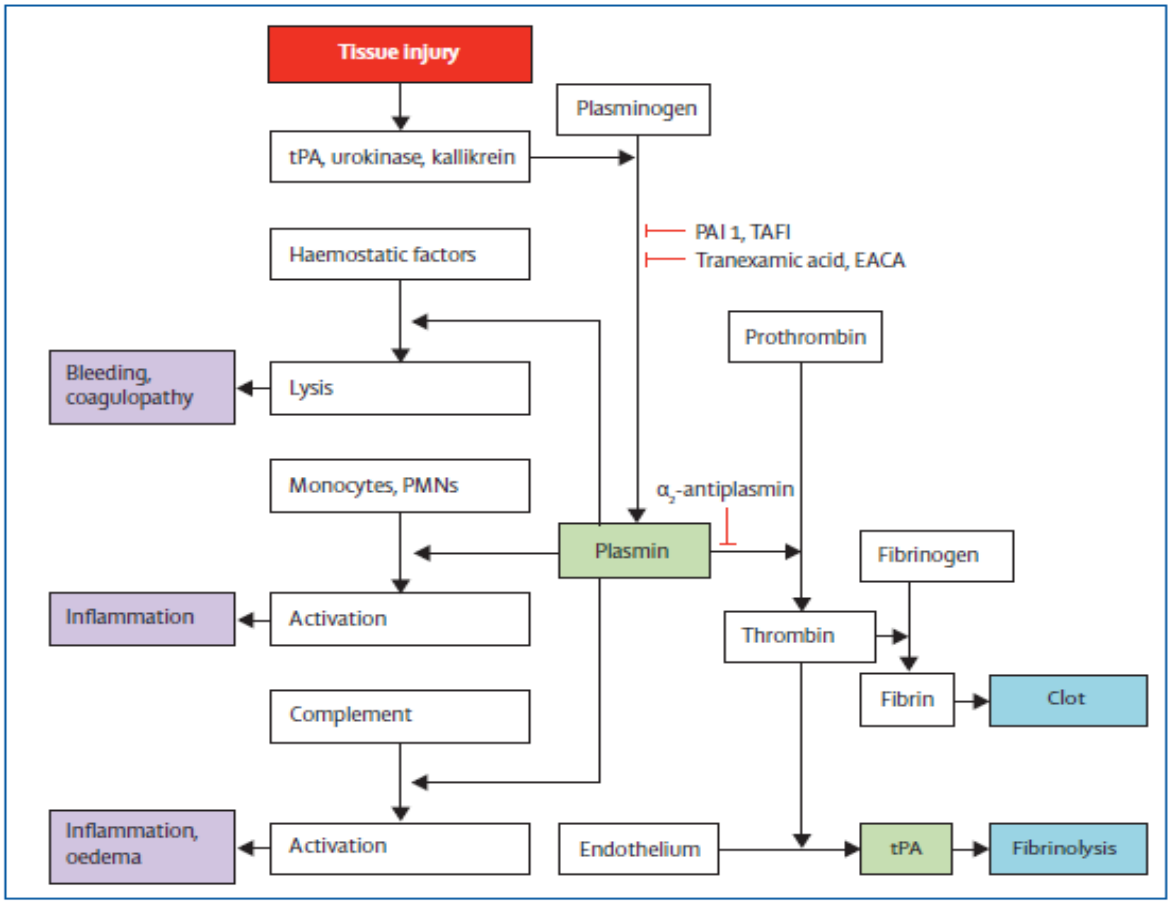


Antifibrinolytic therapy: new data and new concepts

Jerrold H Levy

www.thelancet.com Published online June 15, 2010



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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

Item	Tanzania	India	UK
Non-ICU hospital stay ($)*			
TXA	135,183	213,435	3,272,416
No TXA	134,641	212,315	3,255,244
TXA administration cost ($)*			
TXA	17,483	19,550	30,830
Overall incremental cost ($)*	18,025	20,670	48,002
Life years gained discounted*			
TXA	13,079	18,176	24,162
No TXA	12,707	17,861	23,407
Incremental life year saved*	372	315	755
Incremental cost per life year saved ($)	48	66	64

Ker *et al. BMC Emergency Medicine* 2012, **12**:3
http://www.biomedcentral.com/1471-227X/12/3

BMC Emergency Medicine

RESEARCH ARTICLE Open Access

Avoidable mortality from giving tranexamic acid to bleeding trauma patients: an estimation based on WHO mortality data, a systematic literature review and data from the CRASH-2 trial

Katharine Ker*, Junko Kiriya, Pablo Perel, Phil Edwards, Haleema Shakur and Ian Roberts

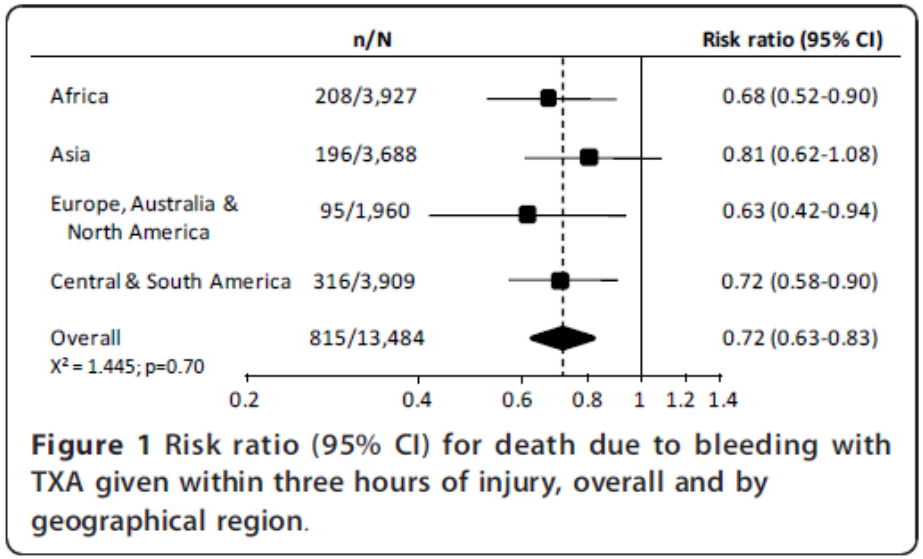

Figure 1 Risk ratio (95% CI) for death due to bleeding with TXA given within three hours of injury, overall and by geographical region.

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/VOL 147 (NO. 2), FEB 2012 WWW.ARCHSURG.COM

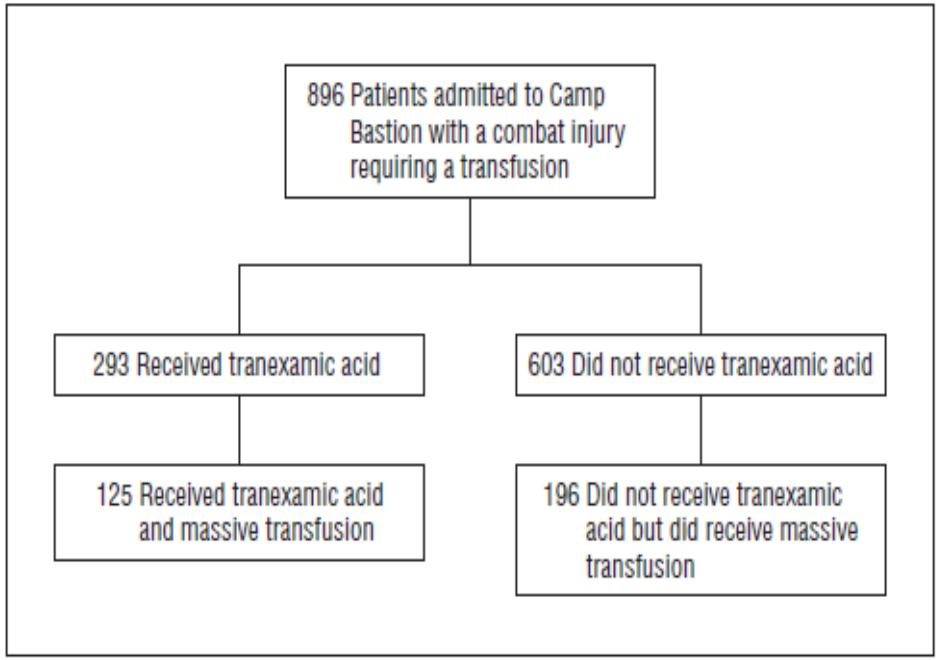

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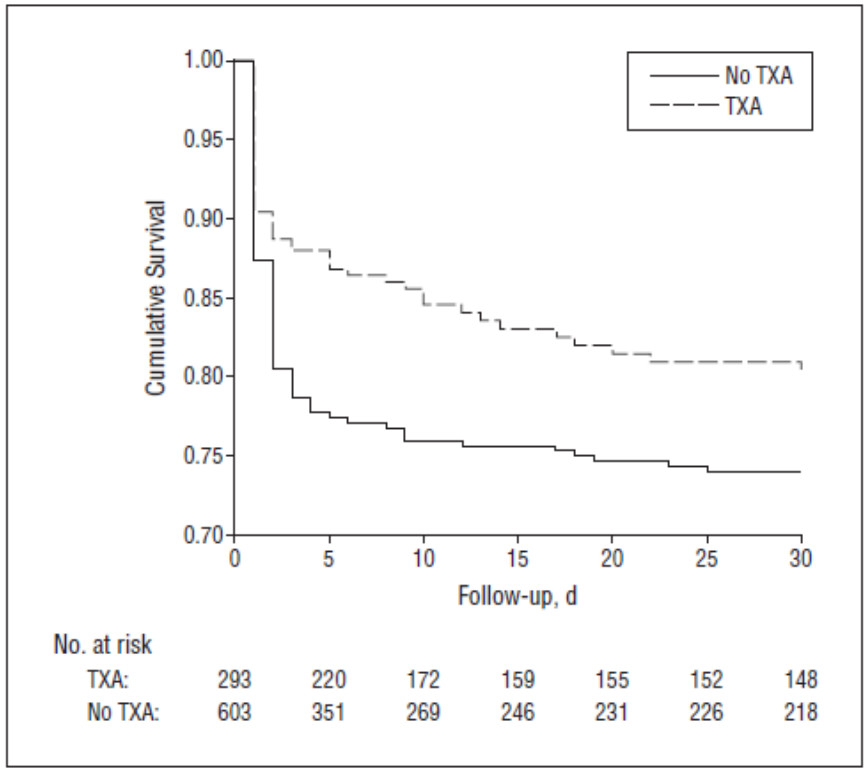
Table 2. All-Cause Mortality of Overall and Massive Transfusion Groups Within 24 Hours, Within 48 Hours, and In-Hospital Mortality

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**



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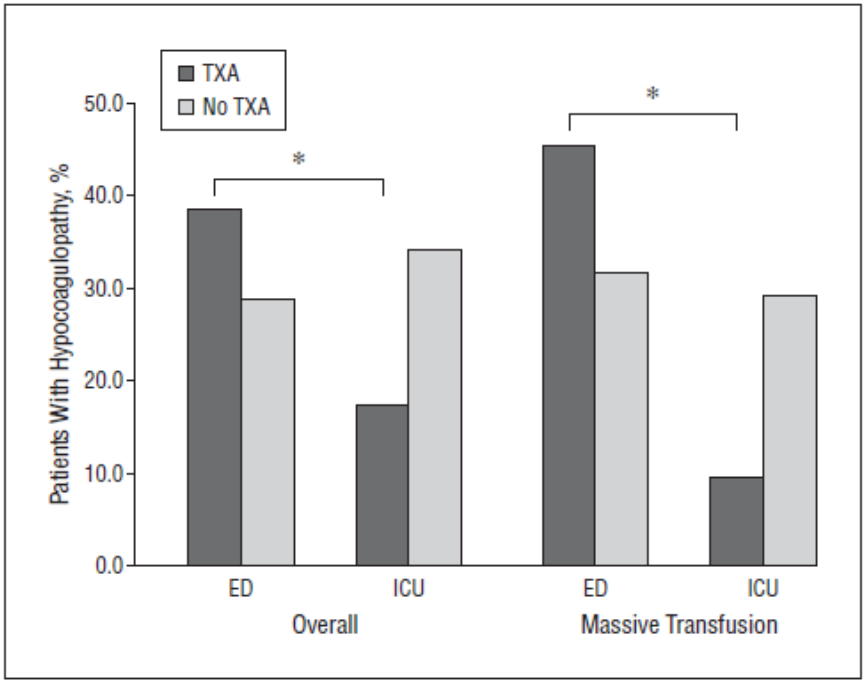


Table 3. Factors Associated With Survival Following Multivariate Analysis of the Overall Group and the Massive Transfusion Group

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**

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

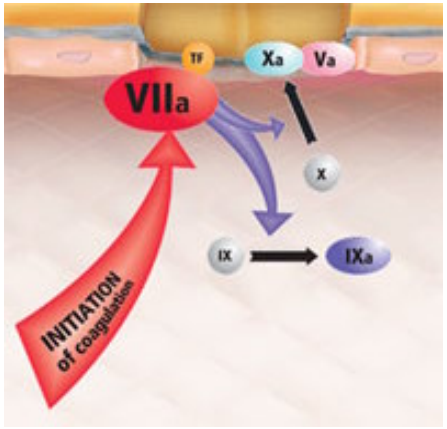
Variable	Overall (N=896)			Massive Transfusion (n=231)		
	TXA (n=293)	No TXA (n=603)	*P* Value[a]	TXA (n=125)	No TXA (n=196)	*P* Value[a]
Demographic data						
Age, mean (SD), y	24.9 (9.6)	23.1 (10.1)	.12	23.8 (7.7)	22.9 (9.2)	.46
Male, %	97.3	94.2	**.04**	98.4	96.9	.49
Host national, No. (%)	116 (39.6)	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
AIS score ≥3, %						
Head	9.9	13.4	.13	9.6	13.8	.26
Chest	22.2	22.2	.99	21.6	23.0	.78
Abdomen	14.7	16.4	.50	13.6	21.0	.06
Extremity	66.6	47.3	**<.001**	68.0	51.0	**.003**
RTS, mean (SD)	5.53 (2.14)	6.04 (2.69)	**.01**	5.58 (2.21)	5.74 (2.88)	.21
Admission physiology, %						
GCS score ≤8	63.3	35.6	**<.001**	64.1	39.3	**<.001**
SBP ≤90 mm Hg	22.8	13.8	**.003**	20.4	18.2	.67
24-h Transfusion, mean (SD), units						
PRBCs	11.8 (12.1)	9.8 (13.1)	**<.001**	21.0 (12.8)	22.5 (15.9)	.47
FFP	10.3 (10.8)	8.6 (11.7)	**<.001**	18.4 (11.5)	19.6 (14.3)	.67
Platelets	1.6 (2.2)	1.4 (2.7)	**.001**	3.2 (2.4)	3.6 (3.6)	.84
Cryoprecipitate	1.6 (2.7)	0.5 (1.3)	**<.001**	1.6 (2.6)	0.7 (1.6)	**<.001**
Miscellaneous						
Time in ED, mean (SD), min	36 (25)	56 (55)	**<.001**	39 (27)	52 (57)	.39
Time in OR, mean (SD), min	170 (121)	115 (74)	**<.001**	180 (126)	113 (74)	**<.001**
Lowest body temperature, mean (SD), °C	36.1 (1.1)	36.4 (0.9)	**.04**	36.5 (0.8)	36.3 (0.9)	.28
Pulmonary embolism, No. (%)	8 (2.7)	2 (0.3)	**.001**	4 (3.2)	0	**.01**
Deep venous thrombosis, No. (%)	7 (2.4)	1 (0.2)	**.001**	2 (1.6)	1 (0.5)	.32

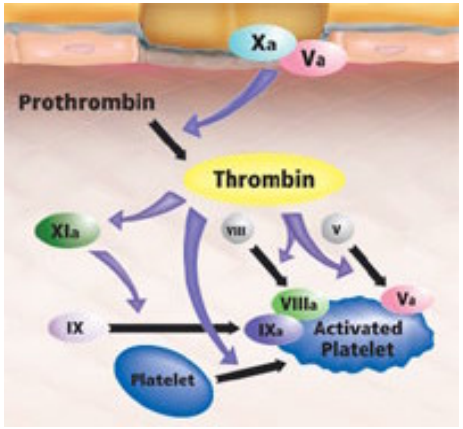
Tranexamic acid use

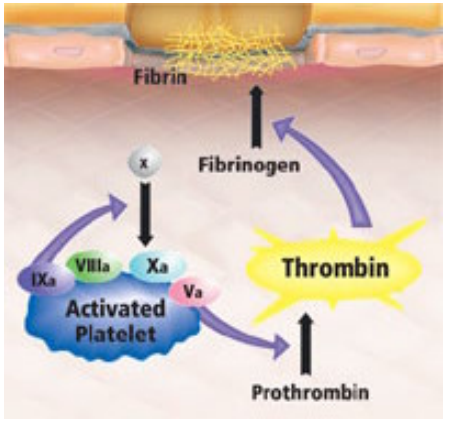
- British army
  - March 2010
- US army
  - 2011
- WHO list of essential medicines
  - March 2011
- UK ambulance service
  - July 2011
- Emergency Departments
  - ?

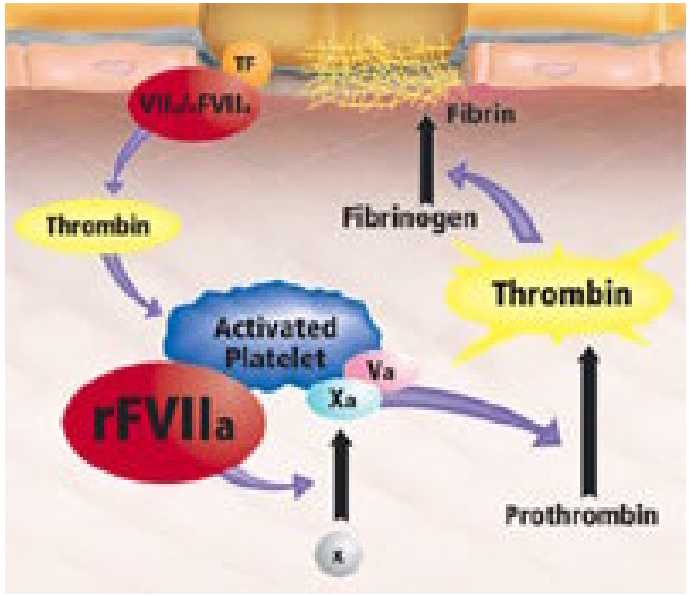
Recombinant Activated Factor VII (rFVIIa)

rFVIIa


TF
Xa
Va
VIIa
X
IX
IXa
INITIATION of coagulation


Xa
Va
Prothrombin
Thrombin
XIa
VIII
V
VIIIa
Va
IX
IXa
Activated Platelet
Platelet


Fibrin
Fibrinogen
X
IXa
VIIIa
Xa
Va
Activated Platelet
Thrombin
Prothrombin


TF
VIIa-FVIIa
Fibrin
Thrombin
Fibrinogen
Thrombin
Activated Platelet
Va
Xa
rFVIIa
Prothrombin
X

rFVIIa

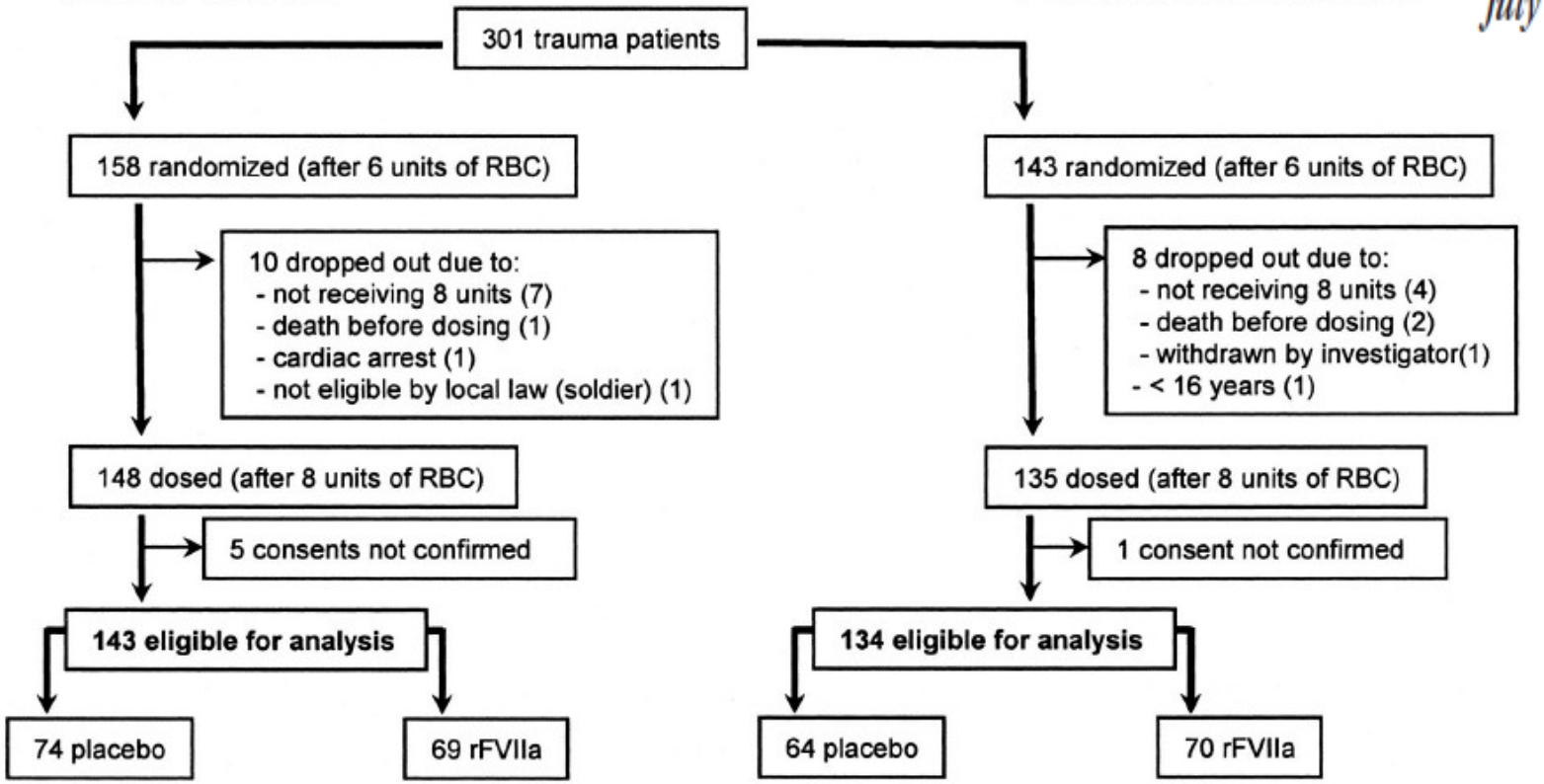
- History
  - 1983
    - Native VIIa halted bleeding in haemophiliacs with antibodies
  - 1988
    - Produced as recombinant product
- Licence
  - Haemophilia A/B with antibodies
  - Factor VII deficiency
  - Glanzmann’s thrombasthenia

The Journal of TRAUMA® Injury, Infection, and Critical Care

Recombinant Factor VIIa as Adjunctive Therapy for Bleeding Control in Severely Injured Trauma Patients: Two Parallel Randomized, Placebo-Controlled, Double-Blind Clinical Trials

Kenneth David Boffard, MD, Bruno Riou, MD, PhD, Brian Warren, MD, Philip Iau Tsau Choong, MD, Sandro Rizoli, MD, Rolf Rossaint, MD, Mads Axelsen, MD, and Yoram Kluger, MD, for the NovoSeven Trauma Study Group

July 2005



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July 2005

Table 2 Total RBC Transfusions (Units) During 48 Hours After First Dose of Trial Drug

	Placebo		rFVIIa		Estimated RBC reduction with 90% CI*	$p^{\dagger}$
	N	Median (range)	N	Median (range)		
Blunt		N = 74		N = 69		
Alive at 48 h	59	7.5 (0–35)	52	7.0 (0–29)	2.6 [0.7;4.6]	0.02
All patients	72	7.2 (0–35)	64	7.8 (0–48)	2.0$^{\diamond}$ [0.0;4.6]	0.07$^{\diamond}$
Penetrating		N = 64		N = 70		
Alive at 48 h	52	4.2 (0–41)	57	3.9 (0–30)	1.0 [0.0;2.6]	0.10
All patients	61	4.8 (0–41)	69	4.0 (0–37)	0.2$^{\diamond}$ [−0.9;2.4]	0.24$^{\diamond}$

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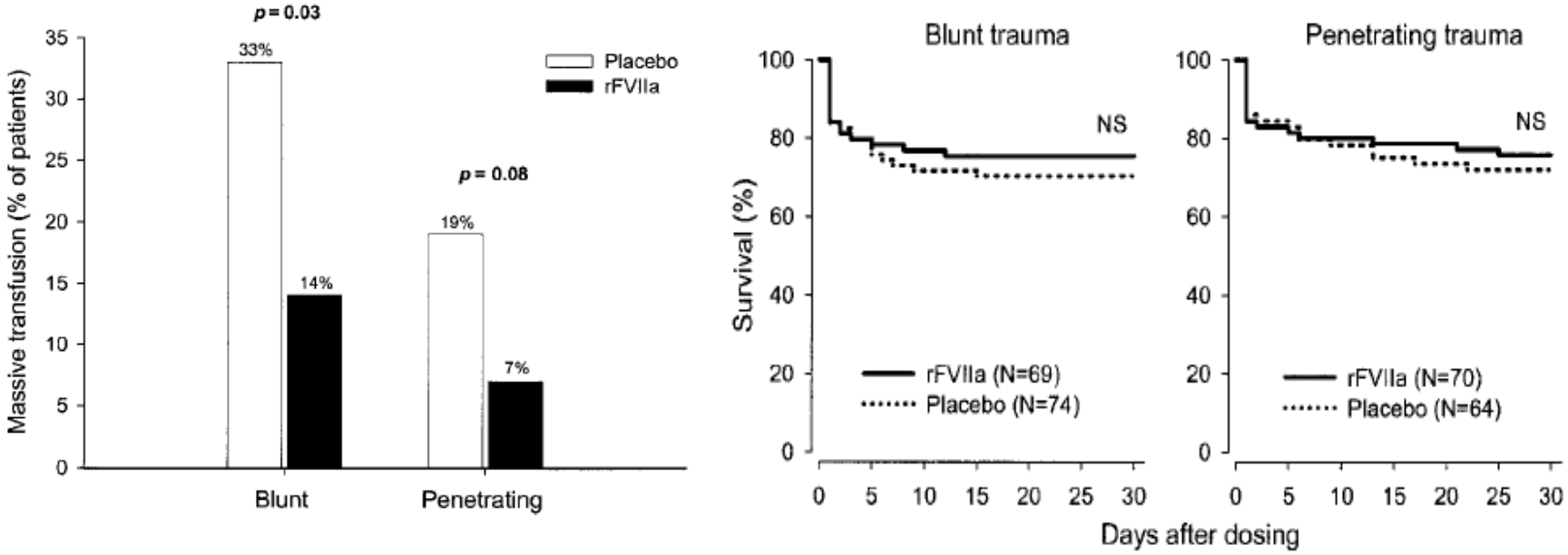

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Table 3 Adverse Events and Clinical Outcomes

	Blunt trauma		Penetrating trauma	
	Placebo (N = 74)	rFVIIa (N = 69)	Placebo (N = 64)	rFVIIa (N = 70)
Serious adverse events				
Patients with events	49 (66%)	44 (64%)	36 (56%)	36 (51%)
Number of events	109	91	76	57
Thromboembolic adverse events				
Patients with events	3 (4%)	2 (3%)	3 (5%)	4 (6%)
Number of events	3	2	3	4

The Journal of **TRAUMA**® *Injury, Infection, and Critical Care* • Volume 69, Number 3, September 2010

Results of the CONTROL Trial: Efficacy and Safety of Recombinant Activated Factor VII in the Management of Refractory Traumatic Hemorrhage

Carl J. Hauser, MD, Kenneth Boffard, MD, Richard Dutton, MD, Gordon R. Bernard, MD, Martin A. Croce, MD, John B. Holcomb, MD, Ari Leppaniemi, MD, Michael Parr, MD, Jean-Louis Vincent, MD, PhD, Bartholomew J. Tortella, MD, MBA, Jeannett Dimsits, MD, and Bertil Bouillon, MD; for the CONTROL Study Group

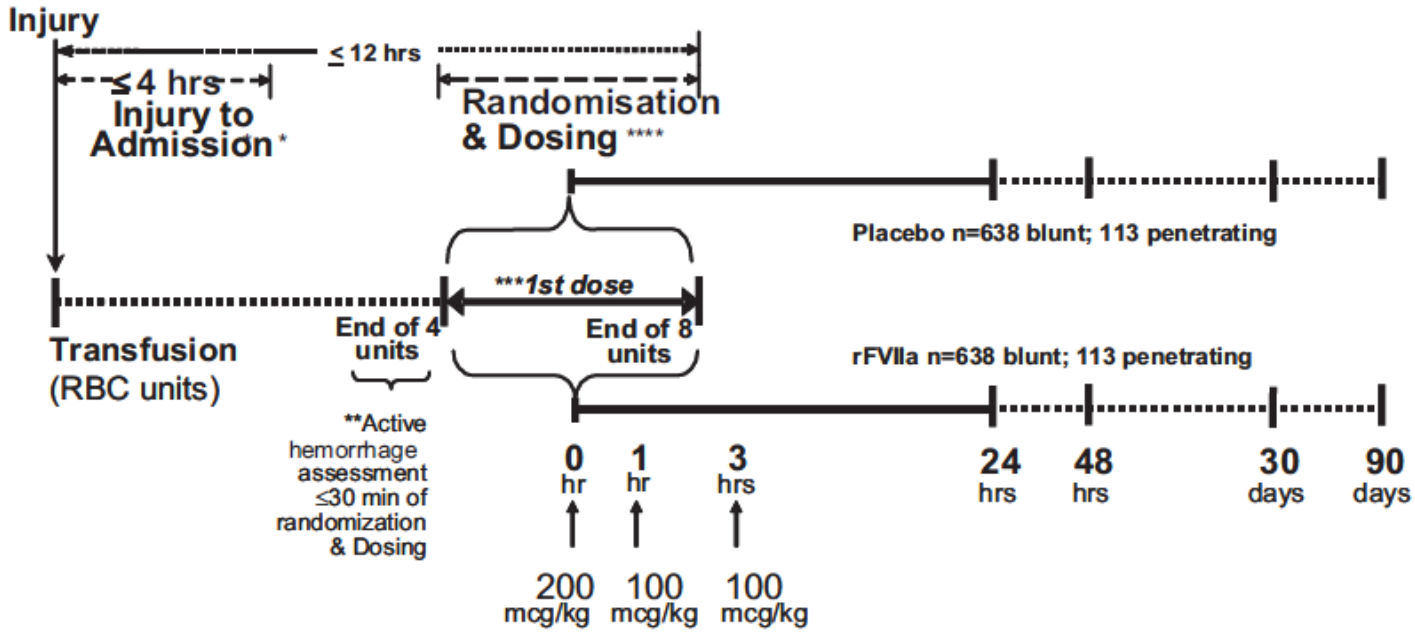

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TABLE 2. Clinical Outcomes (30-d ITT Analysis)

	Blunt Trauma			Penetrating Trauma		
	rFVIIa (n = 218)	Placebo (n = 242)	*p*	rFVIIa (n = 44)	Placebo (n = 38)	*p*
30-d mortality, n (%)	24 (11.0)	26 (10.7)	0.93† 0.37‡	8 (18.2)	5 (13.2)	0.40†
Durable morbidity*, n (%)	19 (8.7)	23 (9.5)	0.75	1 (2.3)	0	1.00
Days alive and free from ventilator/RRT through day 30, mean ± SD	17.2 ± 10.3	16.4 ± 10.3	0.31	21.2 ± 11.1	21.9 ± 10.0	0.73
Days alive and free of ICU through day 30	13.7 ± 10.4	12.9 ± 9.9	0.32	18.7 ± 11.2	19.5 ± 10.6	0.65
MOF through day 30§, n (%)	98 (45.0)	129 (53.3)	0.06	10 (22.7)	9 (23.7)	0.90
Days alive and free from MOF through day 30§, mean ± SD	24.6 ± 9.7	24.4 ± 9.4	0.66	24.1 ± 11.6	25.4 ± 10.2	0.45
SOF through day 30, n (%)	214 (98.2)	235 (97.1)	0.49	40 (90.9)	35 (92.1)	0.91
Days alive and free from SOF through day 30, mean ± SD	19.9 ± 8.9	19.5 ± 8.6	0.53	21.9 ± 11.1	23.1 ± 9.8	0.50
Days alive and free of hospital through day 30	4.0 ± 6.9	3.5 ± 6.4	0.39	13.2 ± 10.4	11.3 ± 9.1	0.71

TABLE 3. Transfusion Requirements (ITT Population)

	Blunt Trauma					Penetrating Trauma				
	rFVIIa (n = 221)		Placebo (n = 247)			rFVIIa (n = 46)		Placebo (n = 40)		
	N*	Mean ± SD	N*	Mean ± SD	$p^{\dagger}$	N*	Mean ± SD	N*	Mean ± SD	$p^{\dagger}$
Units administered from dosing to 24 h										
Allogeneic transfusions	198	17.1 ± 26.8	228	20.7 ± 25.7	0.03	39	11.2 ± 15.0	35	16.8 ± 19.3	0.09
RBC	184	6.9 ± 10.4	222	8.1 ± 10.9	0.04	37	4.5 ± 7.3	33	6.2 ± 6.5	0.11
FFP	160	4.7 ± 6.4	188	6.9 ± 8.6	<0.001	29	3.8 ± 6.0	33	5.7 ± 6.4	0.04
Platelets	112	3.3 ± 8.4	117	3.4 ± 7.0	0.84	15	1.6 ± 3.7	21	2.5 ± 4.1	0.08
Fibrinogen concentrate	28	1.5 ± 6.7	28	1.3 ± 4.7	0.68	1	0.1 ± 0.4	1	0.4 ± 2.7	0.92
Cryoprecipitate	34	0.9 ± 3.3	41	1.3 ± 4.3	0.66	8	1.6 ± 4.1	11	2.0 ± 4.8	0.33
Units administered from dosing to 48 h										
Allogeneic transfusions	201	19.0 ± 27.1	231	23.5 ± 28.0	0.04	39	12.2 ± 15.7	37	18.4 ± 20.7	0.06
RBC	191	7.8 ± 10.6	228	9.1 ± 11.3	0.04	39	5.0 ± 7.4	35	6.8 ± 6.9	0.11
FFP	166	5.3 ± 6.7	195	8.0 ± 10.1	0.001	29	4.0 ± 6.2	33	6.5 ± 7.6	0.02
Platelets	117	3.7 ± 8.6	124	3.9 ± 7.8	0.95	16	1.9 ± 3.9	21	2.7 ± 4.1	0.12
Fibrinogen concentrate	29	1.5 ± 6.7	28	1.3 ± 4.8	0.59	1	0.1	1	0.4	0.92
Cryoprecipitate	34	0.9 ± 3.3	41	1.4 ± 4.5	0.64	8	1.6 ± 4.1	11	2.0 ± 4.8	0.33
Patients requiring massive RBC transfusion (≥10 units of RBC) from injury to 24-h postdose, n (%)[‡]	111 (50.2)		134 (54.3)		0.38	14 (30.4)		21 (52.5)		0.04

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TABLE 4. Adverse Events Through Day 90 (Safety Population)

	Blunt Trauma			Penetrating Trauma		
	rFVIIa (n = 224)	Placebo (n = 250)	*p*	rFVIIa (n = 46)	Placebo (n = 40)	*p*
Serious adverse events						
Patients with events, n (%)	147 (65.6)	177 (70.8)	0.23	18 (39.1)	20 (50.0)	0.31
Number of events	348	390		35	44	
Average number of events per patient	2.4	2.2		1.9	2.2	
Thrombotic AEs*						
Patients with events, n (%)	36 (16.1)	33 (13.2)	0.38	2 (4.3)	4 (10.0)	0.41†
Number of events	45	35		2	5	
Arterial thrombotic AEs, no. events	16	11	0.20	2	1	1.00†
Venous TEs, no. events	29	24	0.25	0	4	0.04†

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Use of Recombinant Factor VIIa in US Military Casualties for a Five-Year Period

Charles E. Wade, PhD, Brian J. Eastridge, MD, John A. Jones, BS, Susan A. West, RN, Philip C. Spinella, MD, Jeremy G. Perkins, MD, Michael A. Dubick, PhD, Lorne H. Blackbourne, MD, and John B. Holcomb, MD

TABLE 1. Criteria for the Use of rFVIIa in the Military Clinical Practice Guidelines

a. Hypotensive from blood loss
b. Base deficit >6 mmol/L
c. Difficult to control bleeding associated with hypothermia (temperature <96°C)
d. Coagulopathic bleeding (clinically or INR >1.5)
e. Require damage control maneuvers
f. Require fresh whole blood
g. Anticipated or actual transfusion of >4 units of PRBC
h. Anticipated significant operative hemorrhage

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TABLE 9. After Propensity Matching Demographic, Admission, and Laboratory Variables of Patients Not Treated and Treated With rFVIIa

Variable	No rFVIIa (n = 266)	rFVIIa (n = 266)
Age (yr)	24 (21–28; 265)	24 (21–29; 266)
ISS	22 (14–30; 266)	25 (16–29; 266)
ISS >15 (%)	71	76
GCS score	15 (7–15; 266)	15 (4–15; 266)
SBP (mm Hg)	114 (93–136; 266)	115 (90–133; 266)
DBP (mm Hg)	64 (47–76; 266)	63 (47–76; 266)
Heart rate (beats per minute)	111 (89–131; 266)	110 (88–130; 266)
Temperature (°C)	98.0 (97.2–99.0; 179)	98.1 (97.3–99.1; 176)
BD	4 (2–8; 209)	5 (2–9; 210)
INR	1.3 (1.2–1.6; 208)	1.4 (1.1–1.8; 209)
Hgb (g/dL)	12 (10–13; 266)	12 (10–14; 266)
Sum PRBC (units)	10 (4–17; 266)	10 (6–16; 266)
Plasma (units)	5 (2–9; 266)	6* (3–10; 266)
Platelets	0 (0–1; 264)	0 (0–1; 266)
Cryoprecipitate	0 (0–0; 264)	0 (0–0; 266)
Massive transfusion (%)	53	51

TABLE 7. The Mortality Rate for the Overall Patient Population and After Propensity Analysis for Patient Treated or Not Treated With rFVIIa

Overall	6 h (%)	24 h (%)	30 d (%)	Overall (%)
No rFVIIa (n = 1544)	7.4	8.5	10.8	11.7
rFVIIa (n = 506)	10.9*	13.6*	22.3*	23.5*
Propensity matched				
No rFVIIa (n = 266)	6.8	9.4	13.5	14.3
rFVIIa (n = 266)	10.5	11.6	18.8	19.9

* Significantly different at $p < 0.01$.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 4, 2010 VOL. 363 NO. 19

Safety of Recombinant Activated Factor VII in Randomized Clinical Trials

Marcel Levi, M.D., Jerrold H. Levy, M.D., Henning Friis Andersen, M.Sc., and David Truloff, D.V.M.

Table 2. Odds Ratios for Thromboembolic Events.

Thromboembolic Event	rFVIIa (N=2583)	Placebo (N=1536)	Odds Ratio (95% CI)*	P Value
	number (percent)†			
All events	264 (10.2)	134 (8.7)	1.17 (0.94–1.47)	0.16
Arterial events	141 (5.5)	49 (3.2)	1.68 (1.20–2.36)	0.003
Venous events	137 (5.3)	88 (5.7)	0.93 (0.70–1.23)	0.61

* Odds ratios were calculated by means of logistic regression with adjustment for age and type of bleeding.

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Table 4. All Arterial Thromboembolic Events, According to Age.

Age Group	rFVIIa	Placebo	Odds Ratio (95% CI)*	P Value†
	no./total no. (%)‡			
<18 yr	1/70 (1.4)	1/51 (2.0)		
18–64 yr	73/1764 (4.1)	34/1107 (3.1)	1.36 (0.89–2.08)	0.15
≥65 yr	67/742 (9.0)	14/372 (3.8)	2.43 (1.34–4.41)	0.003
65–74 yr	33/427 (7.7)	8/225 (3.6)	2.12 (0.95–4.71)	0.07
≥75 yr	34/315 (10.8)	6/147 (4.1)	3.02 (1.22–7.48)	0.02

* Odds ratios were calculated by means of logistic regression with adjustment for indication.

Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia (Review)

Simpson E, Lin Y, Stanworth S, Birchall J, Doree C, Hyde C

THE COCHRANE COLLABORATION®

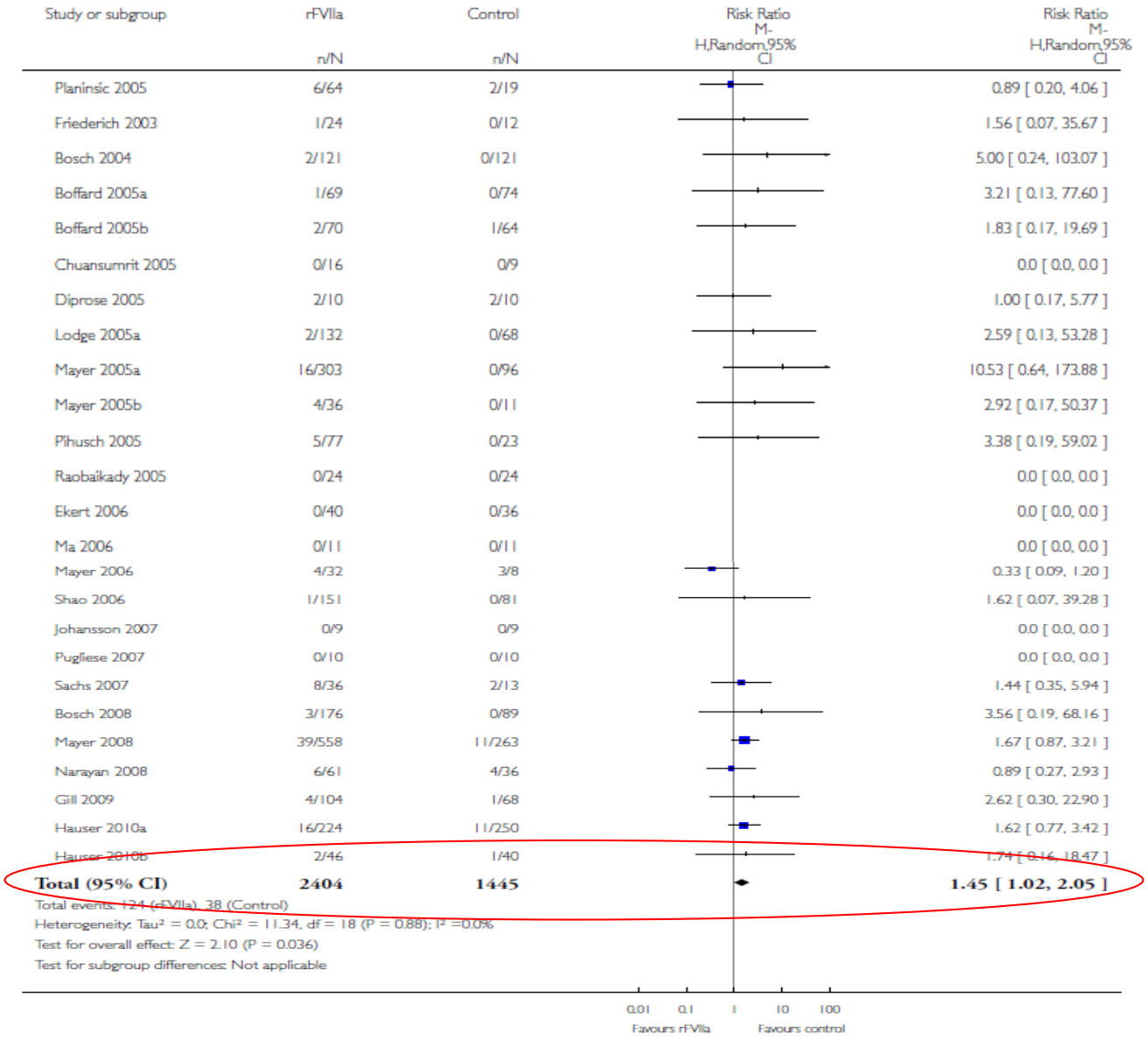
This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2012, Issue 4

Analysis 3.4. Comparison 3 rFVIIa used prophylactically or therapeutically versus placebo (adverse events), Outcome 4 Total arterial events.

Review: Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia

Comparison: 3 rFVIIa used prophylactically or therapeutically versus placebo (adverse events)

Outcome: 4 Total arterial events



rFVIIa use

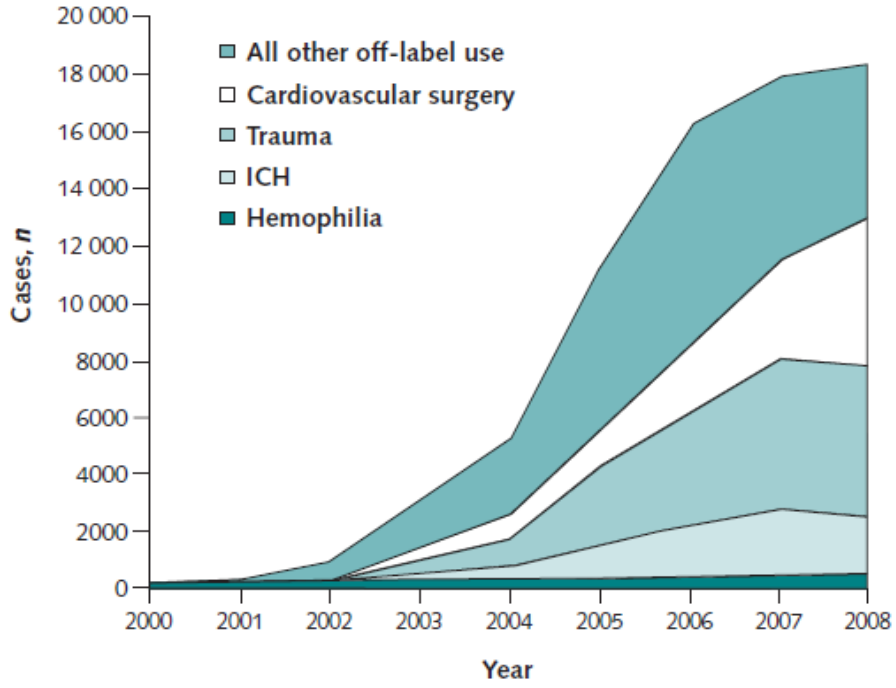
- Major Haemorrhage guidelines
  - Civilian and military
  - “consider” use
  - Low grade of recommendation

ORIGINAL RESEARCH | Annals of Internal Medicine

Off-Label Use of Recombinant Factor VIIa in U.S. Hospitals: Analysis of Hospital Records

Aaron C. Logan, MD, PhD; Veronica Yank, MD; and Randall S. Stafford, MD, PhD

Figure 1. Estimated annual in-hospital cases of recombinant factor VIIa use for hemophilia and off-label indications.

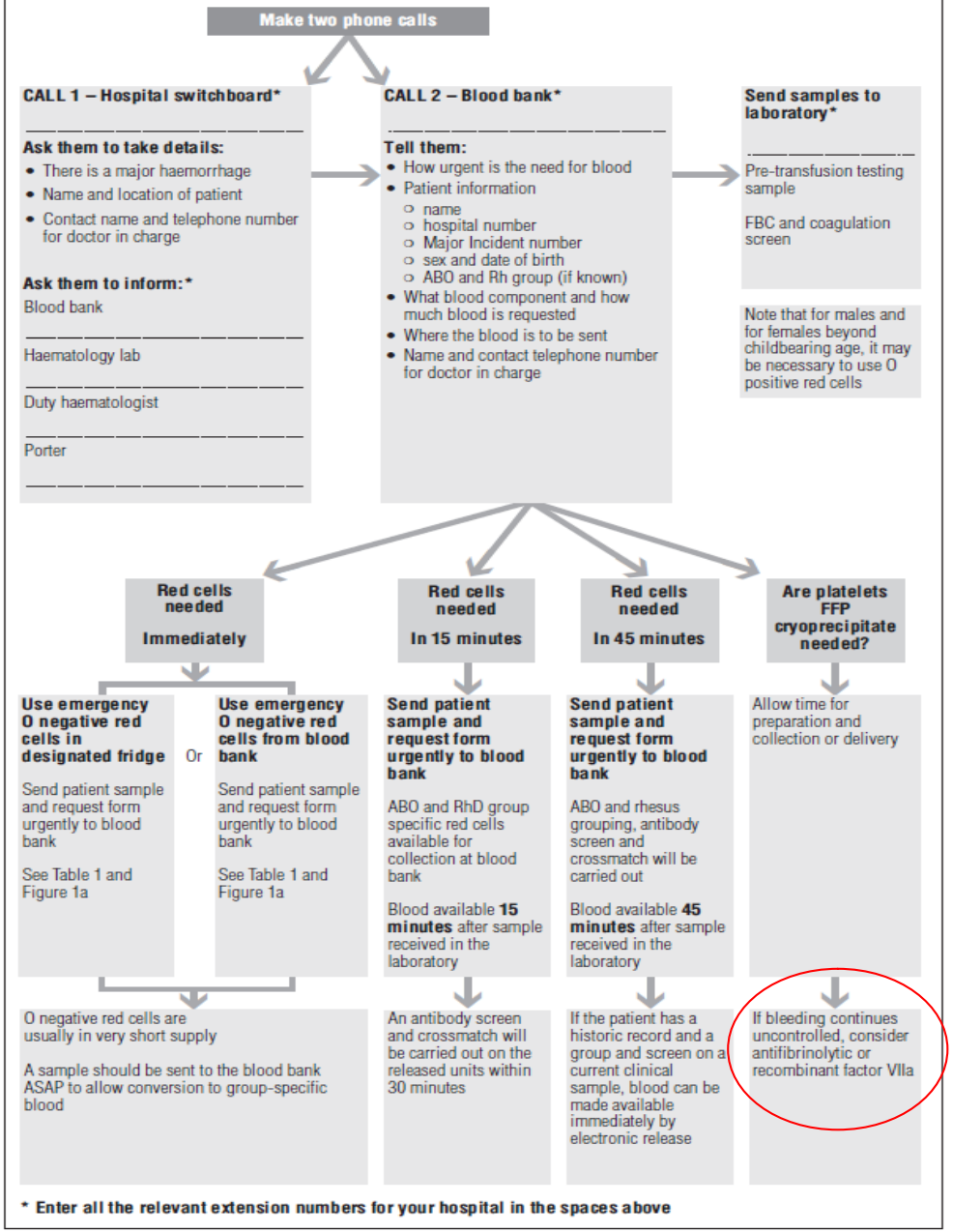


rFVIIa use

- Acidosis
- Hypothermia
- Coagulopathy


Handbook of
Transfusion Medicine
Editor DBL McClelland
United Kingdom Blood Services
4th Edition

Figure 1a An example of a major haemorrhage protocol
If there is a local protocol for your hospital, that should be used



* Enter all the relevant extension numbers for your hospital in the spaces above

AAGBI SAFETY GUIDELINE

Blood Transfusion and the Anaesthetist

Management of Massive Haemorrhage

Published by
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November 2010

Summary

- Tranexamic acid
  - Single large RCT with mortality benefit
  - Safe
  - Lacking supporting data
  - Applicable to low and middle income countries
  - Applicable to high income countries?
  - Widely used

Summary

- rFVIIa
  - Single RCT stopped early with no mortality benefit
  - Questionable safety
  - Secondary benefits of reduced transfusion requirements
  - Widely used?

Thank you