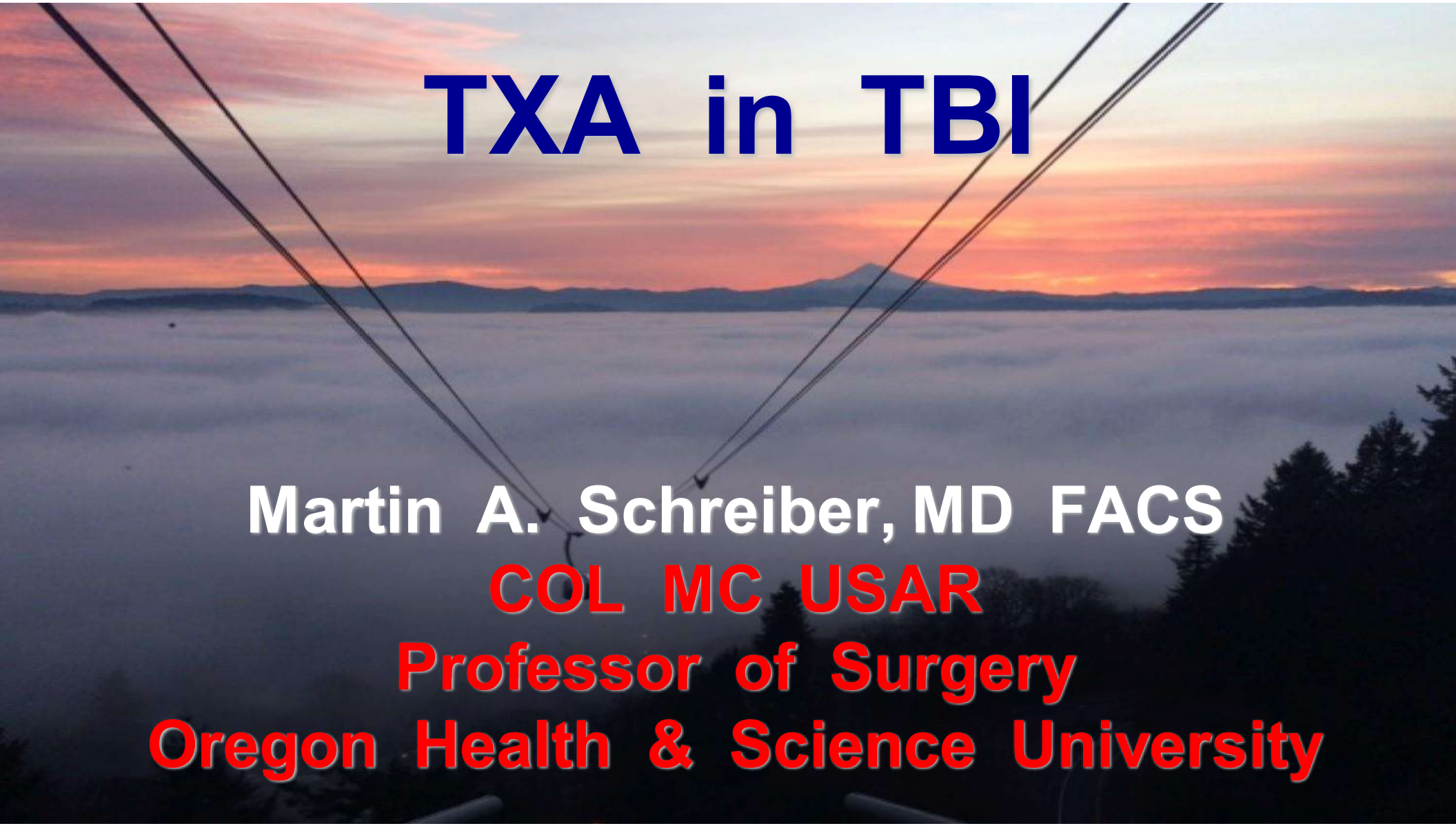


TXA in TBI

Martin A. Schreiber, MD FACS
COL MC USAR
Professor of Surgery
Oregon Health & Science University

Introduction

- Randomized trials
- Coagulation analysis
- Endothelial biomarkers
- Complications
- Timing
- Biomarkers

OHSU TRAUMA Center

Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): a randomised, placebo-controlled trial

*The CRASH-3 trial collaborators**

Summary

Background Tranexamic acid reduces surgical bleeding and decreases mortality in patients with traumatic extracranial bleeding. Intracranial bleeding is common after traumatic brain injury (TBI) and can cause brain herniation and death. We aimed to assess the effects of tranexamic acid in patients with TBI.

Methods This randomised, placebo-controlled trial was done in 175 hospitals in 29 countries. Adults with TBI who were within 3 h of injury, had a Glasgow Coma Scale (GCS) score of 12 or lower or any intracranial bleeding on

Lancet 2019; 394: 1713–23

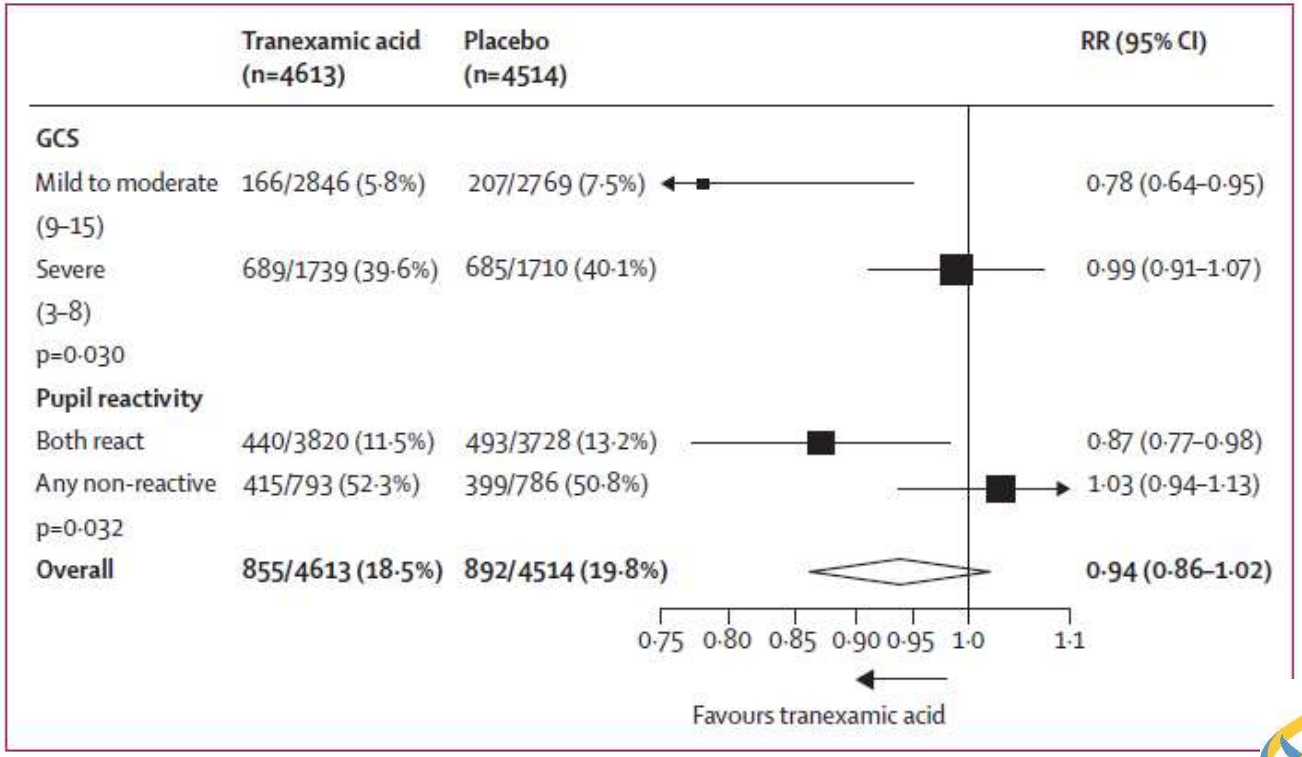
Published Online
October 14, 2019
https://doi.org/10.1016/
S0140-6736(19)32233-0

See Comment page 1687

12,737 patients from 2012 - 2019

OHSU TRAUMA Center

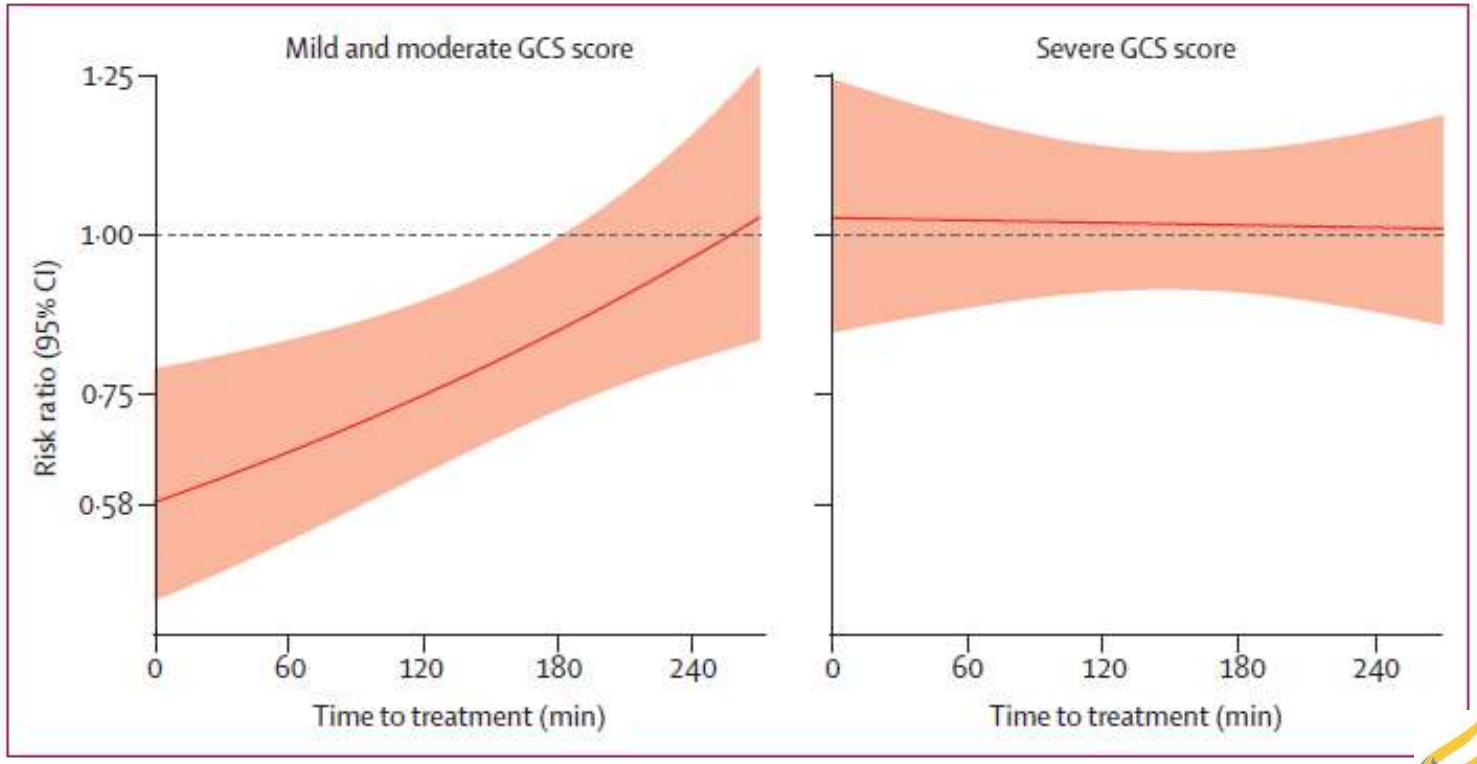
Survival Stratified by Severity



CRASH – 3 Trial Collaborators. *Lancet* 2019;394:1713 – 23.

OHSU TRAUMA Center

Stratification by Severity and Time



CRASH – 3 Trial Collaborators. *Lancet* 2019;394:1713 – 23.

OHSU TRAUMA Center

Research

JAMA | Original Investigation

Effect of Out-of-Hospital Tranexamic Acid vs Placebo on 6-Month Functional Neurologic Outcomes in Patients With Moderate or Severe Traumatic Brain Injury

Susan E. Rowell, MD, MBA; Eric N. Meier, MS; Barbara McKnight, PhD; Delores Kannas, RN, MS, MHA; Susanne May, PhD; Kellie Sheehan, RN; Eileen M. Bulger, MD; Ahamed H. Idris, MD; Jim Christenson, MD; Laurie J. Morrison, MD; Ralph J. Frascone, MD; Patrick L. Bosarge, MD; M. Riccardo Colella, DO, MPH; Jay Johannigman, MD; Bryan A. Cotton, MD; Jeannie Callum, MD; Jason McMullan, MD; David J. Dries, MD; Brian Tibbs, MD; Neal J. Richmond, MD; Myron L. Weisfeldt, MD; John M. Tallon, MD, MSc; John S. Garrett, MD; Martin D. Zielinski, MD; Tom P. Aufderheide, MD; Rajesh R. Gandhi, MD, PhD; Rob Schlamp; Bryce R. H. Robinson, MD; Jonathan Jui, MD, MPH; Lauren Klein, MD, MS; Sandro Rizoli, MD; Mark Gamber, DO; Michael Fleming, BA; Jun Hwang, MS; Laura E. Vincent, RN; Carolyn Williams, RN; Audrey Hendrickson, MPH; Robert Simonson, DO; Patricia Klotz, RN; George Sopko, MD; William Witham, MD; Michael Ferrara, MS; Martin A. Schreiber, MD

Rowell et al *JAMA* 2020;324:961 – 974.

OHSU TRAUMA Center

Subject Selection

Inclusion Criteria

- Blunt or penetrating TBI
- GCS = 3 - 12
- Prehospital SBP ≥ 90 mmHg
- Age ≥15 y/o, or ≥50 kg, if age unknown
- IV placed
- Planned transport to participating hospital

Exclusion Criteria

- GCS = 3 with no reactive pupil
- > 2 hours from time of injury or time unknown
- Any prehospital CPR
- Seizures, MI, stroke, dialysis
- Known or suspected prisoners
- Known/suspected pregnancy
- Drowning or hanging
- Burns >20% TBSA
- TXA or pro-coagulant drug
- Opt out

Rowell et al *JAMA* 2020;324:961 – 974.

OHSU TRAUMA Center

Drug Administration

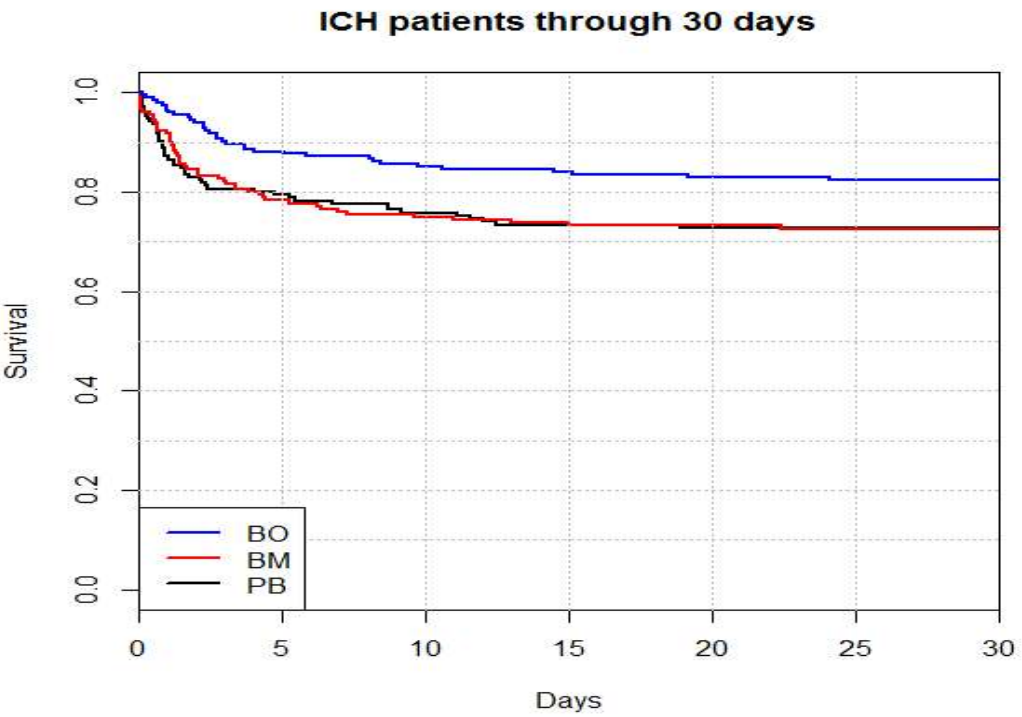
Table 1. Baseline Characteristics of Patients in a Study of the Effect of Tranexamic Acid vs Placebo on Neurologic Outcomes in Patients With Traumatic Brain Injury (continued)

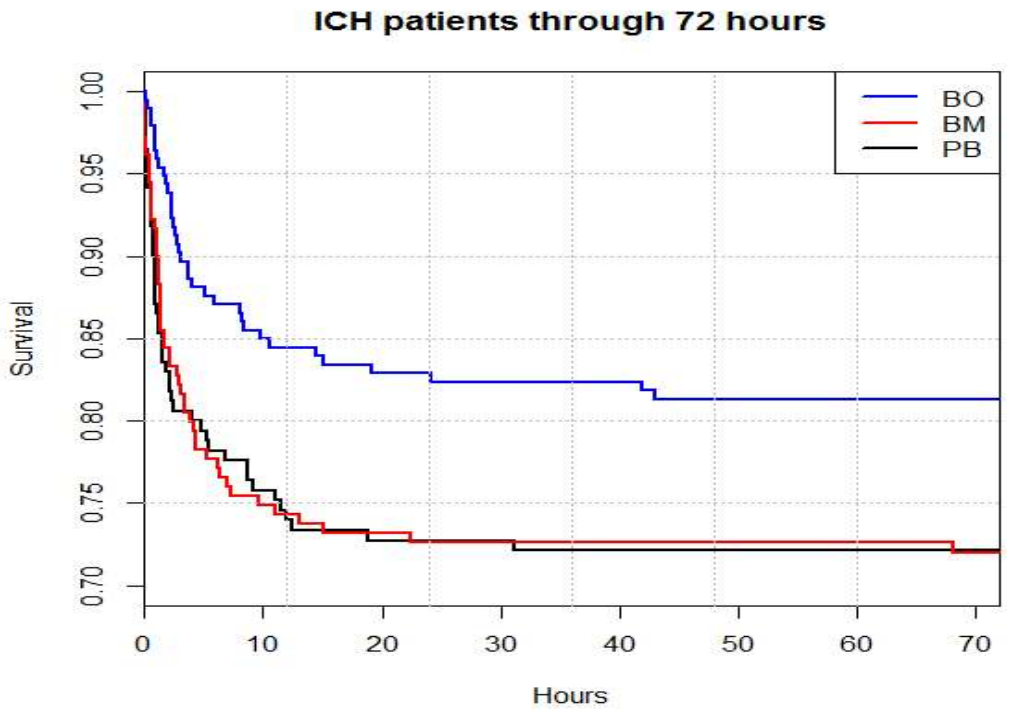
Characteristic	Bolus maintenance (n = 312)	Bolus only (n = 345)	Placebo (n = 309)
Out-of-hospital study drug infusion			
Time from injury to start of infusion, median (IQR), min[g]	43 (29-62)	40 (29-65)	41 (30-58)
Entire bolus infused, No. (%)	285 (93)	327 (95)	290 (94)
No infusion-related deviations, No. (%)[h]	297 (95)	334 (97)	304 (98)
In-hospital study drug infusion			
Started, No. (%)	254 (81)	297 (86)	244 (79)
Time to start of infusion, median (IQR), min[i]	88 (60-130)	94 (65-134)	86 (60-120)
Entire bag infused, No. (%)	229 (73)	266 (77)	214 (69)
No infusion-related deviations, No. (%)[h]	295 (95)	335 (97)	294 (95)

Rowell et al *JAMA* 2020;324:961 – 974.

OHSU TRAUMA Center

Survival





Rowell et al *JAMA* 2020;324:961 – 974.

Why Improved Outcomes? Potential Explanations

- Inhibition of lysis
- Decreased bleeding
- Prevention of endotheliopathy
- Decreased cerebral edema – plasmin mechanism
- Neuroprotection

OHSU TRAUMA Center

Adverse Events

Outcome	Treatment group, No. (%)[a]			Adjusted difference (95% CI)[b]		
	Bolus maintenance	Bolus only	Placebo	Bolus maintenance vs placebo	Bolus only vs placebo	Bolus only vs bolus maintenance
Progression of intracranial hemorrhage[d,e]	26 (17) (n = 154)	27 (15) (n = 178)	30 (20) (n = 148)	−4.2 (−13.0 to 4.6)	−6.3 (−14.4 to 1.7)	−2.2 (−9.9 to 5.6)
Adverse events[f]	(n = 312)	(n = 345)	(n = 309)			
Seizure/seizure-like activity[c]	5 (2)	17 (5)	7 (2)	−0.6 (−2.8 to 1.6)	2.8 (−0.1 to 5.6)	3.4 (0.7 to 6.1)
Any thromboembolic event[c]	13 (4)	31 (9)	30 (10)	−5.8 (−9.8 to −1.8)	−1.0 (−5.4 to 3.4)	4.8 (1.1 to 8.5)
Other adverse events[c,g]	77 (25)	79 (23)	76 (25)	−0.4 (−7.1 to 6.2)	−2.3 (−8.8 to 4.3)	−1.8 (−8.3 to 4.6)

Rowell et al *JAMA* 2020;324:961 – 974.

OHSU TRAUMA Center

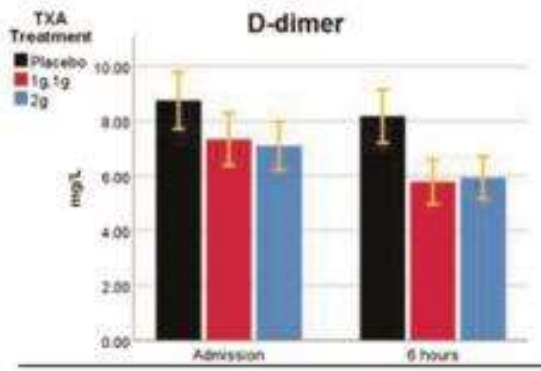
LY30 Breakdown

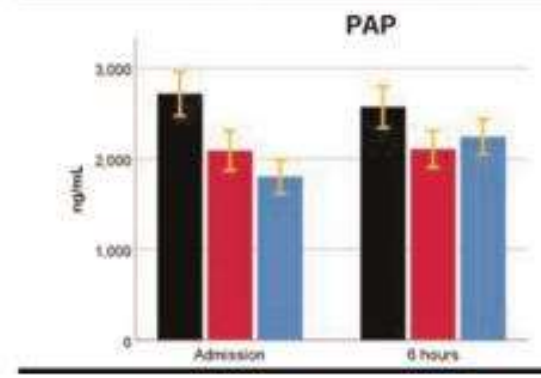
	PCB (n=309)		BM (n=312)		BO (n=345)	
	#	%	#	%	#	%
Had LY30 measure at admission	240	78%	246	79%	261	76%
<0.8% (fibrinolysis shutdown)	148	62%	157	64%	165	63%
0.8-3% (normal)	56	23%	61	25%	65	25%
>3%	36	15%	28	11%	31	12%

OHSU TRAUMA Center

ROC RESUSCITATION OUTCOMES CONSORTIUM

D – Dimers and PAPs





Factor	Time	Treatment	Mean (95% CI)	p
D-dimer	Admission	PB	8.8 (7.7-9.8)	
		BM	7.2 (6.3-8.2)	0.055
		BO	7.1 (6.2-8.0)	
	6 hours	PB	8.2 (7.2-9.2)	
		BM	5.7 (4.9-6.5)	*<0.001*
		BO	5.9 (5.1-6.7)	
PAP	Admission	PB	2733 (2489-2977)	
		BM	2101 (1881-2320)	*<0.001*
		BO	1800 (1612-1987)	
	6 hours	PB	2582 (2350-2814)	
		BM	2120 (1916-2323)	*0.02*
		BO	2240 (2044-2436)	

Dixon et al *JTACS* 2020;89:900 – 907.

OHSU TRAUMA Center

Endothelial Biomarkers

Median baseline marker levels in patients who received placebo versus TXA

Marker	Placebo		TXA		P
	n	Median [IQR]	*n*	Median [IQR]	
Syndecan-1	129	272.4 [219.7–373.1]	156	254.6 [200.9–324.0]	.05
ICAM-1	128	42 879.8 [31 552.3–66 088.9]	155	43 491.3 [32 198.0–58 107.6]	.45
VCAM-1	129	61 206.0 [47 652.8–90 083.6]	156	63 739.9 [49 402.7–87 275.7]	.36
Thrombomodulin	129	598.9 [514.1–760.5]	156	594.2 [505.4–714.6]	.14
Thrombospondin-2	129	2 055.7 [1 537.9–2 787.1]	156	1 975.9 [1456.0–2642.5]	.22
Angiopoietin-1	129	477.7 [303.9–876.2]	155	482.8 [289.1–695.3]	.23
Angiopoietin-2	129	144.2 [103.3–196.0]	156	150.4 [106.6–190.0]	.66

Marker	Early (<45 min)		Late (≥45 min)		P
	n	Median [IQR]	*n*	Median [IQR]	
Syndecan-1	77	234.4 [200.1–293.3]	79	270.1 [201.1–358.0]	.09
ICAM-1	76	40 492.4 [30 446.2–56 903.7]	79	46 502.6 [32 971.5–63 558.4]	.16
VCAM-1	77	63 801.8 [49 866.8–86 826.1]	79	63 678.0 [49 133.7–87 963.5]	.70
Thrombomodulin	77	583.5 [478.4–707.8]	79	605.7 [520.7–723.3]	.42
Thrombospondin-2	77	1 954.9 [1 363.0–2 820.8]	79	1 991.4 [1 516.9–2 596.0]	.46
Angiopoietin-1	77	371.5 [266.7–690.9]	78	532.6 [346.2–768.6]	.08
Angiopoietin-2	77	142.6 [94.0–171.8]	79	155.4 [111.3–211.3]	.05

Anderson et al *J Head Trauma Rehab* 2020;35:317 – 323.

OHSU TRAUMA Center

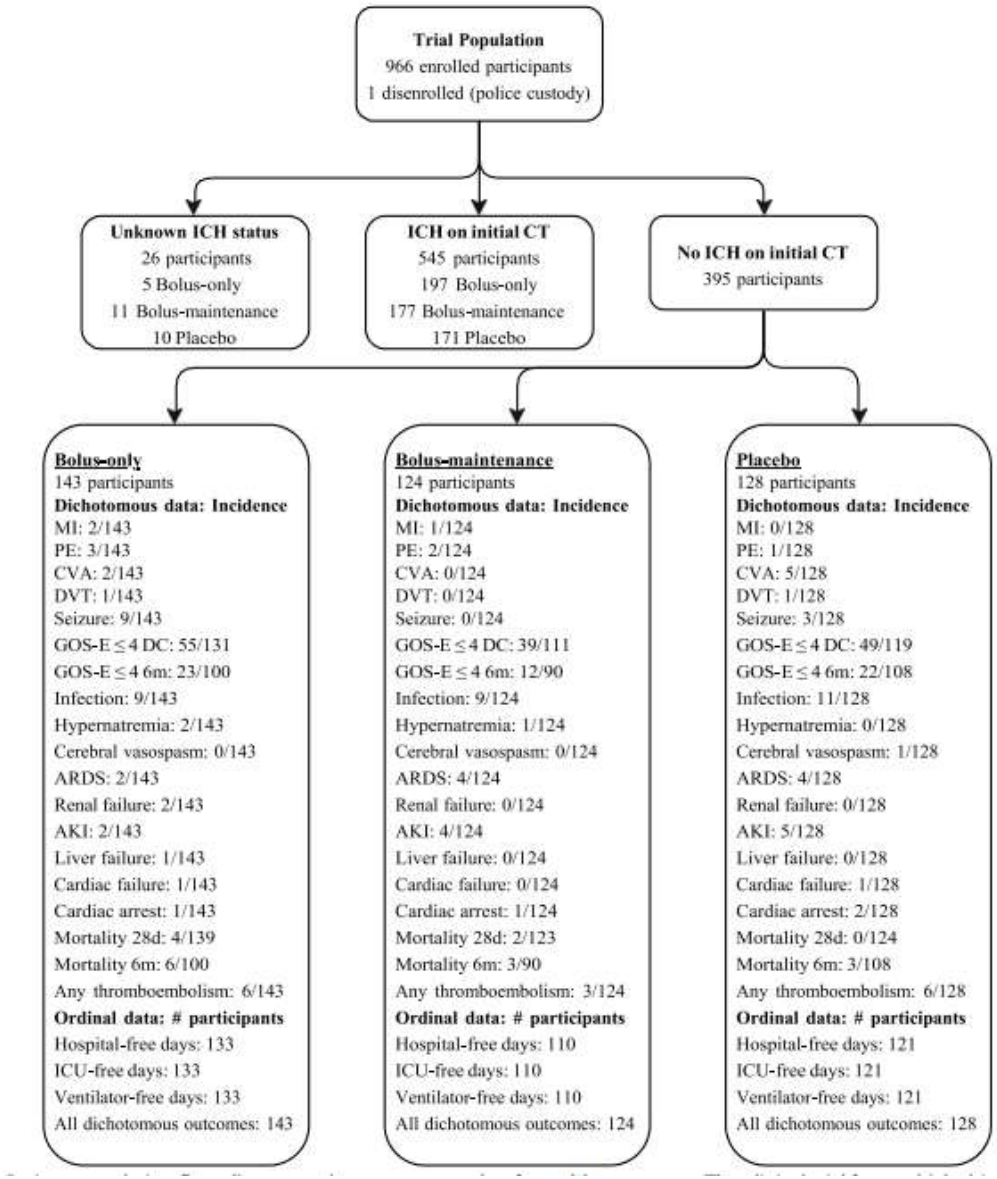
2022 EAST QUICK SHOT

Tranexamic acid is not inferior to placebo with respect to adverse events in suspected traumatic brain injury patients not in shock with a normal head computed tomography scan: A retrospective study of a randomized trial

Jordan W. Harmer, BS, Elizabeth N. Dewey, MS, Eric N. Meier, MS, Susan E. Rowell, MD, MCR, *and* **Martin A. Schreiber, MD, FACS, FCCM**, *Portland, Oregon*

Harmer et al. *JTACS* 2022;93:98 – 105.

OHSU TRAUMA *Center*



OHSU TRAUMA Center

The Effects of Timing of Prehospital Tranexamic Acid on Outcomes after Traumatic Brain Injury;

Sub Analysis of a Randomized Controlled Trial

Alex Brito

1/14/22

Brito AMP et al. *JTACS* 2022;Sep 23. PMID: 3613835.

Patient Demographics	Pooled Dosing		
	<45 min (n = 354)	≥45 min (n = 295)	p
Race (Percent)			**<0.001**
American Indian	2.2	0.4	
Asian	6.1	1.6	
Black/African American	24.7	10	
White	66.3	86.8	
Other	0.6	0.4	

Brito AMP et al. *JTACS* 2022;Sep 23. PMID: 3613835.

Presenting Characteristics	Pooled Dosing		
	<45 min	≥45 min	p
GCS by EMS	9+/-3	7+/-3	0.13
GCS on Presentation	9+/-3	7+/-3	**0.04**
Max Head Injury (AIS)	3+/-2	3+/-2	0.54
Injury Severity Score	17+/-14	17+/-13	0.48
Rotterdam Score	3+/-1	3+/-1	0.89

Brito AMP et al. *JTACS* 2022;Sep 23. PMID: 3613835.

Presenting Characteristics	Pooled Dosing		
	<45 min	≥45 min	p
Prehospital Advanced Airway	29.9 %	73.2 %	**<0.001**
Air Transport	7.1 %	70.5 %	**<0.001**
Advanced Airway Placed (Irrespective of location)	60.5 %	80.7 %	**<0.001**

Brito AMP et al. *JTACS* 2022;Sep 23. PMID: 3613835.

Sequelae	Pooled Dosing		
	<45 min	≥45 min	p
Seizures	4.5	1.7	**0.043**
Acute Kidney Injury	4.5	1.7	**0.043**
Renal Failure	0.6	0.7	0.855

Brito AMP et al. *JTACS* 2022;Sep 23. PMID: 3613835.

Sequelae	Pooled Dosing		
	<45 min	≥45 min	p
Thrombo-embolic Events	5.9	7.5	0.437
Pulmonary Embolism	1.4	1.4	0.951
Thrombotic Cerebrovascular Accident	2	3.1	0.38
Deep Vein Thrombosis	0.8	3.4	**0.021**
Cerebral Vasospasm	0	2	**0.007**

Brito AMP et al. *JTACS* 2022;Sep 23. PMID: 3613835.

Biomarker Predictability

TABLE 2B. *p* Values for Testing Additional Predictive Value of Biomarkers

Models Being Compared	ICH on Initial Scan	Mass Lesion: Marshall 5 + 6	Marshall > 1	ICH Progression	48-h Mortality	28-Day Mortality	6-Month GOS-E ≤ 4	6-Month DRS ≥ 7
PH vs. PH + UCH-L1	0.002	0.258	0.901	0.424	0.205	0.024	0.026	0.128
PH vs. PH + MAP-2	<0.001	0.006	0.1	0.11	0.033	0.001	0.002	0.001
PH vs. PH + GFAP	<0.001	0.001	0.066	0.009	<0.001	<0.001	<0.001	<0.001
PH vs. PH + all biomarkers	<0.001	0.003	0.135	0.078	<0.001	<0.001	<0.001	<0.001
PH + UCH-L1 vs. PH + all biomarkers	<0.001	0.002	0.063	0.045	<0.001	<0.001	<0.001	<0.001
PH + MAP-2 vs. PH + all biomarkers	<0.001	0.042	0.24	0.119	<0.001	<0.001	<0.001	<0.001
PH + GFAP vs. PH + all biomarkers	0.584	0.31	0.336	0.979	0.167	0.967	0.926	0.365

Anderson et al. *JTACS* 2020;89:80 – 86.

OHSU TRAUMA Center

Biomarkers

- GFAP, UCH - L1, MAP – 2 measured serially
- No effect of TXA on biomarker levels
- Biomarkers most closely associated with AIS head and age
- Associated with mortality

Hoefer et al, Submitted to EAST, unpublished


Tranexamic Acid
100 mg/mL