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Tranexamic Acid and Thrombosis Risk: The Last Talk that You Should Ever Hear about this Topic

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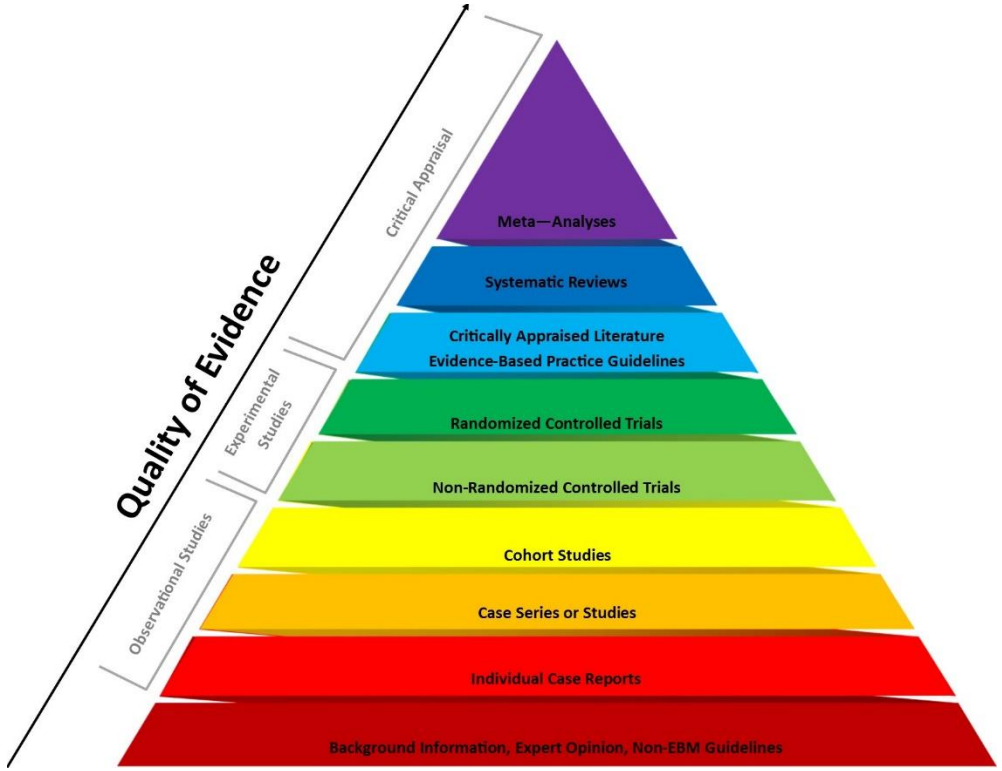
Disclosures

- Research funding: NIH, DoD
- Research funding: Haemonetics, Instrumentation Laboratory
- Honoraria, travel support, consulting: Janssen, CSL Behring, Haemonetics, Meredian
- Scientific advisory board, equity stake: Haima Therapeutics
- US Patents: DIELECTRIC SENSING TO CHARACTERIZE HEMOSTATIC DYSFUNCTION Serial Number: 16/837,704; NOVEL TLR4 INHIBITORS FOR THE TREATMENT OF HUMAN INFECTIOUS AND INFLAMMATORY DISORDERS Serial Number: 17/174,018

Disclosures

The Journal of Trauma and Acute Care Surgery

- I now regret publishing this paper 4 years ago…



AAST 2018 PODIUM PAPER

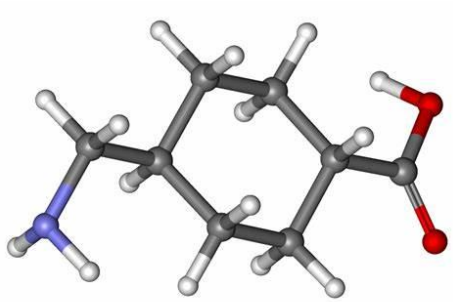
Tranexamic acid administration is associated with an increased risk of posttraumatic venous thromboembolism

Myers, Sara P. MD; Kutcher, Matthew E. MD; Rosengart, Matthew R. MD; Sperry, Jason L. MD; Peitzman, Andrew B. MD; Brown, Joshua B. MD; Neal, Matthew D. MD

Author Information

Journal of Trauma and Acute Care Surgery: January 2019 - Volume 86 - Issue 1 - p 20-27
doi: 10.1097/TA.0000000000002061

Objectives and overview



- Origins of the myth of TXA and thrombosis
- Randomized trials in non-traumatic hemorrhage
- Randomized trials in surgery
- Recent randomized trials in trauma

Does TXA increase risk of VTE?

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

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Does TXA increase risk of VTE? US Military Experience

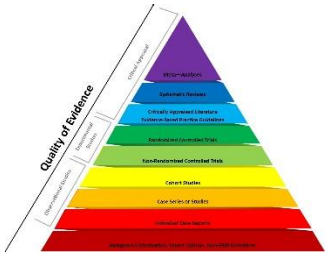


Table 1. Demographic and Clinical Data for Overall Cohort and Subgroups Based on Receipt of Tranexamic Acid (TXA)

Variable	Mean (SD) Overall (n =) TXA (n = 146)	Transfusion (n = 282) No TXA (n = 264)	*P* Value
VTE, No. (%)	50 (34.2)	13 (4.9)	.07

- VTE event rate = 15.6%
- TXA independent risk for VTE (OR 2.58)
- TXA group = higher ISS, transfusion requirement
- 12.4% TXA “overuse”
- “A reevaluation of the use of TXA in combat casualties should be undertaken”

Appropriate tranexamic acid

121 Patients received tranexamic acid <3 h after injury

47 Patients (38.8%) sustained a venous thromboembolism

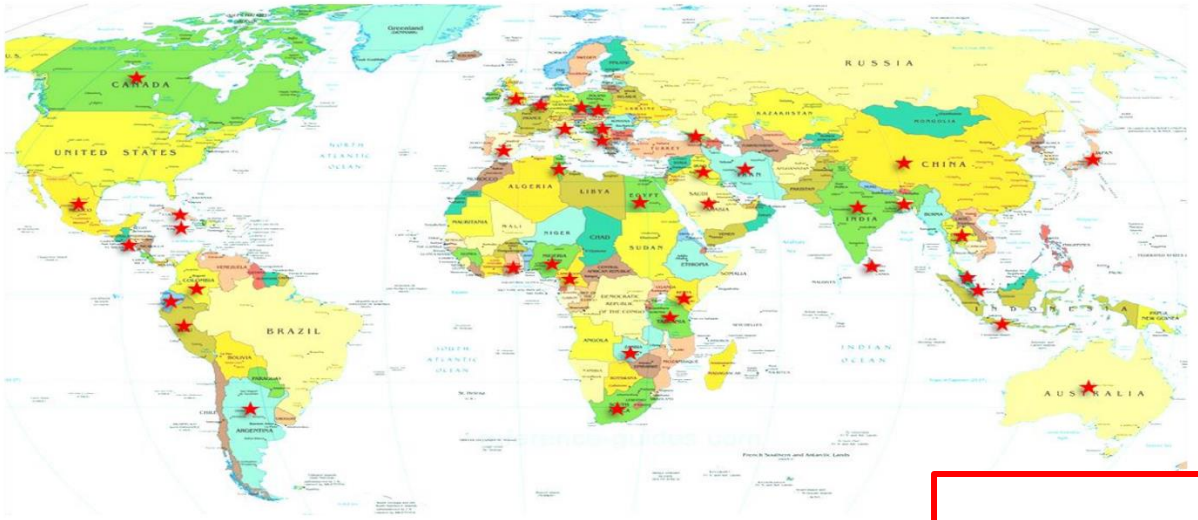
nexamic acid

not receive acid

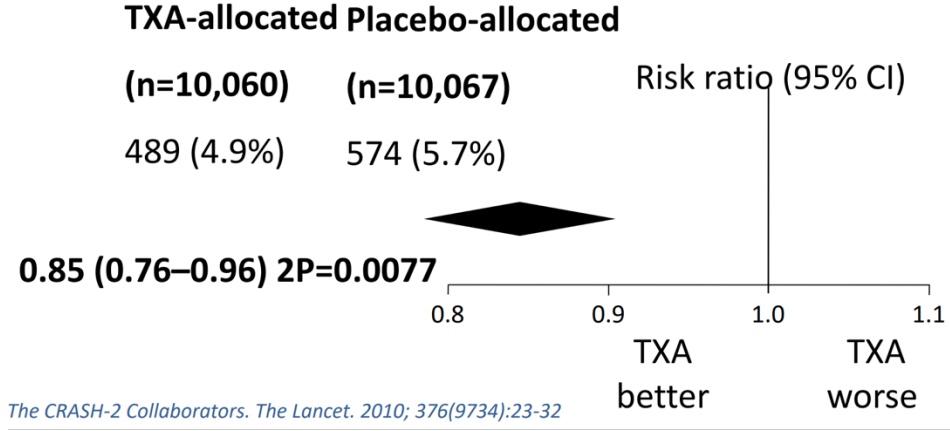
) sustained a oembolism

CRASH-2
Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage

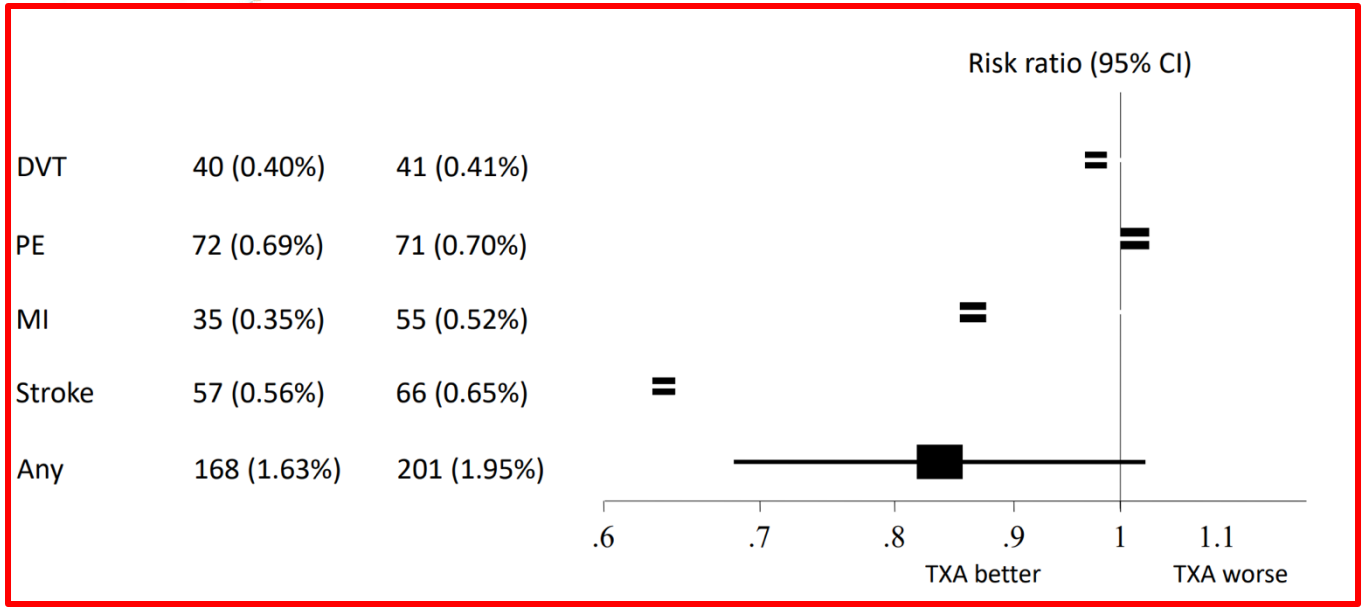
20,211 patients from 274 hospitals in 40 countries

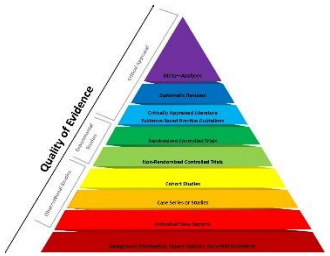


The CRASH-2 trial collaborators
Lancet. 2010 Jul 3;376(9734):23-32.

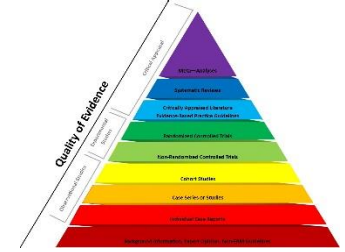


The CRASH-2 Collaborators. The Lancet. 2010; 376(9734):23-32





Slide courtesy of Bev Hunt



woman

World Maternal Antifibrinolytic Trial

A randomised, double blind, placebo controlled trial among 20,060 women with a clinical diagnosis of postpartum haemorrhage.

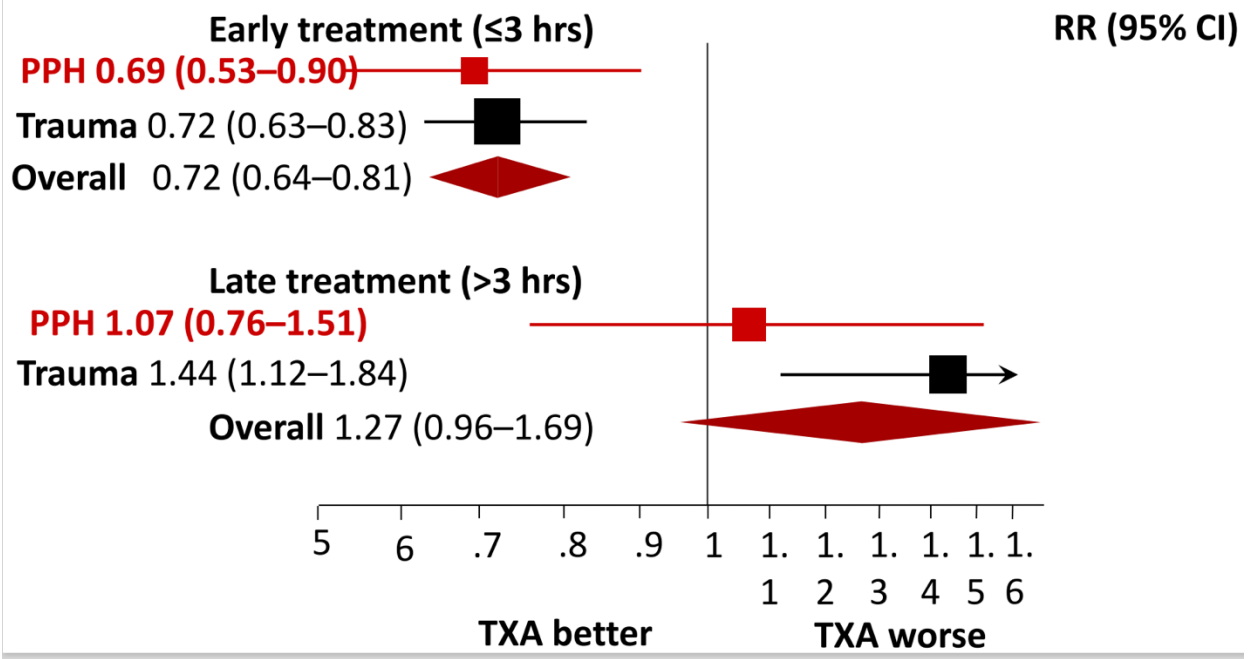
WOMAN Trial Collaborators

Thromboembolic events

	TXA (N=10033) n (%)	Placebo (N=9985) n (%)	Risk ratio (95% CI)	P-value
Any event	30 (0.3)	34 (0.3)	0.88 (0.54–1.43)	0.60
Venous events (DVT, PE)	20 (0.2)	25 (0.3)	0.80 (0.44–1.43)	0.45
Deep vein thrombosis	3 (0.03)	7 (0.1)	0.43 (0.11–1.65)	0.20
Pulmonary embolism	17 (0.2)	20 (0.2)	0.85 (0.44–1.61)	0.61
Arterial events (MI, stroke)	10 (0.1)	9 (0.1)	1.11 (0.45–2.72)	0.83
Myocardial infarction	2 (0.02)	3 (0.03)	0.66 (0.11–3.97)	0.65
Stroke	8 (0.1)	6 (0.1)	1.33 (0.46–3.82)	0.60

No increased thromboembolism

Death due to bleeding



Slide courtesy of Bev Hunt

TXA and Thrombosis Summary

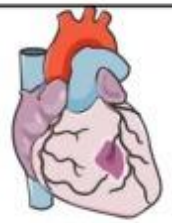
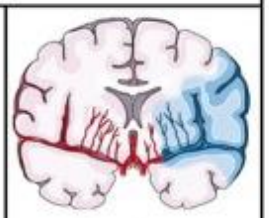
Controversy #1: TXA and Thrombosis

Given the anti-fibrinolytic effects of TXA, concern exists regarding increased risk of **thromboembolic events**

Non-surgical Patients

Risk of arterial and venous thrombosis in **non-surgical patients** receiving systemic TXA[61]:

- Systematic review of 22 RCTs (including CRASH-2 and WOMAN)

		 DVT	 PE	 MI	 Stroke
Number of trials (n)		8 (46630)	6 (43161)	3 (42470)	5 (42815)
Weighted event rates	**TXA**	0.28%	0.52%	0.27%	0.45%
	No TXA	0.29%	0.54%	0.30%	0.41%
RR (95% CI)		0.97 (0.69-1.37)	0.97 (0.75-1.26)	0.88 (0.43-1.84)	1.10 (0.68-1.78)

No increased risk of venous or arterial thrombosis in non-surgical patients receiving systemic TXA

Patients with a known history of thrombosis were excluded from these studies. In the WOMAN trial, patients with a known thrombotic event during pregnancy were excluded

ILLUSTRATED REVIEW

rpth research & practice in thrombosis & haemostasis

Tranexamic acid evidence and controversies: An illustrated review

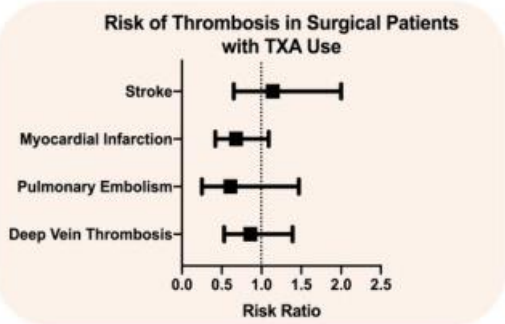
Nicole Relke MD[1] | Nicholas L. J. Chornenki MD[1] |
Michelle Sholzberg MDCM, MSc, FRCPC[2,3,4]

Surgical Patients

Studies of **surgical patients** have also not shown a significant increase in thrombotic events for any surgery type while reducing blood loss[62,63,64]

Did you know?

There was no dose response relationship for reducing surgical blood loss with TXA doses above 1g IV[64]



In the absence of patient specific factors (e.g. history of thrombosis or cirrhosis) **evidence suggests there is no reason to avoid TXA in medical or surgical patients for fear of thrombosis**

Rates of VTE 0.8% (TXA) vs 0.4% (no TXA) (RR 1.85 CI 1.15-2.98)

HALT-IT [55]

ELIGIBILITY Adult with significant **upper or lower gastrointestinal (GI) bleed**

Including: patients with cirrho

METHODS

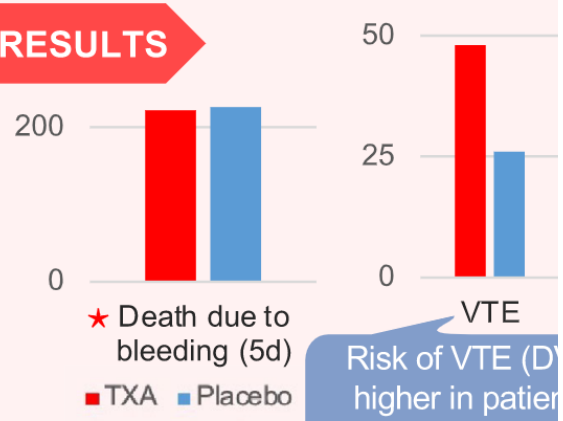
n=12009

TXA n=5994

Pla n=

TXA 1g IV over 10 min the
TXA 3g IV over 24h

RESULTS



Risk of VTE (D higher in patie variceal bleedin disease (*p*=0

CONCLUSION

TXA **did not reduce death** from GI bleeding

- Risk of **VTE** and **seizure** higher in the TXA group

Factors Potentially Increasing ALT-IT Trial[56]

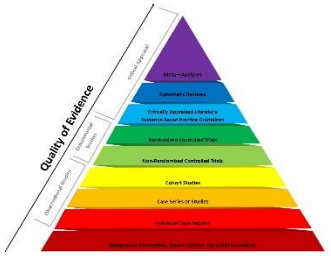
ge (58 yrs vs. 35 yrs
ASH-2 trial)
ies (7% malignancy)

disease (40%):
is in cirrhosis[57] may
ciated with ↑VTE[58]

gher dose
xplain increased risk of
seizure)

Relke, et al. RPTH 2021

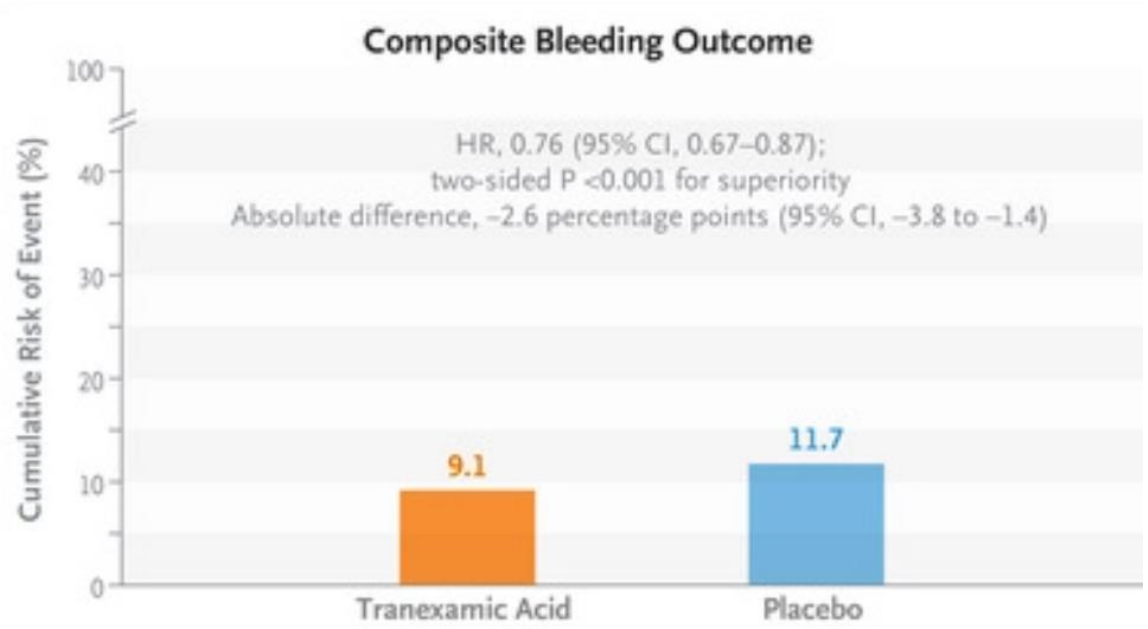
The NEW ENGLAND JOURNAL of MEDICINE

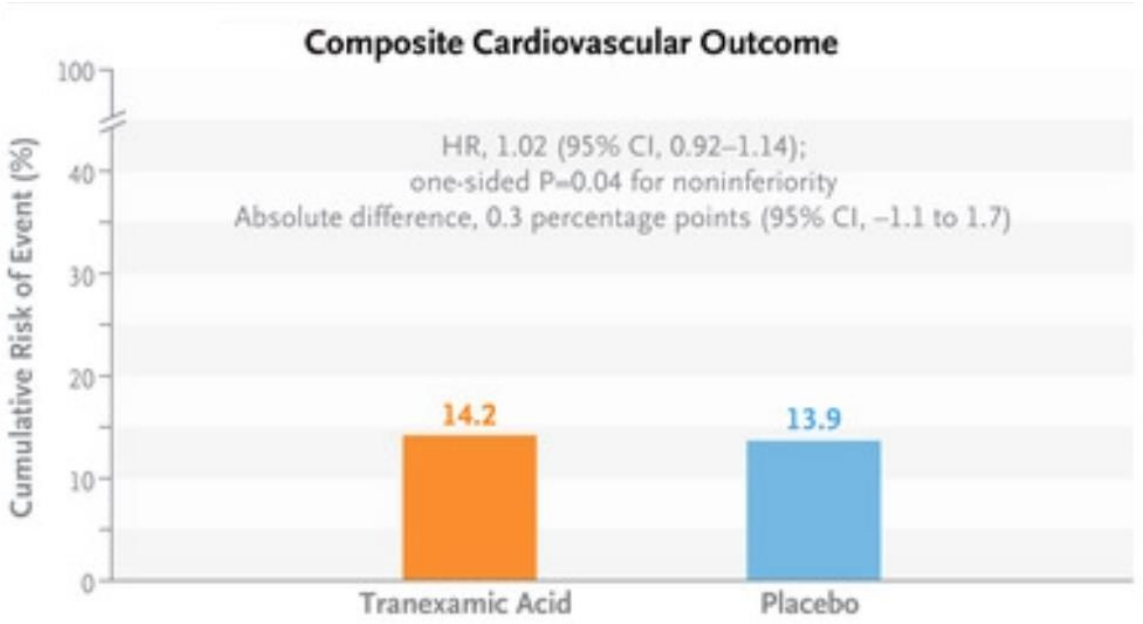


ORIGINAL ARTICLE

Tranexamic Acid in Patients Undergoing Noncardiac Surgery

P.J. Devereaux, M.D., Ph.D., Maura Marcucci, M.D., Thomas W. Painter, M.B., Ch.B., David Conen, M.D., M.P.H., Vladimir Lomivorotov, M.D., Daniel I. Sessler, M.D., Matthew T.V. Chan, M.B., B.S., Ph.D., Flavia K. Borges, M.D., Ph.D., María J. Martínez-Zapata, M.D., Ph.D., Chew Yin Wang, M.B., Ch.B., Denis Xavier, M.D., Sandra N. Ofori, F.W.A.C.P., et al., for the POISE-3 Investigators*





JAMA Surgery

Original Investigation

ONLINE ONLY FREE

April 14, 2021

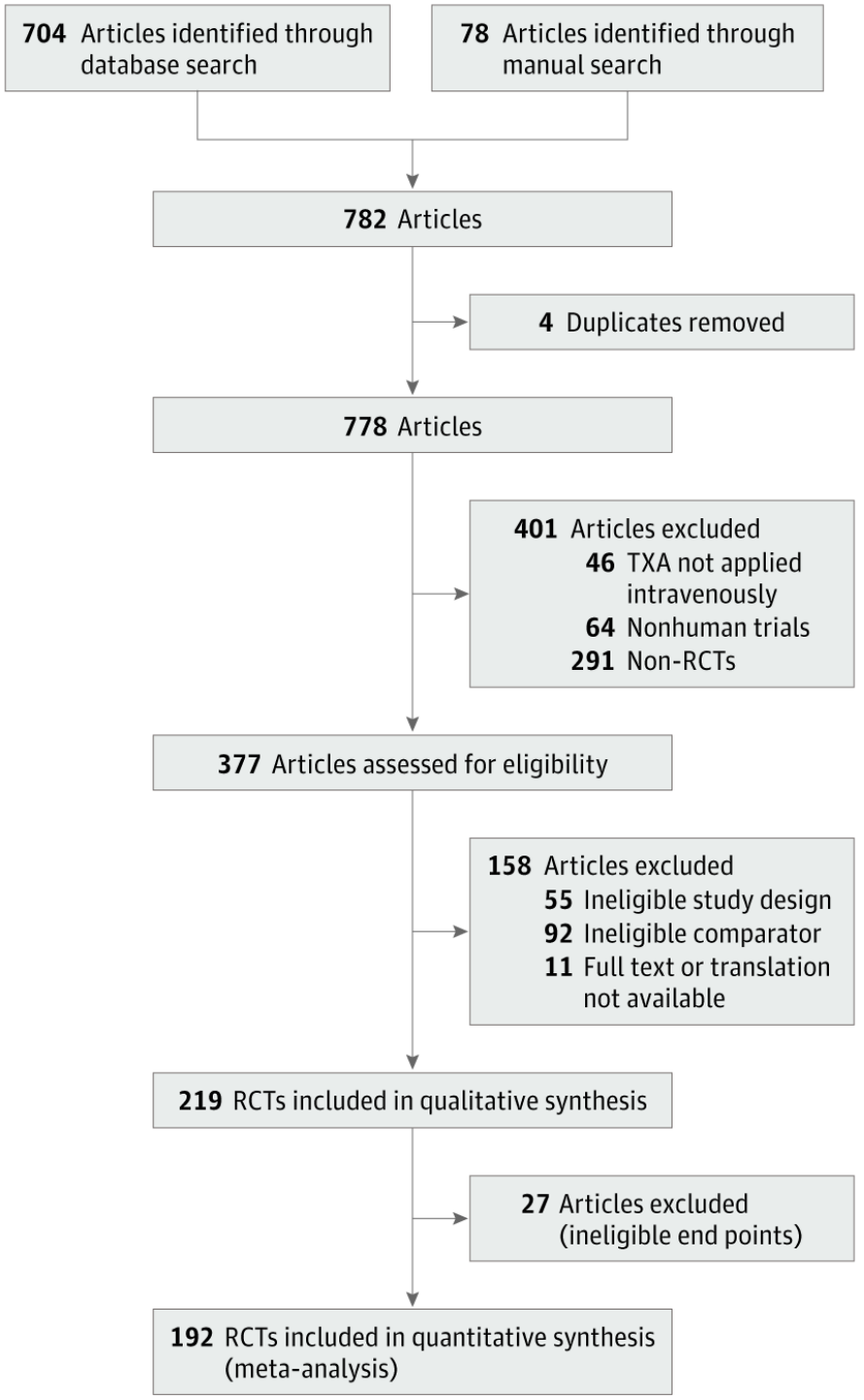
Association of Intravenous Tranexamic Acid With Thromboembolic Events and Mortality

A Systematic Review, Meta-analysis, and Meta-regression

Isabel Taeuber[1]; Stephanie Weibel, PhD[2]; Eva Herrmann, PhD[3]; Vanessa Neef, MD[1]; Tobias Schlesinger, MD[2]; Peter Kranke, MD[2]; Leila Messroghli, MD[1]; Kai Zacharowski, MD, PhD[1]; Suma Choorapoikayil, PhD[1]; Patrick Meybohm, MD[1,2]

» Author Affiliations | Article Information

JAMA Surg. 2021;156(6):e210884. doi:10.1001/jamasurg.2021.0884



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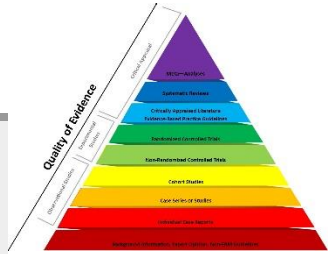


From: **Association of Intravenous Tranexamic Acid With Thromboembolic Events and Mortality: A Systematic Review, Meta-analysis, and Meta-regression**

JAMA Surg. 2021;156(6):e210884. doi:10.1001/jamasurg.2021.0884

Table 1. TXA and Total Thromboembolic Events

		TXA		Control					
Medical discipline	No. of included studies	Events	No. of included patients	Events	No. of included patients	Model	Risk difference (95% CI)	*P* value	I^2, %
Cardiothoracic	16	72	3171	74	3009	Fixed effect	−0.001 (−0.009 to 0.007)	.83	0
						Random effects	−0.001 (−0.007 to 0.008)	.91	
Neurological	12	282	2007	230	2000	Fixed effect	0.026 (0.007 to 0.045)	.01	57
						Random effects	0.018 (−0.013 to 0.048)	.26	
Gynecological	26	35	12 356	41	12 286	Fixed effect	−0.001 (−0.002 to 0.001)	.53	0
						Random effects	−0.001 (−0.002 to 0.001)	.50	
Orthopedic	101	172	4787	113	4149	Fixed effect	0.001 (−0.007 to 0.009)	.79	0
						Random effects	0.001 (−0.004 to 0.007)	.64	
Major trauma	1	204	10 060	233	10 067	Fixed effect	−0.003 (−0.007 to 0.001)	.16	NA
						Random effects	−0.003 (−0.007 to 0.001)	.16	
Maxillofacial	6	0	265	0	192	Fixed effect	0.000 (−0.023 to 0.023)	>.99	0
						Random effects	0.000 (−0.019 to 0.019)	>.99	
Pediatric	2	0	42	0	40	Fixed effect	0.000 (−0.067 to 0.067)	>.99	0
						Random effects	0.000 (−0.064 to 0.064)	>.99	
Other	12	14	799	15	670	Fixed effect	−0.004 (−0.021 to 0.013)	.62	0
						Random effects	−0.004 (−0.018 to 0.011)	.63	
Total	176	779	33 487	706	32 413	Fixed effect	0.001 (−0.002 to 0.003)	.66	0
						Random effects	−0.001 (−0.002 to 0.001)	.39	

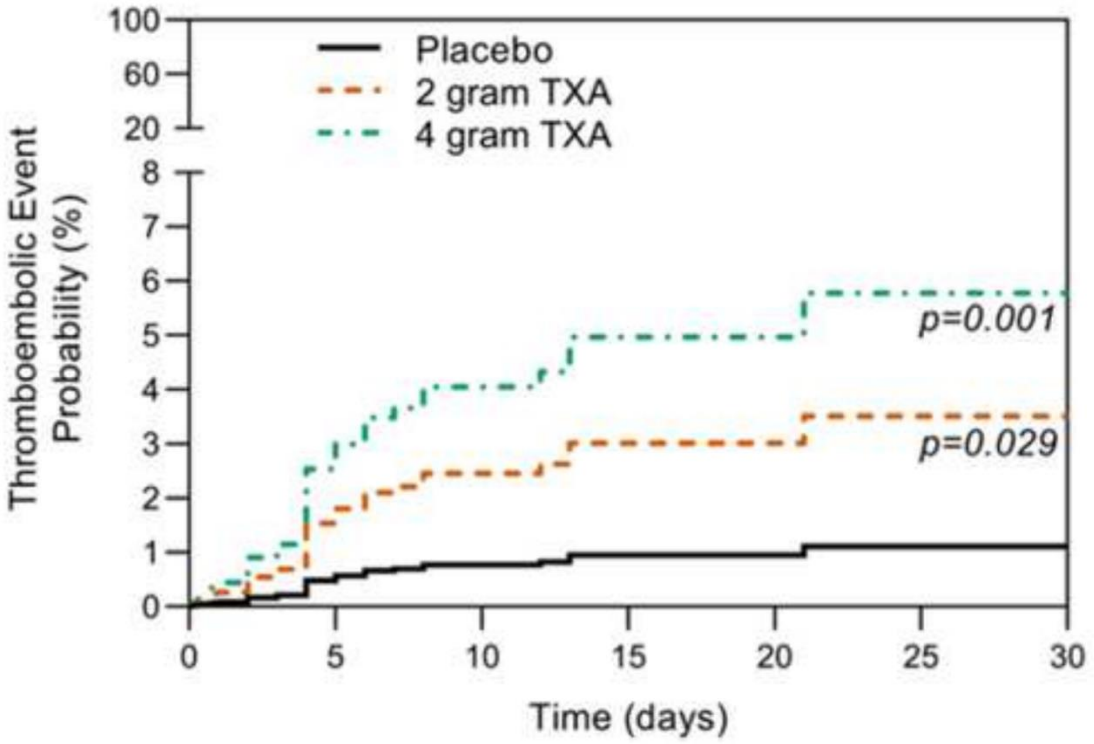
Abbreviations: NA, not applicable; TXA, tranexamic acid.

TAMPITI secondary analysis

The Immunologic Effect of Early Intravenous Two and Four Gram Bolus Dosing of Tranexamic Acid Compared to Placebo in Patients With Severe Traumatic Bleeding (TAMPITI): A Randomized, Double-Blind, Placebo-Controlled, Single-Center Trial

Philip C. Spinella, Kimberly A. Thomas, [...], and for the TAMPITI Investigators

- Placebo N=50, 2gm TXA N=49, 4gm TXA N=50



Spinella, et al, *Transfusion*, in press

Limitations:

- Small (6, 13, 16 patients w/ TE)
- Multiple events in the same patients
- Included “abdominal” TE (not usually quantified)
- ***Screening***
- TE patients: older, sicker, different injuries, required more blood
- Model did not control for all TE risk variables but did include IL-8 (?!?!)

JAMA Surgery | Original Investigation

Tranexamic Acid During Prehospital Transport in Patients at Risk for Hemorrhage After Injury

A Double-blind, Placebo-Controlled, Randomized Clinical Trial

Francis X. Guyette, MD, MPH; Joshua B. Brown, MD, MSc; Mazen S. Zenati, MD, PhD; Barbara J. Early-Young, BSN; Peter W. Adams, BS; Brian J. Eastridge, MD; Raminder Nirula, MD, MPH; Gary A. Vercruysse, MD; Terence O'Keeffe, MD; Bellal Joseph, MD; Louis H. Alarcon, MD; Clifton W. Callaway, MD, PhD; Brian S. Zuckerbraun, MD; Matthew D. Neal, MD; Raquel M. Forsythe, MD; Matthew R. Rosengart, MD, MPH; Timothy R. Billiar, MD; Donald M. Yealy, MD; Andrew B. Peitzman, MD; Jason L. Sperry, MD, MPH; and the STAAMP Study Group

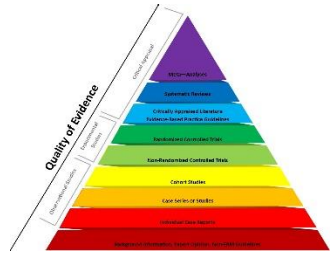
Figure 3. Prespecified Tranexamic Acid Dose Response Analysis, Time to Intervention, and Shock Severity Post Hoc Subgroup Analysis for 30-Day Mortality

A Mortality risk by tranexamic acid prespecified dosing regimens

Tranexamic acid dose	No./total No. (%) of patients	Risk ratio (95% CI)	P value
Placebo (reference)	45/452 (10.0)		
Abbreviated	14/150 (9.3)	0.94 (0.65-1.36)	.74
Standard	11/141 (7.8)	0.78 (0.50-1.24)	.30
Repeat	11/151 (7.3)	0.73 (0.54-0.99)	.04

			5.2)		
Multiple organ failure	33 (7.4)	39 (8.6)	1.2 (−2.4 to 4.7)	.52	.94
Acute respiratory distress syndrome	42 (9.4)	39 (8.6)	−0.8 (−4.6 to 2.9)	.66	.97
Nosocomial infection	88 (19.7)	66 (14.5)	−5.2 (−10.1 to −0.3)	.04	.75
Seizure in first 24 h	5 (1.1)	7 (1.5)	0.4 (−1.0 to 1.9)	.58	.94
Pulmonary embolism	13 (2.9)	7 (1.5)	−1.3 (−3.3 to 0.5)	.16	.78
Deep vein thrombosis	12 (2.7)	7 (1.5)	−1.2 (−3.3 to 0.5)	.23	.83

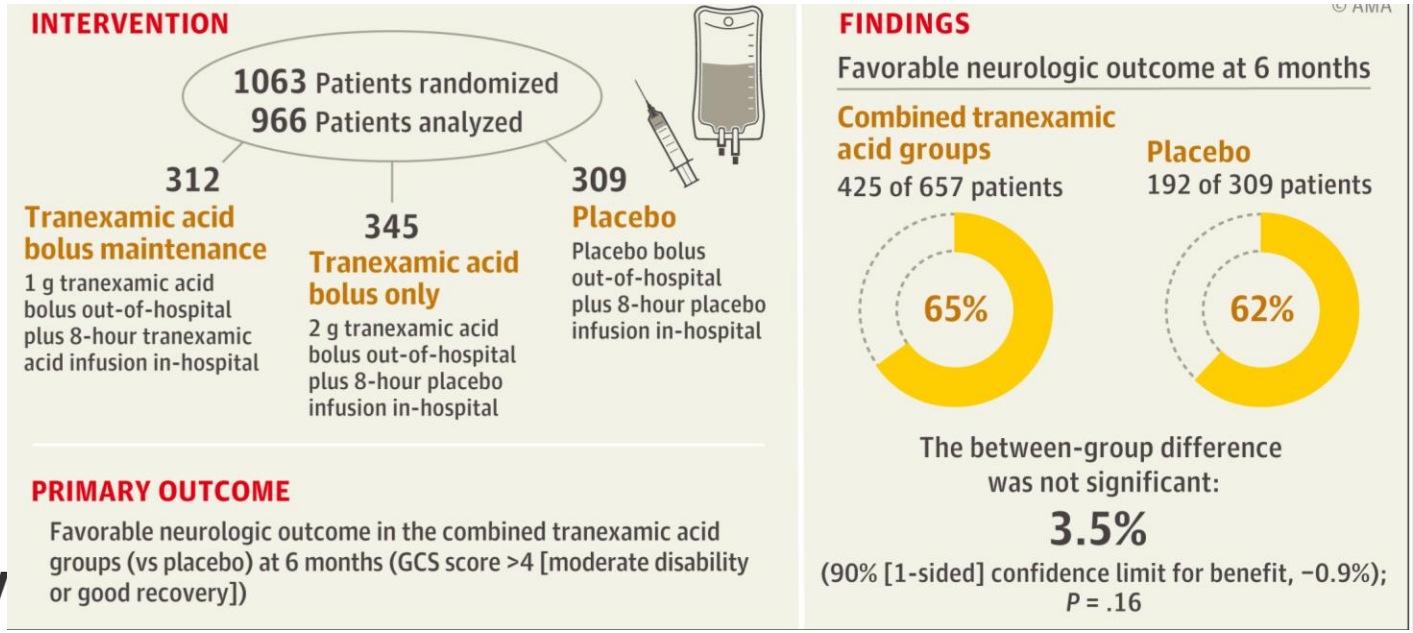
≤1	18/238 (7.6)	10/219 (4.6)	0.60 (0.44-0.83)	.002
>1	27/214 (12.6)	26/223 (11.7)	0.92 (0.52-1.64)	.79
Shock severity				
Tachycardia only	21/320 (6.6)	18/316 (5.7)	0.87 (0.56-1.34)	.52
SBP <90 mm Hg	13/101 (12.9)	13/99 (13.1)	1.02 (0.55-1.90)	.95
SBP <70 mm Hg	11/31 (35.5)	5/27 (18.5)	0.52 (0.34-0.80)	.003



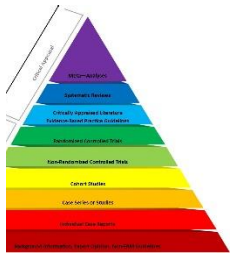
JAMA®
The Journal of the American Medical Association

September 8, 2020

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



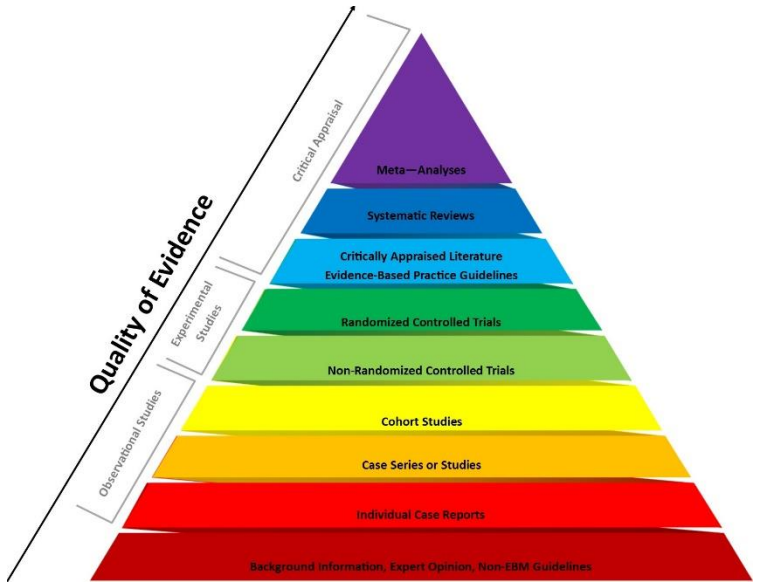
Adverse events, No. (%)[h]	Bolus maintenance	Bolus (2gm)	Placebo
Seizure or seizure-like activity	5 (2)	17 (5)	7 (2)
Any thromboembolic event	13 (4)	31 (9)	30 (10)
Myocardial infarction	3 (1)	2 (1)	1 (<1)
Pulmonary embolism	3 (1)	6 (2)	5 (2)
Thrombotic stroke	3 (1)	13 (4)	10 (3)
Deep vein thrombosis	3 (1)	10 (3)	9 (3)
Other thromboembolic event[i]	1 (<1)	13 (4)	9 (3)
Hospital-free days, mean (SD)[j]	13.6 (10.7)	14.1 (10.4)	13.6 (10.7)
Intensive care unit-free days, mean (SD)[k]	18.1 (10.8)	19.1 (9.7)	18.5 (10.6)
Ventilator-free days, mean (SD)[l]	19.9 (10.8)	20.9 (9.7)	20.2 (10.5)
Mortality	53 (19) (n = 285)	40 (13) (n = 318)	50 (18) (n = 285)



Rowell, et al, JAMA, 2020

Summary

- **There is NO risk of thrombosis**
- **Stop talking about it**



TXA.
i PUT
THAT
SHiT
ON EVERYTHiNG

Questions?

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Neal lab funding

- R35GM119526-07 NIGMS
- R01HL141080-01A1 NHLBI
- OTA # 1OT2HL156812-01 NHLBI
- DM160354 Department of Defense JPC-6 Combat Casualty Care Research Program
- Department of Defense CDMRP JPC-6 Combat Casualty Care Research Program
- Department of Defense W81XWH21107810

NIH National Institute of General Medical Sciences

NIH National Heart, Lung, and Blood Institute

Matthew D. Neal, MD
Co-Director

Phil Spinella, MD
Co-Director

Jason Sperry, MD
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ANESTHESIOLOGY

Temporal Transitions in Fibrinolysis after Trauma: Adverse Outcome Is Principally Related to Late Hypofibrinolysis

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ANESTHESIOLOGY 2022; 136:148–61