Supplementary Online Content

Karl V, Thorn S, Mathes T, Hess S, Maegele M. Association of tranexamic acid administration with mortality and thromboembolic events in patients with traumatic injury: a systematic review and meta-analysis. *JAMA Netw Open*. 2022;5(3):e220625. doi:10.1001/jamanetworkopen.2022.0625

**eMethods.** Search Strategy, Selection Process and Data Items Extracted

**eResults.** Study Selection, Study Characteristics, Outcomes, and Results of Subgroup Analyses

**eFigure 1.** PRISMA Flow Diagram

**eTable 1.** List of Excluded Studies With Reasons

**eTable 2.** Data Extraction Sheet

**eTable 3.** Extracted Data of Blood Transfusions

**eFigure 2.** 24-Hour Mortality

**eFigure 3.** 24-Hour Mortality in Observational Studies Excluding Studies at High Risk for Confounding Bias

**eFigure 4.** 1-Month Mortality in RCTs

**eFigure 5.** 1-Month Mortality in Observational Studies Excluding Studies at High Risk for Confounding Bias

**eFigure 6.** 1-Month Mortality in Multiple Trauma

**eFigure 7.** 1-Month Mortality in TBI

**eFigure 8.** 1-Month Mortality in Standard Protocol Tranexamic Acid Administration

**eFigure 9.** 1-Month Mortality in Nonstandard Protocol Tranexamic Acid Administration

**eFigure 10.** Overall Mortality

**eFigure 11.** Overall Mortality in RCTs

**eFigure 12.** Overall Mortality in Observational Studies Excluding Studies at High Risk for Confounding Bias

**eFigure 13.** Overall Mortality in Multiple Trauma

**eFigure 14.** Overall Mortality in TBI

**eFigure 15.** Overall Mortality in In-hospital Tranexamic Acid Administration

**eFigure 16.** Overall Mortality in Prehospital Tranexamic Acid Administration

**eFigure 17.** Overall Mortality in Standard Protocol Tranexamic Acid Administration

**eFigure 18.** Overall Mortality in Nonstandard Tranexamic Acid Administration

**eFigure 19.** Thromboembolic Events

**eFigure 20.** Thromboembolic Events in RCTs

**eFigure 21.** Thromboembolic Events in Observational Studies Excluding Studies at High Risk for Confounding Bias

**eFigure 22.** Thromboembolic Events in Multiple Trauma

**eFigure 23.** Thromboembolic Events in TBI

**eFigure 24.** Thromboembolic Events in In-hospital Tranexamic Acid Administration

**eFigure 25.** Thromboembolic Events in Prehospital Tranexamic Acid Administration

© 2022 Karl V et al. *JAMA Network Open.*
**eFigure 26.** Thromboembolic Events in Standard Protocol Tranexamic Acid Administration

**eFigure 27.** Thromboembolic Events in Nonstandard Protocol Tranexamic Acid Administration

**eFigure 28.** Funnel Plot for 1-Month Mortality

**eFigure 29.** Funnel Plot for Thromboembolic Events

**eReferences**

This supplementary material has been provided by the authors to give readers additional information about their work.
**eMethods. Search Strategy, Selection Process and Data Items Extracted**

**Search strategy**

The search strategy was prepared by an experienced information specialist in collaboration with clinical experts. The search was limited to English and German language. We searched for studies published from 1986 (when TXA was approved for medical use) onwards. We excluded in vitro studies and animal experiments. The search strategy was based on the Peer Review of Electronic Search Strategies checklist (PRESS) and validated by checking if pre-defined studies that are clearly eligible would have been identified. The detailed search strategy is shown below.

*Medline via Ovid (Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily And Version(R))*

1 *Cranio cerebral Trauma/ or *brain injuries/ or exp brain injuries, traumatic/ or exp head injuries, closed/ or exp head injuries, penetrating/ or exp skull fractures/ 94218

2 (cranio cerebral trauma* or skull fracture* or traumatic brain injur* or tbi or ((head or brain) adj (injur* or trauma*))).ti,ab,kf. 105128

3 exp "Wounds and Injuries"/ 744665

4 (injur* or trauma*).ti,ab,kf 1081710

5 1 or 2 or 3 or 4 1486642

6 exp Tranexamic Acid/ 3675

7 (tranexamic acid or txa).ti,ab,kf. 5579

8 6 or 7 6351

9 5 and 8 1073

10 (english or german).lg. 27969887

11 9 and 10 1018

12 exp animals/ not humans.sh. 4760027

13 11 not 12 885

14 (comment or editorial or letter).pt. 1905379

15 13 not 14 810

16 limit 15 to yr=1986-2021 791

*Embase via Embase*

#1 'head injury'/exp OR 'brain injury'/mj OR 'traumatic brain injury'/mj OR 'skull fracture'/exp 319,284

#2 ("cranio cerebral trauma*" OR "skull fracture*" OR "traumatic brain injur*" OR tbi OR ((head OR brain) NEAR/1 (injur* OR trauma*))):ti,ab,kw 151,460

#3 'injury'/exp 2,401,780

#4 (injur* OR trauma*):ti,ab,kw 1,406,552

#5 tranexamic acid'/exp OR ("tranexamic acid" OR txa):ti,ab,kw 18,874

#6 (english OR german):la 33,439,122

#7 (animals'/exp NOT 'humans'/de) 5,680,425

#8 (comment OR editorial OR letter):it 1,800,517

© 2022 Karl V et al. JAMA Network Open.
Selection process

Titles and abstracts of records identified by the electronic literature search were screened first. Next, full text articles were retrieved and screened for eligibility criteria. Disagreements were solved through discussion between the two reviewers or after consultation with a third or fourth reviewer until consensus. Multiple reports of the same study were merged so that each study is the unit of analyses.

Data items extracted
We extracted data of the latest available follow-up time for the outcomes overall mortality and thromboembolic events. As there are some studies which conducted a subgroup analysis within their trials, there are cases in which we extracted different data from the same study according to the subgroup. Missing data were marked as such and evaluated in the bias assessment and discussion, respectively. Extracted data items were extracted as follows.

1. bibliometric information:
   1.1. name of all author
   1.2. name of the Journal
   1.2. year of publication
2. trial-specific information:
   2.1. number and geographic regions of recruiting centers
   2.2. NCT number, i.e., unique identification code given to each clinical study record registered on ClinicalTrials.gov
   2.3. enrollment start and end dates
   2.4. length of participant follow-up
3. participant-specific information:
   3.1. number of randomized participants
   3.2. detailed inclusion and exclusion criteria
   3.3. baseline characteristics of participants such as age and gender
   3.4. relevant clinical characteristics such as vital signs and ISS
   3.5. Patient ratios of blunt vs. penetrating and TBI vs. multiple trauma
4. intervention(s) and comparison intervention(s)
   4.1. medication
   4.2. doses
   4.3. frequency
5. outcomes:
   5.1. mortality at 24 hours, 28 and 30 days, respectively as well as overall mortality
   5.2. thromboembolic events
   5.3. length of follow-up (if necessary for each outcome separately)
6. subgroup allocation
   6.1. multiple trauma including TBI vs predominantly TBI
   6.2. severely vs. non-severely injured
   6.3. blunt vs. penetrating trauma
   6.4. inhospital vs. prehospital TXA administration
   6.5. administration of TXA within 3 hours of onjury vs. beyond 3 hours of injury
eResults. Study Selection, Study Characteristics, Outcomes, and Results of Subgroup Analyses

Study selection

Our systematic literature search identified 1546 records. Two additional studies were detected through manual reference screening of related articles. After removal of duplicates, 1317 abstracts were screened for inclusion and exclusion criteria. 71 publications were included for full text screening, at which stage 40 studies were excluded (eTable 1). We included 31 studies in the systematic review.

Study Characteristics

Seven studies included trauma patients presenting predominantly with traumatic brain injury while 24 studies included multiple trauma patients. Five studies included trauma patients receiving prehospital TXA and 6 studies described that TXA was first administered in-hospital. The studies were conducted in the United States, United Kingdom, Canada, Germany, France, China, Japan, Tunisia, Thailand, Qatar and worldwide.

Outcomes

During study selection it became apparent that some studies did not report the time at which mortality was measured (follow-up time), whereas others reported follow-up times that differed from the above. In order to avoid excluding many studies due to incorrect follow-up times, we suggested overall mortality in addition. This outcome encompassed mortality of all aforementioned time points plus mortality for which no time frame was given.

It was not possible to conduct a meta-analysis for the amount of blood products given. A lot of data on blood product transfusion were reported as median instead of mean. Moreover, due to major clinical differences between the studies regarding trauma severity, data varied largely and led to significant heterogeneity. Thus, we had to discard the outcome amount of blood products given. Detailed data of blood products given can be seen in the Supplement XIII.

Results of subgroup analyses

After extracting data it was impossible to conduct meta analyses of some subgroups. First, most of the studies included patients that were severely injured, therefore we did not have sufficient data for the non-severely injured cohort to compare. Second, we are missing studies that compare blunt vs. penetrating trauma and TXA administration within 3 hours vs. beyond 3 hours, respectively. Finally, we conducted meta-analyses of the subgroups multiple trauma vs. TBI and in-hospital vs. prehospital TXA administration. For the latter, data availability limited our analysis to the outcomes overall mortality and thromboembolic events.

After recognising that most of our results were statistically heterogenous, we hypothesized that different TXA dosage regimens between trials would be a reason. Some included studies did not define a dosage regimen prior to study initiation while others applied a dosage regimen that differs from the The European guideline on management of major bleeding and coagulopathy following trauma: 1g IV bolus, followed by 1g IV maintenance dose over 8 hours. Therefore we conducted post-hoc meta-analyses comparing standard TXA administration and non-standard administration.

Meta-analysis of one-month mortality

A subgroup analysis of the different types of trauma suggested a greater effect in the TXA groups of multiple trauma patients (RR = 0.77, 95% CI = 0.63-0.94, I² = 43%, 95% PI = 0.48 – 1.25) than of TBI patients (RR = 0.94, 95% CI = 0.85-1.03, I² = 0%, 95% PI = 0.83 – 1.06). Notably, almost 90% of the results of the TBI subgroup analysis were determined by the CRASH-3 study. The post-hoc subgroup analysis regarding TXA standard administration, defined as 1g bolus plus 1g maintenance dose, and non-standard administration resulted in a similar RR of 0.82 while the standard administration was accompanied by larger heterogeneity (95% CI = 0.58 – 1.16, I² = 50%, 95% PI = 0.33 – 2.03) than the non-standard administration (95% CI = 0.69 – 0.97, I² = 0%, 95% PI = 0.69 – 0.98).
**Meta-analysis of overall mortality**

To explore heterogeneity we performed a subgroup analysis. For multiple trauma patients we could not resolve heterogeneity (p < 0.01). RR estimates varied between 0.21 and 2.94. The analysis of TBI patients showed that TXA administration was associated with reduction in overall mortality (RR = 0.94, 95% CI = 0.86-1.03, I² = 0%, 95% PI = 0.86 – 1.03). Prehospital and in-hospital administration of TXA both reduced overall mortality rates with the same estimated RR of 0.82. Thereby, the prehospital subgroup showed a smaller confidence interval and lower heterogeneity (95% CI = 0.61-1.10, I² = 15%, 95% PI = 0.49 – 1.36) compared to the in-hospital subgroup (95% CI = 0.44-1.54, I² = 48%, 95% PI = 0.17 – 3.89). Data of the post-hoc subgroup analysis of TXA standard administration and non-standard administration were not pooled because heterogeneity was significant in both cases (p = 0.04 / p < 0.01).

**Meta-analysis of thromboembolic events**

A subgroup analysis of TBI patients showed that thromboembolic events decreased when TXA was administered. However, the prediction interval that effect estimates in future studies may vary widely (RR = 0.91, 95% CI = 0.43-1.91, I² = 44%, 95% PI= 0.19 – 4.31). Data of the multiple trauma subgroup was not pooled because of heterogeneity (p < 0.01). In-hospital TXA administration suggested that TXA may decrease incidence of thromboembolic events (RR = 0.93, 95% CI = 0.51-1.72, I² = 35%, 95% PI = 0.27 – 3.27), while prehospital TXA administration increase thromboembolic events negligibly (RR = 1.01, 95% CI = 0.53-1.94, p = 0.14, I² = 43%, 95% PI = 0.32 – 3.18). Statistical heterogeneity was high for both comparisons. A post-hoc subgroup analysis regarding standard administration and non-standard administration did not resolve this heterogeneity (p < 0.01 / p < 0.01).
eFigure 1. PRISMA flow diagram

[Diagram showing the PRISMA flow for study selection and exclusion.]

Identification of studies via databases and registers:
- Records identified through database searching (1546):
  - Medline (n = 781)
  - Embase (n = 480)
  - Cochrane (n = 275)
- Duplicate records removed before screening (n = 231)
- Records screened (n = 1315)
  - Records excluded (n = 1182):
    - Non-English/German (1)
    - Non-human (11)
    - Wrong intervention (93)
    - Wrong outcome (49)
    - Wrong population (403)
    - Other background (325)
- Reports sought for retrieval (n = 133)
- Reports assessed for eligibility (n = 69)
- Studies included in review:
  - Randomized controlled trials (n = 6)
  - Observational studies (n = 25)

Identification of studies via other methods:
- Records identified from Citation searching (n = 2)
- Reports sought for retrieval (n = 2)
- Reports assessed for eligibility (n = 2)
- Reports excluded (2): See Supplement VII

© 2022 Karl V et al. JAMA Network Open.
### eTable 1. List of Excluded Studies With Reasons

| Study Title                                                                 | Reason |
|-----------------------------------------------------------------------------|--------|
| Dixon AL, McCully BH, Rick EA, Dewey E, Farrell DH, Morrison LJ, et al. Tranexamic acid administration in the field does not affect admission thromboelastography after traumatic brain injury. The Journal of Trauma and Acute Care Surgery. 2020;89(5):900-7. | O      |
| Ebrahimi P, Mozafari J, Ilkhchi RB, Hanafi MG, Mousavinejad M. Intravenous Tranexamic Acid for Subdural and Epidural Intracranial Hemorrhage: Randomized, Double-Blind, Placebo-Controlled Trial. Reviews on Recent Clinical Trials. 2019;14(4):286-91. | O      |
| Fakharian E, Abedzadeh-Kalahroudi M, Atoof F. Effect of Tranexamic Acid on Prevention of Hemorrhagic Mass Growth in Patients with Traumatic Brain Injury. World Neurosurgery. 2018;109:e748-e53. | P      |
| May S, Prehospital Tranexamic Acid Use for Traumatic Brain Injury (TXA). 2019. | D      |
| Meretoja A, Yassi N, Wu TY, Churilov L, Sibolt G, Jeng JS, et al. Tranexamic acid in patients with intracerebral haemorrhage (STOP-AUST): a multicentre, randomised, placebo-controlled, phase 2 trial. Lancet Neurology. 2020;19(12):980-7. | P      |
| Monsef Kasmaei V, Javadi A, Naseri Alavi SA. Effects of tranexamic acid on reducing blood loss in pelvic trauma: A randomised double-blind placebo controlled study. Journal of Clinical Orthopaedics & Trauma. 2019;10(2):286-9. | P      |
| Schreiber MA. Prehospital tranexamic acid improves survival after traumatic brain injury in patients with intracranial hemorrhage. Shock (Augusta, Ga). 2019;51(6):26. | D      |
| Sperry J. Study of Tranexamic Acid During Air Medical Prehospital Transport Trial (STAAMP Trial) (STAAMP). | D      |
| Acar N, Canakci ME, Bilge U. Early and Ultraearly Administration of Tranexamic Acid in Traumatic Brain Injury: Our 8-Year-Long Clinical Experience. Emergency Medicine International Print. 2020;2020:6593172. | C      |
| Adair KE, Patrick JD, Kliber EJ, Peterson MN, Holland SR. TXA (Tranexamic Acid) Risk Evaluation in Combat Casualties (TRECC). Trauma Surgery & Acute Care Open. 2020;5(1):e000353. | U      |
| Balvers K, van Dieren S, Baksaas-Aasen K, Gaarder C, Brohi K, Eaglestone S, et al. Combined effect of therapeutic strategies for bleeding injury on early survival, transfusion needs and correction of coagulopathy. British Journal of Surgery. 2017;104(3):222-9. | U      |
| Blackwell JR, Leggett T, Kukadia J, Sahemey R, Lopes R, Nasir H, et al. Venous thromboembolism following tranexamic acid in the trauma patient. Trauma (united kingdom) Conference: 17th international trauma care conference United kingdom. 2016;18(4):318. | P      |

© 2022 Karl V et al. JAMA Network Open.
| Author(s)                                                                 | Title                                                                                   | Journal                                                                                     | Year | Page(s) |
|-------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|------|---------|
| Boudreau RM, Deshpande KK, Day GM, Hinckley WR, Harger N, Pritts TA, et al. | Prehospital Tranexamic Acid Administration During Aeromedical Transport After Injury. | Journal of Surgical Research.                                                                  | 2019 | 233:132-8 |
| Chapman N.                                                               | Use of tranexamic acid in trauma patients requiring massive transfusion protocol activation: an audit in a major trauma centre in New Zealand. | New Zealand Medical Journal.                                                                 | 2018 | 131(1483):8-12 |
| Cornelius BG, McCarty K, Hylan K, Cornelius A, Carter K, Smith KWG, et al. | Tranexamic Acid: Promise or Panacea: The Impact of Air Medical Administration of Tranexamic Acid on Morbidity, Mortality, and Length of Stay. | Advanced Emergency Nursing Journal.                                                           | 2018 | 40(1):27-35 |
| Cornelius B, Moody K, Hopper K, Kilgore P, Cvek U, Trutschl M, et al.    | A Retrospective Study of Transfusion Requirements in Trauma Patients Receiving Tranexamic Acid. | Journal of Trauma Nursing.                                                                 | 2019 | 26(3):128-33 |
| Chapman N.                                                               | Use of tranexamic acid in trauma patients requiring massive transfusion protocol activation: an audit in a major trauma centre in New Zealand. | New Zealand Medical Journal.                                                                 | 2018 | 131(1483):8-12 |
| Cornelius BG, McCarty K, Hylan K, Cornelius A, Carter K, Smith KWG, et al. | Tranexamic Acid: Promise or Panacea: The Impact of Air Medical Administration of Tranexamic Acid on Morbidity, Mortality, and Length of Stay. | Advanced Emergency Nursing Journal.                                                           | 2018 | 40(1):27-35 |
| Chapman N.                                                               | Use of tranexamic acid in trauma patients requiring massive transfusion protocol activation: an audit in a major trauma centre in New Zealand. | New Zealand Medical Journal.                                                                 | 2018 | 131(1483):8-12 |
| Cornelius B, Moody K, Hopper K, Kilgore P, Cvek U, Trutschl M, et al.    | A Retrospective Study of Transfusion Requirements in Trauma Patients Receiving Tranexamic Acid. | Journal of Trauma Nursing.                                                                 | 2019 | 26(3):128-33 |
| David JS, Lambert A, Bouzat P, Incagnoli P, Geay-Baillat AM, Taverna XJ, et al. | Fibrinolytic shutdown diagnosed with rotational thromboelastometry represents a moderate form of coagulopathy associated with transfusion requirement and mortality: A retrospective analysis. | European Journal of Anaesthesiology.                                                          | 2020 | 37(3):170-9 |
| DeHoff K, Milligan J, Zimmerman LH, Jurado L, Nakajima S, Acquista E.    | Impact of tranexamic acid on transfusions prevs post-protocol implementation in trauma patients. | Critical care medicine Conference: 46th critical care congress of the society of critical care medicine, SCCM 2016 United states Conference start: 20170121 Conference end: 20170125. 2016;44(12 Supplement 1):461. |      |         |
| Douglas A, Faviere D, Gallo A, VanderSchaaf A, Wall W, Wilson K, et al.   | Impact of Early Tranexamic Acid Administration on Overall Blood Product Utilization at 24 Hours. | Journal of Trauma Nursing.                                                                  | 2020 | 27(2):66-70 |
| Erramouspe PJ, Garcia-Pintos MF, Benipal S, Manoukian MAC, Santamarina JL, Shawagga HG, et al. | Mortality and Complication Rates in Adult Trauma Patients Receiving Tranexamic Acid: A Single-center Experience in the Post-CRASH-2 Era. | Academic Emergency Medicine.                                                                 | 2020 | 27(5):358-65 |
| Gall L, Davenport R, Brohi K.                                            | Effect of early tranexamic acid on the coagulation system in patients with suspected traumatic haemorrhage: a prospective cohort study. |                                                                                              | 2016 |         |
| Fernandez M, Morrison C, Pettineo G.                                     | Pilot study: the use of tranexamic acid in trauma patients at a level one teaching hospital. | Crit Care Med.                                                                               | 2012 |         |
| Ghazi S, Pierson R, Trolinski T.                                         | Military application of tranexamic acid in trauma emergency resuscitation study 2C03, 3C00. | Journal of the Intensive Care Society.                                                        | 2013 | 14(1):86-8 |
| Guth C, Vassal O, Friggeri A, Wey PF, Inaba K, Decullier E, et al.       | Effects of modification of trauma bleeding management: A before and after study.          | Anaesthesia                                                                                   | 2020 |         |

© 2022 Karl V et al. JAMA Network Open.
| Journal | Title | Date |
|---------|-------|------|
| Critical Care & Pain Medicine. | 2019;38(5):469-76. | |
| Jachetti A, Massenat RB, Edema N, Woolley SC, Benedetti G, Van Den Bergh R, et al. | Introduction of a standardised protocol, including systematic use of tranexamic acid, for management of severe adult trauma patients in a low-resource setting: the MSF experience from Port-au-Prince, Haiti. BMC Emergency Medicine. 2019;19(1):56. | I |
| Kheirbek T, Jikaria N, Murray B, Martin TJ, Lueckel SN, Stephen AH, et al. | Unjustified Administration in Liberal Use of Tranexamic Acid in Trauma Resuscitation. Journal of Surgical Research. 2020;258:125-31. | C |
| Kunze-Szikszay N, Krack LA, Wildenauer P, Wand S, Heyne T, Walliser K, et al. | The pre-hospital administration of tranexamic acid to patients with multiple injuries and its effects on rotational thrombelastometry: a prospective observational study in pre-hospital emergency medicine. Scandinavian Journal of Trauma, Resuscitation & Emergency Medicine. 2016;24(1):122. | C |
| Lawson K, Godfrey P. | TXA for HEMS patients with suspected haemorrhage. 2017. | C |
| Lipsky AM, Abramovich A, Nadler R, Feinstein U, Shaked G, Kreiss Y, et al. | Tranexamic acid in the prehospital setting: Israel Defense Forces’ initial experience. Injury. 2014;45(1):66-70. | C |
| Marsden MER, Rossetto A, Duffield CAB, Woolley TGD, Buxton WP, Steynberg S, et al. | Prehospital tranexamic acid shortens the interval to administration by half in Major Trauma Networks: a service evaluation. Emergency Medicine Journal. 2019;36(7):395-400. | P |
| Meizoso JP, Dudaryk R, Mulder MB, Ray JJ, Karcutskie CA, Eidelson SA, et al. | Increased risk of fibrinolysis shutdown among severely injured trauma patients receiving tranexamic acid. The Journal of Trauma and Acute Care Surgery. 2018;84(3):426-32. | P |
| Milligan J, DeHoff K, Jurado L, Zimmerman LH, Nakajima S, Acquista E. | Effects of early versus late tranexamic acid administration in critically ill trauma patients. 2016. | F |
| Morrison JJ, Ross JD, Dubose JJ, Jansen JO, Midwinter MJ, Rasmussen TE. | Association of cryoprecipitate and tranexamic acid with improved survival following wartime injury: findings from the MATTERs II Study. JAMA Surgery. 2013;148(3):218-25. | I |
| Neeki MM, Dong F, Toy J, Vaezazizi R, Powell J, Jabourian N, et al. | Efficacy and Safety of Tranexamic Acid in Prehospital Traumatic Hemorrhagic Shock: Outcomes of the Cal-PAT Study. The Western Journal of Emergency Medicine. 2017;18(4):673-83. | D |
| Nelson Yap KB, Albert Wong SH, Idris Z. | Tranexamic acid in traumatic brain injury. Medical Journal of Malaysia. 2020;75(6):660-5. | P |
Reed MJ, Cooke C, McMahon N, Hands K, Henderson S, Knight E, et al. Improvements in National Code Red transfusion practice in Scotland after adoption of recommendations from the Scottish National Code Red 2015 review. Injury. 2020;51(4):913-8.

Tencza E, Harrell AJ, Sarangarm P. Effect of tranexamic acid administration time on blood product use in urban trauma patients. American Journal of Health-System Pharmacy. 2020;77(Supplement_2):S46-S53.

Van Haren RM, Valle EJ, Thorson CM, Jouria JM, Busko AM, Guarch GA, et al. Hypercoagulability and other risk factors in trauma intensive care unit patients with venous thromboembolism. The Journal of Trauma and Acute Care Surgery. 2014;76(2):443-9.

Vu EN, Schlamp RS, Wand RT, Kleine-Deters GA, Vu MP, Tallon JM. Prehospital use of tranexamic acid for hemorrhagic shock in primary and secondary air medical evacuation. Air Medical Journal. 2013;32(5):289-92.

Walker PF, Schobel S, Caruso JD, Rodriguez CJ, Bradley MJ, Elster EA, et al. Trauma Embolic Scoring System in military trauma: a sensitive predictor of venous thromboembolism. Trauma Surgery & Acute Care Open. 2019;4(1):e000367.

P: wrong patients; I: wrong intervention; O: no relevant outcome; C: Missing control group; F: No full publication; A: Appraisal; U: data not usable, excluded during data extraction; D: Duplicate, Trial within another publication
**Table 2. Data Extraction Sheet**

| Study/Reference | Region, setting, inclusion criteria, exclusion criteria and baseline characteristics (IG/CG) of study population | Intervention(s), control, patient flow (IG/CG) and length of follow-up period |
|-----------------|--------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Chakroun-Walha O, Samet A, Jerbi M, Nasri A, Talbi A, Kanoun H, et al. Benefits of the tranexamic acid in head trauma with no extracranial bleeding: a prospective follow-up of 180 patients. European Journal of Trauma & Emergency Surgery. 2019;45(4):719-26. | **Region/Setting**
Tunisia
August 2016 – September 2017
**Inclusion criteria**
- Age ≥ 18 years
- Admitted to the ED for TBI
- Intracranial bleeding in the first or the second brain CT-scan, and with a delay of management in the study center under 24 h after trauma
**Exclusion criteria**
- Significant extra cranial bleeding (that is not in need of immediate blood transfusion)
- Patients with evidence that TXA improve outcome
- Known renal failure
- History or current evidence suggestive of venous or arterial thrombosis
**Patient characteristics IG/CG**
Age, years, mean(SD)
44 (20) / 39 (18)
Gender
M/F sex ratio 11/8.3
Vital signs
Shock defined as:
- Heart rate, bpm, mean(SD) 87 (16) / 86 (19) |
|                                                                 | TXA bolus 1g, 10 min, maintenance 1g, 8h |
| Control                                                      | None                                           |
| Time of TXA administration after injury                     | N/A                                            |
| Randomized patients                                         | 96/84                                          |
| Follow-up                                                    | 28 days                                        |
| Collaborators C-t, Shakur H, Roberts I, Bautista R, Caballero J, Coats T, et al. 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. Lancet. 2010;376(9734):23-32. | Region/Setting |
|---|---|
| 40 countries worldwide | TXA bolus 1g, 30 min, maintenance 1g, 8h |
| May 2005 - March 2010 | Control |
| NCT00375258 | Placebo bolus, 10 min, maintenance, 8h |
| Inclusion criteria | Time of TXA administration after injury |
| • significant haemorrhage (systolic blood pressure less than 90 mmHg and/or heart rate more than 110 beats per minute), or at risk of significant haemorrhage | ≤ 8 h |
| • TXA administration within 8 hours of the injury | Randomized patients |
| • ≥ 16 years old | 10096/10115 |
| Exclusion criteria | Follow-up |
| • Patients for whom the responsible doctor considers there is a clear indication for antifibrinolytic therapy | 28 days / hospital discharge |
| • Patients for whom there is considered to be a clear contraindication to antifibrinolytic therapy | |
| Patient characteristics IG/CG | |
| Age, years, mean (SD) |  |
| 34.6 (14.1) / 34.5 (14.4) |  |
Gender
Male 8439 (83.6%) 8496 (84.0%)

Vital signs
Shock defined as:
  • Systolic blood pressure, mmHg
    ≤75: 1566 (15.55) / 1608 (15.9)
    76-89: 1615 (16) / 1697 (16.8)
    ≥90: 6901 (68.4) / 6791 (67.1)
    Not know: 11 (0.11) / 18 (0.18)
  • Heart rate, bpm
    ≤77: 875 (8.7) / 871 (8.6)
    77-91: 1727 (17.1) / 1770 (17.5)
    92-107: 2556 (25.3) / 2546 (25.5)
    >107: 4872 (48.3) / 4853 (48)
    not know: 63 (0.62) / 74 (0.73)
If TBI: GCS score, points
3-8: 1799 (17.8) / 1839 (18.2)
9-12: 1353 (13.4) / 1351 (13.4)
13-15: 6934 (68.7) / 6908 (68.3)
Not known: 7 (0.07) / 16 (0.16)

Injury Severity Score, points, mean (SD)
N/A

Blunt vs. Penetrating, n (%)
Collaborators C-t. 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. Lancet. 2019;394(10210):1713-23.

| Region/Setting | 29 countries worldwide |  |
|----------------|------------------------|---|
|                | July 2012 - January 2019 |  |
| NCT01402882    |  |  |

**Inclusion criteria**

Adults with traumatic brain injury who

- are within eight hours of injury (limited to within 3 hours from September, 2016)
- with any intracranial bleeding on CT scan or who have a GCS of 12 or less
- have no significant extracranial haemorrhage
- Responsible clinician's 'uncertainty' as to whether or not to use tranexamic acid in a particular patient with traumatic brain injury

**Exclusion criteria**

None

**Patient characteristics IG/CQ**

| Age, years, mean (SD) | 41.7 (19.0) 41.9 (19.0) |
|----------------------|------------------------|

| Gender |  |
|--------|---|
| Men 3742 (80) 3660 (80) |  |
| Women 906 (19) 893 (20) |  |

| Intervention | TXA bolus 1g, 30 min, maintenance 1g, 8h |
|--------------|-----------------------------------------|
| Control      | Placebo bolus, 10 min, maintenance, 8h |

**Time of TXA administration after injury**

< 3 h

**Randomized patients**

4649 / 4553

**Follow-up**

28 days / hospital discharge / death

© 2022 Karl V et al. JAMA Network Open.
| Vital signs |
|-------------|
| Shock defined as: |
| - Systolic blood pressure, mmHg |
| <90: 89 (0.2) / 85 (2) |
| 90-119: 1508 (32) / 1490 (33) |
| 120-139: 1461 (31) / 1504 |
| ≥140: 1576 (34) / 1466 (32) |
| Not know: 15 (<1) / 8 (<1) |
| If TBI: GCS score, points, n (%): |
| 3: 495 (11) / 506 (11) |
| 4: 213 (5) / 213 (5) |
| 5: 163 (4) / 172 (4) |
| 6: 221 (5) / 232 (5) |
| 7: 311 (7) / 294 (6) |
| 8: 354 (8) / 315 (7) |
| 9: 335 (7) / 292 (6) |
| 10: 371 (8) / 364 (8) |
| 11: 375 (8) / 390 (9) |
| 12: 476 (10) / 478 (10) |
| 13: 297 (6) / 312 (7) |
| 14: 526 (11) / 458 (10) |
| 15: 484 (10) / 492 (11) |
| Unknown: 28 (1) / 35 (1) |
Region/Setting
4 US locations
May 2015 - October 2019
NCT02086500

Inclusion criteria
- Blunt or penetrating injured patients at risk of bleeding being transported via air or ground 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 or ground medical transport
  - Documented at referring hospital prior to air or ground medical transport arrival OR
- Tachycardia (heart rate >110 beats per minute)
  - At scene of injury or during air or ground medical transport
  - Documented at referring hospital prior to air or ground medical transport arrival

Exclusion criteria
- Age > 90 or < 18 years of age
- Inability to obtain intravenous access or intraosseous

Intervention
A) TXA bolus 1g, 10 min + Placebo bolus 10 min + Placebo infusion 8 h
B) TXA bolus 1g, 10 min + Placebo bolus 10 min + TXA infusion 8 h
C) TXA bolus 1g, 10 min + TXA bolus 10 min + TXA infusion 8 h

Control
Placebo bolus, 10 min + Placebo bolus 10 min + Placebo infusion 8 h

Time of TXA administration after injury
Prehospital

Randomized patients
460/467

Follow-up
30 days
- Documented (radiographic evidence) cervical cord injury with motor deficit
- Known prisoner
- Known pregnancy
- Traumatic arrest with > 5 minutes CPR without return of vital signs
- Penetrating cranial injury
- Traumatic brain injury with brain matter exposed
- Isolated drowning or hanging victims
- Wearing an opt out bracelet
- Isolated fall from standing
- Patient or Family Objection at scene

**Patient characteristics IG/CG**

**Age, years, mean (SD)**

|                | IG   | CG   |
|----------------|------|------|
|                | 41 (17) | 42 (18) |

**Gender, n (%)**

| Gender     | IG   | CG   |
|------------|------|------|
| Male       | 327 (73.2) | 341 (74.8) |
|            | 327 (73.2) | 341 (74.8) |

**Vital signs**

**Shock defined as:**

- Systolic blood pressure, mmHg, median (IQR) 123 (88-143) / 126 (87-148)
- Heart rate, bpm, median (IQR) 118 (112-127) / 117 (112-124)

If TBI: GCS score, n (%): GCS <8: 89 (19.9) / 107 (23.5)

**Injury Severity Score, points, median (IQR)**

|                | IG   | CG   |
|----------------|------|------|
|                | 13 (5-22) | 11 (4-22) |

**Blunt vs. Penetrating, n (%)**

|                | IG   | CG   |
|----------------|------|------|
|                | 371 (83) | 389 (85.3) vs. 78 (17.4) | 70 (15.4) |

**TBI vs. multiple trauma, n (%)**

|                | IG   | CG   |
|----------------|------|------|
|                | N/A  |      |
| Region/Setting | 20 US and Canada locations  
May 2015 - November 2015 |
|----------------|--------------------------------------------------|
| 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 (or estimated weight > 50 kg if age is unknown)  
- 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  
- 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 |
| Patient characteristics IG/CG |  
**Age, years, median (IQR)**  
A) 39 (26-57) B) 40 (26 / 56) / 36 (25-55)  
**Gender, n (%)**  
|  
| Intervention | A) 1g bolus TXA and 1g maintenance TXA, 8 h  
B) 2 g bolus TXA, Placebo infusion  
Control | Placebo bolus and maintenance |
| Time of TXA administration after injury | Prehospital  
Randomized patients | 718/345  
Follow-up | 6 months |
### Male

|   | A) 227 (73) | B) 255 (74) | / | 233 (75) |
|---|-------------|-------------|---|----------|

#### Vital signs

**Shock defined as:**

If TBI: GCS score, points, mean (SD)

7.8 (3.3) / 7.6 (3.2)

**Injury Severity Score, points, median (IQR)**

A) 17 (8-27) B) 17 (8-27) / 17 (9-27)

**Blunt vs. Penetrating, n (%)**

A) 302 (97) B) 339 (98) / 294 (95) vs. A) 12 (4) B) 5 (1) / 16 (5)

**TBI vs. multiple trauma, n (%)**

N/A

---

**Region/Setting**

Thailand

October 2008 - October 2009

NCT00755209

**Inclusion criteria**

- moderate to severe injuries (post-resuscitation scores GCS 4-12)
- age ≥ 16 year
- non-penetrating TBI in 8 hours onset
- first CT brain in 8 hours onset
- non neurosurgical OR in 8 hours onset

**Exclusion criteria**

- patients with coagulopathy (only 1 excluded)
- serum creatinine over than 2 mg%
- with associated major organ injury requiring surgery within 8 hours of injury

**Intervention**

TXA

bolus 1g, 30 min

maintenance 1g, 8h

**Control**

Placebo

bolus, 10 min

maintenance, 8h

**Time of TXA administration after injury**

N/A

**Randomized patients**

Yutthakasemsunt S, Kittiwatanagul W, Piyavechvirat P, Thinkamrop B, Phuenpathom N, Lumbiganon P.

Tranexamic acid for patients with traumatic brain injury: a randomized, double-blinded, placebo-controlled trial. BMC Emergency Medicine. 2013;13:20.
- pregnancy
- receiving any medication which affects haemostasis

**Patient characteristics IG/CG**

| Age, years, mean (SD) | 34.8 (16.0) / 34.1 (15.3) |
|-----------------------|---------------------------|

| Gender, n (%)         | Male 103 (86%) / 107 (91%) |
|-----------------------|-----------------------------|

**Vital signs**

Shock defined as:

If TBI: GCS score, n (%): Moderate (9-12): 52 (53) / 47 (47); Severe (4-8): 68 (49) / 71 (51)

**Injury Severity Score, points, mean (SD):**

23.3 / 24.8

**Blunt vs. Penetrating, n (%):**

N/A

**TBI vs. multiple trauma, n (%):**

20 (17) / 16 (14) vs. 100 (83) / 102 (86)

**Region/Setting**

| USA |
|-----|

**Inclusion criteria**

- Adult full trauma team activations (SBP <90mmHg, respiratory compromise, blood transfusions en route, patients requiring IV fluids to

**Intervention**

TXA 1 g bolus, 1 g maintenance

**Control**

No TXA

**Time of TXA administration after injury**

120/120 Follow-up

hospital discharge

© 2022 Karl V et al. JAMA Network Open.
maintain vital signs, penetrating trauma to neck or torso, or GCS <8 with traumatic mechanism)
- Indications for TXA: SBP <90mmHg, receiving blood transfusions, MTP activation or clinical concern for ongoing bleeding

**Exclusion criteria**
- Time since injury >3h
- Contraindications for TXA: >3h since injury, isolated TBI

**Patient characteristics IG/GC**

| Age, years, mean (SD) | N/A |
|-----------------------|-----|
| Gender                | N/A |
| Vital signs           | N/A |
| Injury Severity Score, points, mean (SD) | N/A |
| Blunt vs. Penetrating, n (%) | N/A |
| TBI vs. multiple trauma, n (%) | N/A |

**Inclusion criteria**

| Region/Setting | Six French trauma centers |
|----------------|---------------------------|
| Intervention | TXA |
| Control | No TXA |

© 2022 Karl V et al. JAMA Network Open.
> 16 years of age
- Major hemorrhage (defined by the need of four or more packed red blood cells [pRBC] in the first 6 hours following the trauma) or
- Received at least one pRBC in the emergency room (ER) or
- Received vasopressors either in the prehospital setting or in the ER

### Exclusion criteria
None

### Patient characteristics IG/CG

| Age, years, mean (SD) | 42 (19) (Propensity Score Calculation) |
|-----------------------|----------------------------------------|
| Gender, n (%)         | Male 73.6 / 73.1 %                      |
|                       | Vital signs                             |
|                       | N/A                                    |
| Injury Severity Score, points, n (%) | <16: 143 (17.9%)                        |
|                       | [16–30]: 322 (40.4%)                    |
|                       | >30: 332 (41.7%)                        |
|                       | (Propensity Score Calculation)         |
| Blunt vs. Penetrating, n (%) | N/A                                  |
| TBI vs. multiple trauma, n (%) | N/A                                    |

### Time of TXA administration after injury
Prehospital or ER administration

### Included Patients
403 / 281

### Follow-up
90 days
| Region/Setting | China, neurosurgery registry database January 2010 - December 2016 |
|----------------|---------------------------------------------------------------|
| Inclusion criteria | - Age >18 years  
- Admission to the trauma center as an inpatient  
- International Classification of Diseases (ICD) code of “Cerebral contusion (852.19)” or “Traumatic subarachnoid hemorrhage (852.00)” as the primary diagnosis |
| Exclusion criteria | - Other primary diagnosis ICD code such as “Diffuse axonal injury (850.4),” “Subdural hematoma, acute (852.20),” “Epidural hematoma (852.40),” “Concussion with no loss of consciousness (850.0),” or “Concussion with brief loss of consciousness (850.1)”.  
- Use of novel oral anticoagulants such as dabigatran, rivaroxaban, or apixaban |
| Patient characteristics IG/CG |  
**Age, years, mean (SD)**  
66.4  
**Gender, n (%)**  
Male 410 (62.9)  
**Vital signs**  
If TBI: GCS score, points, mean (SD)  
14-15: 473 (72.7)  
9-13: 110 (16.9) |
| Intervention | 1 g TXA on admission followed by 500 mg every 6 hours for 24 hours |
| Control | No TXA |
| Time of TXA administration after injury | On admission |
| Included Patients | 81 / 570 |
| Follow-up | N/A |
| Injury Severity Score, points, mean (SD) | N/A |
|-----------------------------------------|-----|
| Blunt vs. Penetrating, n (%)            | N/A |
| TBI vs. multiple trauma, n (%)          | N/A |

Cole E, Davenport R, Willett K, Brohi K. Tranexamic acid use in severely injured civilian patients and the effects on outcomes: a prospective cohort study. Annals of Surgery. 2015;261(2):390-4.

| Region/Setting                           | England |
|------------------------------------------|---------|
| Inclusion criteria                       | > 15 years of age |
| Exclusion criteria                       | ISS < 15 |
| Patient characteristics IG/CG           |         |
| Age, years, mean (SD)                    | 42 (17.2) / 40 (18.6) |
| Gender, %                                | Male 78 / 82 |
| Vital signs                              |         |
| Shock defined as:                        |         |
|                                          | • Systolic blood pressure, mmHg, mean (SD) 102 (34) / 127 (31) |

Intervention  
1g TXA bolus followed by 1g TXA infusion  
Control  
No TXA  
Time of TXA administration after injury  
Prehospital or ER, all < 3h  
Included Patients  
160 / 225  
Follow-up  
N/A
Dixon A, Emigh B, Spitz K, Teixeira P, Coopwood B, Trust M, et al. Does tranexamic acid really work in an urban US level I trauma center? A single level 1 trauma center’s experience. American Journal of Surgery. 2019;218(6):1110-3.

| Region/Setting      | USA |
|---------------------|-----|
| Time of TXA administration after injury | Prehospital or ER |

**Inclusion criteria**
- Patients who underwent MTP defined as the receiving of greater than 10 units of pRBCs within the first 24 h of injury

**Exclusion criteria**
None

**Patient characteristics IG/CG**

| Age, years, mean (SD) | 41 (17) / 42 (17) |
|-----------------------|-------------------|
| Gender, n (%)         | Male 47 (76) / 43 (69) |
|                       | Vital signs       |
|                       | Shock defined as:  |
|                       | Systolic pressure, mmHg, mean (SD) 115 (32) / 98 (44) |

**Intervention**
1g TXA bolus, 1 g TXA maintenance

**Control**
No TXA

62 / 62

N/A
| Region/Setting | Intervention |
|----------------|--------------|
| Qatar          | TXA 1 g      |
| January 2017 - September 2018 | Control |
| No TXA         | Time of TXA administration after injury |
| Prehospital   | Prehospital |

**Inclusion criteria**
- Age 16 - 80
- Significant hemorrhage: SBP < 90mmHg and/or HR > 110 beats per minute OR at risk
- Within 3 h of trauma
- Control: No TXA administration but meeting CRASH-2 Criteria and receiving blood transfusion within the first 4 h

**Exclusion criteria**
- First dose of TXA at the ED
- < 16 and > 80 years of age
- Vulnerable population (prisoners and pregnant patients)
- Traumatic brain injury with exposed brain
- Isolated drowning or hanging victims

**Patient characteristics IG/CG**

| Age, years, mean (95% CI) |
|---------------------------|
| 31.4 (29.2 - 33.7) / 31.5 (29.2 - 33.7) |
### Gender, %

Male 96.1 / 89.2

### Vital signs

**Shock defined as:**

- **Systolic blood pressure, mmHg, mean (95 % Cl)** 106.9 (101.9 - 111.8) / 107.1 (101.9 - 112.3)
- **Heart rate, bpm, mean (95 % Cl)** 97.1 (92.4 - 101.8) / 96.6 (90.9 - 102.2)
- **Shock index, mean (SD)** 0.96 (0.33) / 0.96 (0.34)
- **Lactate, mmol/l, median (range)** 3.0 (0.8 - 18.8) / 4.1 (0.6 - 18.0)
- **Base value, mmol/l, median (range)** 7.3 (-22.1 - 4.5) / -7.3 (-26.9 - 0.2)

### Injury Severity Score, points, mean (95 % Cl)

24.0 (21.4 - 26.5) / 25 (22.3 - 27.6)

### Blunt vs. Penetrating, n (%)

N/A

### TBI vs. multiple trauma, n (%)

N/A

---

**Glover TE, Sumpter JE, Ercole A, Newcombe VFJ, Lavinio A, Carrothers AD, et al.** Pulmonary embolism following complex trauma: UK MTC observational study. Emergency Medicine Journal. 2019;36(10):608-12.

### Region/Setting

**UK**

November 2014 - May 2017

### Inclusion criteria

- Age 18 years and older
- Major trauma (undefined)
- Admitted to a level 2 or 3 trauma center

### Exclusion criteria

N/A

### Intervention

**TXA**

**Control**

No TXA

**Time of TXA administration after injury**

N/A

**Included Patients**
| **Patient characteristics IG/CG** |
|-----------------------------------|
| **Age, years, median (range)**    | 45.3 (18 - 95.7) / 51.9 (18 - 96.1) |
| **Gender, %**                     |
| Male 75.7 / 72.1                  |
| **Vital signs**                   |
| N/A                               |
| **Injury Severity Score, points, median (range)** |
| 27 (4 - 75) / 25 (4 - 59)         |
| **Blunt vs. Penetrating, n (%)**  |
| N/A                               |
| **TBI vs. multiple trauma, n (%)**|
| N/A                               |

| **Region/Setting** |
|---------------------|
| **USA**             |
| September 2009 - September 2013 |

| **Inclusion criteria** |
|------------------------|
| ● Age 16 years and older |
| ● Evidence of hyperfibrinolysis (rTEG LY-30 of 3 % or greater) |

| **Exclusion criteria** |
|------------------------|
| ● Burn wounds > 20 % of total body surface |
| ● Dead within 30 minutes of arrival |

| **Follow-up** |
|---------------|
| 6 weeks       |

| **Intervention** |
|------------------|
| TXA 1 g bolus, 1 g infusion over 8 h was implemented in 2011 (study started 2009) where 1g bolus and 1g maintenance dose of TXA was administered —> 2 years without a guideline and missing of dose regime |

| **Control** |
|-------------|
| No TXA      |

| **Time of TXA administration after injury** |
|---------------------------------------------|

© 2022 Karl V et al. JAMA Network Open.
| Patient characteristics IG/CG | < 3 h |
|-------------------------------|------|
| **Age, years, median (IQR)**  |  |
| 37 (26 - 56) / 32 (23 - 46)   | 98 / 934 |
| **Gender, %**                 |  |
| Male 80 / 74                  | N/A  |
| **Vital signs**               |  |
| Shock defined as             |  |
| • Systolic blood pressure, mmHg, median (IQR) 121 (100 - 140) / 126 (104 / 143) |
| • Heart rate, bpm, median (IQR) 105 (84 - 125) / 100 (84 - 120) |
| • Lactate, mmol/l, median (IQR) 4.4 (3.1 - 7.7) / 3 (1.9 - 4.6) |
| • Base value, mmol/l, median (IQR) -5 (-12 - -2) / -2 (-5 - 1) |
| **Injury Severity Score, points, mean (SD)** |  |
| 29 (19 - 41) / 14 (4 - 25)   |  |
| **Blunt vs. Penetrating, n (%)** |  |
| Blunt 78 / 65                |  |
| **TBI vs. multiple trauma, n (%)** |  |
| N/A                         |  |

**Region/Setting**
- USA
- October 2010 - March 2014

**Inclusion criteria**
- Injured in combat in Afghanistan
- Been admitted to role 3 MTF

Howard JT, Stockinger ZT, Cap AP, Bailey JA, Gross KR. Military use of tranexamic acid in combat trauma: Does it matter? The Journal of Trauma and Acute Care Surgery. 2017;83(4):579-88.

**Intervention**
- TXA

**Control**
- No TXA

© 2022 Karl V et al. *JAMA Network Open.*
- Received blood transfusion of at least one unit

**Exclusion criteria**

None

**Patient characteristics IG/CG**

| Age, years, mean (SD) | 24.6 (9) / 24.9 (10.1) |
|-----------------------|------------------------|

| Gender, n (%)         | Male 362 (97.1) / 627 (95.4) |

**Vital signs**

N/A

| Injury Severity Score, points, mean (SD) | 16.8 (10.6) / 16.2 (10.2) |

**Blunt vs. Penetrating, n (%)**

N/A

| TBI vs. multiple trauma, n (%) | N/A |

**Region/Setting**

| USA |

**Inclusion criteria**

Treated at the Walter Reed National Military Medical Center

**Exclusion criteria**

None

**Intervention**

TXA

**Control**

None

**Time of TXA administration after injury**

N/A

**Included Patients**

373 / 657

**Follow-up**

Discharge / 30 days
| N/A | Included Patients |
|-----|-------------------|
|     | 146 / 309         |

| Follow-up |
|-----------|
| through initial hospitalization and readmission |

| Khan M, Jehan F, Bulger EM, O'Keeffe T, Holcomb JB, Wade CE, et al. Severely injured trauma patients with admission hyperfibrinolysis: Is there a role of tranexamic acid? Findings from the PROPPR trial. The Journal of Trauma and Acute Care Surgery. 2018;85(5):851-7. |

| Region/Setting |
|----------------|
| USA            |

| Intervention |
|--------------|
| TXA           |
| Control      |
| No TXA       |

| Time of TXA administration after injury |
|----------------------------------------|
| < 3h                                   |

### Patient characteristics IG/CG

| Age, years, mean (SD) |
|-----------------------|
| 25.3 (4.8) / 27.4 (7.1) |

| Gender, n (%) |
|---------------|
| Male 144 (99.3) / 299 (96.4) |

### Vital signs

- **Shock defined as:**
  - Systolic blood pressure, mmHg, mean (SD) 115.5 (30.8) / 131.4 (23.9)
  - Heart rate, bpm, mean (SD) 120.6 (30) / 92.8 (4.4)

### Injury Severity Score, points, mean (SD)

| 27.8 (12.4) / 15.6 (10.8) |

| Blunt vs. Penetrating, n (%) |
|-----------------------------|
| N/A                         |

| TBI vs. multiple trauma, n (%) |
|-------------------------------|
| N/A                           |

### Inclusion criteria

- Adult trauma patients
- Hyperfibrinolysis, defined as Ly30 >/= 3 %

### Exclusion criteria

- Received TXA > 3h
Patient characteristics IG/CG

Age, years, mean (SD)
42.5 (20) / 38.7 (17)

Gender, %
Male 66 / 68

Vital signs

Shock defined as:

- Systolic blood pressure, mmHg, median (IQR) 100 (76 - 127) / 101 (80 - 131)
- Heart rate, bpm, median (IQR) 115 (76 - 127) / 120 (100 - 134)
- Lactate, mmol/l, median (IQR) 8.3 (5.1 - 11.7) / 9.5 (5.1 - 12.7)
- Base value, mmol/l, median (IQR) -14 (-18 - -8) / -12 (-18 - -6.7)

Injury Severity Score, points, median (IQR)
38 (23 -45) / 35 (21 - 45)

Blunt vs. Penetrating, %
Penetrating 32 / 44

TBI vs. multiple trauma, n (%)
N/A

Included Patients
31 / 62

Follow-up
deadh/ discharge / 30 days after admission

Lewis CJ, Li P, Stewart L, Weintrob AC, Carson ML, Murray CK, et al. Tranexamic acid in life-threatening military injury and the associated risk of infective complications. British Journal of Surgery. 2016;103(4):366-73.

Region/Setting
USA
June 2009 - December 2013

Inclusion criteria

- received blood products (i.e. packed red blood cells, whole blood) within 24 h of injury

Exclusion criteria

Intervention
TXA
Control
No TXA

Time of TXA administration after injury

© 2022 Karl V et al. JAMA Network Open.
| N/A | Patient characteristics IG/CG |
|-----|-------------------------------|
| N/A | Age, years, median (IQR)      |
|     | 24.2 (21.7 - 27.2) / 24.2 (21.8 - 28.7) |
|     | Gender, n (%)                 |
|     | Male 334 (90.7) / 570 (91.1)  |
| Vital signs | Shock defined as: |
|     | • Shock index, median (IQR) 1.1 (0.8 - 1.4) / 0.9 (0.7 - 1.2) |
|     | Injury Severity Score, points, median (IQR) |
|     | 33 (27 - 45) / 33 (26 - 43)  |

| Region/Setting |
|----------------|
| USA            |
| 2013 - 2016    |

| Inclusion criteria |
|--------------------|
| • age 16 and older |
| • no known hypertensivity to TXA |
| • no known severe renal failure |
| • no known history of thromboembolism |
| • patient does not present with aneurismal subarachnoid hemorrhage |
| • patient is seen by qualified medical personnel within 3 h of injury |
| • survived ≥ 8.5 hrs |
| • received at least a single blood product |
| • BPM ≥ 120 and SBP ≤ 90 mmHg |

| Exclusion criteria |
|--------------------|
| N/A | Included Patients |
|     | 335 / 626         |

| Follow-up |
|-----------|
| N/A       |

Luehr E, Grone G, Pathak M, Austin C, Thompson S. Administration of tranexamic acid in trauma patients under stricter inclusion criteria increases the treatment window for stabilization from 24 to 48 hours—a retrospective review. International Journal of Burns & Trauma. 2017;7(6):115-9.

| Intervention |
|--------------|
| TXA          |

| Control |
|---------|
| No TXA  |

| Time of TXA administration after injury |
|----------------------------------------|
| < 3h                                   |

| Included Patients |
|-------------------|
| 53 / 62           |

| Follow-up |
|-----------|
| 30 days   |
- Exclusion of isolated injuries, such as orthopedic, face and neurosurgical patients.

**Patient characteristics IG/CG**

| Age, years, mean (SD) | 41.6 (18.3) / 41.9 (18.6) |
|-----------------------|---------------------------|
| Gender, n %           | 42 (79.3) / 36 (58.1)     |

**Vital signs**

Shock defined as:
- Systolic blood pressure, mmHg, mean (SD) 77.3 (10) / 77 (10.6)
- Heart rate, bpm, mean (SD) 131.5 (8.2) / 135.5 (13)

**Injury Severity Score, points, mean (SD)**

| 21.6 (11.4) / 20.3 (11.7) |

**Blunt vs. Penetrating, n (%)**

| Blunt 43 (81.1) / 53 (85.5) |

**TBI vs. multiple trauma, n (%)**

| N/A |

---

Moore HB, Moore EE, Huebner BR, Stettler GR, Nunns GR, Einsersen PM, et al. Tranexamic acid is associated with increased mortality in patients with physiological fibrinolysis. Journal of Surgical Research. 2017;220:438-43.

**Region/Setting**

- USA
- 2014 - 2016

**Inclusion criteria**

- NISS > 15

**Exclusion criteria**

**Intervention**

- TXA

**Control**

- No TXA

**Time of TXA administration after injury**

© 2022 Karl V et al. JAMA Network Open.
### Patient characteristics IG/CG

| Age, years, median (interquartile values) | 27 (24 - 54) / 34 (27 - 49) |
| Gender, % | Male 85 / 77 |
| Vital signs | N/A |
| New Injury Severity Score, points, median (interquartile values) | 48 (29 - 57) / 29 (22 - 43) |
| Blunt vs. Penetrating, n (%) | Penetrating 42 / 32 |
| TBI vs. multiple trauma, n (%) | N/A |

### Included Patients

- **Morrison JJ, Dubose JJ, Rasmussen TE, Midwinter MJ.**
  - **Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) Study.**
  - **Archives of Surgery.** 2012;147(2):113-9.

### Region/Setting

- **UK**
- **January 2009 - December 2010**

### Inclusion criteria

- Massive transfusion (at least 10 units of packed red blood cells)

### Exclusion criteria

- N/A

### Intervention

- TXA bolus of 1 g, repeated as felt indicated by the managing clinician

### Control

- No TXA

### Time of TXA administration after injury

- N/A

### Included Patients

- 26 / 206
- Discharge/death
| Age, years, mean (SD) | 23.8 (7.7) / 22.9 (9.2) | Gender, % | Male 98.4 / 96.9 |
|--------------------------------------|------------------------|----------------|----------------|
| Vital signs | N/A | Injury Severity Score, points, mean (SD) | 26.1 (17.1) / 25.2 (20.5) |
| Blunt vs. Penetrating, n (%) | N/A | TBI vs. multiple trauma, n (%) | N/A |
| Region/Setting | UK | March 2006 - March 2011 |
| Inclusion criteria | patients who received at least 1 unit of packed red blood cells |
| Exclusion criteria | N/A |
| Patient characteristics IG/CG | Age, years, mean (SD) | 24.2 (11.7) / 23.6 (1.6) |
| Intervention | TXA bolus of 1 g intravenous, further doses at the clinician’s discretion. |
| Control | No TXA |
| Time of TXA administration after injury | N/A |
| Included Patients | 148 / 758 |
| Follow-up | 125 / 196 | discharge/ 30 days |

Morrison JJ, Ross JD, Dubose JJ, Jansen JO, Midwinter MJ, Rasmussen TE. Association of cryoprecipitate and tranexamic acid with improved survival following wartime injury: findings from the MATTERs II Study. JAMA Surgery. 2013;148(3):218-25.
| Gender, n (%)                      | Male 143 (96.6) / 710 (93.7) |
|-----------------------------------|-------------------------------|
| Vital signs                       | N/A                           |
| Injury Severity Score, points, mean (SD) | 23 (19.2) / 21.2 (18.5) |
| Blunt vs. Penetrating, n (%)      | N/A                           |
| TBI vs. multiple trauma, n (%)    | N/A                           |

| Region/Setting                    | USA 2008 - 2015               |
|-----------------------------------|-------------------------------|

| Inclusion criteria                | Adult trauma patients       |
|                                   | Documented Head Abbreviated Injury Scale |
|                                   | Requiring blood product resuscitation or |
|                                   | Likely to require massive transfusion (greater than 10 units of BP over 24 h) |

| Exclusion criteria                | No documented Head Abbreviated Injury Scale |
|                                   | Incomplete data                |

| Patient characteristics IG/CG    | Age, years, mean               |
|-----------------------------------|-------------------------------|

| Intervention                      | 1 g TXA bolus, 1 g TXA maintenance |
|-----------------------------------|-----------------------------------|
| Control                           | No TXA                           |
| Time of TXA administration after injury | N/A                             |
| Included Patients                 | 46 / 46                          |
| Follow-up                         | discharge                       |
| discharge / 30 days               |                                 |
| Gender, n (%) | 24.7 / 25.3 |
|--------------|-------------|
| Male 46 (100) / 46 (100) |

| Vital signs |  |
|-------------|---|
| GCS score, points, n (%) |  |
| GCS 14-15: 23 (50) / 21 (45.7) |
| GCS 10-13: 5 (10.9) / 3 (6.5) |
| GCS <9: 18 (39.1) / 22 (47.8) |

| Injury Severity Score, points, mean (SD) | 25.1 / 25.7 |
|----------------------------------------|-------------|

| Blunt vs. Penetrating, n (%) |  |
|-----------------------------|---|
| Penetrating 43 (93.5) / 39 (82.6) |

| TBI vs. multiple trauma, n (%) | N/A |
|-------------------------------|-----|

| Region/Setting | USA |
|----------------|-----|
| January 2012 - December 2016 |

| Inclusion criteria |  |
|--------------------|---|
| Adult trauma patients |

| Exclusion criteria |  |
|--------------------|---|
| taking prehospital anticoagulation |
| known risk of DVT, PE, or hereditary coagulopathy |
| prehospital TXA administration as part of a separate trial protocol |

| Intervention | TXA |
|--------------|-----|
| Control | No TXA |
| Time of TXA administration after injury | N/A |
| Included Patients | 189 / 189 |

Myers SP, Kutcher ME, Rosengart MR, Sperry JL, Peitzman AB, Brown JB, et al. Tranexamic acid administration is associated with an increased risk of posttraumatic venous thromboembolism. The Journal of Trauma and Acute Care Surgery. 2019;86(1):20-7.
### Patient characteristics IG/CG

| Age, years, median (IQR) | 36 (24 - 53) / 32 (22 - 55) |
|--------------------------|-------------------------------|
| Gender, n (%)            | Male 142 (75) / 132 (70)     |

### Vital signs

**Shock defined as:**
- Systolic blood pressure, mmHg, median (IQR) 83 (70, 98) / 84 (71, 98)
- Heart rate, bpm, median (IQR) 130 (114, 141) / 119 (104, 132)
- Lactate, mmol/l, mean (SD) 6.0 (3.8) / 5.4 (4.8)

### Injury Severity Score, points, median (IQR)

19 (12, 27) / 14 (8, 22)

### Blunt vs. Penetrating, n (%)

- Penetrating 65 (44) / 40 (21)
- TBI vs. multiple trauma, n (%) N/A

### Intervention

1 g TXA bolus, 1 g TXA maintenance

### Control

No TXA

### Time of TXA administration after injury

<3 h

---

Neeki MM, Dong F, Toy J, Vaezazizi R, Powell J, Wong D, et al. Tranexamic Acid in Civilian Trauma Care in the California Prehospital Antifibrinolytic Therapy Study. The Western Journal of Emergency Medicine. 2018;19(6):977-86.

© 2022 Karl V et al. *JAMA Network Open.*
- Bleeding not controlled by direct pressure or tourniquet
- Major amputation of any extremity above the wrists and above the ankles

**Exclusion criteria**

- Any patient <18 years of age
- Any patient more than three hours post-injury
- Any patient with an active thromboembolic event (within the last 24 hours) – i.e., active stroke, myocardial infarction or pulmonary embolism
- Any patient with a hypersensitivity or anaphylactic reaction to TXA
- Traumatic arrest with more than five minutes of cardiopulmonary resuscitation without return of vital signs
- Penetrating cranial injury
- Traumatic brain injury with brain matter exposed
- Isolated drowning or hanging victims
- Documented cervical cord injury with motor deficits

**Patient characteristics IG/CG**

| Age, years, mean (SD) | 37.96 (16.11) / 37.64 (16.33) |
|-----------------------|--------------------------------|
| Gender, n (%)         | Male 293 (80.9) / 293 (80.9)   |

**Vital signs**

**Shock defined as:**

- Systolic blood pressure, mmHg, mean (SD) 78.42 (16.17) / 83.66 (14.13)

| Injury Severity Score, points, mean (SD) | 16.08 (10.69) / 17.15 (11.71) |

| Blunt vs. Penetrating, n (%)             |                                |

**Included Patients**

362 / 362

**Follow-up**

28 days
Neeki MM, Dong F, Toy J, Salameh J, Rabiei M, Powell J, et al. Safety and Efficacy of Hospital Utilization of Tranexamic Acid in Civilian Adult Trauma Resuscitation. The Western Journal of Emergency Medicine. 2020;21(2):217-25.

| Region/Setting          | USA                      |
|-------------------------|--------------------------|
| Time of TXA administration after injury | <3 h                         |
| Included Patients       | 280 / 280              |
| Follow-up               | 28 days                 |

| Inclusion criteria |  |
|--------------------|---|
| ● Blunt or penetrating trauma with signs and symptoms of hemorrhagic shock within three hours of injury (SBP of less than 90 mmHg upon arrival to designated trauma centers, HR > 120, estimated blood loss of 500 milliliters, bleeding not controlled by direct pressure or tourniquet) |  |
| ● Major amputation of any extremity above the wrists and above the ankles |  |

| Exclusion criteria |  |
|--------------------|---|
| ● Any patient <18 years of age |  |
| ● Any patient more than three hours post-injury |  |
| ● Any patient with an active thromboembolic event (within the last 24 hours) – i.e., active stroke, myocardial infarction or pulmonary embolism |  |
| ● Any patient with a hypersensitivity or anaphylactic reaction to TXA |  |
| ● Any patient that received prehospital TXA |  |
| ● Traumatic arrest with more than five minutes of cardiopulmonary resuscitation without return of vital signs |  |
| ● Penetrating cranial injury |  |
| ● Traumatic brain injury with brain matter exposed |  |
| ● Isolated drowning or hanging victims |  |
| ● Documented cervical cord injury with motor deficits |  |

| Patient characteristics IG/CG |  |
|------------------------------|---|
| Age, years, mean (SD) |  |
| Gender, n (%) | Male 236 (84.3) / 241 (86.1) |
|---------------|--------------------------------|
| Vital signs   |                                |
| Shock defined as: |                                |
| Systolic blood pressure, mmHg, mean (SD) | 99.32 (17.84) / 102.32 (23.27) |
| Injury Severity Score, points, mean (SD) | N/A |
| Blunt vs. Penetrating, n (%) | Blunt 159 (56.8) / 160 (57.1) |
| TBI vs. multiple trauma, n (%) | N/A |

| Region/Setting | Japan |
|----------------|-------|
| 2012           |       |

| Inclusion criteria |
|--------------------|
| ● 18 years of age  |
| ● ISS ≥ 16         |

| Exclusion criteria |
|--------------------|
| ● Complications (e.g. out-of-hospital cardiac arrest, burns, liver cirrhosis, isolated cervical spine injury not caused by a high-energy accident) |
| ● Pregnancy        |

| Patient characteristics IG/CG |
|-------------------------------|
|                               |

| Intervention |
|--------------|
| TXA          |
| Control      |
| No TXA       |

| Time of TXA administration after injury |
|----------------------------------------|
| <3 h                                   |

| Included Patients |
|-------------------|
| 250 / 250         |

| Follow-up |
|-----------|
| 28 days   |
| Age, years, median (IQR) | 57 (36 - 72) / 56 (38 - 69) |
|-------------------------|-----------------------------|
| Gender, n (%)           | 181 (72.4) / 186 (74.4)     |
| Vital signs             |                             |
| Shock defined as:       |                             |
| • Systolic blood pressure, mmHg, median (IQR) 136 (110 - 159) / 133 (110 - 157) |
| • Heart rate, bpm, median (IQR) 87 (75 - 100) / 86 (75 - 100) |
| • Lactate, mmol/l, mean (SD) 2.6 (1.7 - 4) / 2.6 (1.6 - 3.9) |
| Injury Severity Score, points, median (IQR) | 25 (17-29) / 25 (17-29) |
| Blunt vs. Penetrating, n (%) |                             |
| Blunt 249 (99.6) / 249 (99.6) |
| TBI vs. multiple trauma, n (%) |                             |
| TBI 188 (75.2) / 190 (76) |

Swendsen H, Galante J, Utter G, Bateni S, Scherer L, Schermer C. Tranexamic Acid use in Trauma: Effective but not Without Consequences. 2013.

| Region/Setting | USA |
|----------------|-----|
| Inclusion criteria | age 18 years and older |
| • Hypotension (SBP <90 mm Hg) upon presentation |
| • Massive transfusion guideline activation in the Emergency Department (ED) |
| • Transport directly to the operating room (OR) or interventional radiology (IR) suite from the ED |

| Intervention | TXA 1 g bolus, 1 g maintenance |
|-------------|-------------------------------|
| Control     | No TXA                         |
| Time of TXA administration after injury | < 3 h |
| Included Patients |                             |
Exclusion criteria
- patients who were transferred from another hospital
- injured more than 3 hours prior the TXA administration

Patient characteristics IG/CG

Age, years, mean (SD)
44.6 (20.3) / 47.6 (18.9)

Gender, %
37 (71.2) / 49 (66.2)

Vital signs
Shock defined as:
- Systolic blood pressure, mmHg, mean (SD) 83 (26) / 74 (20)
- Heart rate, bpm, mean (SD) 127.4 (25.5) / 117 (25)

Injury Severity Score, points, mean (SD)
27.1 (15) / 20.5 (16.8)

Blunt vs. Penetrating, n (%)
N/A

TBI vs. multiple trauma, n (%)
N/A

Valle EJ, Allen CJ, Van Haren RM, Jouria JM, Li H, Livingstone AS, et al. Do all trauma patients benefit from tranexamic acid? The Journal of Trauma and Acute Care Surgery. 2014;76(6):1373-8.

Region/Setting
USA
August 2009 - January 2013

Inclusion criteria
- Adult trauma patients

Intervention
TXA 1 g bolus, 1 g maintenance

Control
No TXA

© 2022 Karl V et al. JAMA Network Open.
- Underwent emergency surgery directly from the resuscitation area

**Exclusion criteria**
- Emergency surgery for isolated orthopedic and/or neurosurgical indications and minor trauma operations such as those for complex wound closures

**Patient characteristics IG/CG**

| Age, years, mean (SD) | 42 (20) / 43 (20) |
|-----------------------|-------------------|
| Gender, %             | Male 85 / 86      |
| **Vital signs**       |                   |
| Shock defined as:     |                   |
| - Systolic blood pressure, mmHg, mean (SD) 98 (30) / 101 (32) |
| - Heart rate, bpm, mean (SD) 105 (26) / 103 (29) |
| - Base value, mmol/l, mean (SD) -7.4 (7) / -7.7 (6.9) |

**Injury Severity Score, points, mean (SD)**

| 28 (16) / 28 (17) |

**Blunt vs. Penetrating, %**

| Penetrating 54 / 54 |

**TBI vs. multiple trauma, n (%)**

| TBI 24 / 26 |

**Time of TXA administration after injury**

| N/A |

**Included Patients**

| 150 / 150 |

**Follow-up**

| N/A |
| Region/Setting | Germany  
January 2012 - December 2014 |
|----------------|---------------------------------|
| Inclusion criteria | 1. ADAC Air Rescue Service database:  
- Primarily admitted trauma patient  
- Critical injury, defined as preclinically assessed NACA IV (potentially life-threatening), NACA V (acute danger) or NACA VI (respiratory and/or cardiac arrest)  
- Admission to a trauma center participating in the TR-DGU  
2. TR-DGU database:  
- Primary admission  
- Treatment in a German trauma centre (i.e., exclusion of trauma centres from other countries) |
| Exclusion criteria | N/A |
| Patient characteristics IG/CG | Age, years, mean (SD)  
43 (19) / 41 (18)  
Gender, n (%)  
Male 187 (72.5) / 187 (72.5)  
Vital signs  
Shock defined as:  
- Systolic blood pressure, mmHg, mean (SD) 118 (34) / 116 (33)  
- Base value, mmol/l, mean (SD) -3.1 (4.7) / -3.5 (5.1) |
| Intervention | TXA  
Control  
No TXA |
| Time of TXA administration after injury | <3 h |
| Included Patients | 258 / 258 |
| Follow-up | 30 days |
| Injury Severity Score, points, mean (SD) | 24 (14) / 24 (16) |
|----------------------------------------|------------------|
| Blunt vs. Penetrating, n (%)           | Blunt 233 (90.3) / 240 (93) |
|                                        | TBI vs. multiple trauma, n (%) |
|                                        | Isolated TBI 7 (2.7) / 8 (3.1) |

Walker PF, Bozzay JD, Johnston LR, Elster EA, Rodriguez CJ, Bradley MJ. Outcomes of tranexamic acid administration in military trauma patients with intracranial hemorrhage: a cohort study. BMC Emergency Medicine. 2020;20(1):39.

| Region/Setting                  | USA |
|---------------------------------|-----|
|                                 | October 2010 - December 2015 |

| Inclusion criteria              | military casualties |
|                                 | diagnosed with military combat-related ICH |

| Exclusion criteria              | no active duties service members |
|                                 | incomplete data |

| Patient characteristics IG/CG   | |
|---------------------------------|------------------|
| Age, years, mean (SD)           | 24.2 (3.1) / 25.5 (5.3) |
| Gender, %                       | N/A |
| Vital signs                     | |
| If TBI: GCS score, points, mean (SD) | 9.2 (4.4) / 12.5 (3.4) |
| Injury Severity Score, points, mean (SD) |  |

| Intervention                    | TXA |
|                                 | No TXA |

| Time of TXA administration after injury | N/A |
| Include Patients                    | 14 / 57 |

Follow-up
| N/A |

© 2022 Karl V et al. JAMA Network Open.
|                        |                   |
|------------------------|-------------------|
| 36.6 (12.5) / 26.2 (11.4) |                   |
| **Blunt vs. Penetrating, n (%)** |                   |
| Penetrating TBI 6 (42.3) / 30 (52.6) |                   |
| TBI vs. multiple trauma, n (%) |                   |
| N/A                     |                   |

Abbreviations: IG: Intervention group; CG: Control group; SD: Standard deviation; GCS: Glasgow Coma Score; TXA: Tranexamic acid; ED: Emergency department; TBI: Traumatic brain injury; N/A: not available; SBP: Systolic blood pressure; HR: Heart rate; ICH: Intracranial hemorrhage

© 2022 Karl V et al. *JAMA Network Open.*
### eTable 3. Extracted Data of Blood Transfusions

| Study                  | Follow-up | PLT mean.e | PLT sd.e | PLT mean.c | PLT sd.c | WB mean.e | WB sd.e | WB mean.c | WB sd.c | PRBC mean.e | PRBC sd.e | PRBC mean.c | PRBC sd.c | Cryo mean.e | Cryo.sd.e | Cryo mean.c | Cryo sd.c | FFP mean.e | FFP sd.e | FFP mean.c | FFP sd.c |
|------------------------|-----------|------------|----------|------------|----------|------------|---------|------------|---------|-------------|-----------|-------------|-----------|-------------|----------|-------------|-----------|------------|---------|-------------|---------|
| Chakroun-Walha 2019    | 24 h      | 1.6        | 0.5      | 0.3        | 1.4      | 0          | 0       | 0.5        | 1.2     | 0.2         | 0.6       | 0.8         | 1.0       | 0.3         | 1.6      | 24 h        |          |            |         |
| CRASH-2 RCT            | D/28 d    | 3          | 3        |            |          |            |         |            |         |             |           |             |           |             |          |             |         |
| Guyette 2020 RCT       | 24 h      | 0          | 0        | 0          | 0        | 0          | 0       | 0          | 0       | 0           | 0         | 0           | 0         | 0           | 0        | 0           | 0       |
| Balvers 2017           | 24 h      | 25         | 28       | 20         | 17       |            |         |            |         |             |           |             |           |             |          |             |         |
| Cole 2015              | 24 h      | 1          | 1        | 0          | 0.7      | 7          | 7.4     | 2          | 5.0     | 1           | 1         | 0           | 0.1       | 5           | 5        | 1           | 4        | 24 h        |
| Dixon 2019             |           | 5          | 4        | 3          | 3        | 23         | 18      | 20         | 11      | 16          | 16        | 15          | 12        | N/A         |          |             |         |
| El-Menyar 2020         | N/A       | 5.2        | 9.7      |            |          |            |         |            |         |             |           |             |           |             |          |             |         |
| Howard 2017            | 24 h      | 1.5        | 1.9      | 1          | 1.6      | 12.5       | 11.5    | 8.4        | 3.2     | 5.7         | 2.2       | 4.8         | 11.1      | 9.9         | 7.7      | 8.2         | 24 h     |
| Johnston 2018          | 24 h      | 34.5       | 25       | 5.2        | 14.5     | 2          | 1.9      | 0.3        | 1.5     | 1.3         | 3.1       | 0.3         | 2.0       | 13.1        | 8.6      | 2.2         | 5        | 6.5         | 9        | 0.8         | 4        | 11.6        | 7.6      | 1.7         | 4.3      | 24 h        |
| Khan 2018              | 24 h      | 13         | 10       |            |          | 15         | 12      |            |         |             |           |             |           |             |          |             |         |
| Lewis 2016             | 24 h      | 17         | 7        |            |          |            |         |            |         |             |           |             |           |             |          |             |         |
| Moore 2017             | N/A       | 3          | 2        |            |          | 28         | 19      | 2          | 0       | 15          | 8         |             |           |             |          |             |         |
| Morrison 2012          | 24 h      | 3.2        | 2.4      | 3.6        | 3.6      | 21         | 12.8    | 22.5       | 15.9    | 1.6         | 2.6       | 0.7         | 1.6       | 18.4        | 11.5     | 19.6       | 14.3     |
| Morrison 2013          | 24 h      | 0.7        | 1.1      | 0.2        | 0.8      | 8          | 6.2     | 5.3        | 7.9     |             |           |             |           |             |          |             |         |
| Morte 2019             | 24 h      | 18.3       | 14.2     | 16.5       | 16.3     |            |         |            |         |             |           |             |           |             |          |             |         |
| Myers 2019             | N/A       | 1.18       | 2.17     | 0.43       | 1.43     | 4.43       | 5.57    | 2.53       | 3.35    | 2.77        | 5.14      | 1.44        | 3.37      | N/A         |          |             |         |
| Neeki 2018             | D         | 1          | 3        |            |          |            |         |            |         |             |           |             |           |             |          |             |         |
| Neeki 2020             | D         | 4          | 7        |            |          |            |         |            |         |             |           |             |           |             |          |             |         |
|                     | unit.e | sd.e | unit.c | sd.c | D: Discharge | ER to ICU |
|---------------------|--------|------|--------|------|---------------|-----------|
| Shiraishi 2017      | 4.5    | 4    | 4.7    | 4    | 24 h          |           |
| Swendsen 2013       | 1      | 0    | 7      | 2    | N/A           |           |
| Wafaisade 2016      | 0.1    | 0.7  | 0.1    | 0.9  | 1.6 1.6 2     | 5.8       |

unit.e: Number of units in the experimental group; sd.e: Standard deviation in the experimental group; unit.c: Number of units in the control group; sd.c: Standard deviation in the control group; D: Discharge; ER to ICU: Time between emergency room and intensive care unit; PLT: Platelets; WB: Whole blood; PRBC: Packed red blood cells; Cryo: Cryoprecipitate; FFP: Fresh frozen plasma.
**Figure 2. 24-Hour Mortality**

| Study               | Experimental Events | Control Events | Total Events | Weight | Risk Ratio IV, 95% CI          |
|---------------------|---------------------|----------------|--------------|--------|-----------------------------|
| Guyette 2020 RCT    | 16                  | 447            | 463          | 0.95   | 0.49; 1.86                  |
| Glover 2019         | 14                  | 333            | 347          | 1.10   | 0.58; 2.07                  |
| Harvin 2015         | 33                  | 98             | 131          | 0.93   | 0.33; 2.81                  |
| Howard 2017         | 20                  | 373            | 393          | 0.93   | 0.55; 1.57                  |
| Khan 2018           | 8                   | 31             | 39           | 0.67   | 0.34; 1.31                  |
| Luehr 2017          | 1                   | 63             | 64           | 0.11   | 0.01; 1.00                  |
| Morrison 2012       | 12                  | 125            | 137          | 0.85   | 0.34; 1.22                  |
| Nekhi 2018          | 7                   | 362            | 369          | 0.54   | 0.22; 1.33                  |
| Nekhi 2020          | 3                   | 280            | 283          | 0.54   | 0.22; 1.33                  |
| Swedensen 2013      | 3                   | 52             | 55           | 0.33   | 0.10; 1.09                  |
| Wafaisade 2016      | 15                  | 258            | 273          | 0.47   | 0.26; 0.84                  |
| **Total**           |                     |                | 1304         |        |                             |
| **Prediction interval** |                |                | [0.17; 3.63] |        |                             |

**Figure 3. 24-Hour Mortality in Observational Studies Excluding Studies at High Risk for Confounding Bias**

| Study               | Experimental Events | Control Events | Total Events | Weight | Risk Ratio IV, Random, 95% CI          |
|---------------------|---------------------|----------------|--------------|--------|-----------------------------|
| Howard 2017         | 12                  | 362            | 374          | 0.54   | 0.22; 1.33                  |
| Khan 2018           | 7                   | 280            | 287          | 0.54   | 0.22; 1.33                  |
| Nekhi 2018          | 3                   | 280            | 283          | 0.54   | 0.22; 1.33                  |
| Nekhi 2020          | 15                  | 258            | 273          | 0.47   | 0.26; 0.84                  |
| Wafaisade 2016      | 20                  | 384            | 404          | 0.47   | 0.26; 0.84                  |
| **Total (95% CI)**  | 1304                | 1619           | 100%         | 0.67   | [0.45; 1.01]                |
| **Prediction interval** |                |                | [0.42; 1.07] |        |                             |

Heterogeneity: Tau² = 0; Chi² = 3.34, df = 4 (P = 0.50); I² = 0%

**Figure 4. 1-Month Mortality in RCTs**

| Study               | Experimental Events | Control Events | Total Events | Weight | Risk Ratio IV, Random, 95% CI          |
|---------------------|---------------------|----------------|--------------|--------|-----------------------------|
| Chakroun-Wahla 2019 RCT | 27                  | 1000          | 1027        | 0.82   | 0.54; 1.24                  |
| CRASH 2 RCT 2010    | 1463                | 10080         | 10243       | 0.91   | 0.86; 0.97                  |
| CRASH 3 2019 RCT    | 855                 | 4613           | 5468        | 0.94   | 0.88; 1.02                  |
| Guyette 2020 RCT    | 36                  | 442            | 478          | 0.82   | 0.54; 1.24                  |
| Rowell 2020 RCT     | 93                  | 803            | 896          | 0.88   | 0.64; 1.20                  |
| **Total (95% CI)**  | 15814               | 15480         | 100%        | 0.92   | [0.87; 0.97]                |
| **Prediction interval** |                |                | [0.87; 0.97] |        |                             |

Heterogeneity: Tau² = 0; Chi² = 2.10, df = 4 (P = 0.72); I² = 0%

© 2022 Karl V et al. JAMA Network Open.
**eFigure 5. 1-Month Mortality in Observational Studies Excluding Studies at High Risk for Confounding Bias**

| Study          | Experimental Events | Total | Control Events | Total | Weight | Risk Ratio IV, Random, 95% CI | Risk Ratio IV, Random, 95% CI |
|---------------|---------------------|-------|---------------|-------|--------|--------------------------------|--------------------------------|
| Boutonnel 2018| 94                  | 403   | 65            | 281   | 17.8%  | 1.01 [0.76; 1.33]              |                                |
| Dixon 2020    | 24                  | 62    | 31            | 62    | 14.6%  | 0.77 [0.52; 1.18]              |                                |
| Howard 2017   | 27                  | 373   | 59            | 657   | 13.7%  | 0.81 [0.52; 1.25]              |                                |
| Khan 2018     | 14                  | 31    | 31            | 62    | 13.1%  | 0.90 [0.57; 1.43]              |                                |
| Neeki 2018    | 13                  | 362   | 30            | 382   | 9.6%   | 0.43 [0.23; 0.82]              |                                |
| Neeki 2020    | 3                   | 280   | 14            | 280   | 3.7%   | 0.21 [0.08; 0.74]              |                                |
| Shrasihi 2017 | 25                  | 250   | 46            | 250   | 13.3%  | 0.54 [0.35; 0.86]              |                                |
| Wafaisade 2016| 36                  | 258   | 42            | 258   | 14.3%  | 0.86 [0.57; 1.29]              |                                |

Total (95% CI) 2019: 2212, 100.0% 0.73 [0.53; 1.00] 0.34; 1.56

**Prediction interval**

Heterogeneity: Tau² = 0.0789; Chi² = 13.80, df = 7 (P = 0.05); I² = 49%

**eFigure 6. 1-Month Mortality in Multiple Trauma**

| Study          | Experimental Events | Total | Control Events | Total | Weight | Risk Ratio IV, Random, 95% CI | Risk Ratio IV, Random, 95% CI |
|---------------|---------------------|-------|---------------|-------|--------|--------------------------------|--------------------------------|
| CRASH II 2010 RCT| 1463               | 10060 | 1613          | 10067 | 21.0%  | 0.91 [0.85; 0.97]              |                                |
| Guyette 2010 RCT| 17                 | 352   | 25            | 374   | 0.2%   | 0.72 [0.40; 1.31]              |                                |
| Boutonnel 2018 | 94                 | 403   | 65            | 281   | 14.1%  | 1.01 [0.76; 1.33]              |                                |
| Dixon 2019     | 24                 | 62    | 31            | 62    | 10.3%  | 0.77 [0.52; 1.16]              |                                |
| Howard 2017    | 27                 | 373   | 59            | 657   | 9.3%   | 0.81 [0.52; 1.25]              |                                |
| Khan 2018      | 14                 | 31    | 31            | 62    | 8.8%   | 0.90 [0.57; 1.43]              |                                |
| Luehr 2017     | 7                  | 53    | 13            | 62    | 3.7%   | 0.63 [0.27; 1.40]              |                                |
| Neeki 2018     | 13                 | 362   | 30            | 362   | 5.7%   | 0.43 [0.23; 0.82]              |                                |
| Neeki 2020     | 3                  | 280   | 14            | 280   | 1.9%   | 0.21 [0.06; 0.74]              |                                |
| Shrasihi 2017  | 25                 | 250   | 46            | 250   | 9.9%   | 0.54 [0.35; 0.86]              |                                |
| Wafaisade 2016 | 36                 | 258   | 42            | 258   | 10.0%  | 0.86 [0.57; 1.29]              |                                |

Total (95% CI) 12484: 12715, 100.0% 0.77 [0.63; 0.94] 0.48; 1.25

**Prediction interval**

Heterogeneity: Tau² = 0.0379; Chi² = 17.48, df = 10 (P = 0.06); I² = 43%

**eFigure 7. 1-Month Mortality in TBI**

| Study          | Experimental Events | Total | Control Events | Total | Weight | Risk Ratio IV, Random, 95% CI | Risk Ratio IV, Random, 95% CI |
|---------------|---------------------|-------|---------------|-------|--------|--------------------------------|--------------------------------|
| Chakroun & Wahtab 2019 RCT | 27         | 96    | 19            | 84    | 2.4%  | 1.24 [0.75; 2.07]              |                                |
| CRASH II 2019 RCT | 855       | 4813  | 892           | 4514  | 89.0%  | 0.94 [0.86; 1.02]              |                                |
| Guyette 2020 RCT | 19         | 90    | 20            | 78    | 2.1%  | 0.82 [0.48; 1.43]              |                                |
| Rowell 2020 RCT | 19         | 90    | 20            | 78    | 2.1%  | 0.82 [0.48; 1.43]              |                                |

Total (95% CI) 5402: 4961, 100.0% 0.94 [0.85; 1.03] 0.83; 1.06

**Prediction interval**

Heterogeneity: Tau² = 0; Chi² = 1.56, df = 3 (P = 0.67); I² = 0%

© 2022 Karl V et al. JAMA Network Open.
eFigure 8. 1-Month Mortality in Standard Protocol Tranexamic Acid Administration

| Study                | Experimental Events | Total Events | Control Events | Weight | IV, Random, 95% CI | Risk Ratio IV, Random, 95% CI |
|----------------------|---------------------|--------------|----------------|--------|---------------------|-----------------------------|
| Chakroun-Walha 2019 RCT | 27                  | 96           | 19             | 84     | 11.7%               | 1.24 [0.75; 2.07]            |
| CRASH-2 2010 RCT     | 1463                | 10060        | 1613           | 10057  | 18.3%               | 0.91 [0.85; 0.97]            |
| CRASH-3 2019 RCT     | 855                 | 4613         | 892            | 4514   | 18.2%               | 0.94 [0.86; 1.02]            |
| Guyette 2020 RCT     | 11                  | 141          | 45             | 452    | 9.8%                | 0.78 [0.42; 1.47]            |
| Rowell 2020 RCT      | 53                  | 285          | 50             | 285    | 14.5%               | 1.06 [0.75; 1.50]            |
| Dixon 2019           | 24                  | 62           | 31             | 62     | 13.0%               | 0.77 [0.52; 1.16]            |
| Neeki 2020           | 13                  | 362          | 30             | 352    | 9.7%                | 0.43 [0.23; 0.82]            |
| Total (95% CI)       | 15899               | 16106        | 100.0%         | 0.82 [0.58; 1.16] | 0.33 [2.03]        |

Heterogeneity: Tau² = 0.1165; Chi² = 14.00, df = 7 (P = 0.06); I² = 50%

Heterogeneity: Tau² = 0; Chi² = 6.36, df = 7 (P = 0.50); I² = 0%

eFigure 9. 1-Month Mortality in Nonstandard Protocol Tranexamic Acid Administration
eFigure 10. Overall Mortality

| Study                        | Experimental Events | Control Events | Risk Ratio IV, 95% CI |
|------------------------------|---------------------|----------------|-----------------------|
| Charkroun-Walha 2019 RCT      | 27                  | 98             | 84, 1.24 [0.75, 2.07]|
| CRASH-2 2010 RCT             | 1463               | 10600          | 1613, 0.91 [0.65, 0.97]|
| CRASH-3 2019 RCT             | 655                | 4613           | 1892, 1.94 [0.86, 1.02]|
| Guyette 2020 RCT             | 36                 | 442            | 45, 0.82 [0.54, 1.24]  |
| Rowell 2020 RCT              | 101                | 551            | 54, 0.92 [0.69, 1.24]  |
| Yuthakasemsunt 2013 RCT      | 12                 | 120            | 17, 0.69 [0.35, 1.39]  |
| Barides 2017                 | 4                  | 32             | 23, 1.19 [0.85, 1.64]  |
| Boutonnet 2018               | 94                 | 403            | 65, 1.01 [0.76, 1.33]  |
| Cole 2015                    | 17                 | 160            | 18, 2.33 [0.71, 2.50]  |
| Dixon 2019                   | 24                 | 62             | 31, 0.77 [0.52, 1.16]  |
| El-Menyar 2020               | 25                 | 102            | 30, 0.83 [0.53, 1.31]  |
| Glover 2019                  | 27                 | 333            | 106, 0.94 [0.68, 1.29]|
| Harnn 2016                   | 39                 | 98             | 169, 3.34 [1.70, 6.10] |
| Howard 2017                  | 27                 | 373            | 59, 0.81 [0.52, 1.25]  |
| Johnston 2018                | 1                  | 146            | 3, 0.71 [0.07, 6.72]   |
| Khan 2018                    | 14                 | 31             | 31, 0.90 [0.57, 1.43]  |
| Lewis 2016                   | 10                 | 335            | 11, 0.70 [0.53, 0.98]  |
| Luehr 2017                   | 7                  | 53             | 13, 0.83 [0.27, 1.40]  |
| Moore 2017                   | 13                 | 26             | 35, 2.06 [1.61, 4.80]  |
| Morrison 2012                | 18                 | 125            | 55, 0.51 [0.32, 0.83]  |
| Morrison 2013                | 27                 | 148            | 179, 0.78 [0.54, 1.11] |
| Morte 2019                   | 0                  | 48             | 5, 0.09 [0.01, 1.60]   |
| Myers 2019                   | 53                 | 189            | 28, 0.89 [1.25, 2.86]  |
| Neeki 2018                   | 13                 | 362            | 30, 0.43 [0.23, 0.82]  |
| Neeki 2020                   | 3                  | 280            | 24, 0.21 [0.06, 0.74]  |
| Shahriar 2017                | 25                 | 250            | 45, 0.54 [0.35, 0.86]  |
| Swensden 2013                | 9                  | 52             | 17, 0.75 [0.30, 1.60]  |
| Valle 2014                   | 47                 | 150            | 35, 1.34 [0.92, 1.95]  |
| Wafaisade 2016               | 38                 | 258            | 42, 0.90 [0.60, 1.35]  |
| Walker 2020                  | 1                  | 14             | 4, 57, 1.02 [0.12, 8.41]|

Prediction Interval [0.40; 2.17]

---

eFigure 11. Overall Mortality in RCTs

| Study                        | Experimental Events | Control Events | Risk Ratio IV, Random, 95% CI |
|------------------------------|---------------------|----------------|-----------------------------|
| Charkroun-Walha 2019 RCT      | 27                  | 96             | 84, 1.24 [0.75, 2.07]      |
| CRASH-2 (RCT)                | 1463               | 10600          | 1613, 0.91 [0.65, 0.97]    |
| CRASH-3 (RCT)                | 655                | 4613           | 1892, 1.94 [0.86, 1.02]    |
| Guyette 2020 RCT             | 36                 | 442            | 45, 0.82 [0.54, 1.24]      |
| Rowell 2020 RCT              | 101                | 551            | 54, 0.92 [0.69, 1.24]      |
| Yuthakasemsunt 2013 RCT      | 12                 | 120            | 17, 0.69 [0.35, 1.39]      |

Total (95% CI) 15882 15507 100.0% 0.92 [0.86; 0.98]

Prediction Interval [0.88; 0.99]

Heterogeneity: Tau² = 0; Chi² = 2.65, df = 5 (P = 0.75); I² = 0%
eFigure 12. Overall Mortality in Observational Studies Excluding Studies at High Risk for Confounding Bias

| Study              | Experimental Events | Control Events | Risk Ratio IV, 95% CI |
|--------------------|---------------------|----------------|----------------------|
| Barde 2017         | 4                   | 23             | 119.05 [0.24; 1.74]  |
| Boutonnet 2018     | 94                  | 281            | 1.01 [0.76; 1.33]    |
| Cole 2015          | 17                  | 18             | 2.33 [0.71; 2.50]    |
| Dixon 2019         | 24                  | 62             | 0.77 [0.52; 1.16]    |
| El-Menyar 2020     | 25                  | 102            | 0.83 [0.53; 1.31]    |
| Howard 2017        | 27                  | 373            | 0.81 [0.52; 1.25]    |
| Khan 2018          | 14                  | 31             | 0.90 [0.57; 1.43]    |
| Morrison 2013      | 27                  | 148            | 0.77 [0.54; 1.11]    |
| Morte 2019         | 0                   | 46             | 0.09 [0.01; 1.60]    |
| Myers 2019         | 53                  | 189            | 1.89 [1.25; 2.66]    |
| Neeki 2018         | 13                  | 362            | 0.43 [0.23; 0.82]    |
| Neeki 2020         | 3                   | 280            | 0.21 [0.06; 0.74]    |
| Shririshi 2017     | 25                  | 250            | 0.54 [0.35; 0.86]    |
| Valle 2014         | 47                  | 150            | 1.34 [0.92; 1.95]    |
| Wefaiwade 2016     | 36                  | 258            | 0.90 [0.60; 1.35]    |

Prediction interval [0.35; 2.65]

0.01 0.1 1 10 100 Tranexamcaine Control

Approximately 0.2% of control deaths were not counted.

eFigure 13. Overall Mortality in Multiple Trauma

| Study              | Experimental Events | Control Events | Risk Ratio IV, 95% CI |
|--------------------|---------------------|----------------|----------------------|
| CRASH-2 2010 RCT   | 1453                | 10060          | 0.91 [0.85; 0.97]    |
| Guette 2020 RCT    | 17                  | 352            | 0.72 [0.40; 1.31]    |
| Barthe 2017        | 4                   | 32             | 0.68 [0.24; 1.74]    |
| Boutonnet 2018     | 94                  | 65             | 1.01 [0.76; 1.33]    |
| Cole 2015          | 17                  | 18             | 1.33 [0.71; 2.50]    |
| Dixon 2019         | 24                  | 31             | 0.77 [0.52; 1.16]    |
| El-Menyar 2020     | 25                  | 102            | 0.83 [0.53; 1.31]    |
| Glover 2019        | 47                  | 106            | 0.94 [0.68; 1.29]    |
| Harrison 2015      | 39                  | 98             | 1.34 [1.76; 3.10]    |
| Howard 2017        | 20                  | 373            | 0.93 [0.55; 1.57]    |
| Johnston 2018      | 1                   | 146            | 0.71 [0.07; 6.72]    |
| Khan 2018          | 14                  | 31             | 0.90 [0.57; 1.43]    |
| Lewis 2016         | 10                  | 335            | 1.70 [0.73; 3.96]    |
| Luehr 2017         | 7                   | 53             | 0.63 [0.27; 1.48]    |
| Moors 2017         | 13                  | 26             | 2.94 [1.81; 4.80]    |
| Morrison 2012      | 18                  | 55             | 0.51 [0.32; 0.83]    |
| Morrison 2013      | 27                  | 148            | 0.77 [0.54; 1.11]    |
| Myers 2019         | 53                  | 189            | 1.89 [1.25; 2.66]    |
| Neeki 2018         | 13                  | 362            | 0.43 [0.23; 0.82]    |
| Neeki 2020         | 3                   | 280            | 0.21 [0.06; 0.74]    |
| Shririshi 2017     | 25                  | 250            | 0.54 [0.35; 0.86]    |
| Swendsen 2013      | 9                   | 52             | 0.75 [0.36; 1.56]    |
| Valle 2014         | 25                  | 109            | 1.72 [0.95; 3.12]    |
| Wefaiwade 2016     | 38                  | 258            | 0.90 [0.60; 1.35]    |

Prediction interval [0.35; 2.47]

0.1 0.5 1 2 10 Tranexamcaine Control

Approximately 1% of control deaths were not counted.

© 2022 Karl V et al. JAMA Network Open.
eFigure 14. Overall Mortality in TBI

| Study                             | Experimental Total | Control Total | Weight | Risk Ratio IV, Random, 95% CI |
|-----------------------------------|--------------------|---------------|--------|-----------------------------|
| Chakroun Walha 2019 RCT           | 27                 | 96            | 91     | 1.24 [0.75; 2.07]            |
| CRASH-3 2019 RCT                  | 855                | 4613          | 4541   | 0.94 [0.80; 1.02]            |
| Guyette 2020 RCT                  | 19                 | 90            | 78     | 0.82 [0.48; 1.43]            |
| Rowell 2020 RCT                   | 101                | 551           | 272    | 0.92 [0.69; 1.24]            |
| Yuthakasomsunt 2013 RCT           | 12                 | 120           | 118    | 0.89 [0.35; 1.49]            |
| Morte 2019                        | 0                  | 40            | 40     | 0.09 [0.01; 1.60]            |
| Valle 2014                        | 13                 | 32            | 34     | 1.53 [0.70; 3.09]            |
| Walker 2020                       | 1                  | 14            | 5      | 1.02 [0.12; 8.41]            |

Total (95% CI) 5562 5203 100.0% 0.94 [0.88; 1.03] [0.88; 1.03]

Heterogeneity: Tau² = 0, Chi² = 6.58, df = 7 (P = 0.47), I² = 0%

eFigure 15. Overall Mortality in In-hospital Tranexamic Acid Administration

| Study                             | Experimental Total | Control Total | Weight | Risk Ratio IV, Random, 95% CI |
|-----------------------------------|--------------------|---------------|--------|-----------------------------|
| Chakroun Walha 2019 RCT           | 1463               | 10060         | 10067  | 0.91 [0.85; 0.97]            |
| CRASH-2 2010 RCT                  | 855                | 4613          | 4514   | 0.94 [0.88; 1.02]            |
| CRASH-3 2019 RCT                  | 12                 | 120           | 118    | 0.69 [0.35; 1.39]            |
| Yuthakasomsunt 2013 RCT           | 3                  | 280           | 280    | 0.21 [0.06; 0.74]            |

Total (95% CI) 15169 15063 100.0% 0.82 [0.44; 1.54] [0.17; 3.80]

Heterogeneity: Tau² = 0.1671, Chi² = 7.68, df = 4 (P = 0.10), I² = 48%

eFigure 16. Overall Mortality in Prehospital Tranexamic Acid Administration

| Study                             | Experimental Total | Control Total | Weight | Risk Ratio IV, Random, 95% CI |
|-----------------------------------|--------------------|---------------|--------|-----------------------------|
| Guyette 2020 RCT                  | 36                 | 442           | 452    | 0.82 [0.54; 1.24]            |
| Rowell 2020 RCT                   | 101                | 551           | 54     | 0.92 [0.69; 1.24]            |
| El-Menyar 2020                    | 25                 | 102           | 102    | 0.83 [0.53; 1.31]            |
| Neeki 2018                        | 13                 | 362           | 362    | 0.43 [0.23; 0.82]            |
| Wafaisade 2016                    | 38                 | 258           | 258    | 0.90 [0.60; 1.35]            |

Total (95% CI) 1715 1446 100.0% 0.82 [0.61; 1.10] [0.49; 1.36]

Heterogeneity: Tau² = 0.0136, Chi² = 4.71, df = 4 (P = 0.32), I² = 15%

© 2022 Karl V et al. JAMA Network Open.
eFigure 17. Overall Mortality in Standard Protocol Tranexamic Acid Administration

| Study                        | Experimental Events | Control Events | Risk Ratio IV, 95% CI |
|------------------------------|---------------------|----------------|----------------------|
| Chalrroux-Walha 2019 RCT      | 27                  | 96             | 84.124 [0.75; 2.07]  |
| CRASH-2 2010 RCT             | 1463                | 10060          | 10067 0.91 [0.85; 0.97] |
| CRASH-3 2019 RCT             | 855                 | 4613           | 4514 0.94 [0.86; 1.02] |
| Guyette 2020 RCT             | 11                  | 141            | 452 0.78 [0.42; 1.47] |
| Rowell 2020 RCT              | 55                  | 262            | 272 1.06 [0.76; 1.48] |
| Yuthakasemwut 2013 RCT       | 12                  | 120            | 17 118 0.69 [0.35; 1.39] |
| Bardes 2017                  | 4                   | 32             | 23 119 0.85 [0.24; 1.74] |
| Cole 2015                    | 17                  | 180            | 18 225 1.33 [0.71; 2.50] |
| Dixon 2019                   | 24                  | 62             | 31 62 0.77 [0.52; 1.16] |
| Morte 2019                   | 0                   | 46             | 5 46 0.09 [0.01; 1.60] |
| Neeki 2018                   | 13                  | 362            | 30 362 0.43 [0.23; 0.82] |
| Neeki 2020                   | 3                   | 280            | 14 280 0.21 [0.06; 0.74] |
| Swendsen 2013                | 9                   | 52             | 17 74 0.75 [0.38; 1.56] |
| Valle 2014                   | 47                  | 150            | 35 150 1.34 [0.92; 1.99] |

Prediction interval [0.42; 1.75]

eFigure 18. Overall Mortality in Nonstandard Tranexamic Acid Administration

| Study                        | Experimental Events | Control Events | Risk Ratio IV, 95% CI |
|------------------------------|---------------------|----------------|----------------------|
| Guyette 2020 RCT             | 25                  | 301            | 452 0.83 [0.52; 1.33] |
| Rowell 2020 RCT              | 40                  | 289            | 54 272 0.80 [0.56; 1.15] |
| Boutonnet 2018               | 94                  | 403            | 65 281 1.01 [0.70; 1.33] |
| El-Menayar 2020              | 25                  | 102            | 30 102 0.83 [0.53; 1.31] |
| Glover 2019                  | 47                  | 333            | 106 706 0.94 [0.68; 1.29] |
| Harwin 2015                  | 39                  | 98             | 159 934 2.34 [1.76; 3.10] |
| Howard 2017                  | 27                  | 373            | 59 657 0.81 [0.52; 1.25] |
| Johnston 2018                | 1                   | 146            | 3 309 0.71 [0.07; 6.72] |
| Khan 2018                    | 14                  | 31             | 31 62 0.90 [0.57; 1.43] |
| Lewis 2016                   | 10                  | 335            | 11 626 1.70 [0.73; 3.90] |
| Lakhrifi 2017                | 7                   | 53             | 13 62 0.63 [0.22; 1.46] |
| Moore 2017                   | 13                  | 26             | 35 206 2.94 [1.81; 4.60] |
| Morrison 2012                | 18                  | 125            | 55 196 0.51 [0.32; 0.83] |
| Morrison 2013                | 27                  | 148            | 179 758 0.77 [0.54; 1.11] |
| Myers 2019                   | 53                  | 189            | 28 189 1.89 [1.25; 2.86] |
| Shirazi 2017                 | 25                  | 250            | 46 250 0.54 [0.35; 0.88] |
| Wafaisade 2016               | 38                  | 268            | 42 268 0.90 [0.60; 1.35] |
| Walker 2020                  | 1                   | 14             | 4 57 1.02 [0.12; 8.41] |

Prediction interval [0.41; 2.49]
**eFigure 19. Thromboembolic Events**

| Study                        | Experimental Events | Control Events | Risk Ratio IV, 95% CI |
|------------------------------|---------------------|----------------|-----------------------|
| Chakroun-Walha 2019 RCT      | 14                  | 98             | 5                      |
| CRASH-2 2010 RCT             | 168                 | 10060          | 201                    |
| CRASH-3 2019 RCT             | 101                 | 6359           | 102                    |
| Guyette 2020 RCT             | 25                  | 447            | 14                     |
| Rollin 2020 RCT              | 44                  | 657            | 30                     |
| Yuthahaksomsunt 2013 RCT     | 0                   | 120            | 3                      |
| Chan 2019                    | 2                   | 81             | 35                     |
| Cole 2015                    | 16                  | 100            | 15                     |
| Dixon 2019                   | 6                   | 62             | 8                      |
| El-Menyar 2020               | 4                   | 102            | 2                      |
| Glober 2019                  | 21                  | 333            | 27                     |
| Harwin 2015                  | 6                   | 98             | 41                     |
| Howard 2017                  | 11                  | 373            | 7                      |
| Johnston 2018                | 50                  | 146            | 21                     |
| Khan 2018                    | 4                   | 31             | 8                      |
| Luehr 2017                   | 7                   | 53             | 11                     |
| Morrison 2012                | 6                   | 125            | 1                      |
| Morte 2019                   | 2                   | 46             | 1                      |
| Myers 2019                   | 29                  | 189            | 14                     |
| Neeeki 2018                  | 2                   | 302            | 2                      |
| Neeki 2020                   | 2                   | 280            | 2                      |
| Slihastra 2017               | 3                   | 250            | 5                      |
| Swensden 2013                | 8                   | 52             | 0                      |
| Walaisade 2016               | 4                   | 71             | 10                     |

**Prediction Interval**

[0.42; 4.35]

**eFigure 20. Thromboembolic Events in RCTs**

| Study                        | Experimental Events | Control Events | Risk Ratio IV, 95% CI |
|------------------------------|---------------------|----------------|-----------------------|
| Chakroun_Walha 2019 RCT      | 14                  | 96             | 5                      |
| CRASH-2 (RCT)                | 168                 | 10060          | 201                    |
| CRASH-3 (RCT)                | 101                 | 6359           | 102                    |
| Guyette 2020 (RCT)           | 25                  | 447            | 14                     |
| Rollin 2020 (RCT)            | 44                  | 657            | 30                     |
| Yuthahaksomsunt 2013 (RCT)   | 0                   | 120            | 3                      |

**Prediction Interval**

[0.24; 4.41]

© 2022 Karl V et al. JAMA Network Open.
eFigure 21. Thromboembolic Events in Observational Studies Excluding Studies at High Risk for Confounding Bias

| Study          | Experimental Events Total | Control Total | Weight | Risk Ratio IV, Random, 95% CI |
|---------------|---------------------------|---------------|--------|-------------------------------|
| Chan 2019     | 2                         | 15            | 0.19   | 0.40 [0.09, 1.84]             |
| Cole 2015     | 16                        | 10            | 0.18   | 1.50 [0.76, 2.94]             |
| Dixon 2019    | 6                         | 8             | 0.36   | 0.75 [0.28, 2.04]             |
| El-Menyar 2020| 4                         | 2             | 0.39   | 3.97 [0.37, 10.88]            |
| Howard 2017   | 11                        | 7             | 0.38   | 2.77 [1.08, 7.06]             |
| Khan 2018     | 4                         | 9             | 0.81   | 0.99 [0.33, 3.07]             |
| More 2019     | 2                         | 1             | 0.37   | 3.19 [0.19, 21.30]            |
| Myers 2019    | 29                        | 14            | 0.14   | 2.07 [1.13, 3.79]             |
| Neeki 2018    | 2                         | 2             | 0.11   | 1.00 [0.14, 7.06]             |
| Neeki 2020    | 2                         | 2             | 0.11   | 1.00 [0.14, 7.05]             |
| Shiraiishi 2017| 3                        | 5             | 0.14   | 0.60 [0.14, 2.48]             |
| Watai 2016    | 4                         | 10            | 0.6     | 0.68 [0.22, 2.09]             |

Total (95% CI) 2007 2926 100.0% 1.31 [0.91; 1.88]

Heterogeneity: Tau² = 0.0195; Chi² = 11.89, df = 11 (P = 0.37); I² = 7%

Tranexamsaure | Control
0.1 | 0.5 | 1 | 2 | 10

Risk Ratio IV, Random, 95% CI [0.81; 2.12]

eFigure 22. Thromboembolic Events in Multiple Trauma

| Study            | Experimental Events Total | Control Total | Risk Ratio IV, 95% CI |
|------------------|---------------------------|---------------|-----------------------|
| CRASH 2 RCT 2010 | 108                        | 201           | 0.84 [0.68, 1.02]     |
| Guye 2020 RCT    | 25                         | 447           | 1.81 [0.95, 3.44]     |
| Cole 2015        | 16                         | 100           | 1.50 [0.76, 2.94]     |
| Dixon 2019       | 6                          | 52            | 0.75 [0.28, 2.04]     |
| El-Menyar 2020   | 4                          | 102           | 2.00 [0.37, 10.68]    |
| Glover 2019      | 21                         | 333           | 1.85 [0.95, 3.07]     |
| Han 2015         | 6                          | 58            | 1.39 [0.61, 3.20]     |
| Howard 2017      | 11                         | 373           | 2.77 [1.08, 7.08]     |
| Johnston 2018    | 50                         | 146           | 5.04 [3.15, 8.06]     |
| Khan 2018        | 4                          | 31            | 1.00 [0.33, 3.07]     |
| Luehr 2017       | 7                          | 53            | 0.74 [0.31, 1.78]     |
| Morrison 2012    | 6                          | 125           | 1.94 [1.15, 7.72]     |
| Myers 2019       | 29                         | 189           | 2.07 [1.13, 3.79]     |
| Neeki 2018       | 2                          | 362           | 1.00 [0.14, 7.08]     |
| Neeki 2020       | 2                          | 280           | 1.00 [0.14, 7.05]     |
| Shiraiishi 2017  | 3                          | 250           | 0.60 [0.14, 2.48]     |
| Swensden 2013    | 8                          | 52            | 7.42 [1.42, 39.88]    |
| Watai 2016       | 4                          | 71            | 0.68 [0.22, 2.09]     |

Prediction interval

Tranexamsaure | Control
0.01 | 0.1 | 1 | 10 | 100

Risk Ratio IV, 95% CI [0.47; 4.51]
eFigure 23. Thromboembolic Events in TBI

| Study                     | Experimental Events | Control Events | Total Events | Total Weight | Risk Ratio IV, Random, 95% CI |
|--------------------------|---------------------|----------------|--------------|--------------|-------------------------------|
| ChakrounWalha 2019 RCT   | 14                  | 96             | 5            | 84           | 17.4%                         |
| CRASH-3 2019 RCT         | 101                 | 6359           | 102          | 6280         | 33.4%                         |
| Rowell 2020 RCT          | 44                  | 887            | 30           | 309          | 29.6%                         |
| Yuthakasemsut 2013 RCT   | 0                   | 120            | 3            | 118          | 3.3%                          |
| Chan 2019                | 2                   | 81             | 35           | 570          | 11.2%                         |
| Morte 2019               | 2                   | 46             | 1            | 46           | 4.9%                          |
| Total (95% CI)           | 7359                | 7407           | 100.0%       |              | 0.91 [0.43; 1.81]             |
| Prediction Interval      |                     |                |              |              | 0.19 [0.09; 0.21]             |

Heterogeneity: Tau² = 0.2302; Chi² = 8.96, df = 5 (P = 0.11); I² = 44%

---

eFigure 24. Thromboembolic Events in In-hospital Tranexamic Acid Administration

| Study                     | Experimental Events | Control Events | Total Events | Total Weight | Risk Ratio IV, Random, 95% CI |
|--------------------------|---------------------|----------------|--------------|--------------|-------------------------------|
| ChakrounWalha 2019 RCT   | 14                  | 96             | 5            | 84           | 14.3%                         |
| CRASH-2 2010 RCT         | 168                 | 10060          | 201          | 10667        | 35.9%                         |
| CRASH-3 2019 RCT         | 101                 | 6359           | 102          | 6280         | 34.0%                         |
| Yuthakasemsut 2013 RCT   | 0                   | 120            | 3            | 118          | 2.3%                          |
| Chan 2019                | 2                   | 81             | 35           | 570          | 8.6%                          |
| Neeki 2020               | 2                   | 280            | 2            | 280          | 5.0%                          |
| Total (95% CI)           | 16996               | 17399          | 100.0%       |              | 0.93 [0.51; 1.72]             |
| Prediction Interval      |                     |                |              |              | 0.27; 3.27                    |

Heterogeneity: Tau² = 0.1471; Chi² = 7.67, df = 5 (P = 0.18); I² = 35%

---

eFigure 25. Thromboembolic Events in Prehospital Tranexamic Acid Administration

| Study                     | Experimental Events | Control Events | Total Events | Total Weight | Risk Ratio IV, Random, 95% CI |
|--------------------------|---------------------|----------------|--------------|--------------|-------------------------------|
| Guyotto 2020 RCT         | 25                  | 447            | 14           | 453          | 30.4%                         |
| Rowell 2020 RCT          | 44                  | 657            | 30           | 309          | 43.9%                         |
| El-Menbari 2020          | 4                   | 102            | 2            | 102          | 6.8%                          |
| Neeki 2019               | 2                   | 362            | 2            | 362          | 5.2%                          |
| Wafaisade 2016           | 4                   | 71             | 10           | 121          | 13.7%                         |
| Total (95% CI)           | 1639                | 1347           | 100.0%       |              | 1.01 [0.53; 1.94]             |
| Prediction Interval      |                     |                |              |              | 0.32; 3.18                    |

Heterogeneity: Tau² = 0.0742; Chi² = 6.98, df = 4 (P = 0.14); I² = 43%

© 2022 Karl V et al. JAMA Network Open.
eFigure 26. Thromboembolic Events in Standard Protocol Tranexamic Acid Administration

| Study                | Experimental Events | Total | Control Events | Total | Risk Ratio IV, 95% CI |
|----------------------|---------------------|-------|----------------|-------|-----------------------|
| Chakroun-Walha 2019 RCT | 14                  | 98    | 5              | 84    | 2.45 [0.92, 6.52]     |
| CRASH-2 2010 RCT     | 108                 | 10069 | 201            | 10087 | 0.84 [0.68, 1.02]     |
| CRASH-2 2019 RCT     | 101                 | 6359  | 102            | 6280  | 0.98 [0.74, 1.32]     |
| Rowell 2020 RCT      | 13                  | 312   | 30             | 309   | 0.43 [0.23, 0.81]     |
| Yutthakasemmsunt 2013 RCT | 0               | 120   | 3              | 118   | 0.14 [0.01, 2.69]     |
| Cole 2015            | 16                  | 150   | 15             | 225   | 1.50 [0.76, 2.94]     |
| Dixon 2019           | 6                   | 52    | 8              | 60    | 0.75 [0.28, 2.04]     |
| Mote 2019            | 29                  | 189   | 14             | 199   | 2.07 [1.13, 3.79]     |
| Neeki 2018           | 2                   | 362   | 2              | 362   | 1.00 [0.14, 7.06]     |
| Neri 2020            | 2                   | 280   | 2              | 280   | 1.00 [0.14, 7.06]     |
| Swendsen 2013        | 8                   | 52    | 0              | 74    | 2.42 [1.42, 408.88]   |

Prediction interval [0.25; 4.78]

Risk Ratio IV, 95% CI

Tranexamsaure Control

0.01 0.1 1 10 100

eFigure 27. Thromboembolic Events in Nonstandard Protocol Tranexamic Acid Administration

| Study                | Experimental Events | Total | Control Events | Total | Risk Ratio IV, 95% CI |
|----------------------|---------------------|-------|----------------|-------|-----------------------|
| Gouette 2020 RCT     | 25                  | 447   | 14             | 461   | 1.81 [0.95, 3.44]     |
| Rowell 2020 RCT      | 31                  | 345   | 30             | 375   | 0.93 [0.57, 1.49]     |
| Chen 2019            | 2                   | 81    | 35             | 116   | 0.40 [0.10, 1.64]     |
| El-Menyar 2020       | 4                   | 102   | 2              | 104   | 2.00 [0.37, 10.08]    |
| Glover 2019          | 21                  | 333   | 27             | 360   | 1.65 [0.95, 2.87]     |
| Harvin 2015          | 6                   | 98    | 41             | 139   | 1.39 [0.61, 3.20]     |
| Howard 2017          | 11                  | 373   | 7              | 380   | 2.77 [1.08, 7.08]     |
| Johnston 2018        | 50                  | 149   | 21             | 170   | 3.04 [3.15, 6.08]     |
| Khan 2018            | 4                   | 31    | 8              | 39    | 1.00 [0.33, 3.07]     |
| Luhr 2017            | 7                   | 53    | 11             | 64    | 0.74 [0.31, 1.78]     |
| Morrison 2012        | 6                   | 125   | 1              | 126   | 9.41 [1.15, 77.22]    |
| Myers 2019           | 29                  | 189   | 14             | 203   | 2.07 [1.13, 3.79]     |
| Shriarshi 2017       | 3                   | 250   | 5              | 255   | 0.60 [0.14, 2.48]     |
| Wafaisade 2016       | 9                   | 27    | 25             | 52    | 1.25 [0.67, 2.35]     |

Prediction interval [0.48; 5.36]

Risk Ratio IV, 95% CI

Tranexamsaure Control

0.1 0.5 1 2 10

© 2022 Karl V et al. JAMA Network Open.
eFigure 28. Funnel Plot for 1-Month Mortality

eFigure 29. Funnel Plot for Thromboembolic Events
References

1. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol. Jul 2016;75:40-6. doi:10.1016/j.jclinepi.2016.01.021

2. Deeks JJ, Higgins JP, Altman DG, Group CSM. Analysing data and undertaking meta-analyses. Cochrane handbook for systematic reviews of interventions. 2019:241-284.

3. Langan D, Higgins JPT, Jackson D, et al. A comparison of heterogeneity variance estimators in simulated random-effects meta-analyses. Res Synth Methods. Mar 2019;10(1):83-98. doi:10.1002/jrsm.1316

4. Mathes T, Kuss O. A comparison of methods for meta-analysis of a small number of studies with binary outcomes. Res Synth Methods. Sep 2018;9(3):366-381. doi:10.1002/jrsm.1296

5. Kuss O. Statistical methods for meta-analyses including information from studies without any events-adding nothing to nothing and succeed nevertheless. Stat Med. Mar 30 2015;34(7):1097-116. doi:10.1002/sim.6383

6. Balduzzi S, Rucker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. Evid Based Ment Health. Nov 2019;22(4):153-160. doi:10.1136/ebmental-2019-300117

7. Chakroun-Walha O, Samet A, Jerbi M, et al. Benefits of the tranexamic acid in head trauma with no extracranial bleeding: a prospective follow-up of 180 patients. European Journal of Trauma & Emergency Surgery. 2019;45(4):719-726.

8. CRASH-3 trial collaborators. 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. Lancet. 2019;394(10210):1713-1723.

9. Rowell SE, Meier EN, McKnight B, et al. Effect of Out-of-Hospital Tranexamic Acid vs Placebo on 6-Month Functional Neurologic Outcomes in Patients With Moderate or Severe Traumatic Brain Injury. JAMA. Sep 8 2020;324(10):961-974. doi:10.1001/jama.2020.8958

10. Yuthakasemsunt S, Kittiwatanagul W, Piyavechvirat P, Thinkamrop B, Phuenpathom N, Lumbiganon P. Tranexamic acid for patients with traumatic brain injury: a randomized, double-blind, placebo-controlled trial. BMC Emergency Medicine. 2013;13:20.

11. Chan DYC, Tsang ACO, Li LF, et al. Improving Survival with Tranexamic Acid in Cerebral Contusions or Traumatic Subarachnoid Hemorrhage: Univariate and Multivariate Analysis of Independent Factors Associated with Lower Mortality. World Neurosurgery. 2019;125:e665-e670.

12. Morte D, Lammers D, Bingham J, Kuckelman J, Eckert M, Martin M. Tranexamic acid administration following head trauma in a combat setting: Does tranexamic acid result in improved neurologic outcomes? The Journal of Trauma and Acute Care Surgery. 2019;87(1):125-129.

13. Walker PF, Bozzay JD, Johnston LR, Elster EA, Rodriguez CJ, Bradley MJ. Outcomes of tranexamic acid administration in military trauma patients with intracranial hemorrhage: a cohort study. BMC Emergency Medicine. 2020;20(1):39.

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

15. Guyette FX, Brown JB, Zenati MS, et al. Tranexamic Acid During Prehospital Transport in Patients at Risk for Hemorrhage After Injury: A Double-blind, Placebo-Controlled, Randomized Clinical Trial. JAMA Surgery. 2020;05:05.

16. Bardes JM, Palmer A, Con J, Wilson A, Schaefer G. Antifibrinolytics in a rural trauma state: assessing the opportunities. Trauma Surgery & Acute Care Open. 2017;2(1):e000107.

17. Boutonnet M, Abbach P, Le Sache F, et al. Tranexamic acid in severe trauma patients managed in a mature trauma care system. The Journal of Trauma and Acute Care Surgery. 2018;84(6S Suppl 1):S54-S62.

18. Cole E, Davenport R, Willett K, Brohi K. Tranexamic acid use in severely injured civilian patients and the effects on outcomes: a prospective cohort study. Annals of Surgery. 2015;261(2):390-4.

19. Dixon A, Emigh B, Spitz K, et al. Does tranexamic acid really work in an urban US level I trauma center? A single level 1 trauma center's experience. American Journal of Surgery. 2019;218(6):1110-1113.

20. El-Menyar A, Sathian B, Wahlen BM, et al. Prehospital administration of tranexamic acid in trauma patients: A 1:1 matched comparative study from a level 1 trauma center. American Journal of Emergency Medicine. 2020;38(2):266-271.

21. Glover TE, Sumpter JE, Ercole A, et al. Pulmonary embolism following complex trauma: UK MTC observational study. Emergency Medicine Journal. 2019;36(10):608-612.

22. Harvin JA, Peirce CA, Mims MM, et al. The impact of tranexamic acid on mortality in injured patients with hyperfibrinolysis. The Journal of Trauma and Acute Care Surgery. 2015;78(5):905-9; discussion 909-11.

23. Howard JT, Stockinger ZT, Cap AP, Bailey JA, Gross KR. Military use of tranexamic acid in combat trauma: Does it matter? The Journal of Trauma and Acute Care Surgery. 2017;83(4):579-588.
24. Johnston LR, Rodriguez CJ, Elster EA, Bradley MJ. Evaluation of Military Use of Tranexamic Acid and Associated Thromboembolic Events. JAMA Surgery. 2018;153(2):169-175.
25. Khan M, Jehan F, Bulger EM, et al. Severely injured trauma patients with admission hyperfibrinolysis: Is there a role of tranexamic acid? Findings from the PROPPR trial. The Journal of Trauma and Acute Care Surgery. 2018;85(5):851-857.
26. Lewis CJ, Li P, Stewart L, et al. Tranexamic acid in life-threatening military injury and the associated risk of infective complications. British Journal of Surgery. 2016;103(4):366-73.
27. Luehr E, Grone G, Pathak M, Austin C, Thompson S. Administration of tranexamic acid in trauma patients under stricter inclusion criteria increases the treatment window for stabilization from 24 to 48 hours—a retrospective review. International Journal of Burns & Trauma. 2017;7(6):115-119.
28. Moore HB, Moore EE, Huebner BR, et al. Tranexamic acid is associated with increased mortality in patients with physiological fibrinolysis. Journal of Surgical Research. 2017;220:438-443.
29. Morrison JJ, Dubose JJ, Rasmussen TE, Midwinter MJ. Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) Study. Archives of Surgery. 2012;147(2):113-9.
30. Morrison JJ, Ross JD, Dubose JJ, Jansen JO, Midwinter MJ, Rasmussen TE. Association of cryoprecipitate and tranexamic acid with improved survival following wartime injury: findings from the MATTERs II Study. JAMA Surgery. 2013;148(3):218-25.
31. Myers SP, Kutcher ME, Rosengart MR, et al. Tranexamic acid administration is associated with an increased risk of posttraumatic venous thromboembolism. J Trauma Acute Care Surg. Jan 2019;86(1):20-27. doi:10.1097/TA.0000000000002061
32. Neeki MM, Dong F, Toy J, et al. Tranexamic Acid in Civilian Trauma Care in the California Prehospital Antifibrinolytic Therapy Study. The Western Journal of Emergency Medicine. 2018;19(6):977-986.
33. Neeki MM, Dong F, Toy J, et al. Safety and Efficacy of Hospital Utilization of Tranexamic Acid in Civilian Adult Trauma Resuscitation. The Western Journal of Emergency Medicine. 2020;21(2):217-225.
34. Shiraishi A, Kushimoto S, Otomo Y, et al. Effectiveness of early administration of tranexamic acid in patients with severe trauma. British Journal of Surgery. 2017;104(6):710-717.
35. Swendsen H, Galante J, Utter G, Bateni S, Scherer L, Schermer C. Tranexamic Acid use in Trauma: Effective but not Without Consequences. 2013;
36. Valle EJ, Allen CJ, Van Haren RM, et al. Do all trauma patients benefit from tranexamic acid? The Journal of Trauma and Acute Care Surgery. 2014;76(6):1373-8.
37. Wafaisade A, Lefering R, Bouillon B, et al. Prehospital administration of tranexamic acid in trauma patients. Critical Care (London, England). 2016;20(1):143.
38. Spahn DR, Bouillon B, Cerny V, et al. The European guideline on management of major bleeding and coagulopathy following trauma: fifth edition. Crit Care. Mar 27 2019;23(1):98. doi:10.1186/s13054-019-2347-3