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Appendix 1. MEDLINE search strategy

The searches used to identify trials for this study were run to 1 July 2018 and were not restricted by date, language or publication status.

Database: Ovid MEDLINE(R) <1946 to March Week 26 2018>

1 exp Antifibrinolytic Agents/
2 (anti-fibrinolytic* or antifibrinolytic* or antifibrinolysin* or anti-fibrinolysin* or antiplasmin* or anti-plasmin* or ((plasmin or fibrinolysis) adj3 inhibitor*)).ab,ti.
3 exp Aprotinin/
4 (Aprotinin* or kallikrein-trypsin inactivator* or bovine kunitz pancreatic trypsin inhibitor* or bovine pancreatic trypsin inhibitor* or basic pancreatic trypsin inhibitor* or BPTI or contrykal or contrykal or kontrikal or dilmintal or iniprol or zymofren or traskolan or antilysin or pulmin or amicar or caprocid or epsamon or episkapron or antilysin or iniprol or kontrikal or kontrikal or pulmin* or Trasylol or Antilysin Spofa or rp79921 or antagogan or antilysin or antilysin or apronitin* or apronitrine or bayer a?128 or bovine pancreatic secretory trypsin inhibitor* or contrykal or frey inhibitor* or gordox or kallikrein trypsin inhibitor* or kazal type trypsin inhibitor* or (Kunitz adj3 inhibitor*) or midran or (pancrea* adj2 antitrypsin) or (pancrea* adj2 trypsin inhibitor*) or riker?52g or rp?9921or trascolan or trasilol or trazylol or zymofren).ab,ti.
5 exp Tranexamic Acid/
6 (tranexamic or Cyclohexanecarboxylic Acid* or Methylamine* or amcha or trans-4-aminomethyl-cyclohexanecarboxylic acid* or t-amcha or amca or kabi 2161 or transamin* or exacyl or amchafibrin or anvitoff or spotof or cyklokapron or ugurol oramino methylcyclohexane carboxylate or aminomethylene glycolohexanecarboxylic acid or AMCHA or amchafibrin or anvitoff or spotof or cyklokapron or ugurol).ab,ti.
7 exp Aminocaproic Acids/ or exp 6-Aminocaproic Acid/
8 ((((aminocaproic or amino?caproic or aminohexanoic or amino caproic or amino caproic or amino n hexanoic or epsilon-aminocaproic or E-aminocaproic) adj2 acid*) or episkapron or cy-116 or cy116 or epsamon or amicar or caprocid or ledelre or Aminocaproic or aminohexanoic acid or amino caproic or amino n hexanoic or akipkaprin or afibrin or capradi or capramol or caprogel or caprolest or caprolisine or caprolysin or capromol or cl 10304 or EACA or eaca roche or ecapron or cyklokapron or cyclokapron or cyclocapron or exacyl or frenalose or hexacapron or hexakapron or tranex or TXA).ab,ti.
9 exp 4-Aminobenzoic Acid/ or 6-Aminocaproic Acid/ or PAMBA or para-aminomethylbenzoic or p-aminomethylbenzoic or amino?methylbenzoic or Gumbix or Stytopur or H-4-AMB-0H or CAS:56-91-7 or H-4AMBZ-0H or NH2-CH2-PH4-COOH or TIMTEC-BB SBB006704 or "RARECHEM AL BW 0005" or Amino-p-toluicacid).ti,ab.
10 (animals not (humans and animals)).sh.
11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 10
12 randomi?ed.ab,ti.
13 randomized controlled trial.pt.
14 controlled clinical trial.pt.
15 placebo.ab.
16 clinical trials as topic.sh.
17 randomly.ab.
18 trial.ti.
19 12 or 13 or 14 or 15 or 16 or 17 or 18
20 (animals not (humans and animals)).sh.
21 19 not 20
22 11 and 21
Appendix 2. Equations of the different models.

1) Logistic regression assessing overall treatment effect and homogeneity of treatment effect across trials

\[
\text{Logit (p}(Y = 1)) = \beta_0 + \beta_1 S + \beta_2 X + \beta_3 (X*S) \tag{model-1}
\]

With \( Y = 1 \), the outcome did not die from bleeding for patient \( i \) in trial \( j \), \( S \) is the trial (CRASH-2 \( S=0 \), CRASH-3 \( S=1 \)), \( X \) is treatment (tranexamic acid is \( X=1 \), placebo is \( X=0 \)).

Then \( \beta_0 \) is the log(odds) in the placebo group in the CRASH-2 trial, \( \beta_1 \) is the difference between trials in placebo group, \( \beta_2 \) the effect of tranexamic acid in CRASH-2 trial, and \( \beta_3 \) is the interaction between treatment effect and trial.

2) Logistic regression assessing overall treatment effect and homogeneity of treatment effect across trials and by time to treatment (triple interaction).

\[
\text{Logit (p}(Y = 1)) = \beta_0 + \beta_1 T + \beta_2 X + \beta_3 S + \beta_4 (X*T) + \beta_5 (S*T) + \beta_6 (S*X) + \beta_7 (S*X*T) \tag{model-2}
\]

With \( Y, X \) coded as in [model-1]. \( T \) is the time to treatment in minutes. \( S \) is the trial.

Then \( \beta_0 \) is the log(odds) in the placebo group when \( T=0 \) (Time 0) and \( S=0 \) (CRASH-2); \( \beta_1 \) is the linear effect of time to treatment in the placebo group for CRASH-2; \( \beta_2 \) the effect of tranexamic acid at \( T=0 \) in CRASH-2 trial; \( \beta_3 \) is the difference between trials in placebo group; \( \beta_4 \) is the interaction between treatment effect and time to treatment for CRASH-2; \( \beta_5 \) is the interaction between time to treatment and trials in the placebo group; \( \beta_6 \) is the interaction of trials with the treatment at \( T=0 \); \( \beta_7 \) is the triple interaction of trials with the treatment and the time to treatment.

3) Logistic regression estimating linear effect of intervention by time to treatment (we assume this interaction is the same in both trials).

\[
\text{Logit (p}(Y = 1)) = \beta_0 + \beta_1 S + \beta_2 X + \beta_3 T + \beta_4 (T*X) \tag{model-3}
\]

With \( Y, S, X, T \) coded as in [model-1] and [model-2];

Then, \( \beta_0 \) is the log(odds) in the placebo group in the CRASH-2 trial when Time=0; \( \beta_1 \) is the difference between trials; \( \beta_2 \) is the effect of tranexamic when Time=0; \( \beta_3 \) is the linear effect of time to treatment in the placebo group of both trials ; \( \beta_4 \) is the interaction of time to treatment with the treatment.
Appendix 3. Results of risk of bias assessment.

### CRASH-2

| Domain                        | Judgement | Justification                                                                                                                                 |
|-------------------------------|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| Sequence generation           | Low       | Computer-generated.                                                                                                                              |
| Allocation concealment        | Low       | Tranexamic acid and placebo were packaged in identical ampoules. Recruiting hospitals with reliable telephone access used a telephone randomisation service, hospitals without, used a local pack system. |
| Blinding                      | Low       | Participants, clinicians and trial staff were blinded to treatment allocation.                                                                   |
| Incomplete outcome data       | Low       | Over 99% of patients were followed up and contributed outcome data.                                                                                |
| Selective outcome reporting   | Low       | Prospectively registered and data on all pre-specified outcomes available for analysis.                                                         |

### CRASH-3

| Domain                        | Judgement | Justification                                                                                                                                 |
|-------------------------------|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| Sequence generation           | Low       | Computer-generated.                                                                                                                              |
| Allocation concealment        | Low       | Tranexamic acid and placebo were packed in sequentially numbered, sealed, treatment boxes.                                                     |
| Blinding                      | Low       | Participants, clinicians and trial staff were blinded to treatment allocation.                                                                   |
| Incomplete outcome data       | Low       | Over 99% of patients were followed up and contributed outcome data.                                                                                |
| Selective outcome reporting   | Low       | Prospectively registered and data on all pre-specified outcomes available for analysis.                                                         |
Appendix 4. Safety outcomes. Fatal and non-fatal thrombotic events.

| Safety outcomes | Odds ratio  |
|-----------------|------------|
|                 | (95% CI)   |
| Fatal and non-fatal thrombotic events |          |
| - Time 0-60 min | 0.86 (0.62, 1.19) |
| - Time 60-180 min | 0.78 (0.60, 1.02) |
| - Time >180 min | 1.01 (0.77, 1.34) |
| - Pooled        | 0.88 (0.74, 1.04) |
| P value for heterogeneity=0.42 |

Fatal thrombotic events

| - Time 0-60 min | 0.80 (0.39, 1.67) |
| - Time 60-180 min | 0.89 (0.49, 1.63) |
| - Time >180 min | 0.85 (0.63, 1.96) |
| - Pooled        | 0.95 (0.68, 1.36) |
| P value for heterogeneity=0.76 |

Non-fatal thrombotic events

| - Time 0-60 min | 0.88 (0.61, 1.26) |
| - Time 60-180 min | 0.78 (0.58, 1.03) |
| - Time >180 min | 0.98 (0.72, 1.35) |
| - Pooled        | 0.88 (0.72, 1.04) |
| P value for heterogeneity=0.51 |

Fewer thrombotic events with TXA ← | ← More thrombotic events with TXA →