

# THE LANCET

## Supplementary appendix 8

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: The 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; published online Oct 14. [http://dx.doi.org/10.1016/S0140-6736\(19\)32233-0](http://dx.doi.org/10.1016/S0140-6736(19)32233-0).

## Web appendix

**Web appendix Table 1. Baseline characteristics prior to randomisation in all patients and in those randomised beyond 3 hours of injury**

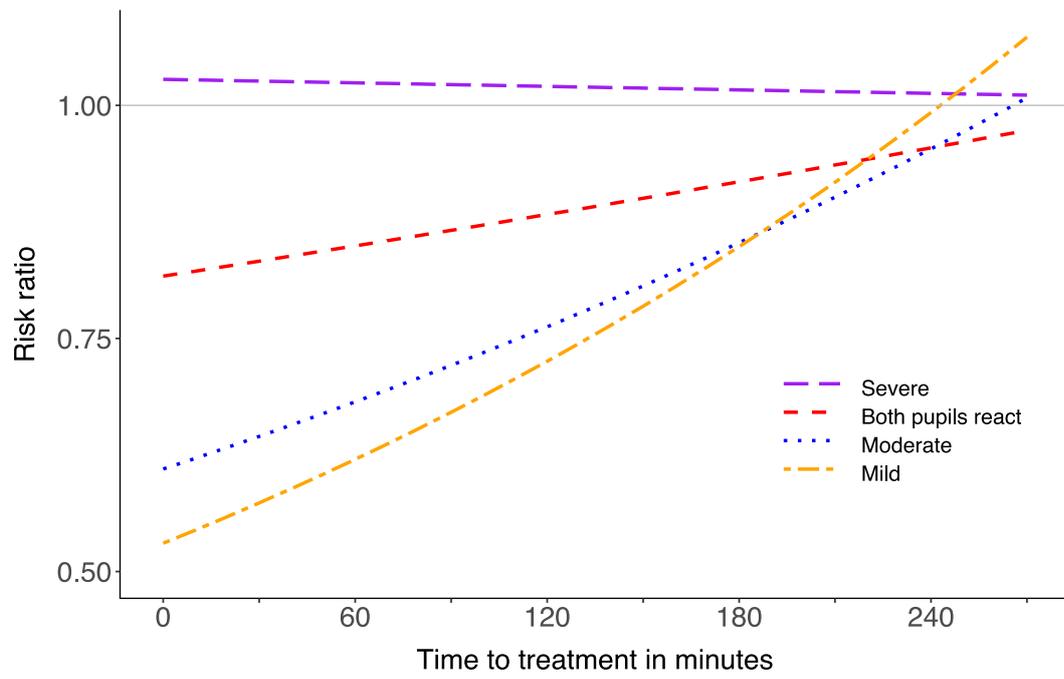
|  | All             |        |                     |        | ≥3 hours        |        |                     |        |
|--|-----------------|--------|---------------------|--------|-----------------|--------|---------------------|--------|
|  | TXA<br>(n=6406) |        | Placebo<br>(n=6331) |        | TXA<br>(n=1757) |        | Placebo<br>(n=1778) |        |
|  | n               | (%)    | n                   | (%)    | n               | (%)    | n                   | (%)    |
| <b>Sex</b>                             |                 |        |                     |        |                 |        |                     |        |
| Male                                   | 5104            | (80)   | 5013                | (79)   | 1362            | (78)   | 1353                | (76)   |
| Female                                 | 1301            | (20)   | 1318                | (21)   | 395             | (22)   | 425                 | (24)   |
| Unknown                                | 1               | (<1)   | 0                   | (0)    | 0               | (0)    | 0                   | (0)    |
| <b>Age (years)</b>                     |                 |        |                     |        |                 |        |                     |        |
| <i>Mean (SD)</i>                       | 43              | (19.8) | 43.1                | (19.7) | 46.4            | (21.3) | 46.2                | (21.1) |
| <24                                    | 1362.0          | (21)   | 1326                | (21)   | 320             | (18)   | 330                 | (19)   |
| 24-44                                  | 2285            | (36)   | 2264                | (36)   | 569             | (32)   | 592                 | (33)   |
| 44-64                                  | 1625            | (25)   | 1613                | (25)   | 456             | (26)   | 429                 | (24)   |
| >64                                    | 1134            | (18)   | 1128                | (18)   | 412             | (23)   | 427                 | (24)   |
| <b>Time since injury (hours)</b>       |                 |        |                     |        |                 |        |                     |        |
| <i>Mean (SD)</i>                       | 2.9             | (3.2)  | 2.9                 | (2.3)  | 5.5             | (5.2)  | 5.4                 | (2.9)  |
| ≤1                                     | 877             | (14)   | 869                 | (14)   | -               | -      | -                   | -      |
| 1-3                                    | 3772            | (59)   | 3684                | (58)   | -               | -      | -                   | -      |
| 3-8                                    | 1737            | (27)   | 1760                | (28)   | 1737            | (99)   | 1760                | (99)   |
| >8                                     | 20              | (<1)   | 18                  | (<1)   | 20              | (1)    | 18                  | (1)    |
| <b>Systolic blood pressure (mm Hg)</b> |                 |        |                     |        |                 |        |                     |        |
| <90                                    | 108             | (2)    | 109                 | (2)    | 19              | (1)    | 24                  | (1)    |
| 90-119                                 | 2001            | (31)   | 1988                | (31)   | 493             | (28)   | 498                 | (28)   |
| 120-139                                | 2107            | (33)   | 2120                | (33)   | 646             | (37)   | 616                 | (35)   |
| ≥140                                   | 2167            | (34)   | 2097                | (33)   | 591             | (34)   | 631                 | (35)   |
| Unknown                                | 23              | (<1)   | 17                  | (<1)   | 8               | (<1)   | 9                   | (1)    |
| <b>Glasgow Coma Scale (GCS)</b>        |                 |        |                     |        |                 |        |                     |        |
| 3                                      | 630             | (10)   | 642                 | (10)   | 135             | (3)    | 136                 | (3)    |
| 4                                      | 261             | (4)    | 275                 | (4)    | 48              | (1)    | 62                  | (1)    |
| 5                                      | 211             | (3)    | 242                 | (4)    | 48              | (1)    | 70                  | (2)    |
| 6                                      | 304             | (5)    | 308                 | (5)    | 83              | (2)    | 76                  | (2)    |
| 7                                      | 413             | (6)    | 400                 | (6)    | 102             | (2)    | 106                 | (2)    |
| 8                                      | 465             | (7)    | 406                 | (6)    | 111             | (2)    | 91                  | (2)    |
| 9                                      | 416             | (6)    | 382                 | (6)    | 81              | (2)    | 90                  | (2)    |
| 10                                     | 463             | (7)    | 444                 | (7)    | 92              | (2)    | 80                  | (2)    |
| 11                                     | 465             | (7)    | 502                 | (8)    | 90              | (2)    | 112                 | (2)    |
| 12                                     | 600             | (9)    | 601                 | (9)    | 124             | (3)    | 123                 | (3)    |
| 13                                     | 460             | (7)    | 453                 | (7)    | 163             | (4)    | 141                 | (3)    |
| 14                                     | 790             | (12)   | 754                 | (12)   | 264             | (6)    | 296                 | (7)    |
| 15                                     | 899             | (14)   | 886                 | (14)   | 415             | (9)    | 394                 | (9)    |
| Unknown                                | 29              | (<1)   | 36                  | (1)    | 1               | (<1)   | 1                   | (<1)   |
| <b>Pupil reaction</b>                  |                 |        |                     |        |                 |        |                     |        |
| None react                             | 536             | (8)    | 575                 | (9)    | 111             | (6)    | 135                 | (8)    |
| One reacts                             | 511             | (8)    | 482                 | (8)    | 137             | (8)    | 129                 | (7)    |
| Both react                             | 5174            | (81)   | 5113                | (81)   | 1468            | (84)   | 1477                | (83)   |
| Unable to assess/unknown               | 185             | (3)    | 161                 | (3)    | 41              | (2)    | 37                  | (2)    |

SD=standard deviation; TXA=tranexamic acid

**Web appendix Table 2. Effect of tranexamic acid on non-head injury deaths in all patients**

| Cause of death        | TXA<br>(n=6359) |        | Placebo<br>(n=6280) |        | RR (95% CI)       |
|-----------------------|-----------------|--------|---------------------|--------|-------------------|
|                       | n               | (%)    | n                   | (%)    |                   |
| Bleeding              | 9               | (0.1)  | 7                   | (0.1)  | 1.27 (0.47-3.41)  |
| Pulmonary embolism    | 9               | (0.1)  | 7                   | (0.1)  | 1.27 (0.47-3.41)  |
| Stroke                | 10              | (0.2)  | 4                   | (0.1)  | 2.47 (0.77-7.87)  |
| Myocardial infarction | 9               | (0.1)  | 3                   | (<0.1) | 2.96 (0.80-10.94) |
| Multi-organ failure   | 27              | (0.4)  | 24                  | (0.4)  | 1.11 (0.64-1.92)  |
| Aspiration/pneumonia  | 30              | (0.5)  | 34                  | (0.5)  | 0.87 (0.53-1.42)  |
| Sepsis                | 9               | (0.1)  | 6                   | (0.1)  | 1.48 (0.53-4.16)  |
| Cervical spine injury | 3               | (<0.1) | 4                   | (0.1)  | 0.74 (0.17-3.31)  |
| Other                 | 16              | (0.3)  | 11                  | (0.2)  | 1.44 (0.67-3.09)  |

CI=confidence interval, RR=risk ratio, SD=standard deviation, TXA=tranexamic acid.



**Web appendix Figure 1: Effectiveness of tranexamic acid versus time to treatment stratified by severity in all patients**

**Web appendix Table 3: Adverse events by MedDRA term**

|  | <b>TXA</b><br><b>(N=6359)</b> | <b>Placebo</b><br><b>(N=6280)</b> | <b>Total</b><br><b>(N=12639)</b> |
|--|-------------------------------|-----------------------------------|----------------------------------|
| <b>Any adverse event</b>                   | <b>198</b>                    | <b>168</b>                        | <b>366</b>                       |
| Pneumonia                                  | 51                            | 50                                | 101                              |
| Respiratory infection                      | 10                            | 7                                 | 17                               |
| Fall                                       | 11                            | 5                                 | 16                               |
| Urinary tract infection                    | 9                             | 5                                 | 14                               |
| Abnormal liver function tests              | 6                             | 6                                 | 12                               |
| Allergic reaction                          | 4                             | 5                                 | 9                                |
| Cellulitis                                 | 4                             | 4                                 | 8                                |
| Wound infection                            | 4                             | 3                                 | 7                                |
| Atrial fibrillation                        | 5                             | 1                                 | 6                                |
| Headache                                   | 5                             | 1                                 | 6                                |
| Pneumothorax                               | 4                             | 2                                 | 6                                |
| Supraventricular tachycardia               | 3                             | 2                                 | 5                                |
| Cerebral haemorrhage                       | 1                             | 3                                 | 4                                |
| Ileus                                      | 1                             | 3                                 | 4                                |
| Pyrexia                                    | 2                             | 2                                 | 4                                |
| Urinary retention                          | 3                             | 1                                 | 4                                |
| Cardiac arrest                             | 3                             | 0                                 | 3                                |
| Chest pain                                 | 3                             | 0                                 | 3                                |
| Constipation                               | 1                             | 2                                 | 3                                |
| Haemothorax                                | 1                             | 2                                 | 3                                |
| Heart block                                | 1                             | 2                                 | 3                                |
| Infection MRSA                             | 1                             | 2                                 | 3                                |
| Intracranial venous sinus thrombosis       | 1                             | 2                                 | 3                                |
| Meningitis                                 | 1                             | 2                                 | 3                                |
| Pulmonary embolism                         | 3                             | 0                                 | 3                                |
| Respiratory failure                        | 0                             | 3                                 | 3                                |
| Acute respiratory distress syndrome        | 1                             | 1                                 | 2                                |
| Anaemia                                    | 0                             | 2                                 | 2                                |
| Atrial flutter                             | 1                             | 1                                 | 2                                |
| Cerebral haematoma                         | 2                             | 0                                 | 2                                |
| Clostridium difficile infection            | 2                             | 0                                 | 2                                |
| Diarrhoea                                  | 2                             | 0                                 | 2                                |
| Epilepsy                                   | 0                             | 2                                 | 2                                |
| Gangrene                                   | 2                             | 0                                 | 2                                |
| Hypertension                               | 0                             | 2                                 | 2                                |
| Hypokalaemia                               | 1                             | 1                                 | 2                                |
| Intestinal pseudo-obstruction              | 1                             | 1                                 | 2                                |
| Ischaemic stroke                           | 2                             | 0                                 | 2                                |
| Neutropenia                                | 2                             | 0                                 | 2                                |
| Pancreatitis                               | 1                             | 1                                 | 2                                |
| Rash                                       | 1                             | 1                                 | 2                                |
| Respiratory arrest                         | 1                             | 1                                 | 2                                |
| Seizure                                    | 1                             | 1                                 | 2                                |
| Sepsis                                     | 1                             | 1                                 | 2                                |
| Thrombocytopenia                           | 2                             | 0                                 | 2                                |
| Thrombocytosis                             | 1                             | 1                                 | 2                                |
| Traumatic brain injury                     | 1                             | 1                                 | 2                                |
| Unintended unilateral bronchial intubation | 1                             | 1                                 | 2                                |
| Wound dehiscence                           | 0                             | 2                                 | 2                                |
| Abdominal compartment syndrome             | 1                             | 0                                 | 1                                |
| Abdominal distension                       | 0                             | 1                                 | 1                                |
| Acute alcoholic intoxication               | 1                             | 0                                 | 1                                |
| Agitation                                  | 1                             | 0                                 | 1                                |
| Atelectasis                                | 0                             | 1                                 | 1                                |
| Bacteraemia                                | 0                             | 1                                 | 1                                |
| Bowel obstruction                          | 1                             | 0                                 | 1                                |

|                                    |   |   |   |
|------------------------------------|---|---|---|
| Bradycardia                        | 0 | 1 | 1 |
| Central line infection             | 1 | 0 | 1 |
| Cerebral salt-wasting syndrome     | 1 | 0 | 1 |
| Cerebrospinal fluid leakage        | 0 | 1 | 1 |
| Cerebrospinal infection            | 1 | 0 | 1 |
| Cervical pain                      | 0 | 1 | 1 |
| Corneal ulcer                      | 1 | 0 | 1 |
| Cranial nerve palsies multiple     | 0 | 1 | 1 |
| Cranial nerve paralysis            | 1 | 0 | 1 |
| Depression                         | 1 | 0 | 1 |
| Diabetic ketoacidosis              | 1 | 0 | 1 |
| ECG signs of myocardial ischaemia  | 0 | 1 | 1 |
| Eye injury                         | 1 | 0 | 1 |
| Facial palsy                       | 0 | 1 | 1 |
| Foot drop                          | 0 | 1 | 1 |
| Fractured zygomatic arch reduction | 0 | 1 | 1 |
| Haematoma                          | 1 | 0 | 1 |
| Haematuria                         | 0 | 1 | 1 |
| Haemophilus influenza pneumonia    | 0 | 1 | 1 |
| Herpes zoster                      | 1 | 0 | 1 |
| Hip dislocation                    | 0 | 1 | 1 |
| Humerus fracture                   | 1 | 0 | 1 |
| Hydrocephalus                      | 0 | 1 | 1 |
| Hyperbilirubinaemia                | 1 | 0 | 1 |
| Hypernatraemia                     | 1 | 0 | 1 |
| Hyponatraemia                      | 1 | 0 | 1 |
| Hypotension                        | 1 | 0 | 1 |
| Hypothermia                        | 0 | 1 | 1 |
| Jaw pain                           | 1 | 0 | 1 |
| Laceration of head                 | 1 | 0 | 1 |
| Laryngopharyngitis                 | 1 | 0 | 1 |
| Leg pain                           | 0 | 1 | 1 |
| Liver failure                      | 0 | 1 | 1 |
| Metabolic encephalopathy           | 1 | 0 | 1 |
| Necrotising fasciitis              | 0 | 1 | 1 |
| Neuroleptic malignant syndrome     | 0 | 1 | 1 |
| Obstructive jaundice               | 0 | 1 | 1 |
| Overdose                           | 0 | 1 | 1 |
| Painful urination                  | 0 | 1 | 1 |
| Paraesthesia                       | 1 | 0 | 1 |
| Pleural effusion                   | 0 | 1 | 1 |
| Post procedural infection          | 0 | 1 | 1 |
| Psychotic episode                  | 1 | 0 | 1 |
| Pulmonary haemorrhage              | 1 | 0 | 1 |
| Pulmonary oedema                   | 0 | 1 | 1 |
| Rectal bleeding                    | 1 | 0 | 1 |
| Shunt infection                    | 1 | 0 | 1 |
| Sinus pause                        | 1 | 0 | 1 |
| Stroke                             | 1 | 0 | 1 |
| Thrombocythaemia                   | 0 | 1 | 1 |
| Thyroid haemorrhage                | 1 | 0 | 1 |
| Toothache                          | 0 | 1 | 1 |
| Tracheostomy                       | 0 | 1 | 1 |
| Tracheostomy complication          | 0 | 1 | 1 |
| Tracheostomy infection             | 1 | 0 | 1 |
| Vasovagal reaction                 | 0 | 1 | 1 |
| Ventricular fibrillation           | 0 | 1 | 1 |
| Ventricular tachycardia            | 0 | 1 | 1 |
| Ventriculitis                      | 1 | 0 | 1 |
| Vocal cord paresis                 | 1 | 0 | 1 |

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TXA=tranexamic acid