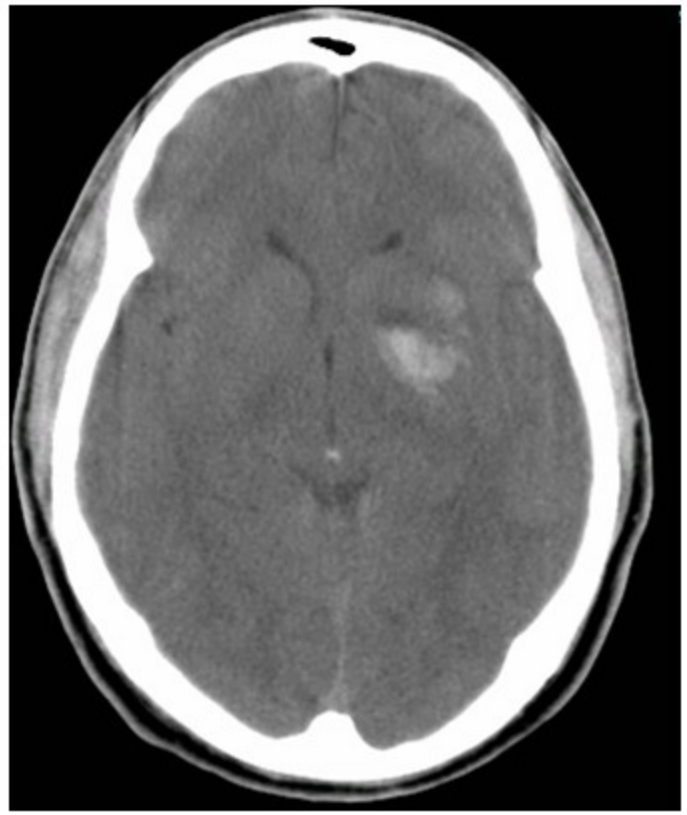
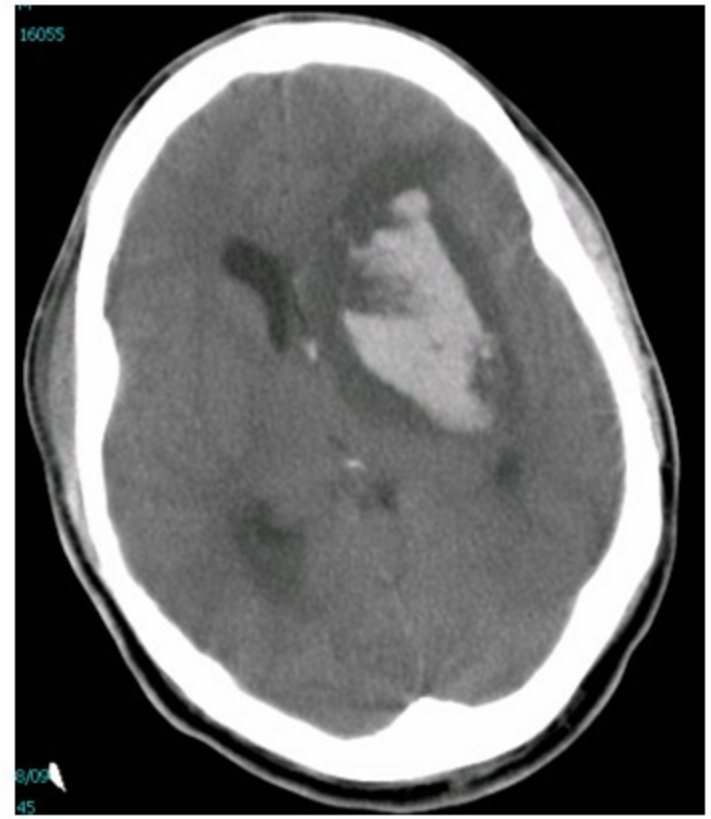
CRASH

Clinical Randomisation of an
Antifibrinolytic in Significant Head Injury

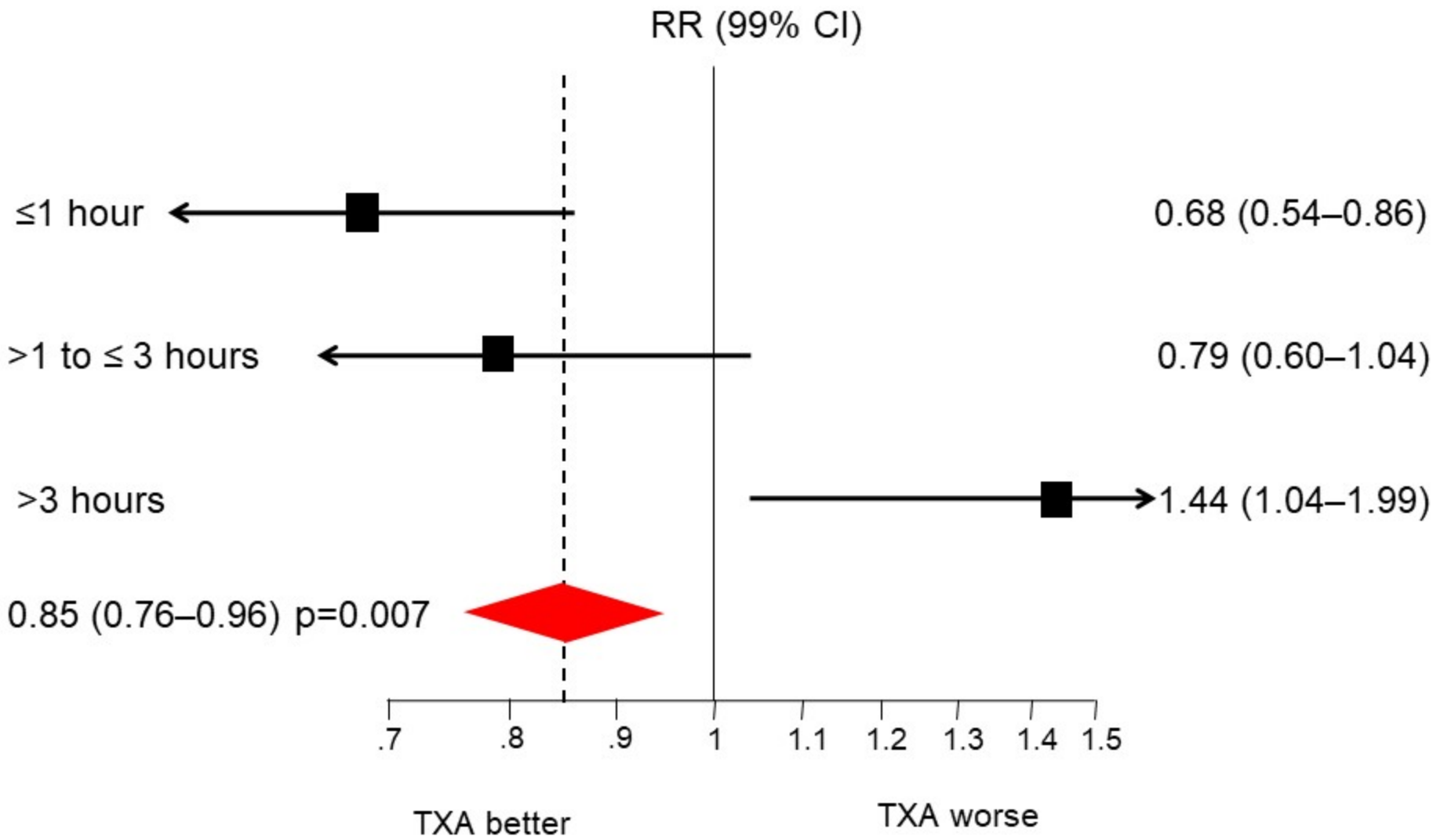
# Tranexamic acid for significant traumatic brain injury: an international randomised placebo controlled trial


TOYOTA
adidas




16055
8/09
45

# CRASH-2: TXA reduces traumatic extra-cranial bleeding deaths

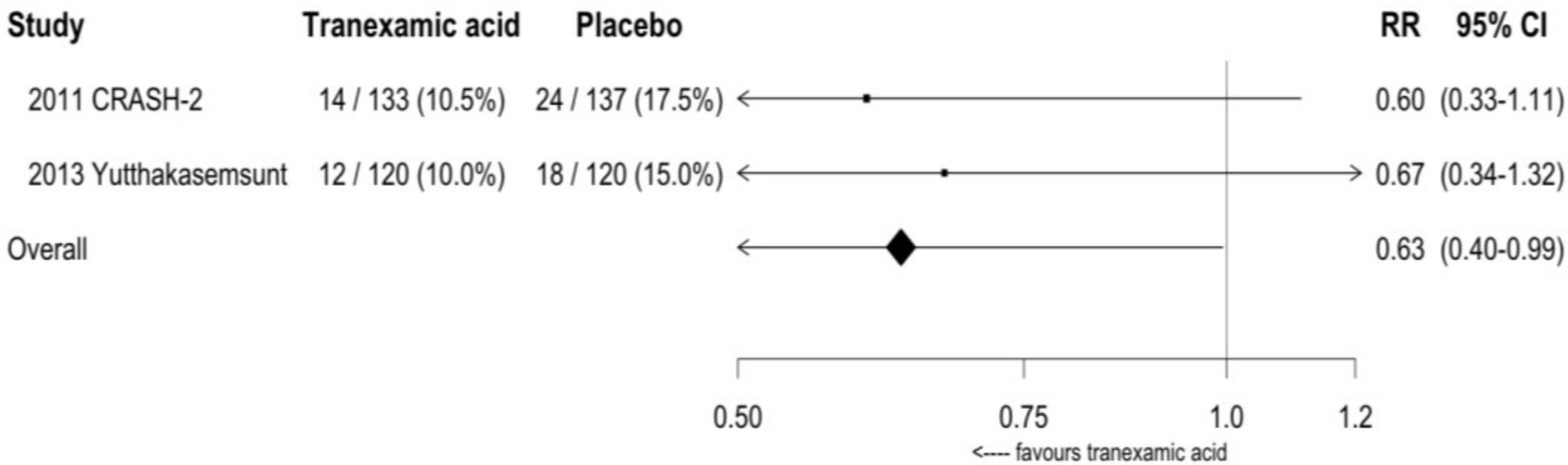



7
CRASH2

# Evidence before CRASH-3

## Effect of TXA on mortality in TBI

**Previous evidence**



# Overview

**ELIGIBILITY**

- adult
- with traumatic brain injury
- within 3 hours of injury
- any intracranial bleeding on CT scan OR GCS ≤12
- no significant extracranial haemorrhage

↓

Appropriate **CONSENT PROCESS** for patient
eg prior relative agreement or waiver

↓

**RANDOMISE** (tranexamic acid or placebo)

↓

**Loading dose 1g TXA or placebo over 10 minutes**

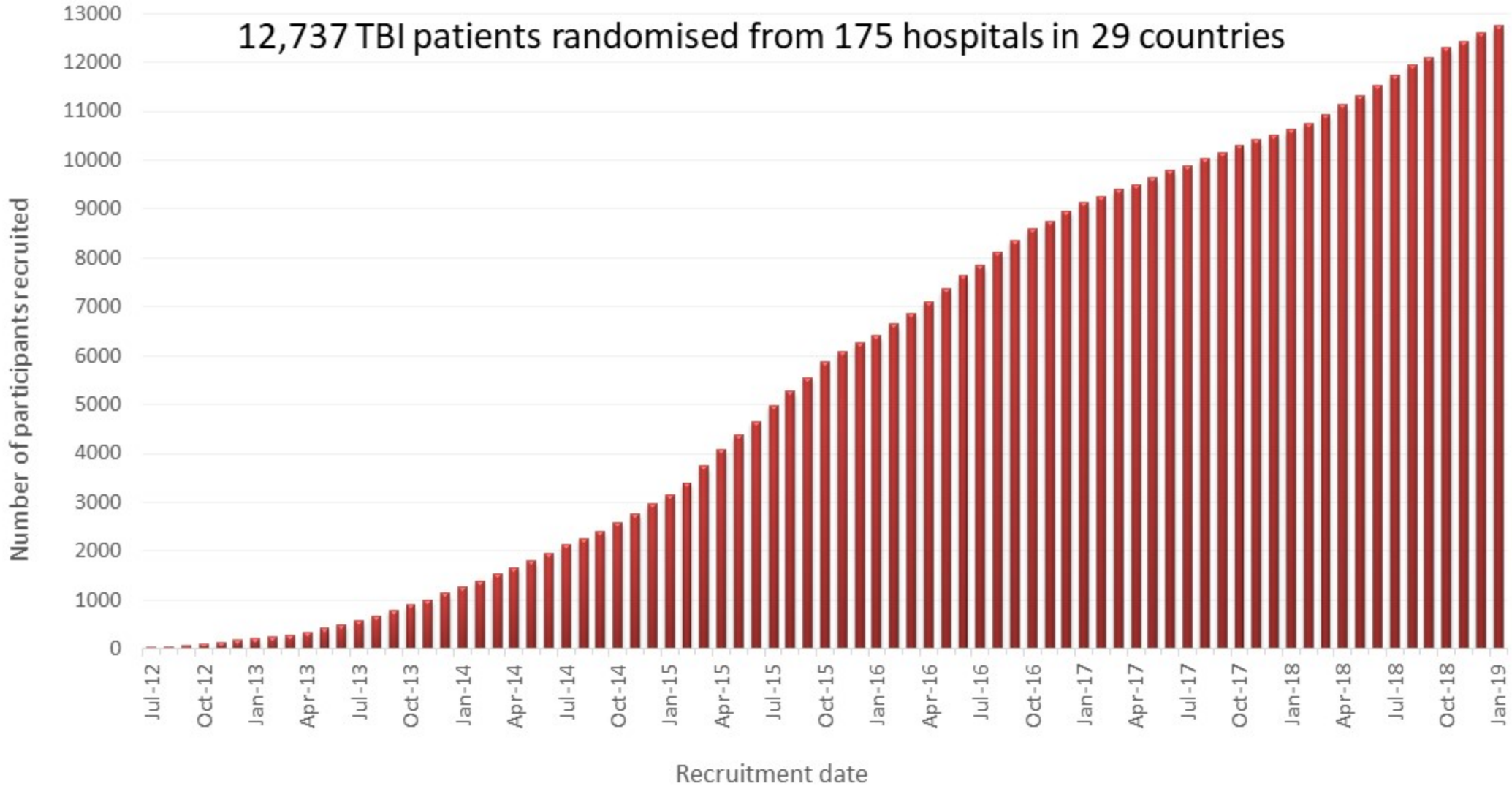
↓

**Maintenance dose 1g TXA or placebo over 8 hours**

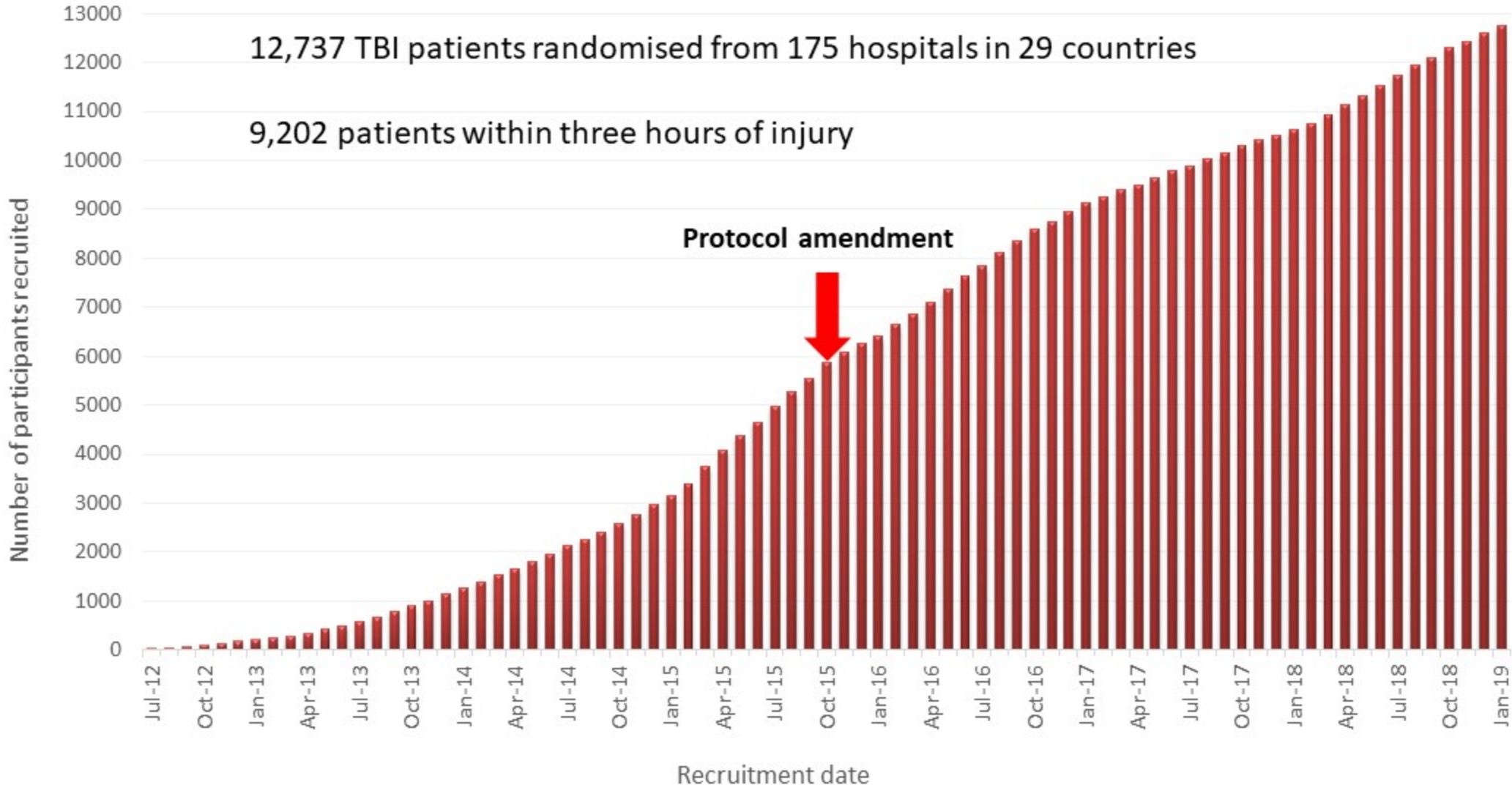
↓

Complete **outcome form** at prior discharge, death, or day 28

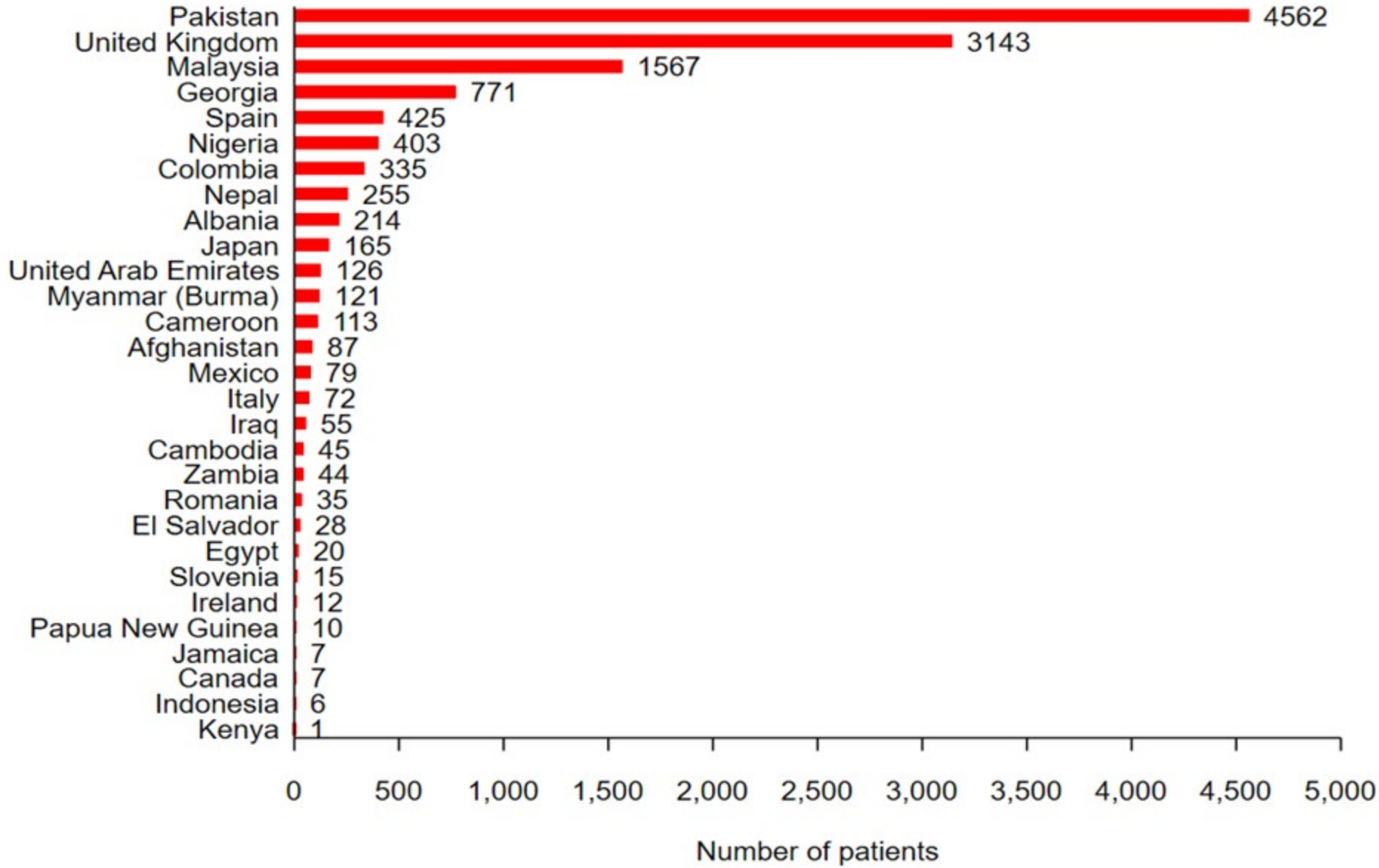
# CRASH-3 trial recruitment



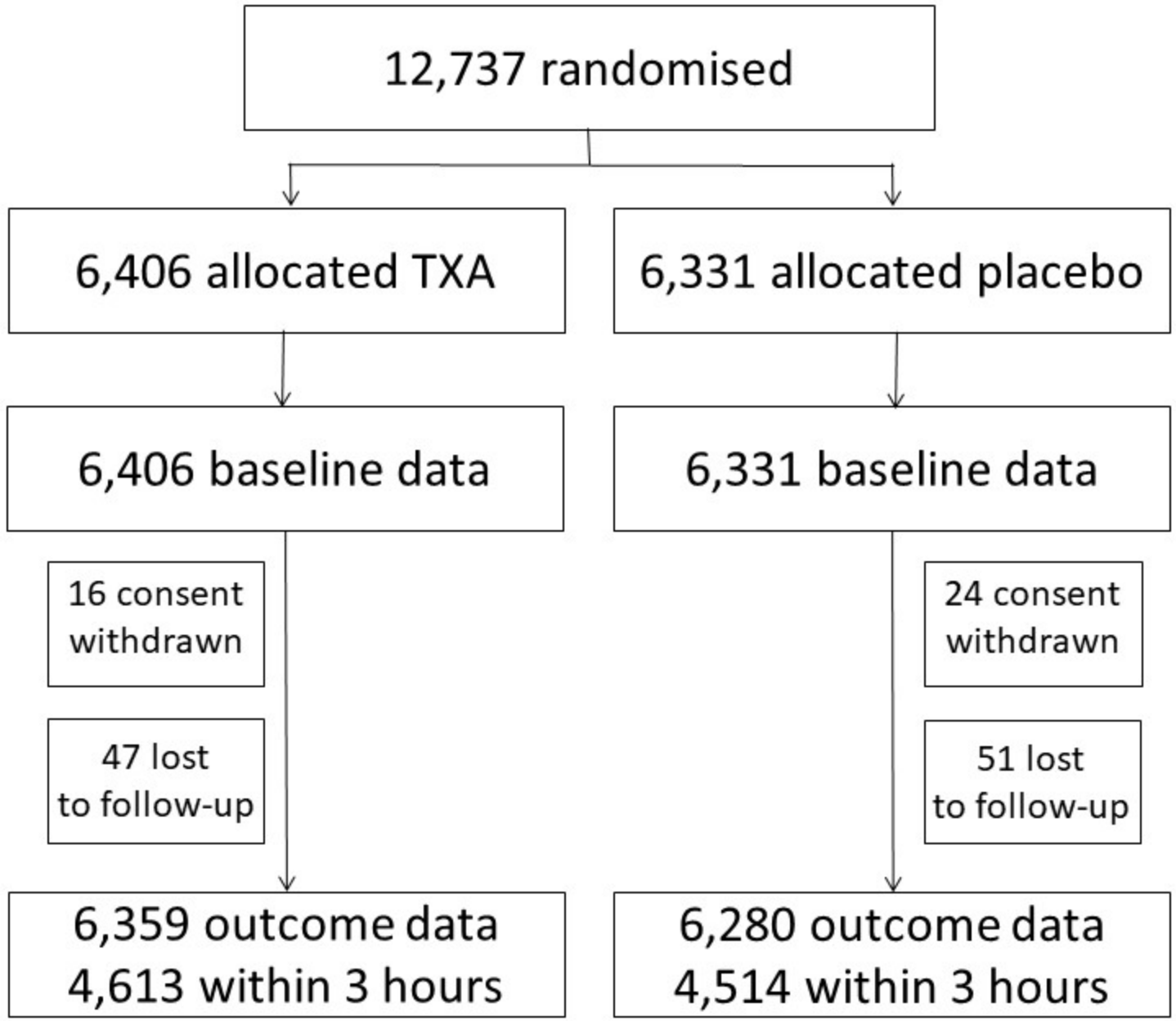
# CRASH-3 trial recruitment



# Trial recruitment by country



# Trial profile



# Baseline characteristics

(Randomised within 3 hours of injury)

| | TXA (n=4649) | | Placebo (n=4553) | |
|---|---|---|---|---|
| | n | (%) | n | (%) |
| **Glasgow Coma Scale** | | | | |
| Severe (3-8) | 1757 | (38) | 1732 | (38) |
| Moderate (9-12) | 1557 | (33) | 1524 | (33) |
| Mild (13-15) | 1307 | (28) | 1262 | (28) |
| Unknown | 28 | (1) | 35 | (1) |
| | | | | |
| **Pupil reaction** | | | | |
| None react* | 425 | (9) | 440 | (10) |
| One reacts | 374 | (8) | 353 | (8) |
| Both react | 3706 | (80) | 3636 | (80) |
| Unable to assess/unknown | 144 | (3) | 124 | (3) |

* pre-specified sensitivity analysis: excludes patients with GCS 3 and those with bilateral unreactive pupils

# Baseline characteristics

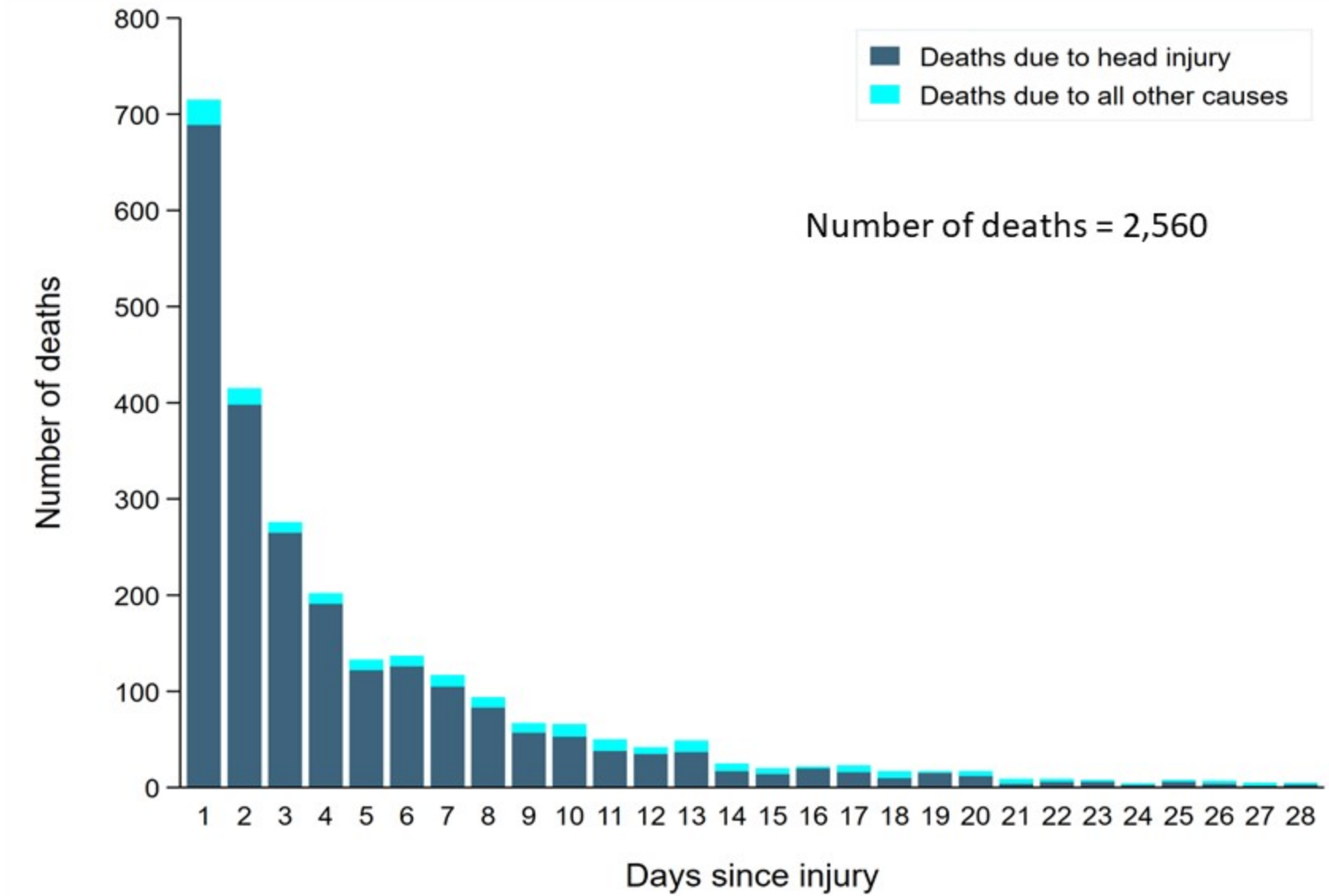
(Randomised within 3 hours of injury)

| GCS | TXA (n=4649) | | Placebo (n=4553) | |
|---|---|---|---|---|
| | n | (%) | 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) |

* pre-specified sensitivity analysis: excludes patients with GCS 3 and those with bilateral unreactive pupils

# Time from injury to death

(All patients)



# Statistical Analysis Plan (published July 2018)

Wellcome Open Research

Wellcome Open Research 2018, 3:86 Last updated: 25 SEP 2018

Check for updates

METHOD ARTICLE

## REVISED Tranexamic acid for significant traumatic brain injury (The CRASH-3 trial): Statistical analysis plan for an international, randomised, double-blind, placebo-controlled trial

Ian Roberts [1], Antonio Belli[2], Amy Brenner [1], Rizwana Chaudhri [3], Bukola Fawole [4], Tim Harris[5], Rashid Jooma[6], Abda Mahmood [1], Temitayo Shokunbi [4], Haleema Shakur [1], CRASH-3 trial collaborators

[1]Clinical Trials Unit, LSHTM, London, WC1E 7HT, UK
[2]The National Institute for Health Research Surgical Reconstruction and Microbiology Research Centre, Queen Elizabeth Hospital, Birmingham, UK
[3]RMC-LSHTM Research Collaboration Centre (RLRCC), Holy Family Hospital, Rawalpindi, Pakistan
[4]COMUI-LSHTM Research Collaboration Centre (CLRCC), University College Hospital, Ibadan, Nigeria
[5]Barts Health and Queen Mary University, London, UK
[6]Aga Khan University Hospital, Karachi, Pakistan

**v2** **First published:** 20 Jul 2018, **3**:86 (doi: 10.12688/wellcomeopenres.14700.1)
**Latest published:** 20 Jul 2018, **3**:86 (doi: 10.12688/wellcomeopenres.14700.1)

### Abstract

**Background:** Worldwide, traumatic brain injury (TBI) kills or hospitalises over 10 million people each year. Early intracranial bleeding is common after TBI, increasing the risk of death and disability. Tranexamic acid reduces blood loss in surgery and death due to bleeding in trauma patients with extra-cranial injury. Early administration of tranexamic acid in TBI patients might limit intracranial bleeding, reducing death and disability. The CRASH-3 trial aims to provide evidence on the effect of tranexamic acid on death and disability in TBI patients. We will randomly allocate about 13,000 TBI patients (approximately 10,000 within 3 hours of injury) to an intravenous infusion of tranexamic acid or matching placebo in addition to usual care. This paper presents a protocol update (version 2.1) and statistical analysis plan for the CRASH-3 trial.
**Results:** The primary outcome is head injury death in hospital within 28 days of injury for patients treated within 3 hours of injury (deaths in patients treated after 3 hours will also be reported). Because there are reasons to expect that tranexamic acid will be most effective in patients treated immediately after injury and less effective with increasing delay, the effect in patients treated within one hour of injury is of particular interest. Secondary outcomes are all-cause and cause-specific mortality, vascular occlusive events, disability based on the Disability Rating Scale and measures suggested by patient representatives, seizures, neurosurgical intervention, neurosurgical blood loss, days in intensive care and adverse events. Sub-group analyses will examine the effect of tranexamic acid on head injury death stratified by time to treatment, severity of TBI and baseline risk.
**Conclusion:** The CRASH-3 trial will provide reliable evidence of the effectiveness and safety of tranexamic acid in patients with acute TBI.

**Open Peer Review**

**Referee Status:** ✓ ✓ ✓ ?

| | Invited Referees 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| version 1 published 20 Jul 2018 | ✓ report | ✓ report | ✓ report | ? report |

1 **Paul S. Myles**, Monash University, Australia

2 **Shahriar Zehtabchi**, State University of New York, Downstate Medical Center, USA

3 Anna Teresa Mazzeo, Università di Torino, Italy
**Deepak Kumar Gupta**, All India Institute of Medical Sciences, Delh (AIIMS), India

4 **Susanne May**, University of Washington, USA

**Discuss this article**

# Statistical Analysis Plan (published July 2018)

**Primary outcome**

"The primary outcome is head injury death in hospital within 28 days of injury among patients randomised within 3 hours of injury…"

**Sensitivity analysis**

TBI patients who have a GCS of 3 and bilateral un-reactive pupils have a very poor prognosis….The inclusion in the CRASH-3 trial of such severely injured patients, who may have little potential to benefit from the trial treatment, **would bias the treatment effect towards the null.** We will therefore conduct a sensitivity analysis that excludes patients with a GCS 3 and bilateral un-reactive pupils.

# Primary outcome

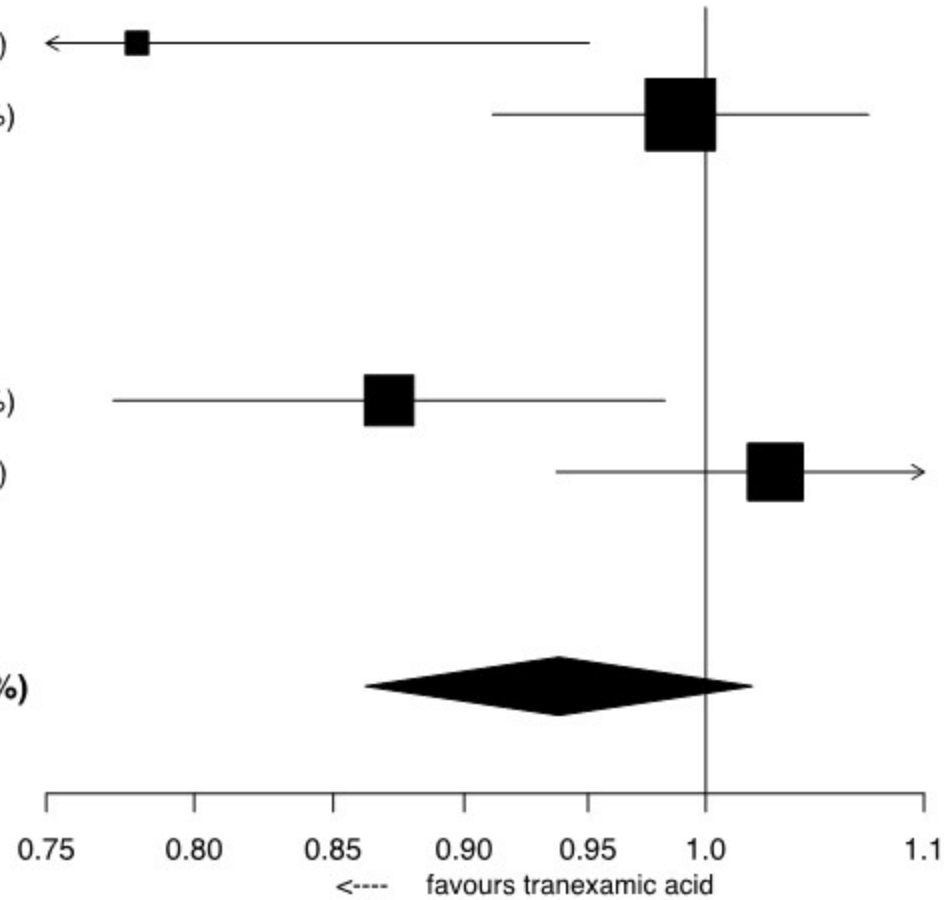
(Head injury death randomised within 3 hours)

| Outcome | TXA n / N | (%) | Placebo n / N | (%) | RR (95% CI) |
|---|---|---|---|---|---|
| **Head injury death** | | | | | |
| All patients | 855 / 4613 | (18.5) | 892 / 4514 | (19.8) | 0.94 (0.86-1.02) |
| **Excl. GCS 3, both unreactive*** | **485 / 3880** | **(12.5)** | **525 / 3757** | **(14.0)** | **0.89 (0.80-1.00)** |

*** Pre-specified analysis: excluding patients with GCS 3 and those with bilateral unreactive pupils**

# Head injury death by severity

| Subgroup | Tranexamic acid (N=4613) | Placebo (N=4514) | RR | 95%CI |
|---|---|---|---|---|
| GCS | | | | |
| Mild to moderate (9-15) | 166 / 2846 (5.8%) | 207 / 2769 (7.5%) | 0.78 | (0.64-0.95) |
| Severe (3-8) | 689 / 1739 (39.6%) | 685 / 1710 (40.1%) | 0.99 | (0.91-1.07) |
| p=0.030 | | | | |
| Pupil reactivity | | | | |
| Both react | 440 / 3820 (11.5%) | 493 / 3728 (13.2%) | 0.87 | (0.77-0.98) |
| Any non reactive | 415 / 793 (52.3%) | 399 / 786 (50.8%) | 1.03 | (0.94-1.13) |
| p=0.032 | | | | |
| **Overall** | **855 / 4613 (18.5%)** | **892 / 4514 (19.8%)** | **0.94** | **(0.86-1.02)** |




**Analysis includes patients with GCS 3 and those with bilateral unreactive pupils**

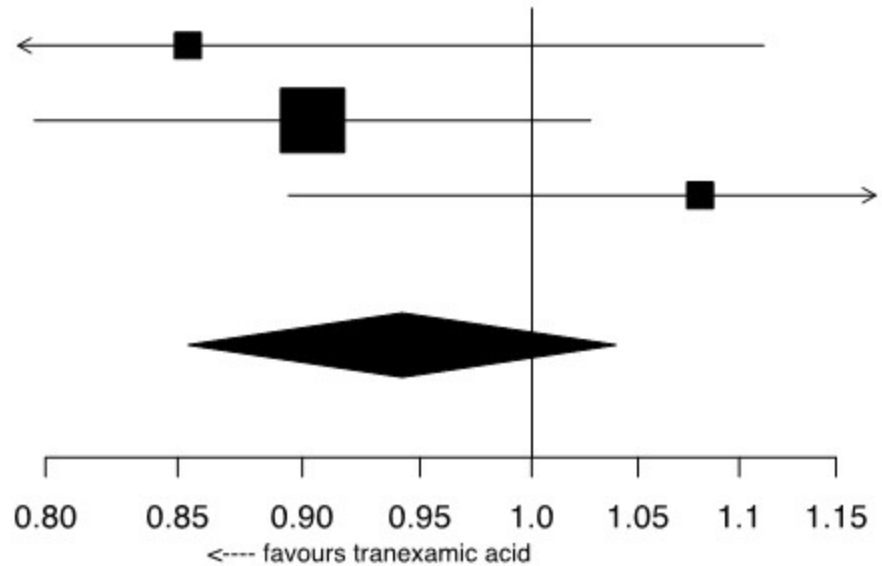
# Head injury death by severity

**Pre-specified analysis:**
"We will assess the impact of baseline severity on the treatment effect in a regression analysis that includes continuous terms for severity and its square (because of potential non-linearity of the treatment effect)."

**Results**:
Strong evidence (heterogeneity p value=0.007) that the treatment effect varies by severity - TXA treatment most effective in less severely injured patients.

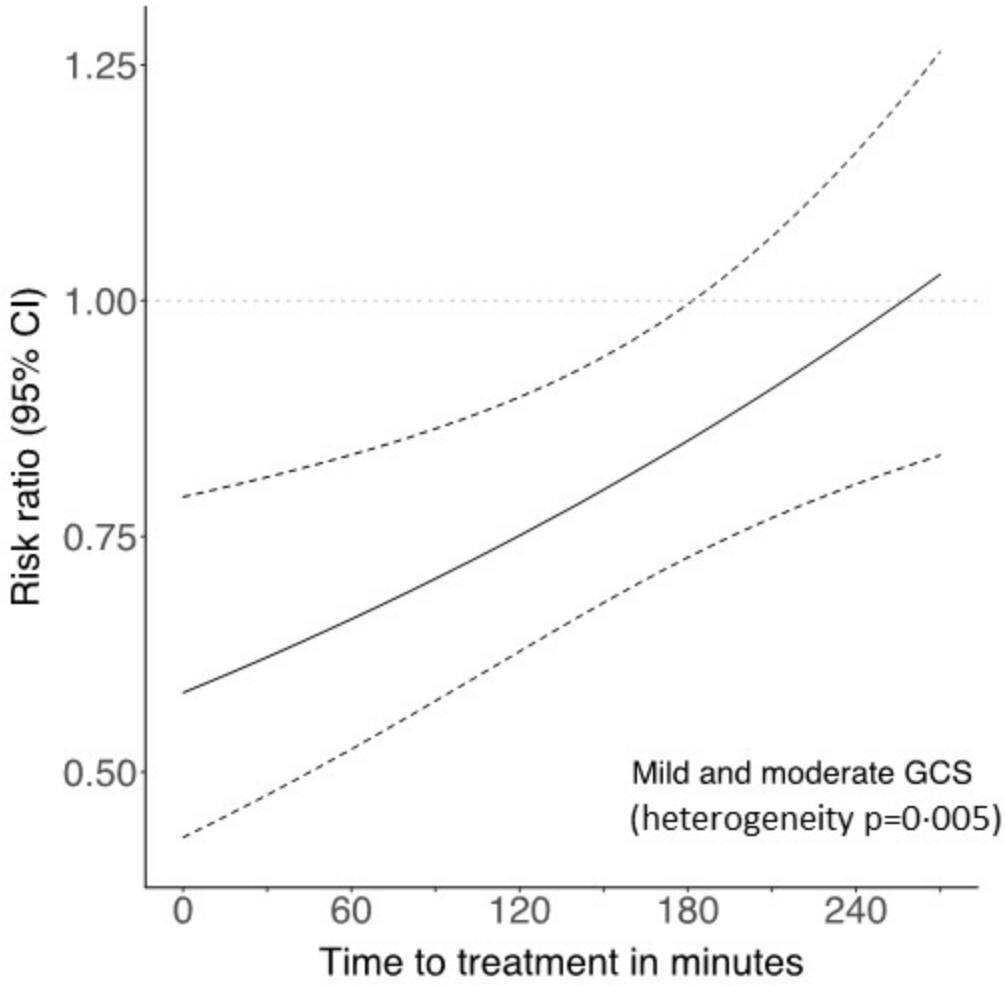
# Head injury death by time to treatment

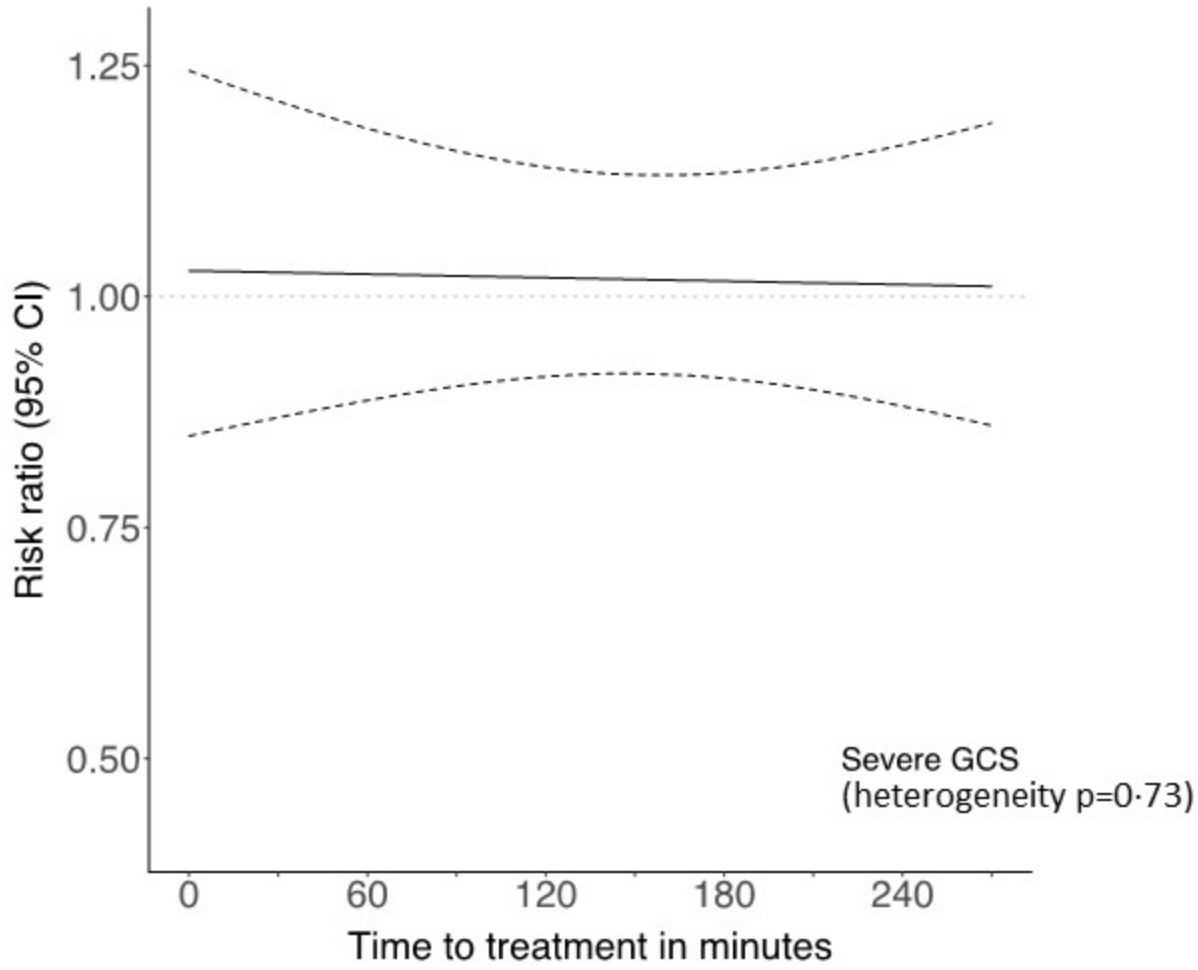
| Subgroup | Tranexamic acid | Placebo | RR | 95%CI |
|---|---|---|---|---|
| Time since injury (hours) † | (N=5420) | (N=5302) | | |
| ≤1 | 90 / 747 (12.0%) | 102 / 723 (14.1%) | 0.85 | (0.66-1.11) |
| 1-3 | 395 / 3133 (12.6%) | 423 / 3034 (13.9%) | 0.90 | (0.80-1.03) |
| 3+ | 196 / 1540 (12.7%) | 182 / 1545 (11.8%) | 1.08 | (0.89-1.31) |
| p=0.23 | | | | |
| **Overall** | **681 / 5420 (12.6%)** | **707 / 5302 (13.3%)** | **0.94** | **(0.85-1.04)** |




† Excluding patients with GCS 3 and bilateral non-reactive pupils at baseline

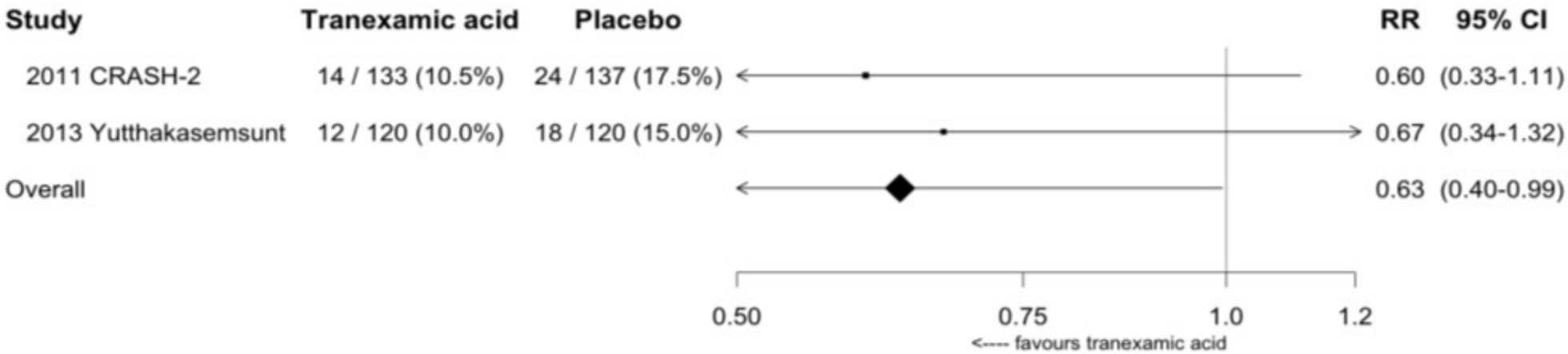
# Head injury death by time to treatment and severity



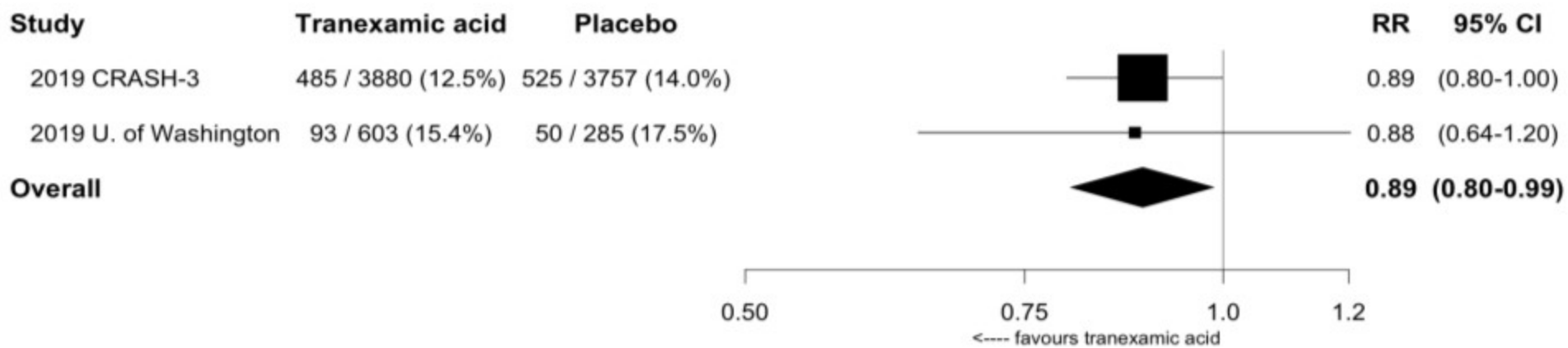



# CRASH-3 trial in context

**Previous evidence**




**New evidence**



# Non-head injury and all-cause mortality

| Outcome | TXA | | Placebo | | RR (95% CI) |
|---|---|---|---|---|---|
| | n / N | (%) | n / N | (%) | |
| Non-head injury death | 75/ 4613 | (1.6) | 56/ 4514 | (1.2) | 1.31 (0.93-1.85) |
| All-cause mortality | 930/ 4613 | (20.2) | 948/ 4514 | (21.0) | 0.96 (0.89-1.04) |

# Disability in survivors

(Low DRS score means less disabled)

| | TXA | Placebo | |
|---|---|---|---|
| | **mean (SD)** | **mean (SD)** | **Difference** |
| **<3h** | 4.99 (7.6) | 5.03 (7.6) | 0.04 |
| **>3h** | 4.52 (7.0) | 5.00 (7.4) | 0.48 |
| **All patients** | 4.86 (7.5) | 5.02 (7.5) | 0.16 |

Includes survivors only

# Disability in survivors

(Randomised within 3 hours of injury)

| | TXA (N=4613) | | Placebo (N=4514) | | RR (95% CI) |
|---|---|---|---|---|---|
| | n | (%) | n | (%) | |
| Confined to bed | 579 | (13) | 549 | (12) | 1.03 (0.93-1.15) |
| Unable to wash or dress | 580 | (13) | 583 | (13) | 0.97 (0.87-1.08) |
| Extreme pain or discomfort | 38 | (1) | 29 | (1) | 1.28 (0.79-2.08) |
| Extreme anxiety or depression | 43 | (1) | 41 | (1) | 1.03 (0.67-1.57) |
| Extreme agitation or aggression | 53 | (1) | 53 | (1) | 0.98 (0.67-1.43) |
| Extreme fatigue | 100 | (2) | 101 | (2) | 0.97 (0.74-1.27) |

# Pre-specified adverse events

(Randomised within 3 hours of injury)

| | TXA (N=4613) | | Placebo (N=4514) | | RR (95% CI) |
|---|---|---|---|---|---|
| | n | (%) | n | (%) | |
| All vascular occlusive events | 69 | (1) | 60 | (1) | 1.13 (0.80-1.59) |
| Pulmonary embolism | 18 | (<1) | 18 | (<1) | 0.98 (0.51-1.88) |
| Deep vein thrombosis | 15 | (<1) | 12 | (<1) | 1.22 (0.57-2.61) |
| Stroke | 29 | (1) | 23 | (1) | 1.23 (0.71-2.13) |
| Myocardial infarction | 9 | (<1) | 12 | (<1) | 0.73 (0.31-1.74) |
| Renal failure | 73 | (2) | 56 | (1) | 1.28 (0.90-1.80) |
| Sepsis | 297 | (6) | 279 | (6) | 1.04 (0.89-1.22) |
| Seizure | 130 | (3) | 105 | (2) | 1.21 (0.94-1.56) |
| Gastrointestinal bleeding | 16 | (<1) | 22 | (<1) | 0.71 (0.37-1.35) |

# Pre-specified adverse events

(Randomised at any time)

| | TXA (N=6359) | | Placebo (N=6280) | | RR (95% CI) |
|---|---|---|---|---|---|
| | n | (%) | n | (%) | |
| All vascular occlusive events | 101 | (2) | 102 | (2) | 0.98 (0.74-1.28) |
| Pulmonary embolism | 24 | (<1) | 32 | (1) | 0.74 (0.44-1.26) |
| Deep vein thrombosis | 19 | (<1) | 16 | (<1) | 1.17 (0.60-2.28) |
| Stroke | 46 | (1) | 42 | (1) | 1.08 (0.71-1.64) |
| Myocardial infarction | 18 | (<1) | 20 | (<1) | 0.89 (0.47-1.68) |
| Renal failure | 100 | (2) | 84 | (1) | 1.18 (0.88-1.57) |
| Sepsis | 411 | (6) | 412 | (7) | 0.99 (0.86-1.12) |
| Seizure | 206 | (3) | 186 | (3) | 1.09 (0.90-1.33) |
| Gastrointestinal bleeding | 24 | (<1) | 35 | (1) | 0.68 (0.40-1.14) |


Tranexamic acid is safe in TBI patients

Tranexamic acid reduces head injury deaths

No increase in disability in survivors

Patients should be treated as soon as possible after injury







Website: crash3.lshtm.ac.uk/ Twitter: @ctu_LSHTM