BACKGROUND AND SCIENTIFIC RATIONALE

Protocol Code: ISRCTN15088122
V 1.1 date 6 Jan 2017

Traumatic Brain Injury

- 10 million killed or hospitalised every year
- 90% in low and middle income countries
- Mostly young adults and long lasting disability
- The incidence of TBI is predicted to rise

•Bruns J, Hauser W. The epidemiology of traumatic brain injury: a review. Epilepsia 2003;44: Supplement 10:2-10.
•Peden M, Scurfield R, Sleet D, et al. World Report on Road Traffic Injury Prevention. Geneva: World Health Organization, 2004.

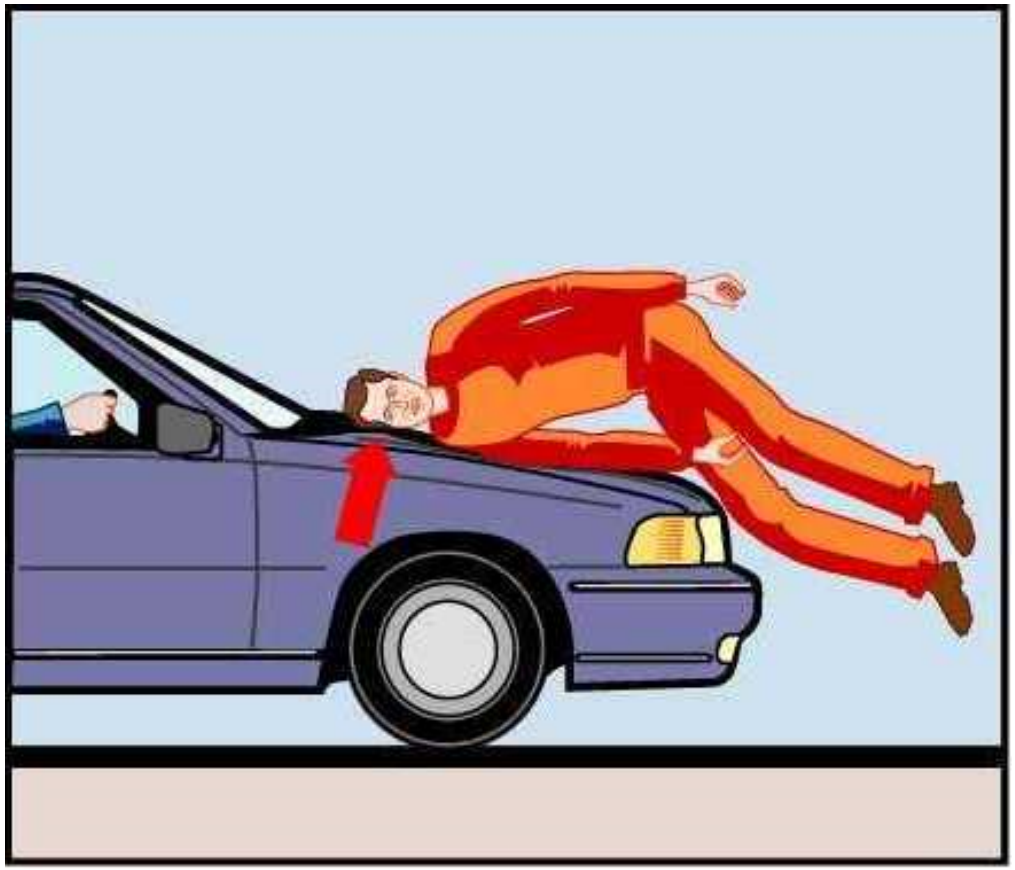
Rankings of Deaths & DALYs: 1990–2020

	Deaths		DALYs	
	1990 rank	2020 rank	1990 rank	2020 rank
Road Traffic Injuries	9 →	6	9 →	3
Self Inflicted Injuries	12 →	10	17 →	14
Interpersonal Violence	16 →	14	19 →	12
War	20 →	15	16 →	8

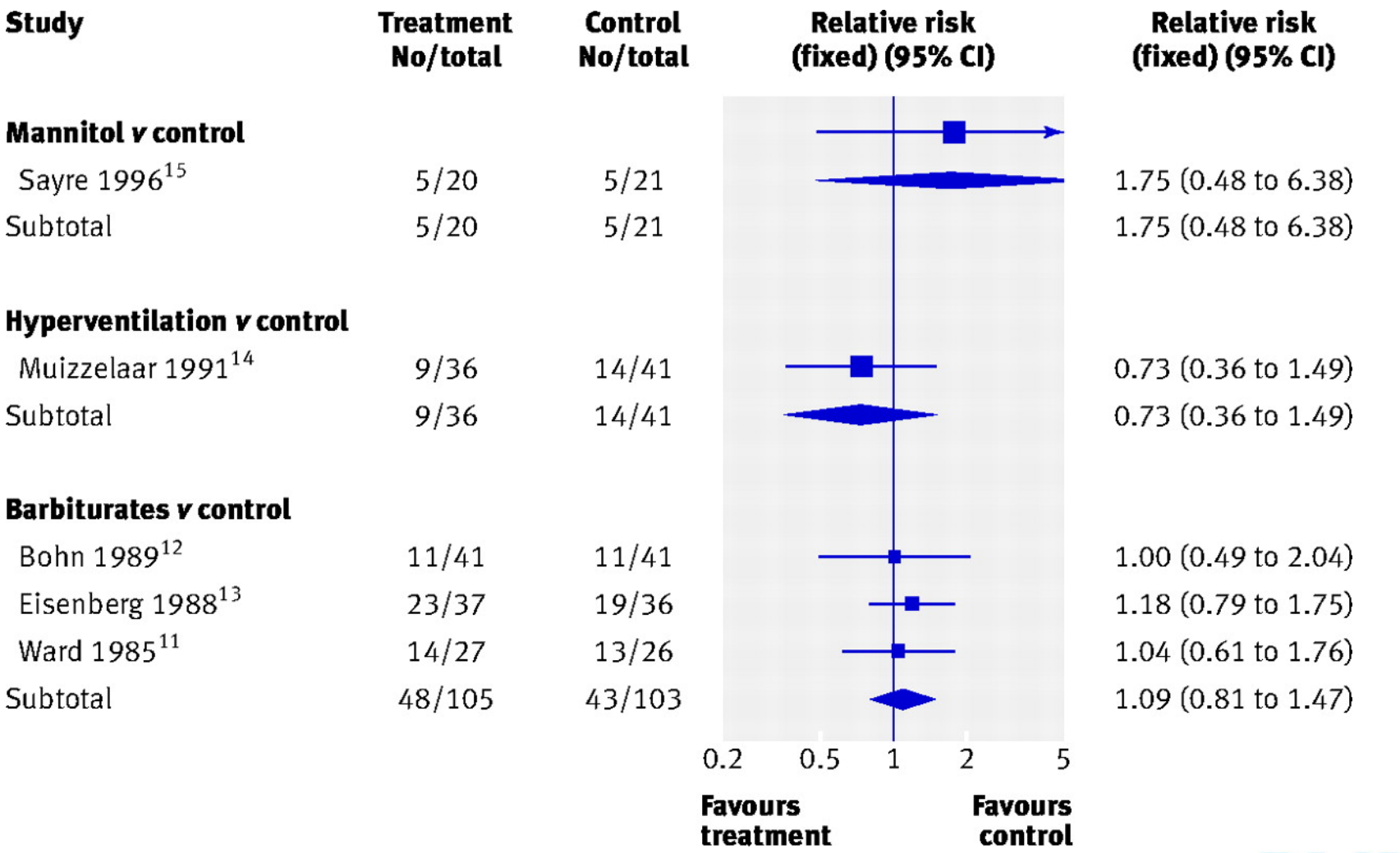
If current trends continue, road traffic and intentional injuries will all rank in the 15 leading causes of death and burden of disease.

Murray CJL, Lopez AD. Global health statistics: a compendium of incidence, prevalence and mortality estimates for over 200 conditions. Harvard School of Public Health, Boston: Harvard University Press, 1996.

Traumatic Brain Injury



Summary of relative risks for death at the end of studies on mannitol, hyperventilation, and barbiturates.



Ker K et al. BMJ 2008;337:bmj.a865

Traumatic Brain Injury

What works in head injury?

- We don’t know
- Large treatment effects unlikely
- But even moderate effects worthwhile

Traumatic Brain Injury

To detect moderate effects trials must be

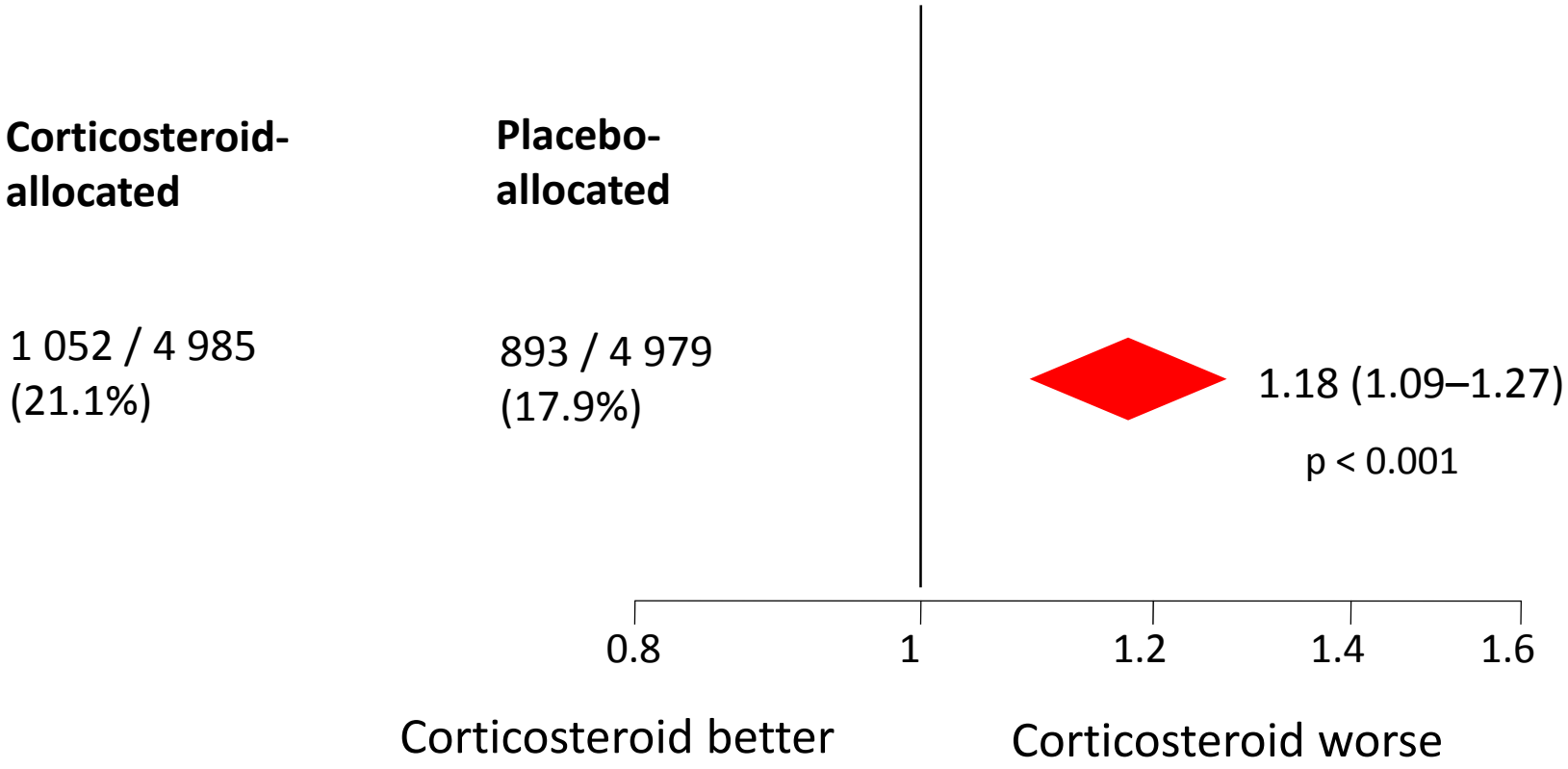
- Large
- Well designed

MRC
Medical Research Council

CRASH

A large simple placebo controlled trial, among adults with head injury and impaired consciousness, of the effects of a 48-hour infusion of corticosteroids on death and neurological disability

Death within 14 days



9 October 2004

ELSEVIER

THE LANCET

Volume 364 Number 9442 October 9–15, 2004 www.thelancet.com

"The administration of corticosteroids to brain-injured patients has seemingly caused more than 10 000 deaths during the 1980s and earlier."

See **Comment** page 1291

£5.00 Registered as a newspaper-ISSN 0140-6736
Founded 1823 · Published weekly

Effect of intravenous corticosteroids on death within 14 days in 10 008 adults with clinically significant head injury (MRC CRASH trial): randomised placebo-controlled trial

*CRASH trial collaborators**

Lancet 2004; 364: 1321–28

See **Comment** page 1291

*Listed at end of report

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crash@lshtm.ac.uk

Summary

Background Corticosteroids have been used to treat head injuries for more than 30 years. In 1997, findings of a systematic review suggested that these drugs reduce risk of death by 1–2%. The CRASH trial—a multicentre international collaboration—aimed to confirm or refute such an effect by recruiting 20 000 patients. In May, 2004, the data monitoring committee disclosed the unmasked results to the steering committee, which stopped recruitment.

Methods 10 008 adults with head injury and a Glasgow coma score (GCS) of 14 or less within 8 h of injury were randomly allocated 48 h infusion of corticosteroids (methylprednisolone) or placebo. Primary outcomes were death within 2 weeks of injury and death or disability at 6 months. Prespecified subgroup analyses were based on injury severity (GCS) at randomisation and on time from injury to randomisation. Analysis was by intention to treat. Effects on outcomes within 2 weeks of randomisation are presented in this report. This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN74459797.

Findings Compared with placebo, the risk of death from all causes within 2 weeks was higher in the group allocated corticosteroids (1052 [21·1%] *vs* 893 [17·9%] deaths; relative risk 1·18 [95% CI 1·09–1·27]; p=0·0001). The relative increase in deaths due to corticosteroids did not differ by injury severity (p=0·22) or time since injury (p=0·05).

Interpretation Our results show there is no reduction in mortality with methylprednisolone in the 2 weeks after head injury. The cause of the rise in risk of death within 2 weeks is unclear.

Introduction

Every year, millions of people worldwide are treated for head injury. A substantial proportion die or are permanently disabled. Although much damage is done at the time of injury, post-traumatic inflammatory changes are believed to contribute to neuronal degeneration.[1,2] Corticosteroids have been used to treat head injury for more than 30 years. A survey of UK neurosurgical intensive-care units in 1996 showed that these drugs were used in 14% of units to treat head injuries,[3] and a survey of intensive-care management of patients with a head injury in the USA reported that corticosteroids were used in 64% of trauma centres.[4] Corticosteroids are also used for management of head injury in Asia.[5]

Previous randomised trials of corticosteroids in head injury have included no more than a few hundred patients, and altogether only about 2000 patients have been studied. In 1997, a systematic review of available trials suggested that the absolute risk of death in the corticosteroid-treated group was about 1–2% lower than in controls, but the 95% CI was from 6% fewer to 2% more deaths.[6]

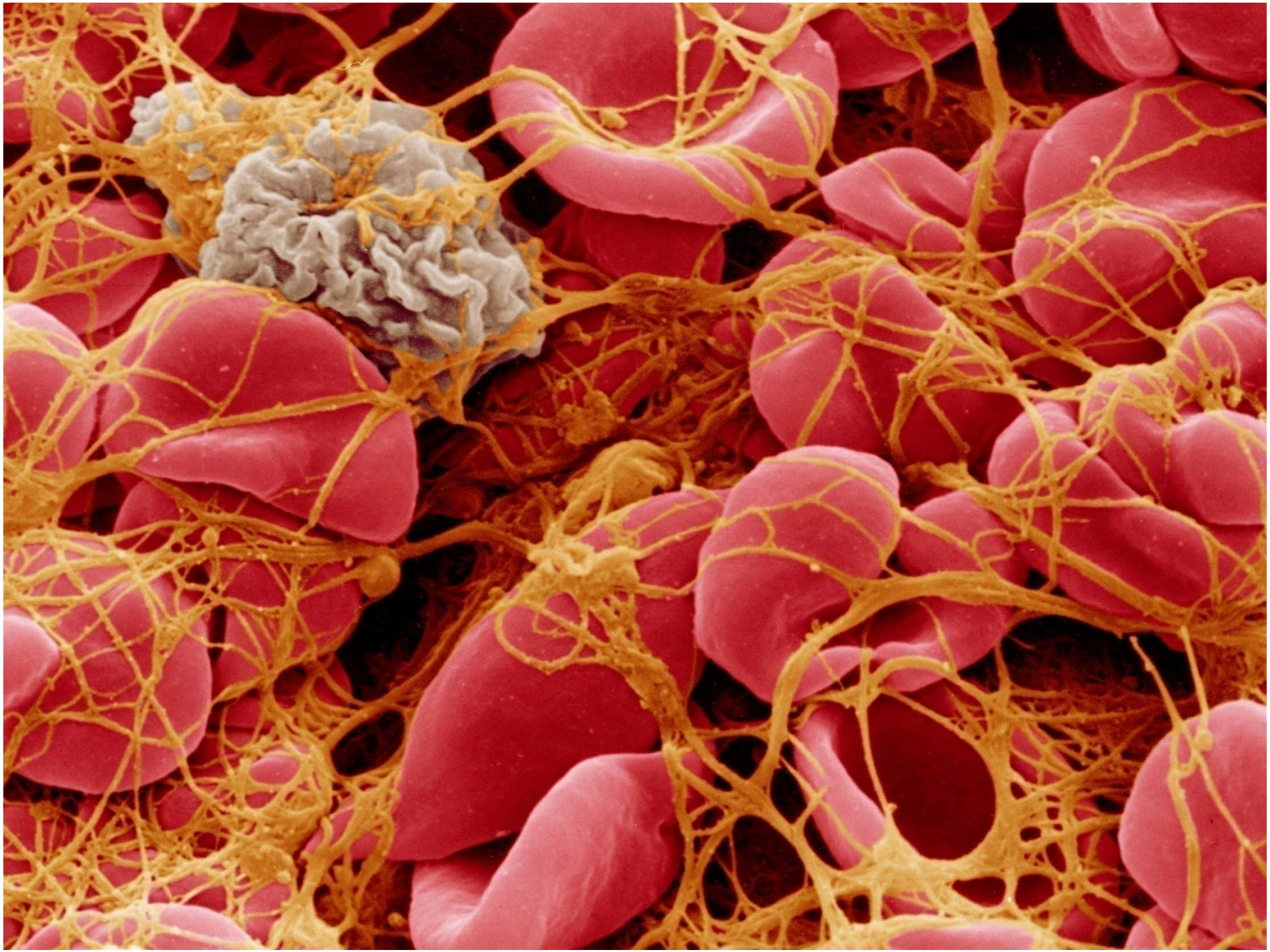
The second US National Acute Spinal Cord Injury Study (NASCIS-2) compared 24 h of methylprednisolone with placebo in 333 patients with acute spinal-cord injury.[7] At 6 months, people receiving methylprednisolone within 8 h of injury seemed to have greater improvement in motor function and sensation to pinprick and touch than did those given placebo. Similar results were reported in a Japanese trial of the same regimen.[8] Results of NASCIS-3 indicated slightly more neurological recovery with 48 h of treatment than with 24 h.[9] Use of corticosteroids to treat acute spinal-cord injury led to renewed interest in their role in the treatment of head injury.[10]

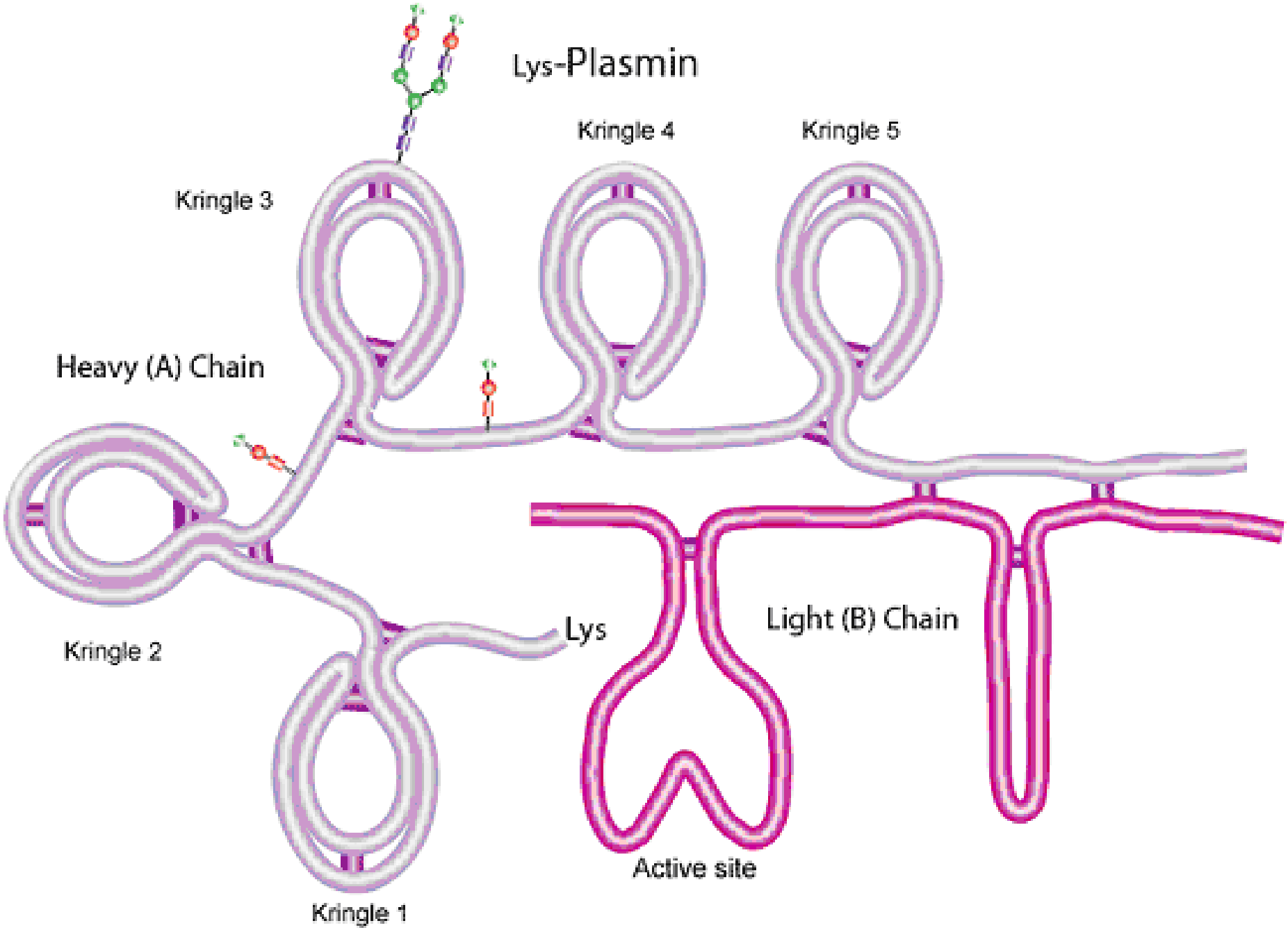
The CRASH trial (corticosteroid randomisation after significant head injury) is a large, international, randomised placebo-controlled trial of the effect of early administration of 48 h infusion of methylprednisolone on risk of death and disability after head injury. The trial aimed to inform clinical decision-making in an area of increasing global health importance. Reliable demonstration of even a small absolute benefit from corticosteroids would have the potential to avoid thousands of deaths and disabilities. Similarly, because corticosteroids are widely used to treat head injury, reliable refutation of any benefit would protect thousands of patients from possible side-effects and avoid unnecessary cost.

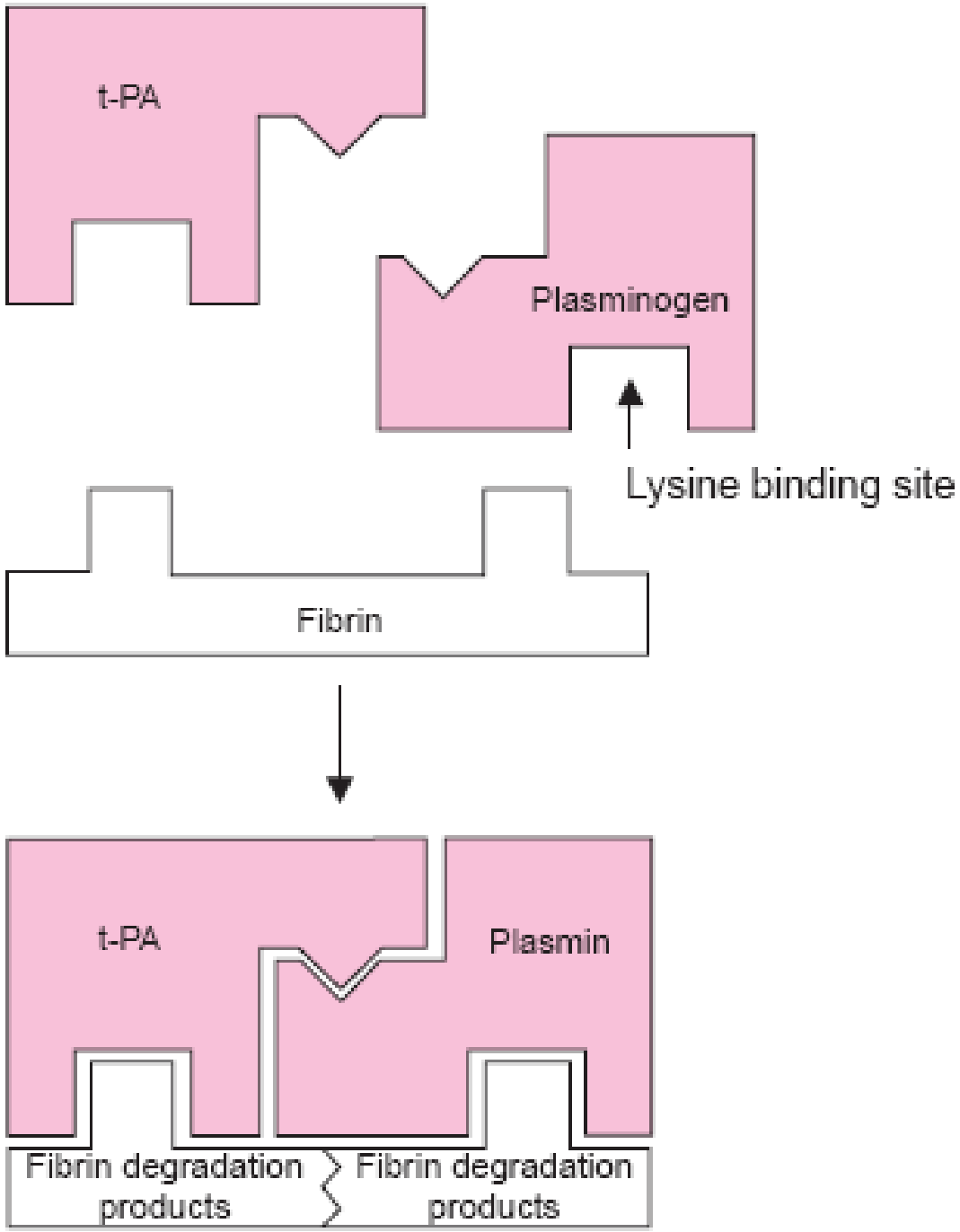
Patients and methods

The protocol for the CRASH trial has been published elsewhere (http://www.crash.lshtm.ac.uk). All collaborating investigators were required to secure local ethics or research committee approval before recruitment could begin. Patients with clinically significant head injury are


TOYOTA
adidas




Lys-Plasmin
Kringle 4
Kringle 5
Kringle 3
Heavy (A) Chain
Kringle 2
Lys
Light (B) Chain
Active site
Kringle 1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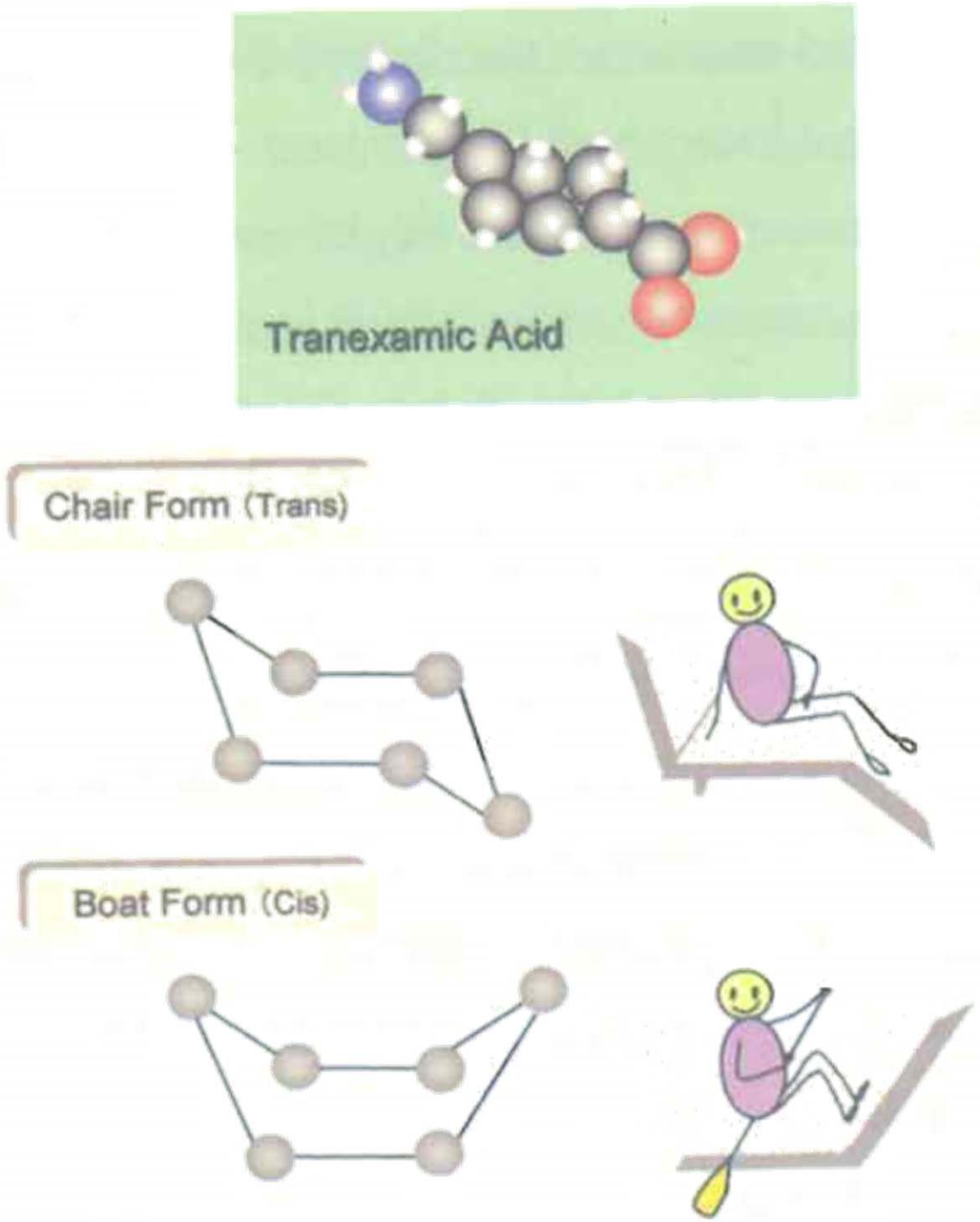
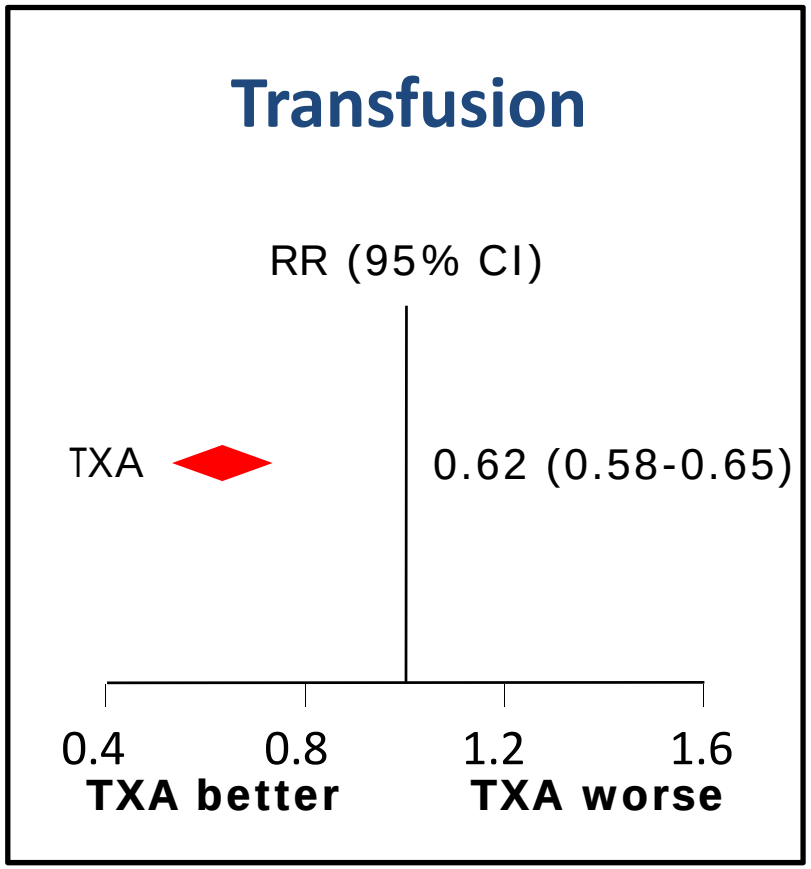


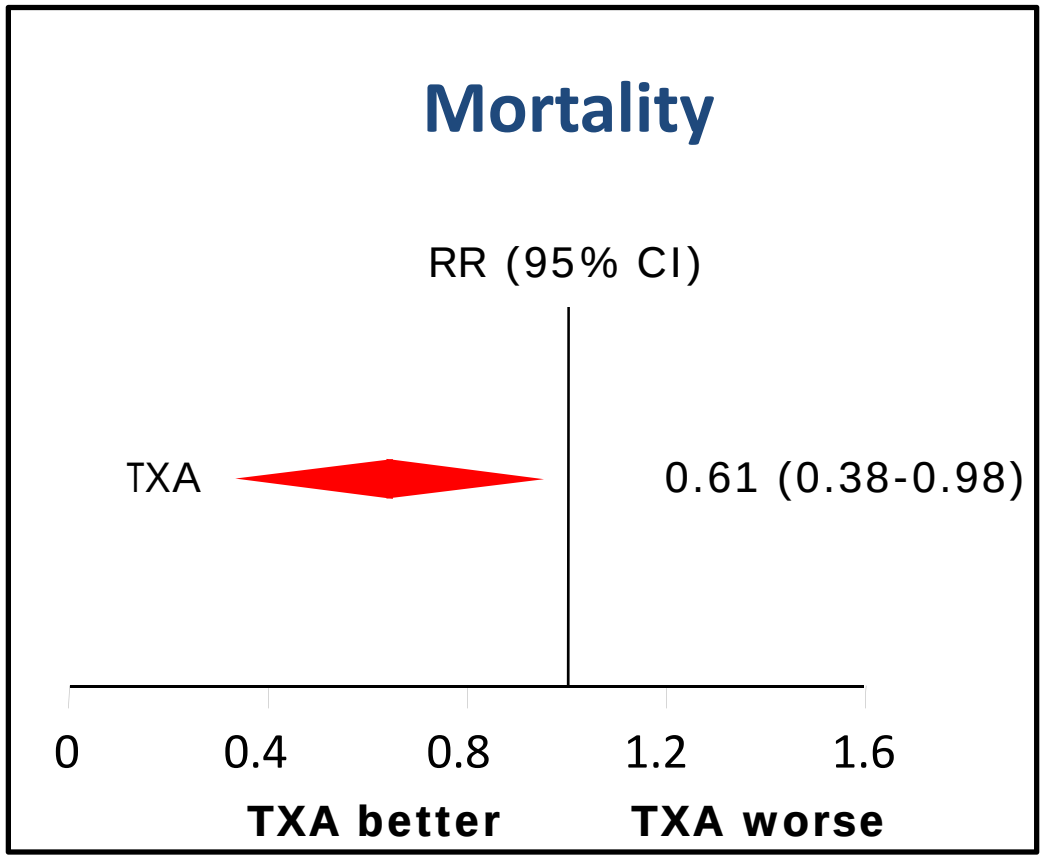
Figure 3. Stereoisomers of cyclohexane

TXA and bleeding

TXA reduces bleeding in surgery



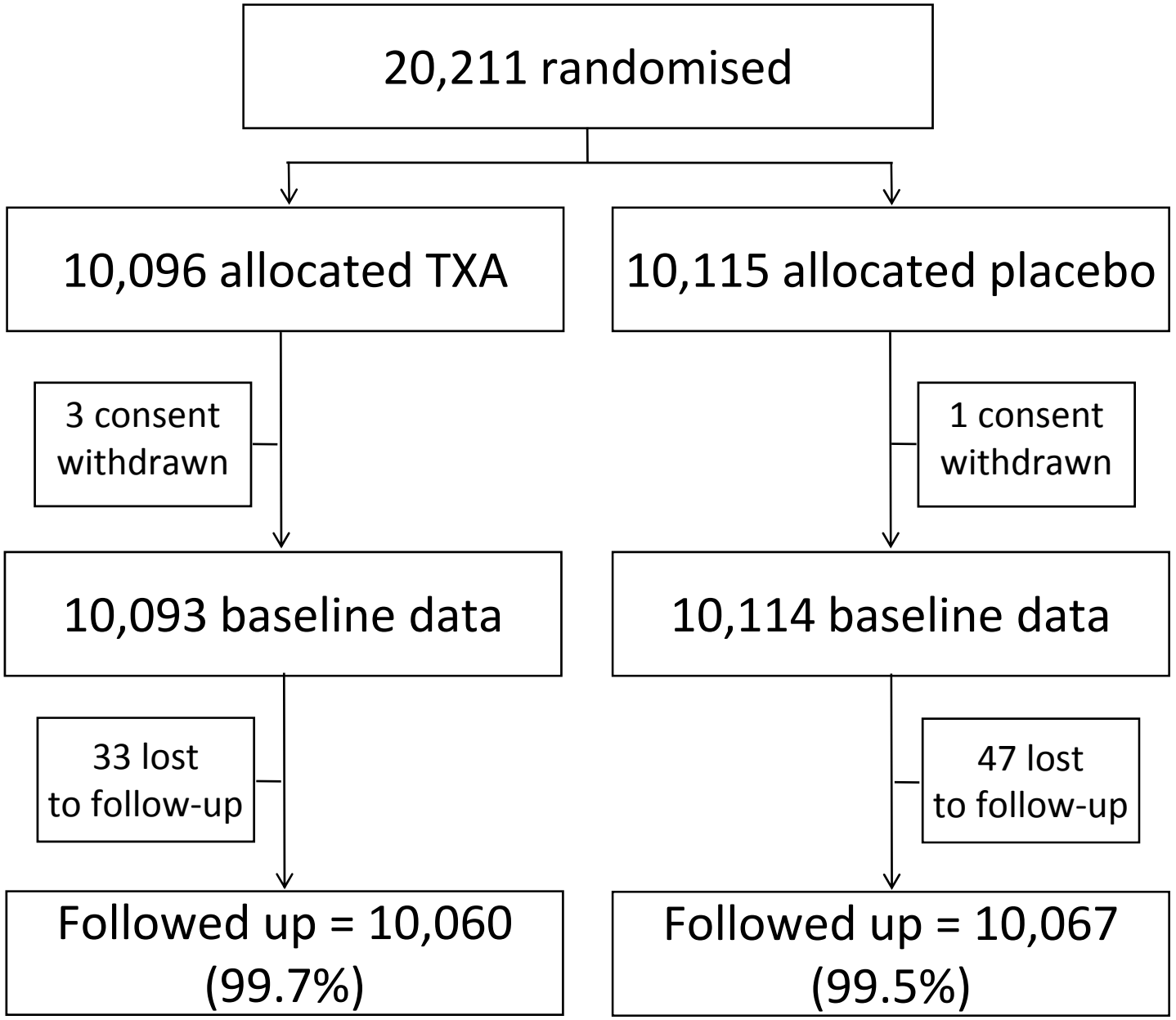
95 trials



72 trials

Ker et al. BMC Emergency Medicine 2012, 12:3

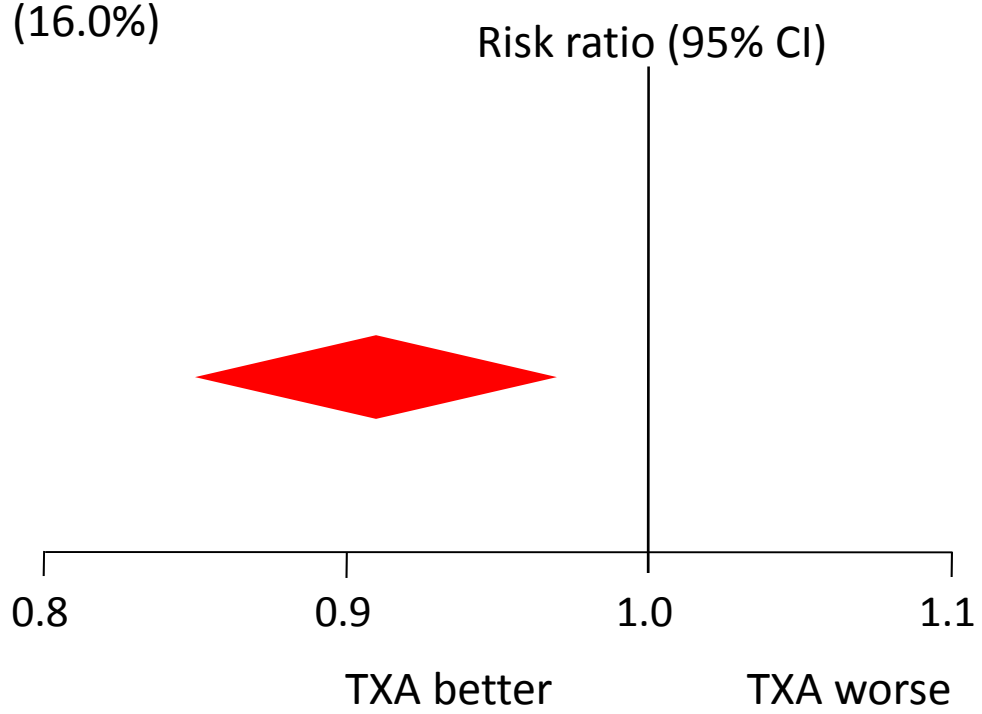
CRASH-2 trial profile



Tranexamic acid and trauma

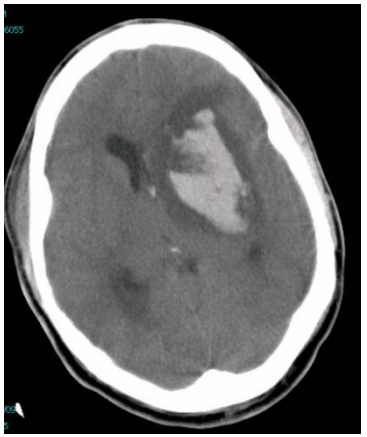
TXA-allocated	**Placebo-allocated**
(n=10,060)	**(n=10,067)**
1,463 (14.5%)	1,613 (16.0%)

0.91 (0.85–0.97) 2P=0.0035



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

Traumatic Intracranial Bleeding



- Bleeding is a common complication of traumatic brain injury
- It is associated with poor outcome
- It can develop or worsen after hospital admission
- Early intervention may prevent enlargement

•Perel P, Roberts I, Bouamra O, Woodford M, Mooney J, Lecky F. Intracranial bleeding in patients with traumatic brain injury: A prognostic study. BMC Emergency Medicine 2009, 9:15

•Oertel M, Kelly DF, McArthur D, Boscardin WJ, Glenn TC, Lee JH, et al. Progressive hemorrhage after head trauma: predictors and consequences of the evolving injury. J Neurosurg. 2002;96(1):109-16.

•Narayan RK, Maas AI, Servadei F, Skolnick BE, Tillinger MN, Marshall LF. Progression of traumatic intracerebral hemorrhage: a prospective observational study. J Neurotrauma. 2008; 25(6):629-39.

Tranexamic acid and Intracranial Bleeding

- Coagulopathy affects about one third of patients with TBI
- Increased fibrinolysis is a common feature of coagulopathy
- Two randomised controlled trials of TXA in TBI

•Harhangi BS, Kompanje EJ, Leebeek FW, Maas AI. Coagulation disorders after traumatic brain injury. Acta Neurochir (Wien). 2008;150(2):165-75.

•Bayir A, Kalkan E, Koçak S, Ak A, Cander B, Bodur S. Fibrinolytic markers and neurologic outcome in traumatic brain injury. Neurol India. 2006; 54(4):363-5.

Tranexamic acid and Intracranial Bleeding

	TXA n (%)	Placebo n (%)	OR (95% CI) n=249
Significant haemorrhage growth (n 123/126)	44 (36)	56 (44)	0.70 (0.42–1.16)
New focal ischaemic regions (n 123/126)	6 (5)	12 (9)	0.49 (0.18–1.35)
Death (n 133/137)	14 (10.5)	24 (17.5)	0.55 (0.27–1.22)

•*CRASH-2 collaborators (Intracranial Bleeding Study). Effect of tranexamic acid in traumatic brain injury: a nested randomised, placebo controlled trial (CRASH-2 Intracranial Bleeding Study). BMJ 2011; 343:d3795.*

Tranexamic acid and Intracranial Bleeding

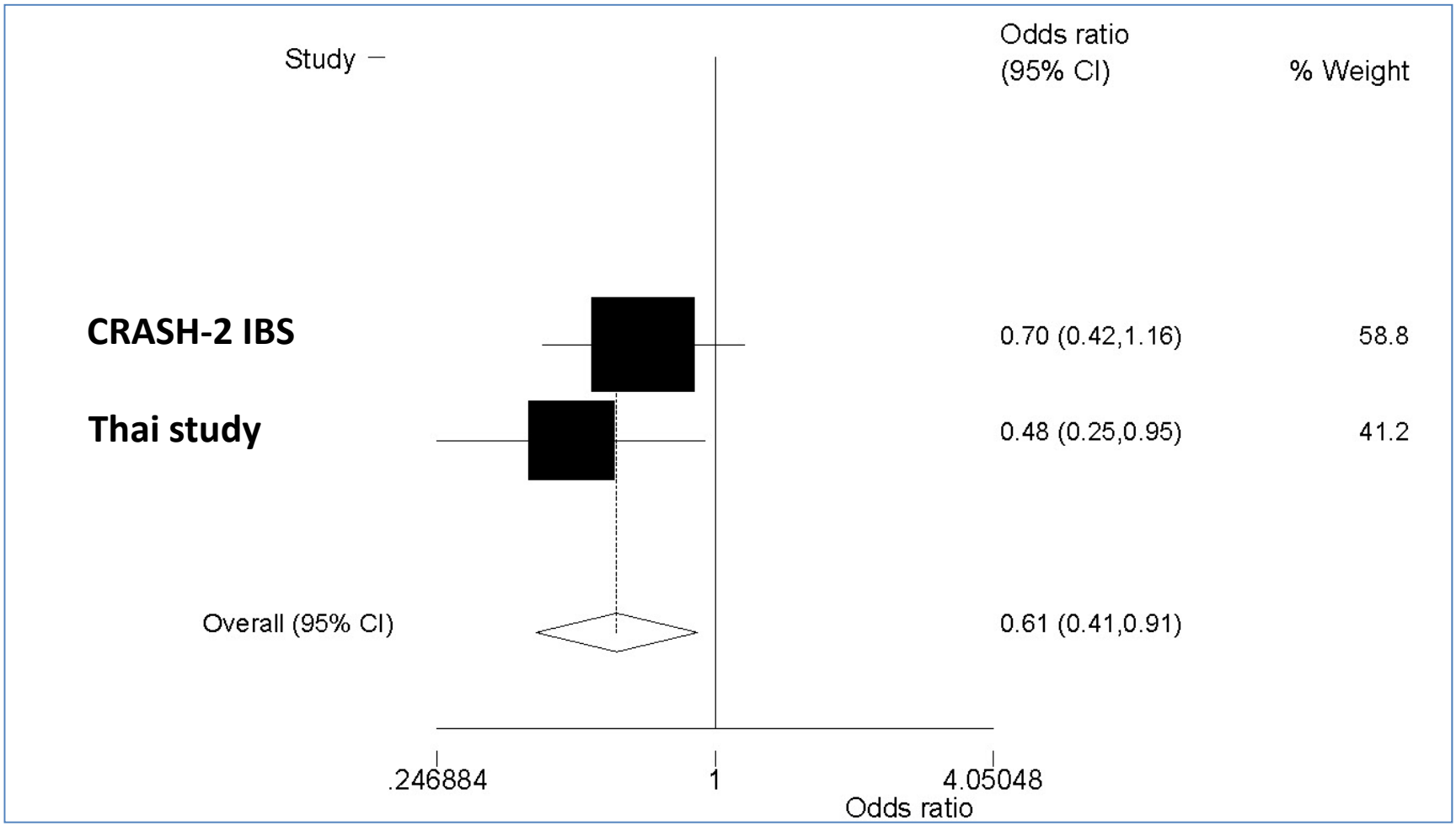
240 patients with isolated TBI

	RR (95% CI)
Haemorrhage growth	0.56 (0.32–0.96)
Mortality	0.67 (0.34–1.32)

- *Yutthakasemsunt S, et al. Tranexamic Acid for preventing progressive intracranial hemorrage in adults with traumatic brain injury; a preliminary report presented at the National Neurotrauma Symposium 2010.*
- *Available from http://www.neurotrauma.org/2010/abstracts.htm*

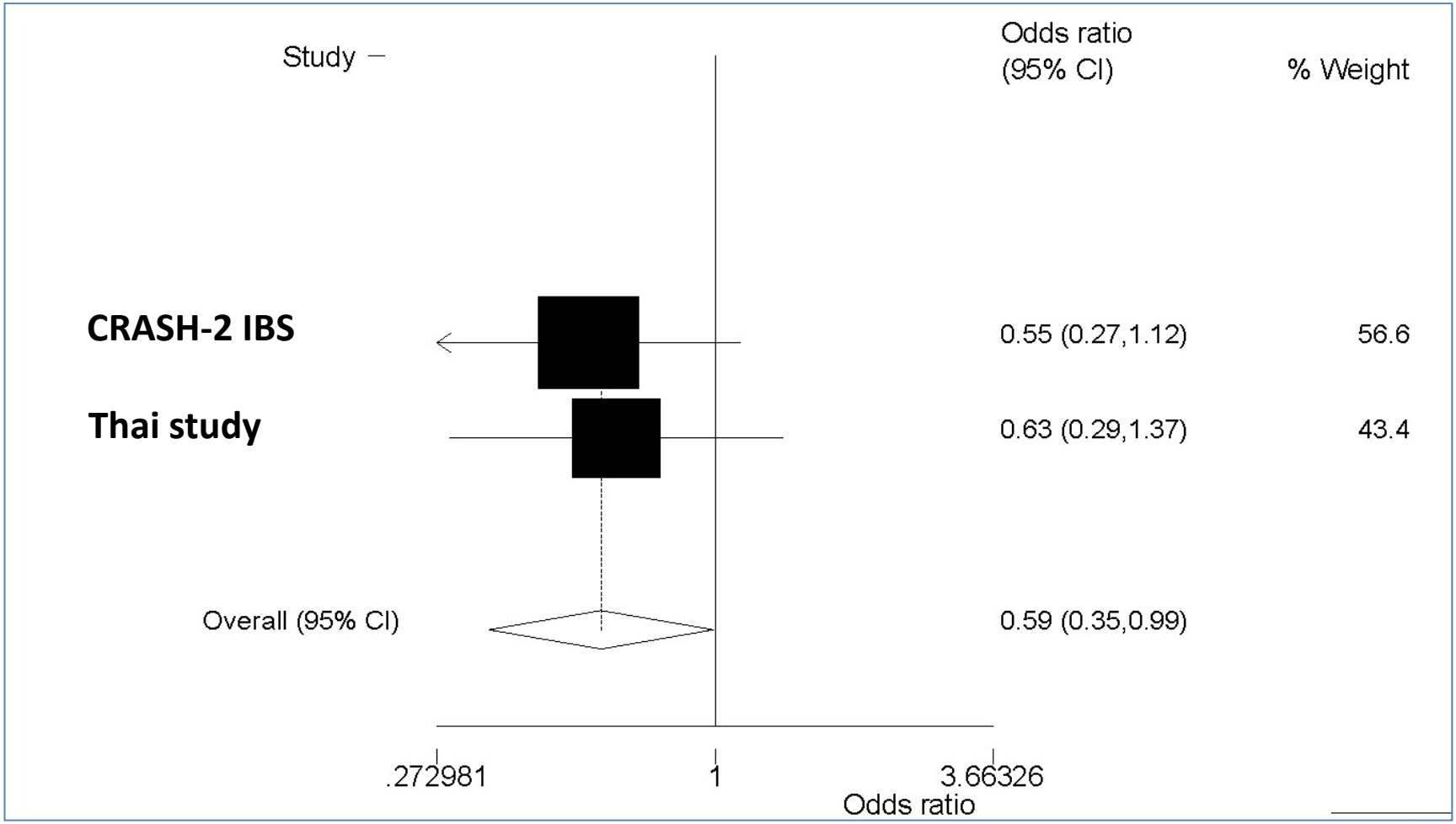
Meta-analysis

Significant Haemorrhage growth



Meta-analysis

Mortality



Randomised Placebo Controlled Clinical Trial

The CRASH-3 trial will provide reliable evidence about the effect of tranexamic acid on mortality and disability in patients with TBI. The effect of TXA on the risk of vascular occlusive events and seizures will also be assessed.

Overview

ELIGIBILITY

- adult
- with traumatic brain injury
- within 8 hours of injury (for the remainder of the trial we will limit recruitment to patients who are within 3 hours of injury)
- any intracranial bleeding on CT scan **OR** GCS ≤12
- no significant extra-cranial haemorrhage
- where the responsible clinician is substantially uncertain as to the appropriateness of antifibrinolytic agents in a patient

↓

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

↓

RANDOMISE (tranexamic acid or placebo)
Entry form completed

↓

Give **loading dose** over 10 minutes

↓

Give **maintenance dose** over 8 hours

↓

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

All clinically indicated treatment is given in addition to trial enrolment

Adverse events are reported up to day 28

If prior consent waiver used, consent from patient or representative required after emergency is over

Rationale for eligibility

Adult

Within 8 hours of injury (for the remainder of the trial we will limit recruitment to patients who are within 3 hours of injury)

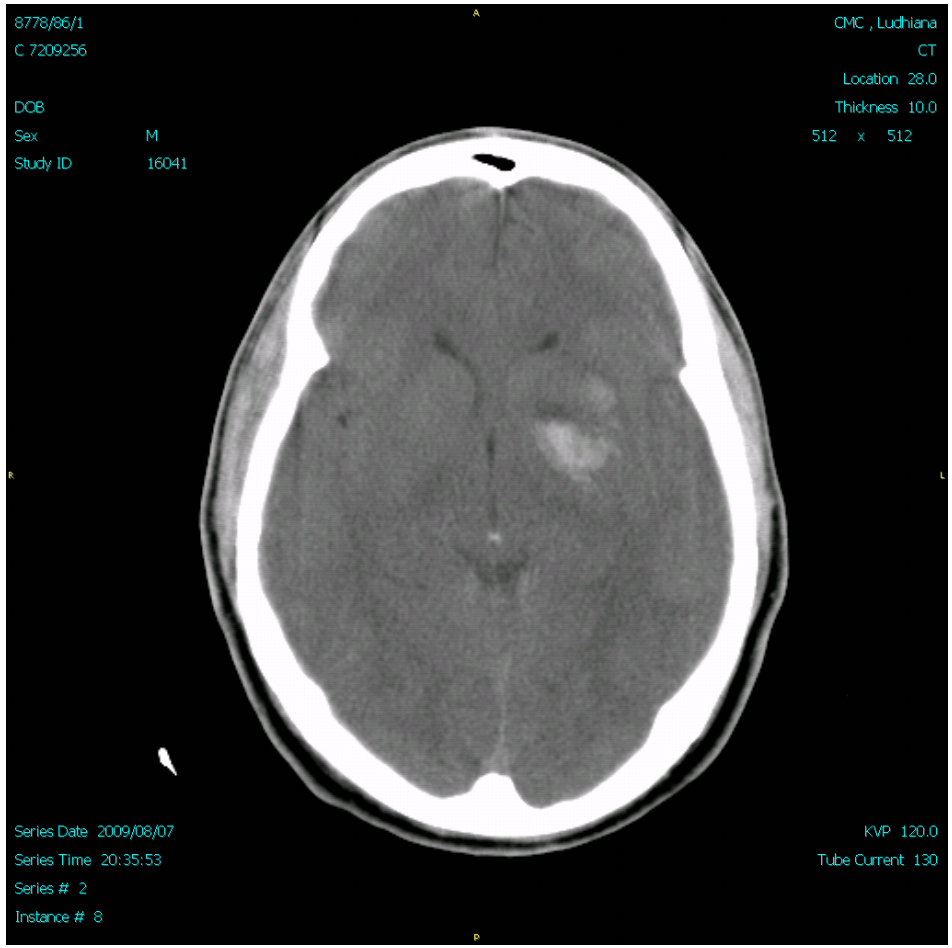
Intracranial bleeding on CT scan OR GCS ≤12

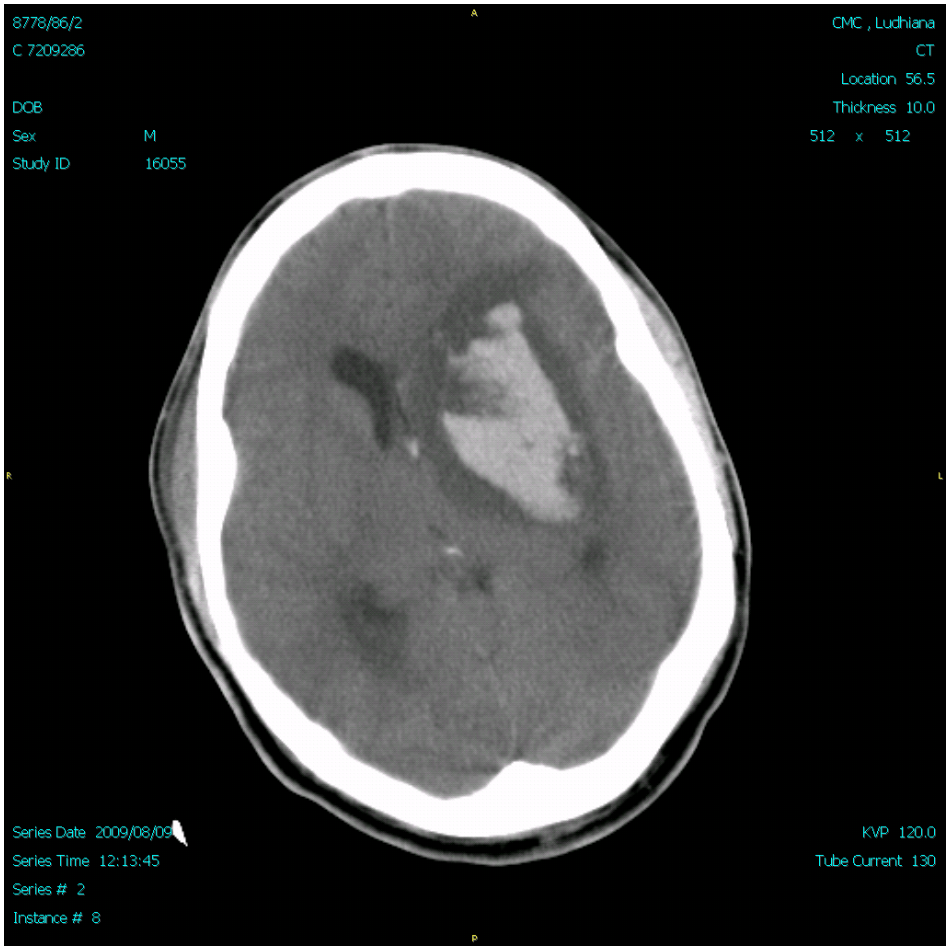
Any intracranial bleeds included

Uncertainty principle

Why exclude CRASH-2 type patients?

Give trial treatment as soon as possible





Safety overview

Data Monitoring Committee

Primary outcome

- Death in hospital within four weeks of injury among patients randomised within 3 hours of injury

Secondary outcomes

- Vascular occlusive events – MI, Stroke, PE, DVT
- Seizures
- Disability
- Other adverse events – any AE and SAE

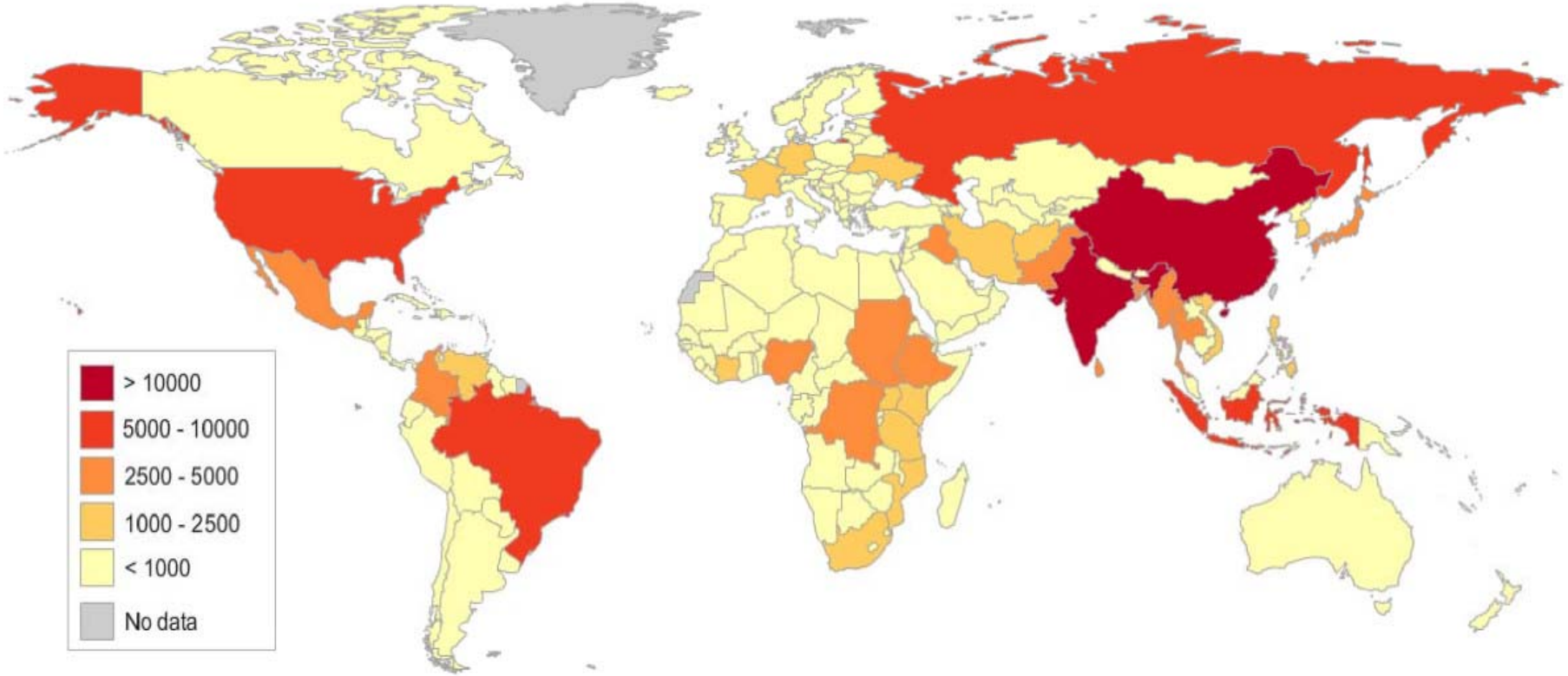
Ker et al. BMC Emergency Medicine 2012, 12:3
http://www.biomedcentral.com/1471-227X/12/3

BMC Emergency Medicine

RESEARCH ARTICLE Open Access

Avoidable mortality from giving tranexamic acid to bleeding trauma patients: an estimation based on WHO mortality data, a systematic literature review and data from the CRASH-2 trial

Deaths prevented each year giving TXA < 1 hour = 128,000 lives
Deaths prevented each year giving TXA < 3 hours =112,000 lives



Ker et al. BMC Emergency Medicine 2012, 12:3

CRASH

Clinical Randomisation of an Antifibrinolytic in Significant Head Injury

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