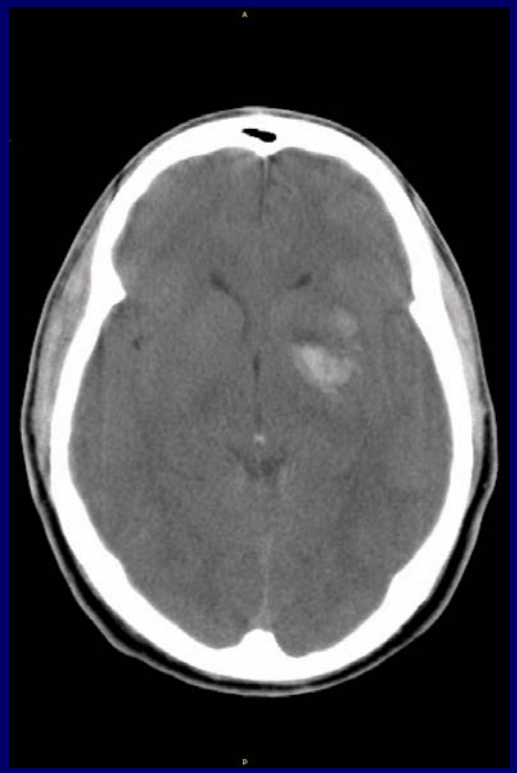
Why urgent randomisation and treatment is critical

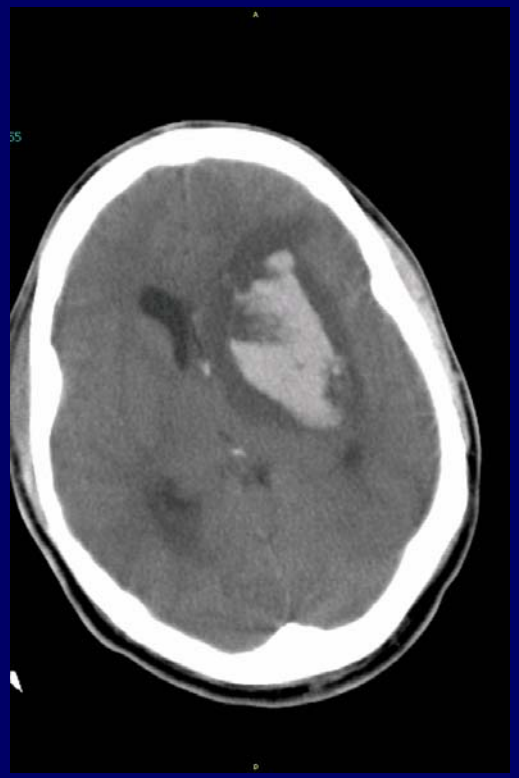
Early randomisation and treatment is critical because:

1. Intracranial bleeding occurs soon after injury and so to prevent early bleeding we must give TXA soon after injury

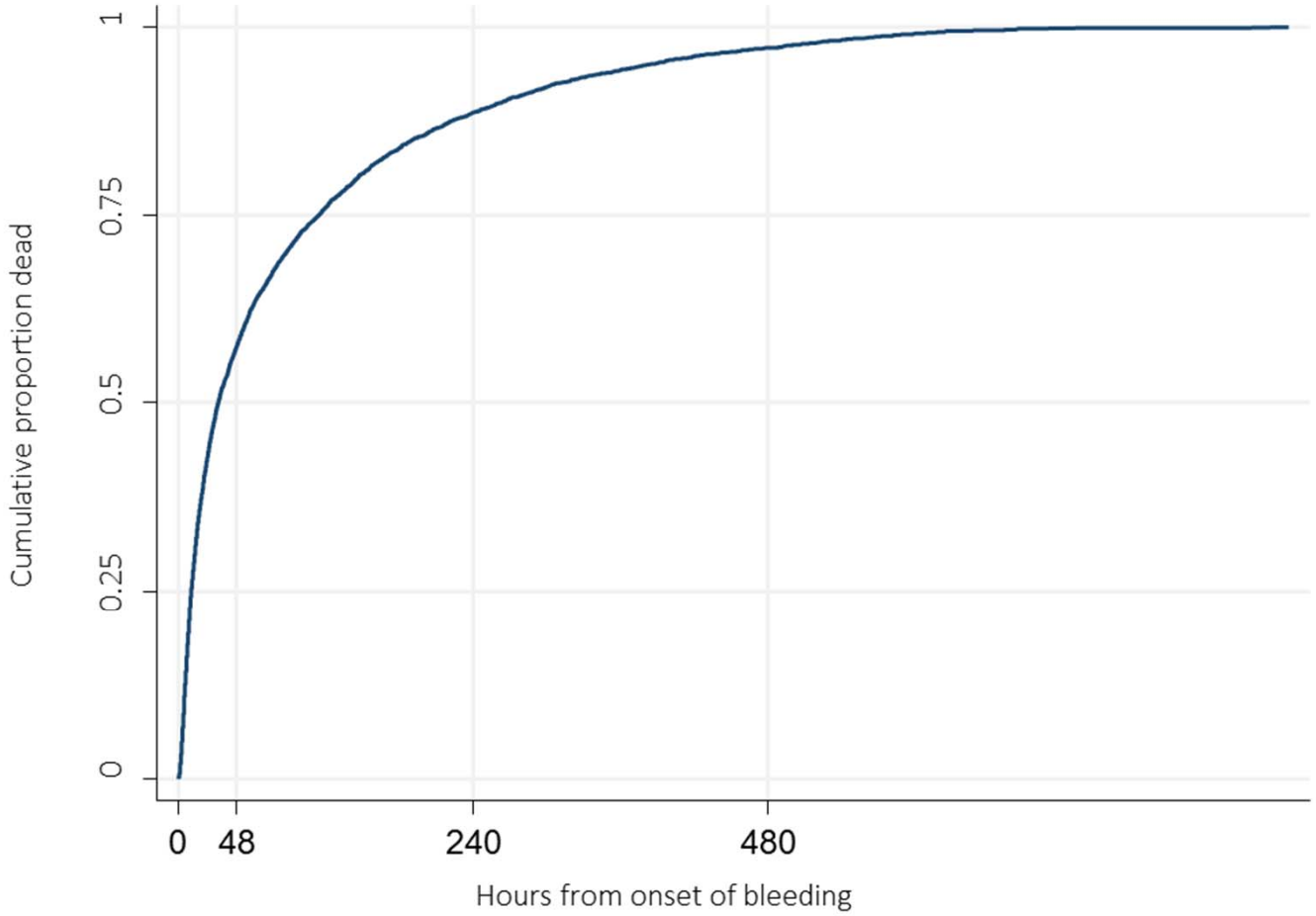
2. The CRASH-2 trial showed that early treatment (<3 hours) is far more effective - this could be the same in TBI patients

CT on admission and 12 hours later



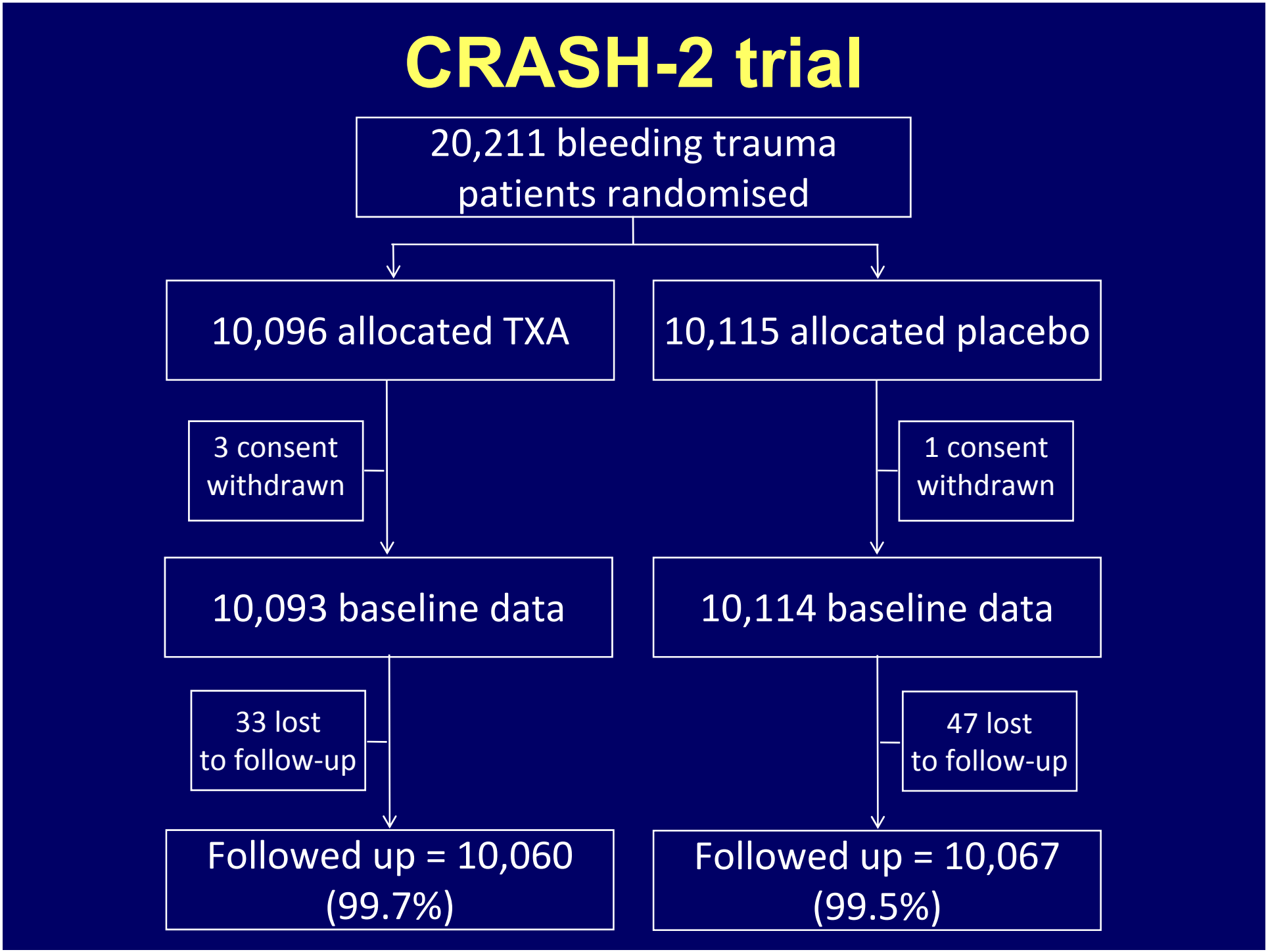


Time to death in acute severe bleeding: most deaths occur soon after injury.



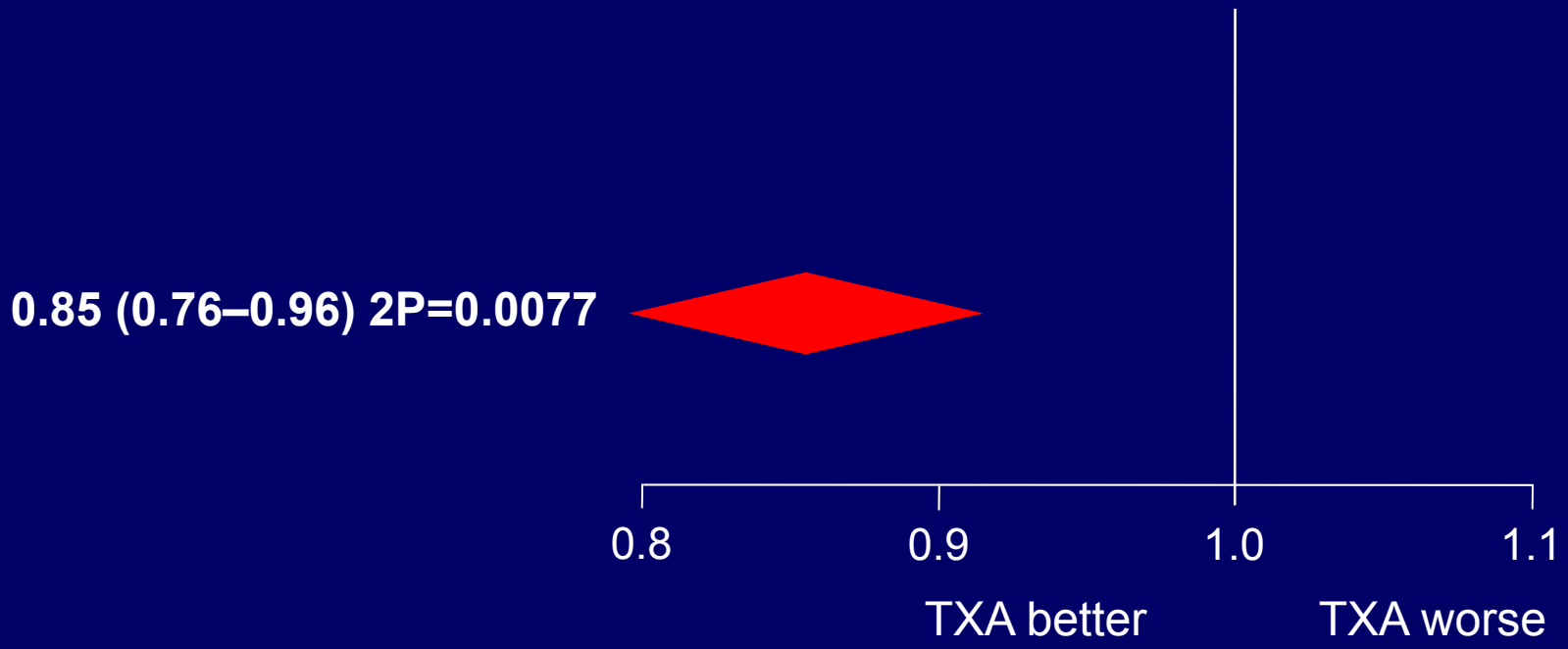
Edwards et al. When and why do bleeding patients die. (Unpublished)

The CRASH-2 trial showed that tranexamic acid (TXA) reduces death due to bleeding and all-cause mortality in trauma patients with extra cranial bleeding.


CRASH-2 trial
20,211 bleeding trauma patients randomised
10,096 allocated TXA
10,115 allocated placebo
3 consent withdrawn
1 consent withdrawn
10,093 baseline data
10,114 baseline data
33 lost to follow-up
47 lost to follow-up
Followed up = 10,060 (99.7%)
Followed up = 10,067 (99.5%)

CRASH-2 results: Death due to bleeding

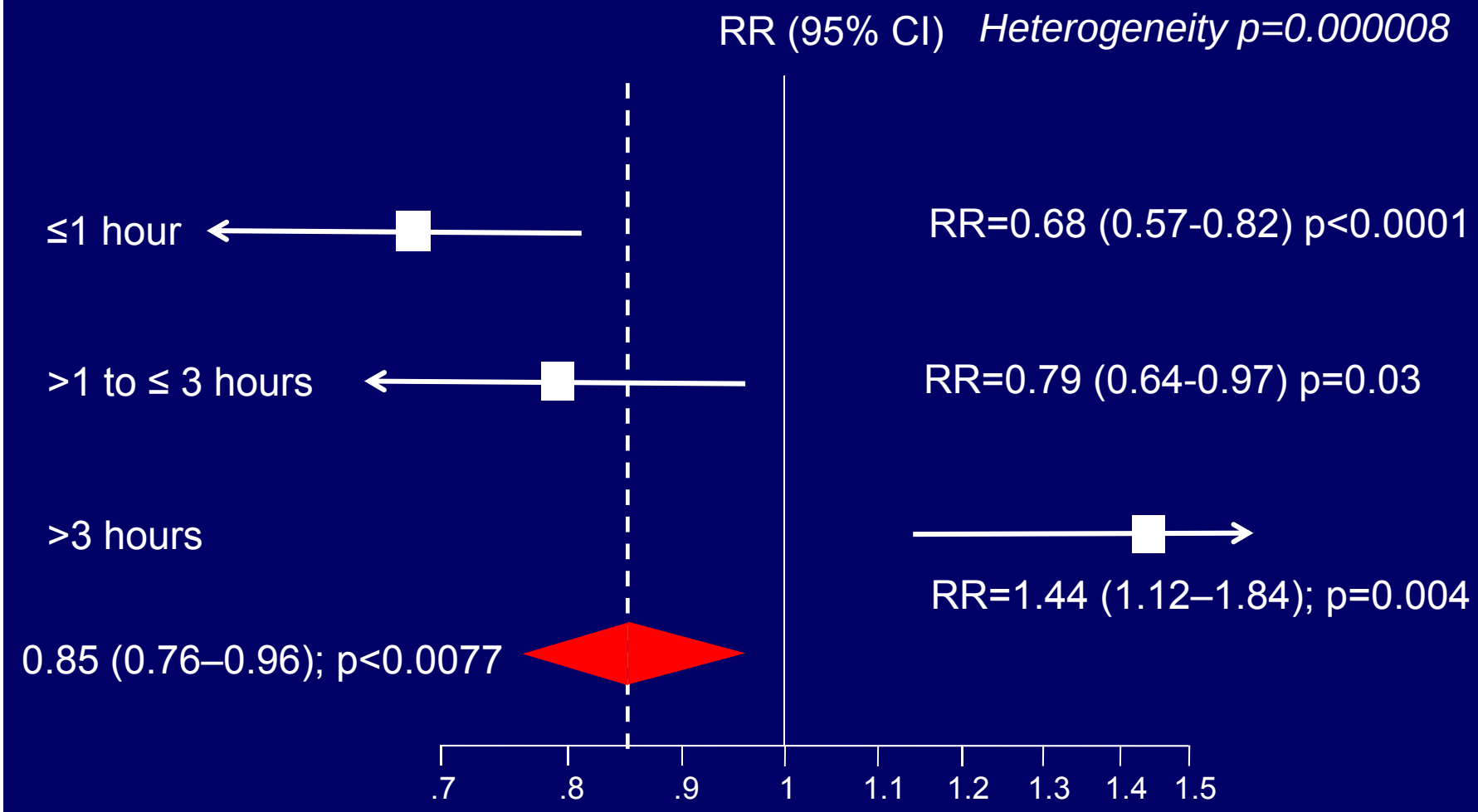
TXA	Placebo	RR (95% CI)
(n= 10,060)	**(n= 10,067)**	
489 (5%)	574 (6%)	



We expected that TXA would be most effective soon after injury (when the blood is thin and bleeding profuse) and less effective later (when the blood is sticky and bleeding is less).

We tested this in a pre-specified sub-group analysis and found very strong evidence in support!

TXA and haemorrhage death by time since injury



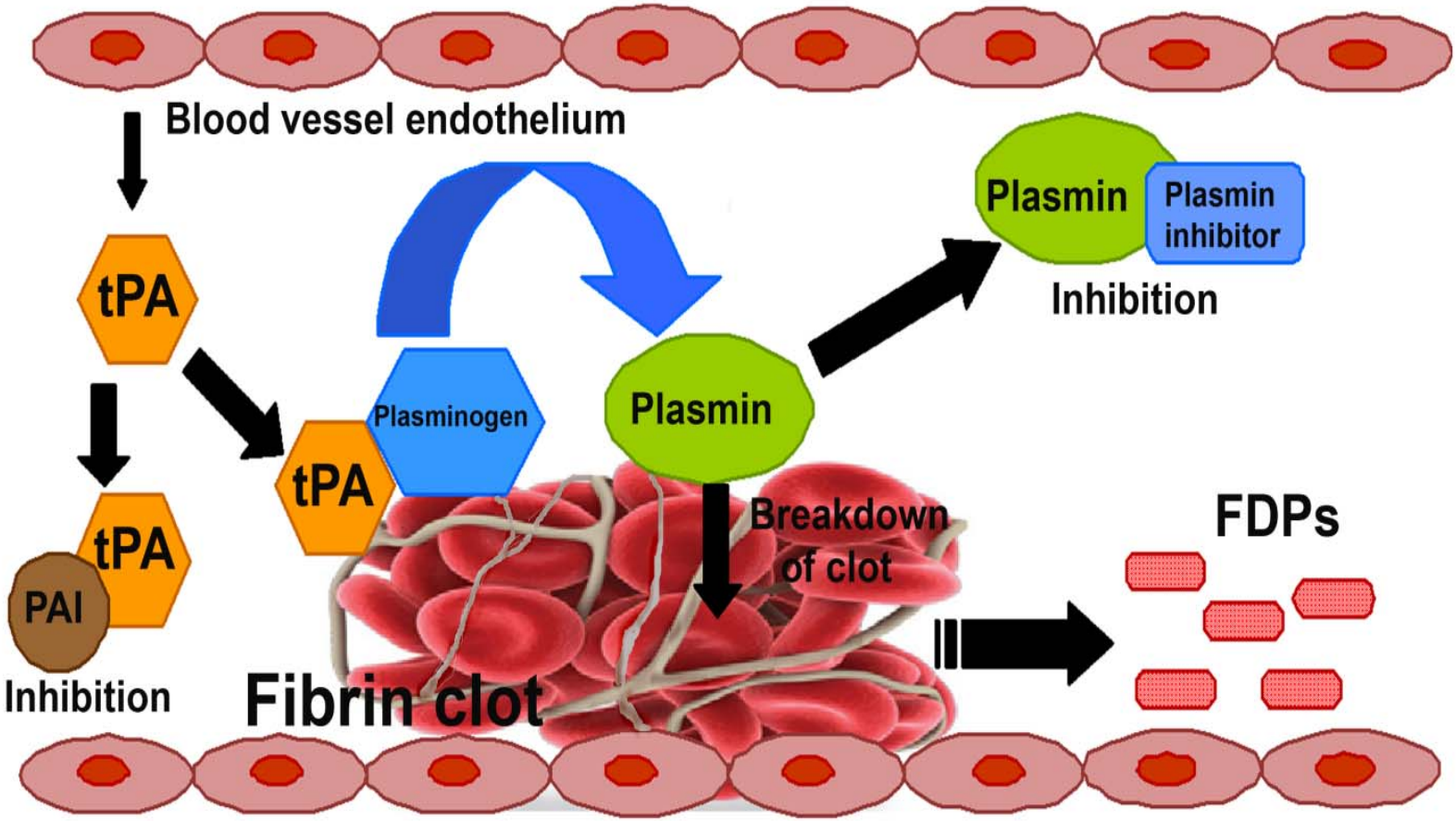
Treatment within three hours of injury was highly effective but late treatment seemed to increase bleeding

Since the results were published new research has been conducted that may explain the results…

t-PA and PAI-1 are the key players

Early t-PA release causes fibrinolysis and bad bleeding

Late PAI-1 release causes fibrinolytic shutdown and thrombotic DIC


Blood vessel endothelium
tPA
tPA
PAI
Inhibition
tPA
Plasminogen
Fibrin clot
Plasmin
Breakdown of clot
Plasmin
Plasmin inhibitor
Inhibition
FDPs

t-PA activates plasminogen and turns on fibrinolysis

Hypotension and hypoxia cause release of stored t-PA

Early fibrinolysis increases bleeding soon after injury

PAI-1 inactivates t-PA and turns off fibrinolysis

PAI-1 is released later because it has to be synthesised

Fibrinolytic shutdown may increase the risk of thrombotic DIC

Hypotension and Hypoxia

t-PA
(early release from endothelial stores)

Early fibrinolysis

PAI-1
(expression can take hours)

Thrombotic DIC

Animal models of poly-trauma show these changes

They have also been seen in trauma patients

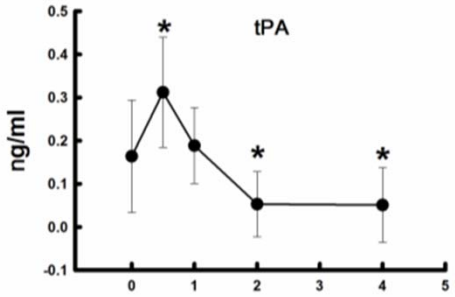
Early t-PA release and fibrinolysis

followed by

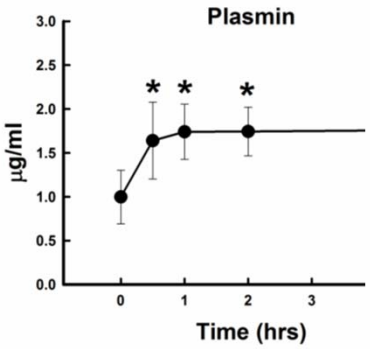
PAI-1 release and fibrinolytic shutdown

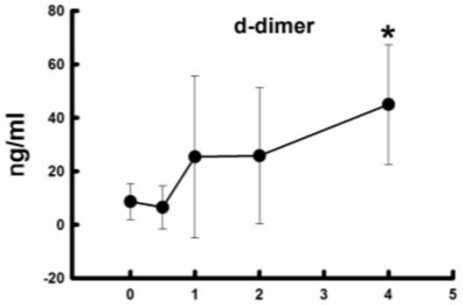
Wu X, Darlington D, Cap A. Procoagulant and Fibrinolytic Activity after Polytrauma in Rat. Am J Physiol Regul Integr Comp Physiol (December 2, 2015). doi:10.1152/ajpregu.00401.2015.

Chapman M et al. Overwhelming tPA release, not PAI-1 degradation, is responsible for hyperfibrinolysis in severely injured trauma patients. J Trauma 2016;80:16-25

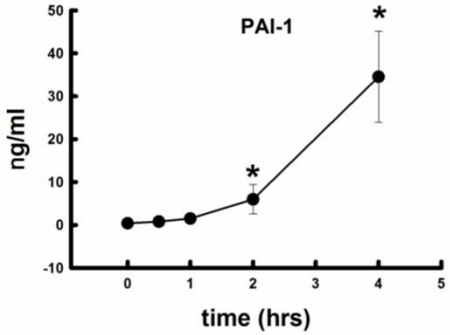


t-PA released soon after injury





Plasmin activation and fibrinolysis



Late PAI-1increase and fibrinolytic shutdown

Wu X, Darlington D, Cap A. Procoagulant and Fibrinolytic Activity after Polytrauma in Rat. Am J Physiol Regul Integr Comp Physiol (December 2, 2015). doi:10.1152/ajpregu.00401.2015.

We hope that TXA will prevent intracranial bleeding

We hope that it will prevent bleeding in the first place and prevent small bleeds becoming large bleeds

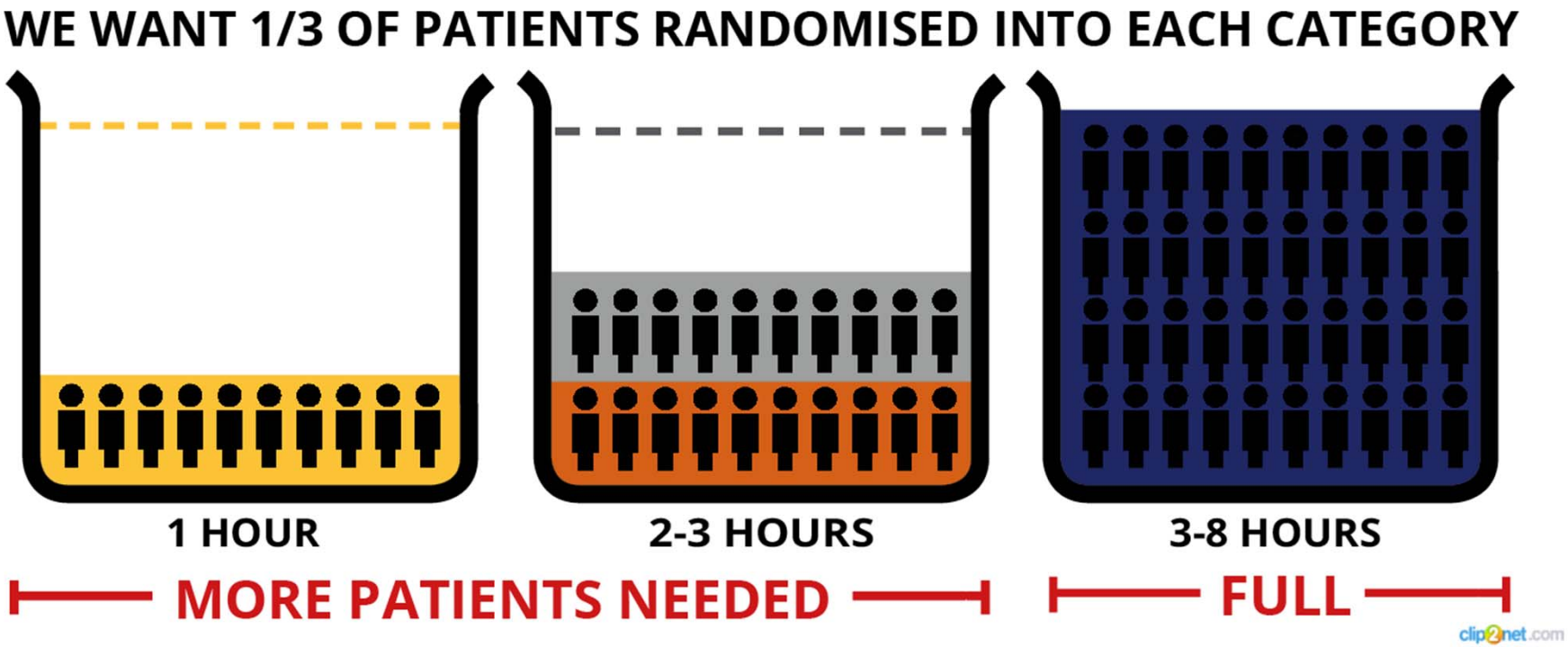
Recent research shows the coagulation changes in TBI are similar to those in extra-cranial bleeding.

If the effect of TXA in TBI is similar to that in extra-cranial bleeding we need to know this and so have planned sub-group analyses by time to treatment.

We need enough patients in each of the time groups (<1 hour, 1-3 hours, 3-8 hours). We already have enough in the 3-8 hour group and so only patients within 3 hours of injury should be recruited in the CRASH-3 trial.

Epstein et al. Acute traumatic coagulopathy in the setting of isolated traumatic brain injury: Definition, incidence and outcomes. Br J Neurosurg 2015;29:118-122.

Zhang et al. Coagulation Parameters and Risk of Progressive Hemorrhagic Injury after Traumatic Brain Injury: A Systematic Review and Meta-Analysis. *BioMed Research International*, vol. 2015, Article ID 261825, 10 pages, 2015.



We need more early patients – especially within 1 hour of injury.

Top tips for reducing time to treatment

- **Identifying eligible patients as soon as they are admitted:**

Including Emergency Department staff in your trial team is essential to identify eligible patients as soon as they are admitted.

- **Randomising patients with a GCS of ≤ 12 prior to CT scan:**

Patients with GCS ≤12 can and should be randomised before CT - waiting for a CT scan can incur treatment delays.

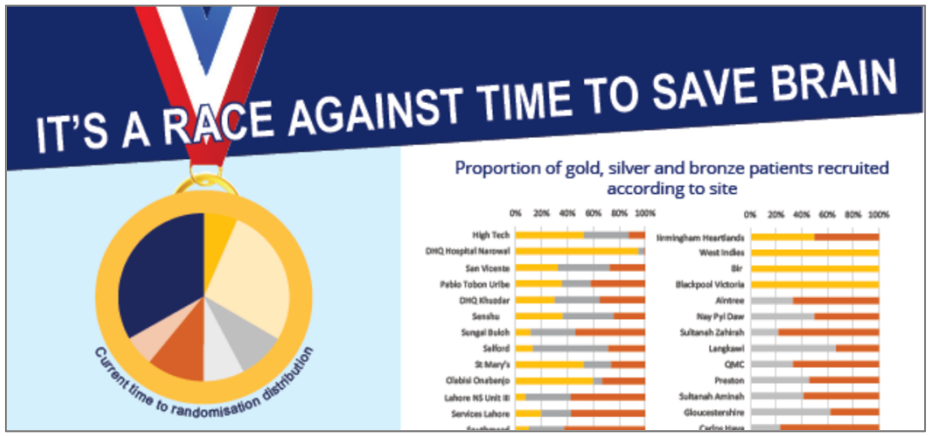
- **Being notified for every positive CT scan:**

If the patient has a GCS > 12 but shows any intracranial bleed on the CT scan you should randomise – consider involving the radiologist in your trial team to alert you to all positive scans.

- **Waiving prior informed consent:**

If your Ethics Committee have approved the use of the consent waiver, please consider using it. We do not expect patients to have capacity to consent due to the nature of their injury and relatives may not be present or may be too distressed to give fully informed written consent at that time. In this instance, it may be more appropriate to agree with a doctor independent of the trial that consent should be waived and then fully informed written consent obtained once the emergency is over.

The message to collaborators



Randomise within the golden hour