Presenter Disclosure Information

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The Spot Sign and Tranexamic Acid on Preventing ICH Growth – Australasia Trial (STOP-AUST): A Multicenter, Randomized, Double-blind, Placebo-controlled Trial

FINANCIAL DISCLOSURE:

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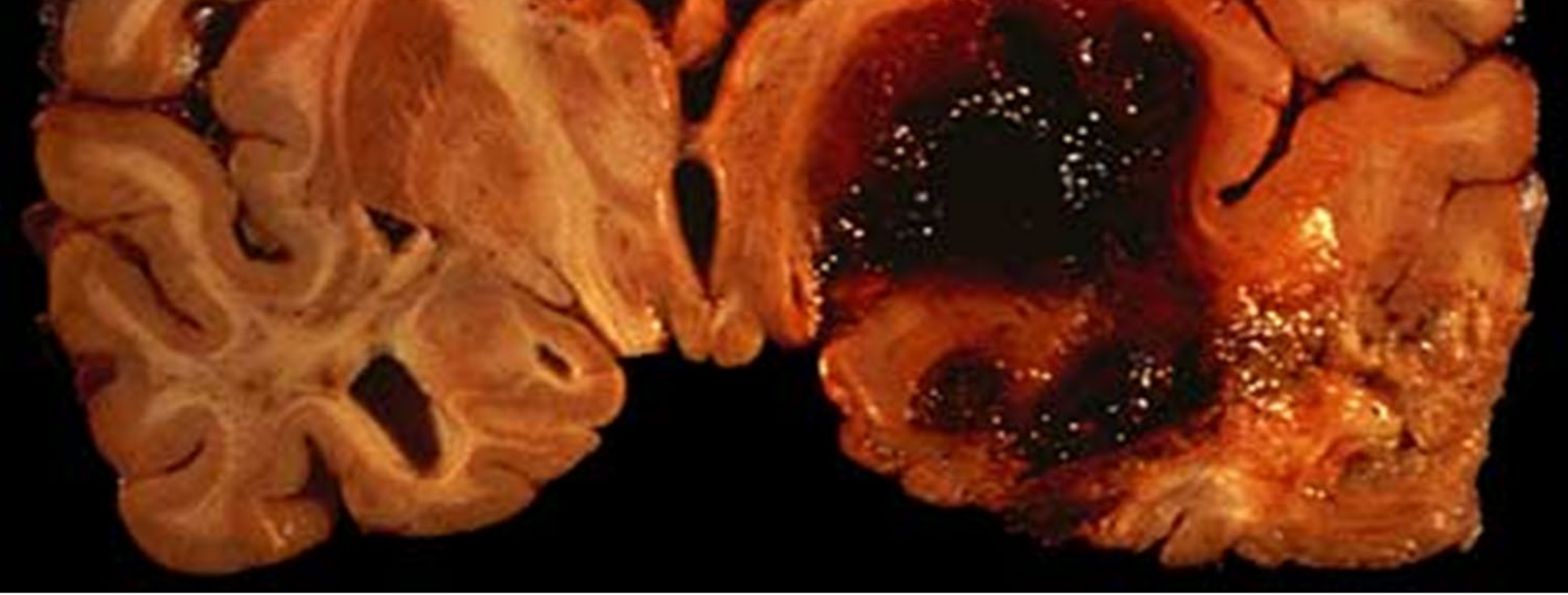
UNLABELED/UNAPPROVED USES DISCLOSURE:

Intravenous tranexamic acid for intracerebral hemorrhage



STOP-AUST

The Spot sign and Tranexamic acid On Preventing ICH growth - AUStralasia Trial

Australian Government
National Health and Medical Research Council

THE UNIVERSITY OF MELBOURNE

The Royal Melbourne Hospital

Atte Meretoja (Principal Investigator, Medical Coordinator)
Geoffrey Donnan (Principal Investigator, Co-chair of Executive Committee)
Stephen Davis (Principal Investigator, Co-chair of Executive Committee)

Background

- Intracerebral hemorrhage (ICH) affects approximately 2 million people in the world every year.
- Mortality after ICH is ~40% in the first 30 days.
- Much of the global burden is in low- and middle-income countries.
- Compared to ischemic stroke, treatments for ICH are extremely limited

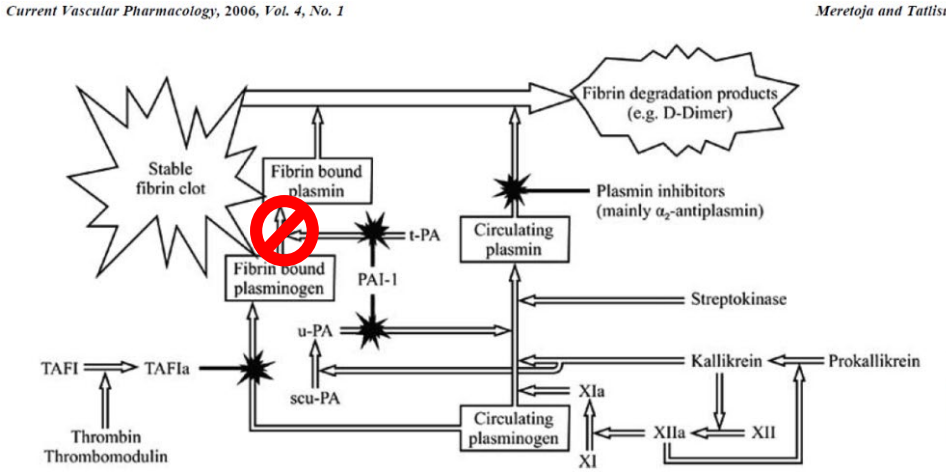
Background

- Early hematoma growth after ICH is a strong predictor of mortality and poor outcome.
- Hemostatic therapies may attenuate ICH growth and improve outcome
- rFVIIa (80mg/kg within 4 hours of onset) led to reduced hematoma growth compared to placebo (Mayer et al, NEJM, 2008)
  - Did not translate to improved outcomes
  - Associated with increased thromboembolic events
  - May be prohibitively expensive in many settings
- In a metanalysis of the SPOTLIGHT and STOP-IT trials, rFVIIa in spot-sign positive ICH patients did not significantly reduce ICH growth (although growth was small in both groups) (Gladstone et al, JAMA Neurology, 2019)

Tranexamic Acid – An Antifibrinolytic

A reversible direct inhibitor of plasminogen lysine binding sites

- Prevents the activation of plasmin and degradation of fibrin = “antithrombolysis”
- Excreted unchanged in urine with 90% clearance in 24h
- Crosses the blood-brain barrier
- Has no relevant interactions
- Inexpensive and used for decades
- Excellent safety profile in phase 3 trials



Tranexamic Acid in ICH

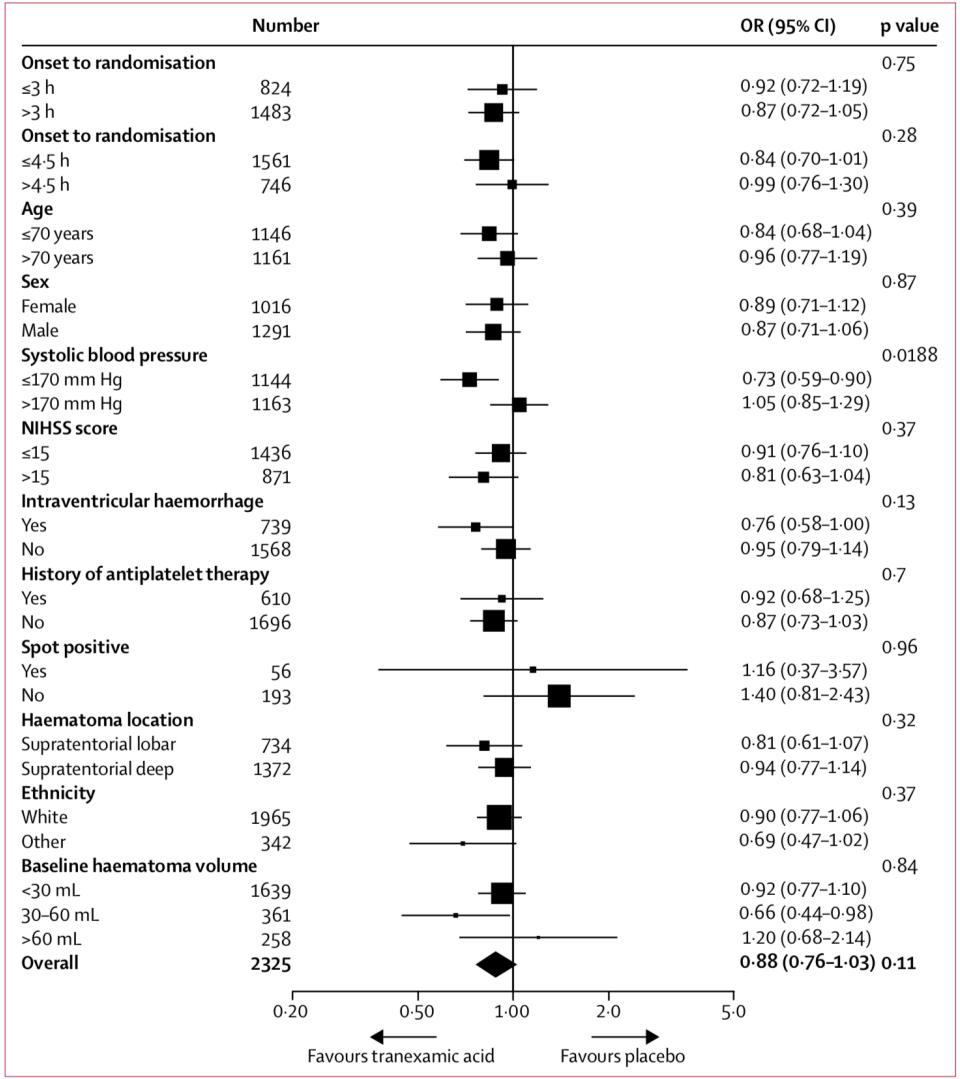
Tranexamic acid for hyperacute primary IntraCerebral Haemorrhage (TICH-2): an international randomised, placebo-controlled, phase 3 superiority trial

*Nikola Sprigg, Katie Flaherty, Jason P Appleton, Rustam Al-Shahi Salman, Daniel Bereczki, Maia Beridze, Hanne Christensen, Alfonso Ciccone, Ronan Collins, Anna Czlonkowska, Robert A Dineen, Lelia Duley, Juan Jose Egea-Guerrero, Timothy J England, Kailash Krishnan, Ann Charlotte Laska, Zhe Kang Law, Serefnur Ozturk, Stuart J Pocock, Ian Roberts, Thompson G Robinson, Christine Roffe, David Seiffge, Polly Scutt, Jegan Thanabalan, David Werring, David Whynes, Philip M Bath, for the TICH-2 Investigators**

2018

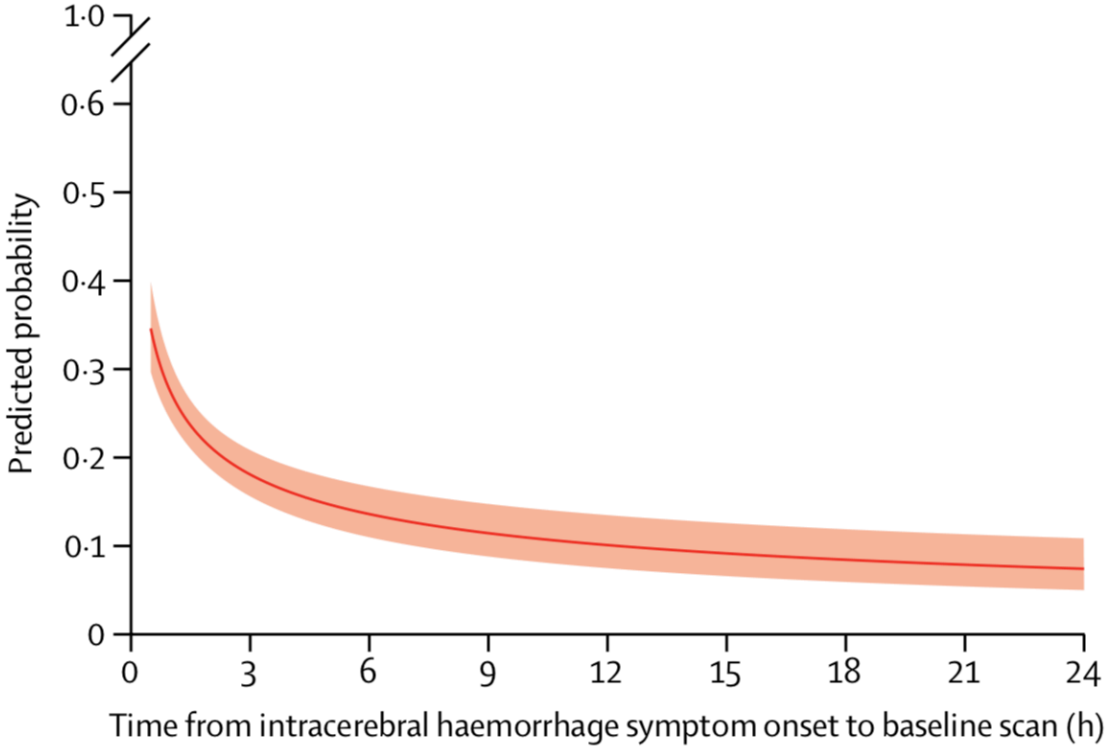
n=2325

Up to 8 hours from onset



Reduced hematoma growth 25% vs 29% (p=0.03)

Reduced absolute growth ~1.4mL (p=0.04)



ICH growth occurs early

Salman et al, *Lancet Neurology*, 2018

STOP AUST Synopsis

STOP-AUST

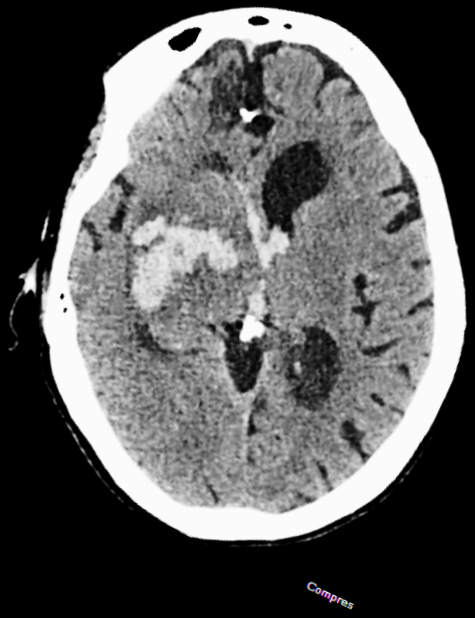
The Spot sign and Tranexamic acid On Preventing ICH growth – AUStralasia Trial

ClinicalTrials.gov NCT01702636

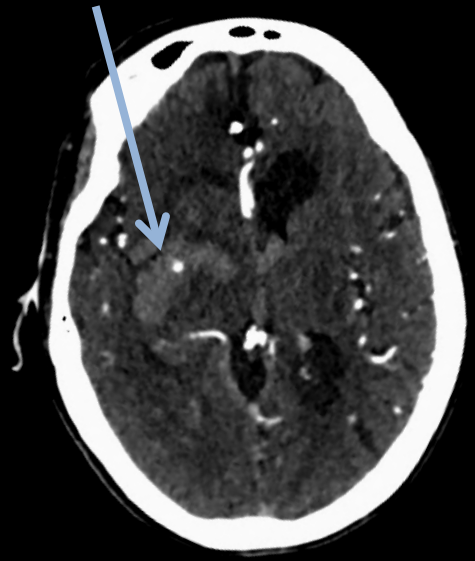
Design:	Phase II investigator-initiated randomized, double-blind, placebo-controlled trial of tranexamic acid in spot sign positive patients within 4½ h of ICH
No. of Subjects and Centres:	Maximum adaptive sample size 150 – Final Sample Size 100, from 13 centres in Australia, Taiwan, and Finland
Recruitment Period:	March 2013 to August 2019
Primary Hypothesis:	ICH patients with CTA "spot sign" will have lower rates of hematoma growth when treated with intravenous tranexamic acid within 4½ hours of stroke onset compared to placebo.
Primary Outcome:	ICH growth by 24±3 h as defined by either >33% or >6 mL increase from baseline, adjusted for baseline ICH volume
Secondary Outcomes:	Absolute ICH growth by 24±3 h, mRS at 3 months, Major Thromboembolic Events (MI, Ischemic stroke, PE), Death

CTA Spot Sign – A marker of risk for hematoma expansion

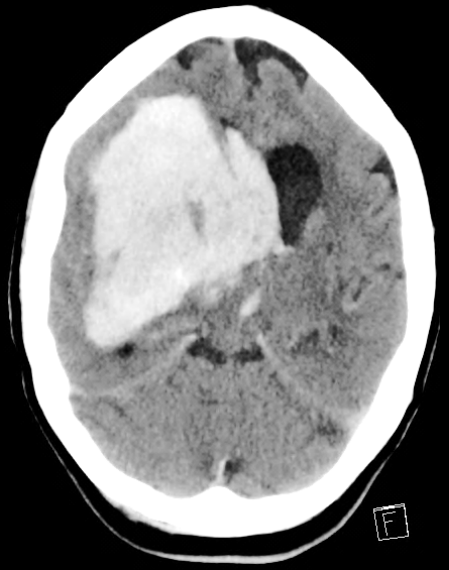
Baseline CT
ICH volume 35 mL



Baseline CT angiography
spot-sign

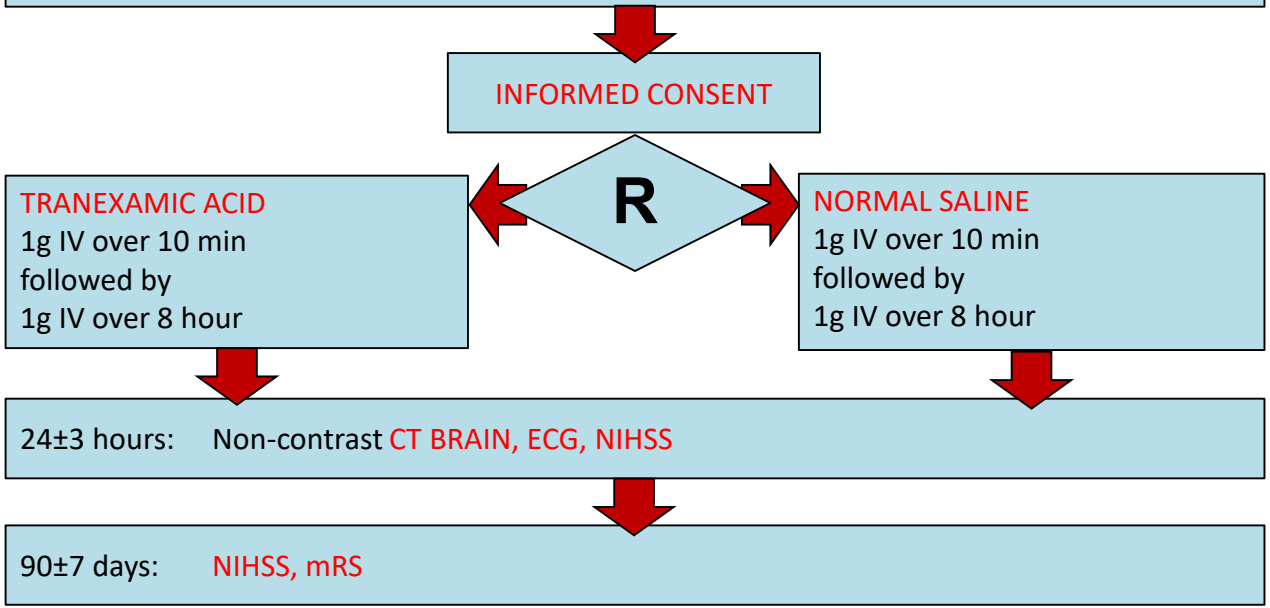


2hr CT
ICH volume 150 mL



SPOT SIGN on CTA
FAST TREATMENT POSSIBLE within 1 hour of CT and 4½ hours of symptom onset
MAIN EXCLUSIONS:

1. History of thrombotic events within the previous 12 months
2. Anticoagulation use within the last 2 weeks
3. Aetiology of ICH known or suspected to be secondary to trauma, tumour, AVM, aneurysm, venous thrombosis, ischaemia, thrombolysis or infection
4. Volume of ICH >70 mL as measured by the ABC/2 method
5. Brainstem ICH
6. GCS <8
7. Planned surgery for ICH



Baseline Demographics

	TXA (n=50)	Placebo (n=50)
Age, median (IQR)	72.5 (55.0-78.0)	71.0 (58.0-79.0)
Female, n (%)	15 (30.0)	23 (46.0)
NIHSS, median (IQR)	14 (8-19)	12 (8-17)
GCS, median (IQR)	14 (11-15)	14.5 (13-15)
Premorbid mRS, n (%) 0 1 2 3 4	 37 (74.0) 3 (6.0) 1 (2.0) 3 (6.0) 6 (12.0)	 41 (82.0) 6 (12.0) 2 (4.0) 0 (0) 1 (2.0)
Admission Glucose, mean (SD)	8.4 (5.3)	7.3 (2.9)
Admission Systolic BP, mean (SD)	168 (25)	173 (25)
Admission Diastolic BP, mean (SD)	91 (20)	90 (17)
Admission Antiplatelet Therapy, n (%)	16 (32.0)	12 (24.0)
Admission Statin Therapy, n (%)	14 (28.0)	16 (32.0)

Imaging and Operational Characteristics

	TXA (n=50)	Placebo (n=50)
ICH Volume, median (IQR)	13.8 (7.8 – 32.0)	15.6 (7.9 – 33.4)
ICH Location, n(%) Cerebellar Hemispheric Cortical Hemispheric Deep	 1 (2.0) 15 (30.0) 34 (68.0)	 0 (0) 15 (30.0) 35 (70.0)
Intraventricular Hemorrhage, n (%)	13 (26.0)	9 (18.0)
SMASH-U Amyloid Angiopathy Hypertension Undetermined	 12 (24.0) 23 (46.0) 15 (30.0)	 14 (28.0) 23 (46.0) 13 (26.0)
TIME METRICS		
Onset to Imaging, median (IQR)	98.5 (66– 153)	88 (69 – 142)
Imaging to Treatment, median (IQR)	50.5 (40– 62)	52 (43-73)
Onset to Treatment, median (IQR)	156 (114 – 225)	150 (121 – 195)

Primary Outcome

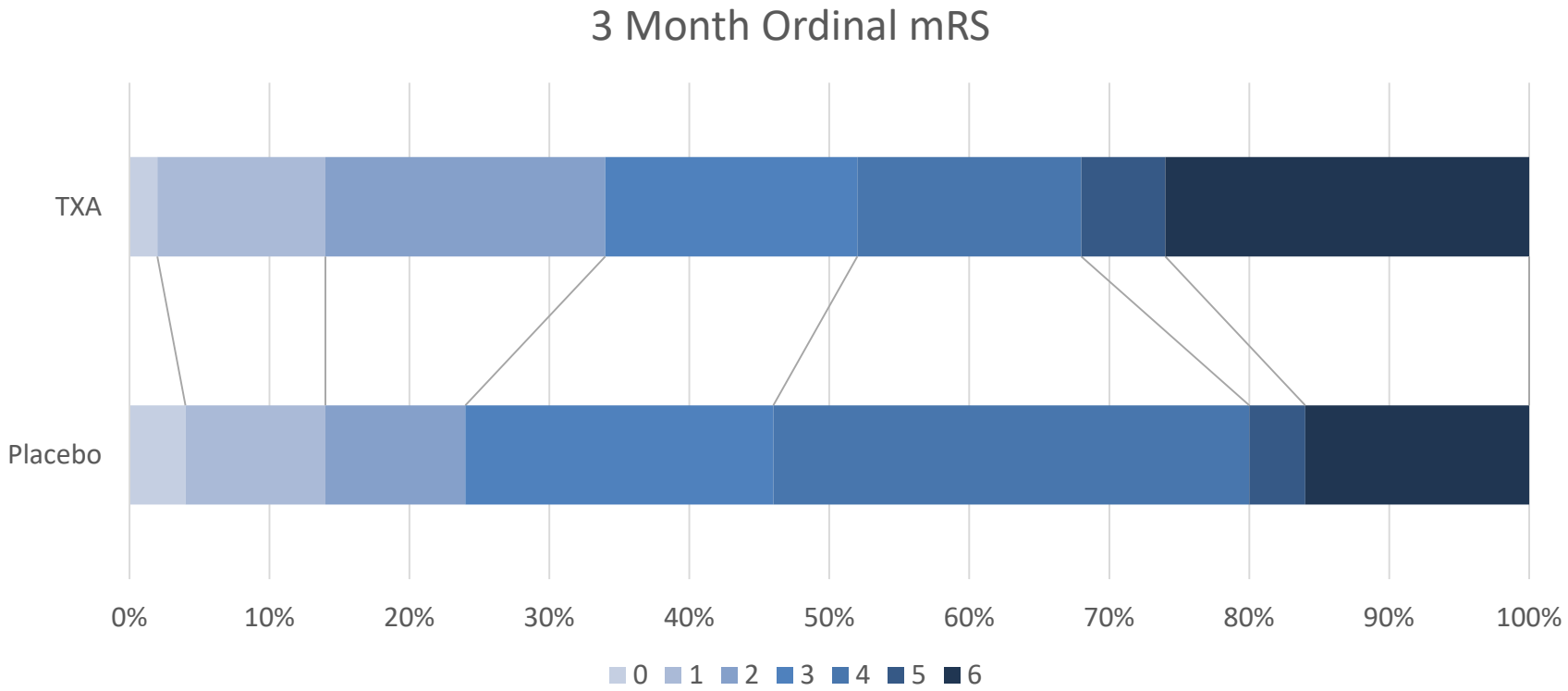
	TXA	Placebo	Effect Size	p
ICH Growth (33% or 6mL)	22/50 (44%)	26/50 (52%)	aOR 0.72 (0.32 – 1.59)*	0.41

*Adjusted for baseline ICH volume

Secondary Outcomes

	TXA	Placebo	Effect Size	p
Absolute Growth, median (IQR)*	1.9 (0.2 – 9.5)	3.4 (0.0 – 16.0)	Adj median difference -1.8 (-5.2 – 1.5)	0.28
Absolute IVH Growth, median (IQR)+	0.0 (0.0 – 0.0)	0.0 (0 – 0.6)	Adj median difference 0 (-0.04 – 0.04)	>0.99
mRS 0-3 or return to baseline, n(%) %	28 (56.0)	23 (46.0)	aOR 1.64 (0.63 – 4.24)	0.31
mRS 0-4 or return to baseline, n(%) %	34 (68.0)	40 (80.0)	aOR 0.33 (0.09 – 1.23)	0.099

*Adjusted for baseline ICH volume
+Adjusted for baseline IVH volume
%Adjusted for age and baseline ICH volume



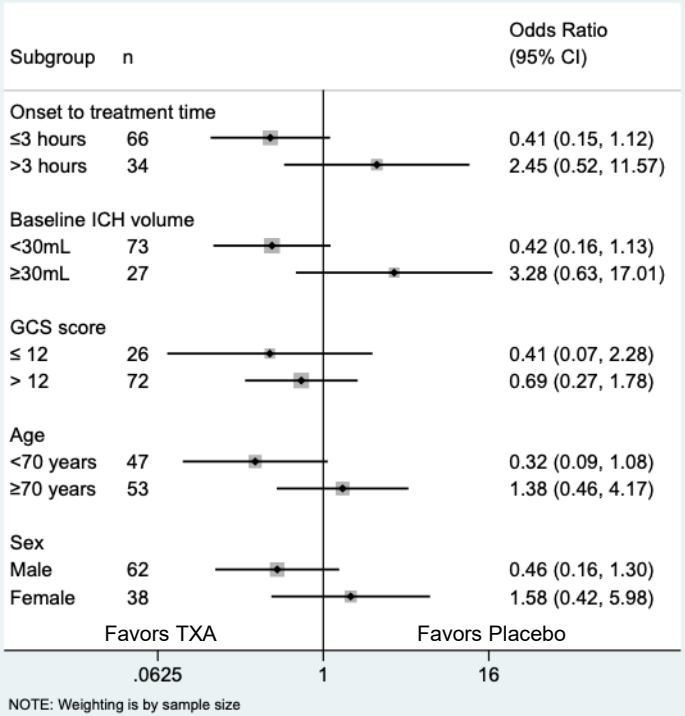
GenOR = 1.01 (0.63 – 1.61), p=0.97
Stratified by age≥70 and volume≥30mL
Assumption free analysis

Safety

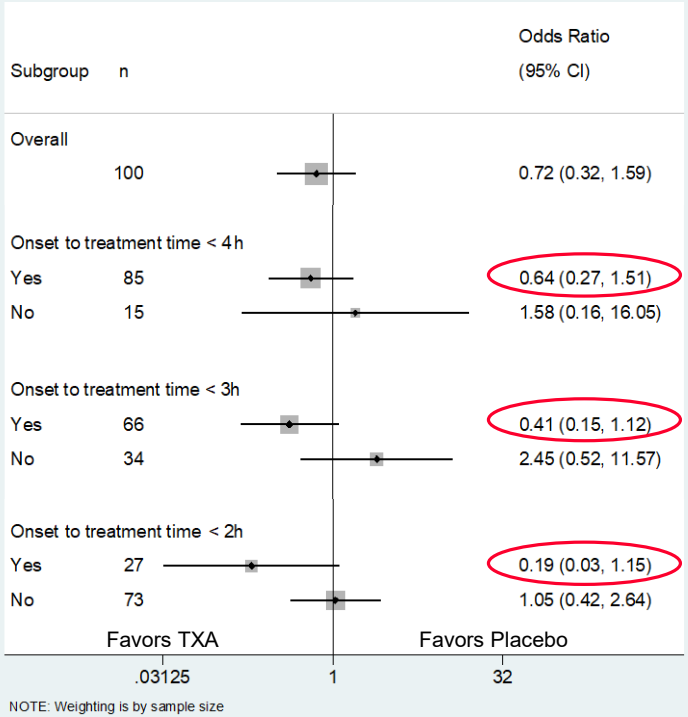
	TXA	Placebo	Effect Size	p
Major Thromboembolic Events	1 (2.0)	2 (4.0)	OR 0.49 (0.04 – 5.58)	0.57
Death*	13 (26.0)	8 (16.0)	aOR 2.38 (0.66 – 8.67)	0.19

*Adjusted for age and baseline ICH volume

Subgroups


Subgroup n
Odds Ratio (95% CI)
Onset to treatment time
≤3 hours 66 0.41 (0.15, 1.12)
>3 hours 34 2.45 (0.52, 11.57)
Baseline ICH volume
<30mL 73 0.42 (0.16, 1.13)
≥30mL 27 3.28 (0.63, 17.01)
GCS score
≤ 12 26 0.41 (0.07, 2.28)
> 12 72 0.69 (0.27, 1.78)
Age
<70 years 47 0.32 (0.09, 1.08)
≥70 years 53 1.38 (0.46, 4.17)
Sex
Male 62 0.46 (0.16, 1.30)
Female 38 1.58 (0.42, 5.98)
Favors TXA
Favors Placebo
.0625
1
16
NOTE: Weighting is by sample size

Subgroups by time epoch



Limitations

- Small sample size
- Results are trends which require replication

Conclusions

- TXA treatment led to a non-statistically significant reduction in ICH growth, both in binary and absolute terms.
- The overall prevalence of ICH growth (48%) was higher in this <4.5h spot-sign selected trial compared to TICH-2 (27%).
- Tranexamic acid is safe in primary ICH
- The trends towards greater effect in the ≤3hr and ≤2hr warrant further exploration of tranexamic acid therapy in the ultra-early time window (STOP-MSU *clinicaltrials.gov* NCT03385928)

Site Investigators

Royal Melbourne Hospital – Prof Stephen Davis*, Prof Geoffrey Donnan*, Prof Bruce Campbell, Prof Peter Mitchell, Prof Bernard Yan, Prof Mark Parsons

Helsinki University Hospital – Dr Marjaana Tiainen, Prof Turgut Tatlisumak, A/Prof Atte Meretoja+

National Taiwan University Hospital – A/Prof Jiann-Shing Jeng

Royal Adelaide Hospital – Prof Timothy Kleinig

John Hunter Hospital – Prof Neil Spratt

Austin Hospital – Prof Vincent Thijs

Western Health – Prof Tissa Wijeratna

Princess Alexandra Hospital – Dr Darshan Shah

The Alfred Hospital – Prof Geoffrey Cloud

Monash Medical Centre – Prof Thanh Phan, Prof Henry Ma

China Medical University Hospital – Prof Chung Hsu, Dr Der-Yang Cho

Lyell McEwin Hospital - Dr Andrew Moey

Eastern Health – Prof Helen Dewey, Prof Christopher Bladin

Imaging
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Mr Gagan Sharma

Biostatistics
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Ms Michele Salleberger

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*Co-chairs of the trial steering committee +Principal Investigator