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TITLE Tranexamic acid in patients with intracerebral haemorrhage (STOP-AUST): a multicentre, randomised, placebo-controlled, phase 2 trial

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DECLARATIONS OF INTEREST

Atte Meretoja	None exist.
Nawaf Yassi	None exist.
Teddy Y Wu	None exist.
Leonid Churilov	None exist.
Gerli Sibolt	None exist.
Jiann-Shing Jeng	None exist.
Timothy Kleinig	None exist.
Neil Spratt	None exist.
Vincent Thijs	Honoraria paid for advisory board, speaker fees, and travel (Boehringer Ingelheim, Pfizer/BMS, Bayer, Amgen, Medtronic)
Tissa Wijeratne	None exist.
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Christopher Bladin	None exist.
Andrew Moey	None exist.
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Christen Barras	None exist.
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Henry Ma	None exist.
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Marjaana Tiainen	None exist.
Sami Curtze	None exist.
Daniel Strbian	Advisory Board (Portola)
Sung-Chun Tang	None exist.
Jackson Harvey	None exist.
Christopher Levi	
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ABSTRACT

Background While intracerebral haemorrhage (ICH) causes 5% of global deaths, few evidence-based therapies other than stroke unit care exist. Tranexamic acid, a reversible direct inhibitor of plasminogen lysine binding sites, decreases haemorrhage in other conditions. We aimed to test whether tranexamic acid reduces ICH growth in patients with confirmed ongoing haemorrhage.

Methods We performed a prospective, 1:1 randomised, double-blind, placebo-controlled, investigator-initiated, academic trial across 13 stroke centres in Australia, Finland, and Taiwan. ICH patients fulfilling clinical criteria and demonstrating contrast extravasation on CT angiography received either 2 g of intravenous tranexamic acid over 8 h, or placebo, started within 4·5 h of symptom onset. The primary outcome, analysed intention-to-treat, was ICH growth (>33% relative or >6 mL absolute) at 24 h, with 3 month safety and functional secondary outcomes. The trial was registered at ClinicalTrials.gov (NCT01702636).

Findings We recruited 100 participants between March 1, 2013 and August 13, 2019. Median age was 71 years and ICH volume was 14·6 mL at baseline. The primary outcome of ICH growth occurred in 26 (52%) placebo and 22 (44%) tranexamic acid group participants (adjusted odds ratio [aOR] 0·72, 95% CI 0·32–1·59, p=0·41). No difference was detected in mortality 8 (16%) *vs* 13 (26%) (aOR 2·38, 0·66–8·67, p=0·19), thromboembolic complications 2 (4%) *vs* 1 (2%) (OR 0·49, 0·04–5·58, p=0·57), or functional outcome distribution (adjusted generalised OR 1·01, 0·63–1·61, p=0·97) between the placebo and tranexamic acid groups. Treatment effect was modified by time, favouring earlier therapy (interaction-p=0·04).

Interpretation Tranexamic acid did not reduce ICH growth or improve functional outcome when given within 4·5 h to patients with ongoing intracerebral haemorrhage. Treatment was safe with no increase in thromboembolic complications. Larger trials with tranexamic acid in earlier time windows are justified.

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Introduction

Globally, 18 million people live with sequelae of intracerebral haemorrhage (ICH) and 3 million die due to the condition each year, comprising 5% of all human deaths.[1,2] Although specialised multidisciplinary treatment in stroke units benefits all stroke patients, there are no strongly evidence-based acute therapies specific to ICH.[3,4]

The main determinants of clinical outcome in ICH are age, neurological deficit, haematoma aetiology, location, and volume.[5,6] Of these, volume is the most significant factor. As with ischaemic stroke, ICH is frequently a dynamic process, with growth occurring in most patients over the first few hours from symptom onset, presenting an intervention target.[7-9] Some haemostatic agents have been tested for attenuating ICH growth. Recombinant activated coagulation factor VII (rFVIIa) was tested in two trials of a total of 1240 ICH patients within 4 hours of symptom onset, but failed to significantly improve outcomes.[10,11] Tranexamic acid was tested in 2325 patients within 8 hours of symptom onset, but did not improve functional outcome.[12] Both agents reduced ICH growth, but the absolute effect on growth was modest, ranging from 1 mL[12] to 5 mL[10,11].

While most ICH growth occurs prior to presentation, significant growth takes place in a third of ICH patients after hospital presentation. CT angiography (CTA) contrast extravasation, the "spot sign", can be used as a biomarker for identifying these patients with ongoing bleeding.[13-15] Here we report our trial results using the spot sign to select ICH patients for haemostatic therapy.

The aim of the STOP-AUST randomised controlled trial was to test the hypothesis that ICH patients selected with CTA spot sign will have lower rates of haematoma growth when treated with intravenous tranexamic acid within 4·5 hours of stroke onset, compared to placebo.

Methods

Study design and participants

STOP-AUST was a phase 2 randomised placebo-controlled (two arm 1:1) double-blind multinational investigator-led academic trial of tranexamic acid within 4·5 hours of intracerebral haemorrhage in patients with contrast extravasation on CT angiography, the "spot sign". Participants were recruited from 13 hospitals across Australia, Finland, and Taiwan. Ethics approval was obtained for each site and country before patient recruitment. The trial was registered at ClinicalTrials.gov (NCT01702636), EudraCT (2013-001262-42) and the protocol has been published.[16]

Adult patients were eligible if they had a non-traumatic ICH with a spot sign, were treatable within 4·5 hours of symptom onset and within 1 hour of CT angiography, were not severely obtunded (Glasgow coma scale >7), and did not have contraindications for antifibrinolytic therapy. Imaging for participant selection mandated a CT angiography prior to randomisation in order to demonstrate a spot sign. The spot sign was defined as contrast extravasation within the haemorrhage, evaluated according to three criteria, all of which must be present: a) serpiginous or spot-like appearance within the margin of a parenchymal haematoma without connection to an outside vessel; b) the density (in Hounsfield units) should be greater than that of the background haematoma (site investigators are not required to document the density); and c) no hyperdensity at the corresponding location on non-contrast CT (to exclude calcium mimics). Key exclusion criteria were very large (>70 mL) or brainstem haematomas, thromboembolic events in the past 12 months, or planned surgery for the ICH. The full list of inclusion and exclusion criteria is provided in the full protocol provided as a supplementary appendix.

Investigators sought written informed consent from each participant if they had the capacity to provide it. If the participant had capacity but could not write, oral informed consent in the presence of a witness was allowed. When participants did not have capacity, a relative or representative gave proxy consent. The ethics approval at some sites allowed for deferred consent when patient did not have

capacity and representatives were not available. When consent was deferred or given by a proxy, we informed the participant about the trial as soon as possible and sought their consent.

Randomisation and masking

Patients were randomised to receive either the placebo or tranexamic acid based on an online central computer-generated code list, using block randomisation with randomly varied block sizes. STOP-AUST was a double-blind trial, with the patient and all those involved in patient management or clinical or imaging assessment of adverse events or outcomes blinded to treatment allocation. The investigational product was distributed to participating centres in externally indistinguishable sealed treatment kits containing either tranexamic acid or placebo (0·9% NaCl) in non-identical standard off-the-shelf ampoules. After randomization, the sealed treatment kit corresponding to the randomization kit number was handed to an external unblinded person (a person not involved in patient management or evaluation, either pharmacist, nurse or other professional based on local practices) who inserted the two ampoules into two bags of normal saline, and gave the appropriately labelled blinded investigational product to the study personnel for administration to the patient.

Procedures

All participants received either intravenous tranexamic acid 1000 mg in 100 mL 0·9% NaCl over 10 minutes followed by 1000 mg in 500 mL 0·9% NaCl infusion over 8 hours or undistinguishable placebo. A second CT scan was performed at 24±3 hours to evaluate haematoma growth. Vital signs were recorded during and after the period of infusion, and blood pressure managed as per standard care. The protocol mandated an electrocardiography at baseline and 24 hours, but troponin was only evaluated if ECG or clinical symptoms were suggestive of myocardial ischaemia. Neurological deficit was evaluated at 24±3 hours and functional outcome at 90±7 days. All investigators were trained and certified for the modified Rankin Scale (mRS), National Institutes of Health Stroke Scale (NIHSS) and spot sign detection. Dr Aviv provided the spot sign training and certification website (http://www.stopauststudy.com/).

Outcomes

The primary outcome measure was presence of ICH growth by 24±3 hours as defined by either >33% or >6 mL increase from baseline, adjusted for baseline ICH volume. The baseline volume was assessed on the most recent scan prior to randomisation, whether that was the noncontrast CT or CT angiogram. Both baseline and 24 hours ICH volumes were obtained in Osirix using planimetric techniques as described previously.[17] Intraventricular haemorrhage (IVH) volumes were also analysed with the same planimetric technique, but were not be included in ICH volumes.

Secondary efficacy outcome measures included absolute ICH growth volume and absolute IVH growth volume by 24±3 hours, both adjusted for baseline volumes, and functional outcome at 90 days, measured using the mRS. The mRS distribution was analysed after evaluation of the proportional odds assumption, and was additionally dichotomised at 0–3 and 0–4. Secondary safety outcome measures included major thromboembolic events (myocardial infarction, ischaemic stroke, or pulmonary embolism) and death due to any cause, both by 90 days.

Statistical analyses

The total sample size of 100 was based on 80% power to detect a significant absolute difference of 30% in the proportion of patients with haematoma enlargement at 24 hours (31% in treatment vs. 61% in control arm) at a two-sided statistical significance threshold of p=0·05. The control arm rate was based on the PREDICT study.[15] Justified by lack of previous efficacy data, our protocol dictated an adaptive sample size re-estimation with a potential increase up to 150, after the first 75 participants.[18,19] This interim analysis did not recommend a sample increase.

The statistical analysis followed an analysis plan fixed prior to database lock. The primary efficacy analysis was on an intention-to-treat basis. Missing primary outcome data was imputed assuming worst possible outcome. The primary outcome was compared between treatment and control arms adjusted for baseline volume using binary logistic regression.

For functional outcome, the analysis plan mandated testing for mRS dichotomised at 0–3 and 0–4, where getting back to pre-stroke level counted as the better outcome, using binary logistic regression adjusting for age and baseline ICH volume. Additionally, mRS categorical shift (common odds ratio on logistic regression) was to be estimated on the full range of the mRS if proportional odds assumptions were met (both Brant test and Approximate likelihood-ratio test of proportionality of odds not significant) or otherwise by using the assumption-free Wilcoxon-Mann-Whitney Generalised Odds Ratios.[20]

For analysis of absolute ICH and IVH growths by 24 hours, a median regression model with bootstrapped standard error estimation and 500 repetitions was estimated, with treatment group as independent and absolute ICH or IVH growth as dependent variables, adjusting for baseline ICH or IVH volumes correspondingly. The safety outcomes of major thromboembolic event and death due to any cause by 90 days were analysed using binary logistic regression, with age and baseline ICH volume adjustment for the mortality outcome only. Predefined subgroup analyses are provided for the primary outcome measure, the results of which were regarded as hypothesis generating only.

The study was run by an executive committee co-chaired by Prof Davis and Prof Donnan and a steering committee including all site primary investigators. An independent data safety monitoring board reviewed the unmasked data after every 25 participants and performed a formal safety interim analysis after 60 patients. The trial was performed in accordance with the principles of good clinical practice and the Declaration of Helsinki.

Role of the funding source

The study was funded by the Australian National Health and Medical Research Council (NHMRC) grant number 1081718 and the Royal Melbourne Hospital Foundation. The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had overall responsibility for the decision to submit for publication.

Results

We recruited 100 participants across 13 centers in 3 countries between Mar 1, 2013 and Aug 13, 2019. All participants were randomised 50:50 and received the allocated treatment (Figure 1.). One participant did not have a follow-up scan due to early palliation and was assigned ICH growth outcome as per the statistical analysis plan. All had complete 3 month-follow-up and study blind was not broken in any individual.

Median age of the participants was 71 years (interquartile range 57 to 79), median ICH volume was 14·6 (7·9 to 32·7) mL, and median baseline NIHSS was 13 (8 to 18) at baseline. Median time from onset to baseline scan was 105 minutes (77 to 155), from baseline scan to treatment 41 minutes (29 to 56), and onset to treatment 150 minutes (118 to 203). Participant characteristics were well balanced among the treatment groups (Table 1).

The primary efficacy outcome, growth of ICH from baseline to 24 hours, occurred in 26 (52%) of the placebo patients and 22 (44%) of the tranexamic acid patients, with the difference being statistically non-significant, OR 0·72 (0·32 to 1·59), p=0·41. The distribution of functional outcome at 3 months did not fulfil the proportional odds assumptions, and the assumption-free analysis demonstrated no difference among the treatment groups (Figure 2). All-cause mortality by 3 months was 8 (16%) in the placebo group and 13 (26%) in the tranexamic acid group and did not significantly differ between the two groups (Figure 3). There were two thromboembolic complications in the placebo group and one in the tranexamic acid group (Table 2). Of the predefined subgroups, only time from stroke onset to treatment demonstrated a significant interaction with the treatment effect (p=0·04), with a stronger effect in patients treated within 3 hours of onset (Figure 4).

The median ICH growth from baseline to 24 hours was 2·7 (0·1 to 13·7) mL, being 3·4 (0·0 to 16·0) mL for placebo and 1·9 (0·2 to 9·5) mL for tranexamic acid patients (p=0·81). The baseline-volume adjusted absolute ICH growth from baseline to 24 hours was –1·8 (–5·2 to 1·5) mL, a non-significant difference at p=0·28 (Figure 5).

One or more protocol violations, mainly issues in delivering the therapy within one hour of baseline imaging, occurred in 26 participants (Figure 1). Baseline characteristics, outcomes, and subgroup analyses in the per-protocol cohort mirrored those of the full analysis set with details provided in the supplementary appendix.

Discussion

Our study of tranexamic acid or placebo within 4·5 hours or symptom onset in patients with ongoing haemorrhage failed to demonstrate a significant reduction in ICH growth. There were no treatment-related safety concerns. Of the pre-specified subgroups, only early treatment within 3 hours of symptom onset appeared to modify the treatment effect.

We chose the 4·5 hour window for this study as haematoma growth in ICH is known to occur early and therefore earlier treatment is likely to be more beneficial.[8] While patients with ischaemic stroke and ICH cannot be distinguished from each other on clinical grounds, emergency medical services are traditionally organized to bring in acute stroke patients with haste for diagnosis and treatment within 4·5 hours of symptom onset.[21]

In stroke patients, tranexamic acid was initially extensively tested in clinical trials for subarachnoid haemorrhage. A Cochrane meta-analysis of 1904 patients concluded that there was no benefit, as the treatment effect on re-bleeds (OR 0.65; 95% confidence interval 0.44 to 0.97) was offset by an excess of cerebral ischaemic events (OR 1.41; 1.04 to 1.91).[22] The trials were mostly performed in the 1970's and 80's with doses much larger than in the present trial, typically 6 grams daily for 3-6 weeks.

Interest in tranexamic acid was revived in 2010 after positive results of the placebo-controlled CRASH-2 trial in trauma patients (n=20,211) using an identical dose to the present study.[23,24] Patient outcomes were improved, especially when treatment was initiated early within 3 hours of trauma. Importantly, thromboembolic complications were not increased. The recent HALT-IT trial in

gastrointestinal bleeding (n=12,009) with a larger dose of 4 grams over 24 hours did not show clinical benefit and demonstrated an increase in venous thromboembolic events. (ADD REF)

Tranexamic acid was first tested in ICH in the two TICH trials and a small Malaysian trial (n=30).[25] Following the TICH pilot trial (n=24), 2325 ICH patients in the TICH-2 trial received tranexamic acid or placebo in a dose identical to the present study.[12,26] Patients were not selected based on ongoing haemorrhage and the time window was longer, up to 8 hours from onset, although half of the patients were treated within 4 hours. Functional outcome at 90 days did not differ between the groups (adjusted odds ratio 0·88, 95% CI 0·76–1·03, p=0·11), despite there being less haematoma growth in the tranexamic acid group (25% vs 29%, OR 0·80, 0·66 to 0·98, p=0·03). Fifty six patient were spot sign positive, but the treatment effect of tranexamic acid on this subgroup has not been published.

Two previous phase II trials using the spot sign as a selection criterion have been reported, namely the STOP-IT and SPOTLIGHT trials, published in 2019.[27] These trials recruited a total of 69 ICH patients over 6 years to receive rFVIIa or placebo, with a median time from CT scan to treatment at 79 minutes in the rFVIIa group, and did not demonstrate significant reductions in ICH growth (41% vs 43%, p=0·83) or severe disability (30% vs 38%, p=0·60).

The main positive signal in our trial comes from the subgroup of patients treated early, within 3 hours of symptom onset. In acute trauma, tranexamic acid has had a strong time to treatment interaction, with earlier treatment being better, preferably within an hour of trauma, with treatment effect possibly lost beyond three hours.[25] Similarly, time is known to be of the essence in reperfusion therapies of acute ischaemic stroke where most benefits are seen with early treatment and treatment effect is lost beyond 4·5 or 6 hours in most patients – only selected patients can still be identifiable in later time windows using advanced imaging.[28] In line with previous literature, our findings favour further trials of tranexamic acid in intracerebral haemorrhage in the early time window, some of which are already ongoing (EudraCT 2012-005594-30 and ClinicalTrials.gov NCT03385928).

Our study has limitations. First, the small sample size makes a type II error possible. The growth rate of 52% in the placebo group was less than the 61% expected based on previous literature. Still, the effect size point estimate of our trial at OR 0·72 (0·32 to 1·59) was similar to that of the TICH-2 trial OR 0·80 (0·66 to 0·98). Several tranexamic acid trials are underway and an individual patient meta-analysis will be performed to address study power issues.[29] Second, the median delay from baseline scan to treatment of 41 minutes was suboptimal to test the study hypothesis, as much of the potential haematoma growth may have already occurred before treatment commenced. Third, recruitment using advanced imaging in a very tight time schedule is difficult and complicates a trial for many sites less familiar and comfortable with the technique. While 13 sites successfully recruited participants into the present trial, two thirds came from two sites only, and several sites were unable to recruit a single patient. This limits the generalisability of our findings and suggests that simpler trials using solely a very early time window may be more applicable in clinical practice.

In summary, tranexamic acid did not significantly reduce ICH growth or improve functional outcome, although the treatment was safe with no increase in thromboembolic complications. As haematoma growth is a major cause of morbidity and mortality in acute ICH, new, safe, and effective treatments to stem ongoing haemorrhage are urgently required. Larger trials with tranexamic acid in earlier time windows are justified.

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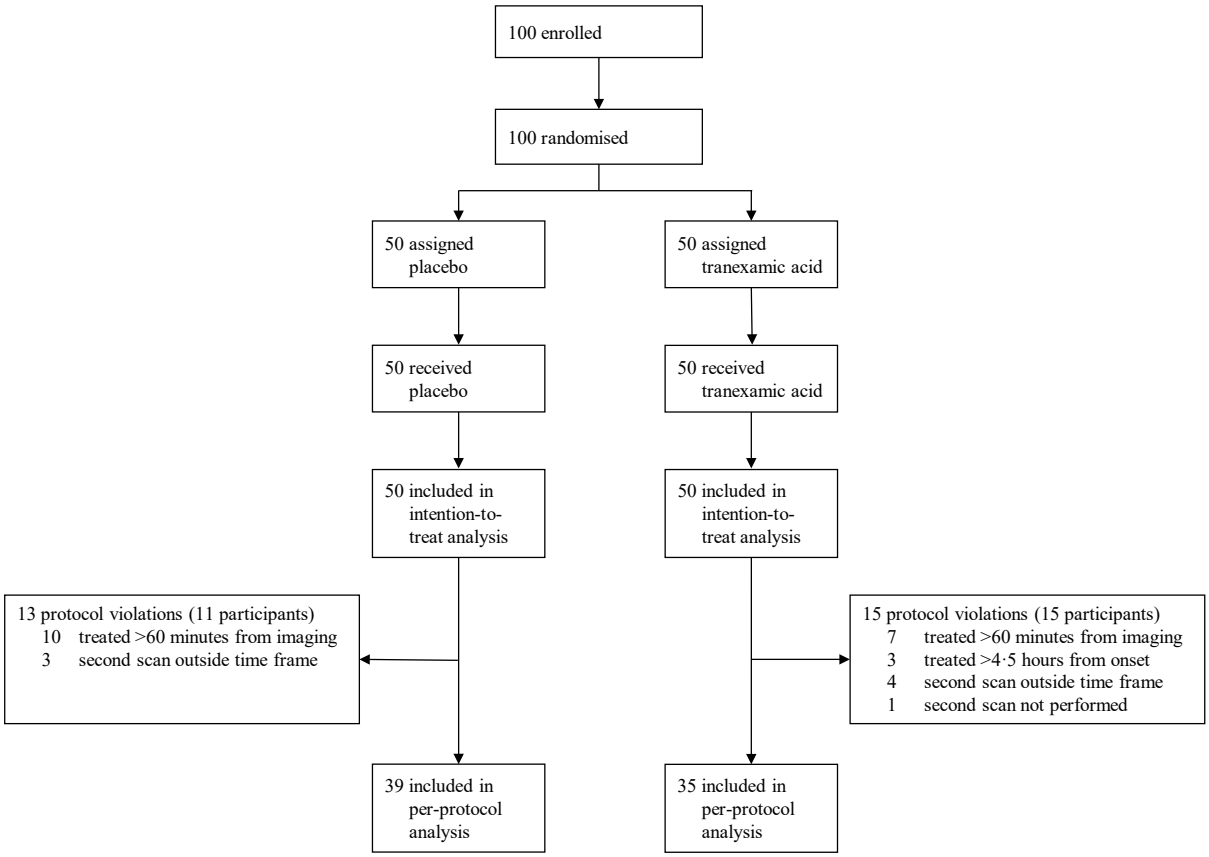

Figure 1: **Study flowchart**

The second scan was to be performed in the time frame of 21 to 27 hours from the first scan. However, the scan was considered within an acceptable time frame also if performed before 21 hours but demonstrated significant growth as per primary outcome (e.g. in the setting of second scans performed prior to surgical evacuation) or if performed beyond 27 hours but without demonstrating significant growth as per primary outcome.

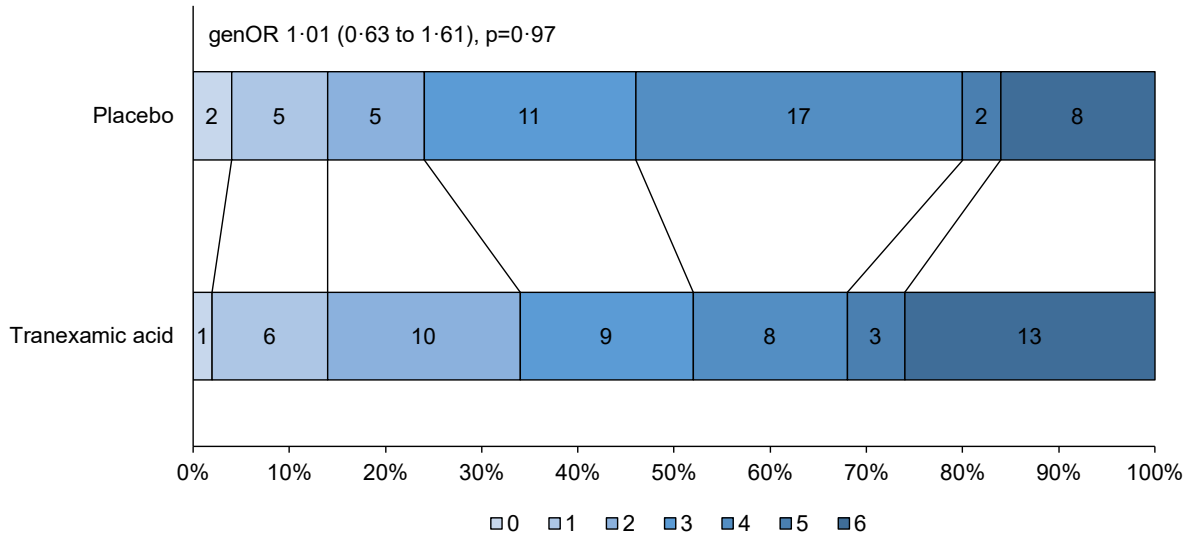

Figure 2: **Modified Rankin Scale distribution at 3 months**

A score of 0 represents no symptoms, 1 represents no disability despite symptoms, 2 represents slight disability but able to look after own affairs, 3 represents moderate disability but able to walk without assistance, 4 represents moderately severe disability (unable to walk or attend to own bodily needs), 5 represents severely disabled (bedridden and requiring constant nursing care), and 6 represents death.

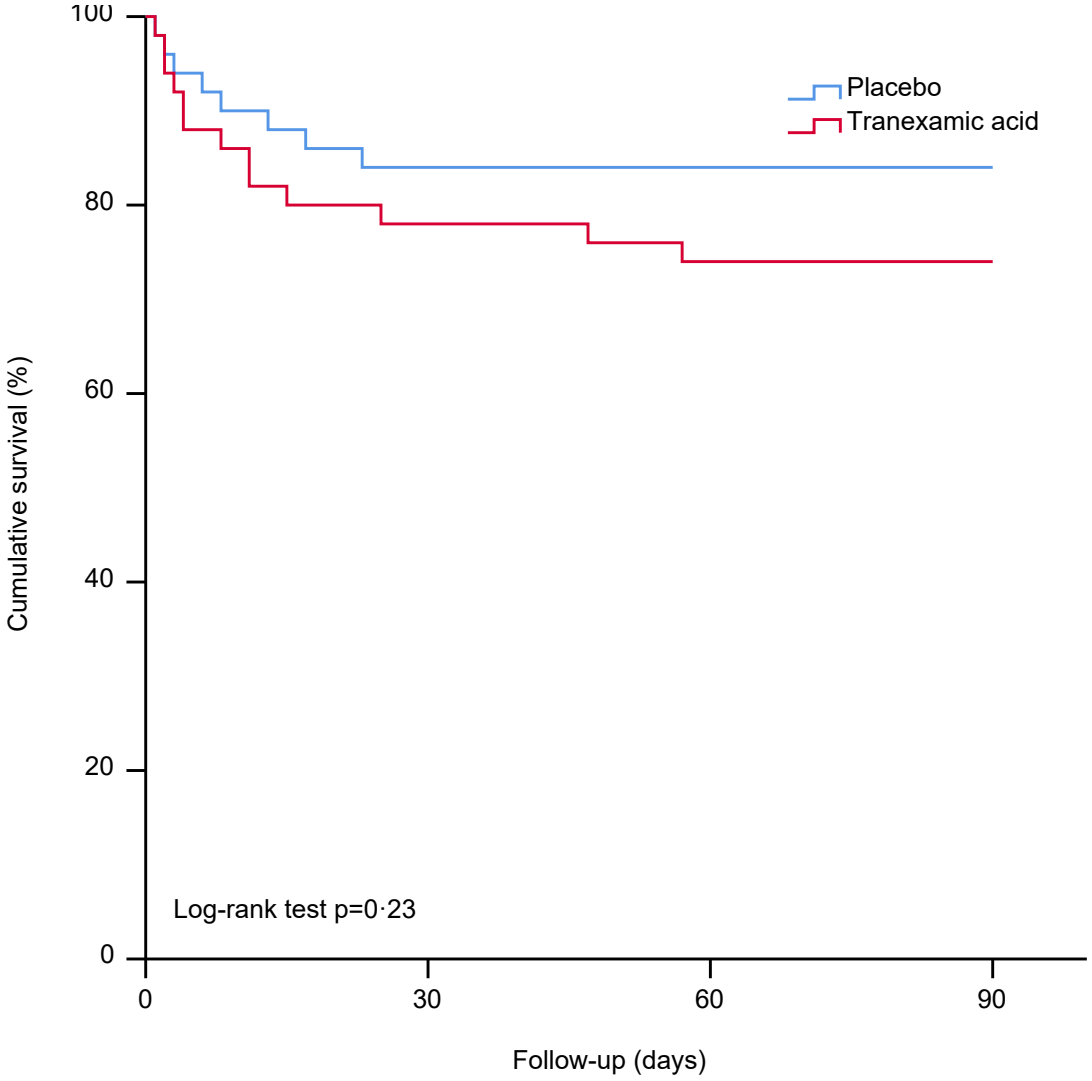

Figure 3: **Kaplan-Meier plot**

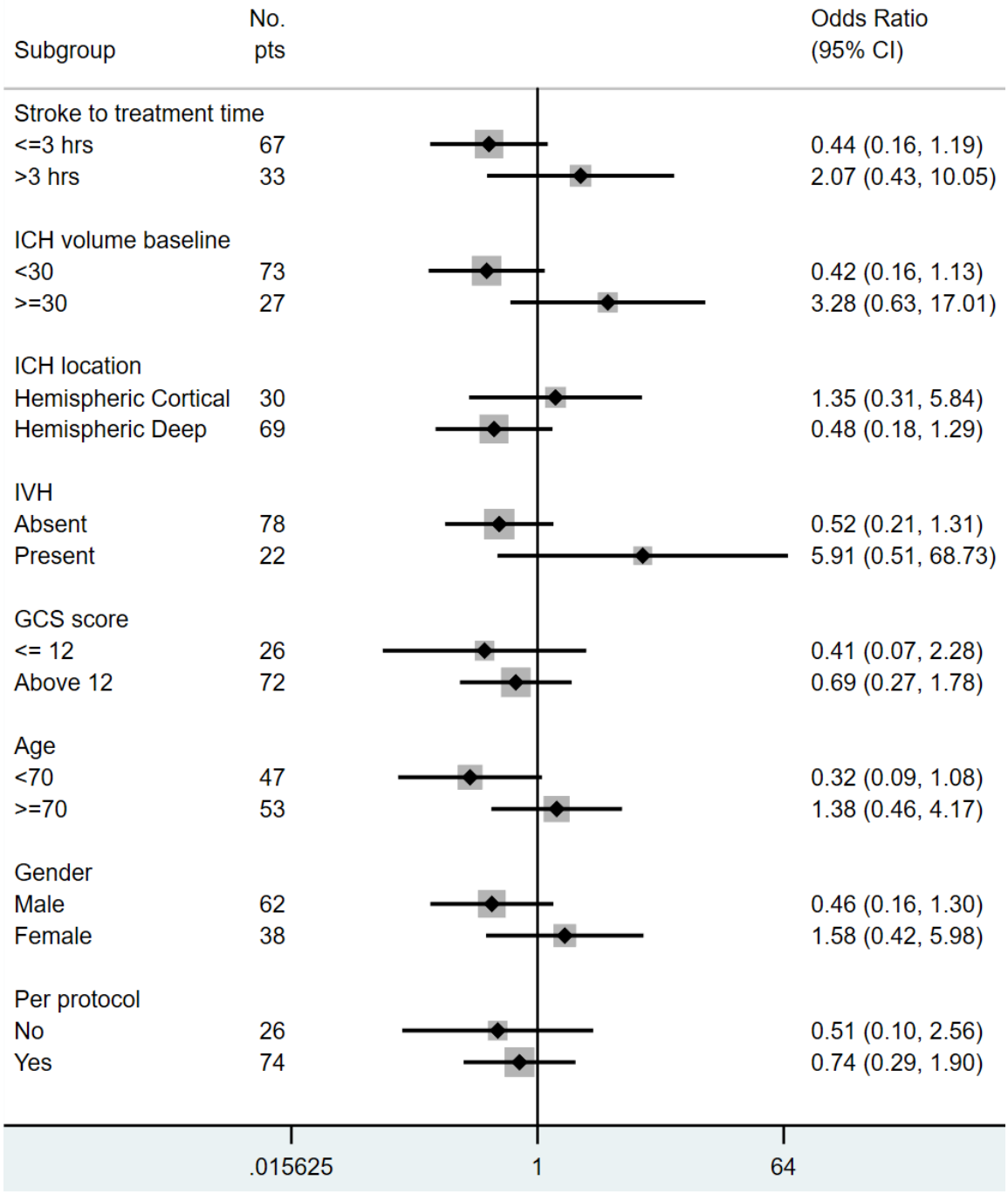

Figure 4: **Forest plot of primary outcome in predefined subgroups**

Odds ratios less than 1 favour tranexamic acid over placebo. P-value for treatment effect interaction by subgroup was 0·04 for stroke to treatment time and non-significant for all others.

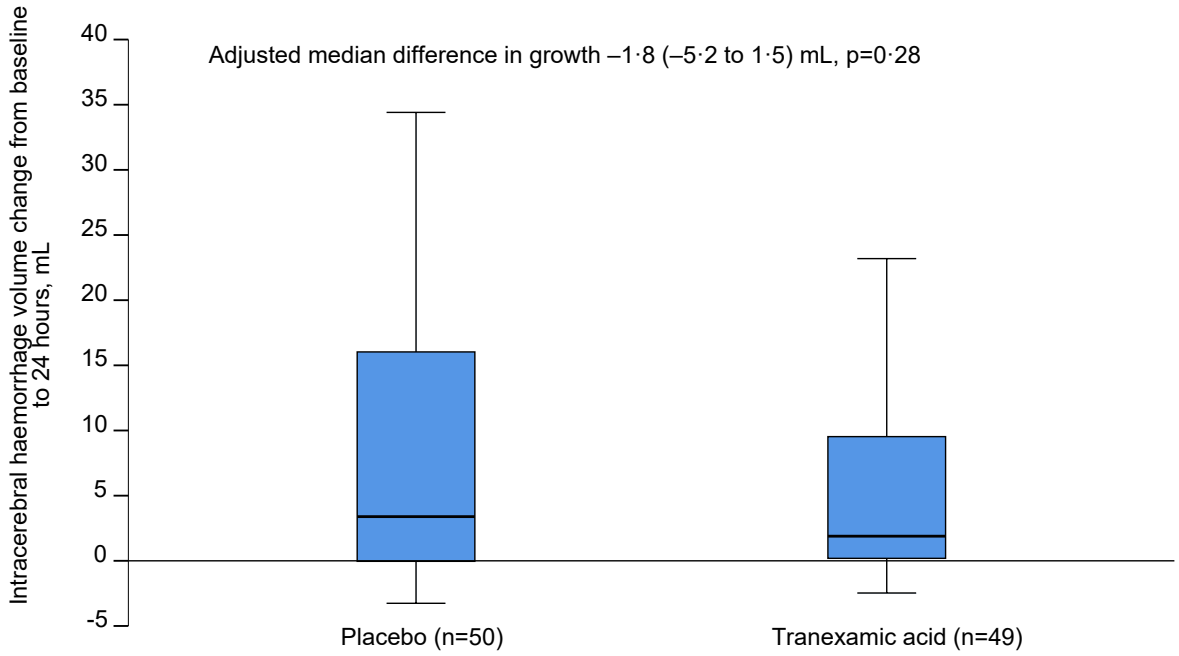

Figure 5: **Box plot of intracerebral haematoma growth from baseline to 24 hours**

	Placebo (n=50)	Tranexamic acid (n=50)
Age, years	71 (58–79)	73 (55–78)
Male sex	27 (54%)	35 (70%)
Country		
Australia	31 (62%)	34 (68%)
Finland	11 (22%)	12 (24%)
Taiwan	8 (16%)	4 (8%)
NIHSS score	12 (8–17)	14 (8–19)
Glasgow coma scale	15 (13–15)	14 (11–15)
Prestroke mRS	0 (0–0)	0 (0–1)
History		
Ischaemic stroke / TIA	5 (10%)	6 (12%)
ICH	3 (6%)	5 (10%)
Hypertension	33 (66%)	36 (72%)
Diabetes	9 (18%)	10 (20%)
Current smoking	6 (12%)	7 (14%)
Current antiplatelet therapy	12 (24%)	16 (32%)
Current statin therapy	16 (32%)	14 (28%)
Admission blood pressure, mmHg		
systolic, mean (SD)	173 (25)	168 (25)
systolic, median (IQR)	172 (157–189)	165 (150–181)
diastolic, mean (SD)	90 (17)	91 (21)
diastolic, median (IQR)	90 (78–101)	90 (80–100)
Serum glucose, mmol/L	6·3 (5·6–7·9)	7·2 (6·6–8·7)
SMASH U Classification		
Hypertensive angiopathy	23 (46%)	23 (46%)
Amyloid angiopathy	14 (28%)	12 (24%)
Undetermined	13 (26%)	15 (30%)
ICH location		
Pure cerebellar	0 (0%)	1 (2%)
Hemispheric cortical	15 (30%)	15 (30%)
Hemispheric deep	35 (70%)	34 (68%)
Mixed	0 (0%)	0 (0%)
Intraventricular extension	9 (18%)	13 (26%)
Baseline haematoma volume, mL		
intracerebral haemorrhage	15·6 (7·9–33·4)	13·8 (7·8–32·0)
intraventricular haemorrhage	0·0 (0·0–0·0)	0·0 (0·0–0·5)
Spot-sign central adjudication	50 (100%)	50 (100%)
Time metrics, minutes		
Onset / last known well to baseline scan	99 (77–150)	111 (75–171)
Baseline scan to treatment	43 (31–56)	40 (29–55)
Onset / last known well to treatment	150 (121–195)	153 (114–215)

Table 1: **Baseline characteristics**
Data are n (%) or median (interquartile range, IQR) unless otherwise stated.

	Placebo (n=50)	Tranexamic acid (n=50)	Effect Size (95%CI)	p-value
Primary efficacy outcome				
ICH growth*	26 (52%)	22 (44%)	0·72 (0·32–1·59)†	0·41
Secondary Outcomes				
modified Rankin Score at 90 days			1·01 (0·63–1·61)‡	0·97
mRS 0	2 (4%)	1 (2%)		
mRS 1	5 (10%)	6 (12%)		
mRS 2	5 (10%)	10 (20%)		
mRS 3	11 (22%)	9 (18%)		
mRS 4	17 (34%)	8 (16%)		
mRS 5	2 (4%)	3 (6%)		
mRS 6, death	8 (16%)	13 (26%)		
mRS 0–3 or back to baseline	23 (46%)	28 (56%)	1·64 (0·63–4·24)§	0·31
mRS 0–4 or back to baseline	40 (80%)	34 (68%)	0·33 (0·09–1·23)§	0·10
Imaging at 24±3 hours, mL¶				
Absolute ICH growth	3·4 (0·0–16·0)	1·9 (0·2–9·5)	–1·8 (–5·2–1·5)†	0·28
Absolute IVH growth	0·0 (0·0–0·6)	0·0 (0·0–0·0)	0 (0·0–0·0)‖	0·99
Safety				
Major thromboembolic events	2 (4%)	1 (2%)	0·49 (0·04–5·58)	0·57
Myocardial infarction	0 (0%)	0 (0%)		
Pulmonary embolism	1 (2%)	0 (0%)		
Ischaemic stroke	1 (2%)	1 (2%)		
Death within 90 days	8 (16%)	13 (26%)	2·38 (0·66–8·67)§	0·19

Table 2: **Outcomes**

Data are n (%) or median (IQR). Effect size reported as adjusted median difference for mL volumes and odds ratios for all other outcomes. *Defined as >33% relative growth or >6 mL absolute growth by 24±3 hours. †Adjusted for baseline ICH volume. ‡Assumption free analysis, stratified by baseline age ≥70 and volume ≥30 mL. §Adjusted for age and baseline ICH volume. ¶Missing 24 hour data for one tranexamic acid patient. ‖Adjusted for baseline IVH volume.

Panel: **Research in context**

Evidence before this study

Tranexamic acid has been studied in other intracranial conditions, in subarachnoid haemorrhage, with a Cochrane review from 2013, and more recently in traumatic brain injury, with several recent meta-analyses. A PubMed search using the terms “tranexamic acid” AND (“intracerebral” OR “ICH”) yielded some case reports and observational series, several trial protocols, and three published trials (TICH n=24, Arumugam n=30, TICH-2 n=2325). Despite recruiting well, the TICH-2 trial failed to demonstrate a significant functional benefit from tranexamic acid, with an adjusted odds ratio of 0·88, 95% CI 0·76–1·03, p=0·11 trending towards benefit. Treatment, given at median of around 4 hours from onset, was safe, reduced growth marginally, and did not increase thromboembolic complications.

Added value of this study

The STOP-AUST trial is, to our knowledge, the first published trial of tranexamic acid in ICH patients with known ongoing haemorrhage at time of recruitment. Tranexamic acid given within 4·5 hours of symptom onset was not associated with ICH growth, functional outcome, or complications in the study population. There was a significant treatment interaction by time, so that patients treated within 3 hours were more likely to benefit from tranexamic acid than those treated later.

Implications of all the available evidence

Current evidence does not justify routine use of tranexamic acid in intracerebral haemorrhage in unselected patients nor in patients with demonstrated ongoing haemorrhage. Despite combined thousands of ICH patients presenting at the experienced STOP-AUST trial sites annually, it took several years to recruit the trial target of 100 participants, suggesting a simpler protocol would be more likely to translate into practise. The combination of convincing safety evidence, high mortality, lack of evidence-based therapies,

and often reduced patient capacity may justify the use of deferred consent in future trials. Research efforts should concentrate on ultra-acute streamlined delivery of tranexamic acid.