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Systematic review

Effect of tranexamic acid for acute spontaneous intracerebral haemorrhage: a systematic review and individual patient data meta-analysis

Chaamanti Sivakumar Menon ,[1] Zhe Kang Law ,[2,3] Lisa Jane Woodhouse ,[4] Jingyi Liu ,[5] Chloe Mutimer,[6] Michael Desborough,[7] Liping Liu ,[8] Alexandros A Polymeris ,[9] Atte Meretoja,[10] Nawaf Yassi,[11] Henry Zhao,[6] Stephen Davis,[12] Geoffrey A Donnan,[13,14] Robert A Dineen ,[15] David J Seiffge ,[9,16] Jeyaraj D Pandian,[17] Rustam Al-Shahi Salman ,[18] Philip M Bath ,[19] Nikola Sprigg[20]

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For numbered affiliations see end of article.

Correspondence to
Dr Chaamanti Sivakumar Menon; chaamanti.menon1@nottingham.ac.uk

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ABSTRACT

Background Spontaneous intracerebral haemorrhage (ICH) has high rates of mortality with no proven haemostatic treatment. We conducted the first systematic review and individual patient data meta-analysis (IPDMA) to assess the effect of tranexamic acid on outcomes in spontaneous ICH.

Methods We searched databases such as MEDLINE, EMBASE and CENTRAL for randomised controlled trials comparing intravenous tranexamic acid to placebo in adults with spontaneous ICH treated within 12 hours. The primary outcome was 90-day functional status (modified Rankin scale). Secondary outcomes included early mortality and haematoma expansion. One-stage random-effects analysis used generalised linear mixed models. Risk of bias was assessed using the Cochrane Risk of Bias (RoB) 2 tool.

Results We screened 1131 records; nine trials (3194 participants) met inclusion and five trials (2860 participants; 90%) provided individual patient data. ROB was low in all trials. At 90 days, 53.2% of patients receiving tranexamic acid had a worse functional outcome compared with 53.6% in the placebo (adjusted common OR 0.93, 95% CI 0.81 to 1.07). Mortality at day 7 and haematoma expansion were significantly reduced with tranexamic acid (adjusted OR 0.70, 95% CI 0.51 to 0.95; and OR 0.81, 95% CI 0.68 to 0.97). No between-trial heterogeneity was observed.

Conclusions This systematic review and IPDMA of tranexamic acid for spontaneous ICH found no improvement in 90-day functional outcomes. However, small yet significant reductions in early mortality and haematoma expansion were observed. The early mortality benefit and favourable safety profile support further research into ultra-early treatment and as part of ICH care bundles for selected patient populations.

PROSPERO registration number CRD42017054978.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Spontaneous intracerebral haemorrhage (ICH) has high mortality and no established haemostatic treatment. Tranexamic acid has shown promise in reducing haematoma expansion in individual trials, but prior meta-analyses based on aggregate data have not demonstrated a clear functional benefit. An individual patient data meta-analysis (IPDMA) was needed to more accurately assess clinical efficacy and explore treatment modifiers.

WHAT THIS STUDY ADDS

⇒ This is the first IPDMA of tranexamic acid for spontaneous ICH which pooled data from five randomised controlled trials (n=2860) and found no improvement in 90-day functional outcomes, but a significant reduction in haematoma expansion and day 7 mortality. The treatment effect was consistent across subgroups, and there were no safety concerns.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ While tranexamic acid does not improve long-term disability, its early mortality benefit and safety profile support further investigation in ultra-early treatment windows and in combination with ICH care bundles. Ongoing trials may clarify its role in selected patient populations.

INTRODUCTION

Intracerebral haemorrhage (ICH) represents ~20% of all strokes and is a leading cause of death and long-term disability.[1] Unlike ischaemic stroke, effective acute therapies for ICH remain limited. Haematoma expansion occurs in up to 40% of patients within the first 24 hours and is strongly associated with increased mortality and worse functional outcomes.[2]

The underlying mechanism of haematoma expansion is multifactorial. The initial insult triggers local coagulopathy, clot instability and secondary fibrinolysis. Fibrinolysis is mediated by the conversion of plasminogen to plasmin, which degrades fibrin clots and exacerbates bleeding.[3] Tranexamic acid, a synthetic lysine analogue, acts as an antifibrinolytic,

stabilising the clot and reducing ongoing bleeding. This action has been demonstrated to be successful in various conditions, including traumatic brain injury (Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage 2 (CRASH-2 trial))[4 5] and postpartum haemorrhage (The effect of tranexamic acid on postpartum bleeding in women with moderate and severe anaemia (WOMAN trial).[6] In the context of ICH, tranexamic acid holds promise in halting early haematoma expansion, which is critical in the hyperacute phase, although its impact on clinical outcomes remains uncertain.

This study is the first systematic review and individual patient data meta-analysis (IPDMA) to pool data across multiple randomised controlled trials (RCTs) to assess the efficacy of tranexamic acid in spontaneous ICH, focusing on functional independence, mortality, haematoma expansion and its safety profile.

METHODS

This systematic review with IPDMA was prospectively registered and the protocol has been published on PROSPERO.[7] The review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Individual Participant Data (PRISMA-IPD) statement. The initial protocol was published in 2017, with an update amendment and database lock in 2025, prior to the final analysis.[7]

Search strategy and selection criteria

Searches were conducted in MEDLINE, EMBASE, Cochrane CENTRAL and Web of Science in November 2024. The search terms included "intracerebral haemorrhage", "tranexamic acid", "antifibrinolytic agents" and "haemostatic agents". Additional searches were carried out in ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (WHO ICTRP). The reference lists of relevant trials were also screened. Full details of the search strategy are provided in online supplemental search criteria.

All titles and abstracts were screened by one reviewer (CSM) to identify eligible studies. Full texts were retrieved for potentially relevant articles and assessed for inclusion. Trial eligibility was confirmed by reviewing published protocols, contacting trial investigators and examining data sharing availability. Where individual participant data were not available, aggregated outcome data were included in a secondary analysis. Eligible trials were RCTs comparing tranexamic acid with placebo in patients with acute spontaneous ICH, with treatment initiated within 12 hours of symptom onset. Trials were excluded if they focused on traumatic or secondary causes of ICH, such as arteriovenous malformations, tumours or aneurysms, except for those related to anticoagulation.

Data collection and risk of bias assessment

Principal investigators of eligible trials were contacted and invited to share anonymised individual patient data, trial protocols and related publications. Data sharing agreements were established with all collaborating trialists, and all data were securely stored in line with data protection regulations. Data were accepted in various formats and were checked for completeness and accuracy against published results. Any discrepancies, outliers or missing data were queried with the original trialists. Variables were harmonised to enable consistent analysis across trials. Continuous variables were retained in their original form where possible, and categorical variables were recoded using standard definitions. Haematoma growth was defined as a relative increase in haematoma volume (HV) of more than 33% or an absolute increase greater than 6 mL on imaging performed within 24±12 hours after randomisation.[8] Early neurological deterioration was defined as a drop of two or more points in the Glasgow Coma Scale (GCS) or an increase of four or more points in the National Institutes of Health Stroke Scale (NIHSS).[9] Haematoma location was categorised as supratentorial deep, supratentorial lobar or infratentorial.

Risk of bias for each included trial was assessed independently by two reviewers (CSM and JL) using the Cochrane Risk of Bias 2 tool.[10] Disagreements were resolved by consensus or by discussion with a third reviewer (MD). The quality of the evidence was further evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework (CSM and JL).

Outcomes

The primary outcome was functional status at 90 days, measured using the modified Rankin Scale (mRS), analysed using ordinal logistic regression to assess for a shift in the overall distribution of scores between treatment groups. Higher mRS scores indicate a worse outcome. Secondary outcomes included mortality at day 7, 28 and 90, haematoma growth,[8] early neurological deterioration,[9] thromboembolic events, seizures and the identification of patient subgroups that may benefit from tranexamic acid. Prespecified effect modifiers included age, sex, haematoma size and location, intraventricular haemorrhage, baseline systolic blood pressure, onset to treatment and prior use of antithrombotic therapy.[7]

Statistical analysis

Baseline characteristics were summarised as counts and percentages for categorical variables, and as mean (SD) or median (IQR) for continuous variables. No statistical comparisons between groups were performed, as all included studies were RCTs; any observed differences were assumed to be due to chance.

A one-stage IPDMA was performed using generalised linear mixed models in SPSS (V.29). The models included a random intercept for trial to account for clustering and between-trial heterogeneity. Heterogeneity was assessed by estimating the variance of the random intercept and formally tested using a likelihood ratio test. The difference in −2 log likelihoods was compared against a χ^2 distribution with one degree of freedom. Binary outcomes were analysed using a binomial distribution with a log link function to estimate risk ratios and 95% CIs. Ordinal outcomes were analysed using cumulative logit (proportional odds) models assuming a multinomial distribution, and results were presented as common ORs with 95% CIs. The proportional odds assumption was assessed using a likelihood ratio test comparing the proportional odds model to a non-proportional alternative. HV absolute difference was analysed using Quade non-parametric analysis of covariance (ANCOVA). Survival analysis was performed using Cox regression survival curves based on the date of death, where available, to compare survival between treatment and placebo arms. Subgroup analyses tested for interactions and stratified effects. All subgroup models included the same adjustment variables and retained the random intercept for trial. The forest plot was created with R software, V.4.2.2, using the 'forestplot' package. Missing data were not imputed.

As a prespecified secondary analysis,[7] a two-step meta-analysis was performed to include trials that were unable to share individual patient data.[11 12] For these trials, treatment effect estimates

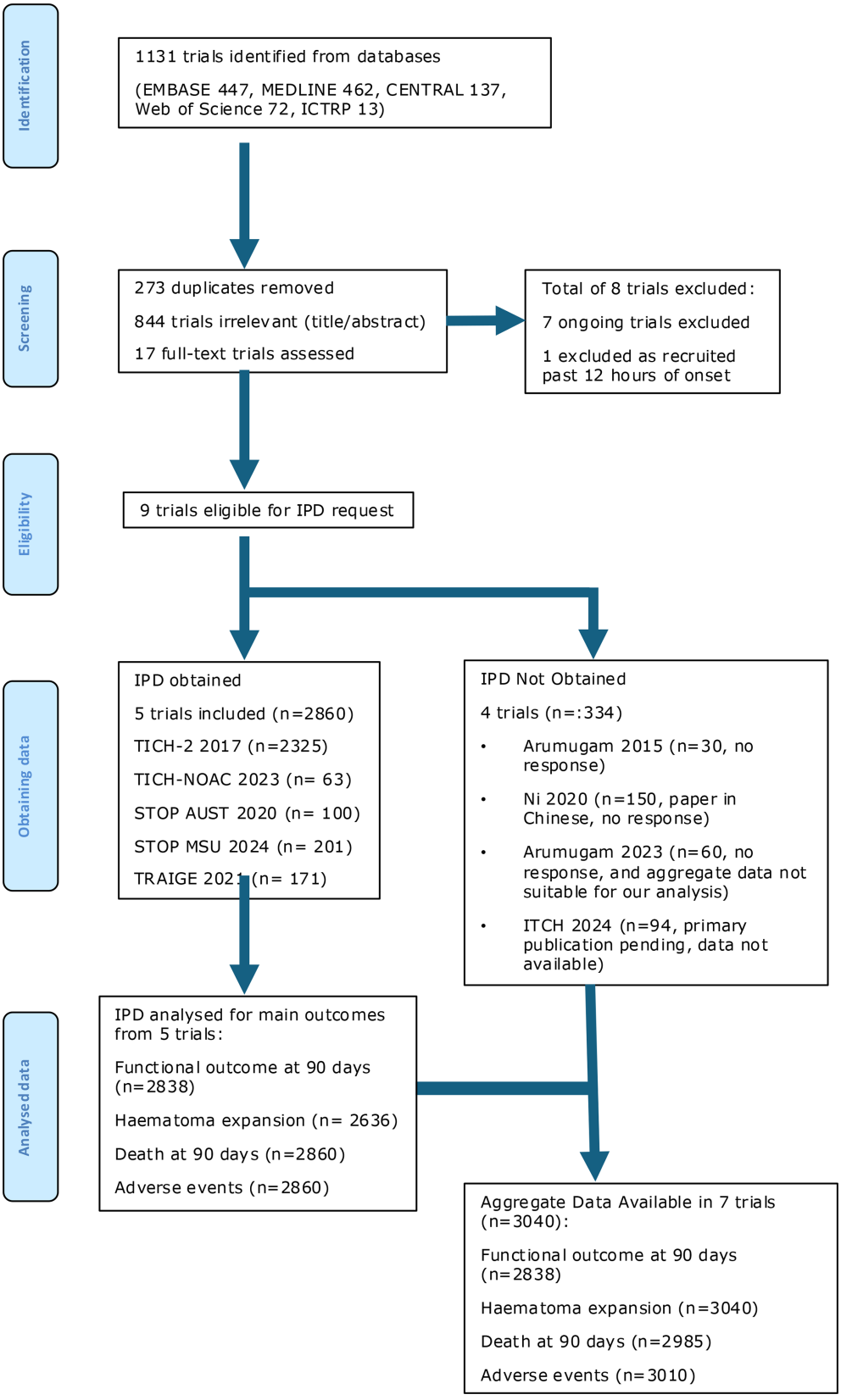

Figure 1 Study selection consort diagram (Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Individual Participant Data (PRISMA-IPD) adapted). Flow diagram showing the identification, screening, eligibility and inclusion of trials for the individual participant data meta-analysis. Reasons for exclusion are indicated. ICTRP, International Clinical Trials Registry Platform. Tranexamic acid for hyperacute primary IntraCerebral Haemorrhage (TICH 2). Tranexamic acid in patients with intracerebral haemorrhage (STOP-AUST). Tranexamic acid for acute intracerebral haemorrhage growth based on imaging assessment (TRAIGE). Tranexamic Acid for Intracerebral Hemorrhage in Patients on Non-Vitamin K Antagonist Oral Anticoagulants (TICH NOAC). Tranexamic acid versus placebo in individuals with intracerebral haemorrhage treated within 2 h of symptom onset (STOP-MSU). Intravenous Tranexamic Acid in Primary Intracerebral Hemorrhage Trial (ITCH)

Table 1 Characteristics of included randomised controlled trials

Study (year)	Country	Sample size (tranexamic acid/control)	Tranexamic acid dose and route	Onset to treatment (hours)	Key inclusion criteria	Key exclusion criteria	Imaging criteria	Risk of bias
Tranexamic acid for hyperacute primary IntraCerebral Haemorrhage (TICH-2) (2017)	UK, Denmark, Georgia, Hungary, Ireland, Italy, Malaysia, Poland, Spain, Sweden, Switzerland, Turkey	2325 (1161/1164)	2 g intravenous	8 hours	Age ≥18 years, spontaneous ICH confirmed on CT, randomised within 8 hours of symptom onset	Secondary ICH (trauma, tumour, AVM), planned surgical evacuation, GCS<5, known thromboembolic event within previous 90 days, contraindication to tranexamic acid	Baseline CT head±CTA, 24-hour CT head	Low
Tranexamic acid in patients with intracerebral haemorrhage (STOP AUST) (2020)	Australia, Finland, Taiwan	100 (50/50)	2 g intravenous	4.5 hours	Age ≥18 years, ICH on CT with spot sign on CTA, randomisation within 4.5 hours of onset, GCS>7, ICH volume <70 mL	GCS<5, pre-existing disability (mRS>4), secondary ICH (trauma, tumour, AVM), planned neurosurgical evacuation within 24 hours, recent DVT/PE (within 2 weeks)	Baseline CT head and CTA scan, 24-hour CT head	Low
Tranexamic acid for acute intracerebral haemorrhage growth based on imaging assessment (TRAIGE) (2021)	China	171 (89/82)	2 g intravenous	8 hours	Age 18–79 years, spontaneous hypertensive ICH, CTA (spot sign) or CT (blend/black hole sign) within 6 hours of symptom onset, randomisation and treatment within 8 hours, informed consent	Secondary ICH (trauma, tumour, AVM, aneurysm, haemorrhagic stroke conversion, venous sinus thrombosis, CNS infection), infratentorial ICH, GCS<8, ICH volume >70 mL, large IVH (filling one ventricle or >50% of both), major thrombotic event within past 6 months, pregnancy or breastfeeding, anticoagulant use with abnormal labs, pre-stroke mRS >2	Baseline CT head±CTA, 24-hour CT head	Low
Tranexamic Acid for Intracerebral Hemorrhage in Patients on Non-Vitamin K Antagonist Oral Anticoagulants (TICH NOAC) (2023)	Switzerland	63 (32/31)	2 g intravenous	12 hours	Age ≥18 years, non-traumatic ICH, on direct oral anticoagulation (eg, apixaban, dabigatran) with last intake within 48 hours, randomisation within 12 hours of symptom onset	GCS<5, pre-existing disability (mRS>4), secondary ICH (trauma, tumour, AVM), planned neurosurgical evacuation within 24 hours, recent DVT/PE (within 2 weeks)	Baseline CT head, 24-hour CT head	Low
Tranexamic acid versus placebo in individuals with intracerebral haemorrhage treated within 2 h of symptom onset (STOP MSU) (2024)	Australia, Vietnam, New Zealand, Finland, Taiwan	201 (103/98)	2 g intravenous	2 hours	Age ≥18 years, primary ICH confirmed on non-contrast CT, treatment possible within 2 hours of symptom onset	GCS<8, brainstem ICH, ICH volume >70 mL, secondary ICH causes, history of thrombotic events within 90 days, haemorrhagic diathesis	Baseline CT head and 24-hour CT head	Low

Summary of the five trials contributing individual participant data to the meta-analysis. Trials are described by country, sample size, tranexamic acid dosing regimen, treatment time window, imaging protocol and risk of bias assessment.
AVM, arteriovenous malformation; CTA, CT angiography; DVT, deep vein thrombosis; GCS, Glasgow Coma Scale; IVH, intraventricular haemorrhage; mRS, modified Rankin Scale; PE, pulmonary embolism.

were extracted from publications. These were combined with summary results from individual patient data trials using a random-effects model in RevMan. Between-study heterogeneity was assessed using the I^2 statistic.

Sensitivity analyses were conducted to test the robustness of findings. These included analysis of the 90-day mRS as a binary outcome (0–3 vs 4–6) and included early deaths (within 24 hours) as a surrogate for haematoma expansion. The prespecified random-effects model was retained for the primary analysis, with a fixed-effect model analysis done to confirm robustness of the findings given the evidence of no heterogeneity.

RESULTS

Study identification and selection

A total of 1131 records were identified through database searches, including EMBASE (n=447), MEDLINE (n=462), CENTRAL (n=137), Web of Science (n=72) and ICTRP (n=13). Three additional trials were identified from other systematic reviews. After removing 273 duplicates and excluding 844 irrelevant records based on title and abstract, 17 full-text trials were screened for eligibility. Of these, one trial was excluded because participants were recruited beyond 12 hours from symptom onset, and seven trials were ongoing at the time of screening. Nine trials met criteria for individual participant data requests, totalling 3194 participants. Individual patient data were successfully obtained from five RCTs, contributing a combined total of 2860 participants (94% of all participants). The remaining four trials did not provide individual patient data due to lack of author response, ongoing publication or language barriers. Relevant aggregate data were available for seven, comprising 3040 participants in total. This is illustrated in figure 1.

Study characteristics

The five included trials were conducted in multiple countries between 2017 and 2024. All trials investigated the effect of 2 g intravenous tranexamic acid administered within 2–12 hours of ICH onset. Most trials also included baseline CT imaging and follow-up CT at 24 hours. The trials also incorporated baseline CT angiography. All included trials were judged to be at low risk of bias and used blinded outcome assessment (online supplemental figure 1). A summary of trial characteristics is provided in table 1.[13–17] There were no important issues identified when checking individual patient data.

The two-stage aggregate data analysis incorporated data from Arumugam *et al* 2014 (n=30) and Ni *et al* 2020 (n=150), extending the evidence base.[11 18] The TANICH trial (n=60) was identified, but its published outcome data were not suitable for inclusion.[12] The Intravenous Tranexamic Acid in Primary Intracerebral Hemorrhage Trial (ITCH) trial (n=96) was unable to share their data with us as they were awaiting publication of their primary results (NCT04742205).

Baseline characteristics

A total of 2860 patients were included, with 1435 assigned to tranexamic acid and 1425 to placebo. Baseline demographic, clinical and radiological characteristics were well balanced between groups. The mean age was 68 (±14.1) years and 54% were female. Median NIHSS was 13 (7–18) in the tranexamic acid group and 12 (6–18) in the placebo group, and median GCS was 15 (12–15) in both arms. Median onset to randomisation was 3.5 hours in both groups. Baseline HV, intraventricular haemorrhage, haematoma location, and imaging markers of haematoma expansion were similar between groups. Full baseline characteristics are presented in table 2.

Table 2 Participant-level baseline demographic, clinical and radiographic characteristics by treatment group

Baseline patient characteristics variables	N	Tranexamic acid (n=1435)	Placebo (n=1425)
Age, years; mean (SD)*	2860	68.2 (14.1)	68.0 (14.1)
Female sex (n, %)	2860	760 (54)	770 (53)
Premorbid mRS; median (IQR)*	2860	0 (0–1)	0 (0–1)
Medical history (n, %)			
Hypertension	2689	830 (61.7)	842 (62.7)
Diabetes	2858	213 (14.9)	185 (13.0)
Ischaemic heart disease	2796	127 (9.1)	112 (8.1)
Prior stroke or transient ischaemic attack	2856	199 (13.9)	181 (12.7)
Antiplatelet use	2857	360 (25.2)	330 (23.2)
Statin use	2346	359 (25.2)	354 (24.9)
NIHSS; median (IQR)*	2839	13 (7–18)	12 (6–18)
Glasgow Coma Scale; median (IQR)	2840	15 (12–15)	15 (12–15)
Systolic blood pressure, mm Hg; median (IQR)*	2856	170 (153–189)	171 (153–190)
Diastolic blood pressure, mm Hg; median (IQR)	2855	91.5 (80–105)	92 (81–105)
Weight, kg; median (IQR)	1997	73.4 (63.5–85.0)	75 (65–88.7)
Glucose, mmol/L; median (IQR)	2357	6.7 (5.7–8.1)	6.5 (5.7–7.8)
Onset to randomisation, hours; median (IQR)*	2857	3.5 (2.4–5.0)	3.5 (2.3–4.9)
Onset to treatment, hours; median (IQR)	2835	3.8 (2.8–5.5)	3.8 (2.7–5.4)
ICH cause (n, %)	2858		
Cerebral amyloid angiopathy		63 (4.4)	63 (4.4)
Hypertension		755 (52.6)	768 (54)
Secondary causes		45 (3.1)	57 (4)
Unknown		572 (39.9)	535 (37.6)
Baseline radiological variables			
Onset to CT scan; median (IQR)	2860	2.17 (1.5–2.2)	2.15 (1.4–3.6)
Baseline intraparenchymal volume, mL; median (IQR)*	2807	14.1 (6.0–31.9)	12.8 (5.3–30.5)
Intraventricular haemorrhage presence at baseline (n, %)	2854	412 (28.7)	404 (28.4)
Baseline intraventricular volume, mL; median (IQR)	816	6.6 (2.1–14.8)	5.6 (1.7–12.7)
Intracerebral haemorrhage location (n, %)*	2829		
Supratentorial deep		933 (65.9)	929 (65.9)
Supratentorial lobar		406 (28.8)	410 (28.9)
Infratentorial		76 (5.4)	74 (5.2)
CT angiography spot sign (n, %)	739	142 (38.2)	138 (37.6)
CT blackhole sign (n, %)	2331	205 (17.4)	200 (17.3)
CT island sign (n, %)	1386	111 (15.6)	111 (16.5)
CT blend sign (n, %)	2645	263 (19.8)	253 (19.2)

Data are n (%), mean (SD) or median (IQR).
*Minimisation criteria.
GCS, Glasgow Coma Scale; ICH, intracerebral haemorrhage; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

Table 3 One-stage individual patient data analysis

Outcomes:	N	Tranexamic acid (n, %)	Placebo (n, %)	Adjusted OR	95% CI
Clinical outcomes					
Primary outcome					
mRS at 90 days (n, %)	2741			Ordinal 0.93	0.81 to 1.07
mRS 0		37 (2.6)	32 (2.3)		
mRS 1		152 (10.7)	167 (11.8)		
mRS 2		242 (17.0)	217 (15.3)		
mRS 3		235 (16.5)	240 (17)		
mRS 4		261 (18.3)	287 (20.3)		
mRS 5		192 (13.5)	179 (12.7)		
mRS 6		304 (21.4)	293 (20.7)		
mRS (median)		4 (2–5)	4 (2–5)		
mRS>3* (n, %)	2741	757 (53.2)	759 (53.6)	Binary 0.87	0.72 to 1.06
Secondary outcome					
Early neurological deterioration (n, %)	2372	268 (22.6)	268 (22.6)	Binary 0.92	0.73 to 1.15
Death by day 7 (n, %)	2343	123 (10.1)	142 (11.8)	Binary 0.70	0.51 to 0.95
Death by day 28 (n, %)	2343	232 (19.1)	235 (19.5)	Binary 0.82	0.63 to 1.07
Death by day 90 (n, %)	2760	304 (21.2)	293 (20.2)	Binary 0.96	0.76 to 1.21
Death by day 90 (Cox regression) (n, %)	2761	295 (21.7)	276 (20.3)	Hazard 0.96	0.81 to 1.13
SAE at 90 days**					
Seizures (n, %)	2760	86 (5.9)	90 (6.4)	Binary 0.92	0.67 to 1.27
Thromboembolic (n, %)	2760				
Arterial		29 (1.6)	23 (2.0)	Binary 1.04	0.70 to 1.54
Venous		49 (3.4)	43 (3.0)	Binary 1.11	0.73 to 1.70
All		77 (4.6)	66 (5.4)	Binary 1.07	0.78 to 1.47

Radiological outcomes	N	Tranexamic acid (n, %)	Placebo (n, %)	Adjusted OR/group comparison (Quade F test)	95% CI/degree of freedom
HV absolute growth (median (IQR), mL)	2636	0.78 (−0.22–4.83)	0.80 (−0.12–5.50)	F 4.48	1, 2594
HV growth (>6 mL or 33%)	2594	376 (28.5)	412 (31.3)	Binary 0.81	0.68 to 0.97
HV growth (>6 mL or 33%) or died within 24 hours*	2625	394 (29.4)	429 (32.2)	Binary 0.82	0.69 to 0.98

Primary, secondary and radiological outcome measures by treatment group.
Data are n (%), mean (SD) or median (IQR). Adjusted common OR, 95% CI and p values are reported for each comparison.
*Sensitivity analyses.
†SAEs have been reported per patient, not per event.
HV, haematoma volume; mRS, modified Rankin Score; SAE, serious adverse event.

Primary outcomes

The primary outcome was functional status at 90 days, measured using the mRS and analysed using ordinal logistic regression to assess for a shift in the distribution of scores between treatment groups. The adjusted common OR in the ordinal analysis testing for a shift towards worse mRS was insignificant, 0.93 (95% CI 0.81 to 1.07) (table 3). The proportional odds assumption was held (p=0.08). The likelihood ratio test comparing fixed and random-effects models showed no evidence of meaningful between-trial heterogeneity (χ^2=42 102.96, p<0.001), supporting consistency of treatment effect across trials. The mRS shift plot confirmed the similarity in functional outcome distribution, with no significant directional effect (online supplemental figure 2). There was also no evidence of publication bias (online supplemental figure 3). Summary of findings assessed on GRADE suggests that tranexamic acid likely does not reduce long-term dependence (low certainty) (online supplemental table 1).

Secondary outcomes

Early neurological deterioration occurred in 268/1188 (22.6%) of patients receiving tranexamic acid and 268/1184 (22.6%) of those receiving placebo, yielding an adjusted OR of 0.92 (95% CI 0.73 to 1.15) (table 3). All-cause mortality at day 7 was significantly lower in the tranexamic acid group compared with placebo 123/1213 (10.1%) versus 142/1203 (11.8%); adjusted OR 0.70, 95% CI 0.51 to 0.95, very low certainty (table 3). However, this difference was not sustained at day 28, 232/1213 (19.1%) versus 235/1203 (19.5%); adjusted OR 0.82, 95% CI 0.63 to 1.07) or at day 90 304/1435 (21.0%) versus 293/1425 (20.2%); adjusted OR 0.96, 95% CI 0.76 to 1.21, low certainty) (table 3). The Cox regression survival analysis showed that cumulative survival was similar between the tranexamic acid and placebo groups over the 90-day follow-up period (online supplemental figure 4). The HR for death with tranexamic acid compared with placebo is insignificant (adjusted HR 0.96 (95% CI 0.81 to 1.13)) (table 3).

There was a small but statistically significant difference in absolute HV growth between treatment groups after adjusting for baseline covariates using the Quade non-parametric ANCOVA (F(1, 2594)=4.48) (table 3). This significant difference was consistent across categorical definitions of haematoma expansion: HV growth >6 mL or >33% from baseline occurred in 376/1321 (28.5%) in the tranexamic acid group versus 412/1315

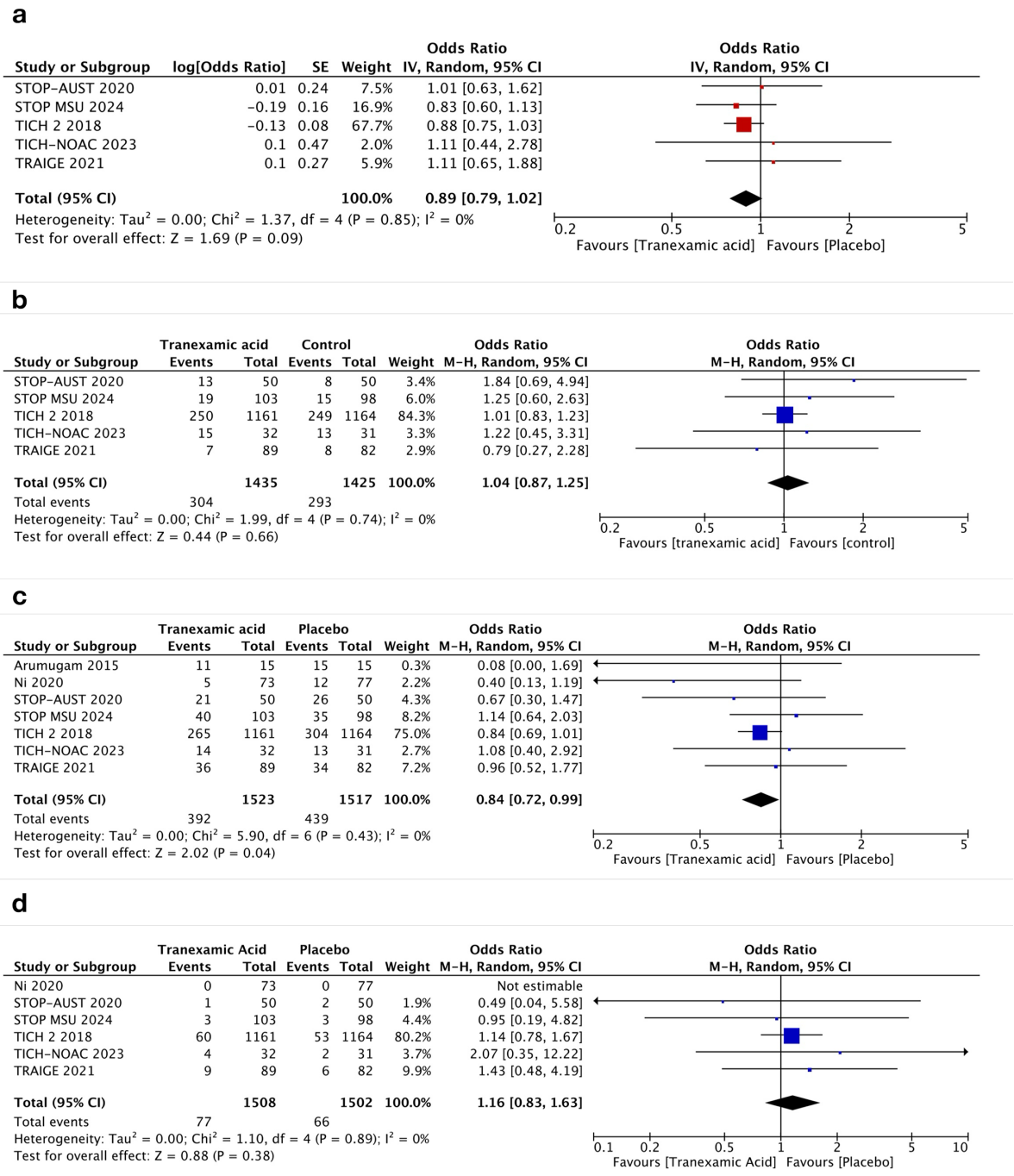

Figure 2 Aggregate study-level meta-analyses. (a) Modified Rankin scale at 90 days (ordinal analysis). OR<1 would indicate lower odds of a worse functional outcome with tranexamic acid. (b) Death at 90 days. OR<1 would indicate lower odds of death at 90 days with tranexamic acid. (c) Haematoma expansion. OR<1 would indicate lower odds haematoma expansion with tranexamic acid. (d) Thromboembolic adverse events. OR<1 would indicate lower odds of thromboembolic events with tranexamic acid. Tranexamic acid for hyperacute primary IntraCerebral Haemorrhage (TICH 2). Tranexamic acid in patients with intracerebral haemorrhage (STOP-AUST). Tranexamic acid for acute intracerebral haemorrhage growth based on imaging assessment (TRAIGE). Tranexamic Acid for Intracerebral Hemorrhage in Patients on Non-Vitamin K Antagonist Oral Anticoagulants (TICH NOAC). Tranexamic acid versus placebo in individuals with intracerebral haemorrhage treated within 2 h of symptom onset (STOP-MSU). Intravenous Tranexamic Acid in Primary Intracerebral Hemorrhage Trial (ITCH).

(31.3%) in the placebo group (adjusted OR 0.81, 95% CI 0.68 to 0.97, low certainty) (table 3).

Serious adverse events at 90 days were comparable between the tranexamic acid and placebo groups. Seizures occurred in 86/1435 (5.9%) of patients receiving tranexamic acid and 90/1425 (6.4%) receiving placebo (adjusted OR 0.92, 95% CI 0.67 to 1.27; moderate certainty). Thromboembolic events occurred in 77/1435 (4.6%) of the tranexamic acid group and 66/1425 (5.4%) of the placebo group (adjusted OR 1.06, 95% CI 0.77 to 1.45, moderate certainty). When disaggregated, arterial events were reported in 29/1435 (2%) and 23/1425 (1.6%), and venous events in 49/1435 (3.4%) and 43/1425 (3.0%) of patients in the tranexamic acid and placebo groups, respectively (table 3). None of these differences was statistically significant. These results suggest that tranexamic acid was not associated with an increased risk of seizures or thromboembolic complications at 90 days.

Characteristic	N	OR (95% CI)	P	Interaction P
Onset to treatment				0.93
...<=2 hours	337	1.09 [0.729 - 1.629]	0.67	
...>2 - <=4.5 hours	1366	0.87 [0.712 - 1.052]	0.15	
...>4.5hr -12hours	1008	0.95 [0.758 - 1.190]	0.7	
Age				0.24
...<70	1343	0.805 [0.662- 0.978]	0.03	
...>=70	1400	1.008 [0.828 - 1.227]	0.94	
Sex				1
...Female	1473	0.921 [0.764 - 1.110]	0.387	
...Male	1268	0.927 [0.757 - 1.135]	0.462	
Systolic blood pressure				0.58
...<170 mmHg	1473	0.874 [0.718 -1.064]	0.18	
...>=170 mmHg	1331	0.954 [0.785 -1.160]	0.18	
NIHSS score				0.39
...<15	1635	0.922 [0.776 - 1.096]	0.254	
...>=15	1106	0.874 [0.694 - 1.101]	0.254	
Intra-ventricular haemorrhage				0.63
...Yes	799	0.963 [0.740 - 1.252]	0.777	
...No	1942	0.900 [0.766 - 1.058]	0.201	
History of antiplatelet therapy				0.7
...Yes	661	0.983 [0.737 - 1.312]	0.909	
...No	2080	0.917 [0.784 - 1.071]	0.274	
History of anticoagulant therapy				0.69
...Yes	60	0.764 [0.206 - 2.833]	0.68	
...No	2681	0.925 [0.806 - 1.062]	0.27	
CT angiogram Spot positive				0.97
...Yes	264	1.058 [0.671- 1.670]	0.807	
...No	436	1.006 [0.709 - 1.429]	0.971	
Non-contrast CT postive				0.05
...Yes	888	0.924 [0.723 - 1.181]	0.527	
...No	822	0.907 [0.709-1.160]	0.436	
Haematoma location				0.51
...Supra-tentorial lobar	801	0.888 [0.624 - 1.263]	0.766	
...Supra-tentorial deep	1793	0.936 [0.791 - 1.107]	0.776	
...Infratentorial	146	0.559 [0.300 - 1.041]	0.067	
Baseline ICH volume				1
...<30	2022	0.943 [0.807 - 1.103]	0.465	
...30-60	442	0.810 [0.573 - 1.145]	0.232	
...>60	277	1.060 [0.618 - 1.819]	0.832	
Overall	**2741**	**0.929 [0.81-1.065]**	**0.292**	

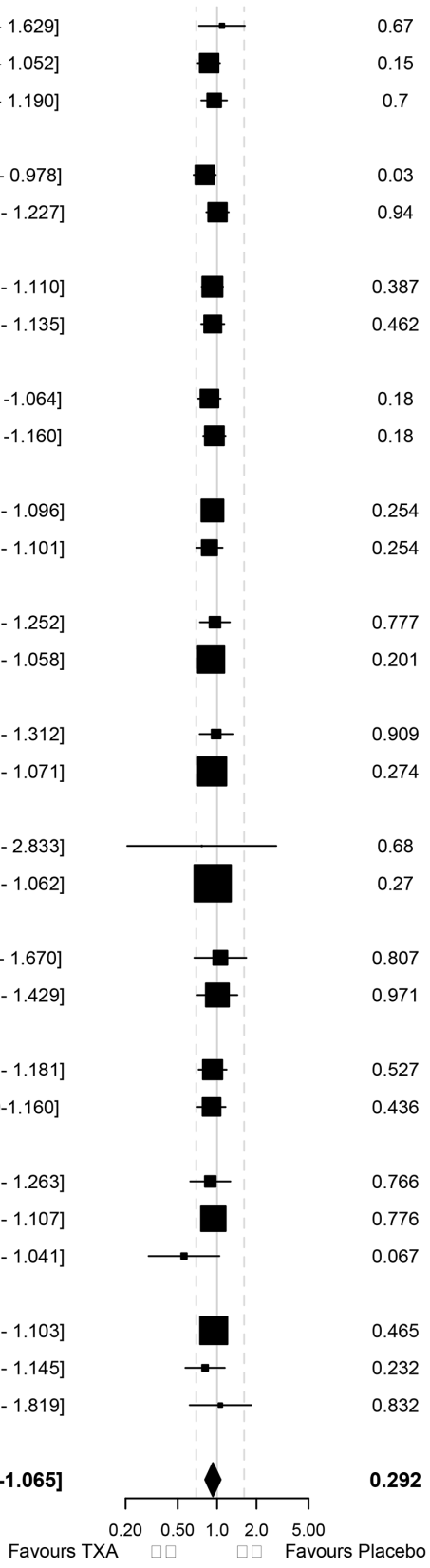

Figure 3 One-stage subgroup analysis of the effect of tranexamic acid on modified Rankin Scale at 90 days. Forest plot of adjusted common ORs (with 95% CIs) for the primary outcome across prespecified subgroups. ICH, intracerebral haemorrhage; NIHSS, National Institutes of Health Stroke Scale.

In the study level aggregate data analysis, the proportion of patients with a shift towards worse functional outcome using the mRS at 90 days showed no significant difference between the tranexamic acid and placebo groups (OR 0.90, 95% CI 0.78 to 1.03; I^2=0%, 5 trials, 2838/3040 (93%)). For mortality, there was no significant difference in death at 90 days (OR 1.04, 95% CI 0.87 to 1.25; I^2=0%, 7 trials, 3040/3040 (100%)) (figure 2a). Tranexamic acid was associated with a statistically significant reduction in haematoma expansion compared with placebo (OR 0.84, 95% CI 0.72 to 0.99; I^2=0%, 7 trials, 3040/3040 (100%)). With regards to safety outcomes, there was no significant difference in the incidence of thromboembolic adverse events (OR 1.16, 95% CI 0.83 to 1.63; I^2=0%, 6 trials, 3010/3040 (99%)) (figure 2). There was no significant heterogeneity observed across any of the outcomes, in keeping with the primary analysis (figure 2).

Subgroup analyses

Prespecified subgroup analyses were performed to assess whether the effect of tranexamic acid varied across clinical and radiological strata. No statistically significant interaction was observed in any subgroup, including by age, sex, blood pressure, NIHSS score, onset-to-treatment time, HV or location, presence of intraventricular haemorrhage, prior antiplatelet or anticoagulant use, or CT/CT angiography features such as spot sign and non-contrast haematoma markers (figure 3). Any possible signals noted were not supported by an interaction effect across the variable and may represent a chance finding (figure 3).

Sensitivity analyses

There were no single-centre trials, trials with high risk of bias or trials lacking a published protocol included in the one-stage IPDMA.

Binary analysis of the mRS, categorising outcomes into favourable (mRS≤3) and unfavourable (mRS>3), showed no significant treatment effect. Poor outcome occurred in 757/1423 (53.2%) of patients in the tranexamic acid group compared with 759/1415 (53.6%) in the placebo group (adjusted OR 0.87, 95% CI 0.71 to 1.06) (table 3).

Sensitivity analysis for haematoma expansion accounted for participants who died within the first 24 hours, as these patients would not have undergone repeat imaging. When including early death (within 24 hours) in the composite outcome, the event occurred in 394/1338 (29.4%) in the tranexamic acid group compared with 429/1331 patients (32.2%) in the placebo group (adjusted OR 0.82, 95% CI 0.69 to 0.98), again showing a statistically significant reduction with tranexamic acid (table 3).

A fixed-effect model was performed as a sensitivity analysis due to the lack of formal statistical evidence for between-trial heterogeneity in baseline outcome risk. Results were consistent with the primary analysis (online supplemental table 2).

CONCLUSIONS

This systematic review and IPDMA of five RCTs, including patients with direct oral anticoagulant (DOAC) associated ICH, found no significant difference in functional outcome at 90 days. Tranexamic acid was associated with a small yet significant reduction in haematoma expansion and early mortality at day 7. These findings were consistent across clinical and radiological subgroups and robust in sensitivity analyses.

The reduction in early mortality likely reflects early stabilisation of the haematoma through limitation of rebleeding or expansion. However, this effect did not translate into improved long-term functional outcome. This may relate to modest absolute reductions in HV, treatment being administered too late in the course of injury or insufficient power to detect small but clinically meaningful differences. Late harm appears unlikely, as large, randomised trials have not demonstrated increased vascular occlusive events,[4 13 19] and the short half-life of tranexamic acid limits sustained biological effects. Longer-term outcomes are more plausibly driven by peri-haematomal oedema, haematoma location, intraventricular extension and comorbidity.

In the subgroup of patients with DOAC-associated ICH, no interaction between anticoagulant status and treatment effect was observed. Theoretically, tranexamic acid may have a greater benefit in anticoagulant-related haemorrhage by stabilising clot formation in the setting of impaired haemostasis. The number of DOAC-associated cases was limited in our analysis and may have been underpowered to detect a modest effect.

Previous meta-analyses, including a recent Cochrane review, reported similar findings; tranexamic acid appeared to reduce haematoma expansion, but there was no convincing evidence of improved functional outcomes.[20–26] In our subgroup analysis, tranexamic acid was not associated with better clinical outcomes with positive radiological markers such as the CT angiogram spot sign and non-contrast CT markers. This is in keeping with findings from another IPDMA.[27 28] Our IPDMA approach allowed harmonisation of outcome definitions, covariate adjustment and detailed subgroup analyses across 90% of available individual patient data. However, the dataset was numerically dominated by TICH-2 (81% of participants), and pooled estimates largely reflect that study population. Effect estimates were consistent across trials, reproduced in sensitivity analyses and showed no between-trial heterogeneity. Missing data were not imputed, and individual participant data were unavailable from some smaller trials, which may have reduced precision.

In summary, tranexamic acid may reduce early haematoma growth and short-term mortality, but without improving long-term outcomes in unselected patients with spontaneous ICH. Larger ongoing trials such as TICH-3 and INTRINSIC will be important in clarifying tranexamic acid's role in early mortality, particularly in patients treated in less than 4.5 hours, on anticoagulants and with expansion-prone bleeds.[29 30] Tranexamic acid may also have a greater impact when delivered as part of a structured care bundle incorporating rapid blood pressure control, anticoagulation reversal and timely neurosurgical evaluation.[31 32] Even a small treatment may have public health significance, especially in the context of an effective care bundle, given the global burden of ICH.

Author affiliations
[1]Stroke Medicine, University of Nottingham, Nottingham, UK
[2]Department of Medicine, National University of Malaysia Faculty of Medicine, Cheras, Malaysia
[3]Stroke, Division of Clinical Neuroscience, University of Nottingham, Nottingham, UK
[4]Stroke, Mental Health & Clinical Neurosciences, University of Nottingham, Nottingham, UK
[5]Neurology, Beijing Tiantan Hospital, Beijing, China
[6]Department of Medicine, Melbourne Brain Centre, Parkville, Victoria, Australia
[7]Department of Clinical Haematology, Oxford University Hospitals NHS Foundation Trust, Oxford, UK
[8]Neurology, Beijing Tiantan Hospital Affiliated to Capital Medical University, Beijing, China
[9]Neurology and Stroke Center, University Hospital Basel, Basel, Switzerland
[10]Helsinki University Central Hospital, Helsinki, Finland
[11]The Royal Melbourne Hospital City Campus, Parkville, Victoria, Australia
[12]Neurology, The Royal Melbourne Hospital, Melbourne, Victoria, Australia
[13]Melbourne Medical School, Melbourne Brain Centre, Parkville, Victoria, Australia
[14]Melbourne Brain Centre, The Royal Melbourne Hospital, Melbourne, Victoria, Australia

[15]Radiological Sciences, Division of Clinical Neuroscience, University of Nottingham, Nottingham, UK
[16]Brain Repair and Rehabilitation, University College London Institute of Neurology, London, UK
[17]Neurology, Christian Medical College and Hospital Ludhiana, Ludhiana, Punjab, India
[18]Centre for Clinical Brain Sciences, The University of Edinburgh Centre for Clinical Brain Sciences, Edinburgh, UK
[19]Stroke Trials Unit, University of Nottingham, Nottingham, UK
[20]Stroke, University of Nottingham Division of Stroke, Nottingham, UK

Contributors CSM: protocol development, statistical analysis, data interpretation, manuscript writing, risk of bias and GRADE analysis. ZKL: protocol development. LJW: statistical analysis and data interpretation. JL: risk of bias and GRADE analysis. CM: collaborator. MD: protocol development, risk of bias analysis. LL: collaborator. AAP: collaborator. AM: collaborator. NY: collaborator. HZ: collaborator. SD: collaborator. GAD: collaborator. JDP: collaborator. RAD: collaborator. DJS: collaborator. RA-SS: protocol development. PMB: protocol development, statistical analysis, data interpretation, manuscript writing. NS: protocol development, statistical analysis, data interpretation, manuscript writing. Guarantor. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Competing interests CSM: involved in the ongoing TICH-3 trial. ZKL: contributor to the TICH-2 trial. LJW: contributor to TICH-2 and TICH-3 trials. JL: involved in the TRIAGE trial. LL: holds research grant and is involved in the TRIAGE trial. NY: holds research grants and involved in STOP-AUST and STOP-MSU trials. Received honoraria for educational activities from Eli Lilly and Novo Nordisk. CSM, HZ, SD, GAD, AM: involved in STOP-AUST and STOP-MSU trials. AM: receives consulting fees from Boehringer-Ingelheim and sits on the committee board for World Stroke Forum. JDP: involved in the INTRINSIC trial; President of the World Stroke Congress. RAD: contributor to TICH-2 and TICH-3 trials. DJS and AAP: holds research and is involved in TICH NOAC. PMB: contributor to TICH-2 and TICH-3 trials. Holds NIHR and BHF grants paid to the University of Nottingham. Receives lecture/consulting fees from Phagenesis, Roche, DiaMedica; holds stock options in CoMind. Industry Committee Co-Chair, WSC. RA-SS: involved in grant applications and delivery of TICH-2 and TICH-3 trials. Holds two NIHR grants paid to the University of Edinburgh. Past President, British & Irish Association of Stroke Physicians. NS: holds research grants for TICH-2, DASH and TICH-3 trials.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants. Ethical approval was not required for our study as only anonymised data from previously published trials were used. Participants gave informed consent to participate in the study before taking part. No participant withdrew consent for sharing anonymised data.

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ORCID iDs
Chaamanti Sivakumar Menon https://orcid.org/0009-0006-3298-3234
Zhe Kang Law https://orcid.org/0000-0002-7900-9037
Lisa Jane Woodhouse https://orcid.org/0000-0002-4472-1999
Jingyi Liu https://orcid.org/0000-0001-7360-0267
Liping Liu https://orcid.org/0000-0003-2943-055X
Alexandros A Polymeris https://orcid.org/0000-0002-9475-2208
Robert A Dineen https://orcid.org/0000-0002-9523-2546
David J Seiffge https://orcid.org/0000-0003-3890-3849
Rustam Al-Shahi Salman https://orcid.org/0000-0002-2108-9222
Philip M Bath https://orcid.org/0000-0003-2734-5132

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