Tenecteplase versus standard medical treatment for basilar artery occlusion within 24 h (TRACE-5): a multicentre, prospective, randomised, open-label, blinded-endpoint, superiority, phase 3 trial

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Summary

Background The efficacy and safety of intravenous thrombolysis with tenecteplase within 24 h after stroke onset due to basilar artery occlusion are not well studied. We aimed to assess whether intravenous tenecteplase administered within 24 h after symptom onset improved functional outcome compared with standard medical treatment in patients with basilar artery occlusion.

Methods TRACE-5 was a prospective, randomised, open-label, blinded-endpoint, superiority, phase 3 trial conducted at 66 stroke centres in China. We included patients aged 18 years or older with stroke due to basilar artery occlusion who were eligible for intravenous thrombolytics within 24 h of stroke onset or the time they were last known to be well and had a pre-stroke modified Rankin scale (mRS) score of 3 or less (scores range from 0 to 6, with higher scores indicating greater disability). Patients were randomly assigned to receive a single intravenous bolus of tenecteplase (0·25 mg/kg; maximum 25 mg) within 24 h after symptom onset or standard medical treatment (which could include intravenous alteplase at 0·9 mg/kg, maximum 90 mg, within 4·5 h of symptom onset; anticoagulation; or antiplatelets), with or without endovascular thrombectomy. The primary outcome was a score of 0–1 on the mRS or return to the baseline mRS score (if the baseline pre-stroke mRS score was 2–3) at 90 days. Safety outcomes were symptomatic intracranial haemorrhage and death. The primary outcome and safety outcomes were assessed in all randomly assigned participants included in their originally assigned groups. This trial is registered with ClinicalTrials.gov, NCT06196320.

Findings Between Jan 24, 2024, and June 20, 2025, 452 patients were enrolled (mean age 66·4 years [SD 11·2], 321 [71%] males, and 131 [29%] females), of whom 222 (49%) subsequently underwent thrombectomy; 221 were randomly assigned to receive tenecteplase and 231 to receive standard medical treatment. Alteplase was used in 80 (35%) of the patients in the standard medical treatment group. An mRS score of 0–1 or return to the baseline mRS score occurred in 83 (38%) patients in the tenecteplase group and 66 (29%) patients in the standard medical treatment group (adjusted relative rate 1·50 [95% CI 1·09–2·08], p=0·014). Symptomatic intracranial haemorrhage within 36 h occurred in four (2%) patients in the tenecteplase group and seven (3%) patients in the standard medical treatment group (adjusted relative rate 0·58 [95% CI 0·17–1·99]). All-cause mortality at 90 days was similar between groups (65 [29%] patients in the tenecteplase group and 71 [31%] patients in the standard medical treatment group; adjusted relative rate 0·87 [95% CI 0·62–1·22]), as was the proportion of patients with an mRS score of 5–6 at 90 days (82 [37%] *vs* 89 [39%]; 0·87 [0·65–1·18]).

Interpretation In this trial involving Chinese patients with ischaemic stroke due to basilar artery occlusion, tenecteplase within 24 h after stroke onset improved functional outcome compared with standard medical treatment. The incidence of symptomatic intracranial haemorrhage and death was similar.

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Introduction

Basilar artery occlusion is a rare but devastating subtype of large-vessel occlusion ischaemic stroke with high rates of disability and mortality (up to 80–90%) if recanalisation does not occur.[1,2] An individual patient data meta-analysis of four randomised controlled trials supports the robust

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See Online for appendix

Research in context

Evidence before this study

Endovascular thrombectomy is established as an effective treatment for basilar artery occlusion within 24 h of stroke onset according to four phase 3 randomised controlled trials. However, access to endovascular thrombectomy remains limited worldwide, particularly in low-income and middle-income countries. As the first-line therapy for ischaemic stroke within 4·5 h, intravenous thrombolysis is widely used and might offer additional benefits for patients with basilar artery occlusion presenting within 24 h after onset, especially with the use of the newer-generation thrombolytic, tenecteplase. We searched PubMed and MEDLINE for randomised trials published between Jan 1, 2000, and Oct 31, 2025, using the terms "tenecteplase", "basilar artery occlusion", and "study" or "clinical trial". To date, no phase 3 randomised controlled trial has been published evaluating the efficacy and safety of tenecteplase in patients with confirmed basilar artery occlusion within 24 h of symptom onset. One phase 3 trial compared alteplase with control, administered between 4·5 h and 24 h in patients with posterior circulation stroke, but it mainly included patients with mild strokes, did not require basilar artery occlusion, and excluded patients intended for thrombectomy.

Added value of this study

TRACE-5 is the first phase 3 trial to compare tenecteplase with standard medical treatment in patients with basilar artery occlusion presenting within 24 h of symptom onset. Our findings showed that tenecteplase administered within 24 h of symptom onset improved excellent functional outcomes without increased safety concerns for patients with basilar artery occlusion. This pragmatic trial allowed the use of alteplase in the control group and thrombectomy in both groups, closely reflecting real-world clinical practice.

Implications of all the available evidence

The TRACE-5 trial supports tenecteplase as an effective option for treating basilar artery occlusion within 24 h, both in centres that can provide endovascular thrombectomy and those that cannot. Using single-bolus tenecteplase to complement endovascular thrombectomy without advanced imaging for patient selection enhances its feasibility for future implementation.

benefit of endovascular thrombectomy for basilar artery occlusion within 24 h of stroke onset.[3–7] However, immediate access to endovascular thrombectomy is currently limited, with a median global thrombectomy access rate of about 3% and access rates of less than 1% in 27% of countries.[8,9] Therefore, intravenous thrombolytic therapies within 4·5 h of onset remain the standard of care in basilar artery occlusion, particularly in patients who initially present to stroke centres without the capacity to perform endovascular thrombectomy.[10,11] Given the dismal prognosis of basilar artery occlusion, further research on whether the time window for intravenous thrombolysis can be extended up to 24 h is warranted.

A previous trial showed the possibility of extending the time window for intravenous thrombolysis to 24 h in patients with posterior circulation stroke using alteplase.[12] However, the trial population primarily included patients with mild strokes, basilar artery occlusion was not required, and those scheduled for thrombectomy were excluded. Therefore, evidence for thrombolytics, with or without endovascular thrombectomy, in the extended time window for patients with basilar artery occlusion is scarce. Tenecteplase, a modified form of human tissue plasminogen activator with higher fibrin specificity and longer half-life,[11] was shown to be non-inferior to alteplase in randomised trials and even superior to alteplase by a study-level meta-analysis,[13] and proven to be effective for anterior circulation large-vessel occlusion in patients not receiving endovascular thrombectomy within 24 h after onset with a numerically higher rate of symptomatic intracranial haemorrhage.[14,15] Tenecteplase was also associated with increased reperfusion before endovascular thrombectomy versus alteplase in basilar artery occlusion, potentially offering additional benefit for these patients.[16,17]

The Tenecteplase Reperfusion Therapy in Acute Ischaemic Cerebrovascular Events-5 (TRACE-5) trial was designed to test whether intravenous tenecteplase at a dose of 0·25 mg per kilogram of bodyweight, administered within 24 h after symptom onset, improved functional outcome compared with standard medical treatment in patients with basilar artery occlusion. The use of endovascular thrombectomy was at the discretion of the treating physician.

Methods

Study design and participants

TRACE-5 was a prospective, randomised, open-label, blinded-endpoint, superiority, phase 3 trial conducted at 66 stroke centres in China. The trial included patients with acute ischaemic stroke due to basilar artery occlusion who were aged 18 years or older and eligible for intravenous thrombolytics within 24 h of stroke onset or the time they were last known to be well. Basilar artery occlusion was defined as a potentially retrievable occlusion of the basilar artery, which could be a near (defined as 99% stenosis with string sign) or complete occlusion of the basilar artery on CT angiography (CTA) or magnetic resonance angiography (MRA). There was no restriction on the National Institutes of Health Stroke Scale (NIHSS) score (which ranges from 0 to 42, with higher scores representing increased neurological deficits). Eligible patients had a pre-stroke modified Rankin scale (mRS) score of 3 or less (scores range from 0 to 6, with higher scores indicating greater disability).

Patients were ineligible if there was an intracranial haemorrhage or other diagnosis (eg, brain tumour) identified by baseline imaging; posterior circulation Acute Stroke Prognosis Early CT Score (pc-ASPECTS)[18] of less than 6 (scores range from 0 [extensive ischaemia, poor prognosis] to 10 [no ischaemia, excellent prognosis][19]) on diffusion weighted imaging or non-contrast CT or CTA source images; significant cerebellar mass effect or acute hydrocephalus; established frank hypodensity on non-contrast CT indicating subacute infarction; or bilateral extensive brainstem ischaemia. The complete list of eligibility criteria is provided in the appendix (p 9).

The trial adhered to the principles outlined in the Declaration of Helsinki and complied with the International Council for Harmonization Guidelines for Good Clinical Practice. The study was approved by the ethics committee of Beijing Tiantan Hospital (KY2023-227-02). There was no patient or public involvement in the study design, conduct, and reporting. Before participant enrolment, the trial protocol received approval from the institutional review board of each participating site and was subsequently published.[20] All of the enrolled patients or their legally authorised representatives provided written informed consent. This trial is registered with ClinicalTrials.gov, NCT06196320.

Randomisation and masking

Patients were randomly assigned (1:1) to intravenous tenecteplase or standard medical treatment with the Central Interactive Management System for Clinical Research, which is a secure, Good Clinical Practice-compliant electronic web-based server that robustly preserves allocation concealment. The randomisation system used computer-generated allocation sequences, stratified by the investigator's intention for endovascular thrombectomy and intention for intravenous alteplase (if randomly assigned to standard medical treatment), and using covariate-adjusted minimisation to balance age (≤70 years *vs* >70 years), NIHSS score (<10 *vs* ≥10), and time from onset to randomisation (<6 h *vs* 6–24 h).

Qualified physicians and members of the Endpoint Adjudication Committee, who were masked to treatment allocation, independently conducted study outcome assessments and endpoint event adjudication, respectively.

Procedures

Immediately after randomisation, the intervention group received tenecteplase as a single intravenous bolus over 5–10 s, dosed at 0·25 mg/kg (maximum 25 mg). The standard medical treatment group could receive intravenous alteplase (0·9 mg/kg, maximum 90 mg; starting with an initial bolus of 10% of the total dose, followed by continuous infusion of the remaining 90% over 60 min) within 4·5 h of stroke onset, anticoagulation, such as heparin infusion, or antiplatelets as per standard care, with or without endovascular thrombectomy based on clinician judgement. Other management for endovascular thrombectomy patients adhered to the *Chinese Guideline for Endovascular Treatment of Acute Ischemic Stroke 2023*,[21] which recommends endovascular thrombectomy for acute basilar artery occlusion within 12 h of onset if the inclusion criteria of the Endovascular Treatment for Acute Basilar-Artery Occlusion (ATTENTION)[6] and Basilar Artery Occlusion Chinese Endovascular (BAOCHE)[7] trials are met (class I; level of evidence A). For acute basilar artery occlusion, endovascular thrombectomy within 12–24 h of onset is recommended if the BAOCHE inclusion criteria are met (class IIa; level of evidence B).

All outcome assessments were conducted by certified clinicians masked to treatment allocation and trained in their administration at each participating site. The screening log systematically captured demographic data, medical history, concomitant medications, laboratory parameters, neurological evaluations (including mRS and NIHSS scores), and imaging findings. Non-contrast CT or MRI at 24–36 h post intervention evaluated intracranial haemorrhage, and 90-day mRS scores were determined through in-person visits or structured telephone interviews.

Study monitoring was managed by the TRACE-5 Coordinating Centre. Monitors conducted on-site visits to verify protocol compliance by auditing study records, cross-referencing source documentation, and engaging with investigators to assess trial conduct. Monitors were tasked with ensuring protocol adherence and verifying accurate completion of electronic case report forms.

Outcomes

The primary outcome, which was chosen on the basis of precedent in previous thrombolytic trials, was the proportion of participants with no disability (defined as an mRS score of 0–1) or return to the baseline mRS score at 90 days (if the baseline pre-stroke mRS score was 2–3). Secondary outcomes were the proportion of participants with functional independence (defined as an mRS score of 0–2) or return to the baseline mRS score at 90 days, the proportion of patients with an mRS score of 0–3 at 90 days, the ordinal distribution of mRS scores at 90 days (scores 5–6 were combined to avoid counting a shift from death [mRS score of 6] to severe disability requiring constant nursing care [mRS score of 5] as a treatment success), the proportion of patients with early clinical improvement (reduction in acute 72 h NIHSS score of ≥8 points compared with the baseline score or 72 h NIHSS score of 0–1), and the proportion of patients with complete occlusion at baseline who reached an expanded Thrombolysis in Cerebral Infarction[22] grade of 2B–3 on initial digital subtraction angiography run before thrombectomy (grades range from 0 [no reperfusion] to 3 [complete reperfusion]).

Safety outcomes were symptomatic intracranial haemorrhage within 36 h (defined according to the Safe

Implementation of Thrombolysis in Stroke-Monitoring Study criteria as local or remote parenchymal haemorrhage type 2, combined with a neurological deterioration of ≥4 NIHSS points, or leading to death),[23] all-cause mortality within 90 days, and the proportion of patients with an mRS score of 5–6 at 90 days. Adverse effects were systematically assessed at 24 h, 7 days or discharge, and 90 days from randomisation (including central review of all brain imaging performed during admission).

The data and safety monitoring board monitored safety outcomes after the first 50 patients were enrolled and every subsequent 100 patients. Severe adverse events within 90 days were also recorded.

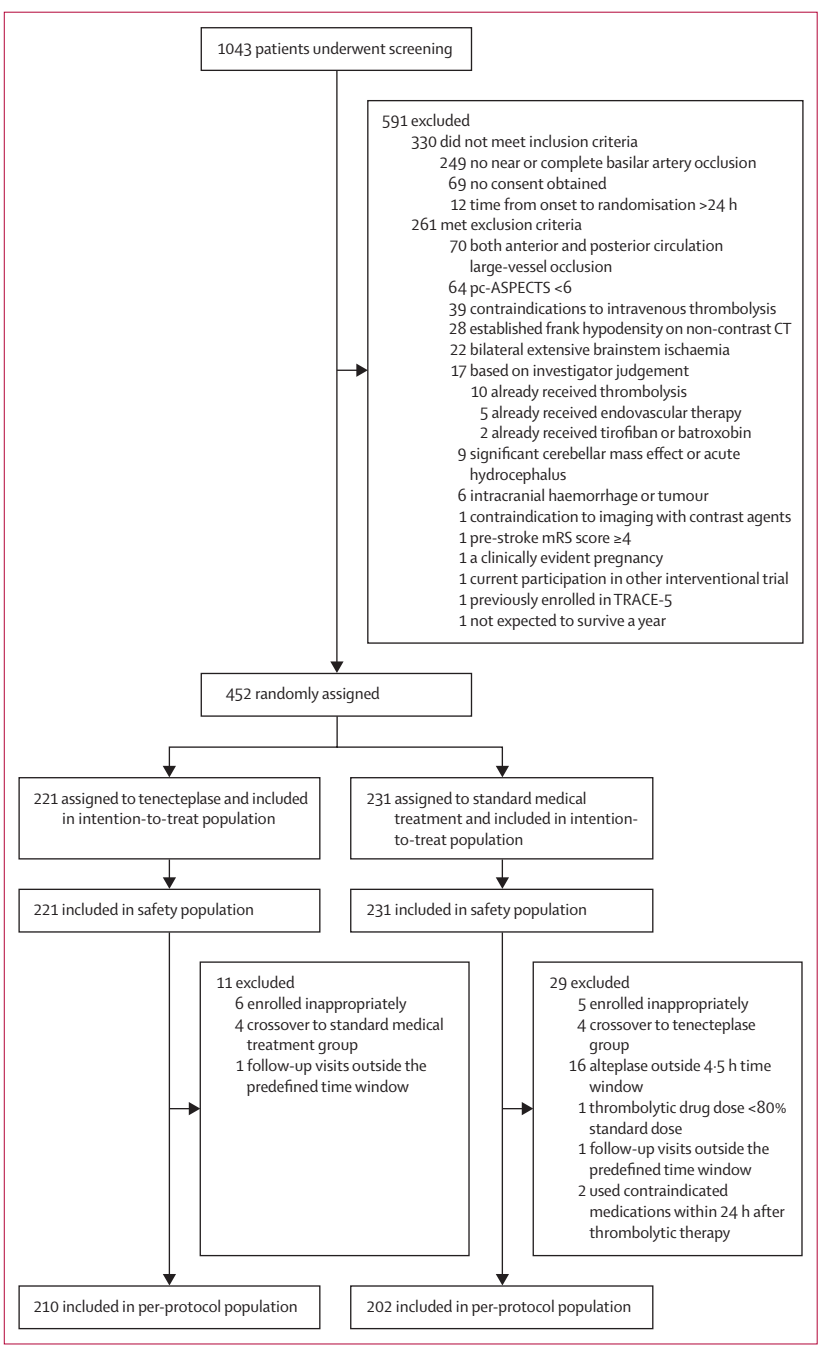


Figure 1: **Trial profile**
mRS=modified Rankin scale. pc-ASPECTS=posterior circulation Acute Stroke Prognosis Early CT Score.

Statistical analysis

On the basis of previous studies,[6,7,17,24] the sample size of 452 patients provided 80% power to detect a 12% difference in the proportions of patients reaching an mRS score of 0–1 (33% intervention *vs* 21% control), assuming a one-sided alpha level of 0·025, an attrition rate of 5%, and a 3-month follow-up period. No interim analyses were planned or performed.

Analyses, including safety, adhered to the intention-to-treat principle, with all randomly assigned participants included in their originally assigned groups. Per-protocol analysis was performed in the per-protocol population, which comprised all participants who completed the assigned interventions as required and in whom there were no major violations of the trial protocol. Major violations defined during data audit included substantial deviation from inclusion or exclusion criteria, use of disallowed concomitant treatments that seriously interfere with efficacy assessment after inclusion, substantial non-compliance with the assigned treatment regimen, excessive delay in drug administration, or non-adherence to the scheduled follow-up windows. Per-protocol analysis was prespecified and considered as a secondary population for efficacy analysis. Outcomes and statistical analyses were prospectively predefined as primary, secondary, or exploratory in the trial protocol. Treatment effect estimates are reported as point estimates with corresponding 95% CIs. Descriptive statistics (means and SDs, medians and IQRs, and numbers and proportions) were computed for all study variables, including baseline characteristics and outcome measures. We did not have missing data for the primary or secondary outcomes.

A prespecified statistical analysis plan was finalised before database lock. The primary outcome and dichotomous secondary outcomes were analysed using modified Poisson regression with robust SE[25] adjusted for age, baseline NIHSS score, and onset-to-randomisation time (dichotomised as <6 h *vs* 6–24 h). Treatment effects were expressed as adjusted relative rates accompanied by 95% CIs. Ordinal analysis of 90-day mRS outcomes, merging scores 5 and 6, used ordinal logistic regression, adjusted for the same covariates, contingent on validation of the proportional odds assumption.

Prespecified subgroups included age (≤70 years *vs* >70 years), sex (male *vs* female), baseline severity of stroke (NIHSS score <10 *vs* ≥10), pc-ASPECTS (≤7 *vs* 8–10), intention for intravenous alteplase (yes *vs* no), intention for endovascular thrombectomy (yes *vs* no), early (≤60 min

after randomisation) versus delayed (>60 min after randomisation) endovascular thrombectomy versus no endovascular thrombectomy, time from stroke onset to randomisation (<6 h *vs* 6–24 h *vs* wake-up stroke), pre-stroke mRS score (0–1 *vs* 2–3), glucose concentration (<7·8 mmol/L *vs* ≥7·8 mmol/L), site of basilar artery occlusion (distal *vs* mid *vs* proximal), stroke mechanism by Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification (cardioembolic stroke *vs* embolic stroke of undetermined source *vs* atherothrombotic stroke), Basilar Artery Tomography Angiography (BATMAN) score on baseline CTA (<7 *vs* ≥7, scores range from 0 [extensive thrombus in the basilar artery, poor collaterals] to 10 [no thrombus in the basilar artery, robust collaterals]),[26] and Posterior Circulation Collateral Score (PC-CS) on baseline CTA (0–3 *vs* 4–5 *vs* ≥6; PC-CS scores range from 0 [no collateral flow] to 10 [robust collateral circulation]).[27] Unadjusted efficacy and safety analyses were performed as post-hoc analyses in the intention-to-treat and per-protocol populations. We also did a post-hoc sensitivity analysis of efficacy and safety outcomes, including adjustment for patient or family refusal to consent for endovascular thrombectomy, along with additional endovascular thrombectomy characteristics, recanalisation at end of procedure, haemorrhagic transformation classifications, and exploratory post-hoc subgroup analysis stratified by imaging modality (CT *vs* MRI). Significance was defined as two-sided p value of less than 0·05. No adjustment for multiple testing was made, and CIs for secondary outcomes and subgroups should not be used for hypothesis testing.

Analyses were conducted with SAS software (version 9.4).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. No confidentiality agreements existed between the manufacturer and investigators, and the manufacturer had no authority to delay or restrict publication of trial findings.

Results

Between Jan 24, 2024, and June 20, 2025, 1043 patients were screened across sites. Following eligibility assessment, 452 qualified for study inclusion, and 221 patients were randomly assigned to the tenecteplase group and 231 to the standard medical treatment group (figure 1). Protocol non-adherence was recorded in 40 (9%) patients, including crossover, alteplase use beyond 4·5 h, and inappropriate enrolment (figure 1).

Baseline characteristics are shown in table 1 and the appendix (pp 11–12). Mean age was 66·4 years (SD 11·2); 321 (71%) patients were male and 131 (29%) were female. The median baseline NIHSS score was 12 (IQR 7–23). The median interval from symptom onset to randomisation was 6·4 h (IQR 3·7–11·5). The median interval from thrombolytic to arterial puncture for the 222 (49%) patients receiving endovascular thrombectomy was 45 min (IQR 25–80). The reasons for not proceeding with endovascular thrombectomy in the study overall and in the subgroup in whom endovascular thrombectomy was intended at the time of randomisation are shown in the appendix (pp 13–14). Alteplase was used in

	Tenecteplase group (n=221)	Standard medical treatment group (n=231)
Age, years	66·5 (10·9)	66·2 (11·6)
Sex		
Male	159 (72%)	162 (70%)
Female	62 (28%)	69 (30%)
Hypertension	165 (75%)	170 (74%)
Diabetes	55 (25%)	58 (25%)
Atrial fibrillation	16 (7%)	21 (9%)
mRS score before stroke*		
0–1	211 (95%)	220 (95%)
2–3	10 (5%)	11 (5%)
Baseline NIHSS score†	13 (7–25)	11 (6–21)
<10	86 (39%)	99 (43%)
≥10	135 (61%)	132 (57%)
Basilar artery occlusion‡		
Complete occlusion	208/218 (95%)	220/230 (96%)
Near-complete occlusion	10/218 (5%)	10/230 (4%)
Basilar artery occlusion site		
Proximal	126/218 (58%)	125/230 (54%)
Mid	64/218 (29%)	74/230 (32%)
Distal	28/218 (13%)	31/230 (13%)
pc-ASPECTS§	8 (6–8)	8 (7–8)
≤7	91 (41%)	88 (38%)
8–10	130 (59%)	143 (62%)
TOAST classification		
Large-artery atherosclerosis	191 (86%)	190 (82%)
Cardioembolism	29 (13%)	40 (17%)
Embolic stroke of undetermined source	1 (<1%)	1 (<1%)
Time from symptom onset to randomisation, h	6·1 (3·8–11·3)	6·5 (3·4–11·6)
<4·5	70 (32%)	85 (37%)
4·5–24	113 (51%)	102 (44%)
Wake-up stroke	38 (17%)	44 (19%)
Intravenous alteplase¶	1 (<1%)	80 (35%)
Intention at time of randomisation to perform endovascular thrombectomy	130 (59%)	125 (54%)
Endovascular thrombectomy	112 (51%)	110 (48%)

Data are mean (SD), n (%), or median (IQR). mRS=modified Rankin scale. NIHSS=National Institutes of Health Stroke Scale. pc-ASPECTS=posterior circulation Acute Stroke Prognosis Early CT Score. TOAST=Trial of Org 10172 in Acute Stroke Treatment. *Scores on the mRS range from 0 to 6, with higher scores indicating greater disability. †Scores on the NIHSS range from 0 to 42, with higher scores indicating a greater deficit. ‡Four patients did not have near-complete or complete basilar artery occlusion on core laboratory assessment. §Scores on the pc-ASPECTS were assessed on baseline CT angiography source images, non-contrast CT brain images, or diffusion weighted imaging, ranging from 0 to 10, with higher scores indicating fewer early ischaemic changes. ¶Four patients assigned to tenecteplase crossed over to control (one received alteplase and three received no intravenous thrombolysis) but were analysed in the tenecteplase group as per the intention-to-treat principle.

Table 1: **Baseline characteristics**

	Tenecteplase group (n=221)	Standard medical treatment group (n=231)	Adjusted effect size* (95% CI)†	p value
Primary outcome				
mRS score 0–1 or return to baseline mRS score at 90 days‡	83 (38%)	66 (29%)	1·50 (1·09–2·08)	0·014
Secondary outcomes				
mRS score of 0–2 or return to baseline mRS score at 90 days	98 (44%)	99 (43%)	1·16 (0·88–1·54)	0·29
mRS score of 0–3 at 90 days	114 (52%)	123 (53%)	1·06 (0·82–1·37)	0·66
Ordinal distribution of mRS scores at 90 days	..	..	1·51 (1·06–2·15)	0·022
0	36 (16%)	30 (13%)	..	..
1	43 (19%)	34 (15%)	..	..
2	17 (8%)	34 (15%)	..	..
3	18 (8%)	25 (11%)	..	..
4	25 (11%)	19 (8%)	..	..
5–6§	82 (37%)	89 (39%)	..	..
Early clinical improvement¶	65 (29%)	64 (28%)	1·08 (0·76–1·52)	0·68
Substantial reperfusion at initial angiogram‖	34/141 (24%)	16/126 (13%)	1·90 (1·04–3·49)	0·038
Safety outcomes				
Symptomatic intracranial haemorrhage within 36 h**	4 (2%)	7 (3%)	0·58 (0·17–1·99)	0·39
All-cause mortality within 90 days	65 (29%)	71 (31%)	0·87 (0·62–1·22)	0·41
mRS score 5–6 at 90 days	82 (37%)	89 (39%)	0·87 (0·65–1·18)	0·38

Data are n (%) or n/N (%) unless otherwise stated. mRS=modified Rankin scale. NIHSS=National Institutes of Health Stroke Scale. *The common odds ratio is shown for the ordinal score on the mRS, and the relative rate is shown for other outcomes. †The primary, secondary, and safety outcomes were adjusted for age, baseline NIHSS score, and onset-to-randomisation time (dichotomised as <6 h vs 6–24 h). ‡Scores on the mRS range from 0 to 6, with higher scores indicating greater disability; the primary outcome also included patients who returned to their baseline mRS score (if the baseline pre-stroke mRS score was 2–3) at 90 days. §mRS scores 5–6 were prespecified to be merged in ordinal analysis to avoid counting a shift from death (mRS score 6) to severe disability requiring constant nursing care (mRS score 5) as a treatment success. ¶Early clinical improvement defined by a reduction on NIHSS score of ≥8 compared with the initial deficit or a score of 0–1 at 72 h. ‖Proportion of patients with complete occlusion at baseline who reached the expanded Treatment in Cerebral Infarction grade of 2B–3 (reperfusion of ≥50% of the affected territory) on initial digital subtraction angiography run before thrombectomy. Two patients did not go for digital subtraction angiography due to significant improvement of NIHSS scores, and repeated CT angiography showed complete recanalisation of occlusion (Arterial Occlusive Lesion score of 3). **Symptomatic intracranial haemorrhage within 36 h (defined as local or remote parenchymal haemorrhage type 2, combined with a neurological deterioration of ≥4 NIHSS points, or leading to death).

Table 2: **Efficacy and safety outcomes**

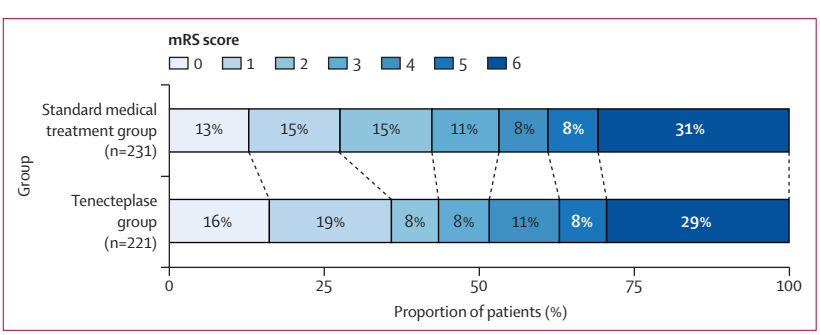
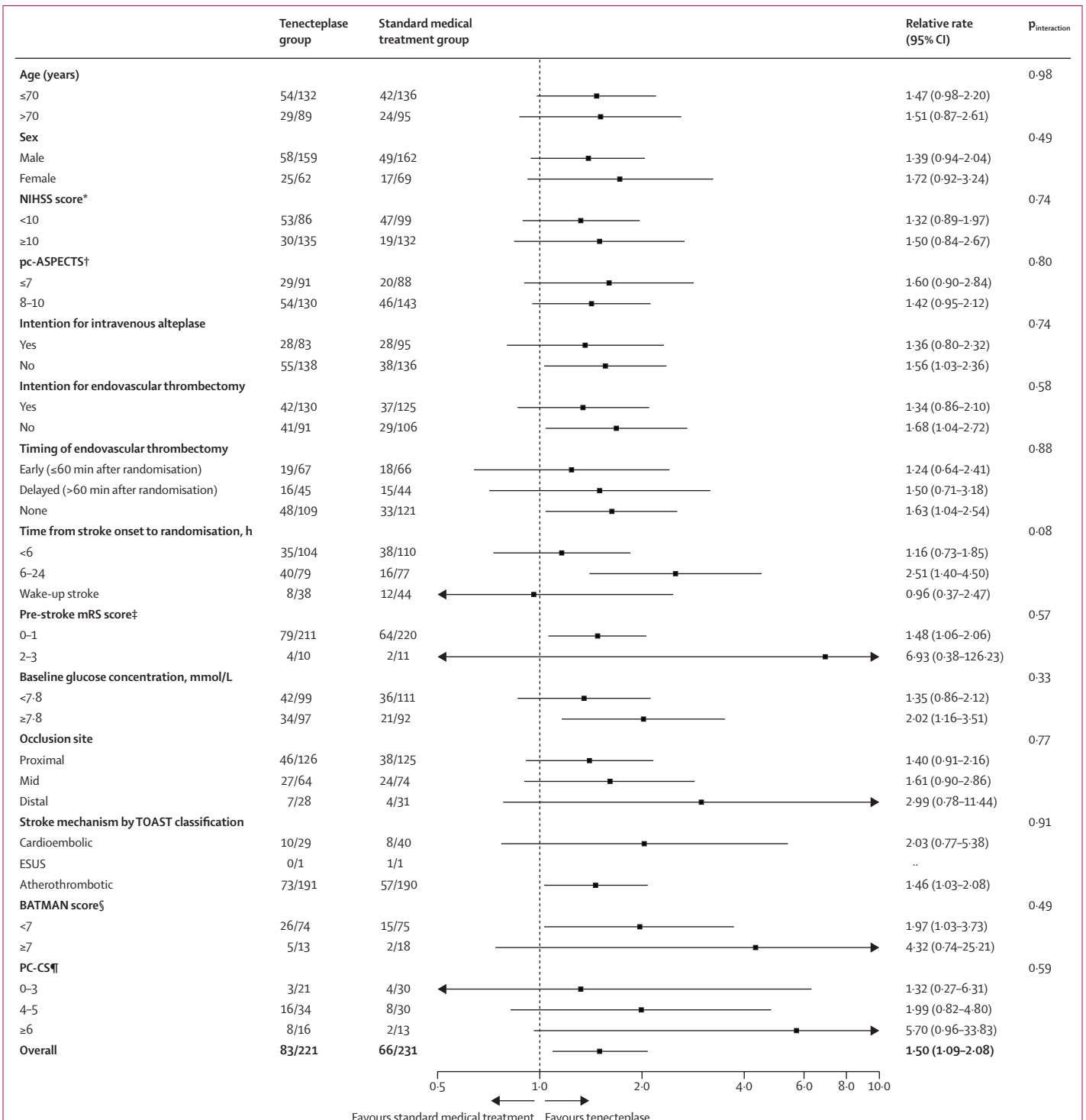


Figure 2: **Distribution of scores on the mRS at 90 days in the intention-to-treat population**
Scores on the modified Rankin scale range from 0 to 6, with 0 indicating no symptoms, 1 indicting symptomatic but not disabled, 2 indicating disabled but independent, 3 indicating dependent but ambulatory, 4 indicating not ambulatory or capable of body self-care, 5 indicating requiring constant nursing care, and 6 indicating death. Percentages might not total 100 because of rounding. mRS=modified Rankin scale.

80 (35%) of 231 patients in the standard medical treatment group.

The primary endpoint of no disability (mRS score 0–1) or return to the baseline mRS score at the 90-day follow-up was reached in 83 (38%) of 221 patients in the tenecteplase group versus 66 (29%) of 231 patients in the standard medical treatment group (adjusted relative rate 1·50 [95% CI 1·09–2·08]; two-tailed p=0·014; table 2; figure 2). In patients with a pre-stroke mRS score of 2–3, four (40%) of ten in the tenecteplase group versus two (18%) of 11 in the standard medical treatment group returned to their baseline mRS scores. Secondary outcome measures and safety data are shown in table 2. The proportional odds assumption for ordinal logistic regression (scores 5 and 6 were combined) was satisfied based on the Brandt test (p=0·40). Stratified subgroup evaluations of treatment effects on the primary endpoint are shown in figure 3. Results in the per-protocol analysis were aligned with those of the primary intention-to-treat analysis (appendix pp 15–16, 26). The appendix shows post-hoc efficacy and safety outcomes using unadjusted analyses in the intention-to-treat and per-protocol analysis (pp 17–20) and post-hoc analysis including an additional adjustment for patient or family refusal to consent to endovascular thrombectomy (pp 21–22). The appendix (p 23) shows post-hoc endovascular thrombectomy procedural characteristics, including final recanalisation. Post-hoc exploratory subgroup analysis stratified by imaging modality is provided in the appendix (p 27).

Symptomatic intracranial haemorrhage within 36 h post randomisation occurred in four (2%) of 221 patients



	Tenecteplase group	Standard medical treatment group	Relative rate (95% CI)	$P_{interaction}$
Age (years)				0·98
≤70	54/132	42/136	1·47 (0·98–2·20)	
>70	29/89	24/95	1·51 (0·87–2·61)	
Sex				0·49
Male	58/159	49/162	1·39 (0·94–2·04)	
Female	25/62	17/69	1·72 (0·92–3·24)	
NIHSS score*				0·74
<10	53/86	47/99	1·32 (0·89–1·97)	
≥10	30/135	19/132	1·50 (0·84–2·67)	
pc-ASPECTS†				0·80
≤7	29/91	20/88	1·60 (0·90–2·84)	
8–10	54/130	46/143	1·42 (0·95–2·12)	
Intention for intravenous alteplase				0·74
Yes	28/83	28/95	1·36 (0·80–2·32)	
No	55/138	38/136	1·56 (1·03–2·36)	
Intention for endovascular thrombectomy				0·58
Yes	42/130	37/125	1·34 (0·86–2·10)	
No	41/91	29/106	1·68 (1·04–2·72)	
Timing of endovascular thrombectomy				0·88
Early (≤60 min after randomisation)	19/67	18/66	1·24 (0·64–2·41)	
Delayed (>60 min after randomisation)	16/45	15/44	1·50 (0·71–3·18)	
None	48/109	33/121	1·63 (1·04–2·54)	
Time from stroke onset to randomisation, h				0·08
<6	35/104	38/110	1·16 (0·73–1·85)	
6–24	40/79	16/77	2·51 (1·40–4·50)	
Wake-up stroke	8/38	12/44	0·96 (0·37–2·47)	
Pre-stroke mRS score‡				0·57
0–1	79/211	64/220	1·48 (1·06–2·06)	
2–3	4/10	2/11	6·93 (0·38–126·23)	
Baseline glucose concentration, mmol/L				0·33
<7·8	42/99	36/111	1·35 (0·86–2·12)	
≥7·8	34/97	21/92	2·02 (1·16–3·51)	
Occlusion site				0·77
Proximal	46/126	38/125	1·40 (0·91–2·16)	
Mid	27/64	24/74	1·61 (0·90–2·86)	
Distal	7/28	4/31	2·99 (0·78–11·44)	
Stroke mechanism by TOAST classification				0·91
Cardioembolic	10/29	8/40	2·03 (0·77–5·38)	
ESUS	0/1	1/1	..	
Atherothrombotic	73/191	57/190	1·46 (1·03–2·08)	
BATMAN score§				0·49
<7	26/74	15/75	1·97 (1·03–3·73)	
≥7	5/13	2/18	4·32 (0·74–25·21)	
PC-CS¶				0·59
0–3	3/21	4/30	1·32 (0·27–6·31)	
4–5	16/34	8/30	1·99 (0·82–4·80)	
≥6	8/16	2/13	5·70 (0·96–33·83)	
Overall	**83/221**	**66/231**	**1·50 (1·09–2·08)**	

0·5 1·0 2·0 4·0 6·0 8·0 10·0

Figure 3: **Subgroup analyses for the primary outcome of mRS score of 0–1 or return to baseline mRS score at 90 days**

BATMAN=Basilar Artery Tomography Angiography. ESUS=embolic stroke of undetermined source. mRS=modified Rankin scale. NIHSS=National Institutes of Health Stroke Scale. pc-ASPECTS=posterior circulation Acute Stroke Prognosis Early CT Score. PC-CS=Posterior Circulation Collateral Score. TOAST=Trial of Org 10172 in Acute Stroke Treatment. *Scores on the NIHSS range from 0 to 42, with higher scores indicating greater deficit. †The pc-ASPECTS was determined by use of baseline CT angiogram source images, non-contrast CT brain images, or diffusion weighted imaging, and ranges from 0 to 10, with higher scores indicating fewer early ischaemic changes. ‡Scores on the mRS range from 0 to 6, with higher scores indicating greater disability. §BATMAN scores were evaluated on baseline CT angiography, ranging from 0 to 10, with higher scores indicating better vascular perfusion and collateral circulation. ¶The PC-CS was calculated on baseline CT angiography, ranging from 0 to 10, with higher scores indicating better collateral blood flow.

in the tenecteplase group versus seven (3%) of 231 patients in the standard medical treatment group (adjusted relative rate 0·58 [95% CI 0·17–1·99]; table 2). Among the seven patients in the standard medical treatment group, all had endovascular thrombectomy; one had alteplase before endovascular thrombectomy and two had complications during endovascular thrombectomy (vessel perforation). Post-hoc haemorrhagic transformation classifications are listed in the appendix (p 24). All-cause mortality at 90 days was similar between groups (65 [29%] patients in the tenecteplase group and 71 [31%] patients in the standard medical treatment group; adjusted relative rate 0·87 [95% CI 0·62–1·22]), as was the proportion of patients with an mRS score of 5–6 at 90 days (82 [37%] *vs* 89 [39%]; 0·87 [0·65–1·18]; table 2). Severe adverse events did not differ between the groups (appendix p 25).

Discussion

The TRACE-5 trial showed that, in patients with ischaemic stroke due to basilar artery occlusion, treatment with intravenous tenecteplase within 24 h of symptom onset led to a larger proportion of patients with no disability at 90 days than that observed with standard medical treatment. Of note, the magnitude of treatment effect in this trial is similar to that reported in patients with anterior circulation large-vessel occlusion not receiving endovascular thrombectomy in the TRACE-3 trial.[14] The magnitude of effect in secondary outcomes using mRS score 0–2 and mRS score 0–3 dichotomies was smaller, but there was evidence of net benefit in the ordinal analysis of mRS (scores 5–6 were combined). The proportion of patients with substantial reperfusion before endovascular therapy was significantly higher in the tenecteplase group than in the standard medical treatment group. The incidence of symptomatic intracranial haemorrhage within the first 36 h after treatment and 90-day all-cause mortality were similar between the two groups.

TRACE-5 was designed to evaluate the efficacy and safety of tenecteplase in an extended time window in patients with basilar artery occlusion. Endovascular thrombectomy within 24 h of symptom onset is highly effective for basilar artery occlusion,[3] but access is limited in many countries. Consistent with the majority of previous thrombolytic trials, we chose an mRS score of 0–1 as the primary outcome. A study-level meta-analysis of 11 randomised controlled trial results showed superiority of tenecteplase over alteplase, with the strongest signal also observed at mRS score 0–1.[13] Our trial supports wider use of thrombolytic therapies up to 24 h after onset of basilar artery occlusion, analogous to trials in anterior circulation stroke[14] but without the need for perfusion mismatch imaging. This could greatly expand access to reperfusion therapies for patients requiring long transfers to centres with endovascular thrombectomy capability or in settings in which endovascular thrombectomy is not available or affordable, including low-income countries. The 2024 European Stroke Organisation and European Society of Minimally Invasive Neurological Therapy guidelines for the acute management of basilar artery occlusion explicitly recommended extending the intravenous thrombolysis window in basilar artery occlusion up to 24 h, although this recommendation was based on expert consensus rather than randomised evidence.[16]

The safety profile of tenecteplase was favourable, with no differences observed in symptomatic intracranial haemorrhage or 90-day mortality compared with standard medical treatment. Importantly, the risk of symptomatic intracranial haemorrhage in the tenecteplase group was low (~2%), which is lower than the risk reported in anterior circulation stroke.[14] This finding is consistent with previous evidence suggesting that the risk of haemorrhagic transformation in posterior circulation stroke might be lower than in anterior circulation[28] and further supports the safety of extending intravenous thrombolysis beyond 4·5 h in basilar artery occlusion.

A previous trial[29] showed no benefit of tenecteplase in the late time window for anterior circulation large-vessel occlusion (when most patients underwent immediate endovascular thrombectomy). By comparison, the TRACE-5 population was younger, had a longer interval between thrombolysis and arterial puncture (45 min *vs* 15 min), and a lower rate of endovascular thrombectomy because most sites in this trial did not have endovascular thrombectomy capability at all times. In contrast to the Extending the Time Window for Thrombolysis in Posterior Circulation Stroke without Early CT Signs (EXPECTS) trial,[12] which focused on the use of intravenous alteplase in an extended time window in a population of patients with very mild posterior circulation stroke with a median NIHSS score of 3, our trial focused on expanding intravenous thrombolysis eligibility to patients with basilar artery occlusion, a devastating condition with a dismal prognosis. However, as a thrombolytic trial without a lower limit on the NIHSS, a lower baseline NIHSS score was observed in this trial than in the BAOCHE and ATTENTION trials.[6,7]

Importantly, subgroup analyses demonstrated a consistent treatment effect, regardless of the underlying cause of stroke or NIHSS score, with a benefit of tenecteplase preserved in patients with basilar artery occlusion and NIHSS scores of less than 10, a subgroup in which the efficacy of thrombectomy remains uncertain.[3] As suggested by the results of the Basilar Artery International Cooperation Study (BASICS) trial,[4] intravenous thrombolysis beyond 4·5 h of symptom onset might be a preferred treatment option for patients with basilar artery occlusion with NIHSS scores of less than 10.[16] The trial was not powered to show a significant benefit in the subgroup of patients who were intended for endovascular thrombectomy. However, there was no

evidence of a differential treatment effect. The ongoing POST-ETERNAL trial (NCT05105633) and the planned individual patient data pooled analysis with TRACE-5 will shed more light on this question. The predefined subgroup analyses showed significantly higher rates of excellent functional outcome with tenecteplase in patients with basilar artery occlusion who did not undergo endovascular thrombectomy and did not receive alteplase in the extended time window (>4·5 h).

TRACE-5 was a pragmatic trial and predominantly used non-contrast CT brain images, CTA source images, or diffusion weighted imaging to assess baseline ischaemic changes, with no requirement for advanced imaging to select patients with basilar artery occlusion for treatment in the late time window. This approach facilitates the implementation and translation of the trial results in settings in which advanced imaging might not be available. Patients enrolled based on MRI versus CT had similar treatment effect in post-hoc analysis. Diffusion weighted imaging–FLAIR mismatch was not used in selection of patients. The convenience of single-bolus administration of tenecteplase in patients with basilar artery occlusion is a major practical advantage that will further facilitate implementation of the trial results in metropolitan and rural settings.

This trial has several limitations. First, the trial was open label. However, outcomes were assessed by clinicians who were unaware of the treatment assignments. Second, we restricted enrolment to patients who did not have large baseline infarcts in the posterior circulation (consistent with previous trials in patients with basilar artery occlusion), so the generalisability of results to patients with larger established infarction is uncertain.[6,7] Further studies are needed to address these questions. Third, the trial was performed in Chinese patients, an ethnic group characterised by a higher prevalence of intracranial atherosclerosis than other ethnicities, which might limit the generalisability of the trial results. Fourth, the tenecteplase used in this trial was the same formulation used in TRACE-2,[30] which demonstrated similar results compared with alteplase as other formulations of tenecteplase available internationally. However, formal comparability data between tenecteplase formulations have not been published.

In conclusion, tenecteplase administered within 24 h of symptom onset improved functional outcomes in patients with basilar artery occlusion compared with standard medical treatment, including alteplase and thrombectomy in those eligible, without increasing the haemorrhagic risk. Our results support the use of tenecteplase up to 24 h after stroke onset as an effective therapeutic option in patients with basilar artery occlusion in both endovascular thrombectomy-capable and endovascular thrombectomy-limited settings.

Contributors

YX and FA prepared the first draft of the report. YoW, BCVC, LHS, MF, and MWP conceptualised the study design and provided critical comments for the manuscript. YoW and BCVC were principal investigators of the study. SZ and YH contributed to the trial execution and participant recruitment. JY calculated the sample size, formulated the statistical plan, and performed the statistical analysis. All other authors served as local investigators or co-investigators, with responsibilities encompassing participant recruitment, data collection, and the critical review, revision, and final approval of the manuscript before submission. The steering committee (YoW, BCVC, LHS, MF, and MWP) was responsible for the overall design, protocol development, interpretation, and supervision of the trial. YoW, YX, and JY had access to and verified all the underlying data reported in the manuscript, and all authors had final responsibility for the decision to submit for publication.

Declaration of interests

LHS serves as a scientific consultant regarding trial design and conduct for Genentech and is a member of the steering committee of the TIMELESS trial (NCT03785678); is a consultant on user interface design and usability to LifeImage; and is a member of a data safety monitoring board for Penumbra (MIND; NCT03342664). MF serves as a consultant for Simcere USA, Revalesio, and Lumosa, and is a member of a data safety monitoring board for Moleac. All other authors declare no competing interests.

Data sharing

Data collected for the study, including de-identified individual participant data and a data dictionary defining each field in the set, can be made available to others on reasonable request to the corresponding author and after signing appropriate data sharing agreements. Such requests must be approved by all the respective ethics boards and appropriate data custodians.

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