Tenecteplase versus alteplase in acute ischaemic cerebrovascular events (TRACE-2): a phase 3, multicentre, open-label, randomised controlled, non-inferiority trial

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Summary

Background There is increasing interest in replacing alteplase with tenecteplase as the preferred thrombolytic treatment for patients with acute ischaemic stroke. We aimed to establish the non-inferiority of tenecteplase to alteplase for these patients.

Methods In this multicentre, prospective, open-label, blinded-endpoint, randomised controlled, non-inferiority trial, adults with an acute ischaemic stroke who were eligible for standard intravenous thrombolysis but ineligible for endovascular thrombectomy were enrolled from 53 centres in China and randomly assigned (1:1) to receive intravenous tenecteplase (0·25 mg/kg, maximum dose of 25 mg) or intravenous alteplase (0·9 mg/kg, maximum dose of 90 mg). Participants had to be able to receive treatment within 4·5 h of stroke, have a modified Rankin Scale (mRS) score of no more than 1 before enrolment, and have a National Institutes of Health Stroke Scale score of 5–25. Patients and treating clinicians were not masked to group assignment; clinicians evaluating outcomes were masked to treatment type. The primary e cacy outcome was the proportion of participants who had a mRS score of 0–1 at 90 days, assessed in the modified intention-to-treat population (all randomly assigned participants who received the allocated thrombolytic), with a non-inferiority margin of 0·937 for the risk ratio (RR). The primary safety outcome was symptomatic intracranial haemorrhage within 36 h, assessed in all participants who received study drug and had a safety assessment available. The trial is registered with ClinicalTrials.gov, NCT04797013, and has been completed.

Findings Between June 12, 2021, and May 29, 2022, 1430 participants were enrolled and randomly assigned to tenecteplase (n=716) or alteplase (n=714). Six patients assigned to tenecteplase and seven to alteplase did not receive study product, and five participants in the tenecteplase group and 11 in the alteplase group were lost to follow-up at 90 days. The primary outcome in the modified intention-to-treat population occurred in 439 (62%) of 705 in the tenecteplase group versus 405 (58%) of 696 in the alteplase group (RR 1·07, 95% CI 0·98–1·16). The lower limit of the RR's 95% CI was greater than the non-inferiority margin. Symptomatic intracranial haemorrhage within 36 h was observed in 15 (2%) of 711 in the tenecteplase group and 13 (2%) of 706 in the alteplase group (RR 1·18, 95% CI 0·56–2·50). Mortality within 90 days occurred in 46 (7%) individuals in the tenecteplase group versus 35 (5%) in the alteplase group (RR 1·31, 95% CI 0·86–2·01).

Interpretation Tenecteplase was non-inferior to alteplase in people with ischaemic stroke who were eligible for standard intravenous thrombolytic but ineligible for or refused endovascular thrombectomy.

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Introduction

Intravenous alteplase has been recommended as a standard therapy for eligible people who have had acute ischaemic strokes.[1–3] Tenecteplase, which differs from alteplase in three amino acids, has a well characterised mechanism of action.[4] The ease of administration gives tenecteplase (given as a single, intravenous bolus) unique practical advantages compared with alteplase (given as an intravenous bolus with the remainder injected over the course of an hour).[5] The recent Tenecteplase In Patients with Acute Ischaemic Stroke (AcT) trial (NCT03889249), a registry linked trial, showed that tenecteplase (0·25 mg/kg) was non-inferior to alteplase (0·9 mg/kg) for excellent functional outcomes at 90 days and had a similar safety profile. The results of this trial support the use of tenecteplase in routine clinical practice.[6] The efficacy and safety of tenecteplase need further assessment in other populations.

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See Online for appendix

There has been a long debate about the appropriate dose of thrombolytics in Asian people with acute ischaemic stroke. The SITS-NEW study[7] aimed to evaluate the efficacy and safety of intravenous alteplase (0·9 mg/kg) as thrombolytic therapy within 3 h of onset of acute ischaemic stroke in an Asian population. This study showed the safety and efficacy of the standard dose of intravenous alteplase (0·9 mg/kg) in an Asian population, as previously observed in the European population studied in SITS-MOST.[8] Guidelines for intravenous thrombolysis in China,[1] Europe,[3] and the USA[2] all recommend the dose of 0·9 mg/kg. The ENCHANTED study,[9] which assessed low-dose (0·6 mg/kg) intravenous alteplase, did not meet the prespecified non-inferiority criteria for standard-dose intravenous alteplase. There is a paucity of data on the appropriate dosage, efficacy, and safety of tenecteplase as compared with alteplase in Asian populations with acute ischaemic stroke.

TRACE-1, a phase 2, dose-finding, randomised clinical trial in China showed that 0·25 mg/kg tenecteplase was well tolerated in Chinese people who had acute ischaemic stroke, and the safety profile of tenecteplase was similar to that of 0·9 mg/kg alteplase.[10] The aim of the Tenecteplase Reperfusion therapy in Acute ischaemic Cerebrovascular Events-2 (TRACE-2) trial was to test whether tenecteplase, at a dose of 0·25 mg/kg, is non-inferior to alteplase in people with an acute ischaemic stroke who were eligible for intravenous thrombolytic but ineligible for or refused endovascular thrombectomy within 4·5 h of symptom onset.

Methods

Study design

The TRACE-2 trial was a phase 3, multicentre, prospective, open-label, blinded-endpoint, randomised controlled, non-inferiority trial across 53 centres in China. The trial protocol was published in 2022.[11] The trial/Span <</MC5ein p4(

Randomisation and masking

Eligible participants were randomly assigned (1:1) to receive intravenous tenecteplase or alteplase. Block randomisation was done with the use of a central web-based randomisation system (Randomisation and Trial Supply Management version 3.1.2, Beijing Bioknow Information Technology, China) with a block length of four without stratification. The local investigators visited the web-randomisation system and obtained the random codes, and the treatment assignment was done according to the random code. All other treatments were guided by the standard of care for ischaemic stroke.

The intravenous thrombolytic treatment was open label. Evaluators for the clinical assessments and the independent clinical-event adjudication committee, which adjudicated primary and secondary efficacy endpoints and bleeding events, were blinded to treatment allocation.

Procedures

Tenecteplase was given as a single, intravenous bolus (over 5–10 s) at a dose of 0·25 mg/kg of bodyweight (maximum dose 25 mg) immediately after randomisation. Intravenous alteplase was given at a dose of 0·9 mg/kg (maximum dose 90 mg), with 10% of the dose given as a bolus and the remainder over 1 h. Other treatments were carried out adhering to established clinical principles and medical practice guidelines. Participants who planned to undergo endovascular thrombectomy were excluded from the study. However, the recruited participants were not prohibited from subsequently receiving endovascular thrombectomy on the basis of the judgment of the treating neurologists or physicians. NCCT imaging or MRI was done to detect any haemorrhage at 24–36 h after randomisation.

Clinical assessments (including clinical symptoms, laboratory tests, and imaging data) were done at each site by trained and certified evaluators who were unaware of the trial group assignments at 24 h, 7 days or hospital discharge (whichever occurred first), and 90 days. The mRS score at 90 days was assessed in person or by telephone. The clinical events committee adjudicated the endpoint events on the basis of clinical symptoms, laboratory tests, and imaging data. Serious adverse events and adverse events were categorised according to standard terminology.

Outcomes

The primary efficacy outcome was the proportion of participants with an excellent functional outcome, defined as an mRS score of 0–1 at 90 days. The secondary efficacy outcomes consisted of the proportion of patients with favourable functional outcomes (defined as an mRS score of 0–2 at 90 days); mRS score at 90 days; the proportion of patients with a substantial neurological improvement on the NIHSS (defined as a decrease of at least 4 points, a score no more than 1 at 24 h and at 7 days, or discharge, whichever occurred first); European health-related quality of life at 90 days; and the proportion of those with a Barthel Index score of at least 95 points at 90 days.

The primary safety outcome was the rate of symptomatic intracranial haemorrhage within 36 h defined by the European Cooperative Acute Stroke Study III.[12] Other safety outcomes included parenchymal haematoma 2 defined by the Safe Implementation of Thrombolysis in Stroke-Monitoring study;[8] any intracranial haemorrhage or other significant haemorrhagic event as defined by the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries criteria;[13] and death from all causes within 90 days of disease onset. Both serious adverse events and adverse events were collected until 90 days. Definitions of outcomes are included in the protocol in the appendix (p 4).

Statistical analysis

Based on a meta-analysis of previous trials, the risk ratio (RR) for the effect of alteplase versus placebo for the excellent functional outcome (mRS score of 0–1) was 1·24 (95% CI 1·14–1·36).[14] The non-inferiority boundary was defined to preserve at least 50% of the most

calculated using binary logistic regression. Non-inferiority would be established if the lower bound of the two-sided 95% CI of the RR for the primary outcome was greater than the predefined non-inferiority margin of 0·937. A superiority test in the modified intention-to-treat population was planned if non-inferiority was found. For secondary efficacy outcomes, a common OR with its 95% CI was calculated using ordinal logistic regression

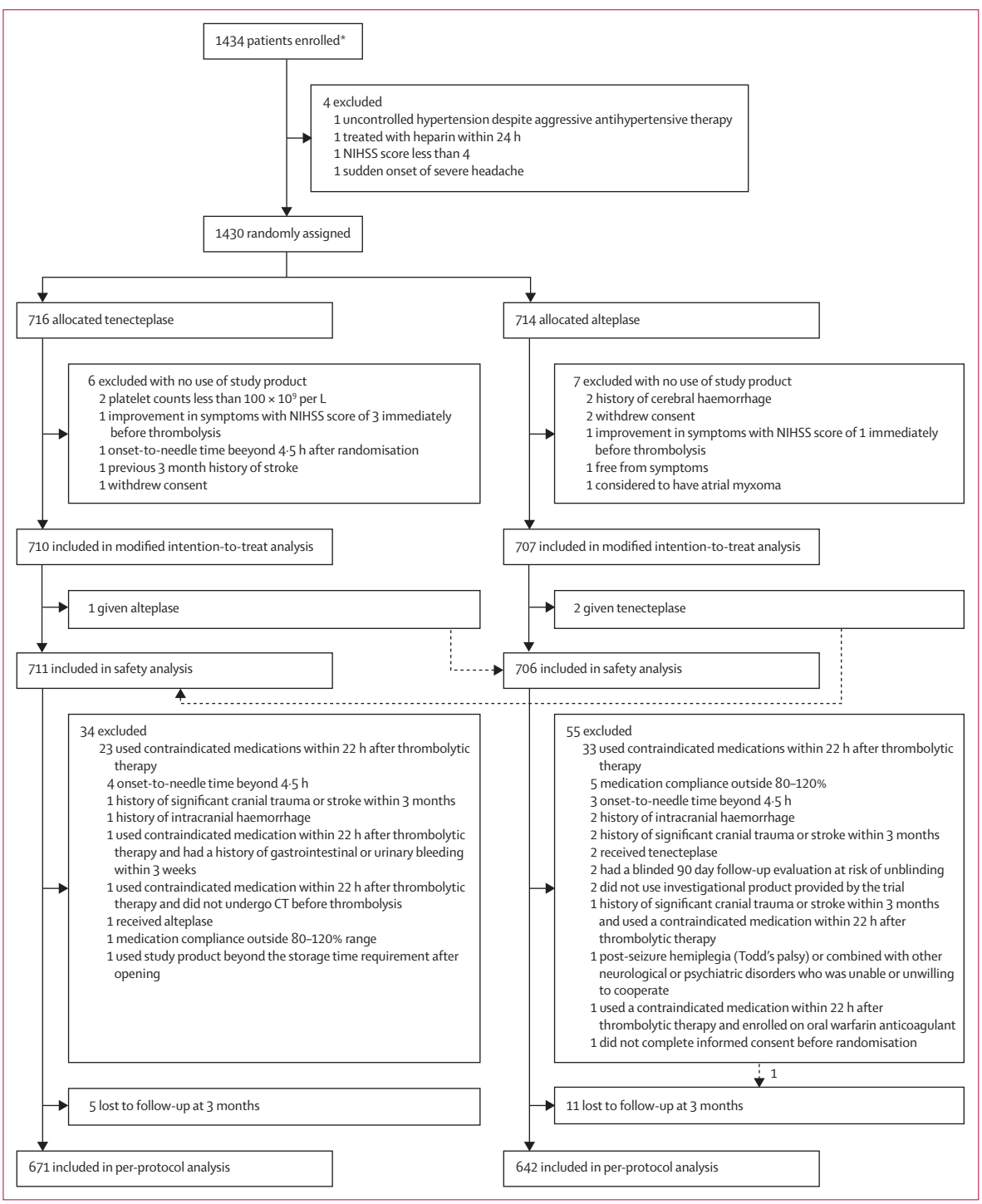

Figure 1: **Enrolment and randomisation**
NIHSS=National Institutes of Health Stroke Scale. *Physicians only obtained informed consent for this trial from patients who were suitable for intravenous thrombolytic but not for endovascular thrombectomy.

for the ordinal 90-day mRS score, and ORs with their 95% CIs were calculated using the Cochran-Mantel-Haenszel method adjusting for the pooled-site effect for other secondary efficacy outcomes. The complete data were used to perform the main efficacy analyses without imputation for missing data. In sensitivity analysis, multiple imputation by fully conditional specification logistic regression was done to impute the missing data of the primary efficacy outcome. We used the Breslow-Day test to examine the heterogeneity of treatment effects across prespecified subgroups of bridging thrombectomy. Post-hoc subgroup analyses were also done for subgroups of sex, bridging thrombectomy, age, NIHSS, and onset-to-needle time.

Safety analyses were done in the safety analysis population, defined as all participants who received at least some of the study drug and had a safety assessment available. ORs were calculated with their 95% CIs using binary logistic regression. For comparison of adverse events and serious adverse events, χ^2 or Fisher's exact test were done, as appropriate.

A single primary efficacy variable was defined for this study and therefore there were no requirements to adjust for multiple comparisons in this study and n

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	Tenecteplase	Alteplase	Effect size (95% CI)	p value
Primary outcome (modified intention-to-treat)				
mRS score 0–1 at 3 months (n=1401)*	439/705 (62%)	405/696 (58%)	..	..
Risk ratio	..	..	1·07 (0·98 to 1·16)†	..
Odds ratio	..	..	1·19 (0·96 to 1·47)	..
Difference in proportion	..	..	3·86 (–1·23 to 8·95)	..
Primary outcome (per-protocol)				
mRS score 0–1 at 3 months (n=1313)*	421/671 (63%)	380/642 (59%)	..	..
Risk ratio	..	..	1·05 (0·97 to 1·15)†	..
Odds ratio	..	..	1·16 (0·93 to 1·45)	..
Difference in proportion	..	..	3·14 (–2·08 to 8·37)	..
Secondary outcomes (modified intention-to-treat)‡				
mRS score 0–2 at 3 months (n=1401)	516/705 (73%)	502/696 (72%)	1·01 (0·95 to 1·08)	0·74
mRS at 3 months (n=1401)	1 (0 to 3)	1 (0 to 3)	1·09 (0·90 to 1·31)	0·38
Improvement on NIHSS of ≥4 points or a score ≤1 at 24 h (n=1388)§	342/690 (50%)	345/698 (49%)	0·97 (0·88 to 1·08)	0·58
Improvement on NIHSS of ≥4 points or a score ≤1 at 7 days or discharge (n=1362)	456/676 (68%)	451/686 (66%)	1·01 (0·94 to 1·09)	0·73
European quality of life visual analogue scale (n=1309)	77·7 (57·6 to 97·8)	76·4 (55·1 to 97·7)	1·38 (–0·87 to 3·63)	0·23
Barthel Index ≥95 (n=1320)	462/658 (70%)	454/662 (69%)	1·03 (0·96 to 1·10)	0·49

Data are n/N (%), effect size (95% CI), median (IQR), or p value. mRS=modified Rankin Scale. NIHSS=National Institutes of Health Stroke Scale. *Scores on the mRS range from 0 to 6, with 0 indicating no disability, 3 indicating moderate disability, and 6 indicating death. †Lower limit of 95% CI did not cross the non-inferiority margin of 0·937. ‡Common odds ratio with its 95% CI was calculated using ordinal logistic regression for the outcome of (342/690 (52oTf 0)T eriority 8((Impor=Nationon)17(odassump=Natfor)2est p=of 0)T

interpretation, or writing of the report. The responsibility for submission was that of the corresponding author, agreed by the trial steering committee.

Results

Recruitment took place between June 12, 2021, and May 29, 2022. Physicians only obtained informed consent for this trial from patients who were suitable for intravenous thrombolytic but not for endovascular thrombectomy. 1434 patients were screened after written informed consent and 4 were ineligible. 1430 patients with ischaemic stroke were enrolled at 53 clinical sites in China (appendix pp 5–6), of whom 716 were assigned to receive tenecteplase and 714 to receive alteplase (figure 1). All enrolled participants were Chinese. Six participants in the tenecteplase group and seven in the alteplase group did not receive the study drug and were excluded from the modified intention-to-treat analysis; the modified intention-to-treat population therefore included 710 participants allocated to the tenecteplase group and 707 to the alteplase group. The safety analysis set had 711 in the tenecteplase group and 706 in the alteplase group as two patients randomised to alteplase were given tenecteplase, and one patient randomised to tenecteplase was given alteplase; patients were classified according to the real treatment. The characteristics of the patients at baseline were similar between the two groups (table 1). The median age of the patients was 66 years (IQR 58–73), 68·5% were men and 31·5% were women. The median baseline NIHSS score was 7 (IQR 6–10) across all participants and the median time from stroke onset to treatment was 180 min (IQR 135–222) in the tenecteplase group and 178·5 min (IQR 135–230) in the alteplase group. 34 tenecteplase-treated and 55 alteplase-treated participants were excluded from the per-protocol analysis due to major deviation from protocol (appendix p 7). Five

towards superior efficacy. Together with the results of other previous studies, 0·25 mg/kg (maximum dose of 25 mg) appears to be the optimal dosage for intravenous tenecteplase. Both the AcT and TRACE-2 trials used this dose of tenecteplase, and 0·9 mg/kg (maximum dose of 90 mg) alteplase was used as a comparison.

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