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 efficacy 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

Research in context

Evidence before this study

We searched PubMed for randomised trials published in English between Jan 1, 2000, and July 31, 2022, with the terms "tenecteplase", "ischaemic stroke", and "clinical trial" or "study". Clinical effectiveness of tenecteplase has been shown in randomised controlled trials, and off-label routine use is endorsed by national practice guidelines, although the strength of recommendation is low. The dosages of tenecteplase used for acute ischaemic stroke have ranged from 0·1 mg/kg to 0·4 mg/kg. However, the NOR-TEST 2 (part A) trial (NCT03854500) showed worse safety and functional outcomes with tenecteplase at 0·4 mg/kg compared with alteplase at the same dose. The AcT trial (NCT03889249) of 1600 individuals showed non-inferiority of tenecteplase at 0·25 mg/kg to alteplase at the same dose for excellent functional outcomes at 90 days, with similar safety profiles between the two treatments. TRACE-1 was a phase 2, dose-finding, randomised clinical trial in China (NCT04676659). The proportion of people with acute ischaemic stroke who had a modified Rankin Scale score of 0–1 at 90 days when treated with tenecteplase at 0·1 mg/kg was 55%, at 0·25 mg/kg was 64%, and at 0·32 mg/kg was 62% compared with 59% for those treated with 0·9 mg/kg alteplase. For those receiving tenecteplase, symptomatic intracerebral haemorrhage occurred in three (5%) in the 0·1 mg/kg group, none in the 0·25 mg/kg group, and two (3%) in the 0·32 mg/kg group, compared with one (2%) individual in the 0·9 mg/kg alteplase group. TRACE-2 was a phase 3 randomised clinical trial informed by TRACE-1.

Added value of this study

There is a paucity of data on the appropriate dosage, efficacy, and safety of tenecteplase compared with alteplase in Asian populations with acute ischaemic stroke. TRACE-2 was done across 53 hospitals in China. In this study, patients who planned to have endovascular thrombectomy were excluded to avoid confounding of results. Therefore, TRACE-2 improves understanding of the efficacy and safety of tenecteplase in a different population.

Implications of all the available evidence

TRACE-2 found that tenecteplase was non-inferior to alteplase for patients with acute ischaemic stroke ineligible for endovascular thrombectomy. This randomised controlled trial provides further evidence to support a worldwide switch to tenecteplase as the preferred thrombolytic for acute ischaemic stroke.

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 was done in accordance with the guidelines for Good Clinical Practice and the Declaration of Helsinki and was designed and supervised by a steering committee. The trial was ethically approved by the institutional review board at the Beijing Tiantan Hospital and at each participating site.

Participants

Participants were eligible if they were aged at least 18 years; could receive intravenous thrombolytics within 4·5 h of their ischaemic stroke; had a modified Rankin Scale (mRS) score of no more than 1 before enrolment; and had a disabling ischaemic stroke with a National Institutes of Health Stroke Scale (NIHSS) score of 5–25. Eligibility for thrombolytic treatment in this trial was based on guidelines by the Chinese Stroke Association,[1] which are consistent with other national guidelines including US[2] and European[3] guidelines. Both non-contrast CT (NCCT) imaging and MRI methods were acceptable for baseline screening. People were ineligible for participation if they had received or intended to proceed to endovascular thrombectomy. Additional information on inclusion and exclusion criteria is provided in the appendix (pp 2–3). Written informed consent was provided by all participants or their representatives before their enrolment.

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 conservative estimate of the efficacy of alteplase from the meta-analysis. The non-inferiority limit was calculated as exp(–1[(Log[1·14])/2])=0·937. Tenecteplase would be declared non-inferior if the lower 97·5% one-sided CI of the RR for the primary outcome did not cross 0·937 (corresponding to 3·74% absolute risk difference). Assuming a power of 85%, a one-sided α level of 0·025, and an absolute RR of 1·07 based on the phase 2 data (response rates of 63·64% for the tenecteplase group *vs* 59·32% for for the alteplase group),[10] the target sample size for each group was 643 patients. Allowing for a dropout rate of 10%, the final target sample size estimate was 1430 patients (715 in each treatment group).

Efficacy analyses were done in the modified intention-to-treat population and in the per-protocol population. The modified intention-to-treat population was defined as all randomly assigned participants who received the allocated thrombolytic; the per-protocol population was defined as all participants who completed the assigned treatment without major violation of the trial protocol or missing data for primary efficacy endpoints. A χ^2 test or Fisher's exact probability method was used for comparison of categorical variables, Wilcoxon rank sum test for comparison of ordinal variables, and *t* test or rank sum test for comparison of continuous variables. The Cochran-Mantel-Haenszel χ^2 test adjusting for the pooled-site effect (≥20 patients for each stratum) was used for comparison of primary endpoints between groups, and the 95% CI of RR was calculated. We used the normal approximation (Wald formula) to derive the 95% CI of absolute risk differences adjusting for the pooled-site effect. Odds ratio (OR) with 95% CIs were

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

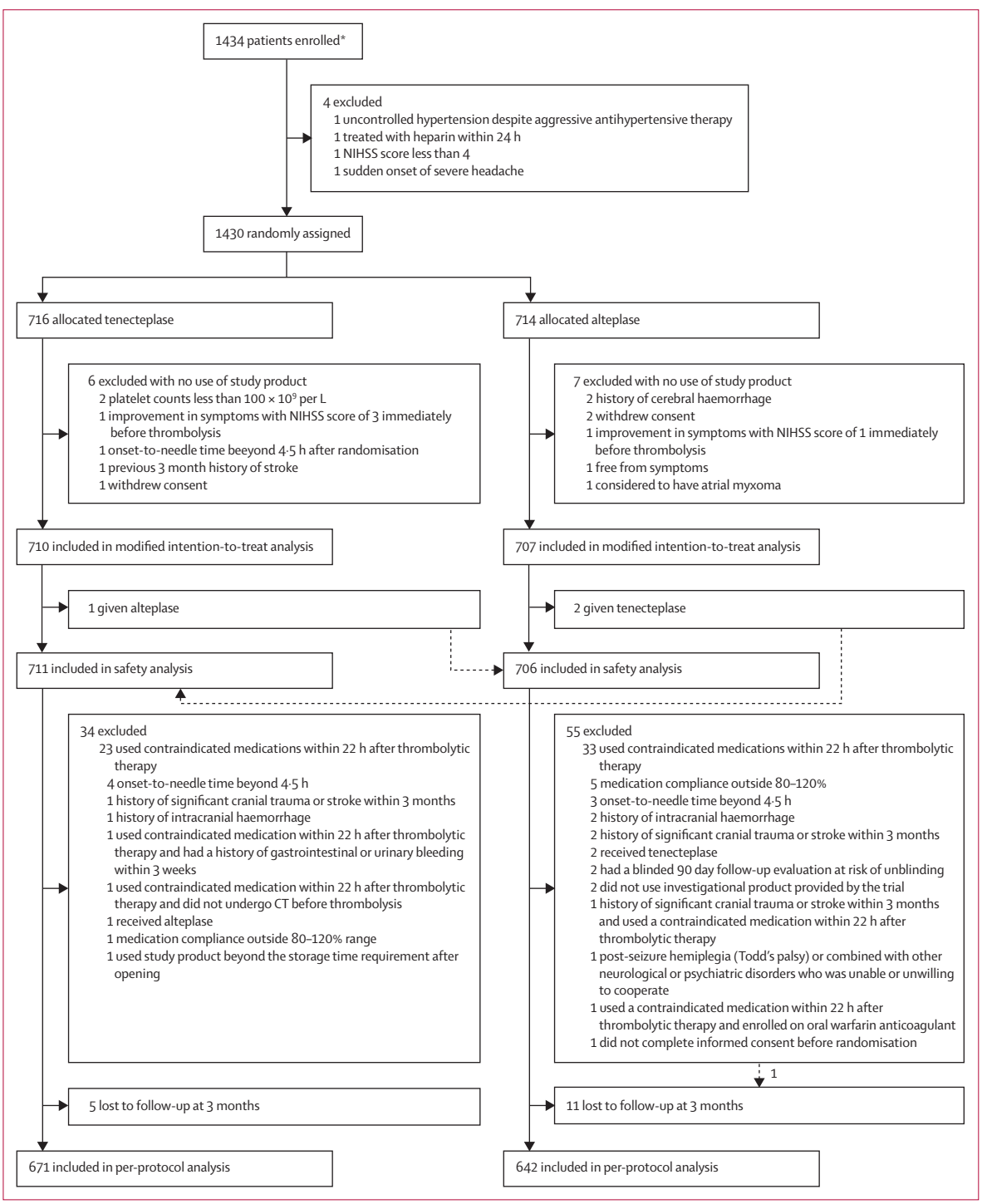

Figure 1: **Enrolment and randomisation**
NIHSS=National Institutes of Health Stroke Scale. *Physicians only obtained informed consent for this trial from patients who were suitable for intravenous thrombolytic but not for endovascular thrombectomy.

	Tenecteplase (n=710)	Alteplase (n=707)
Age, years	67 (58–73)	65 (58–72)
Age		
18–59 years	211 (30%)	218 (31%)
60–79 years	423 (60%)	428 (61%)
≥80 years	76 (11%)	61 (9%)
Sex		
Male	492 (69%)	479 (68%)
Female	218 (31%)	228 (32%)
Ethnicity		
Chinese	710 (100%)	707 (100%)
Weight, kg	65 (59–75)	67 (60–75)
Medical history		
Hypertension	510 (72%)	512 (72%)
Diabetes	172 (24%)	207 (29%)
Hyperlipidaemia	130 (18%)	160 (23%)
Coronary heart disease	167 (24%)	166 (24%)
Arrhythmia	137 (19%)	146 (21%)
Current smoking		
Yes	266 (38%)	276 (39%)
No	443 (62%)	430 (61%)
Data missing	1 (<1%)	1 (<1%)
History of medication use		
Antiplatelet agents	90 (13%)	92 (13%)
Anticoagulant agents	5 (1%)	7 (1%)
Lipid-lowering drugs	67 (9%)	60 (9%)
Hypoglycaemic drugs	108 (15%)	118 (17%)
Antihypertensive drugs	296 (42%)	318 (45%)
mRS score before stroke		
0	634 (89%)	633 (90%)
1	76 (11%)	74 (11%)
(Continued from previous column)		
Baseline NIHSS score*	7 (5–10)	7 (6–10)
Baseline NIHSS score categories		
≤7	419 (59%)	387 (55%)
8–14	228 (32%)	261 (37%)
≥15	63 (9%)	59 (8%)
Onset-to-needle time, min	180 (135–222)	178·5 (135–230)
Onset-to-needle time categories, hours		
<3	353 (50%)	353 (50%)
≥3	357 (50%)	354 (50%)
Door-to-needle time, min	58 (45–78)	61 (48–84)
Bridging thrombectomy	27 (4%)	24 (3%)
Total costs, yuan†	11 255·45 (7537·13–16849·64)	12 094·25 (8039·37–17809·93)
Costs for thrombolysis, yuan	7376·00 (3688·00–7376·00)	5340·24 (5340·24–5340·24)
Duration of hospital stay		
≤7 days	125 (18%)	117 (17%)
>7 days	561 (79%)	574 (81%)
Data missing	24 (3%)	16 (2%)

Data are median (IQR) or n (%). NIHSS=National Institute of Health Stroke Scale. *NIHSS scores range from 0 to 42, with higher scores indicating more severe stroke. †Data available for 1360 patients (675 tenecteplase, 685 alteplase).

Table 1: **Baseline characteristics of participants in the modified intention-to-treat population**

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 no adjustment for multiple testing was done for secondary outcomes. No interim analysis was planned in this trial. An independent data-monitoring committee reviewed the safety data regularly and assessed whether the study should continue. All statistical analyses were done with use of SAS software (version 9.4).

The trial is registered with ClinicalTrials.gov, NCT04797013.

Role of the funding source

The trial drugs, tenecteplase and alteplase, were provided free of charge to the trial sites by China Shijiazhuang Pharmaceutical Company Recomgen Pharmaceutical (Guangzhou), which was the sponsor of this trial but had no role in design, conduct, and report of the trial. The investigators were responsible for data collection and conduct of the trial. The database was managed by the independent Giant contract research organisation. The statistical and data management centre at the China National Clinical Research Center for Neurological Diseases was responsible for the statistical analysis. The sponsors of the study had no role in study design, data collection, data analysis, data

	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 ordinal mRS at 90 days (proportional odds assumption test p=0·11), β coefficient with its 95% CI was calculated using general linear model for the outcome of European quality of life visual analogue scale, and risk ratios with their 95% CIs were calculated using the Cochran-Mantel-Haenszel method considering the site effect for other secondary outcomes. §NIHSS scores range from 0 to 42, with higher scores indicating more severe stroke.

Table 2: **Efficacy outcomes at 3 months**

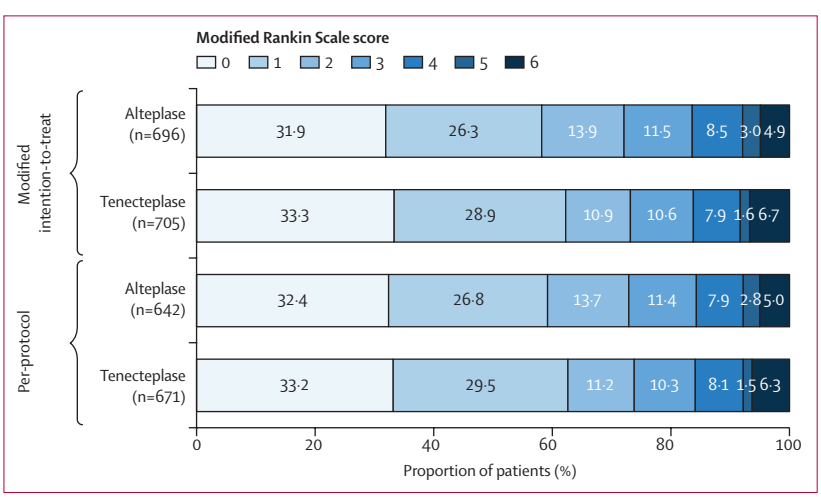

Figure 2: **Distribution of modified Rankin Scale scores at 90 days in the modified intention-to-treat analysis and per-protocol populations, according to assigned treatment**

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

tenecteplase-treated and 11 alteplase-treated participants (including one participant who did not meet the inclusion criteria) were lost to follow-up at 90 days with missing data for the primary outcomes; these participants were excluded from the per-protocol analysis. The concomitant medications used during hospital stay are presented in the appendix (p 8).

In the modified intention-to-treat analysis, 439 (62%) of 705 patients in the tenecteplase group and 405 (58%) of 696 patients in the alteplase group reached the primary outcome (mRS score of 0–1 at 3 months; RR 1·07, 95% CI 0·98 to 1·16; proportion difference 3·86, 95% CI –1·23 to 8·95; table 2, figure 2). The lower limit of the 95% CI of the RR was larger than the non-inferiority margin of 0·937 indicating that tenecteplase was non-inferior but not superior to alteplase. The sensitivity analysis with multiple imputation for missing data of the primary efficacy outcome showed similar results to the main analysis (appendix p 9). The proportion of patients with a favourable functional outcome (mRS score 0–2) in the tenecteplase group was 73% compared with 72% in the alteplase group (RR 1·01, 95% CI, 0·95–1·08). No

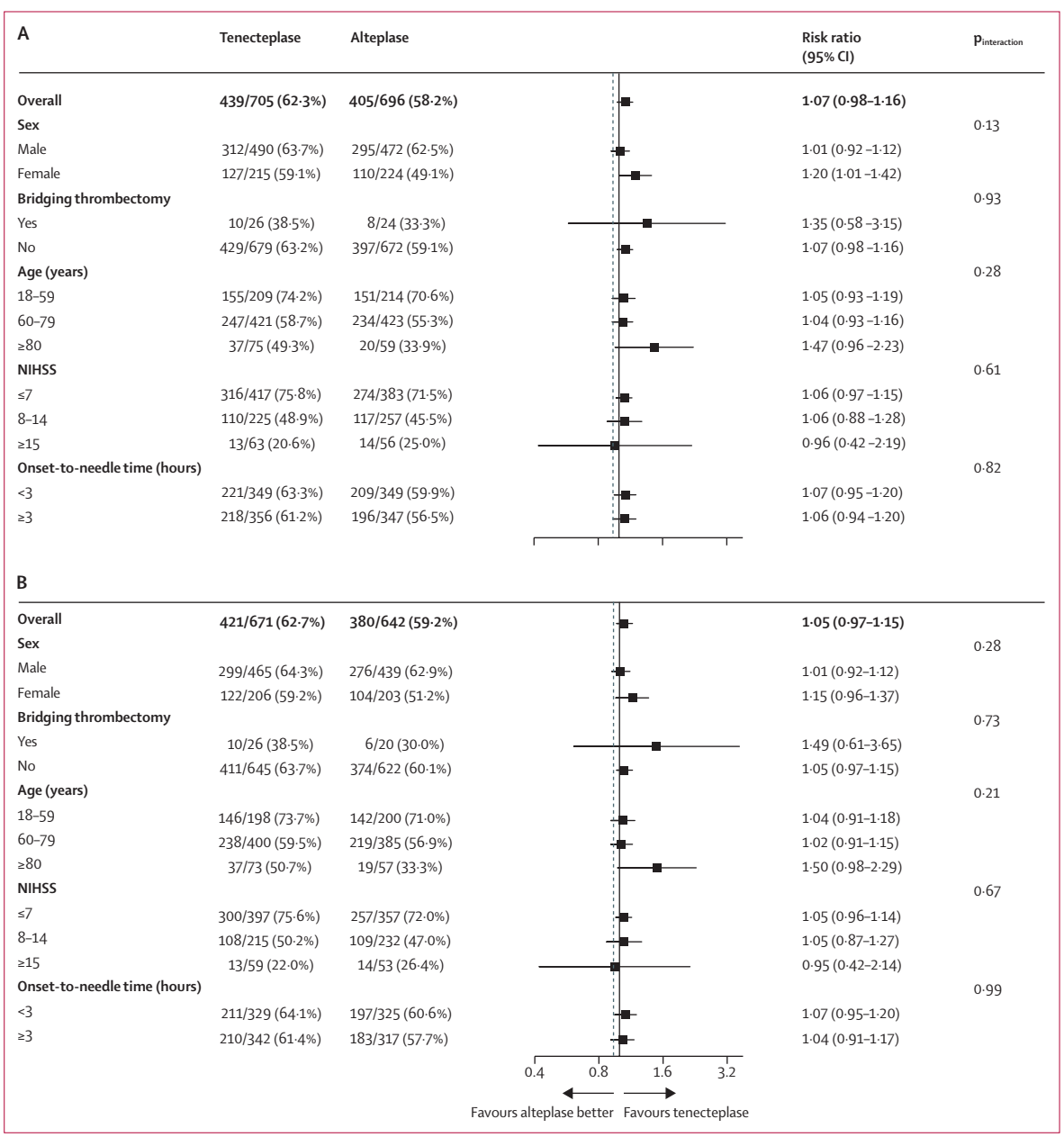

Figure 3: **Effects of tenecteplase as compared with alteplase for the primary efficacy outcome in prespecified subgroups according to the modified intention-to-treat population (A) and the per-protocol population (B)**
The dashed vertical line indicates the non-inferiority limit of 0·937.

significant treatment effect was observed in all other secondary outcomes. The results of the per-protocol analysis were consistent with those of the modified intention-to-treat analysis (table 2, appendix pp 9–10). Similar efficacy was observed in the prespecified subgroups (figure 3).

Symptomatic intracranial haemorrhage within 36 h occurred in 15 (2%) of 711 patients in the tenecteplase group and 13 (2%) of 706 in the alteplase group (RR 1·18, 95% CI 0·56–2·50; table 3). Symptomatic parenchymal haematoma 2 intracranial haemorrhage within 36 h occurred in ten (1%) patients in the tenecteplase group and three (<1%) in the alteplase group (RR 3·73, 95% CI 0·99–14·13). 46 (7%) participants in the tenecteplase group and 35 (5%) participants in the alteplase group died within 90 days (RR 1·31, 95% CI 0·86–2·01). Similar rates of adverse events and serious adverse events were observed between the two groups (appendix p 11–13). No orolingual angioedema was found in this trial.

Discussion

In this trial, among patients with acute ischaemic stroke within 4·5 h of last known well who were eligible for intravenous thrombolysis treatment but ineligible for or refused endovascular thrombectomy, we found that 0·25 mg/kg of intravenous tenecteplase was non-inferior to 0·9 mg/kg of intravenous alteplase for achieving an excellent functional outcome. Although participants who received tenecteplase had numerically more mortality and symptomatic intracranial haemorrhage than those receiving alteplase, we did not observe statistically significant differences in the proportions of symptomatic intracranial haemorrhage nor rates of mortality between the two treatment groups in the 90 days after symptom onset.

Our findings are consistent with the results of the AcT trial and other published non-randomised clinical reports assessing off-label use of tenecteplase versus alteplase.[6,15] The AcT trial was designed as a pragmatic, registry-linked trial and the characteristics of its participants were similar to those of individuals treated in real-world practice. The findings of the AcT trial, therefore, can be readily generalised to the patient populations that the two registries represent. Our TRACE-2 trial was done in Chinese individuals. The consistent results of non-inferiority from these two large clinical trials with participants of very different ethnic backgrounds provide robust evidence for the use of intravenous tenecteplase for the treatment of people with disabling acute ischaemic stroke who are not candidates for thrombectomy. In our TRACE-2 trial, the percentage of participants with an mRS score of 0–1 was consistent with the TRACE-1 trial (NCT04676659), but higher than that from the AcT trial. Participants in TRACE-2 had lower median baseline NIHSS score compared with those in the AcT trial because TRACE-2 excluded those eligible for endovascular thrombectomy. In the AcT trial, approximately 25% of the participants presented with large vessel occlusion on CT angiography and 505 participants underwent endovascular thrombectomy. The subgroup analysis of participants with large vessel occlusion in the AcT trial did not show superiority of tenecteplase. In TRACE-2, however, participants eligible for or who were planned to undergo endovascular thrombectomy were excluded from the study and only 51 (4%) individuals subsequently had endovascular thrombectomy after thrombolytic treatment during the trial. A phase 2 trial (EXTEND-IA TNK part 1 and part 2) in patients with large vessel occlusion who underwent thrombectomy after tenecteplase or alteplase suggested that tenecteplase might be superior to alteplase in terms of functional outcome.[16,17] A meta-analysis that included four randomised controlled trials with a total of 433 patients suggested that people with acute ischaemic stroke and large vessel occlusion receiving intravenous tenecteplase might have better recanalisation and clinical outcomes than those receiving intravenous alteplase.[18] The findings of TRACE-2 trial in combination with the AcT trial further strengthen the evidence for non-inferiority of tenecteplase compared with alteplase in treating patients with acute ischaemic stroke.

The dose choice for thrombolytics is crucial for eligible patients with acute ischaemic stroke. The safety and efficacy of tenecteplase was previously investigated at doses of 0·10 mg/kg, 0·25 mg/kg, and 0·40 mg/kg.[19–25] A dose of 0·40 mg/kg did not show better efficacy than that at 0·25 mg/kg,[18] but resulted in higher rates of symptomatic haemorrhage and worse clinical outcomes than with 0·9 mg/kg alteplase.[25] In the TRACE-1 trial in Chinese individuals with acute ischaemic stroke, the safety and efficacy of tenecteplase at doses of 0·10 mg/kg, 0·25 mg/kg, and 0·32 mg/kg were compared with 0·9 mg/kg alteplase.[10] Tenecteplase at a dose of 0·32 mg/kg had a worse safety profile than either 0·25 mg/kg tenecteplase or 0·9 mg/kg alteplase, without any trend

	Tenecteplase (n=711)	Alteplase (n=706)	Effect size (95% CI)*	p value
Symptomatic intracranial haemorrhage within 36 h	15 (2%)	13 (2%)	1·18 (0·56–2·50)	0·72
Symptomatic intracranial haemorrhage within 90 days	17 (2%)	15 (2%)	1·18 (0·59–2·37)	0·74
Parenchymal haematoma 2 intracranial haemorrhage within 36 h	10 (1%)	3 (<1%)	3·73 (0·99–14·13)	0·053
Any intracranial haemorrhage within 90 days	44 (6%)	50 (7%)	0·92 (0·62–1·36)	0·50
Other significant haemorrhage events within 90 days	5 (1%)	5 (1%)	1·05 (0·29–3·90)	0·99
Deaths	46 (7%)	35 (5%)	1·31 (0·86–2·01)	0·22
Adverse events	610 (86%)	613 (87%)	0·99 (0·95–1·03)	0·57
Serious adverse events	116 (16%)	107 (15%)	1·10 (0·87–1·41)	0·55

Data are n (%), effect size (95% CI), or p value. *Risk ratios with their 95% CIs were calculated using Cochran-Mantel-Haenszel method considering the centre effect.

Table 3: **Safety outcomes at 3 months in the safety analysis population**

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.

This study had several limitations. First, for practical reasons including the importance of not delaying intravenous thrombolytic, the study design only blinded the clinicians performing outcome evaluations. Therefore, bias caused by the open-label design cannot be excluded. Second, this study excluded patients with more disabling strokes eligible for endovascular thrombectomy, which might limit the generalisability of the findings to more severely affected patients who could have a higher risk of intracranial haemorrhage.

Given the ease of administration for tenecteplase, it is worth evaluating the efficacy and safety of intravenous tenecteplase with extended time window from 4·5 h to 24 h. Future research could also look to examine whether there is a time-dependent treatment effect of intravenous tenecteplase as compared with alteplase.

In conclusion, tenecteplase was non-inferior (and not superior) to alteplase for acute ischaemic stroke within 4·5 h of symptom onset. The trial results support the implementation of intravenous tenecteplase 0·25 mg/kg as an alternative thrombolytic agent to the standard-of-care alteplase in patients with disabling ischaemic stroke within 4·5 h of stroke onset.

Contributors

YoW, SL, and YP prepared the first draft of the report. YoW, HL, BCVC, LHS, MF, and MWP conceptualised the study design and provided critical comments for the manuscript. YoW was the study principal investigator. SL was involved with the implementation and recruitment to the trial. YP calculated the sample size, developed the statistical plan, and did the statistical analysis. All other authors were local investigators or co-investigators and recruited participants, collected data, revised the final version of the manuscript, and critically reviewed the report and approved the final version before submission. The steering committee was responsible for the overall design, protocol development, interpretation, and supervision of the trial. All the authors guarantee the completeness and accuracy of the reported data and the fidelity of the trial to the protocol. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

LHS reports grants or contracts from the National Institutes of Health; consulting fees from Medtronic and Genentech; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Prime Education; and participation on a Data Safety Monitoring Board or Advisory Board for Diffusion Pharma and Penumbra. MF reports consulting fees from Simcere USA; participation on a Data Safety Monitoring Board or Advisory Board for NoNo and NINOs; and is president of the World Stroke Association. 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 and after signing appropriate data sharing agreements. Please send data access requests to the corresponding author. Such requests must be approved by the respective ethics boards and appropriate data custodians.

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