










Tenecteplase versus alteplase for acute ischaemic stroke in the elderly patients: a post hoc analysis of the TRACE-2 trial

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To cite: Xiong Y, Wang L, Pan Y, *et al.* Tenecteplase versus alteplase for acute ischaemic stroke in the elderly patients: a post hoc analysis of the TRACE-2 trial. *Stroke & Vascular Neurology* 2024;**0**. doi:10.1136/svn-2023-003048

► Additional supplemental material is published online only. To view, please visit the journal online (<https://doi.org/10.1136/svn-2023-003048>).

Received 18 December 2023
Accepted 20 May 2024



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ABSTRACT

Background The benefit–risk profile of tenecteplase in the elderly patients with acute ischaemic stroke (AIS) is uncertain. We sought to investigate the efficacy and safety of 0.25 mg/kg tenecteplase compared with alteplase for AIS patients aged ≥80 years.

Methods We performed a post hoc analysis of the Tenecteplase Reperfusion Therapy in Acute Ischaemic Cerebrovascular Events-2 Trial, a randomised, phase 3, non-inferiority clinical trial. Disabling AIS patients aged ≥80 years who initiated intravenous thrombolytics within 4.5 hours of symptom onset were enrolled from June 2021 to May 2022 across 53 centres in China and were randomly allocated to receive 0.25 mg/kg tenecteplase or 0.9 mg/kg alteplase. The primary efficacy outcome was the proportion of participants with a modified Rankin Scale (mRS) score of 0–1 at 90 days. Symptomatic intracranial haemorrhage (sICH) within 36 hours was the safety outcome.

Results Of 137 participants, mRS 0–1 at 90 days occurred in 37 (49.3%) of 75 in the tenecteplase group vs 20 (33.9%) of 59 in the alteplase group (risk ratio (RR) 1.47, 95% CI 0.96 to 2.23). sICH within 36 hours was observed in 3 (4.0%) of 76 in the tenecteplase group and two (3.3%) of 61 in the alteplase group (RR 1.30, 95% CI 0.20 to 8.41).

Conclusions The risk–benefit profile of tenecteplase thrombolysis was preserved in the elderly patients, which lends further support to intravenous 0.25 mg/kg tenecteplase as an alternative to alteplase in these patients.

INTRODUCTION

The prevalence and severity of stroke markedly increase with age.¹ About 30% of acute strokes occur among people aged over 80 years.² The clinical benefits and potential risks of intravenous thrombolysis in acute ischaemic stroke (AIS) in elderly patients have always been a topic of concern. Intravenous alteplase is the only approved thrombolytic agent for ischaemic stroke and was equally recommended for patients ≤80 and >80 years of age in the American Heart Association/American Stroke Association

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Alteplase was equally recommended by current guidelines for acute ischaemic stroke (AIS) patients of ≤80 or >80 years. The safety and efficacy profile of tenecteplase in patients ≥80 years old was lacking.

WHAT THIS STUDY ADDS

⇒ 0.25 mg/kg tenecteplase was not statistically different from alteplase regarding efficacy and safety outcomes in AIS patients who were ≥80 years old within 4.5 hours of symptom onset.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Intravenous 0.25 mg/kg tenecteplase can be an alternative thrombolytic agent to the standard-of-care alteplase in patients of ≥80 years old.

guideline (Class of Recommendations of I and Level of Evidence of A)³ and European Stroke Organisation guidelines.⁴ The odds of independent recovery favoured alteplase for elderly patients in the third international stroke trial⁵ including 1617 (53%) patients older than 80 years of age and meta-analysis of alteplase trials⁶ including 1729 (26%) patients >80 years showed that there were no significant differences in alteplase effect based on age group. A recent pooled analysis, based on the individual patient data of seven randomised trials found that among patients aged >80 years, alteplase was associated with a higher proportion of good stroke outcome and similar 90-day mortality compared with placebo.⁷

Tenecteplase, the third-generation thrombolytic drug, is a genetically modified tissue plasminogen activator with a longer half-life, higher affinity for fibrin, and stronger tolerance to plasminogen activator inhibitor-1 than alteplase.⁸ A pooled analysis from EXTEND-IA TNK (Tenecteplase vs Alteplase Before Endovascular Therapy for Ischaemic Stroke) trials showed that tenecteplase with

a dose of 0.25 mg/kg was associated with improved 90-day functional outcome and less mortality compared with 0.40 mg/kg tenecteplase or 0.9 mg/kg alteplase for patients older than 80 years in bridging endovascular procedure.⁹ The phase 3 trials AcT (Intravenous tenecteplase compared with alteplase for AIS in Canada),¹⁰ TRACE-2 (Tenecteplase Reperfusion Therapy in Acute Ischaemic Cerebrovascular Events-2)¹¹ and ATTEST-2 (Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis-2),¹² performed recently provided robust evidence for 0.25 mg/kg tenecteplase not inferior to alteplase within 4.5 hours of symptom onset and the post hoc subgroup analysis showed that there was no statistical heterogeneity of tenecteplase treatment effect by age group. However, the efficacy and safety of tenecteplase for patients aged over 80 years was not yet well investigated, especially in the patients without endovascular thrombectomy.

Our study is a post hoc subgroup analysis from the TRACE-2 trial¹¹ and aimed to test the safety and efficacy of tenecteplase 0.25 mg/kg compared with alteplase 0.9 mg/kg in patients older than 80 years and without endovascular treatment (EVT).

METHODS

Study design and settings

This study was a post hoc subgroup analysis of the TRACE-2 trial data. TRACE-2 was a phase 3, multicentre, prospective, open-label, blinded-endpoint, randomised controlled, non-inferiority trial with 1430 AIS patients enrolled within 4.5 hours of stroke onset in China. Patients were randomly assigned to receive 0.25 mg/kg tenecteplase (max 25 mg) or 0.9 mg/kg alteplase (max 90 mg). The design, rationale, baseline patient characteristics, and primary results of the trial have been previously published (online supplemental file 1).^{11 13}

In the present study, patients ≥ 80 years were included in the analyses. TRACE-2 was performed under the guidelines of the Chinese Stroke Association.¹⁴ Written informed consent of all patients was obtained before participation. The study followed the Consolidated Standards of Reporting Trials reporting guideline.¹⁵

Outcomes

The primary efficacy outcome was the proportion of participants with modified Rankin Scale (mRS) 0–1 at 90 days. Secondary outcomes were mRS 0–2 at 90 days; mRS score at 90 days; substantial neurological improvement, which was defined as a decrease of ≥ 4 points or a score of 0 or 1 on the National Institute of Health Stroke Scale (NIHSS) at 24 hours and at 7 days or discharge, whichever occurred first; the rate of Barthel Index score ≥ 95 points and European health-related quality of life at 90 days. The primary safety outcome was symptomatic intracranial haemorrhage (sICH) within 36 hours defined by the European Cooperative Acute Stroke Study III.¹⁶ Other evaluated safety outcomes included parenchymal

hematoma 2 (PH2) defined by the Safe Implementation of Thrombolysis in Stroke-Monitoring study¹⁷; any intracranial haemorrhage or other significant haemorrhagic events as defined by the Global Utilisation of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries criteria¹⁸; and deaths from all causes within 90 days of disease onset. Both adverse events and serious adverse events were also documented up to 90 days. Detailed definitions of outcomes in the TRACE-2 trial have been reported previously.^{11 13}

Statistical analysis

We analysed the primary efficacy outcomes in the modified intention-to-treat (mITT) population defined as participants who received the allocated thrombolytics and in the per-protocol (PP) population. The χ^2 test adjusting for the pooled-site effect (≥ 20 patients for each stratum) was used to compare the primary outcome between the two groups with the 95% CI of risk ratio (RR). We used the normal approximation (Wald formula) adjusting for the pooled-site effect to derive the 95% CI of absolute risk differences and binary logistic regression to calculate the OR with 95% CIs.

Secondary efficacy outcomes analyses were based on mITT population. We used ordinal logistic regression to calculate a common OR with its 95% CI for the ordinal 90-day mRS score, and the Cochran-Mantel-Haenszel method adjusting for the pooled-site effect to derive ORs with 95% CIs for other secondary efficacy outcomes. The main efficacy analyses were performed without imputation for missing data.

In the safety analyses, RRs with their 95% CIs were calculated using Cochran-Mantel-Haenszel method considering the centre effect. χ^2 or Fisher's exact test was done as appropriate to compare adverse events and serious adverse events.

A two-sided $p < 0.05$ was considered to be statistically significant. All statistical analyses were performed by SAS software (V.9.4).

RESULTS

Study participants

Among 1430 randomised participants in the TRACE-2 trial, 137 (9.6%) 80 years or older patients were included in the present post hoc subgroup analysis, of whom 76 were assigned to tenecteplase group and 61 to alteplase group (figure 1). Table 1 shows baseline characteristics of the participants.

Efficacy outcomes

In the mITT analysis, 37 (49.3%) of 75 patients in the tenecteplase group and 20 (33.9%) of 59 patients in the alteplase group had mRS 0–1 at 90 days (RR 1.47 (95% CI 0.96 to 2.23); table 2, figure 2). The p value for interaction was 0.08 for the primary outcome with the cohort that was less than 80 years of age. The results of the PP analysis were consistent (table 2). 46/75 (61.3%) in the tenecteplase group and 26/59 (44.1%) in the alteplase

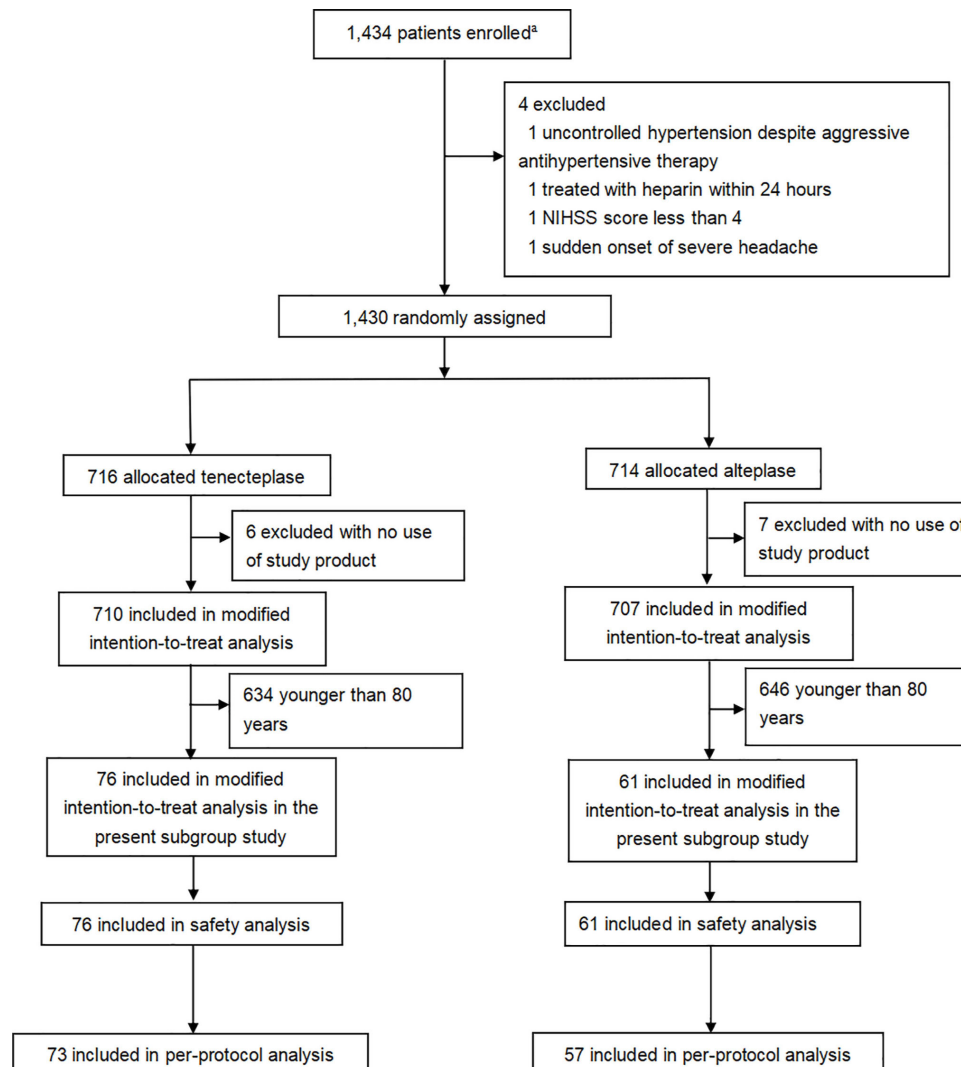


Figure 1 Flow diagram. ^aPhysicians only obtained informed consent for this trial from patients who were suitable for intravenous thrombolytic but not for endovascular thrombectomy. NIHSS, National Institutes of Health Stroke Scale.

group had mRS score 0–2 (OR 2.01 (95% CI 1.01 to 4.03), $p=0.048$). Patients in the tenecteplase group achieved a better functional outcome (the median mRS score: 2 vs 3; OR 1.90 (95% CI 1.04 to 3.50); $p=0.04$) and a higher rate of Barthel Index ≥ 95 (36/64 (56.3%) vs 17/47 (36.2); OR 2.27 (1.05 to 4.92); $p=0.04$). Analyses for other secondary outcomes within 90 days showed no significant treatment effect.

Safety outcomes

Table 3 shows the safety outcomes of patients classified according to the actual treatment. The safety analysis set had 76 patients assigned to tenecteplase and 61 to alteplase. sICH within 36 hours occurred in 3 (4.0%) of 76 patients treated with tenecteplase and 2 (3.3%) of 61 treated with alteplase (RR 1.30, 95% CI 0.20 to 8.40). One symptomatic PH 2 and intracranial haemorrhages within 36 hours were found in the tenecteplase group. The rates of deaths were not significantly different between the two groups (14.5% vs 19.7%; RR 0.68, 95% CI 0.31 to 1.51). Rates of adverse events and serious adverse events were

similar between the two groups (online supplemental table S1 and S2).

DISCUSSION

In this post hoc subgroup analysis of the TRACE-2 trial including 9.6% patients with AIS within 4.5 hours of symptom onset who were >80 years old and eligible for intravenous thrombolysis treatment without access to thrombectomy, we found that intravenous 0.25 mg/kg tenecteplase was not statistically different with 0.9 mg/kg alteplase for an excellent functional outcome without increasing risk of sICH or deaths at 90 days. Hence, increased age should not be a reason to withhold treatment with tenecteplase in AIS.

Thrombolysis in elderly patients has drawn great attention from clinicians and researchers. The benefit of intravenous alteplase was well established for adult patients with disabling stroke symptoms regardless of age and stroke severity.^{3,6} In clinical trials investigating tenecteplase, a potential alternative to alteplase, most studies did

Table 1 Baseline characteristics of the participants

Characteristics	Tenecteplase (n=76)	Alteplase (n=61)	P value
Age (IQR), years	82.0 (81.0–86.0)	83.0 (81.0–85.0)	0.86
Sex, n (%)			0.66
Male	32 (42.1)	28 (45.9)	
Female	44 (57.9)	33 (54.1)	
Weight (IQR), kg	55.0 (47.0–65.0)	57.0 (50.0–65.0)	0.63
Medical history, n (%)			
Hypertension	56 (73.7)	44 (72.1)	0.84
Diabetes	13 (17.1)	15 (24.6)	0.28
Dyslipidaemia	8 (10.5)	15 (24.6)	0.03
Coronary heart disease	26 (34.2)	22 (36.1)	0.82
Current smoking, n (%)	8 (10.5)	8 (13.1)	0.51
History of medication use, n (%)			
Antiplatelet agents	10 (13.2)	9 (14.8)	0.79
Anticoagulant agents	0 (0.0)	1 (1.6)	0.45
Lipid-lowering drugs	8 (10.5)	7 (11.5)	0.86
Hypoglycaemic drugs	4 (5.3)	6 (9.8)	0.49
Antihypertensive drugs	29 (38.2)	27 (44.3)	0.47
mRS score before stroke, n (%)			0.77
0	66 (86.8)	54 (88.5)	
1	10 (13.2)	7 (11.5)	
Baseline NIHSS score (IQR)	9 (6–14)	9 (6–12)	0.87
Baseline NIHSS score categories, n (%)			0.66
≤7	31 (40.8)	22 (36.1)	
8–14	29 (38.2)	28 (45.9)	
≥15	16 (21.1)	11 (18.0)	
Onset-to-needle time (IQR), min	174.0 (138.5–207.0)	184.0 (146.0–230.0)	0.14
Onset-to-needle time categories, n (%)			0.26
<3 hours	41 (54.0)	27 (44.3)	
≥3 hours	35 (46.1)	34 (55.7)	
Door-to-needle time (IQR), min	64.0 (50.0–82.0)	65.0 (50.0–90.0)	0.84
Bridging thrombectomy, n (%)	3 (4.0)	2 (3.3)	>0.99
Total costs (IQR), yuan	9725.76 (7382.68–13552.70)	12701.15 (7819.84–19371.11)	0.11
Thrombolysis costs (IQR), yuan	3688.00 (3688.00–7376.00)	5340.24 (3570.00–5340.24)	0.01
Hospital stay, n (%)			0.10
≤7 days	14 (20.0)	19 (32.8)	
>7 days	56 (80.0)	39 (67.2)	
Data missing	6	3	

Data are median (IQR) or n (%).

mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale.

not employ an upper age-limit exclusion criterion.^{11 19–23} However, studies of tenecteplase in these patients are limited. The subgroup analysis from NOR-TEST (Norwegian Tenecteplase Stroke Trial) including 273 patients ≥80 years identified no significant differences between 0.40 mg/kg tenecteplase and 0.90 mg/kg alteplase

regarding the rates mRS 0–1 at 3 months and sICH within 48 hours.²⁴ Similar conclusion was drawn in the context of large vessel occlusion (LVO) and EVT in a pooled analysis of the EXTEND-IA TNK trials.⁹ However, the later NOR-TEST 2 trial enrolled 24.5% (50/204) patients older than 80 years and found that a dose of 0.40 mg/kg

Table 2 Efficacy outcomes within 90 days

	Tenecteplase	Alteplase	Effect size (95% CI)	P value
Primary outcome				
mRS score 0–1 at 90 days (n=134)	37/75 (49.3%)	20/59 (33.9%)	–	–
Risk ratio	–	–	1.47 (0.96 to 2.23)	–
OR	–	–	1.90 (0.94 to 3.84)	–
Difference in proportion	–	–	0.16 (–0.01 to 0.33)	–
Primary outcome (per-protocol)				
mRS score 0–1 at 90 days (n=130)	37/73 (50.7%)	19/57 (33.3%)	–	–
Risk ratio	–	–	1.50 (0.98 to 2.29)	–
OR	–	–	2.06 (1.00 to 4.21)	–
Difference in proportion	–	–	0.17 (–0.002 to 0.35)	–
Secondary outcomes (modified intention-to-treat)				
mRS score 0–2 at 90 days (n=134)	46/75 (61.3%)	26/59 (44.1%)	2.01 (1.01 to 4.03)	0.048
mRS at 3 months (n=134)	2 (0 to 4)	3 (1 to 5)	1.90 (1.04 to 3.50)	0.04
Major neurological improvement at 24 hours (n=134)	38/74 (51.4%)	21/60 (35.0%)	1.96 (0.97 to 3.95)	0.06
Major neurological improvement at 7 days or discharge (n=122)	49/68 (72.1%)	33/54 (61.1%)	1.64 (0.77 to 3.52)	0.20
European quality of life visual analogue scale (n=110)	80.0 (60.0 to 90.0)	80.0 (60.0 to 90.0)	–3.38 (–12.11 to 5.36)	0.44
Barthel Index≥95 (n=111)	36/64 (56.3%)	17/47 (36.2)	2.27 (1.05 to 4.92)	0.04

mRS, modified Rankin Scale.

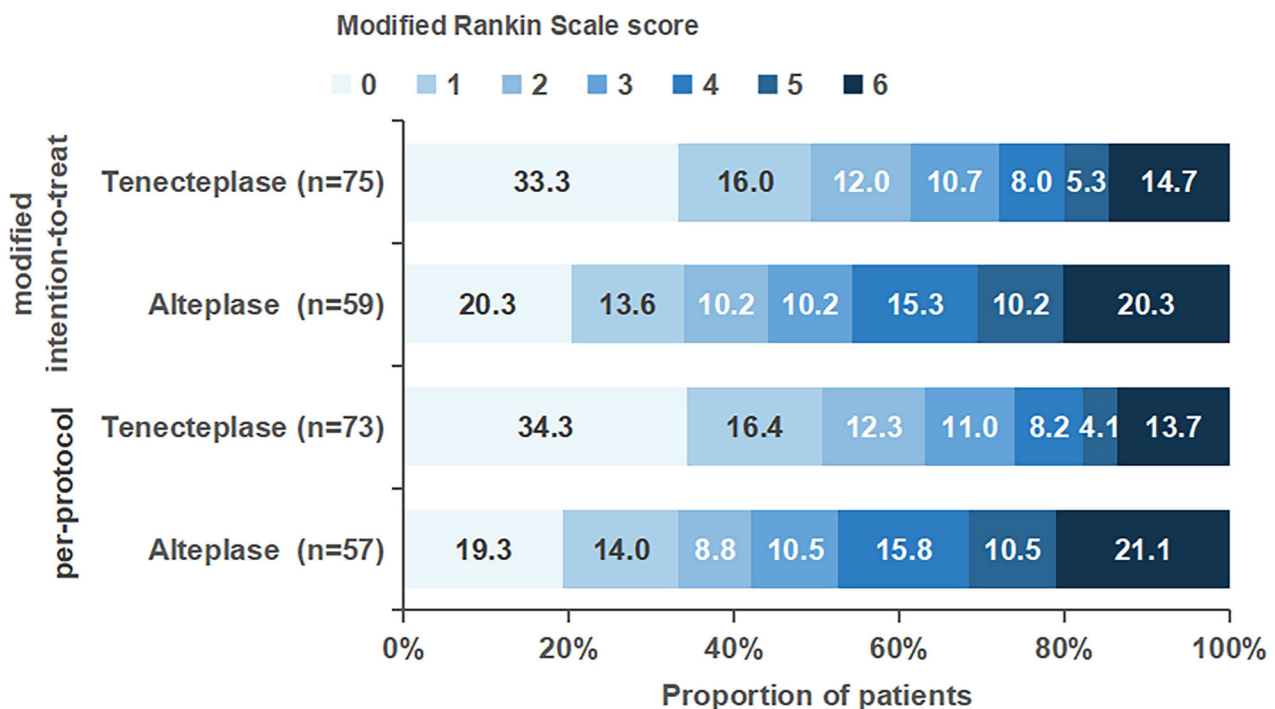
**Figure 2** Distribution of modified Rankin Scale scores at 90 days in the modified intention-to-treat analysis and per-protocol populations, according to assigned treatment.

Table 3 Safety outcomes within 90 days in the safety analysis population

	Tenecteplase (n=76)	Alteplase (n=61)	Effect size (95% CI)*	P value
sICH within 36 hours	3 (4.0%)	2 (3.3%)	1.30 (0.20 to 8.41)	0.78
sICH within 90 days	3 (4.0%)	2 (3.3%)	1.30 (0.20 to 8.41)	0.78
Parenchymal haematoma two intracranial haemorrhage within 36 hours*	1 (1.3%)	0 (0.0%)	–	–
Any intracranial haemorrhage within 90 days	10 (13.2%)	7 (11.5%)	1.22 (0.45 to 3.32)	0.68
Deaths	11 (14.5%)	12 (19.7%)	0.68 (0.31 to 1.51)	0.36
Adverse events	70 (92.1%)	56 (91.8%)	1.02 (0.92 to 1.13)	0.66
Serious adverse events	15 (19.7%)	16 (26.2%)	0.79 (0.40 to 1.56)	0.50

*Risk ratio with its 95% CI was not able to be calculated due to the small size of outcome events.

sICH, symptomatic intracranial haemorrhage.

tenecteplase did not show better mRS 0–1 after 3 months than that at 0.25 mg/kg but resulted in higher rates of sICH during the first 48 hours than with 0.9 mg/kg alteplase.²⁵ In the subgroup analysis of the EXTEND-IA TNK trials including 137 patients >80 years and with LVO, a lower dose of 0.25 mg/kg tenecteplase was significantly associated with improved 90-day mRS compared with 0.40 mg/kg tenecteplase and alteplase after adjusting for baseline NIHSS score, age and time from symptom onset to arterial puncture, despite that there was no efficacy and safety difference of the three treatment groups (0.25 mg/kg TN, 0.4 mg/kg tenecteplase and alteplase) in the younger group.⁹ The rate of excellent functional outcome (mRS 0–1) reached 42% in the tenecteplase group compared with 17% in the alteplase group, and there was no sICH associated with tenecteplase thrombolysis. These supported that 0.25 mg/kg is the recommended dose of tenecteplase regardless of age. 0.25 mg/kg tenecteplase was non-inferior to alteplase in the Intravenous tenecteplase compared with alteplase for AIS in the recent AcT¹⁰ and ATTEST-2¹² trials and there was no statistical heterogeneity of tenecteplase treatment effect by age group. Consistent with these findings, our study found that tenecteplase was not statistically different with alteplase in ITT and PP patients. Moreover, elderly patients in the tenecteplase group achieved similar safety outcomes to the alteplase group. Additionally, the 0.25 mg/kg tenecteplase thrombolysis was significantly economical as the median costs for thrombolysis were around 30% lower than 0.90 mg/kg alteplase in our study. The total costs in the tenecteplase group were also numerical lower. The findings further indicated that the tenecteplase thrombolysis may be beneficial in patients aged ≥80 years.

The results in the subgroup ≥80 years were not statistically heterogeneous compared with the overall TRACE-2 effect based on inferiority boundary 0.937. Tenecteplase in AIS patients aged 80 years and over also reached non-inferiority, but not superiority, while in this subgroup analysis, we tested difference between tenecteplase versus alteplase and observed no significant effect difference

between the two arms. The AcT trial including 506 (32.1%) patients with thrombectomy and 542 (34.6%) patients ≥80 years¹⁰ and the ATTEST-2 trial including 12.3% thrombectomy and 26% patients ≥80 years¹² did not find statistical heterogeneity of tenecteplase effect versus alteplase by age group. But the baseline characteristics of the elderly subgroup were not further investigated. Therefore, it was difficult for researchers to conduct cross-comparisons. 0.25 mg/kg tenecteplase among elderly patients in the EXTEND-IA TNK trials achieved significantly better mRS score at 3 months, which was consistent with the positive benefit–risk profile shown in the secondary efficacy analysis in our study. However, the 95% CIs of effect estimates for freedom from disability were relatively too wide in both studies to reach any definite conclusion.⁹ The recently published large observational CERTAIN study (The Comparative Effectiveness of Routine Tenecteplase vs Alteplase in Acute Ischaemic Stroke Collaboration) included around a quarter of patients ≥80 years and found that the tenecteplase group was more likely to achieve an mRS score 0–1 at 90 days than alteplase.²⁶ However, the age subgroup was not further investigated and real-world studies for tenecteplase in octogenarians are warranted. From the safety perspective, more frequent sICH was seen in the elderly patients compared with the overall trial. The TRACE-2 trial excluded more disabling strokes eligible for endovascular thrombectomy and had fewer older patients with previous antithrombotic drugs. Unexpectedly, we detected a higher risk of sICH in the tenecteplase group in the present analysis than that in the EXTEND-IA TNK trials. The rate of sICH in the tenecteplase group of our study was also higher than 1.8% found in the CERTAIN study, which involved 9238 patients with ischaemic stroke in New Zealand, Australia and the USA.²⁶ The higher proportion of sICH in the present study might derive from the small sample size and regional and racial differences.

This is a novel post hoc analysis to evaluate the efficacy and safety of tenecteplase for AIS among Asian patients aged ≥80 years. However, there were several limitations to be acknowledged. First, type I errors can be introduced

in such an exploratory and subgroup analysis of a randomised clinical trial. Second, although the TRACE-2 trial is a large-scale trial, the number of patients older than 80 years was 137 of 1430 patients (9.6%) with only modest power to detect differences, which was smaller compared with the elderly subjects in the ACT¹⁰ or ATTEST-2.¹² Our findings, due to the small sample size, should be interpreted with caution. Furthermore, since patients with LVO eligible for endovascular thrombectomy were excluded, the comparison of the two treatment strategies in elderly patients with/without LVO, which was of great interest to clinicians, was not investigated in the present study and our findings cannot be generalised to patients with LVO for whom thrombectomy is intended. Our analysis adds complementary evidence to the pooled analysis of EXTEND-IA TNK trials⁹ which was conducted exclusively in the context of LVO and EVT. Finally, the TRACE-2 trial was conducted exclusively in China and the generalisability of the results in other population should be further validated.

CONCLUSIONS

Within 4.5 hours of symptom onset, 0.25 mg/kg tenecteplase thrombolysis was comparable with alteplase for achieving excellent functional outcome with a similar safety profile in AIS patients who were ≥ 80 years old and did not receive endovascular thrombectomy. The trial results lend further support to intravenous 0.25 mg/kg tenecteplase as an alternative to the standard-of-care alteplase in patients of increased age.

Contributors YW had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: YX and YW. Acquisition, analysis, or interpretation of data: YX, LW, YP, MW and SL. Drafting of the manuscript: YX, YW and CD. Critical revision of the manuscript for important intellectual content: LHS and BCVC. Statistical analysis: YP, MW and SL. Administrative, technical, or material support: ZL, MH, NW, ZC and SW. Guarantors: YW and YX.

Funding This study was funded by Beijing Municipal Science & Technology Committee (Z211100003521019) China Shijiazhuang Pharmaceutical Company Recomgen Pharmaceutical (Guangzhou) Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences(2019-I2M-5-029). National Natural Science Foundation(82111530203, 82171272).

Competing 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. All other authors report no disclosures relevant to the manuscript.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and the principles of the Declaration of Helsinki. All participants gave informed consent before taking part. This study obtained Ethics approval of Institutional Review Board of Beijing Tiantan Hospital, Capital Medical University with number YW2020-046-04. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

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REFERENCES

- Wang Y-J, Li Z-X, Gu H-Q, et al. China stroke Statistics 2019: a report from the National center for Healthcare quality management in neurological diseases, China National clinical research center for neurological diseases, the Chinese stroke Association, national center for chronic and non-communicable disease control and prevention, Chinese center for disease control and prevention and Institute for global Neuroscience and stroke Collaborations. *Stroke Vasc Neurol* 2020;5:211–39.
- Mishra NK, Ahmed N, Andersen G, et al. Thrombolysis in very elderly people: controlled comparison of SITS International stroke Thrombolysis Registry and virtual International stroke trials Archive. *BMJ* 2010;341:c6046.
- Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for Healthcare professionals from the American heart Association/American stroke Association. *Stroke* 2019;50:e344–418.
- Berge E, Whiteley W, Audebert H, et al. European stroke Organisation (ESO) guidelines on intravenous Thrombolysis for acute ischaemic stroke. *Eur Stroke J* 2021;6:L–LXII.
- Wardlaw JM, Murray V, Berge E, et al. Recombinant tissue plasminogen activator for acute ischaemic stroke: an updated systematic review and meta-analysis. *Lancet* 2012;379:2364–72.
- Emberson J, Lees KR, Lyden P, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous Thrombolysis with Alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. *Lancet* 2014;384:1929–35.
- Bluhmki E, Danays T, Biegert G, et al. Alteplase for acute ischemic stroke in patients aged >80 years: pooled analyses of individual patient data. *Stroke* 2020;51:2322–31.
- Keyt BA, Paoni NF, Refino CJ, et al. A faster-acting and more potent form of tissue plasminogen activator. *Proc Natl Acad Sci U S A* 1994;91:3670–4.
- Yogendrakumar V, Churilov L, Mitchell PJ, et al. Safety and efficacy of Tenecteplase in older patients with large vessel occlusion: A pooled analysis of the EXTEND-IA TNK trials. *Neurology* 2022;98:e1292–301.
- Menon BK, Buck BH, Singh N, et al. Act trial investigators. intravenous Tenecteplase compared with Alteplase for acute ischaemic stroke in Canada (act): a pragmatic, Multicentre, open-label, Registry-linked, randomised, controlled, non-inferiority trial. *Lancet* 2022;400:161–9.
- Wang Y, Li S, Pan Y, et al. Tenecteplase versus Alteplase in acute ischaemic cerebrovascular events (TRACE-2): a phase 3, Multicentre, open-label, randomised controlled, non-inferiority trial. *Lancet* 2023;401:645–54.
- Muir GF, Ford I, Wardlaw JM, et al. TENECTPLASE VERSUS ALTEPLASE FOR ACUTE STROKE WITHIN 4.5H OF ONSET: THE SECOND ALTEPLASE-TENECTPLASE TRIAL EVALUATION

- FOR STROKE THROMBOLYSIS (ATTEST-2). 15th world stroke Congress. In: *International Journal of Stroke*. Toronto, Canada, 2023: 18. 3–420.
- 13 Li S, Campbell BCV, Schwamm LH, *et al*. Tenecteplase reperfusion therapy in acute ischaemic cerebrovascular events-II (TRACE II): rationale and design. *Stroke Vasc Neurol* 2022;7:71–6.
 - 14 Dong Q, Dong Y, Liu L, *et al*. The Chinese stroke Association scientific statement: intravenous Thrombolysis in acute ischaemic stroke. *Stroke Vasc Neurol* 2017;2:147–59.
 - 15 Schulz KF, Altman DG, Moher D, *et al*. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;340:c332.
 - 16 Hacke W, Kaste M, Bluhmki E, *et al*. Thrombolysis with Alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* 2008;359:1317–29.
 - 17 Wahlgren N, Ahmed N, Dávalos A, *et al*. Thrombolysis with Alteplase for acute ischaemic stroke in the safe implementation of Thrombolysis in stroke-monitoring study (SITS-MOST): an observational study. *Lancet* 2007;369:275–82.
 - 18 investigators G. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med* 1993;329:673–82.
 - 19 Huang X, Cheripelli BK, Lloyd SM, *et al*. Alteplase versus Tenecteplase for Thrombolysis after ischaemic stroke (ATTEST): a phase 2, randomised, open-label, blinded Endpoint study. *Lancet Neurol* 2015;14:368–76.
 - 20 Campbell BCV, Mitchell PJ, Churilov L, *et al*. Tenecteplase versus Alteplase before Thrombectomy for ischemic stroke. *N Engl J Med* 2018;378:1573–82.
 - 21 Parsons M, Spratt N, Bivard A, *et al*. A randomized trial of Tenecteplase versus Alteplase for acute ischemic stroke. *N Engl J Med* 2012;366:1099–107.
 - 22 Bivard A, Zhao H, Churilov L, *et al*. Comparison of Tenecteplase with Alteplase for the early treatment of ischaemic stroke in the Melbourne mobile stroke unit (TASTE-A): a phase 2, randomised, open-label trial. *Lancet Neurol* 2022;21:520–7.
 - 23 Roaldsen MB, Eltoft A, Wilsgaard T, *et al*. Safety and efficacy of Tenecteplase in patients with wake-up stroke assessed by non-contrast CT (TWIST): a Multicentre, open-label, randomised controlled trial. *Lancet Neurol* 2023;22:117–26.
 - 24 Thommessen B, Næss H, Logallo N, *et al*. Tenecteplase versus Alteplase after acute ischemic stroke at high age. *Int J Stroke* 2021;16:295–9.
 - 25 Kvistad CE, Næss H, Helleberg BH, *et al*. Tenecteplase versus Alteplase for the management of acute ischaemic stroke in Norway (NOR-TEST 2, part A): a phase 3, randomised, open-label, blinded Endpoint, non-inferiority trial. *Lancet Neurol* 2022;21:511–9.
 - 26 Warach SJ, Ranta A, Kim J, *et al*. Symptomatic intracranial hemorrhage with Tenecteplase vs Alteplase in patients with acute ischemic stroke: the comparative effectiveness of routine Tenecteplase vs Alteplase in acute ischemic stroke (CERTAIN) collaboration. *JAMA Neurol* 2023;80:732–8.