JAMA | Original Investigation

Tenecteplase for Acute Non–Large Vessel Occlusion 4.5 to 24 Hours After Ischemic Stroke
The OPTION Randomized Clinical Trial

Gaoting Ma, MD; Ran Mo, MD; Yingting Zuo, PhD; Qingfeng Ma, MD; Guangjian Zhao, MD; Xiaoxi Yao, MS; Ji Liang, MD; Li Zhou, MS; Yong He, MS; Faqing Long, MD; Zhengzhou Yuan, MD; Lei Liu, MS; Guosheng Han, MS; Yan Tan, MS; Zhibing Ai, MD; Chunsheng Cai, MS; Juan Liu, MS; Liyong Zhang, MD; Haihua Yang, MD; Tingyu Yi, MD; Li Li, MD; Yao Fu, MS; Yanxing Zhang, MS; Xiangzhong Shao, MS; Zhipeng Yu, MD; Saizhen Wu, MS; Yanqiu Du, MS; Lingqun Mao, MS; Hongling Guo, MS; Xufeng Chen, MD; Yifei Chen, MD; Qiong Zhao, MS; Liyi Chi, MS; Yi Liu, MD; Haochun Zhang, MS; Guangzong Li, MS; Shujuan Meng, MD; Yifan Wu, MD; Jieying Wu, MD; Ziying Jiang, MD; Shaoyuan Lei, PhD; Daiquan Gao, MD; Lianmei Zhong, MD; Jens Fiehler, MD; Duolao Wang, PhD; Thanh N. Nguyen, MD; Jeffrey L. Saver, MD; Junwei Hao, MD, PhD; for the OPTION Investigators

IMPORTANCE The efficacy and safety of intravenous tenecteplase in non–large vessel occlusion acute ischemic stroke beyond 4.5 hours after symptom onset remain uncertain.

OBJECTIVE To assess the efficacy and safety of intravenous tenecteplase administered 4.5 to 24 hours after stroke onset in patients with non–large vessel occlusion and salvageable brain tissue.

DESIGN, SETTING, AND PARTICIPANTS This randomized, open-label, blinded end-point clinical trial was conducted at 48 centers in China. A total of 566 patients with non–large vessel occlusion stroke and evidence of potentially salvageable tissue determined on perfusion imaging presenting within 4.5 to 24 hours of the time last seen well were recruited between June 2, 2023, and August 4, 2025 (final follow-up, October 28, 2025).

INTERVENTIONS Patients were randomly assigned 1:1 using a minimization algorithm to receive intravenous tenecteplase (0.25 mg/kg; maximum dose, 25 mg; n = 282) or standard medical treatment (n = 284).

MAIN OUTCOMES AND MEASURES The primary efficacy outcome was an excellent functional outcome, defined as a score of 0 or 1 on the modified Rankin Scale at 90 days. Safety outcomes included symptomatic intracranial hemorrhage within 36 hours and mortality within 90 days.

RESULTS Among the 570 patients randomized, 566 were included in the primary analysis (median age, 68 [IQR, 59-75] years; 196 female [34.6%]). An excellent functional outcome was observed in 123 of 282 patients (43.6%) in the tenecteplase group and 97 of 284 (34.2%) in the control group (risk ratio, 1.28 [95% CI, 1.04-1.57]; *P* = .02). The incidence of symptomatic intracranial hemorrhage at 2.8% was higher with tenecteplase than with standard medical treatment at 0% (risk difference, 2.85% [95% CI, 1.16%-5.54%]; *P* = .004), and the mortality at 90 days was 5.0% and 3.2%, respectively (risk ratio, 1.57 [95% CI, 0.69-3.57]; *P* = .28).

CONCLUSIONS AND RELEVANCE Among patients with non–large vessel occlusion acute ischemic stroke and salvageable brain tissue, intravenous tenecteplase administered 4.5 to 24 hours after onset resulted in a greater likelihood of an excellent functional outcome at 90 days than standard care but had an increased risk of symptomatic intracranial hemorrhage.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT05752916

JAMA. doi:10.1001/jama.2026.0210
Published online February 5, 2026.

Visual Abstract

Research Summary

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The OPTION Investigators appear listed in Supplement 4.

Corresponding Author: Junwei Hao, MD, PhD, Department of Neurology, Xuanwu Hospital Capital Medical University, National Center for Neurological Disorders, 45 Changchun St, Beijing, China (haojunwei@vip.163.com).

Acute ischemic stroke caused by an occlusion of the internal carotid artery, proximal middle cerebral artery, vertebral artery, or basilar artery (collectively termed *large vessel occlusions*) is associated with poor functional outcomes and high mortality in the absence of reperfusion.[1,2] Endovascular thrombectomy within 24 hours of symptom onset is effective for acute large vessel occlusion stroke in selected patients.[1-4] When thrombectomy is unavailable or not planned, intravenous thrombolysis is effective within 4.5 hours of symptom onset (albeit conferring lesser benefit) and potentially when administered between 4.5 and 24 hours.[5,6]

Non–large vessel occlusion acute ischemic stroke is more common than stroke due to large vessel occlusion. Such stroke generally arises from medium vessel occlusion, small vessel occlusion (including deep and long pial penetrator vessels), hemodynamic watershed ischemia, and unusual or disseminated conditions.[7] Endovascular thrombectomy has generally not been shown to benefit these patients,[8,9] and intravenous thrombolysis within 4.5 hours is the standard of care for eligible patients.[10,11] Evidence remains scarce from direct comparisons of intravenous thrombolysis vs standard medical treatment for acute ischemic stroke due to non–large vessel occlusion beyond 4.5 hours after onset.

Tenecteplase, a modified human tissue plasminogen activator, has been shown to be noninferior to—and potentially superior to—alteplase within 4.5 hours after stroke onset.[12] Therefore, the Tenecteplase for Acute Non-Large Vessel Occlusion in the Extended Time Window (OPTION) trial was designed to test the hypothesis that intravenous tenecteplase thrombolysis initiated between 4.5 and 24 hours after symptom onset would provide a benefit in patients with acute ischemic stroke due to non–large vessel occlusion with salvageable brain tissue.

Key Points

Question Does intravenous tenecteplase administered 4.5 to 24 hours after onset improve clinical outcomes among patients with non–large vessel occlusion acute ischemic stroke and salvageable brain tissue?

Findings This randomized clinical trial that included 566 patients found that 43.6% of patients receiving tenecteplase and 34.2% of patients receiving standard medical treatment achieved an excellent functional outcome (measured by a modified Rankin Scale score of 0 or 1) at 90 days. This resulted in a risk ratio of 1.28, a difference that was statistically significant.

Meaning Findings from this study support intravenous tenecteplase given 4.5 to 24 hours after stroke onset for patients with acute non–large vessel occlusion and salvageable brain tissue.

Methods

Trial Design and Oversight

We conducted a multicenter, randomized, open-label trial with blinded outcome assessment at 48 Chinese centers. The trial was approved by the institutional review board at Xuanwu Hospital Capital Medical University and all participating centers. The study protocol was published and is available in Supplement 1, and the statistical analysis plan in Supplement 2.[13] Written informed consent was obtained from all patients or their legal representatives before randomization.

The trial was designed, conducted, and overseen by the steering committee, with safety monitored by an independent data and safety monitoring board (DSMB). It was conducted in accordance with the principles of the Declaration of Helsinki[14] and the International Council for Harmonisation guidelines for Good Clinical Practice. This article followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.

Participants

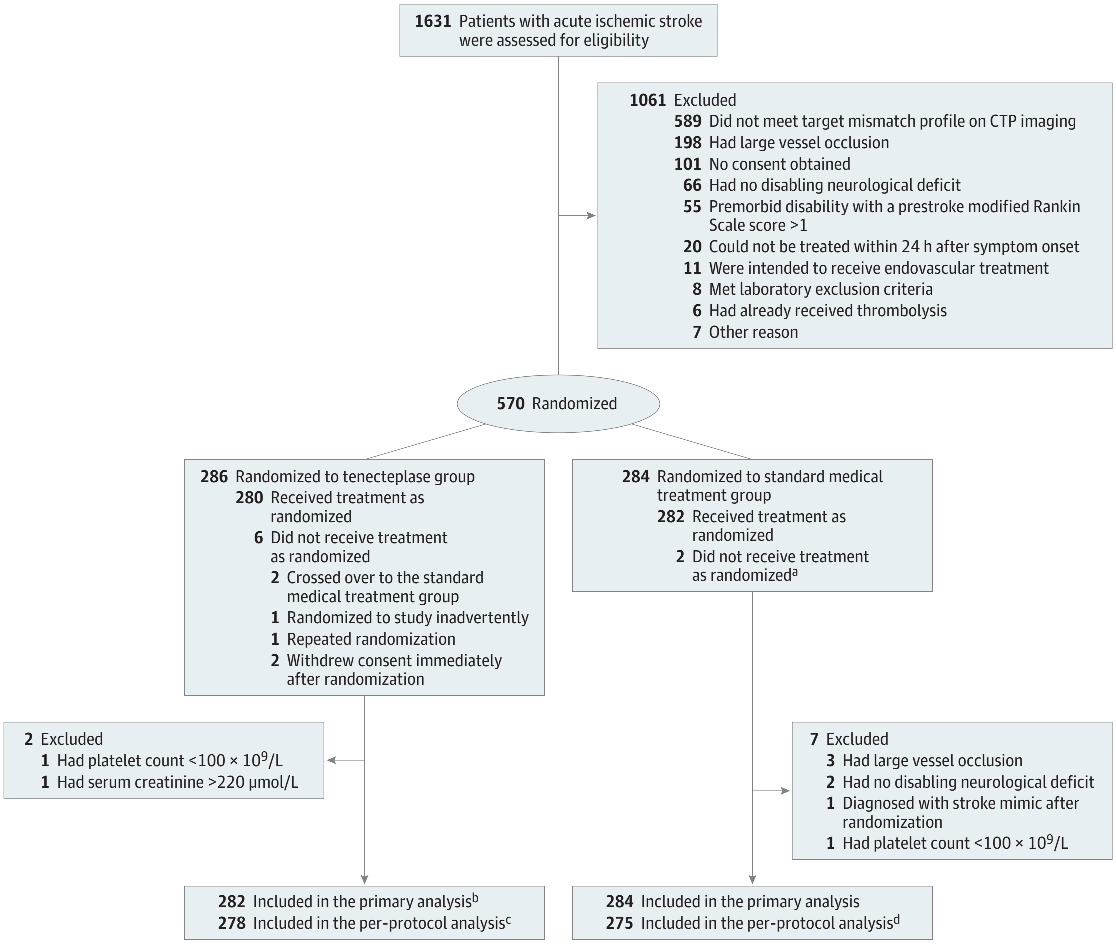
Patients were eligible for inclusion if they were 18 years or older; had a prestroke score of 0 or 1 on the modified Rankin Scale (mRS; scores range from 0 [no neurological deficit] to 6 [death]); had an acute ischemic stroke and could receive tenecteplase 4.5 to 24 hours after the time they were last seen well; had a baseline National Institutes of Health Stroke Scale (NIHSS) score of 6 to 25 (scores range, 0-42, with higher scores indicating more severe neurological deficits) or a score of 4 or 5 with a disabling deficit (eg, hemianopia, aphasia, and loss of hand function). The presence of potentially salvageable tissue on penumbral imaging (by automated computed tomographic [CT] perfusion imaging, using CTPdoc software, version 6.11; Shukun Technology Co; a research version of CTPdoc software was provided to the trial sites by Shukun Technology[15]) was a prerequisite for enrollment (**Figure 1** and **Table 1**). Patients were excluded if there was a large vessel occlusion defined as occlusion of the internal carotid artery, the M1 segment of the middle cerebral artery, or the vertebrobasilar artery, regardless of planned thrombectomy.

The ischemic core was defined as a region of relative cerebral blood flow less than 30% of that in normal tissue, as measured by CT perfusion imaging.[16] The critically hypoperfused tissue was defined by a delayed arrival of the injected tracer agent, as a time to maximum of the residue function exceeding 6 seconds.[17] Patients were required to have an ischemic core volume of less than 50 mL, a ratio of the volume of critically hypoperfused tissue to the ischemic core volume of at least 1.2, and a difference in volume between the critically hypoperfused tissue and the ischemic core of at least 10 mL. These criteria indicate potentially salvageable brain tissue by reflecting a mismatch between a small ischemic core and a larger region of critically hypoperfused but viable brain tissue. Additional details regarding inclusion and exclusion criteria are provided in eMethods 1 in Supplement 3.

Randomization

Eligible patients were randomly assigned in a 1:1 ratio via a centralized web-based randomization system to intravenous tenecteplase (CSPC Recomgen Pharmaceutical Co, Ltd) or standard medical treatment. A stochastic minimization algorithm balanced the 2 groups by vessel occlusion location (anterior or posterior circulation), age (<65 or ≥65 years),

Figure 1. Flow of Patients in the OPTION Trial



[a]Two patients in the standard medical treatment group did not receive treatment as randomized, with one receiving tenecteplase and the other alteplase.

[b]Four patients were excluded due to withdrawal of consent, repeated randomization, and inadvertent randomization.

[c]Four patients were excluded due to protocol violations, including 2 who had crossed over to the standard medical treatment group, 1 with platelet count lower than 100 × 10^9/L, and 1 with a serum creatinine level higher than 220 μmol/L (2.26 mg/dL).

[d]Nine patients were excluded due to protocol violations, including 2 who did not receive standard medical treatment, 1 diagnosed with stroke mimic, 3 with large vessel occlusion, 1 with platelet count lower than 100 × 10^9/L, and 1 who lacked a disabling neurological deficit.

CTP indicates computed tomographic perfusion: OPTION, Tenecteplase for Acute Non–Large Vessel Occlusion in the Extended Time Window.

baseline NIHSS (<16 or ≥16), and center. Treatment assignment was open label. However, the assessment of trial outcomes was performed by qualified physicians who were blinded to the treatment assignments.

Interventions

The tenecteplase group received a bolus of intravenous tenecteplase (0.25 mg/kg; maximum dose, 25 mg) over 5 to 10 seconds immediately after randomization, whereas the control group received antiplatelet therapy. All other treatments followed the Chinese Guidelines for Diagnosis and Treatment of Acute Ischemic Stroke (2018 updated to 2023 during the trial).[18,19] Although patients with planned endovascular thrombectomy during screening were excluded, rescue thrombectomy was permitted for clinical deterioration per local clinician judgment.

Outcomes

The primary efficacy outcome was an excellent functional outcome, defined as mRS score of 0 or 1 at 90 days. The mRS score at 90 days was obtained via structured telephone interview by an assessor who was unaware of the treatment assignment. An independent neurologist, who was unaware of group allocation, reviewed the audio recordings.[20] If audio recordings were unavailable, outcomes were assessed in person by local certified investigators, who were also unaware of the treatment assignment.

Secondary efficacy outcomes were the ordinal distribution of the mRS scores at 90 days, functional independence (mRS score, 0-2) at 90 days, reperfusion at 24 hours (defined as >90% reduction in the volume of the lesion in which there had been a delayed arrival of an injected tracer agent of >6 seconds), infarct volume on 24 hours' follow-up imaging, early

Table 1. Characteristics of the Patients at Baseline

Characteristic	Tenecteplase (n = 282)	Standard medical treatment (n = 284)
Age, median (IQR), y	69 (59-75)	67 (59-74)
Sex, No. (%)		
Male	176 (62.4)	194 (68.3)
Female	106 (37.6)	90 (31.7)
Medical history, No. (%)		
Hypertension	211 (74.8)	200 (70.4)
Diabetes	73 (25.9)	73 (25.7)
Atrial fibrillation	36 (12.8)	38 (13.4)
Hyperlipidemia	21 (7.4)	23 (8.1)
NIHSS score at randomization, median (IQR)[a]	7 (5-9)	6 (5-9)
Systolic blood pressure, median (IQR), mm Hg	153 (137-165)	153 (140-166.5)
Serum glucose, median (IQR), mg/dL	124.0 (104.6-155.5)	122.9 (101.0-167.0)
Modified Rankin Scale score before stroke, No. (%)[b]		
0	265 (94.0)	255 (89.8)
1	17 (6.0)	29 (10.2)
Circulation with stento-occlusion, No. (%)[c]		
Anterior circulation	219 (77.7)	218 (76.8)
Posterior circulation	63 (22.3)	65 (22.9)
Unknown	0	1 (0.4)
Stroke etiology, No (%)		
Large-artery atherosclerosis	101 (35.8)	108 (38.0)
Cardioembolism	67 (23.8)	66 (23.2)
Undetermined or other cause	114 (40.4)	110 (38.7)
Qualifying artery, No. (%)[d]		
Occlusion		
M2 segment of middle cerebral artery	86 (30.5)	93 (32.8)
Anterior cerebral artery	48 (17.0)	38 (13.4)
Posterior cerebral artery	37 (13.1)	41 (14.4)
M3-M4 segment of middle cerebral artery	24 (8.5)	19 (6.7)
Other	18 (6.4)	11 (3.9)
M1 segment of middle cerebral artery	0	3 (1.1)
Stenosis	65 (23.0)	67 (23.6)
No occlusion or stenosis	4 (1.4)	12 (4.2)
Volume of irreversibly injured ischemic core at initial imaging, median (IQR), mL[e]	0 (0-3.7)	1 (0-4.2)
Volume of perfusion lesion at initial imaging, median (IQR), mL[f]	34.8 (20.6-58.2)	37.6 (20.1-67.3)
Category of onset of stroke, No. (%)		
Known onset time	190 (67.4)	190 (66.9)
Stroke on awakening	91 (32.3)	90 (31.7)
Unwitnessed onset	1 (0.4)	4 (1.4)
Onset to randomization time, median (IQR), h	12.4 (8.7-16.8)	11.5 (8.3-16.6)

SI conversion factor: To convert glucose from mg/mL to mmol/L, multiply by 0.0555.

[a] Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating a more severe neurological deficit.

[b] Scores on the modified Rankin Scale range from 0 to 6, with higher scores indicating more severe disability.

[c] One patient whose posterior circulation stroke was initially described by the investigators at the trial site was later determined to be a stroke mimic.

[d] Other types included occlusion of the anterior or posterior inferior cerebellar artery, and superior cerebellar artery. Stenosis locations were the internal carotid artery, the M1 segment of the middle cerebral artery, the M2 or M3 segment of the middle cerebral artery, the anterior cerebellar artery, the posterior cerebellar artery, and the basilar artery (exact percentages are shown in eTable 2 in Supplement 3). Three patients were identified as having an M1 occlusion by the independent core laboratory.

[e] The volume of irreversibly injured ischemic core was calculated with the use of a threshold for relative cerebral blood flow of less than 30% of that in normal brain tissue as measured with the use of computed tomographic perfusion imaging.

[f] To define the critically hypoperfused tissue, volume of perfusion lesion was calculated as the volume of tissue in which there had been delayed arrival of an injected tracer agent exceeding 6 seconds.

clinical response at 24 hours (defined as a reduction from baseline of ≥8 points on the NIHSS or achieving an NIHSS score ≤1), the change from baseline in NIHSS score at 7 days (or at discharge if earlier), and health-related quality of life at 90 days, assessed with the EuroQol Group 5-Dimension 5-Level questionnaire (range, −0.391 to 1.00, with higher scores indicating better quality of life). Baseline and follow-up images were independently adjudicated at an imaging core laboratory (eMethods 2 in Supplement 3).

Safety outcomes were symptomatic intracranial hemorrhage within 36 hours after randomization, as defined by the Heidelberg Bleeding Classification (an increase in the NIHSS score of ≥4 points or an increase in a NIHSS subcategory of ≥2 points with any intracranial hemorrhage on imaging),[21] moderate or severe systemic bleeding within 90 days (as defined by the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries [GUSTO] trial),[22] and all-cause mortality within 90 days. Adverse events were reported according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. In post hoc analyses, intracranial hemorrhage was assessed based on the Heidelberg Bleeding Classification, while symptomatic intracranial hemorrhage was defined per the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST), the European Cooperative Acute Stroke Study III (ECASS III), the National Institute of Neurological Disorders and Stroke (NINDS), and the Third International Stroke Trial (IST-3) definitions (eMethods 2 in Supplement 3).

Sample Size Calculation

The sample size calculation was based on the occlusion-site subgroup data from a previous meta-analysis,[23] assuming a 12% absolute difference in the rate of excellent functional outcome (50.0% in the tenecteplase group and 38.0% in the standard medical treatment group). We calculated that a total sample size of 568 patients would provide 80% power to detect the target difference at a 2-sided α of .049 (after adjustment for 1 interim efficacy analysis when 50% of the target sample size, 284 patients, had reached the 90-day outcome), and a 5% dropout rate. Due to rapid recruitment, a substantial number of additional patients were enrolled during the time it took for the 284th patient to reach the 90-day assessment. Consequently, the original interim analysis plan was deemed unfeasible following a review by the DSMB. No formal efficacy assessment was conducted and no α was spent.

Statistical Analysis

The primary analysis was performed in a population that included all patients who had undergone randomization (no consent withdrawal), analyzed according to randomization group. The efficacy analyses were repeated in the per-protocol population, which included all patients who received the assigned treatment and had no major protocol violations. The safety analyses were performed in the safety population, which consisted of all patients who had undergone randomization and had received any amount of trial treatment, classified according to the treatment they actually received.

The primary efficacy outcome was analyzed by a modified Poisson regression model with robust error estimation to estimate the risk ratio (RR) and 95% CI as a measurement of treatment effect. The crude analysis served as the primary analysis. The post hoc risk difference (RD) was also calculated from analysis of the dichotomized outcomes using a generalized linear model. The number needed to treat for the primary outcome was derived by taking the inverse of the absolute risk reduction. No imputation for missing data was performed because the data for the primary efficacy analysis were complete. The secondary outcome of mRS score at 90 days was analyzed by ordinal logistic regression following confirmation (score test) that the proportional odds assumption was met. Nonnormal continuous secondary efficacy outcomes were analyzed with the win-ratio approach. We also performed prespecified secondary analyses adjusted for 4 prespecified covariates (age, baseline NIHSS score, anterior vs posterior circulation as the location of the stento-occlusion, and time from symptom onset to randomization; eMethods 3 in Supplement 3).

We performed subgroup analysis of the primary outcome by assessing the test for interaction with 7 prespecified subgroup variables including age, time between stroke onset and randomization, NIHSS score, anterior vs posterior circulation as the location of the stento-occlusion, qualifying artery, baseline serum glucose, and baseline systolic blood pressure. A post hoc subgroup variable was stroke etiology. A sensitivity analysis of the primary outcome was conducted to assess the center effect on treatment effect by performing a generalized estimating equation model with center as a cluster effect. In addition to the prespecified analyses, we conducted 2 main post hoc analyses. First, to evaluate the impact of medium or distal vessel occlusion on the primary outcome, we analyzed patients who met the criteria for the Endovascular Treatment to Improve Outcomes for Medium Vessel Occlusions (ESCAPE-MeVO)[8] or Endovascular Therapy Plus Best Medical Treatment (BMT) versus BMT Alone for Medium Vessel Occlusion Stroke (DISTAL)[9] trials. Second, to remove the effect of rescue endovascular treatment, the primary outcome was multiply imputed based on baseline characteristics for those who received rescue endovascular intervention (eMethods 3 in Supplement 3).

Analyses were performed with a 2-sided α level of .05. Secondary analyses and subgroup analyses were considered exploratory and performed without adjustment for multiplicity. All analyses were performed with SAS software, version 9.4 (SAS Institute Inc), and R software, version 4.1.1 (R Foundation).

Results

Patient Characteristics

From June 2, 2023, to August 4, 2025, a total of 570 patients underwent randomization (eFigure 2 in Supplement 3). Four patients were excluded from all the analyses owing to withdrawal of consent, repeated randomization, and inadvertent randomization, leaving 282 patients assigned to the tenecteplase group and 284 patients to the standard medical treatment group (Figure 1). The enrolled patients were generally representative of the expected study population (eTable 1 in Supplement 3). No patients were lost to follow-up. Two patients in the tenecteplase group crossed over to receive standard medical treatment, whereas 2 patients in the standard medical treatment group received tenecteplase and alteplase, respectively. Rescue thrombectomy was performed in 6 patients in the tenecteplase group and 1 patient in the standard medical treatment group, all of whom had mild symptoms at randomization and experienced neurological deterioration and reassessment before thrombectomy.

Baseline demographic and clinical characteristics were balanced between the 2 groups (Table 1; eTable 2 in Supplement 3). The median age was 68 (IQR, 59-75) years, and 196 of the 566 patients (34.6%) were female. The median NIHSS score at randomization was 7 (IQR, 5-9), and the median interval between the time that the patient was last seen well and randomization was 12.0 (IQR, 8.6-16.7) hours. Salvageable brain tissue was present in all patients on CT perfusion imaging. There were 21 patients whose CT hypodensities were larger than the core defined by CT perfusion criteria and were subsequently identified as having a mismatch inconsistency,

Table 2. Efficacy and Safety Outcomes

Outcome	Tenecteplase (n = 282)	Standard medical treatment (n = 284)	Unadjusted			Adjusted[a]	
			Risk difference (95% CI)[b]	Treatment difference (95% CI)	*P* value	Treatment difference (95% CI)	*P* value
Primary efficacy outcome							
mRS score 0-1 at 90 d, No. (%)[c]	123 (43.6)	97 (34.2)	9.46 (1.47 to 17.46)	RR, 1.28 (1.04 to 1.57)	.02	RR, 1.32 (1.08 to 1.61)	.007
Secondary efficacy outcomes							
mRS score at 90 d, median (IQR)[c]	2 (0 to 3)	2 (1 to 3)		Common OR, 1.39 (1.04 to 1.86)[d]	.03	Common OR, 1.50 (1.12 to 2.01)	.007
mRS score 0-2 at 90 d, No. (%)[c]	177 (62.8)	157 (55.3)	7.48 (−0.59 to 15.56)	RR, 1.14 (0.99 to 1.30)	.07	RR, 1.16 (1.02 to 1.32)	.03
Reperfusion at 24 h, No./total (%)[e]	95/252 (37.7)	76/264 (28.8)	8.91 (0.81 to 17.01)	RR, 1.31 (1.02 to 1.68)	.03	RR, 1.31 (1.03 to 1.68)	.03
Infarct volume at 24 h, median (IQR), mL[f]	5.6 (1.2 to 19.8)	6.2 (1.2 to 19.9)		WR, 1.02 (0.83 to 1.24)	.87	WR, 1.01 (0.83 to 1.24)	.89
Early clinical response at 24 h, No./total (%)[g]	32/280 (11.4)	14/282 (5.0)	6.46 (1.96 to 10.97)	RR, 2.30 (1.26 to 4.22)	.007	RR, 2.37 (1.30 to 4.34)	.005
Change in the NIHSS score at 7 d, median (IQR)[h]	−3 (−5 to −1)	−2 (−4 to −1)		WR, 1.16 (0.94 to 1.43)	.16	WR, 1.15 (0.93 to 1.42)	.19
EQ-5D-5L score at 90 d, median (IQR)[i]	0.9 (0.6 to 1.0)	0.9 (0.6 to 1.0)		WR, 1.02 (0.82 to 1.27)	.83	WR, 1.08 (0.86 to 1.34)	.52
Safety outcomes[j]							
Symptomatic intracranial hemorrhage within 36 h, No./total (%)[k]	8/281 (2.8)	0	2.85 (1.16 to 5.54)[l]		.004[l]		
Moderate or severe systemic bleeding within 90 d, No./total (%)[m]	2/281 (0.7)	2/284 (0.7)	0.01 (−1.38 to 1.39)	RR, 1.01 (0.14 to 7.12)	.99	RR,1.02 (0.14 to 7.45)	.98
Death within 90 d, No./total (%)	14/281 (5.0)	9/284 (3.2)	1.81 (−1.45 to 5.07)	RR, 1.57 (0.69 to 3.57)	.28	RR, 1.48 (0.65 to 3.36)	.35

Abbreviations: EQ-5D-5L, EuroQol Group 5-Dimension 5-Level self-report questionnaire; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; RR, risk ratio; WR, win ratio.

[a] Adjusted for age, baseline NIHSS score, circulation with stento-occlusion, and time from symptom onset to randomization. The win ratio was adjusted using the inverse probability of treatment weighting method.

[b] Post hoc analyses were performed to calculate the risk difference using the generalized linear model.

[c] The mRS scores range from 0 to 6, with higher scores indicating greater disability and a score of 6 indicating death.

[d] The proportional odds assumption was met (*P* = .35 by the score test).

[e] Reperfusion was defined as a reduction of greater than 90% in the volume of the lesion in which there had been a delayed arrival of an injected tracer agent exceeding 6 seconds.

[f] The infarct volume was measured on computed tomographic (CT) imaging 24 hours after randomization. Forty-four patients (16 in the tenecteplase group and 28 in the standard medical treatment group) could not be assessed because of severe intracranial hemorrhage or death (3 patients), follow-up CT scan quality (10 patients), or CT was not performed for other reasons (31 patients).

[g] Early clinical response at 24 hours was defined as an improvement (reduction) from baseline of at least 8 points on the NIHSS or an NIHSS score of 1 or lower.

[h] Data were missing for 2 patients (for 1 patient in tenecteplase group and for 1 in the standard medical treatment group).

[i] The EQ-5D-5L is a standard instrument for the measurement of health status. Scores range from −0.391 to 1.00, with higher scores indicating better quality of life and death coded as 0.

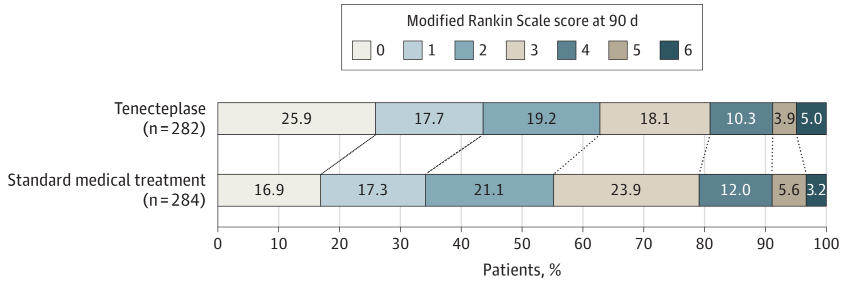
[j] The safety population included all patients who underwent randomization, and received any amount of tenecteplase or standard medical treatment.

[k] Symptomatic intracranial hemorrhage was defined by Heidelberg Bleeding Classification. RR values were not calculated due to a 0 denominator in the control group.

[l] Calculated using Fisher exact test.

[m] Moderate or severe systemic bleeding was defined according to the criteria established in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial. Symptomatic intracranial hemorrhage was not included in this category.

Figure 2. Horizontal Stacked Bar Chart Depicting Scores on the Modified Rankin Scale at 90 Days



Scores on the modified Rankin Scale (mRS) range from 0 (no symptoms) to 6 (death). A score of 1 indicates no clinically meaningful disability (patients are able to perform usual work, leisure, and school activities); 2, slight disability (patients are able to look after their own affairs without assistance but are unable to carry out all previous activities); 3, moderate disability (patients require some help but are able to walk unassisted); 4, moderately severe disability (unable to attend to bodily needs without assistance or unable to walk unassisted); and 5, severe disability (patients are bedridden and require constant care). Percentages may not total 100 because of rounding.

but they were retained in the analyses. The most common arterial lesions on baseline CT angiography were occlusions of the M2-M4 segments of the middle cerebral artery (39.2% [n = 222]), the anterior cerebral artery (15.2% [n = 86]), or the posterior cerebral artery (13.8% [n = 78]) and cerebral artery stenosis without occlusion (23.3% [n = 132]). Among cases of cerebral artery stenosis without occlusion, the M1-M3 segments of the middle cerebral artery (16.1% [n = 91]) were the most common sites.

Primary Efficacy Outcome

An excellent functional outcome (mRS score, 0 or 1) at 90 days was observed in 123 of 282 patients (43.6%) in the tenecteplase group and in 97 of 284 patients (34.2%) in the standard medical treatment group, yielding an unadjusted RD of 9.46% (95% CI, 1.47%-17.46%) and an unadjusted RR of 1.28 (95% CI, 1.04-1.57; *P* = .02; **Table 2** and **Figure 2**). The number needed to treat to achieve an excellent functional outcome was 11. The analyses of the primary outcome adjusted for prespecified or post hoc covariates were consistent with the findings in the primary analysis (Table 2; eTable 3 in Supplement 3). The per-protocol analyses yielded similar results (eFigure 3 and eTable 4 in Supplement 3). The primary outcome was assessed by a blinded central rater using audio recordings from 552 patients, including 15 patients who died after discharge and by local blinded investigators for 6 patients. Eight patients died in the hospital.

Secondary Efficacy Outcomes

The results for secondary outcomes are shown in Table 2. The common odds ratio for the ordinal distribution of mRS scores at 90 days was 1.39 (95% CI, 1.04-1.86; *P* = .03) in favor of the tenecteplase group. Functional independence (mRS score, 0-2) at 90 days occurred in 177 patients (62.8%) in the tenecteplase group and 157 (55.3%) in the standard medical treatment group (unadjusted RR, 1.14 [95% CI, 0.99-1.30]; *P* = .07). Reperfusion at 24 hours was achieved in 95 of 252 (37.7%) of the tenecteplase group vs 76 of 264 (28.8%) of the standard treatment group (unadjusted RR, 1.31 [95% CI, 1.02-1.68]; *P* = .03).

Subgroup, Sensitivity, and Post Hoc Analyses

The subgroup analyses of the primary outcome are shown in **Figure 3**. There was no evidence of treatment effect heterogeneity across all 7 baseline features evaluated. The primary findings were supported by the sensitivity analysis for center effects and the post hoc analysis that demonstrated absence of endovascular treatment effect (eTable 5 in Supplement 3). For the post hoc analysis among patients with medium or distal vessel occlusion, the primary outcome occurred in 42.6% of those in the tenecteplase group compared with 33.0% of those in the standard medical treatment group (unadjusted RR, 1.29 [95% CI, 0.995-1.67]; *P* = .054; eTable 6 in Supplement 3).

Adverse Events

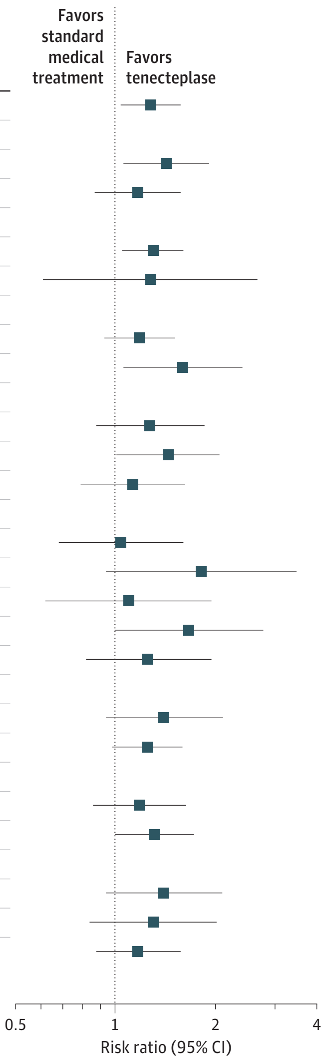
Symptomatic intracranial hemorrhage within 36 hours after treatment occurred in 8 patients (2.8%) in the tenecteplase group vs none in the standard medical treatment group (unadjusted RD, 2.85% [95% CI, 1.16% -5.54%]; *P* = .004; Table 2; eTables 7, 8, and 9 in Supplement 3 show additional data by intracranial hemorrhage type and using various definitions). Of note, symptomatic intracranial hemorrhage developed in 2 of the 21 patients with CT hypodensities larger than the core defined by CT perfusion scan with post hoc mismatch inconsistency. The incidence of moderate or severe systemic bleeding within 90 days was 0.7% in both groups (unadjusted RR, 1.01 [95% CI, 0.14-7.12]; *P* = .99; Table 2). Mortality within 90 days was 5.0% (14 of 281) with tenecteplase and 3.2% (9 of 284) with standard medical care (unadjusted RR, 1.57 [95% CI, 0.69-3.57]; *P* = .28; Table 2; eFigure 4 and eTable 10 in Supplement 3). The results for other adverse events and serious adverse events are provided in eTables 11 and 12 in Supplement 3.

Discussion

Among patients with acute ischemic stroke who had a favorable perfusion-imaging profile detected by automated perfusion imaging and non-large vessel occlusion, treatment

Figure 3. Dot Plot Subgroup Analysis of Modified Rankin Scale Score of 0 or 1 at 90 Days

Subgroup	Patients with mRS score of 0 or 1 at 90 d, No./total (%): Tenecteplase	Standard medical treatment	Risk ratio (95% CI)[a]	P value for interaction
Overall	123/282 (43.6)	97/284 (34.2)	1.28 (1.04-1.57)	
Age, y				
<65	60/114 (52.6)	43/116 (37.1)	1.42 (1.06-1.91)	.35
≥65	63/168 (37.5)	54/168 (32.1)	1.17 (0.87-1.57)	
NIHSS score[b]				
<10	109/214 (50.9)	87/222 (39.2)	1.30 (1.05-1.60)	.96
≥10	14/68 (20.6)	10/62 (16.1)	1.28 (0.61-2.66)	
Circulation with steno-occlusion[c]				
Anterior	89/219 (40.6)	75/218 (34.4)	1.18 (0.93-1.51)	.21
Posterior	34/63 (54.0)	22/65 (33.9)	1.59 (1.06-2.40)	
Time from symptom onset to randomization, h				
4.5-9.0	33/67 (49.3)	29/75 (38.7)	1.27 (0.88-1.85)	
>9.0-24	51/124 (41.1)	34/119 (28.6)	1.44 (1.01-2.05)	.65
Stroke on awakening	39/91 (42.9)	34/90 (37.8)	1.13 (0.79-1.62)	
Qualifying artery				
M2 segment of middle cerebral artery	28/86 (32.6)	29/93 (31.2)	1.04 (0.68-1.60)	
M3-M4 segment of middle cerebral artery	16/24 (66.7)	7/19 (36.8)	1.81 (0.94-3.48)	
Anterior cerebral artery	18/48 (37.5)	13/38 (34.2)	1.10 (0.62-1.94)	.49
Posterior cerebral artery	21/37 (56.8)	14/41 (34.2)	1.66 (0.99-2.77)	
Stenosis	28/65 (43.1)	23/67 (34.3)	1.25 (0.82-1.94)	
Serum glucose, mg/dL				
<100	30/57 (52.6)	24/64 (37.5)	1.40 (0.94-2.10)	.62
≥100	93/225 (41.3)	73/220 (33.2)	1.25 (0.98-1.59)	
Systolic blood pressure, mm Hg				
≤140	46/90 (51.1)	35/81 (43.2)	1.18 (0.86-1.63)	.63
>140	77/192 (40.1)	62/203 (30.5)	1.31 (1.00-1.72)	
Stroke etiology[d]				
Large artery atherosclerosis	38/101 (37.6)	29/108 (26.9)	1.40 (0.94-2.09)	
Cardioembolism	29/67 (43.3)	22/66 (33.3)	1.30 (0.84-2.01)	.77
Undetermined or other cause	56/114 (49.1)	46/110 (41.8)	1.17 (0.88-1.57)	



[a]The widths of the CIs have not been adjusted for multiplicity and cannot be used to infer treatment effects.

[b]The National Institutes of Health Stroke Scale (NIHSS) score is a measure of the severity of stroke. NIHSS scores range from 0 to 42, with higher scores indicating more severe neurological deficits.

[c]The circulation with stento-occlusion and qualifying artery were assessed at an independent core laboratory.

[d]Subgroup analysis according to stroke etiology was unplanned.

mRS indicates modified Rankin Scale. To convert glucose from mg/dL to mmol/L, multiply by 0.0555.

with tenecteplase between 4.5 and 24 hours after stroke onset led to a higher proportion of an excellent functional outcome at 90 days than standard medical care. For 1 additional patient to have an excellent functional outcome, the number needed to treat was 11. However, tenecteplase was associated with a higher rate of symptomatic intracranial hemorrhage.

Recent meta-analyses have demonstrated thrombolysis efficacy beyond the 4.5-hour window, advancing understanding of extended thrombolysis.[24,25] The Teneteplase Reperfusion Therapy in Acute Ischemic Cerebrovascular Events-III (TRACE-III) trial demonstrated that intravenous tenecteplase administered between 4.5 and 24 hours was beneficial for patients with anterior circulation large vessel occlusion who did not have access to endovascular thrombectomy.[26] Also, 81.4% of patients in the TRACE-III trial had intracranial internal carotid artery or the first segment of the middle cerebral artery occlusions. The Treatment With Intravenous Alteplase in Ischemic Stroke Patients With Onset Time Between 4.5 and 24 Hours (HOPE) trial, evaluating intravenous alteplase administered 4.5 to 24 hours in patients with salvageable brain tissue of whom 63% presented with proximal large vessel occlusion, showed improved nondisabled outcomes.[27] Unlike these trials, the current study focused on patients with non-large vessel occlusion and excluded candidates for endovascular thrombectomy, providing evidence for tenecteplase use beyond 4.5 hours in this population.

The benefit of the primary outcome in the OPTION trial was corroborated by higher early reperfusion and neurological improvement rates. In line with the Chinese Acute Tissue-Based Imaging Selection for Lysis in Stroke–Tenecteplase II (CHABLIS-T II)[28] trial, the current study demonstrated that intravenous tenecteplase at 4.5 to 24 hours increased reperfusion, with comparable reperfusion rates (37.7% reported in OPTION, 33.3% reported in CHABLIS-T II). Despite that, the reperfusion rate was notably lower than that reported in an earlier phase 2b study (79.3% reported in the Tenecteplase versus Alteplase for Acute Ischaemic Stroke [TAAIS] trial).[29] Possible explanations include differences in the treatment time window and variations in imaging modality and in the definition for reperfusion assessment.

The OPTION trial used a perfusion-imaging selection strategy analogous to prior late-window thrombolysis trials but excluded patients with acute large vessel occlusion.[27,30] Based on this imaging selection approach, the trial enrolled a population in which 68.2% (386 of 566 patients) of patients had medium or distal vessel occlusion, as defined separately in the ESCAPE-MeVO[8] and DISTAL[9] trials. A post hoc analysis of this subgroup showed rates of excellent functional outcomes at 90 days of 42.6% for the tenecteplase group vs 33.0% for the standard medical treatment group, a 9.6% difference that approached but did not formally achieve statistical significance. Notably, the Tenecteplase vs Alteplase for Stroke Thrombolysis Evaluation (TASTE)[31] trial enrolled a nearly identical proportion of patients with non-large vessel occlusion and compared the efficacy and safety of intravenous tenecteplase vs alteplase. In the intention-to-treat population, patients treated with tenecteplase in the TASTE trial had a higher rate of excellent functional outcomes than those in the OPTION trial (57% vs 43.6%), a difference likely attributable to a shorter median onset-to-thrombolysis time (2.5 hours vs 12.8 hours).

The incidence of symptomatic intracranial hemorrhage was higher with tenecteplase regardless of the definition used to denote this complication. This finding is consistent with data from the pooled analysis of extended time window thrombolysis.[24,25]

Limitations

The trial has several limitations. First, it used an open-label design, although all outcomes were adjudicated by assessors blinded to treatment assignment. Second, some patients were not enrolled in the trial and instead treated with endovascular thrombectomy, but there were only 11 such individuals. Third, the trial did not exclude patients with occlusions of the dominant M2 segment of middle cerebral artery—a subgroup for which thrombectomy has shown a trend toward benefit in prior trials.[1] Fourth, the optimal perfusion threshold for ischemic core and penumbra volume in posterior circulation strokes are not well established, which may have resulted in the inclusion of patients with inaccurate penumbral assessment; however, these patients showed homogeneous benefit with patients with anterior circulation. Fifth, on central imaging review, we identified 21 patients whose CT hypodensities were larger than the core defined by CT perfusion criteria and led to the numerically negative mismatch, with symptomatic intracranial hemorrhage developing in 2 of these cases. Therefore, careful evaluation of noncontrast CT hypodensity is advisable when considering late-window thrombolytic therapy. Finally, this study was performed in a Chinese population, and findings may not fully generalize to populations of other races or ethnicities.

Conclusions

Intravenous tenecteplase administered 4.5 to 24 hours after stroke onset in patients with non-large vessel occlusion and salvageable brain tissue resulted in a higher likelihood of an excellent functional outcome than standard medical care, although an increased risk of symptomatic intracranial hemorrhage existed. These results support extending the thrombolysis time window in this patient population.

ARTICLE INFORMATION

Accepted for Publication: January 8, 2026.

Published Online: February 5, 2026. doi:10.1001/jama.2026.0210

Author Affiliations: Department of Neurology, Xuanwu Hospital Capital Medical University, National Center for Neurological Disorders, Beijing, China (G. Ma, Mo, Zuo, Q. Ma, Yu, Meng, Y. Wu, J. Wu, Jiang, Gao, Zhong, Hao); Stroke Center, Linyi People's Hospital, Linyi, China (G. Zhao); Department of Neurology, First People's Hospital of Chenzhou, First Clinical College of Xiangnan University, Chenzhou, China (Yao); Department of Neurology, Changde Hospital, Xiangya School of Medicine, Central South University (First People's Hospital of Changde City), Changde, China (Liang); Department of Neurology, Weifang People's Hospital, Weifang, China (Zhou); Department of Neurology, Liuyang Jili Hospital, Changsha, China (He); Department of Neurology, Second Affiliated Hospital of Hainan Medical University, Haikou, China (Long); Department of Neurology, Affiliated Hospital of Southwest Medical University, Luzhou, China (Yuan); Department of Emergency, Xiangtan Central Hospital (Affiliated Hospital of Hunan University), Xiangtan, China (L. Liu); Department of Neurology, Affiliated Hospital of Shandong Second Medical University, Weifang, China (Han); Department of Cerebrovascular Diseases Center, Guigang People's Hospital, Guigang, China (Tan); Department of Neurology, Taihe Hospital, Hubei University of Medicine, Shiyan, China (Ai); Department of Neurology, Qingpu Branch of Zhongshan Hospital, Affiliated to Fudan University, Shanghai, China (Ai); Department of Cerebrovascular Disease, Huizhou First Hospital, Huizhou, China (Cai); Department of Neurology, Zhuozhou Hospital, Zhuozhou, China (J. Liu); Department of Neurosurgery, Liaocheng People's Hospital, Liaocheng, China (L. Zhang); Department of Neurology, Daxing Teaching Hospital, Capital Medical University, Beijing, China (Yang); Department of Neurointervention, Zhangzhou Municipal Hospital, Fujian Medical University, Zhangzhou, China (Yi); Department of Neurology, Shenyang First People's Hospital, Shenyang, China (L. Li); Department of Neurology, Anshan Changda Hospital, Anshan, China (Fu); Department of Neurology, Shaoxing People's Hospital, First Hospital of Shaoxing University, Shaoxing, China (Y. Zhang); Department of Neurology, Hai'an People's Hospital, Hai'an, China (Shao); Department of Neurology, Inner Mongolia Hospital of Xuanwu Hospital Capital Medical University, Chifeng, China (Yu); Department of Neurology, Affiliated Yueqing Hospital of Wenzhou Medical University, Yueqing, China (S. Wu); Department of Neurology, Tongliao City People's Hospital, Tongliao, China (Du); Department of Neurology, Taizhou Central Hospital (Taizhou University Hospital), School of Medicine, Taizhou University, Taizhou, China (Mao); Department of Neurology, Huaxian People's Hospital, Anyang, China (Guo); Department of Emergency Medicine, First Affiliated Hospital with Nanjing Medical University, Nanjing, China (X. Chen); Department of Neurology, Beijing Pinggu Hospital, Beijing, China (Y. Chen); Department of Neurology, People's Hospital of Shaodong, Shaoyang, China (Q. Zhao); Department of Neurology, Xijing Hospital 986 Hospital, Fourth Military Medical University, Xi'an, China (Chi); Department of Neurology, Shanxi Provincial People's Hospital, Fifth Clinical Medical College of Shanxi Medical University, Taiyuan, China (Y. Liu); Department of Cerebrovascular Diseases, Dazhou Central Hospital, Dazhou, China (H. Zhang); Department of Neurology, Chengdu Sixth Hospital, Chengdu, China (G. Li); Evidence-Based Medicine Center, Xuanwu Hospital Capital Medical University, Beijing, China (Lei); Department of Diagnostic and Interventional Neuroradiology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany (Fiehler); Global Health Trials Unit, Liverpool School of Tropical Medicine, Liverpool, United Kingdom (Wang); Department of Neurology, Radiology, Boston Medical Center, Boston, Massachusetts (Nguyen); Department of Neurology, David Geffen School of Medicine at UCLA, Los Angeles (Saver).

Author Contributions: Dr Hao 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. Drs G. Ma, Mo, Zuo, and Q. Ma contributed equally to this article as co–first authors.
Concept and design: G. Ma, Mo, Q. Ma, Nguyen, Saver, Hao.
Acquisition, analysis, or interpretation of data: G. Ma, Mo, Zuo, Q. Ma, G. Zhao, Yao, Liang, Zhou, He, Long, Yuan, L. Liu, Han, Tan, Ai, Cai, J. Liu, L. Zhang, Yang, Yi, L. Li, Fu, Y. Zhang, Shao, Yu, S. Wu, Du, Mao, Guo, X. Chen, Y. Chen, Q. Zhao, Chi, Y. Liu, H. Zhang, G. Li, Meng, Y. Wu, J. Wu, Jiang, Lei, Gao, Zhong, Fiehler, Wang, Saver, Hao.
Drafting of the manuscript: G. Ma, Mo, Zuo, Q. Ma, G. Zhao, Yao, Liang, Zhou, He, Long, Yuan, L. Liu, Han, Tan, Ai, Cai, J. Liu, L. Zhang, Yang, Yi, L. Li, Fu, Y. Zhang, Shao, Yu, S. Wu, Du, Mao, Guo, X. Chen, Y. Chen, Q. Zhao, Chi, Y. Liu, H. Zhang, G. Li, Meng, Y. Wu, J. Wu, Jiang, Lei, Gao, Zhong, Wang, Hao.
Critical review of the manuscript for important intellectual content: G. Ma, Mo, Zuo, Q. Ma, Yuan, Yang, Fiehler, Wang, Nguyen, Saver, Hao.
Statistical analysis: Zuo, Wang.
Obtained funding: Hao.
Administrative, technical, or material support: G. Zhao, Yao, Liang, Zhou, He, Long, Yuan, L. Liu, Han, Tan, Ai, Cai, J. Liu, L. Zhang, Yang, Yi, L. Li, Fu, Y. Zhang, Shao, Yu, S. Wu, Du, Mao, Guo, X. Chen, Y. Chen, Q. Zhao, Chi, Y. Liu, H. Zhang, G. Li, Meng, Y. Wu, J. Wu, Jiang, Lei, Gao, Zhong, Nguyen.
Supervision: Q. Ma, Yuan, Fiehler, Wang, Nguyen, Hao.

Conflict of Interest Disclosures: Dr Fiehler reported being the managing director of Eppdata, an imaging core laboratory, which was not involved in this study. Dr Nguyen reported serving as an associate editor for the American Stroke Association, speaker for Genentech, advisory board member of Bayer and Route 92, and consultant to Medtronic outside the submitted work. Dr Saver reported receiving personal fees from Abbott, Aeromics, Bayer, Biogen, Boehringer Ingelheim, BrainQ, BrainsGate, CSL Bering, Medtronic USA, Roche, Stream Medical, Johnson & Johnson, MIVI Neuroscience, Occlutech, MindRhythm, Neuronics Medical, and Rapid Medical outside the submitted work. No other disclosures were reported.

Funding/Support: This study was supported by the Beijing Hospitals Authority Clinical Medicine Development of special funding support (ZLRK 202514); The China Shijiazhuang Pharmaceutical Company (CSPC) Recomgen Pharmaceutical (Guangzhou) Co LTD. The study drug was provided by CSPC Recomgen Pharmaceutical (Guangzhou) Co LTD.

Role of the Funder/Sponsor: The Beijing Hospitals Authority Clinical Medicine Development of special funding support (ZLRK202514) and China Shijiazhuang Pharmaceutical Company (CSPC) Recomgen Pharmaceutical (Guangzhou) Co LTD had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Group Information: The OPTION Investigators appear listed in Supplement 4.

Disclaimer: Dr Saver is an Associate Editor of *JAMA* but was not involved in any of the decisions regarding review of the manuscript or its acceptance.

Meeting Presentation: This article was presented at 2026 International Stroke Conference of the American Heart Association; February 5, 2026; New Orleans, Louisiana.

Data Sharing Statement: See Supplement 5.

Additional Contributions: We thank Jieli Chen, MD, Tianjin Huanhu Hospital, Tianjin Key Laboratory of Cerebral Vascular and Neurodegenerative Diseases, Tianjin, China, for her assistance in revising the article. Dr Chen did not receive any compensation for her contribution.

REFERENCES

1. Goyal M, Menon BK, van Zwam WH, et al; HERMES collaborators. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet*. 2016;387(10029):1723-1731. doi:10.1016/S0140-6736(16)00163-X

2. Nogueira RG, Jovin TG, Liu X, et al; ATTENTION, BASICS, BAOCHE, and BEST investigators. Endovascular therapy for acute vertebrobasilar occlusion (VERITAS): a systematic review and individual patient data meta-analysis. *Lancet*. 2025;405(10472):61-69. doi:10.1016/S0140-6736(24)01820-8

3. Jovin TG, Nogueira RG, Lansberg MG, et al. Thrombectomy for anterior circulation stroke beyond 6 h from time last known well (AURORA): a systematic review and individual patient data meta-analysis. *Lancet*. 2022;399(10321):249-258. doi:10.1016/S0140-6736(21)01341-6

4. Liu C, Abdalkader M, Sang H, et al. Endovascular thrombectomy for large-ischemic core stroke: a systematic review and meta-analysis of randomized controlled trials. *Neurology*. 2025;104(9):e213443. doi:10.1212/WNL.0000000000213443

5. Lees KR, Emberson J, Blackwell L, et al; Stroke Thrombolysis Trialists' Collaborators Group. Effects of alteplase for acute stroke on the distribution of functional outcomes: a pooled analysis of 9 trials. *Stroke*. 2016;47(9):2373-2379. doi:10.1161/STROKEAHA.116.013644

6. Wang Z, Li J, Wang X, Yuan B, Li J, Ma Q. Tenecteplase for acute ischemic stroke at 4.5 to 24 hours: a meta-analysis of randomized controlled trials. *Stroke*. 2026;57(1):50-62. doi:10.1161/STROKEAHA.125.053256

7. Saver JL, Chapot R, Agid R, et al; Distal Thrombectomy Summit Group*†. Thrombectomy for distal, medium vessel occlusions: a consensus statement on present knowledge and promising directions. *Stroke*. 2020;51(9):2872-2884. doi:10.1161/STROKEAHA.120.028956

8. Goyal M, Ospel JM, Ganesh A, et al; ESCAPE-MeVO Investigators. Endovascular treatment of stroke due to medium-vessel occlusion. *N Engl J Med*. 2025;392(14):1385-1395. doi:10.1056/NEJMoa2411668

9. Psychogios M, Brehm A, Ribo M, et al; DISTAL Investigators. Endovascular treatment for stroke due to occlusion of medium or distal vessels. *N Engl J Med*. 2025;392(14):1374-1384. doi:10.1056/NEJMoa2408954

10. 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(12):e344-e418. doi:10.1161/STR.0000000000000211

11. Alamowitch S, Turc G, Palaiodimou L, et al. European Stroke Organisation (ESO) expedited recommendation on tenecteplase for acute ischaemic stroke. *Eur Stroke J*. 2023;8(1):8-54. doi:10.1177/23969873221150022

12. Palaiodimou L, Katsanos AH, Turc G, et al. Tenecteplase vs alteplase in acute ischemic stroke within 4.5 hours: a systematic review and meta-analysis of randomized trials. *Neurology*. 2024;103(9):e209903. doi:10.1212/WNL.0000000000209903

13. Ma G, Mo R, Zuo Y, et al. A multicenter, prospective, randomized, open-label, blinded endpoint trial of intravenous thrombolysis with tenecteplase for acute non-large-vessel occlusion in extended time window (OPTION): Rationale and design. *J Transl Int Med*. 2025;13(5):472-479. doi:10.1515/jtim-2025-0048

14. World Medical Association. World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Participants. *JAMA*. 2025;333(1):71-74. doi:10.1001/jama.2024.21972

15. Xu XQ, Ma G, Shen GC, et al. Spatial accuracy of computed tomography perfusion to estimate the follow-up infarct on diffusion-weighted imaging after successful mechanical thrombectomy. *BMC Neurol*. 2023;23(1):31. doi:10.1186/s12883-023-03075-z

16. Campbell BC, Christensen S, Levi CR, et al. Cerebral blood flow is the optimal CT perfusion parameter for assessing infarct core. *Stroke*. 2011;42(12):3435-3440. doi:10.1161/STROKEAHA.111.618355

17. Zaro-Weber O, Moeller-Hartmann W, Heiss WD, Sobesky J. Maps of time to maximum and time to peak for mismatch definition in clinical stroke studies validated with positron emission tomography. *Stroke*. 2010;41(12):2817-2821. doi:10.1161/STROKEAHA.110.594432

18. Chinese Society of Neurology. Chinese guidelines for diagnosis and treatment of acute ischemic stroke 2018. *Chin J Neurol*. 2018;51:666-682. doi:10.3760/cma.j.issn.1006-7876.2018.09.004

19. Chinese Society of Neurology. Chinese guidelines for diagnosis and treatment of acute ischemic stroke 2023. *Chin J Neurol*. 2024;57:523-559. doi:10.3760/cma.j.cn113694-20240410-00221

20. Janssen PM, Visser NA, Dorhout Mees SM, Klijn CJ, Algra A, Rinkel GJ. Comparison of telephone and face-to-face assessment of the modified Rankin Scale. *Cerebrovasc Dis*. 2010;29(2):137-139. doi:10.1159/000262309

21. von Kummer R, Broderick JP, Campbell BC, et al. The Heidelberg Bleeding Classification: classification of bleeding events after ischemic stroke and reperfusion therapy. *Stroke*. 2015;46(10):2981-2986. doi:10.1161/STROKEAHA.115.010049

22. Berkowitz SD, Granger CB, Pieper KS, et al; the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) I Investigators. Incidence and predictors of bleeding after contemporary thrombolytic therapy for myocardial infarction. *Circulation*. 1997;95(11):2508-2516. doi:10.1161/01.CIR.95.11.2508

23. Campbell BCV, Ma H, Ringleb PA, et al; EXTEND, ECASS-4, and EPITHET Investigators. Extending thrombolysis to 4.5-9 h and wake-up stroke using perfusion imaging: a systematic review and meta-analysis of individual patient data. *Lancet*. 2019;394(10193):139-147. doi:10.1016/S0140-6736(19)31053-0

24. Günkan A, Ferreira MY, Vilardo M, et al. Thrombolysis for ischemic stroke beyond the 4.5-hour window: a meta-analysis of randomized clinical trials. *Stroke*. 2025;56(3):580-590. doi:10.1161/STROKEAHA.124.048536

25. Palaiodimou L, Papageorgiou NM, Safouris A, et al. Efficacy and safety of intravenous thrombolysis in the extended time window for acute ischemic stroke: a systematic review and meta-analysis. *J Clin Med*. 2025;14(15):5474. doi:10.3390/jcm14155474

26. Xiong Y, Campbell BCV, Schwamm LH, et al; TRACE-III Investigators. Tenecteplase for ischemic stroke at 4.5 to 24 hours without thrombectomy. *N Engl J Med*. 2024;391(3):203-212. doi:10.1056/NEJMoa2402980

27. Zhou Y, He Y, Campbell BCV, et al; HOPE investigators. Alteplase for acute ischemic stroke at 4.5 to 24 hours: the HOPE randomized clinical trial. *JAMA*. 2025;334(9):788-797. doi:10.1001/jama.2025.12063

28. Cheng X, Hong L, Lin L, et al; CHABLIS-T II Collaborators. Tenecteplase Thrombolysis for stroke up to 24 hours after onset with perfusion imaging selection: the CHABLIS-T II randomized clinical trial. *Stroke*. 2025;56(2):344-354. doi:10.1161/STROKEAHA.124.048375

29. 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(12):1099-1107. doi:10.1056/NEJMoa1109842

30. Ma H, Campbell BCV, Parsons MW, et al; EXTEND Investigators. Thrombolysis guided by perfusion imaging up to 9 hours after onset of stroke. *N Engl J Med*. 2019;380(19):1795-1803. doi:10.1056/NEJMoa1813046

31. Parsons MW, Yogendrakumar V, Churilov L, et al; TASTE investigators. Tenecteplase versus alteplase for thrombolysis in patients selected by use of perfusion imaging within 4.5 h of onset of ischaemic stroke (TASTE): a multicentre, randomised, controlled, phase 3 non-inferiority trial. *Lancet Neurol*. 2024;23(8):775-786. doi:10.1016/S1474-4422(24)00206-0