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Intravenous Tenecteplase Prior to Endovascular Treatment for Ischemic Stroke at 4.5 to 24 Hours
The TNK-PLUS Randomized Clinical Trial

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IMPORTANCE Whether intravenous tenecteplase prior to endovascular treatment (EVT) for ischemic stroke reduces disability in the late time window is unclear.

OBJECTIVE To investigate the adverse events and efficacy of tenecteplase prior to EVT in patients 4.5 to 24 hours after ischemic stroke onset due to proximal middle cerebral artery (MCA) occlusion.

DESIGN, SETTING, AND PARTICIPANTS Multicenter, phase 3, randomized, open-label, blinded end point, superiority trial conducted at 40 centers in China. Adult (≥18 years) patients with acute ischemic stroke 4.5 to 24 hours after last known to be well due to MCA-M1 or proximal M2 occlusion with salvageable brain tissue (ischemic core volume <70 mL, mismatch ratio ≥1.8, and mismatch volume ≥15 mL) identified on computed tomography–perfusion or magnetic resonance–perfusion-diffusion imaging were enrolled from January 25, 2024, through July 21, 2025, and followed up for 90 days. Final follow-up occurred on October 14, 2025.

INTERVENTIONS Eligible patients were randomly assigned in a 1:1 ratio to receive intravenous tenecteplase (0.25 mg/kg; maximum dose, 25 mg) before EVT (n = 199) or EVT alone (n = 192).

MAIN OUTCOMES AND MEASURES The primary outcome was functional independence, defined as a score of 0 to 2 on the modified Rankin Scale (range, 0-6, with higher scores indicating greater disability) at 90 days. Adverse events outcomes included symptomatic intracranial hemorrhage and death.

RESULTS All of the 391 patients enrolled (median age, 68 years [IQR, 59-75]; 155 [39.6%] females) completed the trial. Functional independence at 90 days occurred in 88 patients (44.2%) in the tenecteplase before EVT group and 83 patients (43.2%) in the EVT alone group (adjusted relative rate, 1.01 [95% CI, 0.83-1.24]; *P* = .89; risk difference, 0.99% [95% CI, −8.84% to 10.83%]). Mortality within 90 days was 12.7% (25/197) in the tenecteplase before EVT group and 14.2% (27/190) in the EVT alone group. Symptomatic intracranial hemorrhage within 36 hours was 5.1% (10/197) and 2.6% (5/190), respectively.

CONCLUSIONS AND RELEVANCE In patients presenting to EVT-capable centers 4.5 to 24 hours after stroke onset with proximal MCA occlusion, intravenous tenecteplase before EVT did not improve clinical outcomes vs EVT alone.

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Visual Abstract
Research Summary
Supplemental content

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The role of thrombolysis in patients who have immediate access to endovascular treatment (EVT) beyond 4.5 hours after stroke onset is uncertain. A pooled analysis of 6 randomized trials[1-6] did not establish the noninferiority of direct EVT within 4.5 hours.[7] However, intravenous thrombolysis with alteplase administered at a median of 25 minutes prior to EVT was also not superior to direct EVT.[7] The Randomized Trial of Thrombectomy With vs Without Recombinant Human Tenecteplase (TNK) Tissue Plasminogen Activator in Stroke (BRIDGE-TNK) tested intravenous tenecteplase prior to thrombectomy in patients with large vessel occlusion (LVO) within 4.5 hours of stroke onset in patients receiving EVT and found that intravenous tenecteplase before EVT improved 90-day functional independence compared with EVT alone.[8]

In the late time window, the Tenecteplase Reperfusion Therapy in Acute Ischemic Cerebrovascular Events III (TRACE-III) trial revealed that tenecteplase administered within 4.5 to 24 hours after stroke onset significantly reduced disability without concerning adverse events in patients with anterior-circulation LVO and with salvageable tissue who could not access EVT.[9] In contrast, the Thrombolysis in Imaging Eligible, Late Window Patients to Assess the Efficacy and Safety of Tenecteplase (TIMELESS) trial enrolled patients with internal carotid artery or proximal middle cerebral artery (MCA) occlusion and perfusion mismatch 4.5 to 24 hours after onset, 77% of whom received EVT. The TIMELESS trial did not demonstrate benefit of bridging thrombolysis with tenecteplase when it was administered a median of 15 minutes prior to EVT. There were no safety concerns, and the subgroup with occlusion of the first (M1) segment of the MCA appeared to benefit.[10] Although patients with occlusion of the second (M2) segment of the MCA did not benefit from tenecteplase in the TIMELESS trial, there was heterogeneity in EVT use that may have confounded interpretation. It therefore remained unclear whether tenecteplase before EVT could provide additional benefit to EVT alone in reducing disability in the 4.5- to 24-hour time window in patients with MCA occlusion.

The Endovascular Treatment With or Without Preceding Intravenous Tenecteplase in Patients With Late-Window Acute Ischemic Stroke due to Middle Cerebral Artery Occlusion (TNK-PLUS) trial was conducted to explore the adverse events and efficacy of intravenous tenecteplase prior to EVT in patients with ischemic stroke due to MCA M1 or proximal M2 segment occlusion presenting 4.5 to 24 hours after the time they were last known to be well, including patients with wake-up and unwitnessed onset.

Key Points

Question In patients with stroke due to an acute proximal middle cerebral artery occlusion beyond 4.5 hours of onset, is endovascular treatment (EVT) with preceding intravenous tenecteplase superior to EVT alone regarding functional outcomes?

Findings In this randomized clinical trial including 391 patients, functional independence (modified Rankin Scale score 0-2) at 90 days did not differ significantly between those receiving tenecteplase plus EVT (44.2%) and those undergoing EVT alone (43.2%).

Meaning For stroke due to a proximal middle cerebral artery occlusion presenting directly to an EVT-capable center within 4.5 to 24 hours, thrombolysis with tenecteplase before EVT did not improve clinical outcomes vs EVT alone.

Methods

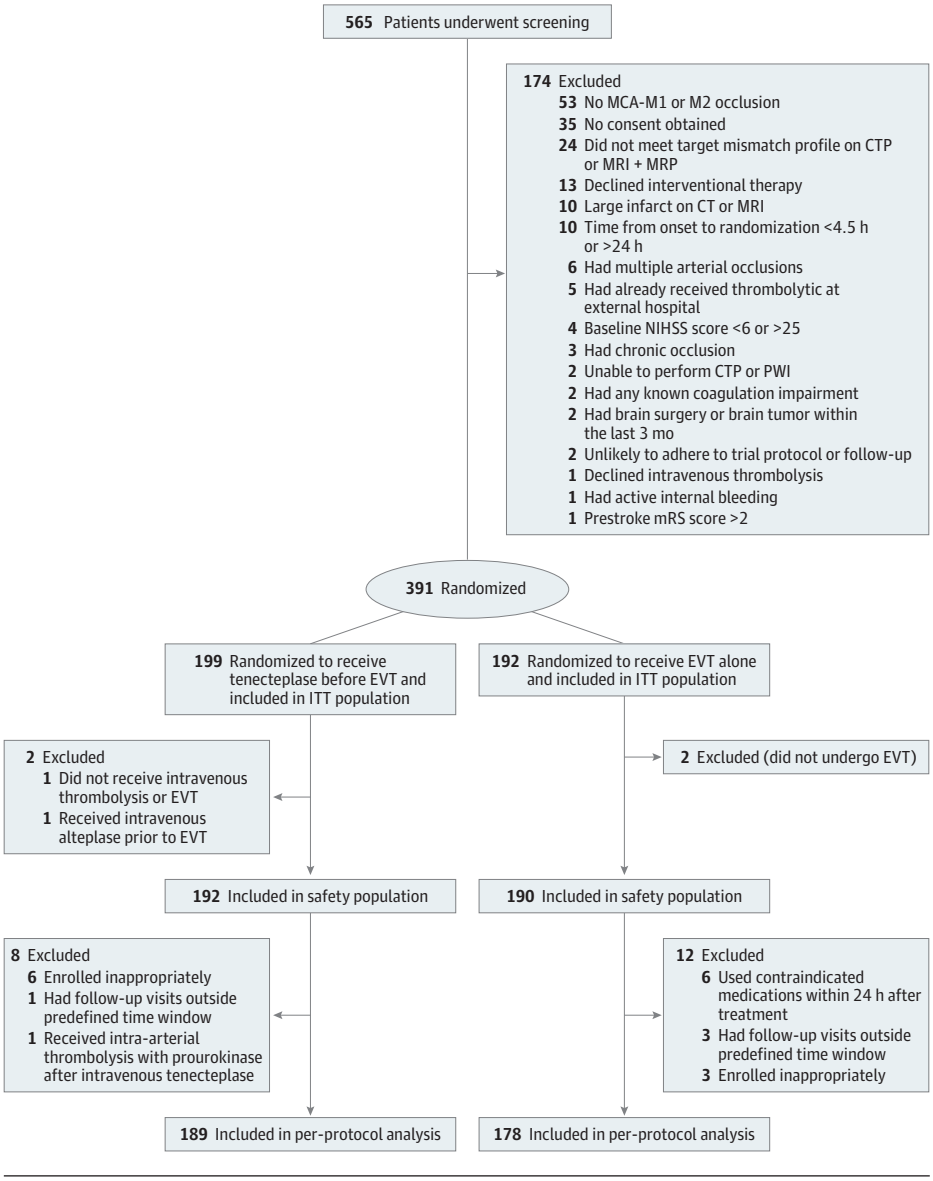
Trial Design and Oversight

The TNK-PLUS study was a multicenter, prospective, open-label, blinded end point, phase 3, randomized controlled clinical trial conducted at 40 centers in China. The study protocol (Supplement 1) was approved by the institutional review boards of all participating centers (eAppendix 1 in Supplement 3). We did not have patient or public involvement in the study design, conduct, and reporting. Written informed consent was obtained from all patients or their legally authorized representative before study-related procedures. The trial was conducted in compliance with the ethical standards of the Declaration of Helsinki[11] and adhered to Good Clinical Practice guidelines. This report followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.[12] The first author wrote the first draft of the manuscript, and the seventh author conducted the statistical analysis. After the database was locked, the first author had full access to the raw dataset and assumed accountability for protocol compliance, including validation of outcome data completeness, adverse-event ascertainment procedures, and source document verification as per regulatory audit requirements. Tenecteplase used in this trial was manufactured by China Shijiazhuang Pharmaceutical Company Pharmaceutical (Guangzhou), which provided an unrestricted grant to support the trial. Perfusion imaging was processed using software that had obtained a class II or higher medical device registration certificate from the National Medical Products Administration (NMPA), China, then centrally evaluated by an NMPA class III medical device (iStroke version 3.13; Biomind).[13]

Patients

Eligible patients were 18 years or older and presenting within a time window of 4.5 to 24 hours after they were last known to be well, including those with wake-up stroke or unwitnessed onset (**Figure 1**). Eligibility criteria included a pre-stroke modified Rankin Scale (mRS) score of 0 to 2 (on a scale from 0 [no symptoms] to 6 [death]) and a National Institutes of Health Stroke Scale (NIHSS) score between 6 and 25 (on a scale from 0 to 42, with higher values reflecting greater neurologic impairment). Enrolled patients had confirmed M1 or proximal M2[14] occlusions of the MCA (the internal carotid artery did not benefit in TIMELESS[10] and rarely responds to intravenous thrombolytics,[15-17] and EVT is not guideline-recommended for anterior cerebral artery occlusion[18,19]) on either computed tomography (CT) angiography or magnetic resonance (MR) angiography and had perfusion-imaging evidence of salvageable brain tissue. Irreversibly injured ischemic core was estimated using a threshold of cerebral blood flow

Figure 1. Flowchart of Enrollment, Randomization, and Treatment of the TNK-PLUS Randomized Clinical Trial



CT indicates computed tomography; CTP, computed tomographic perfusion; EVT, endovascular treatment; ITT, intention to treat; MCA, middle cerebral artery; MRI, magnetic resonance imaging; MRP, magnetic resonance perfusion; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; PWI, perfusion-weighted imaging; and TNK-PLUS, Endovascular Treatment With or Without Preceding Intravenous Tenecteplase in Patients With Late-Window Acute Ischemic Stroke due to Middle Cerebral Artery Occlusion.

less than 30% of normal brain on CT-perfusion or apparent diffusion coefficient less than 620×10^{-6} mm^2/s on diffusion-weighted MR imaging (MRI), and hypoperfused brain was defined as time to maximum (T_{max}) delay greater than 6 seconds on CT or MR perfusion. Eligible patients were required to have an ischemic core volume of less than 70 mL, a ratio of hypoperfused tissue to ischemic core volume of 1.8 or more, and a mismatch volume (difference between hypoperfused tissue and ischemic core) of at least 15 mL. Patients were ineligible if they declined EVT or intravenous thrombolytic at the time of randomization, had large infarct on noncontrast brain CT or MRI (infarct size >1/3 MCA territory), or had multiple arterial occlusions. Full inclusion criteria, exclusion criteria, site requirements, and definition of outcomes are listed in eMethods 1 through 4 in Supplement 3.

Randomization and Blinding

We randomly allocated participants in a 1:1 ratio to the intervention group (tenecteplase before EVT) or the control group (EVT alone) through a centralized web-based system, stratified according to LVO site (M1 or M2), with block size of 4. The block size was not known to investigators. The randomization sequences were generated by an independent statistician who had no involvement in patient enrollment, in the intervention, or in the follow-up. All clinical efficacy and adverse events end points were evaluated by qualified physicians unaware of the treatment allocation. Blinded assessments of neuroimaging were independently adjudicated by the central imaging core laboratory (Beijing Tiantan Hospital) with 3 neurointerventionists, 1 neurologist, and 1 radiologist. Alberta Stroke Program Early CT Score[20] (range, 0-10; lower scores

indicate more extensive infarction) was independently assessed on CT or MRI by 2 raters, with a third rater to determine consensus when required. Occlusion due to intracranial atherosclerosis[21] was assessed by 2 neurointerventionists, with consensus after reviewing patients' medical history and imaging (including digital subtraction angiography). Clinical end point events were adjudicated by an independent clinical events committee consisting of neurologists not involved in patient enrollment.

The intervention group received tenecteplase (0.25 mg/kg; maximum dose, 25 mg), which was given as a single, intravenous bolus (injection over 5 to 10 seconds) immediately after randomization. EVT was performed as soon as possible after tenecteplase administration. The EVT techniques in both groups included stent retriever, aspiration, balloon angioplasty, stent placement, or a combination of techniques.

Outcomes

The primary outcome was the proportion of participants achieving functional independence at 90 days, defined as mRS score of 0 to 2. Secondary outcomes were the proportion of participants with no disability (defined as an mRS score ≤1), the proportion of participants with an mRS score of 3 or less, the ordinal distribution of mRS at 90 days, and the proportion of participants with severe disability or death (mRS score of 5 or 6) at 90 days. We also assessed early neurologic improvement at 72 hours (defined as either a decrease of ≥8 points on the NIHSS score from baseline or an NIHSS score of 0 to 1), the change in NIHSS score from baseline to day 7, reperfusion prior to EVT (>50% reperfusion of the affected arterial territory; ie, expanded Thrombolysis in Cerebral Infarction score[22] of 2b50 [50%-60% reperfusion] to 3 [100% reperfusion]), complete recanalization at 24 hours after randomization (arterial occlusive lesion scale assessed on CT angiography or MR angiography; scores range from 0 [no recanalization] to 3 [complete recanalization]),[23] and successful reperfusion at 24 hours defined as a reduction of more than 90% in the volume of brain tissue, with a T_{max} delay greater than 6 seconds. Adverse events outcomes were symptomatic intracranial hemorrhage within 36 hours (Safe Implementation of Thrombolysis in Stroke-Monitoring Study [SITS-MOST] criteria: local or remote parenchymal hematoma type 2 on the 22- to 36-hour posttreatment imaging scan, combined with a neurologic deterioration of 4 points or more on the NIHSS from baseline, or from the lowest NIHSS value between baseline and 24 hours, or leading to death)[24] and mortality within 90 days.

Trial Conduct

At baseline, eligibility was confirmed by CT perfusion or MR perfusion-diffusion imaging, which was repeated 24 hours after randomization to evaluate vessel recanalization and tissue reperfusion. Intracranial hemorrhage was assessed using noncontrast CT or MRI within 36 hours after randomization. The 90-day mRS score was assessed by certified clinicians at each site who were unaware of the treatment assignment, either through an in-person visit or by telephone interview. Each site designated a certified blinded local investigator who was independent of the treating clinical team. The assessments were conducted in a dedicated area using structured interview forms. These assessments were double-checked by an independent, centrally located blinded evaluator through review of video or telephone recordings to ensure accuracy. All serious adverse events were recorded using standardized classification terminology.

Sample Size Calculation

Based on the results of the TIMELESS study, among participants with stroke due to M1 occlusion, the proportion achieving an mRS score of 0 to 2 at 90 days was 31.0% in the control group and approximately 14% higher in the intervention group.[10] Patients with proximal M2 occlusions had greater effect size (tenecteplase vs standard medical treatment on mRS 0-1 at 90 days) than those with M1 occlusion (18.6% vs 9.7%) in the TRACE-III study in patients without access to EVT.[9] Based on these studies, we estimated a conservative effect size of 10%. An interim analysis based on a prespecified promising-zone adaptive sample size reestimation procedure[25] was conducted when 273 participants completed 90-day mRS follow-up. The minimum calculated sample size was 390 (powered for a 14% effect size) and the maximum sample size was 754, powered for a 10% effect size, with a 2-sided α level of .05, power (1 − β) of 0.8, and an anticipated attrition rate of 5%. Conditional power (0.03) at the interim sample size reestimation was not in the prespecified promising zone (0.33 to 0.80); therefore, no sample size increase was required, and the final sample size remained 390.

Statistical Analysis

The primary and secondary efficacy analyses were carried out in both the full analysis set and in the per-protocol set. The full analysis set was defined as all randomly assigned participants. The per-protocol set was defined as participants who completed the assigned interventions as required without major violations of the trial protocol. The safety analysis set was defined as all participants who were randomized into the group and received treatment procedure as specified in the protocol and had at least 1 safety evaluation. The primary efficacy outcome was analyzed using log-binomial regression with trial site as a random effect, adjusting for age, baseline NIHSS score, and site of LVO (M1 or proximal M2), with calculation of relative rate (RR) and 95% CI in the intervention and control groups. The data used for the primary efficacy analysis were complete; therefore, no imputation for missing values was required. For secondary outcomes with missing data, a multiple imputation approach based on a fully conditional specification method was applied. For secondary and other outcomes, these findings should be interpreted as exploratory because of the potential for type I error and the lack of control for multiple comparisons.

Prespecified subgroup analyses for the primary efficacy outcome were performed based on age (<80 vs ≥80 years), sex (male vs female), stroke severity at baseline (NIHSS score 6-15 vs 16-25), site of vessel occlusion (M1 vs proximal M2), Alberta Stroke Program Early CT Score (<8 vs ≥8), core volume (<10 mL vs ≥10 mL), time from onset of symptoms to randomization (<10 hours vs ≥10 hours), time from randomization to arterial

Table 1. Baseline Characteristics of the Patients

Characteristic	Tenecteplase before EVT (n = 199)	EVT alone (n = 192)
Age, median (IQR), y	68.0 (58.0-74.0)	68.5 (60.0-75.0)
Sex, No. (%)		
Male	122 (61.3)	114 (59.4)
Female	77 (38.7)	78 (40.6)
NIHSS score at admission, median (IQR)[a]	14 (9-17)	13 (10-17)
Comorbidities, No. (%)		
Hypertension	129 (64.8)	122 (63.5)
Diabetes	42 (21.1)	41 (21.4)
Previous stroke/TIA	33 (16.6)	36 (18.8)
Atrial fibrillation	26 (13.1)	28 (14.6)
Occlusion site, No. (%)[b]		
MCA-M1	168 (84.4)	163 (84.9)
MCA-M2	31 (15.6)	29 (15.1)
ASPECTS, median (IQR)[c]	8 (7-9)	8 (7-9)
Cause of stroke, No. (%)[d]		
Intracranial atherosclerosis	133 (66.8)	121 (63.0)
Cardioembolism	63 (31.7)	70 (36.5)
Undetermined	3 (1.5)	1 (0.5)
Time metrics, median (IQR)		
From stroke onset to randomization, h	9.3 (6.4-14.3)	10.8 (6.7-14.3)
From door to intravenous tenecteplase, min	90 (69-130)	NA
From door to arterial puncture, min	123 (95-163)	118 (87-159)
From randomization to tenecteplase administration, min	9 (5-18)	NA
From tenecteplase administration to arterial puncture, min	26 (14-37)	NA
From tenecteplase administration to confirmed arterial occlusion, min	34 (22-50)	NA
From randomization to arterial puncture, min	38 (26-50)	34 (23-47)
From randomization to revascularization, min	97 (69-133)	98 (73-135)
From stroke onset to revascularization, h	11.8 (8.3-15.7)	12.7 (8.5-16.3)
Type of stroke onset, No. (%)		
Known onset time	127 (63.8)	119 (62.0)
Unwitnessed onset	15 (7.5)	18 (9.4)
Wake-up stroke	57 (28.6)	55 (28.6)
Volume on imaging, median (IQR), mL		
Ischemic core[e]	6.8 (1.0-22.5)	13.1 (2.3-24.1)
Perfusion lesion[f]	120.6 (69.0-172.6)	128.4 (79.5-183.1)

Abbreviations: ASPECTS, Alberta Stroke Program Early Computed Tomography Score; EVT, endovascular treatment; MCA, middle cerebral artery; NA, not applicable; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack.

[a] Scores range from 0 to 42, with higher scores indicating a greater deficit.

[b] Sites of MCA occlusion were assessed by the core laboratory based on computed tomography angiography/magnetic resonance angiography at baseline before randomization. The M1 segment is the main trunk of the MCA, and the M2 segment is the first order branch of the main trunk of the MCA.

[c] Scores range from 0 to 10, with lower scores indicating larger infarction.

[d] The etiology of stroke was assessed according to the medical history, clinical features, and results on digital subtraction angiography.

[e] All patients had interpretable perfusion imaging at baseline required for eligibility. The ischemic core was defined as an area with a relative cerebral blood flow of less than 30% of normal brain using computed tomography perfusion imaging or an apparent diffusion coefficient value of less than 620×10^{-6} mm^2 per second using magnetic resonance imaging.

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

puncture (<30 minutes vs ≥30 minutes), time from onset of symptoms to revascularization (<12 hours vs ≥12 hours), time from randomization to revascularization (<1.6 hours vs ≥1.6 hours), collateral grade (0-1 and 2-3),[26] and cause of stroke (cardioembolism, intracranial atherosclerosis, and undetermined). Time metrics were dichotomized approximately at the median of the whole population, as specified in the statistical analysis plan (Supplement 2). To investigate heterogeneity of the treatment effect by different subgroups, an interaction between subgroups by treatment was tested in the primary regression model. The *P* value for interaction was derived from the test of this interaction term.

A 2-sided $P < .05$ was considered to indicate statistical significance. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc) and followed the predetermined statistical analysis plan (Supplement 2).

Results

Patient Characteristics

Between January 2024 and July 2025, 565 patients underwent screening, of whom 391 (69.2%) were enrolled in the trial (due to the last 2 patients providing consent almost simultaneously); 199 were randomly assigned to receive tenecteplase with EVT and 192 to EVT alone (Figure 1). The reasons for nonenrollment and protocol violations are detailed in Figure 1. Protocol violations occurred in 24 patients (6.1%).

Baseline demographic, clinical, imaging characteristics, key time metrics, and EVT techniques were similar between groups, as detailed in **Table 1** and eTable 1 in Supplement 3. The median age was 68 years (IQR, 59-75), with males accounting for 236 (60.4%) of the 391 patients. The median NIHSS score at

Table 2. Efficacy and Adverse Event Outcomes[a]

Outcome	Tenecteplase before EVT (n = 199)	EVT alone (n = 192)	Measure (95% CI)	
			Effect size[b]	Risk difference
Primary outcome				
mRS 0-2 at 90 d, No. (%)[c]	88 (44.2)	83 (43.2)	1.01 (0.83 to 1.24)	0.99 (−8.84 to 10.83)
Secondary outcomes				
Ordinal distribution of mRS at 90 d, No. (%)[c]			1.02 (0.72 to 1.45)	
0	26 (13.1)	20 (10.4)		
1	34 (17.1)	35 (18.2)		
2	28 (14.1)	28 (14.6)		
3	37 (18.6)	36 (18.8)		
4	34 (17.1)	30 (15.6)		
5	15 (7.5)	16 (8.3)		
6	25 (12.6)	27 (14.1)		
mRS score at 90 d, No. (%)[c]				
0-1	60 (30.2)	55 (28.6)	1.01 (0.76 to 1.34)	1.50 (−7.53 to 10.54)
0-3	125 (62.8)	119 (62.0)	1.02 (0.90 to 1.16)	0.83 (−8.77 to 10.44)
5-6	40 (20.1)	43 (22.4)	0.93 (0.65 to 1.34)	−2.3 (−10.41 to 5.81)
Major neurologic improvement at 72 h, No. (%)[d]	49 (24.7)	48 (25.0)	0.97 (0.69 to 1.36)	−0.28 (−2.99 to 2.43)
Change in the NIHSS score at 7 d, median (IQR)	4 (0 to 8)	4 (0 to 8)	−0.83 (−2.34 to 0.68)	
Reperfusion prior to EVT, No. (%)[e]	20 (10.1)	14 (7.3)	1.32 (0.69 to 2.54)	2.81 (1.05 to 4.57)
Reperfusion at 24 h, No. (%)[f]	89 (44.7)	88 (46.0)	0.97 (0.78 to 1.21)	−1.32 (−4.44 to 1.80)
Recanalization at 24 h, No. (%)[g]	106 (53.3)	96 (50.0)	0.99 (0.85 to 1.15)	3.32 (0.19 to 6.45)
Adverse events outcomes[h]				
SICH within 36 h, No. (%)[i]	10 (5.1)	5 (2.6)	1.93 (0.68 to 5.51)	2.44 (−7.53 to 12.45)
Death within 90 d, No. (%)	25 (12.7)	27 (14.2)	0.93 (0.57 to 1.52)	−1.52 (−11.52 to 8.47)

Abbreviations: EVT, endovascular treatment; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SICH, symptomatic intracranial hemorrhage.

[a] Numbers shown are based on multiple imputation for secondary outcomes (major neurologic improvement at 72 hours, change in the NIHSS score at 7 days, successful reperfusion prior to EVT, reperfusion at 24 hours, and recanalization at 24 hours).

[b] Adjusted common odds ratio is shown for the ordinal score on the mRS; β coefficient is shown for the outcome of NIHSS change from baseline to day 7; adjusted relative rates are shown for other outcomes (adjusted for age, NIHSS score, and occlusion site).

[c] Scores range from 0 to 6, with higher scores indicating greater disability.

[d] Major neurologic improvement defined by NIHSS score 1 or less or a decrease of 8 points or more from baseline at 72 hours. Multiple imputation for missing data (1 patient in the tenecteplase before EVT group).

[e] Reperfusion prior to EVT defined as an expanded treatment in cerebral infarction score of 2b50, 2b67, 2c, or 3 on the intracranial angiogram. Multiple imputation for missing data (2 patients in the tenecteplase before EVT group and for 2 in the EVT alone group).

[f] 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. Multiple imputation for missing data (58 patients in the tenecteplase before EVT group and for 46 in the EVT alone group, due to lacking follow-up perfusion imaging).

[g] Recanalization at 24 hours was defined as complete recanalization (arterial occlusive lesion score, 3; scale range, 0 [no recanalization] to 3 [complete recanalization]), as assessed on computed tomography angiography or magnetic resonance angiography. Multiple imputation for missing data (32 patients in the tenecteplase before EVT group and for 23 in the EVT alone group).

[h] Adverse events outcomes were analyzed in the safety population, which included 197 patients in the tenecteplase before EVT group and 190 patients in the EVT alone group.

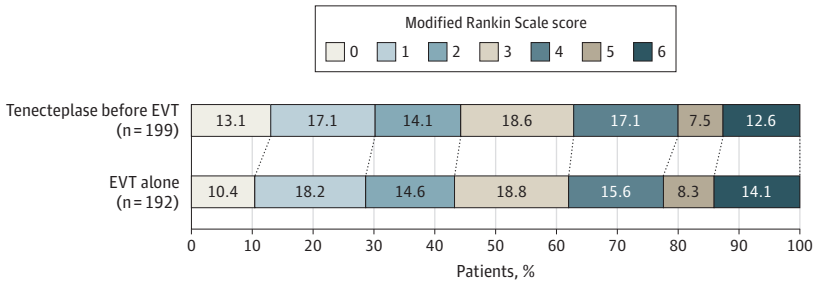
[i] Definition is according to the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) criteria: local or remote parenchymal hemorrhage type 2 on the 22 to 36 hours posttreatment imaging scan, combined with a neurologic deterioration of 4 points or more on the NIHSS from baseline, or from the lowest NIHSS value between baseline and 24 hours, or leading to death.

admission was 13 (IQR, 10-17). The median time from symptom onset to randomization was 10.0 hours (IQR, 6.5-14.3), and the median time from hospital admission to intravenous tenecteplase administration was 90 minutes in the interventional group (IQR, 69-130). An MCA-M1 occlusion was present in 168 patients (84.4%) in the intervention group and in 163 patients (84.9%) in the control group. Intracranial atherosclerosis accounted for 65.0% (254/391) of patients. Regarding imaging modality for reperfusion at 24 hours, 89.9% (302/336) of patients underwent CT angiography, and 10.1% (34/336) underwent MR angiography.

Primary and Secondary Outcomes

The primary outcome of functional independence (mRS score ≤2) at 90 days was achieved by 44.2% of patients in the tenecteplase plus EVT group and 43.2% in the direct EVT group (adjusted RR, 1.01 [95% CI, 0.83-1.24]; 2-sided P = .89) (**Table 2** and **Figure 2**). Secondary and adverse events outcomes are

Figure 2. Distribution of Scores on the Modified Rankin Scale at 90 Days in the Intention-to-Treat Population



EVT indicates endovascular treatment.

presented in Table 2. The required perfusion imaging at 24 hours after randomization was not completed for 104 patients, due to their clinical status. Efficacy and adverse events outcomes in the intention-to-treat population without multiple imputation yielded results similar to those from the main analyses (eTable 2 in Supplement 3). A post hoc analysis of reperfusion after EVT in the intention-to-treat population without multiple imputation was 95.2% (179/188) for the tenecteplase before EVT group and 90.8% (168/185) for the EVT alone group (adjusted RR, 1.04 [95% CI, 0.98-1.10]; P = .19). The results of the primary and secondary efficacy outcomes in the per-protocol analysis were similar to those from the main analysis (eTable 3 and eFigure in Supplement 3). Sensitivity analysis in the CT angiography–assessed patients for recanalization at 24 hours and post hoc analysis of the treatment-effect heterogeneity of subgroups on a continuous scale yielded results similar to those from the main analyses (eTable 4 and eTable 5 in Supplement 3).

Adverse Events Outcomes

A total of 10 patients (5.1%) in the tenecteplase before EVT group and 5 patients (2.6%) in the EVT alone group had symptomatic intracranial hemorrhage within 36 hours after randomization (adjusted RR, 1.93 [95% CI, 0.68-5.51]). Death within 90 days occurred in 25 patients (12.7%) in the tenecteplase before EVT group and 27 (14.2%) in the EVT alone group (adjusted RR, 0.93 [95% CI, 0.57-1.52]). No significant difference was observed between groups in the incidence of serious adverse events (eTable 6 in Supplement 3). Prespecified subgroup analyses of the primary outcome did not indicate heterogeneity (**Figure 3**).

Discussion

This randomized trial of patients presenting to an EVT-capable center with a M1 or proximal M2 occlusion and salvageable tissue within 4.5 to 24 hours of the time they were last known to be well did not demonstrate the superiority of tenecteplase before EVT compared with EVT alone for a favorable functional outcome (defined as an mRS score of 0-2) at 90 days. However, despite a numerically increased rate of symptomatic intracranial hemorrhage, no differences were observed in mortality or severe disability.

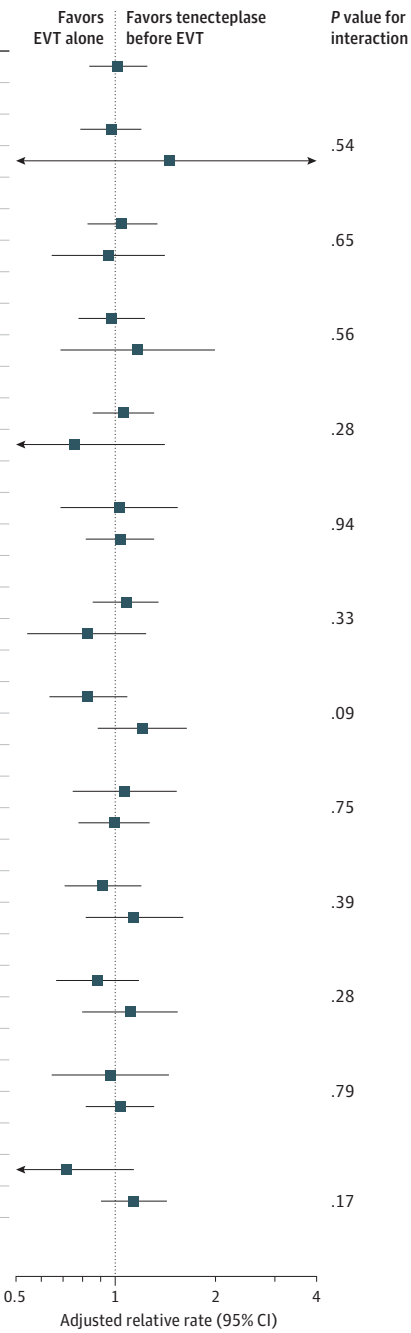
The TNK-PLUS trial was designed based on the TIMELESS trial M1 subgroup analysis result, which suggested benefit of tenecteplase over placebo in patients who predominantly received EVT.[10] However, the TIMELESS post hoc subgroup analysis was considered exploratory, and the TNK-PLUS prospective randomized trial failed to show a benefit of tenecteplase before EVT vs EVT alone, despite the median of 26 minutes between the administration of tenecteplase and arterial puncture being longer than the median of 15 minutes in the TIMELESS trial.[10] Reperfusion prior to EVT in the TNK-PLUS trial (10.1%) was numerically higher than in the BRIDGE-TNK trial (6.1%)[8] but lower than in the Tenecteplase vs Alteplase Before Endovascular Therapy for Ischemic Stroke (EXTEND-IA TNK) trial (22%).[27] Dwell time of tenecteplase may account for the difference (16 minutes for BRIDGE-TNK vs 26 minutes for TNK-PLUS vs 43 minutes for EXTEND-IA TNK).[8,27] The end-of-procedure expanded Thrombolysis in Cerebral Infarction score 2b/3 of 95% in TNK-PLUS was slightly higher than the 91% in BRIDGE-TNK.[8] The lower rate of complete recanalization at 24 hours in the current study (53.3%) compared with that in the TIMELESS trial (76.7% in the tenecteplase group)[10] may be attributable to the increased prevalence of intracranial atherosclerosis in TNK-PLUS.

Viewed in the context of the Extending the Time Window for Tenecteplase by Effective Reperfusion in Patients with Large Vessel Occlusion (ETERNAL-LVO) trial,[28] intravenous tenecteplase before thrombectomy might benefit patients with a delayed time from thrombolytic administration to arterial puncture. Noting that there was no significant effect in this subgroup and that the test for interaction was also not significant, the favorable point estimate for tenecteplase effect in the TNK-PLUS prespecified subgroup analysis of patients who had time from randomization to revascularization of 1.6 hours or longer may support the rationale for trials in patients being transferred for EVT, which require an estimated time from randomization to arterial puncture of 2 hours or longer.

The TNK-PLUS trial adds important data to the field of bridging thrombolytic prior to EVT. The most important difference between the positive BRIDGE-TNK trial and the neutral TNK-PLUS trial is the time window.[8] Although not evident in BRIDGE-TNK, perhaps due to small subgroups, there was a strong relationship between onset to thrombolytic time and benefit of bridging thrombolytic in the large IRIS collaboration meta-analysis,[29] with bridging no longer demonstrating

Figure 3. Dot Plot Showing Subgroup Analysis of Modified Rankin Scale Score of 0 or 2 at 90 Days (Primary Outcome) in Prespecified Subgroups

Subgroup	No. of patients with primary outcome/total No. (%)		Absolute difference (95% CI)	Adjusted relative rate (95% CI)	*P* value for interaction
	Tenecteplase before EVT	EVT alone			
Overall	88/199 (44.2)	83/192 (43.2)	0.99 (-8.84 to 10.83)	1.01 (0.83-1.24)	
Age, y					
<80	85/188 (45.2)	78/166 (47.0)	-1.78 (-12.18 to 8.63)	0.97 (0.78-1.19)	.54
≥80	3/11 (27.3)	5/26 (19.2)	8.04 (-22.33 to 38.41)	1.45 (0.42-5.02)	
Sex					
Male	61/122 (50.0)	52/114 (45.6)	4.39 (-8.35 to 17.13)	1.04 (0.82-1.33)	.65
Female	27/77 (35.1)	31/78 (39.7)	-4.68 (-19.90 to 10.54)	0.95 (0.64-1.40)	
Stroke severity (NIHSS score) at baseline[a]					
6-15	68/137 (49.6)	65/125 (52.0)	-2.36 (-14.48 to 9.75)	0.97 (0.77-1.22)	.56
16-25	19/61 (31.1)	18/66 (27.3)	3.87 (-11.95 to 19.70)	1.16 (0.68-1.98)	
Site of vessel occlusion					
M1	77/168 (45.8)	71/163 (43.6)	2.28 (-8.44 to 12.99)	1.05 (0.85-1.30)	.28
Proximal M2	11/31 (35.5)	12/29 (41.4)	-5.90 (-30.49 to 18.70)	0.75 (0.40-1.40)	
ASPECTS score					
<8	30/87 (34.5)	25/71 (35.2)	-0.73 (-15.67 to 14.21)	1.02 (0.68-1.53)	.94
≥8	58/112 (51.8)	58/121 (47.9)	3.85 (-8.99 to 16.69)	1.03 (0.81-1.30)	
Core volume, mL					
<10	63/110 (57.3)	50/87 (57.5)	-0.20 (-14.10 to 13.71)	1.07 (0.85-1.34)	.33
≥10	25/89 (28.1)	33/105 (31.4)	-3.34 (-16.22 to 9.55)	0.82 (0.54-1.23)	
Time from onset of symptoms to randomization, h					
<10	45/110 (40.9)	44/84 (52.4)	-11.47 (-25.56 to 2.62)	0.82 (0.63-1.08)	.09
≥10	43/89 (48.3)	39/108 (36.1)	12.20 (-1.57 to 25.98)	1.20 (0.88-1.63)	
Time from randomization to arterial puncture, min[b]					
<30	29/65 (44.6)	29/71 (40.8)	3.77 (-12.87 to 20.41)	1.06 (0.74-1.52)	.75
≥30	59/133 (44.4)	54/119 (45.4)	-1.02 (-13.32 to 11.28)	0.99 (0.77-1.26)	
Time from onset of symptoms to revascularization, h[c]					
<12	43/100 (43.0)	44/87 (50.6)	-7.57 (-21.88 to 6.73)	0.91 (0.70-1.19)	.39
≥12	41/89 (46.1)	36/98 (36.7)	9.33 (-4.75 to 23.42)	1.13 (0.81-1.59)	
Time from randomization to revascularization, h[c]					
<1.6	43/92 (46.7)	46/89 (51.7)	-4.95 (-19.50 to 9.60)	0.88 (0.66-1.17)	.28
≥1.6	41/97 (42.3)	34/96 (35.4)	6.85 (-6.87 to 20.57)	1.10 (0.79-1.53)	
Collateral grades[d]					
0-1	26/68 (38.2)	25/68 (36.8)	1.47 (-14.80 to 17.74)	0.96 (0.64-1.44)	.79
2-3	62/131 (47.3)	58/124 (46.8)	0.55 (-11.70 to 12.81)	1.03 (0.81-1.30)	
Cause of stroke					
Cardioembolism	19/63 (30.2)	30/70 (42.9)	-12.70 (-28.91 to 3.51)	0.71 (0.45-1.13)	.17
Intracranial atherosclerosis	68/133 (51.1)	53/121 (43.8)	7.33 (-4.93 to 19.59)	1.13 (0.90-1.42)	
Undetermined	1/3 (33.3)	0/1	33.33 (-20.01 to 86.68)		



ASPECTS indicates Alberta Stroke Program Early CT Score; EVT, endovascular treatment; NIHSS, National Institutes of Health Stroke Scale.

[a]Two patients had a baseline NIHSS score greater than 25.

[b]Three patients refused digital subtraction angiography (DSA) or EVT.

[c]Three patients refused DSA or EVT, 1 patient did not perform DSA, and 13 patients only received DSA.

[d]The presence of collateral flow in the middle cerebral artery (MCA) territory of the affected hemisphere on computed tomography angiography (CTA: single-phase CTA or the arterial phase of multiphase CTA), defined as grade 0 (absent collateral supply), grade 1 (collateral filling ≤50% but >0%), grade 2 (collateral filling >50% but <100%), or grade 3 (100% collateral filling) scored in comparison to the entire contralateral MCA territory.

significant benefit beyond 2 hours and 20 minutes from stroke onset. The precise time would vary as a function of statistical power, but the principle of a time-dependent effect of thrombolytic appears clear and is supported by other studies.[30-34] The reasons for the time dependency are unclear, but it appears that thrombus is more likely to dissolve with shorter delay

between onset and administration of thrombolytic, perhaps due to persistence of flow microchannels through the thrombus.[35] Late-window studies also selected patients based on favorable perfusion mismatch, which is associated with slower infarct progression rate. These patients may demonstrate less response to the potentially earlier reperfusion with bridging thrombolytic. TNK-PLUS and TIMELESS[10] in the anterior circulation and the recently presented ATTENTION-LATE trial (NCT05701956) in the posterior circulation were consistent in not finding benefit of bridging 4.5 to 24 hours in patients with immediate access to EVT. Importantly, the results of these trials, which had a short time between thrombolytic administration and arterial puncture, do not apply to patients with expected delays to accessing EVT, including those being transferred between hospitals.

Limitations

This trial has several limitations. First, the open-label design may have caused bias, but outcomes were assessed by clinicians unaware of the treatment assignments. Second, the trial was performed in China, where intracranial atherosclerosis is more prevalent than in Western countries and atrial fibrillation is less prevalent. However, in this study, one-third of patients had a cardioembolic cause for stroke, which is comparable to Western populations.[36] Increased prevalence of intracranial atherosclerosis in the Chinese population could modulate the effect of thrombolysis, although no evidence of interaction in the data was observed. Third, the door-to-needle time (median, 90 minutes) was longer than the median of less than 60 minutes that sites were required to have for routine 0- to 4.5-hour thrombolysis due to additional imaging, consent, and randomization procedure, which may have reduced the tenecteplase dwell time. Fourth, although neutral, the confidence intervals for the outcomes do not exclude clinically meaningful benefit (or harm), and the trial was likely not powered to detect differences in safety end points. Fifth, the trial enrolled patients directly presenting to a thrombectomy-capable center, so the results are not generalizable to patients presenting to a center without onsite EVT capability.

Conclusions

In this randomized trial of patients with ischemic stroke due to a proximal middle cerebral artery occlusion and who had salvageable tissue presenting directly to an EVT center within 4.5 to 24 hours, treatment with intravenous tenecteplase before EVT did not increase the likelihood of functional independence compared with EVT alone.

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