ORIGINAL ARTICLE

Intravenous Tenecteplase before Thrombectomy in Stroke

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ABSTRACT

BACKGROUND

The safety and efficacy of treatment with intravenous tenecteplase before endovascular thrombectomy in patients with acute ischemic stroke due to large-vessel occlusion remain uncertain.

METHODS

In this open-label trial conducted in China, we randomly assigned patients with acute ischemic stroke due to large-vessel occlusion who had presented within 4.5 hours after onset and were eligible for thrombolysis to receive either intravenous tenecteplase followed by endovascular thrombectomy or endovascular thrombectomy alone. The primary outcome was functional independence (a score of 0 to 2 on the modified Rankin scale; range, 0 to 6, with higher scores indicating more severe disability) at 90 days. Secondary outcomes included successful reperfusion before and after thrombectomy. Safety outcomes included symptomatic intracranial hemorrhage within 48 hours and death within 90 days.

RESULTS

A total of 278 patients were randomly assigned to the tenecteplase–thrombectomy group and 272 to the thrombectomy-alone group. Functional independence at 90 days was observed in 147 patients (52.9%) in the tenecteplase–thrombectomy group and in 120 patients (44.1%) in the thrombectomy-alone group (unadjusted risk ratio, 1.20; 95% confidence interval, 1.01 to 1.43; P=0.04). A total of 6.1% of the patients in the tenecteplase–thrombectomy group and 1.1% of those in the thrombectomy-alone group had successful reperfusion before thrombectomy, and 91.4% and 94.1%, respectively, had successful reperfusion after thrombectomy. Symptomatic intracranial hemorrhage within 48 hours occurred in 8.5% of the patients in the tenecteplase–thrombectomy group and in 6.7% of those in the thrombectomy-alone group; mortality at 90 days was 22.3% and 19.9%, respectively.

CONCLUSIONS

Among patients with acute ischemic stroke due to large-vessel occlusion who had presented within 4.5 hours after onset, the percentage of patients with functional independence at 90 days was higher with intravenous tenecteplase plus endovascular thrombectomy than with endovascular thrombectomy alone. (Funded by the Chongqing Science and Health Joint Medical Research Project and others; BRIDGE-TNK ClinicalTrials.gov number, NCT04733742.)

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*A full list of BRIDGE-TNK Trial Investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Intravenous thrombolysis that precedes endovascular thrombectomy has both the potential benefit of enhancing reperfusion before, during, and after the procedure and the potential risk of increasing intracranial hemorrhage. Since 2018, six randomized, controlled trials have evaluated the role of intravenous thrombolysis before endovascular thrombectomy in the treatment of patients with stroke who had presented within 4.5 hours after onset and were eligible for thrombolysis.[1-6] A pooled analysis of participant-level data from these six trials showed no significant difference in efficacy between intravenous thrombolysis plus endovascular thrombectomy and endovascular thrombectomy alone. It is notable that most of the participants in these trials received alteplase, with only 2.2% receiving tenecteplase, which precluded a meaningful subgroup analysis of the effect of tenecteplase.[7]

Tenecteplase is a genetically modified tissue plasminogen activator that offers pharmacokinetic advantages over alteplase — including a prolonged half-life, enhanced fibrin specificity, and resistance to endogenous inhibitors — that enable rapid, single-bolus administration and may lead to superior efficacy with respect to reperfusion.[8] A randomized trial showed that tenecteplase before endovascular thrombectomy was associated with a higher incidence of early reperfusion and better functional outcomes at 90 days than alteplase before endovascular thrombectomy.[9] In contrast, a target trial emulation analysis indicated that intravenous tenecteplase before endovascular thrombectomy was not associated with a higher likelihood of functional independence than endovascular thrombectomy alone.[10] However, existing evidence is limited by small sample sizes and the lack of a direct comparison of intravenous tenecteplase plus endovascular thrombectomy with endovascular thrombectomy alone. A randomized trial assessing whether treatment with intravenous tenecteplase before endovascular thrombectomy confers incremental clinical benefit without elevating hemorrhagic risk in this population is needed.

We therefore designed and conducted the Randomized Trial of Thrombectomy with versus without Recombinant Human Tenecteplase (TNK) Tissue Plasminogen Activator in Stroke (BRIDGE-TNK) to determine whether intravenous tenecteplase plus endovascular thrombectomy would lead to a higher likelihood of functional independence at 90 days than endovascular thrombectomy alone among patients with stroke due to large-vessel occlusion who had presented within 4.5 hours after onset and were eligible for thrombolysis.

METHODS

TRIAL DESIGN AND OVERSIGHT

BRIDGE-TNK was an investigator-initiated, multicenter, randomized, open-label trial with blinded assessment of outcomes. The trial was conducted in accordance with the principles of the Declaration of Helsinki. The trial protocol (available with the full text of this article at NEJM.org) was approved by the ethics committees of the Second Affiliated Hospital of Army Medical University (Xinqiao Hospital) and all the participating centers, and key aspects have been published previously.[11] Written informed consent was obtained from all the patients or their legal representatives before randomization. The last author had unrestricted access to the data after the database was locked and vouches for the accuracy and completeness of the data and for the fidelity of the trial to the protocol and statistical analysis plan (available with the protocol).

The China Shijiazhuang Pharmaceutical Company (CSPC) provided tenecteplase. CSPC had no role in the trial design; the collection, analysis, or interpretation of the data; or the preparation or approval of the manuscript. There were no confidentiality agreements between CSPC and the investigators, and CSPC could not delay or interdict publication of the trial results. The first draft of the manuscript was written by the first and last authors, and all the authors made critical revisions. Lists of the trial sites, investigators, and administrative staff are provided in the Supplementary Appendix (available at NEJM.org), along with a flowchart showing the trial design (Fig. S1 in the Supplementary Appendix).

PATIENTS

The trial was conducted at 39 hospitals in China (Fig. S2). Patients were eligible for inclusion in the trial if they were 18 years of age or older; had acute ischemic stroke due to occlusion of an internal carotid artery, the first or second segment of the middle cerebral artery, or a vertebrobasilar artery; had presented within 4.5 hours after the time point that they were last known to be well;

and were eligible for intravenous thrombolysis on the basis of Chinese stroke guidelines. Key exclusion criteria were the presence of contraindications to intravenous thrombolysis and the receipt of intravenous thrombolysis before screening. Details regarding the eligibility criteria are provided in the Supplementary Appendix.

RANDOMIZATION

Eligible patients were randomly assigned in a 1:1 ratio to receive either intravenous tenecteplase followed by endovascular thrombectomy (tenecteplase–thrombectomy group) or endovascular thrombectomy alone (thrombectomy-alone group). A fixed-block randomization scheme with block sizes of four was used. Randomization was performed on a secure website immediately after eligibility was confirmed. Patients and clinical staff were informed of the treatment assignments after randomization. However, the randomization codes were concealed from all parties, including the clinical coordinating center, the data-management group, trial statisticians, and CSPC staff and delegates. An independent clinical-events committee, whose members were unaware of the treatment assignments, adjudicated efficacy and safety outcome events, including procedure-related complications and serious adverse events. Findings on imaging studies were adjudicated by an imaging core laboratory in a blinded manner.

INTERVENTIONS

All the patients in both treatment groups were to receive rapid endovascular thrombectomy. Patients who were randomly assigned to the tenecteplase–thrombectomy group were to be treated with intravenous tenecteplase followed by endovascular thrombectomy. Tenecteplase was manufactured by CSPC Recomgen Pharmaceutical (Guangzhou). Tenecteplase was stored as a lyophilized powder in a glass vial (16 mg per vial) and was reconstituted in sterile water (3 ml) for injection. A bolus dose (0.25 mg per kilogram of body weight; maximum dose, 25 mg) was administered intravenously over a period of 5 to 10 seconds and was followed by a saline flush. Patients in both groups could also receive endovascular therapy (the use of stent retrievers, thromboaspiration, balloon angioplasty, stenting, intraarterial thrombolysis, or a combination of these approaches), which was provided at the discretion of the interventionalist. Patients who were randomly assigned to the thrombectomy-alone group were to receive endovascular thrombectomy without intravenous tenecteplase pretreatment.

OUTCOMES

The primary outcome was functional independence, defined as a score of 0 to 2 on the modified Rankin scale, at 90 days. The modified Rankin scale is a 7-point ordinal scale of functional disability; scores range from 0 to 6, with higher scores indicating more severe disability. The scores were adjudicated by two independent neurologists who were certified in the use of the modified Rankin scale and were unaware of the treatment assignments. The assessments were based on video or voice recordings that were taken at the outpatient clinic, during a telephone or video call, or by family members.

Secondary efficacy outcomes included the disability level (the modified Rankin scale score) at 90 days, an excellent outcome (a modified Rankin scale score of 0 or 1) at 90 days, independent ambulation (a modified Rankin scale score of 0 to 3) at 90 days, and health-related quality of life (the score on the EuroQol Group 5-Dimension 5-Level [EQ-5D-5L] questionnaire; range, −0.39 to 1, with higher scores indicating better quality of life) at 90 days, all of which were assessed by the clinical-events committee. The National Institutes of Health Stroke Scale (NIHSS) score (range, 0 to 42, with higher scores indicating more severe neurologic deficits) at 5 to 7 days (or at discharge if it occurred earlier) was assessed by two independent, certified neurologists by video in a blinded manner. Successful reperfusion (an expanded Treatment in Cerebral Infarction [eTICI] grade of 2b, 2c, or 3; range, 0 [no reperfusion] to 3 [complete reperfusion]) on angiography performed before endovascular thrombectomy, successful reperfusion on angiography performed after endovascular thrombectomy, first-pass reperfusion (an eTICI grade of 2c or 3 after the first thrombectomy pass), and modified first-pass reperfusion (an eTICI grade of 2b, 2c, or 3 after the first thrombectomy pass) were adjudicated by the imaging core laboratory.[12]

Safety outcomes were symptomatic intracranial hemorrhage (assessed according to the modified Heidelberg Bleeding Classification) within 48 hours after randomization, any evidence of intracranial hemorrhage on imaging within 48

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Tenecteplase plus Thrombectomy (N=278)	Thrombectomy Alone (N=272)
Median age (IQR) — yr	70 (60–77)	70 (63–76)
Male sex — no. (%)	161 (57.9)	159 (58.5)
Prestroke score on the modified Rankin scale — no. (%)†		
0	263 (94.6)	258 (94.9)
1	11 (4.0)	9 (3.3)
2	3 (1.1)	4 (1.5)
4	1 (0.4)	1 (0.4)
Cause of stroke — no. (%)		
Large-artery atherosclerosis	82 (29.5)	85 (31.2)
Cardioembolism	172 (61.9)	163 (59.9)
Unknown	22 (7.9)	18 (6.6)
Other	2 (0.7)	6 (2.2)
Median ASPECTS at baseline (IQR)‡	8 (6–9)	8 (6–9)
Site of occlusion — no. (%)		
Internal carotid artery	77 (27.7)	87 (32.0)
Middle cerebral artery		
First segment	154 (55.4)	145 (53.3)
Second segment	18 (6.5)	20 (7.4)
Vertebrobasilar artery	29 (10.4)	20 (7.4)
Median systolic blood pressure (IQR) — mm Hg	144 (130–163)	148 (129–169)
Median NIHSS score (IQR)§	16 (12–20)	16 (12–20)
Median glucose level (IQR) — mmol/liter¶	7.3 (6.1–9.1)	7.3 (6.0–8.8)
Median time from the last-known-well time point to randomization (IQR) — min	159.3 (121.2–214.9)	167.6 (130.5–215.5)
Median time from randomization to the start of treatment with intravenous tenecteplase (IQR) — min	6.0 (3.5–10.2)	NA
Median time from the start of treatment with intravenous tenecteplase to the thrombectomy puncture (IQR) — min	16.0 (1.5–35.0)	NA
Median time from randomization to the thrombectomy puncture (IQR) — min‖	28.2 (7.0–45.4)	24.4 (2.3–38.6)
Median time from the thrombectomy puncture to reperfusion (IQR) — min‖	55.0 (35.0–85.0)	64.0 (40.0–102.0)

* IQR denotes interquartile range, and NA not applicable.
† Scores on the modified Rankin scale range from 0 to 6, with higher scores indicating more severe disability. The score on the modified Rankin scale before the onset of stroke was evaluated by the site investigator with the use of information obtained from patients (if possible) or their family members.
‡ The Alberta Stroke Program Early Computed Tomography Score (ASPECTS) ranges from 0 to 10, with higher scores indicating a smaller ischemic core.
§ The National Institutes of Health Stroke Scale (NIHSS) score ranges from 0 to 42, with higher scores indicating more severe neurologic deficits.
¶ For the glucose level, data were missing for 7 patients (3 in the tenecteplase–thrombectomy group and 4 in the thrombectomy-alone group). To convert the values to milligrams per deciliter, divide by 0.05551.
‖ Data were not available for 1 patient in the thrombectomy-alone group.

hours, death within 90 days, procedure-related complications, and serious adverse events. Safety data were collected by site investigators, and data from the source documentation were adjudicated by the imaging core laboratory and clinical-events committee.

STATISTICAL ANALYSIS

On the basis of the results from two randomized trials conducted in China that assessed endovascular thrombectomy alone for the treatment of acute stroke due to large-vessel occlusion,[3,6] we assumed that the percentage of patients with functional independence at 90 days in the thrombectomy-alone group would be 41%. On the basis of the results from a pooled analysis of three randomized trials that assessed intravenous tenecteplase bridging endovascular thrombectomy for the treatment of stroke due to large-vessel occlusion,[9,13,14] we hypothesized that the percentage of patients with functional independence at 90 days in the tenecteplase–thrombectomy group would be 54%. We calculated that a sample size of 231 patients per group (462 total patients) would provide the trial with 80% power to detect a significant difference between the two treatment groups in the percentage of patients with functional independence at 90 days, at a two-sided alpha level of 0.05. The sample size was increased to 272 patients per group (544 total patients) to allow for 15% attrition.

A modified Poisson regression model was used for the analysis of the primary outcome and binary secondary outcomes, with adjustment for prespecified covariates, generating adjusted risk ratios as measurements of treatment effect.[15] The analysis of the modified Rankin scale score at 90 days was performed with the generalized-odds-ratio approach. The analysis of nonnormal continuous secondary outcomes such as the EQ-5D-5L score at 90 days and the NIHSS score at 5 to 7 days (or at discharge) was performed with the win-ratio approach.[16] Although the protocol specified that adjusted treatment effects were to be reported, unadjusted estimates are also presented. The statistical analysis plan did not include a provision for correction for multiplicity in the analysis of secondary outcomes or the subgroup analysis, and the widths of the confidence intervals should not be used to infer definitive treatment effects.

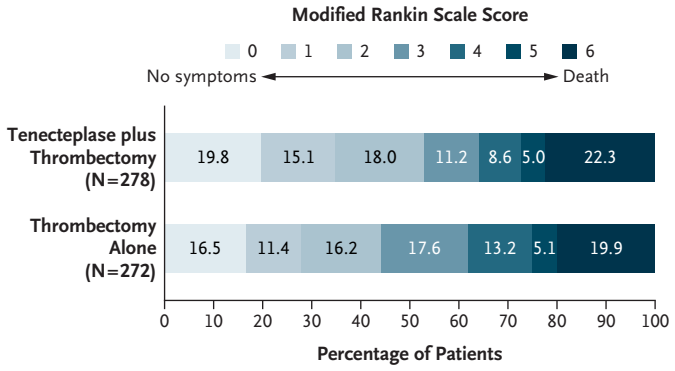


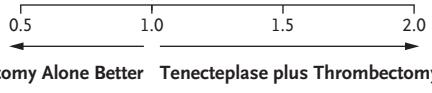
Figure 1. Distribution of Scores on the Modified Rankin Scale at 90 Days in the Intention-to-Treat Population.

Shown is the distribution of scores on the modified Rankin scale at 90 days in the two treatment groups. The scores range from 0 to 6, with a score of 0 indicating no neurologic deficit, 1 no clinically significant disability, 2 slight disability (the ability to handle daily tasks such as shopping, cleaning, and finances without assistance, but the inability to carry out some previously performed activities), 3 moderate disability requiring some help (the ability to walk unassisted, but the inability to handle daily tasks without assistance), 4 moderately severe disability (the inability to walk unassisted or to attend to bodily needs without assistance), 5 severe disability (the need for constant nursing care and attention), and 6 death. The overall distribution of scores is similar in the two treatment groups (adjusted generalized odds ratio, 1.16; 95% CI, 0.94 to 1.43); the analysis was not adjusted for multiplicity. The percentages may not total 100 because of rounding.

The main analyses of efficacy outcomes were performed in the intention-to-treat population, which consisted of all the patients who had undergone randomization, except those for whom consent was withdrawn. The analyses of severe adverse events and procedure-related complications were performed in the safety population, which consisted of all the patients who had undergone randomization (without withdrawal of consent) and had received any trial treatment.

Modification of the treatment effect was assessed in nine prespecified subgroups, which were defined according to the following characteristics: age, sex, NIHSS score at baseline, Alberta Stroke Program Early Computed Tomography Score (ASPECTS; range, 0 to 10, with higher scores indicating a smaller ischemic core) at baseline, site of occlusion, cause of stroke, use of angioplasty or stenting during thrombectomy,

Subgroup	Modified Rankin Scale Score of 0 to 2 at 90 Days		Adjusted Risk Ratio (95% CI)
	Thrombectomy Alone	Tenecteplase plus Thrombectomy	
	no. of events/total no. (%)		
Overall	120/272 (44.1)	147/278 (52.9)	1.18 (1.01–1.39)
Age			
≤70 yr	73/146 (50.0)	86/143 (60.1)	1.18 (0.89–1.56)
>70 yr	47/126 (37.3)	61/135 (45.2)	1.18 (0.97–1.44)
Sex			
Female	45/113 (39.8)	58/117 (49.6)	1.19 (0.90–1.57)
Male	75/159 (47.2)	89/161 (55.3)	1.17 (0.96–1.44)
NIHSS score at baseline			
≤16	82/143 (57.3)	95/144 (66.0)	1.13 (0.95–1.35)
>16	38/129 (29.5)	52/134 (38.8)	1.24 (0.89–1.73)
ASPECTS at baseline			
≤8	73/190 (38.4)	100/197 (50.8)	1.34 (1.08–1.66)
>8	47/82 (57.3)	47/81 (58.0)	0.93 (0.72–1.19)
Site of occlusion			
Internal carotid artery	28/87 (32.2)	31/77 (40.3)	1.36 (0.92–1.99)
Other	92/185 (49.7)	116/201 (57.7)	1.14 (0.97–1.37)
Cause of stroke			
Large-artery atherosclerosis	42/85 (49.4)	38/82 (46.3)	0.99 (0.72–1.36)
Cardioembolism	66/163 (40.5)	96/172 (55.8)	1.28 (1.04–1.58)
Unknown or other	12/24 (50.0)	13/24 (54.2)	1.06 (0.59–1.92)
Angioplasty or stenting during thrombectomy			
No	82/190 (43.2)	110/210 (52.4)	1.18 (0.98–1.44)
Yes	32/72 (44.4)	24/51 (47.1)	1.03 (0.70–1.52)
Time from last-known-well time point to randomization			
≤163 min	68/125 (54.4)	84/149 (56.4)	1.06 (0.87–1.30)
>163 min	52/147 (35.4)	63/129 (48.8)	1.35 (1.04–1.77)
Actual or expected time from last-known-well time point to start of intravenous tenecteplase			
≤140 min	44/69 (63.8)	49/85 (57.6)	0.94 (0.73–1.20)
>140 min	76/203 (37.4)	98/193 (50.8)	1.33 (1.08–1.64)
Actual or expected time from start of intravenous tenecteplase to puncture			
≤16 min	61/135 (45.2)	73/138 (52.9)	1.17 (0.93–1.47)
>16 min	59/137 (43.1)	74/140 (52.9)	1.19 (0.95–1.50)



time from the last-known-well time point to randomization, and actual or expected time from the last-known-well time point to the start of treatment with intravenous tenecteplase.[17] A post hoc analysis was performed in a subgroup defined according to the actual or expected time from the start of treatment with intravenous tenecteplase to the thrombectomy puncture. The actual time was measured in the tenecteplase–thrombectomy group, whereas the expected time was calculated in the thrombectomy-alone group.

No imputation for missing data was performed in this trial because the data for the primary analysis and prespecified covariates for covariate-adjusted analyses were complete. Statistical analyses were conducted with the use of SAS software, version 9.4 (SAS Institute), and R software, version 4.1.1 (R Foundation for Statistical Computing). Details regarding the statistical analysis are provided in the Supplementary Appendix.

RESULTS

PATIENT CHARACTERISTICS

From May 9, 2022, through September 8, 2024, a total of 554 patients underwent randomiza-

Figure 2 (facing page). Subgroup Analysis of Functional Independence at 90 Days.

The forest plot shows the adjusted risk ratio between the two treatment groups for functional independence, defined as a score of 0 to 2 on the modified Rankin scale, at 90 days in ten subgroups. The National Institutes of Health Stroke Scale (NIHSS) score ranges from 0 to 42, with higher scores indicating more severe neurologic deficits; the NIHSS score was assessed by two independent, certified neurologists by video in a blinded manner. The Alberta Stroke Program Early Computed Tomography Score (ASPECTS) ranges from 0 to 10, with higher scores indicating a smaller ischemic core; the ASPECTS was assessed by the imaging core laboratory. The subgroup analysis for age, NIHSS score at baseline, ASPECTS at baseline, and time from the last-known-well time point to randomization were dichotomized relative to the median. For the actual or expected time from the last-known-well time point to the start of treatment with intravenous tenecteplase, the actual time was measured in the tenecteplase–thrombectomy group, whereas the expected time was calculated in the thrombectomy-alone group by adding the time from the last-known-well time point to randomization that was documented for each patient to the mean time from randomization to the start of treatment with intravenous tenecteplase that was derived for the group. For the actual or expected time from the start of treatment with intravenous tenecteplase to the thrombectomy puncture (post hoc subgroup analysis), the actual time was measured in the tenecteplase–thrombectomy group, whereas the expected time was calculated in the thrombectomy-alone group by subtracting the expected time from the last-known-well time point to the start of treatment with intravenous tenecteplase from the median time from the last-known-well time point to the thrombectomy puncture. Adjusted risk ratios are reported in accordance with the prespecified statistical analysis plan. The widths of the confidence intervals were not adjusted for multiplicity and cannot be used to infer definitive treatment effects. The percentages may not total 100 because of rounding.

tion, and 550 were included in the intention-to-treat population; 4 patients were excluded from all the analyses owing to withdrawal of consent (Fig. S3). No patients were lost to follow-up. Of the 550 patients in the intention-to-treat population, 278 were randomly assigned to the tenecteplase–thrombectomy group and 272 to the thrombectomy-alone group. The median age of the patients was 70 years (interquartile range, 61 to 77), and 230 patients (41.8%) were women. The characteristics of the patients at baseline were balanced between the two treatment groups, and the trial population was largely representative of the expected patient population (Table 1, and Tables S1 and S2). The median time from the start of treatment with intravenous tenecteplase to the thrombectomy puncture was 16 minutes (interquartile range, 1.5 to 35). The median time from the thrombectomy puncture to reperfusion was 55 minutes in the tenecteplase–thrombectomy group and 64 minutes in the thrombectomy-alone group. Angioplasty or stenting was used during the procedure in 51 of 261 patients (19.5%) in the tenecteplase–thrombectomy group and in 72 of 262 patients (27.5%) in the thrombectomy-alone group.

PRIMARY OUTCOME

Functional independence at 90 days (the primary outcome) was observed in 147 patients (52.9%) in the tenecteplase–thrombectomy group and in 120 patients (44.1%) in the thrombectomy-alone group (unadjusted risk ratio, 1.20; 95% confidence interval [CI], 1.01 to 1.43; P=0.04; adjusted risk ratio, 1.18; 95% CI, 1.01 to 1.39; P=0.04) (Fig. 1). The results of the prespecified and post hoc subgroup analyses of functional independence at 90 days are shown in Figure 2.

SECONDARY OUTCOMES

The results of the analyses of prespecified secondary outcomes are shown in Table 2 and Table S3. The trial was not powered for the detection of differences between the two treatment groups in these analyses, and the analyses were not adjusted for multiplicity. A total of 17 of 278 patients (6.1%) in the tenecteplase–thrombectomy group and 3 of 271 patients (1.1%) in the thrombectomy-alone group had successful reperfusion before thrombectomy (adjusted risk ratio, 5.19; 95% CI, 1.51 to 17.84). A total of 254 of 278 patients (91.4%) in the tenecteplase–thrombectomy group and 255 of 271 patients (94.1%) in the thrombectomy-alone group had successful reperfusion after thrombectomy (adjusted risk ratio, 0.97; 95% CI, 0.92 to 1.02).

SAFETY OUTCOMES

Symptomatic intracranial hemorrhage within 48 hours occurred in 23 of 271 patients (8.5%) in the tenecteplase–thrombectomy group and in 18 of 269 patients (6.7%) in the thrombectomy-alone group (adjusted risk ratio, 1.35; 95% CI, 0.74 to 2.44; P=0.33). Mortality at 90 days was 22.3% in the tenecteplase–thrombectomy group and 19.9% in the thrombectomy-alone group (ad-

Table 2. Efficacy and Safety Outcomes (Intention-to-Treat Population).

Outcome	Tenecteplase plus Thrombectomy (N=278)	Thrombectomy Alone (N=272)	Measure of Treatment Effect	Adjusted Treatment Effect (95% CI)*	P Value
Primary efficacy outcome					
Modified Rankin scale score of 0 to 2 at 90 days — no. (%)†	147 (52.9)	120 (44.1)	Risk ratio	1.18 (1.01–1.39)	0.04
Secondary efficacy outcomes					
Modified Rankin scale score at 90 days — no. of wins/total no. of pairs (%)†	33,929/75,616 (44.9)	29,814/75,616 (39.4)	Generalized odds ratio	1.16 (0.94–1.43)	—
Modified Rankin scale score of 0 or 1 at 90 days — no. (%)†	97 (34.9)	76 (27.9)	Risk ratio	1.24 (0.98–1.57)	—
Modified Rankin scale score of 0 to 3 at 90 days — no. (%)†	178 (64.0)	168 (61.8)	Risk ratio	1.03 (0.92–1.17)	—
EQ-5D-5L score at 90 days — no. of wins/total no. of pairs (%)‡	33,155/75,616 (43.8)	34,613/75,616 (45.8)	Win ratio	0.94 (0.76–1.18)	—
Successful reperfusion before thrombectomy — no./total no. (%)§	17/278 (6.1)	3/271 (1.1)	Risk ratio	5.19 (1.51–17.84)	—
Successful reperfusion after thrombectomy — no./total no. (%)§	254/278 (91.4)	255/271 (94.1)	Risk ratio	0.97 (0.92–1.02)	—
First-pass reperfusion — no./total no. (%)¶	107/261 (41.0)	104/263 (39.5)	Risk ratio	1.03 (0.84–1.27)	—
Modified first-pass reperfusion — no./total no. (%)¶	146/261 (55.9)	139/263 (52.9)	Risk ratio	1.05 (0.90–1.23)	—
Safety outcomes					
Death within 90 days — no. (%)	62 (22.3)	54 (19.9)	Hazard ratio	1.17 (0.81–1.69)	—
Symptomatic intracranial hemorrhage within 48 hr — no./total no. (%)‖	23/271 (8.5)	18/269 (6.7)	Risk ratio	1.35 (0.74–2.44)	—
Any evidence of intracranial hemorrhage on imaging within 48 hr — no./total no. (%)‖	84/271 (31.0)	87/269 (32.3)	Risk ratio	0.99 (0.78–1.25)	—

* The treatment effect was adjusted for age, NIHSS score at baseline, ASPECTS at baseline, site of occlusion, and time from the last-known-well time point to randomization. For secondary outcomes, the widths of the confidence intervals were not adjusted for multiplicity and cannot be used to infer definitive treatment effects. Unadjusted estimates are provided in Table S3.

† Scores on the modified Rankin Scale range from 0 to 6, with higher scores indicating more severe disability. The scores were adjudicated by two independent neurologists who were certified in the use of the modified Rankin scale and were unaware of the treatment assignments. The neurologists reviewed video or voice recordings that were elicited in accordance with a structured assessment.

‡ Scores on the EuroQol Group 5-Dimension 5-Level (EQ-5D-5L) questionnaire range from –0.39 to 1, with higher scores indicating better quality of life. A score of 0 indicates the health-state equivalent to death.

§ Successful reperfusion was defined as an expanded Treatment in Cerebral Infarction (eTICI) grade of 2b, 2c, or 3. The eTICI grading system ranges from 0 to 3, with a score of 0 indicating no reperfusion, 1 reduction in thrombus without filling of distal arterial branches, 2a reperfusion of less than 50% of the territory, 2b reperfusion of 50% or more of the territory, 2c near-complete reperfusion with distal slow flow or the presence of small cortical emboli, and 3 complete reperfusion. Data were not available for 1 patient in the thrombectomy-alone group.

¶ First-pass reperfusion was defined as an eTICI grade of 2c or 3 after the first thrombectomy pass. Modified first-pass reperfusion was defined as an eTICI grade of 2b, 2c, or 3 after the first thrombectomy pass. Data were not available for 26 patients (17 in the tenecteplase–thrombectomy group and 9 in the thrombectomy-alone group).

‖ Symptomatic intracranial hemorrhage was assessed according to the modified Heidelberg Bleeding Classification and was adjudicated by the clinical-events committee. Evidence of intracranial hemorrhage on imaging was adjudicated by the imaging core laboratory. Data were not available for 10 patients (7 in the tenecteplase–thrombectomy group and 3 in the thrombectomy-alone group), but no hemorrhage was reported by the local radiologist.

Table 3. Severe Adverse Events and Procedure-Related Complications (Safety Population).*

Event	Tenecteplase plus Thrombectomy (N=278)	Thrombectomy Alone (N=272)
	no. of patients with event/total no. (%)	
Severe adverse events within 90 days		
Large or malignant middle-cerebral-artery stroke	32/278 (11.5)	28/272 (10.3)
Hemicraniectomy†	9/278 (3.2)	9/272 (3.3)
Acute respiratory failure‡	80/278 (28.8)	78/272 (28.7)
Acute heart failure§	69/278 (24.8)	69/272 (25.4)
Procedure-related complications		
Arterial perforation¶	6/278 (2.2)	4/271 (1.5)
Arterial dissection¶	7/278 (2.5)	3/271 (1.1)
Clot migration‖	65/278 (23.4)	62/271 (22.9)
Contrast extravasation**	74/271 (27.3)	80/269 (29.7)
Complications of vascular access		
Groin hematoma	6/278 (2.2)	1/272 (0.4)
Groin pseudoaneurysm	6/278 (2.2)	2/272 (0.7)

* Severe adverse events and procedure-related complications were adjudicated by the clinical-events committee in a blinded manner.
† The indication for hemicraniectomy was a large or malignant middle-cerebral-artery stroke.
‡ Acute respiratory failure was defined by the receipt of mechanical ventilation or supplemental oxygen through a reservoir mask or a pulmonary severity index of greater than 130.
§ Acute heart failure was defined by the B-type natriuretic peptide (BNP) level, the change in the N-terminal pro-BNP level, or a Killip class of II or higher.
¶ Data were not available for 1 patient in the thrombectomy-alone group.
‖ Clot migration was defined as observed movement of a clot before or during the procedure at the occlusion site. Data were not available for 1 patient in the thrombectomy-alone group.
** Data were not available for 10 patients (7 in the tenecteplase–thrombectomy group and 3 in the thrombectomy-alone group).

justed hazard ratio, 1.17; 95% CI, 0.81 to 1.69; P=0.39). Kaplan–Meier estimates of survival are shown in Figure S4. The results for serious adverse events and procedure-related complications are shown in Table 3.

DISCUSSION

Results from BRIDGE-TNK showed that, among patients with acute ischemic stroke due to large-vessel occlusion who had presented within 4.5 hours after onset and were eligible for intravenous thrombolysis, the percentage of patients with functional independence at 90 days was higher with intravenous tenecteplase plus endovascular thrombectomy than with endovascular thrombectomy alone. The analyses of secondary outcomes, which were not adjusted for multiplicity, showed no meaningful difference between the two treatment groups.

In a meta-analysis of trials of intravenous alteplase before thrombectomy, with a median of 25 minutes between the administration of alteplase and the arterial puncture, reperfusion occurred before thrombectomy in 4% of the patients.[7] In these patients, treatment with alteplase averted the need for endovascular thrombectomy and resulted in a shorter time from stroke onset to reperfusion, which is consistently associated with reduced disability.[18] In BRIDGE-TNK, with a median of 16 minutes between the administration of tenecteplase and the arterial puncture, reperfusion occurred before thrombectomy in 6.1% of the patients in the tenecteplase–thrombectomy group. This percentage was higher than that observed in the thrombectomy-alone group in our trial (1.1%) but was lower than that observed in the group randomly assigned to receive tenecteplase before endovascular thrombectomy in a previous trial (22%), in which the median time

from the administration of tenecteplase to arterial puncture was 43 minutes.[9]

Patients in the tenecteplase–thrombectomy group in our trial had earlier reperfusion than patients in the thrombectomy-alone group, a factor that may, in part, have accounted for the difference in functional outcomes between the two treatment groups. Furthermore, the time from thrombectomy puncture to reperfusion was 9 minutes shorter among patients in the tenecteplase–thrombectomy group, regardless of the use of rescue therapy such as angioplasty or stenting. This factor may also have contributed to the difference in functional outcomes. With regard to safety outcomes, symptomatic intracranial hemorrhage within 48 hours occurred in 8.5% of the patients in the tenecteplase–thrombectomy group and in 6.7% of those in the thrombectomy-alone group; evidence of intracranial hemorrhage on imaging within 48 hours was observed in a similar percentage of patients in the two groups (31.0% and 32.3%, respectively).

A previous meta-analysis of alteplase-based trials suggested that bridging thrombolytic therapy was beneficial only when it was administered within 140 minutes after stroke onset.[17] In our trial, functional independence at 90 days was observed in 98 of the patients (50.8%) in the tenecteplase–thrombectomy group who had an actual time to treatment of more than 140 minutes after stroke onset, as compared with 76 of the patients (37.4%) in the thrombectomy-alone group who had an expected time to treatment of more than 140 minutes after stroke onset. The RESILIENT DIRECT-TNK trial (ClinicalTrials.gov number, NCT05199194) is an ongoing trial investigating the same question that was addressed in our trial. A meta-analysis of participant-level data from both trials would allow for further exploration of the treatment effect in subgroups and of potential mechanisms, such as clot composition and collateral-circulation status.

In our trial, no patients were lost to follow-up, and successful reperfusion occurred in 92.7% of the patients. However, several limitations warrant consideration. First, the trial had an open-label design. It is notable that outcomes were adjudicated by an independent clinical-events committee whose members were unaware of the treatment assignments, which may help mitigate potential bias. Second, although the observed absolute difference in the percentage of patients with functional independence at 90 days of 8.8 percentage points is clinically meaningful (number needed to treat, 11), the effect size fell below the prespecified assumption of 13 percentage points that was used for the sample-size calculation. Third, the exclusion of patients who needed interhospital transfer before thrombectomy limits the generalizability of the findings among patients who are initially evaluated at centers where thrombectomy cannot be performed. The effectiveness of early thrombolysis with tenecteplase before transfer remains unaddressed. Finally, the role of tenecteplase in the treatment of patients presenting more than 4.5 hours after they were last known to be well is uncertain and needs to be validated in randomized trials. The TIMELESS trial, which evaluated the use of intravenous tenecteplase in an extended window of time, showed that tenecteplase was associated with a higher incidence of reperfusion than placebo but had no benefit with respect to functional outcomes.[19] The CHABLIS-T II trial showed that intravenous tenecteplase was associated with a higher incidence of reperfusion than best medical treatment, but with similar functional outcomes.[20]

In this trial, among patients with acute ischemic stroke due to large-vessel occlusion who had presented within 4.5 hours after onset and were eligible for thrombolysis, the combination of intravenous tenecteplase and endovascular thrombectomy resulted in a higher likelihood of functional independence at 90 days than endovascular thrombectomy alone, although the lack of a consistent significant benefit across secondary outcomes makes this finding tenuous.

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REFERENCES

1. Mitchell PJ, Yan B, Churilov L, et al. Endovascular thrombectomy versus standard bridging thrombolytic with endovascular thrombectomy within 4·5 h of stroke onset: an open-label, blinded-endpoint, randomised non-inferiority trial. Lancet 2022;400:116-25.

2. Fischer U, Kaesmacher J, Strbian D, et al. Thrombectomy alone versus intravenous alteplase plus thrombectomy in patients with stroke: an open-label, blinded-outcome, randomised non-inferiority trial. Lancet 2022;400:104-15.

3. Zi W, Qiu Z, Li F, et al. Effect of endovascular treatment alone vs intravenous alteplase plus endovascular treatment on functional independence in patients with acute ischemic stroke: the DEVT randomized clinical trial. JAMA 2021;325:234-43.

4. Suzuki K, Matsumaru Y, Takeuchi M, et al. Effect of mechanical thrombectomy without vs with intravenous thrombolysis on functional outcome among patients with acute ischemic stroke: the SKIP randomized clinical trial. JAMA 2021;325:244-53.

5. LeCouffe NE, Kappelhof M, Treurniet KM, et al. A randomized trial of intravenous alteplase before endovascular treatment for stroke. N Engl J Med 2021;385:1833-44.

6. Yang P, Zhang Y, Zhang L, et al. Endovascular thrombectomy with or without intravenous alteplase in acute stroke. N Engl J Med 2020;382:1981-93.

7. Majoie CB, Cavalcante F, Gralla J, et al. Value of intravenous thrombolysis in endovascular treatment for large-vessel anterior circulation stroke: individual participant data meta-analysis of six randomised trials. Lancet 2023;402:965-74.

8. Tanswell P, Modi N, Combs D, Danays T. Pharmacokinetics and pharmacodynamics of tenecteplase in fibrinolytic therapy of acute myocardial infarction. Clin Pharmacokinet 2002;41:1229-45.

9. Campbell BCV, Mitchell PJ, Churilov L, et al. Tenecteplase versus alteplase before thrombectomy for ischemic stroke. N Engl J Med 2018;378:1573-82.

10. Altersberger VL, Kaesmacher J, Churilov L, et al. Bridging thrombolysis with tenecteplase versus endovascular thrombectomy alone for large-vessel anterior circulation stroke: a target trial emulation analysis. J Neurol Neurosurg Psychiatry 2025 January 22 (Epub ahead of print).

11. Qiu Z, Li F, Xie D, et al. Efficacy and safety of intravenous tenecteplase before endovascular thrombectomy for acute ischemic stroke: the multicenter, randomized, BRIDGE-TNK trial protocol. J Am Heart Assoc 2024;13(21):e036765.

12. EuroQol Research Foundation. EQ-5D-5L user guide, version 3.0. September 2019 (https://euroqol.org/publications/user-guides).

13. Campbell BCV, Mitchell PJ, Churilov L, et al. Effect of intravenous tenecteplase dose on cerebral reperfusion before thrombectomy in patients with large vessel occlusion ischemic stroke: the EXTEND-IA TNK part 2 randomized clinical trial. JAMA 2020;323:1257-65.

14. Bala F, Singh N, Buck B, et al. Safety and efficacy of tenecteplase compared

with alteplase in patients with large vessel occlusion stroke: a prespecified secondary analysis of the ACT randomized clinical trial. JAMA Neurol 2023;80:824-32.
15. Zou G. A modified Poisson regression approach to prospective studies with binary data. Am J Epidemiol 2004;159:702-6.
16. Wang D, Pocock S. A win ratio approach to comparing continuous nonnormal outcomes in clinical trials. Pharm Stat 2016;15:238-45.
17. Kaesmacher J, Cavalcante F, Kappelhof M, et al. Time to treatment with intravenous thrombolysis before thrombectomy and functional outcomes in acute ischemic stroke: a meta-analysis. JAMA 2024;331:764-77.
18. Saver JL, Goyal M, van der Lugt A, et al. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: a meta-analysis. JAMA 2016;316:1279-88.
19. Albers GW, Jumaa M, Purdon B, et al. Tenecteplase for stroke at 4.5 to 24 hours with perfusion-imaging selection. N Engl J Med 2024;390:701-11.
20. Cheng X, Hong L, Lin L, et al. Tenecteplase thrombolysis for stroke up to 24 hours after onset with perfusion imaging selection: the CHABLIS-T II randomized clinical trial. Stroke 2025;56:344-54.