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Intravenous Tenecteplase Before Thrombectomy in Stroke

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Abstract:	BACKGROUND The safety and efficacy of intravenous tenecteplase before endovascular thrombectomy remains uncertain in acute ischemic stroke secondary to large vessel occlusion. METHODS In this open-label randomized trial conducted in China, acute ischemic stroke patients who had occlusion of the internal carotid artery, first or second segment of the middle cerebral artery, or vertebrobasilar artery within 4.5 hours onset and who were eligible for intravenous thrombolysis were randomized in a 1:1 ratio to receive intravenous tenecteplase followed by endovascular thrombectomy or endovascular thrombectomy alone. The primary outcome was functional independence defined as a score of 0 to 2 on the modified Rankin scale at 90 days. Safety outcomes were symptomatic intracranial hemorrhage within 48 hours and mortality at 90 days. RESULTS Among 550 patients randomized, 278 were assigned to the tenecteplase-plus-thrombectomy group and 272 to the thrombectomy-alone group. Functional independence occurred in 147 patients (52.9%) in the tenecteplase-plus-thrombectomy group and 120 patients (44.1%) in the thrombectomy-alone group (adjusted risk ratio 1.18, 95% confidence interval 1.01-1.39, P=0.04). Symptomatic intracranial hemorrhage within 48 hours occurred in 8.5% in the tenecteplase-plus-thrombectomy group and 6.7% in the thrombectomy alone group; and mortality at 90 days was 22.3% and 19.9%, respectively. CONCLUSIONS In this trial conducted in China, patients with acute ischemic stroke due to large vessel occlusion within 4.5 hours after onset, intravenous tenecteplase plus endovascular thrombectomy led to higher rates of functional independence at 90 days compared to endovascular thrombectomy alone. (Funded by the CSHJMRP and others; BRIDGE-TNK ClinicalTrials.gov number, NCT04733742)

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Title

Intravenous Tenecteplase Before Thrombectomy in Stroke

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2. Supplement 2 - Supplementary methods, tables, and figures
3. Supplement 3 - CONSORT checklist

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Abstract

BACKGROUND The safety and efficacy of intravenous tenecteplase before endovascular thrombectomy remains uncertain in acute ischemic stroke secondary to large vessel occlusion.

METHODS In this open-label randomized trial conducted in China, acute ischemic stroke patients who had occlusion of the internal carotid artery, first or second segment of the middle cerebral artery, or vertebrobasilar artery within 4.5 hours onset and who were eligible for intravenous thrombolysis were randomized to receive intravenous tenecteplase followed by endovascular thrombectomy or endovascular thrombectomy alone. The primary outcome was functional independence defined as a score of 0 to 2 on the modified Rankin scale at 90 days. Safety outcomes were symptomatic intracranial hemorrhage within 48 hours and mortality at 90 days.

RESULTS Among 550 patients randomized, 278 were assigned to the tenecteplase-plus-thrombectomy group and 272 to the thrombectomy-alone group. Functional independence occurred in 147 patients (52.9%) in the tenecteplase-plus-thrombectomy group and 120 patients (44.1%) in the thrombectomy-alone group (unadjusted risk ratio 1.20, 95% confidence interval 1.01-1.43, P=0.04; adjusted risk ratio 1.18, 95% confidence interval 1.01-1.39, P=0.04). Successful reperfusion rates pre- and post- thrombectomy were 6.1% and 91.4% in the tenecteplase-plus-thrombectomy group, and 1.1% and 94% in the thrombectomy-alone group.

Symptomatic intracranial hemorrhage within 48 hours occurred in 8.5% in the tenecteplase-plus-thrombectomy group and 6.7% in the thrombectomy alone group; and mortality at 90 days was 22.3% and 19.9%, respectively.

CONCLUSIONS In this trial conducted in China, patients with acute ischemic stroke due to large vessel occlusion within 4.5 hours after onset, intravenous tenecteplase plus endovascular thrombectomy led to higher rates of functional independence at 90 days compared to endovascular thrombectomy alone. (Funded by the Chongqing Science and Health Joint Medical Research Project and others; BRIDGE-TNK ClinicalTrials.gov number, NCT04733742)

Introduction

Intravenous thrombolysis preceding endovascular thrombectomy has both potential benefit of enhancing reperfusion before, during, and after the procedure, and potential risk of increasing intracranial hemorrhage. Since 2018, six randomized controlled trials evaluated the role of intravenous thrombolysis before endovascular thrombectomy in thrombolysis-eligible stroke patients presenting within 4.5 hours from last known well.[1-6] A pooled analysis of individual participant-level data from these six trials did not find a significant difference in efficacy between endovascular thrombectomy alone and intravenous thrombolysis plus endovascular thrombectomy. Notably, these trials predominantly utilized alteplase, with only 2.2% of participants receiving tenecteplase, precluding meaningful subgroup analysis of tenecteplase effect.[7]

Tenecteplase, a genetically modified tissue plasminogen activator, offers pharmacokinetic advantages over alteplase, including prolonged half-life, enhanced fibrin specificity, and resistance to endogenous inhibitors, enabling rapid, single-bolus administration with potentially superior reperfusion efficacy.[8] A randomized trial comparing tenecteplase to alteplase prior to endovascular thrombectomy reported increased early reperfusion and improved 90-day functional outcomes with tenecteplase.[9] In contrast, a target trial emulation analysis indicated that intravenous tenecteplase before endovascular thrombectomy compared with endovascular

thrombectomy alone was not associated with increased likelihood of functional independence.[10] However, existing evidence is limited by small sample sizes and lack of direct comparison between intravenous tenecteplase plus thrombectomy and thrombectomy alone. No randomized trial has established whether adding tenecteplase prior to endovascular thrombectomy confers incremental clinical benefit without elevating hemorrhagic risk in this population.

Therefore, we designed and conducted the Randomized Trial of Thrombectomy With Versus Without rhTNK-tPA in Stroke (BRIDGE-TNK) to determine whether intravenous tenecteplase plus endovascular thrombectomy improves functional outcomes at 90 days compared to endovascular thrombectomy alone in thrombolysis-eligible stroke patients with large vessel occlusion within 4.5 hours of last known well.

Methods

Trial Design and Oversight

BRIDGE-TNK was an investigator-initiated, multicenter, randomized, open-label trial with blinded endpoint assessment. The trial was conducted in accordance with the principles of the Declaration of Helsinki and was registered at www.clinicaltrials.gov (NCT04733742). The trial protocol (**Supplement 1**) was approved by the ethics committees of the Xinqiao Hospital, Army Medical University and all participating centers, and key aspects were published.[11] Written

informed consent was obtained from all patients or their legal representatives before randomization. After the database was locked, the last author had unrestricted access to the data and vouches for the fidelity to the protocol and statistical analysis plan (**Supplement 1**), and for the completeness and accuracy of the reported outcome data and adverse events. The first draft of the manuscript was written by the first and last author with critical revisions from all authors. There were no confidentiality agreements between the sponsor and the investigators, and the sponsor could not delay or interdict publication of the trial results. The China Shijiazhuang Pharmaceutical Company (CSPC) provided tenecteplase and did not have a role in the trial design; the collection, analysis, and interpretation of the data; or the preparation of the manuscript, and did not have to approve the manuscript before submission for publication. **Figure S1** shows the overall flowchart of the trial. A list of the sites and investigators participating in the trial, and administrative staff is provided in the Supplementary Appendix.

Patients

The trial was conducted at 39 hospitals in China (**Figure S2**). Study patients were aged 18 years or older, had acute ischemic stroke secondary to occlusion of the internal carotid artery, the first or second segment of the middle cerebral artery, or the vertebrobasilar artery, presented within 4.5 hours from last known well, and were eligible for intravenous thrombolysis, based on Chinese stroke guidelines. The key exclusion criteria were patients who had contraindications

to intravenous thrombolysis or who had already received intravenous thrombolysis prior to screening. Detailed selection criteria are provided in **Supplement 3**.

Randomization and Blinding

Eligible patients were randomly assigned to receive intravenous tenecteplase followed by endovascular thrombectomy (tenecteplase-plus-thrombectomy group) or endovascular thrombectomy alone (thrombectomy-alone group) in a 1:1 ratio. Fixed block randomization with block sizes of 4 was used. Randomization was conducted immediately via a secure website immediately after the patient's eligibility was confirmed. All subjects and clinical staff were unblinded to treatment allocation after randomization. However, the randomization codes were concealed from all parties, including the clinical coordinating center, the data management group, trial statisticians, and the sponsor staff and delegates. An independent clinical events committee, blinded to treatment allocation, adjudicated efficacy and safety outcomes, procedure-related complications, and serious adverse events. All images were adjudicated by an imaging core laboratory in a blinded manner.

Interventions

All patients in both groups received rapid endovascular thrombectomy. Patients randomized to the tenecteplase-plus-thrombectomy group were treated with intravenous tenecteplase followed by endovascular thrombectomy. Tenecteplase was manufactured and supplied by CSPC

Recomgen Pharmaceutical (Guangzhou) Co., LTD, China. Tenecteplase, as a lyophilized powder stored in glass vials (16 mg per vial), which was reconstituted in 3 ml of sterile water for injection (0.25 mg/kg, maximum dose, 25mg), and delivered intravenously as a bolus over approximately 5-10 seconds followed by a saline flush. Endovascular therapy for both groups included use of stent retrievers, thromboaspiration, balloon angioplasty, stenting, intra-arterial thrombolysis, or a combination of these approaches, at the discretion of the interventionalist. Patients randomized to the thrombectomy-alone group received endovascular thrombectomy without intravenous tenecteplase pretreatment.

Outcomes

The primary outcome was achievement of functional independence, defined as a score of 0 to 2 on the modified Rankin scale (mRS), at 90 days. The mRS is a 7-level ordinal scale with scores ranging from 0 (no symptoms) to 6 (death). The scores were adjudicated by two mRS-certified neurologists who were blinded to treatment allocation, based on video or voice recordings taken at the outpatient clinic, during a telephone or video call, or by their family.

Secondary efficacy outcomes included the disability level measured by the ordinal mRS, excellent outcome (mRS score 0 to 1), independent ambulation (mRS score 0 to 3), and health-related quality of life [European Quality Five-Dimension Five-Level (EQ-5D-5L) scale score], all assessed at 90 days by the clinical events committee; National Institutes of Health Stroke

Scale (NIHSS, range from 0 to 42, with higher scores indicating more severe neurologic deficits) score at 5 to 7 days (or discharge if that occurred earlier) centrally assessed by two independent certified neurologists in a blinded manner via video; successful reperfusion (expanded Treatment in Cerebral Infarction (eTICI, range from 0 [no reperfusion] to 3 [complete reperfusion]) score of 2b50, 2b67, 2c, or 3) at initial angiogram prior to endovascular thrombectomy; successful reperfusion at end-of-procedure angiography; first pass reperfusion (eTICI 2c or greater after the first thrombectomy pass), and modified first pass reperfusion (eTICI 2b50 or greater after the first thrombectomy pass) adjudicated by imaging core laboratory.[12]

Safety outcomes were symptomatic intracranial hemorrhage according to the modified Heidelberg classification within 48 hours, any radiologic intracranial hemorrhage within 48 hours, mortality within 90 days, procedure-related complications, and serious adverse events. Safety data were collected by site investigators and adjudicated through source documentation by imaging core laboratory and clinical events committee.

Statistical analysis

Based on two Chinese randomized trials of endovascular thrombectomy alone for acute large vessel occlusion stroke[3,6], the assumed proportion of functional independence in the

thrombectomy-alone group was 41%. Based on a pooled analysis of three randomized trials of intravenous tenecteplase bridging endovascular thrombectomy in patients with large vessel occlusion stroke [9,13,14], we hypothesized that the proportion of functional independence in the tenecteplase-plus-thrombectomy group would be 54%. Using a two-sided α=0.05 and 80% power, 231 patients per group (total 462) were required. To accommodate a 15% attrition rate, the sample size was inflated to 272 per group (total 544).

A modified Poisson regression model was used for the analysis of binary primary and secondary outcomes, with adjustment for prespecified covariates, generating adjusted risk ratios (aRRs) as measurements of treatment effect.[15] The full-range mRS score at 90 days was analyzed using the generalized odds ratio. Analyses of the nonnormal continuous secondary outcomes such as the EQ-5D-5L scale score and NIHSS score at 5 to 7 days or discharge were performed using the win ratio approach.[16] Additional information regarding secondary outcomes is provided in the Supplementary Appendix. While the protocol specified adjusted treatment effects as primary, unadjusted estimates are also presented in the supplement. Because the statistical analysis plan did not include a provision for correcting for multiplicity when conducting tests for the secondary endpoints or subgroup analyses, the widths of confidence intervals should not be used to infer definitive treatment effects.

The main analysis of the efficacy outcomes was performed in all patients who underwent randomization, unless consent was withdrawn. Analyses of severe adverse events and procedural-associated complications were based on the safety population, which consisted of all randomized patients who received any study treatment. Treatment effect modification was assessed in 9 prespecified subgroups: age, sex, baseline NIHSS score, baseline Alberta Stroke Program Early CT Score (ASPECTS, range 0-10, with higher scores indicating a smaller ischemic core), time from last known well to randomization, occlusion site, cause of stroke, angioplasty or stenting, and expected last known well to start of intravenous tenecteplase. [17] A further subgroup of actual/expected time from start of intravenous tenecteplase to puncture, was added post hoc. No missing data imputation was performed in this trial because the data for the primary outcome analysis and prespecified covariates for covariate adjusted analyses were complete. The significance level for the primary endpoint was a 2-sided α=0.05. Statistical analyses were conducted on the SAS 9.4 system with Windows (SAS Institute, Cary, NC) and R (version 4.1.1.). The statistical analysis plan is provided in **Supplement 1**.

Results

Characteristics of the patients

From May 9, 2022, to September 8, 2024, 554 patients underwent randomization, of whom 550 were included in the intention-to-treat analysis, and 4 were excluded from all analyses owing to withdrawal of consent. No patients were lost to follow-up. The median age of the patients was 70 (interquartile range [IQR], 61-77) years; 230 (41.8%) were women. Of the 550 patients, 278 were assigned to the tenecteplase-plus-thrombectomy group and 272 to the thrombectomy-alone group. **Figure S3** shows the flow of patient enrollment and follow-up in this trial. Baseline characteristics were balanced in both groups and were largely representative of the expected patient population (**Table 1 and Table S1 and S2**). The median time from intravenous tenecteplase to puncture was 16.0 (IQR, 1.5-35.0) min. The median time from puncture to reperfusion was 55 minutes in the tenecteplase-plus-thrombectomy group and 64 minutes in the thrombectomy-alone group. Angioplasty or stenting during the procedure was used in 51 of 261 participants (19.5%) in the tenecteplase-plus-thrombectomy group and in 72 of 262 participants (27.5%) in the thrombectomy-alone group.

Primary outcome

The proportion of patients who had functional independence at 90 days (the primary outcome) was 52.9% (147/278) in the tenecteplase-plus-thrombectomy group as compared with 44.1% (120/272) 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 [aRR], 1.18; 95% CI, 1.01-1.39; P=0.04) (**Table 2, Table S3 and Figure 1**).

Secondary outcomes

Prespecified secondary outcomes are shown in **Table 2 and Table S3**. The trial was not powered for detecting between-group differences in these analyses, and the analyses were not adjusted for multiplicity. The percentage of patients who achieved successful reperfusion at initial angiogram prior to thrombectomy was 6.1% (17/278) in the tenecteplase-plus-thrombectomy group and 1.1% (3/271) in the thrombectomy-alone group (aRR, 5.27; 95% CI, 1.54-18.04). Successful reperfusion (eTICI 2b50 to 3) at end-of-procedure angiography was observed in 91.4% of patients in the tenecteplase-plus-thrombectomy group and 94.1% in the thrombectomy-alone group, aRR 0.97 (95%CI 0.92-1.02).

Safety outcomes

Safety outcomes are shown in **Table 2 and Table S3**. Symptomatic intracranial hemorrhage within 48 hours after randomization occurred in 23 patients (8.5%) in the tenecteplase-plus-thrombectomy group and in 18 patients (6.7%) in the thrombectomy-alone group (aRR, 1.35; 95% CI, 0.74-2.44, P=0.33). Ninety-day mortality was 22.3% with tenecteplase-plus-thrombectomy and 19.9% with thrombectomy-alone (adjusted hazard ratio, 1.18; 95% CI, 0.81-1.70, P=0.39). **Figure S4** shows the Kaplan-Meier estimates of the probability of death. The

incidence of serious adverse events and procedural-associated complications are listed in **Table 3**. The results of the prespecified and post hoc subgroup analyses are presented in **Figure 2**.

Discussion

The BRIDGE-TNK trial showed that, in acute ischemic stroke patients with large vessel occlusion who were eligible for intravenous thrombolysis within 4.5 hours from last known well, intravenous tenecteplase plus endovascular thrombectomy led to a higher proportion of patients with functional independence than that observed with endovascular thrombectomy alone. Secondary outcomes, not adjusted for multiplicity, were not significantly different between the groups.

In a meta-analysis of trials using intravenous alteplase prior to thrombectomy, with a median of 25 min between alteplase and arterial puncture, reperfusion prior to thrombectomy occurred in 4%.[7] This averted the need for endovascular thrombectomy and shortened the time from stroke onset to reperfusion, which is consistently associated with reduced disability.[18] In BRIDGE-TNK, intravenous tenecteplase achieved reperfusion prior to thrombectomy in 6.1%, with a median 16 min between tenecteplase and arterial puncture. This was higher than the 1.1% rate observed in patients treated with thrombectomy alone but lower than the 22% in a previous trial in which the median tenecteplase to arterial puncture time was 43 min.[9] As

reperfusion is achieved earlier in these patients treated with intravenous tenecteplase, this may, in part, account for an increase in the proportion of functional independence in the tenecteplase-plus-thrombectomy group. Furthermore, the tenecteplase-plus-thrombectomy group achieved a 9-minute reduction in the time from puncture to reperfusion compared with the thrombectomy-alone group, independent of rescue therapy, such as angioplasty and/or stenting. This may also potentially contribute to the different outcomes between the two groups. With regards to safety outcomes, symptomatic intracranial hemorrhage was 8.5% in the tenecteplase arm compared with the 6.7% in the thrombectomy-alone arm, and the risk of any radiologic intracranial hemorrhage was similar (31.0% versus 32.3%).

A prior meta-analysis of alteplase-based trials suggested that bridging thrombolytic therapy was beneficial only when it was administered within 140 minutes of stroke onset.[17] In this study, functional independence was achieved in 98 patients (50.8%) who received tenecteplase initiation more than 140 minutes after the last known well time, compared to 76 patients (37.4%) in the thrombectomy-alone group. The RESILIENT DIRECT-TNK (Randomization to Endovascular Treatment Alone or Preceded by Systemic Thrombolysis With Tenecteplase in Acute Ischemic Stroke due to Large Intracranial Vessel Occlusion Trial -DIRECT Thrombectomy vs Intravenous TNK Plus Thrombectomy, NCT05199194) is an ongoing trial investigating the question addressed in this trial. A meta-analysis of individual participant data

from both trials will be conducted and more details will further explore these subgroups and potential mechanisms, such as clot composition and collateral circulation status.

The present trial had no patients lost to follow-up, and achieved a high successful reperfusion rate of 92.7%. However, several limitations warrant consideration. First, the trial used an open-label design. Outcomes were adjudicated by an independent clinical event committee blinded to the treatment assignments, which may help mitigate potential bias. Second, while the observed 8.8% absolute improvement in functional independence is clinically meaningful (number needed to treat=11), this effect size fell below the pre-specified 13% assumption used for sample size calculation. Third, our exclusion of patients requiring inter-hospital transfer prior to thrombectomy limits generalizability in patients who are initially evaluated at non-thrombectomy-capable centers. The effectiveness of early thrombolysis with tenecteplase prior to transfer remains unaddressed. Last, the role of tenecteplase in patients presenting beyond 4.5 hours of last known well is uncertain and needs to be validated by randomized trials. A trial of intravenous tenecteplase in the extended time-window, TIMELESS (The Thrombolysis in Imaging Eligible, Late Window Patients to Assess the Efficacy and Safety of Tenecteplase), showed that tenecteplase improved reperfusion but had no functional outcome benefit, possibly due to limited salvageable tissue.[19] Another trial, CHABLIS-T II (Chinese Acute Tissue-Based

Imaging Selection for Lysis In Stroke Tenecteplase II) also found that intravenous tenecteplase resulted in improved reperfusion, but with similar functional outcomes.[20]

In conclusion, in this trial evaluating thrombolysis-eligible patients with acute ischemic stroke secondary to large vessel occlusion presenting within 4.5 hours of the time they were last known to be well, the combination of intravenous tenecteplase and endovascular thrombectomy resulted in a higher proportion achieving functional independence than the endovascular thrombectomy alone, although the lack of consistent significant benefit in secondary outcomes makes this finding tenuous.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Figures Legends:

Figure 1 Distribution of the modified Rankin scale score at 90 days in the intention-to-treat population.

Shown are scores on the modified Rankin scale for patients in the tenecteplase-plus-thrombectomy group and the thrombectomy-alone group according to randomization. Bars are labelled with percentages. Scores range from 0 to 6, with 0 indicating no neurologic deficit, 1 no clinically significant disability, 2 slight disability (able to handle own affairs without assistance but unable to carry out all previous activities), 3 moderate disability requiring some help (e.g., with shopping, cleaning, and finances but able to walk unassisted), 4 moderately severe disability (unable to attend to bodily needs without assistance and unable to walk unassisted), 5 severe disability (requiring constant nursing care and attention), and 6 death. The overall distribution of scores were similar between the two arms (Adjusted generalized odds ratio, 1.16; 95% confidence interval, 0.94 to 1.43), and the analysis was not adjusted for multiplicity.

Figure 2 Analysis of functional independence at 90 days in prespecified subgroups.

The forest plot displays the adjusted risk ratio for functional independence at 90 days in ten subgroups. Age, baseline NIHSS score, baseline ASPECTS, and onset to randomization time

were dichotomized at the median. The Alberta Stroke Program Early Computed Tomography Score (ASPECTS) ranges from 0 to 10, with higher scores indicating a smaller ischemic core. Listed are values for the core laboratory assessment. Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating worse neurologic deficits. ICA denotes internal carotid artery, CE cardioembolism, LAA large artery atherosclerosis, and NIHSS denotes National Institutes of Health Stroke Scale. Adjusted risk ratios were calculated and reported in accordance with the pre-specified statistical analysis plan. The widths of the confidence intervals were not adjusted for multiple comparisons, and cannot be used to infer treatment effects.

* For the thrombectomy-alone group, the expected time from last known well to expected start of intravenous tenecteplase was derived by summing each subject's documented last known well to randomization duration with the group's mean randomization to start of intravenous tenecteplase latency. For the tenecteplase-plus-thrombectomy group, the measured time from last known well to start of intravenous tenecteplase was directly employed for analysis.

† The expected time from start of intravenous tenecteplase to puncture in the thrombectomy-alone group was mathematically determined by subtracting the expected last known well interval preceding tenecteplase administration from the last known well to puncture timeframe.

For the tenecteplase-plus-thrombectomy group, the measured time from start of intravenous tenecteplase to puncture was directly employed for analysis.

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

	Tenecteplase-plus-thrombectomy (N=278)	Thrombectomy-alone (N=272)
Demographic characteristics		
Median age (IQR), years	70 (60-77)	70 (63-76)
Male sex, no./total no. (%)	161/278 (57.9)	159/272 (58.5)
Prestroke score on the modified Rankin scale, no./total no. (%)†		
0	263/278 (94.6)	258/272 (94.8)
1	11/278 (4.0)	9/272 (3.3)
2	3/278 (1.1)	4/272 (1.5)
4	1/278 (0.4)	1/272 (0.4)
Cause of stroke - no./total no. (%)		
Large artery atherosclerosis	82/278 (29.5)	85/272 (31.3)
Cardioembolism	172/278 (61.9)	163/272 (59.9)
Unknown	22/278 (7.9)	18/272 (6.6)
Other	2/278 (0.7)	6/272 (2.2)
Imaging characteristics‡		
Median baseline ASPECTS (IQR)§	8 (6-9)	8 (6-9)
Occlusion site - no./total no. (%)		
Intracranial internal carotid artery	77/278 (27.7)	87/272 (32.0)
M1 middle cerebral artery segment	154/278 (55.4)	145/272 (53.3)
M2 middle cerebral artery segment	18/278 (6.5)	20/272 (7.4)
Vertebrobasilar artery	29/278 (10.4)	20/272 (7.4)
Clinical examination at arrival		
Median systolic blood pressure (IQR), mmHg	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 workflow times (IQR), min		
Last known well to randomization	159.3 (121.2-214.9)	167.6 (130.5-215.5)
Randomization to start of intravenous tenecteplase	6.0 (3.5-10.2)	NA
Intravenous tenecteplase to puncture	16.0 (1.5-35.0)	NA
Randomization to puncture**	28.2 (7.0-45.4)	24.4 (2.3-38.6)
Puncture to reperfusion††	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 of functional disability range from 0 (no symptoms) to 6 (death). The modified Rankin scale score before stroke onset was evaluated by the site investigator with the use of information obtained from patients (if possible) or their family members.

‡ Imaging characteristics were assessed by the imaging core laboratory.

§ The Alberta Stroke Program Early Computed Tomography Score (ASPECTS) is an imaging measure of the extent of ischemic stroke. Scores ranges from 0 to 10, with higher scores indicating a smaller infarct core.

¶ Scores on National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with less scores indicating less severe neurologic deficits.

‖ For the glucose level, data were missing for 7 patients (3 in the tenecteplase-plus-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.

†† Data were not available for 1 patient in the thrombectomy-alone group.

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

	Tenecteplase-plus-thrombectomy (N=278)	Thrombectomy-alone (N=272)	Effect measure	Adjusted effect value (95% CI) †	*P* value
Primary efficacy outcome					
Modified Rankin scale score of 0 to 2 at 90 days - no./total no. (%)‡	147/278 (52.9)	120/272 (44.1)	Risk Ratio	1.18 (1.01 to 1.39)	0.04
Secondary efficacy outcomes					
Modified Rankin scale score at 90 days, No. of wins/total No. of pairs	33929/75616 (44.9)	29814/75616 (39.4)	Generalized Odds Ratio	1.16 (0.94-1.43)	—
Modified Rankin scale score of 0 to 1 at 90 days - no./total no. (%)	97/278 (34.9)	76/272 (27.9)	Risk Ratio	1.25 (0.99-1.58)	—
Modified Rankin scale score of 0 to 3 at 90 days - no./total no. (%)	178/278 (64.0)	168/272 (61.8)	Risk Ratio	1.04 (0.99-1.58)	—
EQ-5D-5L scale score at 90 days, No. of wins/total No. of pairs §	33155/75616 (43.8)	34613/75616 (45.8)	Win Ratio	0.94 (0.76-1.18)	—
Successful reperfusion at initial angiogram prior to thrombectomy - no./total no. (%)¶	17/278 (6.1)	3/271 (1.1)	Risk Ratio	5.27 (1.54-18.04)	—
Successful reperfusion at end-of-procedure angiography - 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					
Mortality at 90 days - no./total no. (%)	62/278 (22.3)	54/272 (19.9)	Hazard Ratio	1.18 (0.81-1.70)	—
Symptomatic intracranial hemorrhage within 48 hours - no./total no. (%)‡‡	23/271 (8.5)	18/269 (6.7)	Risk Ratio	1.35 (0.74-2.44)	—

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	Tenecteplase-plus-thrombectomy (N=278)	Thrombectomy-alone (N=272)	Effect measure	Adjusted effect value (95% CI) †	*P* value
Any radiologic intracranial hemorrhage within 48 hours - no./total no. (%)‡‡	84/271 (31.0)	87/269 (32.3)	Risk Ratio	0.99 (0.78-1.25)	—

* CI denotes confidence interval, and IQR interquartile range.

† Values adjusted for age, baseline NIHSS score, baseline ASPECTS, occlusion site, and time from last known well to randomization. The widths of confidence intervals for secondary outcomes have not been adjusted for multiplicity and cannot be used to infer treatment effects.

‡ Scores on the modified Rankin Scale of functional disability range from 0 (no symptoms) to 6 (death). The score was evaluated centrally by 2 modified Rankin Scale–certified neurologists who were blinded to treatment allocation and who reviewed the video or voice recordings elicited using a structured assessment.

§ Scores on the European Quality Five-Dimension Five-Level Self-Report Questionnaire (EQ-5D-5L) range from −0.39 to 1, with higher scores indicating a better quality of life; 0 is the value of a health state equivalent to death.

¶ The expanded Thrombolysis In Cerebral Infarction (eTICI) reperfusion grading system is a 6-point scale: 0 indicates no reperfusion noted; 1, reduction in thrombus without filling of distal arterial branches; 2a, reperfusion of <50% of the territory; 2b, a reperfusion of ≥50% of the territory; 2c, near-complete perfusion with distal slow flow or presence of small cortical emboli; and 3, complete reperfusion. Successful reperfusion at initial angiogram prior to thrombectomy was defined as an eTICI grade of 2b, 2c, or 3 on the first intracranial angiogram. Data were not available for 1 patient in the thrombectomy-alone group.

‖ The eTICI grade was determined at the final angiogram. Data were not available for 1 patient in the thrombectomy-alone group.

** First pass reperfusion was defined as achieving eTICI 2c or 3 after the first thrombectomy pass. Data were not available for 26 patients (17 in the tenecteplase-plus-thrombectomy group and 9 in the thrombectomy-alone group).

†† Modified first pass reperfusion was defined as achieving eTICI 2b, 2c or 3 after the first thrombectomy pass. Data were not available for 26 patients (17 in the tenecteplase-plus-thrombectomy group and 9 in the thrombectomy-alone group).

‡‡ Intracranial hemorrhage was adjudicated by a clinical events committee. Symptomatic intracranial hemorrhage was assessed according to the Heidelberg criteria. Data were not available for 10 patients (3 in the tenecteplase-plus-thrombectomy group and 4 in the thrombectomy-alone group) but no hemorrhage was reported by the local radiologist.

Table 3. Severe adverse events and procedural-associated complications*

	Tenecteplase-plus-thrombectomy (N=278)	Thrombectomy-alone (N=272)
Severe adverse events within 90 days - no./total no. (%)		
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)
Procedural-associated complications - no./total no. (%)		
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)
Vascular access complications		
Groin hematoma	6/278 (2.2)	1/272 (0.4)
Groin pseudoaneurysm	6/278 (2.2)	2/272 (0.7)

* All severe adverse events and procedural-associated complications were reported by the independent clinical events committee who were blinded to treatment allocation.

† The indication for hemicraniectomy was large or malignant middle cerebral artery stroke.

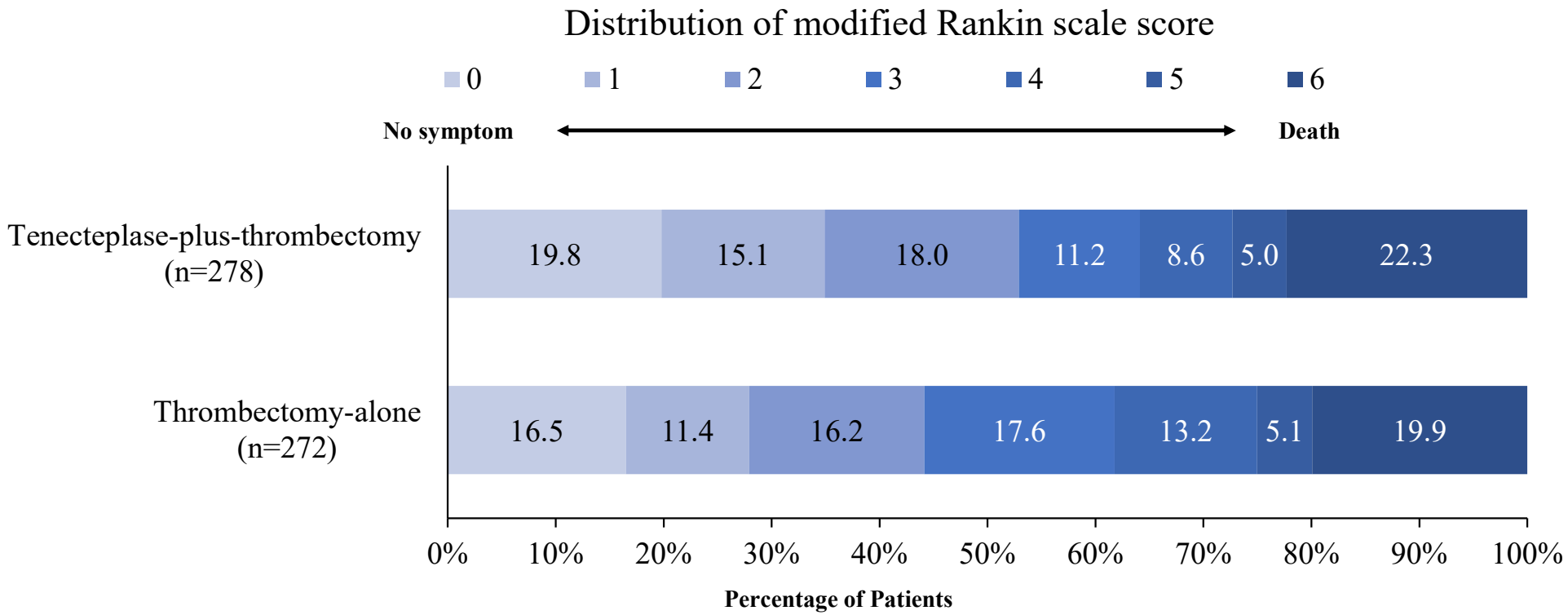
‡ Need for mechanical ventilation or oxygen through a reservoir mask or a Pulmonary Severity Index greater than 130.

§ Brain natriuretic peptide (BNP) concentration, changes in N-terminal pro-BNP (NT-pro-BNP) or Killip class II or higher.

¶ Data were not available for 1 patient in the thrombectomy-alone group.

‖ Clot observed to have moved before and 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-plus-thrombectomy group and 3 in the thrombectomy-alone group).


Distribution of modified Rankin scale score
0
1
2
3
4
5
6
No symptom
Death
Tenecteplase-plus-thrombectomy (n=278)
19.8
15.1
18.0
11.2
8.6
5.0
22.3
Thrombectomy-alone (n=272)
16.5
11.4
16.2
17.6
13.2
5.1
19.9
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%
Percentage of Patients

Variable	mRS score 0 to 2 at 90 days, No./total No. (%) Tenecteplase-plus-thrombectomy	Thrombectomy-alone	Adjusted risk ratios (95% confidence interval)
Overall	147/278 (52.9)	120/272 (44.1)	1.18 (1.01 to 1.39)
Age			
≤70 years	86/143 (60.1)	73/146 (50.0)	1.18 (0.89 to 1.56)
>70 years	61/135 (45.2)	47/126 (37.3)	1.18 (0.97 to 1.44)
Sex			
Women	58/117 (49.6)	45/113 (39.8)	1.19 (0.9 to 1.57)
Men	89/161 (55.3)	75/159 (47.2)	1.17 (0.96 to 1.44)
Baseline NIHSS score			
≤16	95/144 (66.0)	82/143 (57.3)	1.13 (0.95 to 1.35)
>16	52/134 (38.8)	38/129 (29.5)	1.24 (0.89 to 1.73)
Baseline ASPECTS			
≤8	100/197 (50.8)	73/190 (38.4)	1.34 (1.08 to 1.66)
>8	47/81 (58.0)	47/82 (57.3)	0.93 (0.72 to 1.19)
Occlusion site			
ICA	31/77 (40.3)	28/87 (32.2)	1.36 (0.92 to 1.99)
Non-ICA	116/201 (57.7)	92/185 (49.7)	1.14 (0.97 to 1.37)
Cause of stroke			
LAA	38/82 (46.3)	42/85 (49.4)	0.99 (0.72 to 1.36)
CE	96/172 (55.8)	66/163 (40.5)	1.28 (1.04 to 1.58)
Unknown/Other	13/24 (54.2)	12/24 (50.0)	1.06 (0.59 to 1.92)
Angioplasty or stenting			
No	110/210 (52.4)	82/190 (43.2)	1.18 (0.98 to 1.44)
Yes	24/51 (47.1)	32/72 (44.4)	1.03 (0.7 to 1.52)
Last known well to randomization			
≤163 min	84/149 (56.4)	68/125 (54.4)	1.06 (0.87 to 1.3)
>163 min	63/129 (48.8)	52/147 (35.4)	1.35 (1.04 to 1.77)
Last known well to actual/expected start of intravenous tenecteplase*			
≤140 min	49/85 (57.6)	44/69 (63.8)	0.94 (0.73 to 1.2)
>140 min	98/193 (50.8)	76/203 (37.4)	1.33 (1.08 to 1.64)
Actual/expected time from start of intravenous tenecteplase to puncture†			
≤16 min	73/138 (52.9)	61/135 (45.2)	1.17 (0.93 to 1.47)
>16 min	74/140 (52.9)	59/137 (43.1)	1.19 (0.95 to 1.5)