The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 18, 2024 VOL. 391 NO. 3

Tenecteplase for Ischemic Stroke at 4.5 to 24 Hours without Thrombectomy

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ABSTRACT

BACKGROUND

Tenecteplase is an effective thrombolytic agent for eligible patients with stroke who are treated within 4.5 hours after the onset of stroke. However, data regarding the effectiveness of tenecteplase beyond 4.5 hours are limited.

METHODS

In a trial conducted in China, we randomly assigned patients with large-vessel occlusion of the middle cerebral artery or internal carotid artery who had salvageable brain tissue as identified on perfusion imaging and who did not have access to endovascular thrombectomy to receive tenecteplase (at a dose of 0.25 mg per kilogram of body weight; maximum dose, 25 mg) or standard medical treatment 4.5 to 24 hours after the time that the patient was last known to be well (including after stroke on awakening and unwitnessed stroke). The primary outcome was the absence of disability, which was defined as a score of 0 or 1 on the modified Rankin scale (range, 0 to 6, with higher scores indicating greater disability), at day 90. The key safety outcomes were symptomatic intracranial hemorrhage and death.

RESULTS

A total of 516 patients were enrolled; 264 were randomly assigned to receive tenecteplase and 252 to receive standard medical treatment. Less than 2% of the patients (4 in the tenecteplase group and 5 in the standard-treatment group) underwent rescue endovascular thrombectomy. Treatment with tenecteplase resulted in a higher percentage of patients with a modified Rankin scale score of 0 or 1 at 90 days than standard medical treatment (33.0% vs. 24.2%; relative rate, 1.37; 95% confidence interval, 1.04 to 1.81; P=0.03). Mortality at 90 days was 13.3% with tenecteplase and 13.1% with standard medical treatment, and the incidence of symptomatic intracranial hemorrhage within 36 hours after treatment was 3.0% and 0.8%, respectively.

CONCLUSIONS

In this trial involving Chinese patients with ischemic stroke due to large-vessel occlusion, most of whom did not undergo endovascular thrombectomy, treatment with tenecteplase administered 4.5 to 24 hours after stroke onset resulted in less disability and similar survival as compared with standard medical treatment, and the incidence of symptomatic intracranial hemorrhage appeared to be higher. (Funded by the National Natural Science Foundation of China and others; TRACE-III ClinicalTrials.gov number, NCT05141305.)

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*A complete list of the TRACE-III investigators is provided in the Supplementary Appendix, available at NEJM.org.

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This article was published on June 14, 2024, at NEJM.org.

N Engl J Med 2024;391:203-12.
DOI: 10.1056/NEJMoa2402980

CME

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The use of intravenous thrombolytic agents is recommended for eligible patients within 4.5 hours after the onset of stroke,[1] and tenecteplase — a modified form of human tissue plasminogen activator — has been shown to be noninferior to alteplase.[2] However, approximately 67 to 75% of patients present after 4.5 hours after stroke onset or with an unknown time of onset.[3] Alteplase therapy is beneficial when initiated up to 9 hours after the onset of stroke if perfusion imaging results indicate the presence of salvageable ischemic brain tissue.[4,5] However, data on the use of tenecteplase beyond 4.5 hours are limited.

The Thrombolysis in Imaging Eligible, Late Window Patients to Assess the Efficacy and Safety of Tenecteplase (TIMELESS) trial[6] involved patients with large-vessel occlusion and evidence of salvageable brain tissue on perfusion imaging. Most of the patients who had undergone randomization received immediate endovascular thrombectomy, which has since been shown to be effective in a broad range of patients when performed up to 24 hours after stroke onset. The trial showed no significant difference between tenecteplase therapy and placebo in the odds of a lower score on the modified Rankin scale at 90 days. The safety results did not differ substantially between the tenecteplase group and the placebo group. However, immediate access to thrombectomy is limited in many geographic locations, including in developed countries, and is often unavailable in low-income or middle-income countries.[7,8]

The effect of late administration of tenecteplase (i.e., after 4.5 hours after stroke onset) in patients without immediate access to thrombectomy is currently unclear and is relevant to a majority of patients worldwide.[9] The Tenecteplase Reperfusion Therapy in Acute Ischemic Cerebrovascular Events–III (TRACE-III) trial investigated the efficacy and safety of tenecteplase at a dose of 0.25 mg per kilogram of body weight, administered 4.5 to 24 hours after stroke onset (the time that the patient was last known to be well, including after stroke on awakening and unwitnessed stroke), in patients who had had ischemic stroke resulting from large-vessel occlusion, had salvageable tissue, and did not have access to endovascular thrombectomy.

Methods

Trial Design and Oversight

We conducted this phase 3, multicenter, prospective, open-label, randomized, blinded-outcome-assessment (also known as blinded–end-point–evaluation) trial at 58 centers in China. The trial protocol (available with the full text of this article at NEJM.org) was approved by the institutional review board at each participating center before enrollment began. Details regarding the rationale, design, and methods have been described previously.[10] All the enrolled patients or their legally authorized representatives provided written informed consent. The trial was conducted in accordance with the principles of the Declaration of Helsinki and the International Council for Harmonisation guidelines for Good Clinical Practice. The first author wrote the first draft of the manuscript, and the fifth author performed the statistical analysis. After the database was locked, the last author had unrestricted access to the data; this author vouches for the fidelity of the trial to the protocol and for the completeness and accuracy of the reported outcome data and adverse events.

China Shijiazhuang Pharmaceutical Company Recomgen Pharmaceutical (Guangzhou) provided tenecteplase and an unrestricted grant to support trial infrastructure but did not participate in the design or conduct of the trial or the drafting of the manuscript. There were no confidentiality agreements between the manufacturer and the investigators, and the manufacturer could not delay or interdict publication of the trial results. A research version of iStroke software was provided free of charge to the trial centers by Beijing Tiantan Hospital and Biomind.

Patients

Patients who were 18 years of age or older and had had stroke, including stroke on awakening and unwitnessed stroke, were recruited within 4.5 to 24 hours after the time that they were last known to be well. Eligible patients had a prestroke score of 0 or 1 on the modified Rankin scale (scores range from 0 to 6, with higher scores indicating greater disability); a score of 6 to 25 on the National Institutes of Health Stroke Scale

(NIHSS; scores range from 0 to 42, with higher scores indicating more severe neurologic deficits); evidence of occlusion of the intracranial internal carotid artery or the first (M1) or second (M2) segment of the middle cerebral artery on computed tomographic (CT) angiography or magnetic resonance angiography; and evidence of salvageable brain tissue as identified on perfusion imaging with the use of iStroke software, version 3.13.[11,12]

Irreversibly injured ischemic core was defined as an area with a cerebral blood flow of less than 30% of that in the normal brain as measured with the use of CT perfusion imaging or an apparent diffusion coefficient value of less than 620×10^{-6} mm^2 per second as measured with the use of perfusion–diffusion magnetic resonance imaging (MRI). The hypoperfused region of the brain was defined according to a delayed arrival of an injected tracer agent (time to maximum of the residue function of >6 seconds). To be eligible, patients had to have an ischemic core volume of less than 70 ml, a ratio of the volume of hypoperfused tissue to the ischemic core volume of at least 1.8, and a difference in volume between the hypoperfused tissue and the ischemic core of at least 15 ml.

Patients were ineligible if endovascular thrombectomy was planned at the time of randomization or there were guideline-based contraindications to thrombolytic agents. Additional information regarding inclusion and exclusion criteria is provided in the Supplementary Appendix, available at NEJM.org.

RANDOMIZATION AND BLINDING

Patients were randomly assigned in a 1:1 ratio to receive tenecteplase or standard medical treatment (control). Randomization was conducted by means of a centralized permuted-block method with blocks of four and was stratified according to the site of vessel occlusion (internal carotid artery vs. M1 segment of the middle cerebral artery vs. M2 segment of the middle cerebral artery). The assessments of the trial outcomes were performed by qualified physicians, and the outcome events were adjudicated by members of a dedicated adjudication committee, all of whom were unaware of the treatment assignments.

INTERVENTIONS

The tenecteplase group received tenecteplase intravenously as a bolus administered over a period of 5 to 10 seconds at a dose of 0.25 mg per kilogram (maximum dose, 25 mg) immediately after randomization. The control group received antiplatelet therapy (standard medical treatment) at the discretion of the investigators. Other treatments conformed to the 2018 Chinese Guidelines for Diagnosis and Treatment of Acute Ischemic Stroke. Although patients who had access to endovascular thrombectomy during the screening period were excluded, rescue thrombectomy after randomization could be performed at the discretion of the treating clinician if the patient's condition had deteriorated and endovascular thrombectomy was accessible at that time. Such patients were included in the intention-to-treat analysis but were excluded from the per-protocol analysis; these analyses are described below, in the Statistical Analysis section.

OUTCOMES

The primary outcome was the absence of disability (defined as a score of 0 or 1 on the modified Rankin scale) at 90 days. Secondary outcomes were the ordinal distribution of scores on the modified Rankin scale at 90 days, functional independence (defined as a modified Rankin scale score of ≤2) at 90 days, major neurologic improvement at 72 hours after treatment (defined as a reduction from baseline of ≥8 points on the NIHSS or an NIHSS score of ≤1), reperfusion at 24 hours after treatment (defined as >90% reduction in the volume of the lesion in which there had been a delayed arrival of an injected tracer agent of >6 seconds), and the change from baseline in the NIHSS score at 7 days. The exploratory secondary outcome was recanalization at 24 hours after treatment; this outcome was assessed with the use of the Arterial Occlusive Lesion scale (scores range from 0 [no recanalization] to 3 [complete recanalization]).[13]

Safety outcomes were symptomatic intracranial hemorrhage (defined as any intracranial hemorrhage that was either associated with an increase [indicating worsening] of ≥4 points in the NIHSS score or led to death and that was identified as

the predominant cause of the neurologic deterioration) within 36 hours after treatment,[14] death from any cause, moderate or severe systemic bleeding within 90 days (as defined according to the criteria established in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries [GUSTO] trial[15]), and adverse events (including serious adverse events) within 90 days.

Outcome assessments were performed by certified clinicians at each center who were unaware of the treatment assignments. Data obtained at screening included demographic information, medical history, current medications, laboratory test results, neurologic function (modified Rankin scale score and NIHSS score), imaging results, and adverse events. At baseline, CT perfusion imaging or perfusion–diffusion MRI was required in order to confirm eligibility and was repeated at 24 hours to evaluate recanalization and reperfusion. Intracerebral hemorrhage was assessed with the use of CT imaging or MRI that was performed without the use of intravenous contrast material at 24 to 36 hours, and the score on the modified Rankin scale at 90 days was assessed at in-person visits or by telephone. Adverse events were reported according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

STATISTICAL ANALYSIS

The main analysis of the efficacy and safety outcomes was performed according to the intention-to-treat principle and included all the patients who had undergone randomization. Patients who completed the assigned treatment and had no major violations of the trial protocol were included in the per-protocol analysis of the efficacy and safety outcomes. Differences between the trial groups in the percentage of patients with a score of 0 or 1 on the modified Rankin scale at 90 days (the primary outcome) were analyzed by means of log-binomial regression with the trial center as a random effect. Unadjusted relative rate and 95% confidence interval are reported. All effects of tenecteplase, as compared with standard medical treatment, on binary secondary and safety outcomes are reported as relative rates with respective 95% confidence intervals. The distribution of scores on the modified Rankin scale was analyzed with the use of ordinal logistic regression and is reported as a common odds ratio; verification of the proportional-odds assumption was performed with the use of a chi-square test. For the analysis of the change from baseline in the NIHSS score at 7 days, a generalized linear mixed model was fitted, and beta coefficients with 95% confidence intervals are reported.

Because there was no prespecified plan for adjustment of the widths of the confidence intervals for the secondary outcomes or for multiple comparisons in subgroup analyses of the primary outcome, the confidence intervals should not be used for causal inference. The data for the main efficacy analyses were complete; therefore, no imputation for missing data was needed. A multiple imputation method that was based on a fully conditional specification method was used to impute missing data for the secondary outcomes for which data were missing.

Prespecified subgroups were defined according to age (<80 vs. ≥80 years), sex, baseline severity of stroke (NIHSS score <10 vs. ≥10), interval between the time that the patient was last known to be well and treatment (>4.5 to 9.0 hours vs. >9.0 to 24.0 hours vs. stroke on awakening), and large-vessel occlusion site (internal carotid artery vs. M1 segment of the middle cerebral artery vs. M2 segment of the middle cerebral artery). Post hoc analyses of functional outcomes were performed with the use of logistic regression, with adjustment for age, sex, baseline NIHSS score, interval between the time that the patient was last known to be well and randomization, and occlusion site. A post hoc subgroup analysis of the primary end point was added; subgroups were defined according to age (<65 vs. ≥65 years), endovascular thrombectomy (yes vs. no), and volume of ischemic core at baseline (<20 ml vs. 20 to <50 ml vs. ≥50 ml).

A P value of less than 0.05 was considered to indicate statistical significance. All statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute). The statistical analysis plan is available with the protocol.

RESULTS

PATIENT CHARACTERISTICS

From January 2022 through November 2023, a total of 1469 patients underwent screening. Of these patients, 516 (35.1%) were enrolled in the trial; 264 were randomly assigned to receive tenecteplase and 252 to receive standard medical

treatment. The reasons for exclusion from participation, as well as details regarding the protocol violations that occurred during the trial, are provided in Figure S1 in the Supplementary Appendix. Protocol violations were reported in 28 patients (5.4%); of these patients, 9 had violations that were related to unrecognized cerebral infarction in more than one third of the middle-cerebral-artery territory, a finding that was associated with the development of symptomatic intracranial hemorrhage in 5 of the patients. Rescue endovascular thrombectomy was performed in 4 patients in the tenecteplase group and in 5 patients in the standard-treatment group.

The demographic, clinical, and imaging characteristics of the patients were similar in the two groups at baseline and were largely representative of the expected patient population (Table 1 and Tables S1 and S2). The median age of the patients was 67 years (interquartile range, 59 to 75), and 350 of the 516 patients (67.8%) were men. The median score on the NIHSS was 10 (interquartile range, 7 to 14), and the median interval between the time that the patient was last known to be well and randomization was 12.3 hours (interquartile range, 8.5 to 16.4). Salvageable brain tissue was assessed by means of CT perfusion imaging in 457 patients (88.6%) and by perfusion–diffusion MRI in 59 patients (11.4%).

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Tenecteplase (N=264)	Standard Medical Treatment (N=252)
Median age (IQR) — yr	67 (58–75)	68 (59–76)
Male sex — no. (%)	183 (69.3)	167 (66.3)
Hypertension — no. (%)	177 (67.0)	180 (71.4)
Diabetes mellitus — no. (%)	69 (26.1)	71 (28.2)
Atrial fibrillation — no. (%)	49 (18.6)	48 (19.0)
Modified Rankin scale score before stroke — no. (%)†		
0	230 (87.1)	216 (85.7)
1	34 (12.9)	36 (14.3)
Median NIHSS score at randomization (IQR)‡	11 (7–15)	10 (7–14)
Category of onset of stroke — no. (%)		
Known onset time	143 (54.2)	149 (59.1)
Unwitnessed onset	20 (7.6)	19 (7.5)
Stroke on awakening	101 (38.3)	84 (33.3)
Median volume of irreversibly injured ischemic core at initial imaging (IQR) — ml§	16.4 (5.7–28.4)	14.9 (6.0–29.3)
Median volume of perfusion lesion at initial imaging (IQR) — ml¶	119.1 (79.8–177.2)	123.2 (74.6–180.1)

* IQR denotes interquartile range.
† Scores on the modified Rankin scale range from 0 to 6, with higher scores indicating greater disability. A score of 0 indicates no symptoms or disability after stroke, and a score of 1 indicates no clinically meaningful disability (patients are able to perform usual work, leisure, and school activities). The score before stroke was assessed by asking the patient or legal representative about the patient's ability to perform activities of daily living before the hospitalization for stroke.
‡ Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating a more severe neurologic deficit.
§ All the patients had interpretable perfusion imaging results at baseline, as required for eligibility. The ischemic core was defined as an area with a relative cerebral blood flow of less than 30% of that in the normal brain as measured with the use of CT perfusion imaging or an apparent diffusion coefficient value of less than 620×10^{-6} mm^2 per second as measured with the use of perfusion–diffusion MRI.
¶ 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.

PRIMARY AND SECONDARY CLINICAL OUTCOMES

The percentage of patients who had no disability (defined as a modified Rankin scale score of 0 or 1) at 90 days (the primary outcome) was 33.0% in the tenecteplase group as compared with 24.2% in the standard-treatment group (relative rate, 1.37; 95% confidence interval [CI], 1.04 to 1.81; P=0.03) (Table 2 and Fig. 1). Secondary and safety outcomes are also presented in Table 2. The trial was not powered for conclusions to be made on the basis of these analyses, and the analyses were not adjusted for multiplicity. The common odds ratio for the ordinal distribution of scores on the modified Rankin scale at 90 days was 1.33 (95% CI, 0.98 to 1.81). The percentage of patients who were functionally independent (defined as a modified Rankin scale score of ≤2) at 90 days was 43.6% in the tenecteplase group and 33.3% in the standard-treatment group (relative rate, 1.31; 95% CI, 1.05 to 1.63).

The results of subgroup analyses of the effect of tenecteplase on the primary outcome are shown in Figure 2, and the results of post hoc analyses of functional outcomes that were adjusted for age, sex, baseline NIHSS score, interval between the time that the patient was last known to be well and randomization, and occlusion site are provided in Table S3. The results of post hoc subgroup analyses of the primary outcome according to age, endovascular thrombectomy, and

Table 2. Efficacy and Safety Outcomes.

Outcome	Tenecteplase (N=264)	Standard Medical Treatment (N=252)	Effect Size (95% CI)*
Primary outcome			
Score of 0 or 1 on the modified Rankin scale at 90 days — no. (%)†	87 (33.0)	61 (24.2)	1.37 (1.04 to 1.81)
Secondary outcomes			
Ordinal distribution of scores on the modified Rankin scale at 90 days — no. (%)†			1.33 (0.98 to 1.81)
0	26 (9.8)	17 (6.7)	—
1	61 (23.1)	44 (17.5)	—
2	28 (10.6)	23 (9.1)	—
3	46 (17.4)	59 (23.4)	—
4	57 (21.6)	57 (22.6)	—
5	11 (4.2)	19 (7.5)	—
6	35 (13.3)	33 (13.1)	—
Score of ≤2 on the modified Rankin scale, indicating functional independence, at 90 days — no. (%)	115 (43.6)	84 (33.3)	1.31 (1.05 to 1.63)
Major neurologic improvement at 72 hr — no./total no. (%)‡	40/250 (16.0)	15/249 (6.0)	2.66 (1.51 to 4.69)
Reperfusion at 24 hr — no./total no. (%)§	48/239 (20.1)	27/229 (11.8)	1.70 (1.10 to 2.64)
Change in the NIHSS score at 7 days	−4 (−6 to −1)	−2 (−5 to 0)	−1.47 (−2.30 to −0.64)
Safety outcomes			
Symptomatic intracranial hemorrhage within 36 hr after randomization — no. (%)¶	8 (3.0)	2 (0.8)	3.82 (0.82 to 17.87)
Death within 90 days — no. (%)	35 (13.3)	33 (13.1)	1.01 (0.65 to 1.58)
Moderate or severe systemic bleeding within 90 days — no. (%)‖	5 (1.9)	2 (0.8)	2.36 (0.46 to 12.09)
Any adverse event — no. (%)	134 (50.8)	129 (51.2)	0.99 (0.84 to 1.17)
Any serious adverse event — no. (%)	53 (20.1)	43 (17.1)	1.18 (0.82 to 1.69)

* The common odds ratio is shown for the ordinal distribution of scores on the modified Rankin scale. The beta coefficient is shown for the analysis of the change from baseline in the NIHSS score at 7 days. The relative rate is shown for other outcomes. The trial was not powered for conclusions to be made on the basis of these analyses, and the analyses were not adjusted for multiplicity.

† For the primary outcome, the P value was 0.03. Scores on the modified Rankin scale range from 0 (no symptoms) to 6 (death). A score of 1 indicates no clinically meaningful disability (patients are able to perform usual work, leisure, and school activities), 2 slight disability (patients are able to look after their own affairs without assistance but are unable to carry out all previous activities), 3 moderate disability (patients require some help but are able to walk unassisted), 4 moderately severe disability (unable to attend to bodily needs without assistance or unable to walk unassisted), and 5 severe disability (patients are bedridden and require constant care).

‡ Major neurologic improvement was defined as an improvement (reduction) from baseline of at least 8 points on the NIHSS or an NIHSS score 1 or lower.

§ 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.

¶ Symptomatic intracranial hemorrhage was defined according to the criteria established in the European Cooperative Acute Stroke Study (ECASS III) trial[14]: the presence of any extravascular blood in the brain or within the cranium that was associated with clinical deterioration, as defined by an increase of 4 points or more in the score on the NIHSS, or that led to death and that was identified as the predominant cause of the neurologic deterioration.

‖ Moderate or severe systemic bleeding was defined according to the criteria established in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial.[15] Symptomatic intracranial hemorrhage was not included in this category.

volume of ischemic core at baseline are provided in Figure S2. The results of the analysis in which multiple imputation was used for the outcomes with missing data (major neurologic improvement at 72 hours, reperfusion at 24 hours after treatment, and change from baseline in the NIHSS score at 7 days) were similar to those of the main analysis (Table S4). Complete recanaliza-

tion at 24 hours after treatment occurred in 69 patients (27.9%) in the tenecteplase group and in 14 patients (5.9%) in the standard-treatment group (Table S5). The results of the primary and secondary efficacy outcomes in the per-protocol analysis were similar to those of the main analysis (Table S6 and Fig. S3).

SAFETY

Symptomatic intracranial hemorrhage within 36 hours after treatment occurred in 8 patients (3.0%) in the tenecteplase group and in 2 patients (0.8%) in the standard-treatment group (relative rate, 3.82; 95% CI, 0.82 to 17.87) (Table 2). Parenchymal hematoma type 2 was reported in 4 patients (1.5%) in the tenecteplase and in 1 patient (0.4%) in the standard-treatment group (Table S7). Moderate or severe systemic bleeding occurred in 5 patients (1.9%) in the tenecteplase group and in 2 patients (0.8%) in the standard-treatment group (relative rate, 2.36; 95% CI, 0.46 to 12.09). The percentage of patients who died within 90 days after randomization was 13.3% (35 of 264 patients) in the tenecteplase group and 13.1% (33 of 252 patients) in the standard-treatment group. The incidence of other adverse events and serious adverse events did not differ substantially between the two groups (Tables S8 and S9).

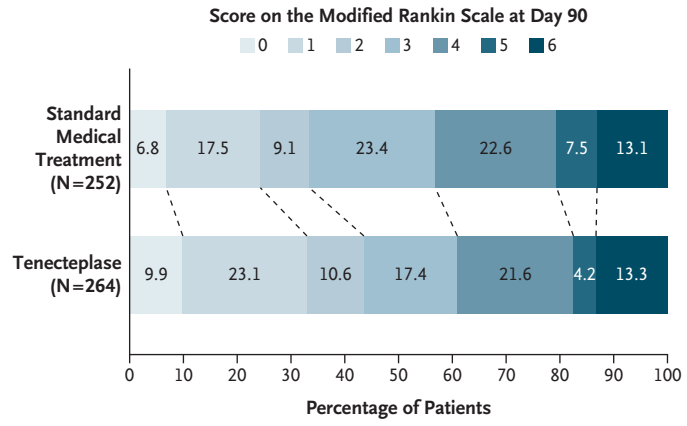

Figure 1. Distribution of Scores on the Modified Rankin Scale at 90 Days (Intention-to-Treat Population).

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

DISCUSSION

The TRACE-III trial showed that, in patients with ischemic stroke due to large-vessel occlusion who had salvageable tissue and did not have access to endovascular thrombectomy, treatment with intravenous tenecteplase between 4.5 hours and 24 hours after stroke onset led to a larger percentage of patients with no disability than that observed with standard medical care. Although there was no marked difference in survival at 90 days, the incidence of symptomatic intracranial hemorrhage within the first 36 hours after treatment appeared to be higher in the tenecteplase group than in the standard-treatment group.

These results can be viewed in the context of the TIMELESS trial, which did not show a benefit of tenecteplase in similar patients with stroke, most of whom underwent endovascular thrombectomy immediately after receiving thrombolytic therapy. As in the TIMELESS trial, the safety of tenecteplase in patients who had been selected for the presence of salvageable brain tissue in the current trial was similar to that seen in the early time window (<4.5 hours after stroke onset), despite the extension of treatment up to 24 hours after stroke onset. The results of the TIMELESS trial are readily generalizable only to patients who present to comprehensive stroke centers, where immediate access to thrombectomy is available; the median time from thrombolytic therapy to arterial puncture in that trial was 16 minutes. In developed countries, most patients present first to hospitals in which endovascular thrombectomy is unavailable and are then transferred to a thrombectomy-capable center. The TRACE-III trial provides evidence that these patients, who may no longer be eligible for thrombectomy by the time they arrive at the thrombectomy center,[16] can benefit from intravenous tenecteplase therapy at the primary stroke center. This approach does require perfusion-imaging capability at these smaller hospitals, but the TRACE-III trial and other trials[5,17] provide evidence for the feasibility of this approach with the use of CT-based methods and automated software. Software such as iStroke, which was used in our trial, adds to the

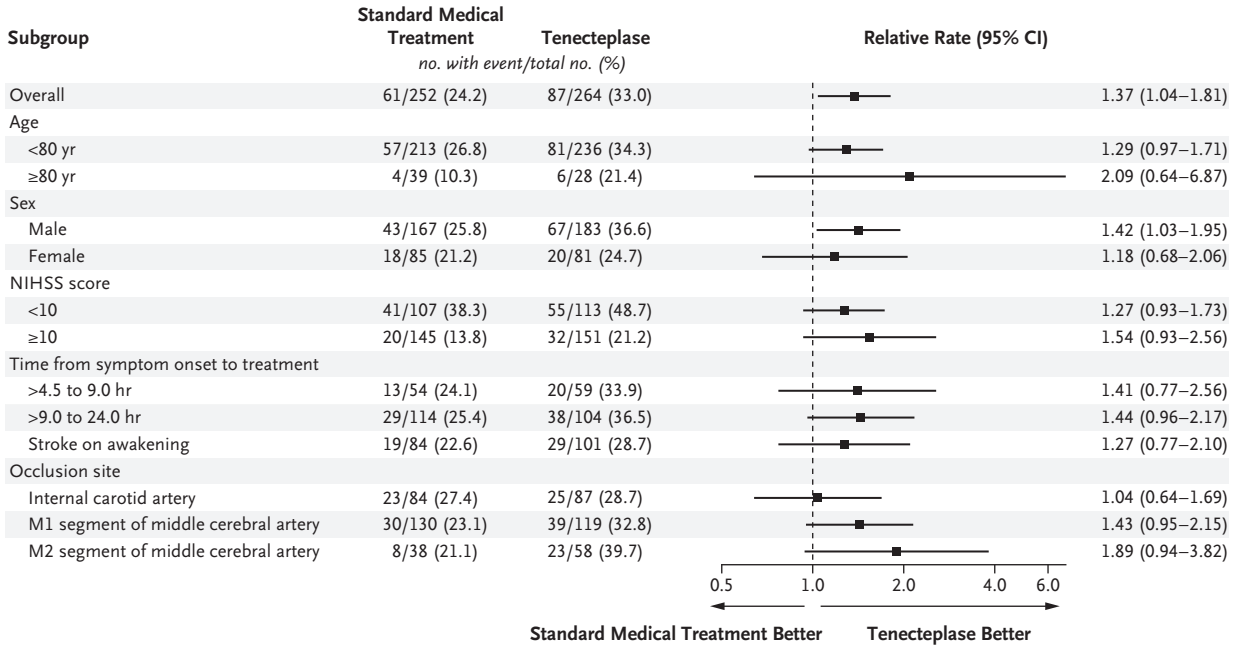

Figure 2. Relative Rate of a Modified Rankin Scale Score of 0 or 1 at 90 Days (Primary Outcome) in Prespecified Subgroups.

The time from symptom onset to treatment refers to the interval between the time that a patient was last known to be well (including after stroke on awakening and unwitnessed stroke) and the time of treatment with tenecteplase or standard medical treatment. Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating more severe neurologic deficits.

available options for computerized-image analysis and may provide a lower-cost option than other commercial software packages.

The TRACE-III trial also builds on the results of the Extending the Time for Thrombolysis in Emergency Neurological Deficits (EXTEND) trial, which showed the benefit of alteplase therapy when initiated up to 9 hours after the onset of stroke in patients who did not undergo thrombectomy.[5] In the TRACE-III trial, extending the initiation of treatment to 24 hours after stroke onset more than doubled the number of patients who were eligible for participation. Tenecteplase was shown to be noninferior to alteplase in multiple trials in which the 0-to-4.5-hour window was used,[18-20] with evidence of superiority in meta-analyses of trials involving patients with large-vessel occlusion.[21,22] Ongoing trials (ClinicalTrials.gov numbers, NCT04454788 and NCT05105633) will provide data on the efficacy of tenecteplase as compared with alteplase when administered beyond 4.5 hours after stroke onset. The median door-to-needle time of 139 minutes in the TRACE-III trial was similar to that in the EXTEND trial, and this interval is likely to be shorter outside the context of a clinical trial that requires written informed consent and randomization. Faster door-to-needle time has consistently been associated with improved functional outcomes and safety.[23]

This trial has several limitations. First, the trial was open-label, although outcomes were assessed by clinicians who were unaware of the treatment assignments. Second, the trial excluded patients who had access to endovascular thrombectomy, so the results may lack applicability to patients who present directly to a thrombectomy-capable center. Third, the trial was performed in China, where intracranial atherosclerosis is more prevalent than in Western countries and atrial fibrillation is less prevalent. Fourth, the effect size — although similar to that seen with thrombolytic therapy at 0 to 3 hours after stroke onset — is smaller than that seen with thrombectomy. Fifth, the median ischemic core volume was relatively small, albeit larger than in previous late-

window thrombecomy trials,[5,16,24] and the severity of stroke was milder. Finally, on central imaging review, nine patients had protocol violations that were related to extensive areas of hypodensity on noncontrast CT, and symptomatic intracranial hemorrhage developed in five of these patients. Therefore, careful evaluation for areas of hypodensity on noncontrast CT is advisable when considering the use of late-window thrombolytic agents, and automated software to detect hypodensity on CT may help to identify patients in whom thrombolytic therapy may not be appropriate.

In this trial involving Chinese patients with ischemic stroke due to anterior-circulation large-vessel occlusion who had salvageable tissue, tenecteplase administered between 4.5 hours and 24 hours after the patients were last known to be well was shown to improve disability-free recovery. In addition to the practical advantage of administration of tenecteplase as a single bolus as compared with alteplase, which is administered as an infusion, our results support the use of tenecteplase in the extended time window when endovascular thrombectomy is not immediately available. However, this approach requires corroboration in trials that are performed in countries in which fewer ischemic strokes are caused by atherogenesis.

Supported by the National Natural Science Foundation of China (grant number, 82171272), the Beijing Municipal Science and Technology Commission and Zhongguancun Science Park Administrative Committee (grant number, Z211100003521019), and China Shijiazhuang Pharmaceutical Company Recomgen Pharmaceutical.

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

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

APPENDIX

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