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Tenecteplase versus Alteplase before Thrombectomy for Ischemic Stroke

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ABSTRACT

BACKGROUND

Intravenous infusion of alteplase is used for thrombolysis before endovascular thrombectomy for ischemic stroke. Tenecteplase, which is more fibrin-specific and has longer activity than alteplase, is given as a bolus and may increase the incidence of vascular reperfusion.

METHODS

We randomly assigned patients with ischemic stroke who had occlusion of the internal carotid, basilar, or middle cerebral artery and who were eligible to undergo thrombectomy to receive tenecteplase (at a dose of 0.25 mg per kilogram of body weight; maximum dose, 25 mg) or alteplase (at a dose of 0.9 mg per kilogram; maximum dose, 90 mg) within 4.5 hours after symptom onset. The primary outcome was reperfusion of greater than 50% of the involved ischemic territory or an absence of retrievable thrombus at the time of the initial angiographic assessment. Noninferiority of tenecteplase was tested, followed by superiority. Secondary outcomes included the modified Rankin scale score (on a scale from 0 [no neurologic deficit] to 6 [death]) at 90 days. Safety outcomes were death and symptomatic intracerebral hemorrhage.

RESULTS

Of 202 patients enrolled, 101 were assigned to receive tenecteplase and 101 to receive alteplase. The primary outcome occurred in 22% of the patients treated with tenecteplase versus 10% of those treated with alteplase (incidence difference, 12 percentage points; 95% confidence interval [CI], 2 to 21; incidence ratio, 2.2; 95% CI, 1.1 to 4.4; P=0.002 for noninferiority; P=0.03 for superiority). Tenecteplase resulted in a better 90-day functional outcome than alteplase (median modified Rankin scale score, 2 vs. 3; common odds ratio, 1.7; 95% CI, 1.0 to 2.8; P=0.04). Symptomatic intracerebral hemorrhage occurred in 1% of the patients in each group.

CONCLUSIONS

Tenecteplase before thrombectomy was associated with a higher incidence of reperfusion and better functional outcome than alteplase among patients with ischemic stroke treated within 4.5 hours after symptom onset. (Funded by the National Health and Medical Research Council of Australia and others; EXTEND-IA TNK ClinicalTrials.gov number, NCT02388061.)

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Intravenous thrombolysis with alteplase is used in eligible patients with acute ischemic stroke before endovascular thrombectomy.[1,2] Alteplase is given as an infusion over a period of approximately 1 hour and has been associated with a low incidence of reperfusion for large-vessel occlusion before thrombectomy in several trials.[3-5] Tenecteplase is a genetically modified variant of alteplase with greater fibrin specificity and a longer half-life that permits bolus administration.[6] In one trial involving patients with ST-segment elevation myocardial infarction, tenecteplase resulted in 30-day mortality similar to that with alteplase and led to a lower incidence of systemic hemorrhage.[7] In patients with stroke, one trial that used computed tomographic (CT) perfusion imaging and large-vessel occlusion for the selection of patients showed a higher incidence of reperfusion at 24 hours and better clinical and functional outcomes with tenecteplase than with alteplase.[8] Other trials that did not use imaging-based selection have shown similar clinical outcomes with tenecteplase and alteplase.[9,10] Tenecteplase can be infused more rapidly than alteplase and is less expensive. We conducted the Tenecteplase versus Alteplase before Endovascular Therapy for Ischemic Stroke (EXTEND-IA TNK) trial to compare tenecteplase with alteplase in establishing reperfusion in patients before endovascular thrombectomy when it was administered within 4.5 hours after the onset of symptoms.

Methods

Trial Design

We conducted an investigator-initiated, multicenter, prospective, randomized, open-label, blinded-outcome trial[11] involving patients with ischemic stroke within 4.5 hours after onset who had large-vessel occlusion of the internal carotid, middle cerebral, or basilar artery and who were eligible to undergo intravenous thrombolysis and endovascular thrombectomy. The methods of the trial have been published previously,[12] and the protocol is available with the full text of this article at NEJM.org.

The design, analysis, and data collection for this trial, as well as the writing of the manuscript, were performed by members of the executive committee and investigators at the trial sites (see the Supplementary Appendix, available at NEJM.org). The first author wrote the first draft of the manuscript, and the third author performed the statistical analysis. The investigators vouch for the accuracy and completeness of the data, for the fidelity of the trial to the protocol, and for the complete reporting of adverse events. Medtronic provided an unrestricted grant to support trial infrastructure but was not involved in the design or conduct of the trial or the preparation of the manuscript. A research version of RAPID software was provided free of charge to trial sites by iSchemaView, which had no other involvement with the trial.

Patients

We enrolled patients at 13 centers in Australia and New Zealand. Patients were eligible if they could undergo intravenous thrombolysis within 4.5 hours after the onset of ischemic stroke and had cerebral vascular occlusion on CT angiography of the internal carotid artery, the first segment of the middle cerebral artery, the second segment of the middle cerebral artery, or the basilar artery and if treatment to retrieve the intraarterial clot could commence (arterial puncture) within 6 hours after stroke onset. There was no upper age limit and no restriction on clinical severity as assessed with the use of the National Institutes of Health Stroke Scale (NIHSS) score (scores range from 0 [normal function] to 42 [death], with lower scores indicating less severe stroke). However, patients with severe preexisting disability, defined as a modified Rankin scale score of more than 3 (scores range from 0 [no neurologic deficit] to 6 [death]), were excluded.

The entry criteria originally required CT-perfusion mismatch for anterior circulation strokes. The hypoperfused region was defined according to a delayed arrival of an injected tracer agent (time to maximum of the residue function exceeding 6 seconds), and irreversibly injured ischemic core was estimated with the use of relative cerebral blood flow less than 30% of that in normal brain. Mismatch was defined as a ratio of greater than 1.2 between the volume of hypoperfusion and the volume of the ischemic core, an absolute difference in volume greater than 10 ml, and an ischemic core volume of less than 70 ml. The criteria of CT-perfusion mismatch were removed on October 12, 2016, after approximately 80 patients had been enrolled, because analysis of pooled data from other trials showed a benefit

of thrombectomy in patients with larger ischemic-core volumes.[13]

The trial was approved by an institutional ethics committee at each site, and written informed consent was obtained from each patient or a legal representative before enrollment except in jurisdictions that allowed deferral of consent for emergency treatment, in which case consent to continue participation was obtained. Detailed inclusion and exclusion criteria are provided in the Supplementary Appendix.

TREATMENT

Patients were randomly assigned in a 1:1 ratio to receive intravenous tenecteplase (at a dose of 0.25 mg per kilogram of body weight; maximum dose, 25 mg) or alteplase (at a dose of 0.9 mg per kilogram; maximum dose, 90 mg). Randomization was performed with the use of a centralized Web server, with stratification according to the site of the involved vessel (internal carotid artery, basilar artery, first segment of the middle cerebral artery, or second segment of the middle cerebral artery). All other treatments were guided by the standard of care for thrombolysis and thrombectomy for ischemic stroke.

ASSESSMENTS AND OUTCOMES

The primary outcome of substantial reperfusion was defined as the restoration of blood flow to greater than 50% of the involved territory or an absence of retrievable thrombus in the target vessel at the time of the initial angiographic assessment. Perfusion was assessed with the use of the modified Treatment in Cerebral Ischemia classification (scores range from 0 [no flow] to 3 [normal flow]).[14] If no lesion was suitable for thrombectomy, the endovascular procedure was terminated. If intracranial angiography could not be performed, the primary outcome was assessed as reperfusion of at least 50% of the involved territory on CT perfusion imaging 1 to 2 hours after thrombolysis.

Secondary outcomes were the modified Rankin scale score at 90 days, assessed centrally by a clinician by means of a telephone conversation, and early neurologic improvement, defined as a reduction of at least 8 points or a score of 0 or 1 on the NIHSS at 72 hours, as assessed by site personnel. Safety outcomes were death due to any cause and symptomatic intracranial hemorrhage, which included subarachnoid hemorrhage that was associated with clinical symptoms and symptomatic intracerebral hemorrhage that was adjudicated centrally by a panel as parenchymal hematoma type 2 within 36 hours after treatment, combined with an increase from baseline in the NIHSS score of at least 4 points.[15] All these assessments were performed by personnel who were unaware of the treatment assignment. An angiogram was obtained at the conclusion of the thrombectomy procedure and graded centrally to gauge angiographic revascularization and embolization into previously unaffected territories. Details of the adverse-event definitions and angiographic criteria are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

A blinded adaptive sample-size reestimation[16] was performed after 100 patients had been enrolled.[12] This reestimation determined a final sample size of 202 patients for the determination of noninferiority. Sequential testing of superiority after testing of noninferiority was planned for the intention-to-treat and per-protocol analyses, but no patients were excluded from the per-protocol analysis of the primary outcome and only one set of analyses is presented.

The noninferiority boundary for the current trial was based on a meta-analysis of the EXTEND-IA (Extending the Time for Thrombolysis in Emergency Neurological Deficits — Intra-Arterial),[3] SWIFT PRIME (Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment),[4] and ESCAPE (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times)[5] endovascular trials, in which 19 of 253 patients (7.5%; 95% confidence interval [CI], 4.6 to 11.5) who received alteplase had reperfusion at the initial angiographic assessment. The noninferiority boundary was defined to preserve at least 50% of the most conservative estimate of the reperfusion efficacy of alteplase from the meta-analysis (that estimate being 4.6%).[12] Noninferiority would be established if the lower boundary of the two-sided 95% confidence interval of the difference in the percentages of patients with substantial reperfusion at the initial angiographic assessment in the tenecteplase group versus the alteplase group was greater than –2.3 percentage points.

The two-sided 95% confidence interval of the incidence difference was estimated by generating incidence differences with corresponding 95% confidence intervals for each of the four strata of patients (those with occlusion of the internal carotid artery, basilar artery, the first segment of the middle cerebral artery, or the second segment of the middle cerebral artery) with subsequent pooling across strata with the use of the Mantel–Haenszel method. If noninferiority was established, superiority of tenecteplase was tested with the use of binary logistic regression, with adjustment for the site of vessel occlusion. Incidence ratios were estimated with the use of modified Poisson regression with robust error estimation,[17] with adjustment for the site of vessel occlusion.

The analysis of the secondary outcome of the modified Rankin scale score was performed with the use of ordinal logistic regression if proportional-odds assumptions were satisfied or, otherwise, with the use of assumption-free ordinal analysis on the full range (0 to 6) of the modified Rankin scale.[18,19] The proportions of patients with a modified Rankin scale score of 0 or 1 (or no change from baseline in patients with a preexisting modified Rankin scale score of 2 or 3) and with a score of 0 to 2 (or no change from baseline in patients with a preexisting modified Rankin scale score of 3) were to be compared between the tenecteplase group and the alteplase group of the trial, with adjustment for age and baseline NIHSS score with the use of a logistic-regression model. The proportions of patients with early neurologic improvement were compared between the two groups, with adjustment for age and baseline NIHSS score, with the use of logistic regression. The differences in the distributions of the NIHSS scores between the tenecteplase group and the alteplase group at 24 hours and at 72 hours were analyzed with the use of Wilcoxon–Mann–Whitney generalized odds ratios, with stratification according to baseline NIHSS score.[18]

RESULTS

CHARACTERISTICS OF THE PATIENTS

From March 2015 through October 2017, we enrolled 204 patients at 12 centers in Australia and at 1 center in New Zealand. A total of 101 patients were assigned to receive tenecteplase, 101 were assigned to receive alteplase, and 2 were excluded owing to withdrawal of consent (1 patient) and to withdrawal by the enrolling physician before treatment was commenced because of an error in assessing patient eligibility (1 patient) (Fig. S1 in the Supplementary Appendix). The characteristics of the patients at baseline are listed in Table 1, and in Table S1 in the Supplementary Appendix. There were no significant differences between the two groups at baseline. In 6 patients, the primary outcome was assessed with the use of CT perfusion imaging only.

OUTCOMES

Reperfusion of greater than 50% of the involved territory or an absence of retrievable thrombus at the time of the initial angiographic assessment was observed in 22 patients (22%) who received tenecteplase, as compared with 10 (10%) who received alteplase (incidence difference, 12 percentage points [95% CI, 2 to 21, not crossing the noninferiority margin of –2.3 percentage points; P=0.002 for noninferiority]; adjusted incidence ratio, 2.2 [95% CI, 1.1 to 4.4; P=0.03 for superiority]; and adjusted odds ratio, 2.6 [95% CI, 1.1 to 5.9; P=0.02 for superiority]) (Table 2). Thrombectomy was not performed in patients who met the primary outcome of reperfusion at the initial angiographic assessment, with the exception of 1 patient in the tenecteplase group who had substantial reperfusion but residual thrombus that was treated with thrombectomy. Of the patients with reperfusion at the initial angiographic assessment, 20 of 22 patients in the tenecteplase group and 6 of 10 in the alteplase group had initial occlusion of the middle cerebral artery. Procedural characteristics and the incidence of reperfusion according to the site of vessel occlusion are shown in Table S2 in the Supplementary Appendix.

In patients who were transferred to another hospital, the delay between thrombolysis and arterial puncture did not differ significantly between the tenecteplase group and the alteplase group (median, 65 minutes [interquartile range, 54 to 80] and 75 minutes [interquartile range, 60 to 81], respectively; P=0.18). Among patients who were treated on-site, the delay did not differ significantly between the tenecteplase group and the alteplase group (median, 32 minutes [interquartile range, 21 to 50] and 37 minutes [interquartile range, 27 to 50], respectively; P=0.44).

Table 1. Characteristics of the 202 Patients at Baseline.*

Characteristic	Tenecteplase Group (N=101)	Alteplase Group (N=101)
Age — yr	70.4±15.1	71.9±13.7
Male sex — no. (%)	58 (57)	52 (51)
Median NIHSS score (IQR)†	17 (12–22)	17 (12–22)
Cause of stroke — no. (%)		
Cardioembolic occlusion	46 (46)	54 (53)
Large-artery occlusion	21 (21)	18 (18)
Undetermined or other	34 (34)	29 (29)
Median time from stroke onset to hospital arrival (IQR) — min	60 (44–89)	72 (53–104)
Median time from stroke onset to initiation of intravenous thrombolysis (IQR) — min	125 (102–156)	134 (104–176)
Median time from initiation of intravenous thrombolysis to arterial puncture (IQR) — min	43 (25–57)	42 (30–63)
Median time from initiation of intravenous thrombolysis to initial angiographic assessment (IQR) — min	54 (34–67)	56 (40–77)
Interhospital transfer for thrombectomy — no. (%)	27 (27)	23 (23)
Site of vessel occlusion — no. (%)		
Internal carotid artery	24 (24)	24 (24)
Basilar artery	3 (3)	3 (3)
Middle cerebral artery		
First segment	59 (58)	60 (59)
Second segment	15 (15)	14 (14)
Median volume at initial imaging (IQR) — ml‡		
Ischemic core	14 (0–33)	11 (0–24)
Perfusion lesion	145 (105–175)	134 (103–170)

* Plus–minus values are means ±SD. There were no significant differences between the two groups. Percentages may not total 100 because of rounding. IQR denotes interquartile range.

† Scores on the National Institutes of Health Stroke Scale (NIHSS), a standardized neurologic examination, range from 0 (normal function) to 42 (death), with lower scores indicating less severe stroke.

‡ Values for the ischemic-core volume were calculated with the use of a threshold of relative cerebral blood volume less than 30% of that in normal brain. The perfusion lesion was defined as the volume of brain with a time to maximum perfusion of more than 6 seconds. CT perfusion imaging was performed, but the requirement for mismatch and an ischemic-core volume of less than 70 ml was removed in a protocol amendment when approximately 80 patients were enrolled.

In an ordinal analysis of the modified Rankin scale score at 90 days, patients in the tenecteplase group had a median score of 2 (interquartile range, 0 to 3), which indicated significantly better function than the median score of 3 (interquartile range, 1 to 5) among patients in the alteplase group (common odds ratio, 1.7; 95% CI, 1.0 to 2.8; P=0.04) (Fig. 1). There was no significant difference in the incidence of recovery to independent function (modified Rankin scale score of 0 to 2 or no change from baseline function) at day 90, which occurred in 65 of 101 patients (64%) in the tenecteplase group and in 52 of 101 (51%) in the alteplase group (adjusted incidence ratio, 1.2; 95% CI, 1.0 to 1.5; P=0.06; adjusted odds ratio, 1.8; 95% CI, 1.0 to 3.4; P=0.06).

There were also no significant differences in the incidence of early neurologic improvement at 72 hours (Table 2). The median NIHSS score at 24 hours was 3 (interquartile range, 1 to 12) among patients in the tenecteplase group and 6 (interquartile range, 2 to 14) among those in the alteplase group (odds ratio, 1.4; 95% CI, 1.0 to

Table 2. Outcomes.

Outcome	Tenecteplase Group (N=101)	Alteplase Group (N=101)	Effect Size (95% CI)	P Value
Primary efficacy outcome				
Substantial reperfusion at initial angiographic assessment — no. (%)*	22 (22)	10 (10)		
Difference — percentage points			12 (2–21)	0.002
Adjusted incidence ratio			2.2 (1.1–4.4)	0.03
Adjusted odds ratio			2.6 (1.1–5.9)	0.02
Secondary outcomes				
Score on the modified Rankin scale at 90 days†				
Median score (IQR) on ordinal analysis‡	2 (0–3)	3 (1–4)	1.7 (1.0–2.8)	0.04
Functionally independent outcome — no. (%)§	65 (64)	52 (51)		
Adjusted incidence ratio			1.2 (1.0–1.5)	0.06
Adjusted odds ratio			1.8 (1.0–3.4)	0.06
Excellent outcome — no. (%)§	52 (51)	43 (43)		
Adjusted incidence ratio			1.2 (0.9–1.6)	0.20
Adjusted odds ratio			1.4 (0.8–2.6)	0.23
Early neurologic improvement — no. (%)§¶	72 (71)	69 (68)		
Adjusted incidence ratio			1.0 (0.9–1.2)	0.70
Adjusted odds ratio			1.1 (0.6–2.1)	0.70
Safety outcomes				
Death — no. (%)§	10 (10)	18 (18)		
Adjusted risk ratio			0.5 (0.3–1.0)	0.049
Adjusted odds ratio			0.4 (0.2–1.1)	0.08
Symptomatic intracerebral hemorrhage — no. (%)§‖	1 (1)	1 (1)		
Risk ratio			1.0 (0.1–15.9)	0.99
Odds ratio			1.0 (0.1–16.2)	0.99
Parenchymal hematoma — no. (%)§**	6 (6)	5 (5)		
Risk ratio			1.2 (0.4–3.8)	0.76
Odds ratio			1.2 (0.4–4.1)	0.76

* Substantial reperfusion was defined as the restoration of blood flow to greater than 50% of the involved territory or no retrievable thrombus at the time of the initial angiographic assessment. The analysis was adjusted for the site-of-vessel-occlusion strata. The P value for the difference is for noninferiority, and the P values for the incidence ratio and odds ratio are for superiority.

† Scores on the modified Rankin scale range from 0 (no neurologic deficit) to 6 (death). A functionally independent outcome was defined as a modified Rankin scale score of 0 to 2 or no change from baseline. An excellent outcome was defined as a modified Rankin scale score of 0 or 1 or no change from baseline.

‡ The analysis was adjusted for the NIHSS score and age at baseline. The effect size was assessed with a common odds ratio from ordinal logistic regression.

§ The analysis was adjusted for the NIHSS score and age at baseline. The effect size was assessed as an incidence or risk ratio from Poisson regression and as an odds ratio from logistic regression.

¶ Early neurologic improvement was defined as a reduction of 8 points in the NIHSS score between baseline and 72 hours or as a score of 0 or 1 at 72 hours. An 8-point reduction is considered to be highly clinically significant.

‖ Symptomatic intracerebral hemorrhage was defined as a large parenchymal hematoma (blood clot occupying >30% of the infarct volume with mass effect) and an increase of 4 points or more in the NIHSS score.

** Parenchymal hematoma was defined as intraparenchymal blood clot with mass effect.

1.9; P=0.06 with adjustment for baseline NIHSS score). At 72 hours, the median NIHSS score was 2 (interquartile range, 0 to 10) among patients in the tenecteplase group and 3 (interquartile range, 1 to 13) among those in the alteplase group (odds ratio, 1.4; 95% CI, 1.0 to 1.9; P=0.053, with adjustment for baseline NIHSS score) (Fig. 2).

SAFETY

Symptomatic intracerebral hemorrhage occurred in two patients. One patient in the tenecteplase group, who also received intravenous heparin during carotid endarterectomy, had symptomatic intracerebral hemorrhage. Symptomatic intracerebral hemorrhage also occurred in one patient in the alteplase group; thrombectomy had not been performed in this patient because of reperfusion before the initial angiographic assessment, but parenchymal hematoma contralateral to the infarction developed, resulting in death.

There were 10 deaths in the tenecteplase group and 18 in the alteplase group, but the difference was not significant in the prespecified logistic-regression analysis (Table 2). A list of adverse events, including causes of death, and a list of serious adverse events are provided in Tables S3 and S4, respectively, in the Supplementary Appendix.

DISCUSSION

Among patients with acute ischemic stroke from major cerebral vessel occlusion within 4.5 hours after the onset of symptoms, intravenous tenecteplase resulted in a higher incidence of reperfusion of the occluded vascular territory before endovascular thrombectomy than did intravenous alteplase. We expected the effect on the clinical outcome of endovascular thrombectomy to obscure any potential difference between tenecteplase and alteplase and therefore chose the technical efficacy of substantial reperfusion for the primary outcome. The trial was powered for noninferiority, not for superiority, and the significance of superiority for the primary outcome of reperfusion was therefore less robust. Patients in the tenecteplase group had significantly better functional outcomes than those in the alteplase group in an ordinal analysis of the modified Rankin scale scores but not according to

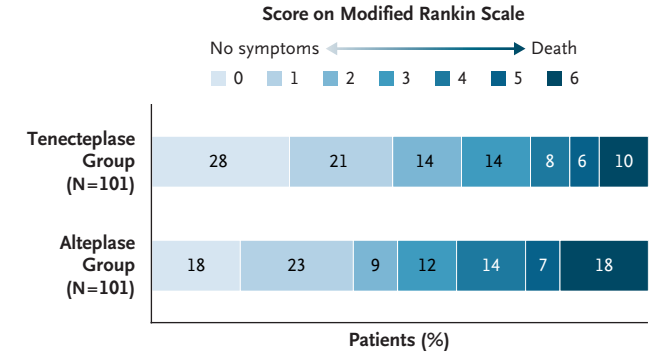

Figure 1. Modified Rankin Scale Scores at 90 Days in the Intention-to-Treat Population.

Shown are the results of the ordinal analysis of the modified Rankin scale scores at 90 days. 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. Patients in the tenecteplase group had a median score of 2, as compared with a median score of 3 among patients in the alteplase group (common odds ratio, 1.7; 95% CI, 1.0 to 2.8; P=0.04). Percentages may not total 100 because of rounding.

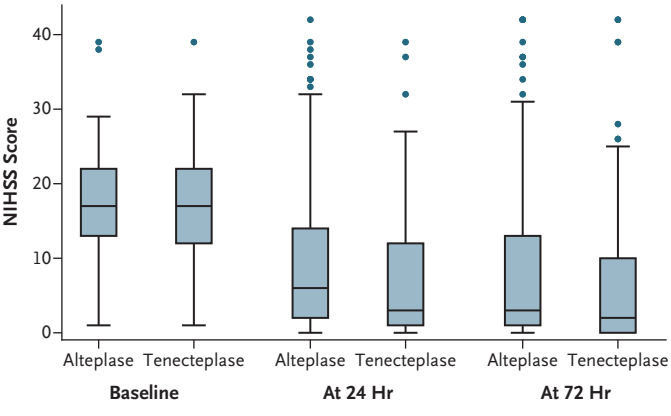

Figure 2. Distribution of National Institutes of Health Stroke Scale (NIHSS) Scores at Baseline, 24 Hours, and 72 Hours.

Scores on the NIHSS, a standardized neurologic examination, range from 0 (normal function) to 42 (death), with lower scores indicating less severe stroke. The horizontal line in each box represents the median, and the top and bottom of the boxes the interquartile range. I bars indicate 1.5 times the interquartile range, and the dots outliers. Differences in early neurologic improvement (defined as a reduction of 8 points in the NIHSS score between baseline and 72 hours or as a score of 0 or 1 at 72 hours) between the tenecteplase group and the alteplase group were not significant.

the proportion of patients who were left with minimal or no deficit or to the proportion of patients with early clinical improvement of their stroke deficit. There was no significant difference in the incidence of symptomatic or asymptomatic cerebral hemorrhage.

Most patients who are treated with intravenous thrombolysis do not have reperfusion of the occluded vessel before thrombectomy. The incidence of reperfusion of 10% that was observed with alteplase in the present trial was similar to the incidence of 11% that was observed in the EXTEND-IA trial of endovascular thrombectomy, which included patients with a distribution of vessel occlusions that is similar to the distribution in the present trial.[3] These two trials enrolled patients at the initial treating hospital, in contrast to most other thrombectomy trials, which enrolled patients after transfer to a center that performs endovascular thrombectomy.[2] Enrollment at the initial hospital ensures the capture of data regarding a potential early response to thrombolysis in patients who otherwise might have been excluded if recruitment had been delayed by interhospital transfer. The higher incidence of early reperfusion that was observed with tenecteplase than with alteplase occurred predominantly among patients with occlusion of the middle cerebral artery.

The median time from the commencement of thrombolysis to arterial puncture in this trial was 46 minutes and did not differ between the treatment groups. Although tenecteplase was associated with a numerically shorter delay than alteplase between the commencement of thrombolysis and arterial puncture of approximately 10 minutes in patients who were transferred and approximately 5 minutes in patients who were treated on site, the between-group differences were not significant.

However, the ability to administer tenecteplase in a single bolus, as compared with the 1-hour infusion of alteplase, may be of practical benefit in patients with stroke with large-vessel occlusion who are transported between, as well as within, hospitals to access endovascular thrombectomy, but this was not formally assessed in this trial. In some systems, transport cannot occur until the infusion of alteplase is complete.

Given the relationship of functional outcome to the time between the onset of stroke symptoms and reperfusion,[20,21] earlier reperfusion by means of thrombolysis in an additional 12% of patients treated with tenecteplase, as compared with alteplase, may have contributed to improved outcomes. However, other mechanisms, including the dissolution of residual thrombus after thrombectomy, may have played a role. Functional outcomes in the alteplase group in our trial were less favorable than those in the EXTEND-IA trial.[3] However, we enrolled a broader group of patients, including patients with a preexisting modified Rankin scale score of 3, who were excluded from the EXTEND-IA trial. Our trial required that the ischemic-core volume be less than 70 ml only for approximately the first 80 patients, which led to the enrollment of patients with larger infarcts than in previous trials. These negative prognostic factors would have been expected to lead to fewer patients with an outcome of a modified Rankin scale score of 0 to 2 than were seen in the EXTEND-IA trial.[3]

A limitation of the trial is that the results apply to patients with ischemic stroke and large-vessel occlusion who are eligible for thrombolysis. These patients represent approximately 13% of all patients with ischemic stroke,[22] although this group contributes disproportionately to the disability burden from ischemic stroke.[23] A phase 3 trial comparing tenecteplase with alteplase in patients in whom endovascular thrombectomy is not planned, with a primary outcome of functional recovery, is ongoing (Tenecteplase versus Alteplase for Stroke Thrombolysis Evaluation [TASTE]; Australian New Zealand Clinical Trials Registry number, ACTRN12613000243718). The results of the present trial are consistent with those of a meta-analysis of previous trials showing a higher incidence of recanalization with tenecteplase than with alteplase among patients with stroke and arterial occlusion.[24]

We chose a dose of tenecteplase of 0.25 mg per kilogram on the basis of previous data that showed better outcomes with this dose than with a dose of 0.1 mg per kilogram.[8] During the recruitment phase of EXTEND-IA TNK, the results of the Norwegian tenecteplase stroke trial (NOR-TEST), in which tenecteplase (at a dose of 0.4 mg per kilogram) was compared with alteplase, were reported.[10] Contrary to results in a previous dose-finding trial,[25] this higher dose was not associated with an increased incidence of symptomatic intracerebral hemorrhage. The use of the dose of 0.4 mg per kilogram in pa-

tients with large-vessel occlusion may be beneficial, given the large clot burden, and this dose is being studied in a trial (EXTEND-IA TNK Part 2; ClinicalTrials.gov number, NCT03340493).

In conclusion, tenecteplase, which can be administered more rapidly than alteplase before thrombectomy in patients with ischemic stroke, was noninferior to alteplase in restoring perfusion in the territory of a proximal cerebral-artery occlusion. Overall functional outcome was better with tenecteplase than with alteplase in the ordinal analysis of the modified Rankin scale scores, but the incidence of recovery to independent function did not differ significantly. There was no significant difference in the incidence of cerebral hemorrhage.

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APPENDIX

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