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ORIGINAL RESEARCH

Tenecteplase, 0.4 mg/kg, in Moderate and Severe Acute Ischemic Stroke: A Pooled Analysis of NOR-TEST and NOR-TEST 2A

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BACKGROUND: The optimal dose of tenecteplase in acute ischemic stroke remains to be defined. We present a pooled analysis of the 2 NOR-TESTs (Norwegian Tenecteplase Stroke Trials) exploring the efficacy and safety of tenecteplase, 0.4 mg/kg.

METHODS AND RESULTS: We retrospectively reviewed 2 PROBE (Prospective Randomized Open, Blinded End-point) trials, NOR-TEST and NOR-TEST 2A. Patients were randomized to either tenecteplase, 0.4 mg/kg, or alteplase, 0.9 mg/kg. The primary end point was favorable functional outcome at 3 months (modified Rankin Scale score, 0–1) or return to baseline if prestroke modified Rankin Scale score was 2. Secondary end points included favorable functional and clinical outcome and safety data. The pooled analysis includes patients with National Institutes of Health Stroke Scale score ≥6 from both trials and an additional post hoc analysis of patients with National Institutes of Health Stroke Scale score ≤5 from NOR-TEST. The per-protocol analysis contains 483 patients, of whom 235 were assigned to tenecteplase and 248 were assigned to alteplase. In per-protocol analysis, functional outcome was better in the alteplase arm with cutoff modified Rankin Scale score of 2 (odds ratio [OR], 0.52 [95% CI, 0.33–0.80]; *P*=0.003) and expressed by ordinal shift analysis (OR, 1.64 [95% CI, 1.17–2.28]; *P*=0.004). Mortality at 3 months was higher in the tenecteplase arm (OR, 2.48 [95% CI, 1.20–5.10]; *P*=0.01). Mortality and intracranial hemorrhage rates were higher in the severe stroke group randomized to tenecteplase, whereas these rates were similar for alteplase and tenecteplase in moderate and mild stroke.

CONCLUSIONS: Tenecteplase, 0.4 mg/kg, is unsafe in moderate and severe stroke, and the risk of death and intracranial hemorrhage probably increases with stroke severity. A lower tenecteplase dose should be tested in future trials.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifiers: NCT01949948, NCT03854500.

Key Words: clinical trial ■ ischemic stroke ■ tenecteplase ■ thrombolytic therapy ■ tissue plasminogen activator

Alteplase is beneficial in patients with acute ischemic stroke (AIS) in all age groups.[1,2] Tenecteplase is preferable compared with alteplase in several aspects.[3,4] Besides better biochemical features, including longer half-life and higher fibrin specificity, the single-bolus administration makes tenecteplase attractive in the acute setting, especially with the *drip-and-ship* strategy for patients with large-vessel occlusions in need of transport for mechanical thrombectomy.

In recent years, there have been increasing research activities aiming to replace alteplase with tenecteplase for AIS. Several phase 2 trials comparing tenecteplase with alteplase, with varying inclusion criteria and tenecteplase doses, have been performed.

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CLINICAL PERSPECTIVE

What Is New?

- This pooled analysis with a substantial database strengthens the conclusion of the 2 trials, NOR-TEST (Norwegian Tenecteplase Stroke Trial) and NOR-TEST 2A.
- Tenecteplase, 0.4 mg/kg, has a worse safety profile than standard-dose alteplase in acute ischemic stroke within 4.5 hours after stroke onset.

What Are the Clinical Implications?

- The implication of the pooled analysis is that tenecteplase dose, 0.4 mg/kg, should not be used in any clinical setting of acute ischemic stroke.
- The future dose should be lower, presumably the advocated 0.25 mg/kg.

The trials have in most cases shown similar efficacy and safety profile of the 2 thrombolytics, but data on the optimal dose have been inconclusive and based on small sample sizes or highly selected patients.[5–11] Accumulated clinical trials indicated that tenecteplase may be preferable compared with alteplase in the treatment of AIS.[12] However, the optimal dose has become a key question. NOR-TEST (Norwegian Tenecteplase Stroke Trial) was the first phase 3 trial comparing tenecteplase, 0.4 mg/kg, with standard alteplase, 0.9 mg/kg.[13] The cohort contained an unproportionally high number of patients with mild AIS and stroke mimics. The results were therefore difficult to apply to the general stroke population but encouraged continued research.[14] A subanalysis of patients with moderate and severe AIS in NOR-TEST showed similar rates of favorable outcome and symptomatic intracranial hemorrhage (sICH) in both treatment arms, although the mortality rate at 3 months was higher in severe AIS.[15] On the basis of these data, closer monitoring of safety parameters in subsequent trials testing tenecteplase, 0.4 mg/kg, was recommended. NOR-TEST 2A was designed to clarify noninferiority of tenecteplase in patients with moderate and severe AIS using the 0.4 mg/kg dose. The trial was, however, prematurely terminated when a per-protocol safety analysis of the first 200 patients showed worse safety and functional outcomes in patients treated with tenecteplase, 0.4 mg/kg, compared with those treated with alteplase, 0.9 mg/kg.[16] We therefore performed a pooled analysis of both NOR-TEST trials, to illuminate efficacy and safety of tenecteplase, 0.4 mg/kg, based on a larger cohort of patients.

METHODS

Anonymized data supporting our findings in the presented article may be provided by Vojtech Novotny or Christopher Elnan Kvistad on reasonable request.

Design and Subjects

NOR-TEST (NCT01949948) and NOR-TEST 2A (NCT03854500) were multicenter, phase 3, randomized, open-label, blinded end point trials.[13,16] NOR-TEST was performed at 13 sites, and NOR-TEST 2A was performed at 11 sites. Patients were enrolled into NOR-TEST from September 1, 2012, until September 30, 2016, and patients were enrolled in NOR-TEST 2A from October 28, 2019, until September 26, 2021.

The 2 trials contain altogether 1323 patients, 1107 patients from NOR-TEST (83.7%) and 216 patients from NOR-TEST 2A (16.3%). For the intention-to-treat (ITT) analysis, 19 patients were excluded either because of withdrawal of informed consent after inclusion or reconsideration of eligibility before medication administration, resulting in a final number of 1304 patients (1100 from NOR-TEST and 204 from NOR-TEST 2). The randomization allocated 649 patients to tenecteplase (49.8%) and 655 patients to alteplase (50.2%). The ITT analysis includes all patients included in the trials regardless of their final diagnosis. The per-protocol (PP) analysis excludes all patients not matching the inclusion criteria (ie, patients with other diagnosis than ischemic stroke, preadmission modified Rankin Scale score ≥3, and admission National Institutes of Health Stroke Scale (NIHSS) score <6, and patients with missing primary outcome data for the final analysis).

The inclusion criteria in the 2 trials differed in terms of NIHSS score on admission. NOR-TEST included all eligible patients with suspected AIS and a neurologic deficit measurable by NIHSS, whereas NOR-TEST 2A included only patients with NIHSS score ≥6 on admission. Otherwise, the inclusion criteria were identical. Patients, aged ≥18 years, with modified Rankin Scale (mRS) score 0 to 2 before the admission and who were admitted within 4.5 hours from stroke onset were eligible for study inclusion. Patients with wake-up stroke or unknown time of stroke onset were considered eligible for study inclusion when diffusion-weighted imaging–fluid-attenuated inversion recovery mismatch was found on admission magnetic resonance imaging. Patients receiving bridging thrombolytic therapy before endovascular treatment were eligible for inclusion. Patients were randomized 1:1 to either 0.4 mg/kg single-bolus tenecteplase (maximum dose of 40 mg) or to standard alteplase dose of 0.9 mg/kg (10% bolus and 90% infusion over 60 minutes with maximum dose of 90 mg). The treating staff in the emergency department was not blinded to treatment randomization, but health personnel in the stroke unit and at follow-up were.

Patients were unaware which drug they had received. Further details about randomization and procedures have been published.[16,17]

The pooling project includes a pooled analysis of patients with moderate (NIHSS score 6–14) or severe (NIHSS score ≥15) AIS from NOR-TEST and NOR-TEST 2A, and an additional post hoc analysis of patients with mild AIS (NIHSS score ≤5) from NOR-TEST.

Outcomes

The primary end point was favorable functional outcome at 3 months, defined as mRS score 0 to 1 or return to baseline if prestroke mRS score was 2. The secondary end points were favorable functional outcome at 3 months, defined as mRS score 0 to 2; major neurologic improvement at 24 hours, measured by NIHSS; any intracranial hemorrhage (ICH) and sICH occurring within 24 to 48 hours after symptom onset; (favorable) ordinal shift analysis of mRS at 3 months; and mortality within 3 months. Any ICH was defined as any hemorrhagic transformations or parenchymal hematoma, according to ECASS (European Cooperative Acute Stroke Study) I criteria.[18] ICH morphology was described according to ECASS I criteria.[19] sICH was defined according to ECASS III criteria.[20] Major neurologic improvement was defined as either NIHSS score of 0 at 24 hours or a reduction in NIHSS score of at least 4 points at 24 hours compared with baseline. In this post hoc analysis, we stratified the cohort into 3 age groups (ie, ≤60, 60–80, and ≥80 years) and 3 stroke severity groups (ie, mild, moderate, and severe).

Statistical Analysis

Primary and secondary end points were essentially identical for both trials and were examined by ITT and PP analysis. PP analysis is presented as the primary point of interest, and ITT analysis is included to provide a full scale of data. The end points were adjusted for age, pretreatment NIHSS score, premorbid mRS score, time from onset to intravenous thrombolysis, endovascular treatment (EVT), and source trial. For the demographics, the continuous variables were tested by *t* test in case of normally distributed data and by Mann-Whitney *U*-test in case of uneven distribution. Variations were expressed by SD or interquartile range, respectively. The categorical variables were tested by Pearson χ^2 test. For the final analyses, a logistic regression analysis expressed by odds ratio (OR) was used. The significance of *P* value was set to <0.05. The primary and secondary outcomes are illustrated using appropriate histograms. An additional post hoc analysis of patients with mild stroke from NOR-TEST was included in the graphics to better illustrate an overall difference between the stroke severity groups.

The study was approved by the regional Committee for Medical and Health Research Ethics and the Norwegian Medicines Agency. Written informed consent was obtained from study participants or their legal representatives in both trials. The funding company had no role in study design, data analysis, interpretation, or writing of the article.

RESULTS

In the pooled analysis of patients with moderate or severe stroke, the ITT population contained 597 patients, of whom 287 (48.1%) were assigned to tenecteplase and 310 (51.9%) were assigned to alteplase. The exclusion scheme for the PP analysis followed the criteria of the original trials. The following patients were excluded for the PP analysis: 60 (10%) patients diagnosed as having stroke mimic, 36 (6%) patients with prestroke mRS score ≥3, 17 (3%) patients with missing end point data at 3 months, and 1 patient having NIHSS score <6. The final PP population included 483 patients, of whom 235 (48.7%) were assigned to tenecteplase and 248 (51.3%) were assigned to alteplase (Figure S1). The demographics between the 2 treatment arms in the PP analysis were similar, except for a higher occurrence of prestroke myocardial infarction in the alteplase arm (Table 1). Similar pattern applies for the demographics in the ITT analysis (Table S1).

The PP analysis showed in the alteplase arm a better functional outcome at 3 months expressed by ordinal shift analysis (OR, 1.64 [95% CI, 1.17–2.28]; *P*=0.004) and by mRS cutoff 0 to 2 (OR, 0.52 [95% CI, 0.33–0.80]; *P*=0.003). There was a higher rate of any ICH (OR, 1.66 [95% CI, 0.97–2.82]; *P*=0.06) and sICH (OR, 2.39 [95% CI, 0.79–7.24]; *P*=0.12) in the tenecteplase arm, but none of these reached statistical significance. Mortality was significantly higher in the tenecteplase arm (OR, 2.48 [95% CI, 1.20–5.10]; *P*=0.01) (Table 2 and Figure 1).

When stratified by age, patients 60 aged to 80 years in the tenecteplase arm showed more any ICH and sICH (22.1% versus 9% and 8.2% versus 1.5%, respectively) and a higher mortality rate (9.8% versus 3.7%), whereas favorable functional outcome was more common in the alteplase arm (56.1% versus 40.2%). There was no difference for ICH rates or functional outcome in the age groups <60 and >80 years (Figure 2).

When stratified by stroke severity, favorable outcome was similar in both treatment arms, but mortality in patients with severe stroke was higher in the tenecteplase arm (27.3% versus 8.3%). Both any ICH (31.8% versus 15.3%) and sICH (9.1% versus 1.4%) were more common in patients with severe stroke treated with tenecteplase. Patients with mild and moderate stroke

Table 1. Demographics and Characteristics in the Per-Protocol Analysis

Variable	Tenecteplase (N=235)	Alteplase (N=248)
Age, y		
Mean (SD)	70.8 (13.9)	70.5 (13.8)
Median (IQR)	73 (62–81)	73 (62–80)
Weight, kg		
Mean (SD)	77.8 (15.2)	78.95 (14.5)
Median (IQR)	76 (68–87)	80 (70–88.5)
Age groups, y, N (%)		
<60	52 (22.1)	53 (21.4)
60–80	122 (51.9)	134 (54.0)
>80	61 (26.0)	61 (24.6)
Sex, N (%)		
Women	105 (44.7)	105 (42.3)
Men	130 (55.3)	143 (57.7)
Unknown time of stroke symptom onset, N (%)	19 (8.1)	13 (5.3)
Major arterial vessel occlusion, N (%)	97 (41.3)	113 (45.6)
Endovascular treatment, N (%)	45 (19.2)	59 (23.8)
Final diagnosis, N (%)		
Ischemic stroke	220 (93.6)	233 (93.95)
Transitory ischemic attack	14 (5.96)	13 (5.24)
Stroke mimics	0 (0)	0 (0)
Stroke risk factors, N (%)		
Hypertension	120 (51.1)	128 (51.6)
Atrial fibrillation	27 (11.5)	36 (14.5)
Diabetes	29 (12.3)	31 (12.5)
Hypercholesterolemia	49 (20.9)	50 (20.2)
Smoker	54 (22.98)	57 (22.98)
Cardiovascular history, N (%)		
Prior ischemic stroke	37 (15.7)	35 (14.1)
Prior myocardial infarction	23 (9.8)	42 (16.94)
Premorbid mRS score, N (%)		
0	176 (74.9)	196 (79.03)
1	41 (17.45)	36 (14.52)
2	18 (7.66)	16 (7.1)
≥3	…	…
NIHSS score on admission		
Mean (SD)	12.1 (6.5)	12.1 (5.8)
Median (IQR)	10 (7–15)	10 (8–15)
Moderate (6–14), N (%)	169 (71.91)	176 (70.97)
Severe (≥15), N (%)	66 (28.09)	72 (29.03)
TOAST classification, N (%)		
Large-vessel disease	69 (29.4)	59 (23.8)
Cardioembolism	69 (29.4)	83 (33.5)
Small-vessel disease	19 (8.1)	16 (6.5)
Other causes	12 (5.1)	16 (6.5)
Unknown or several causes	63 (26.8)	66 (26.6)
Time from onset to thrombolysis, median (IQR), min	100 (70–146)	94 (70–136)

IQR indicates interquartile range; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and TOAST, Trial of ORG 10172 in Acute Stroke Treatment.

had similar rates of any ICH and sICH regardless of the type of thrombolytic treatment (Figure 3).

Compared with the main analysis, there was no significant change in the primary or secondary outcomes after exclusion of patients with unknown stroke onset (Table S2). In the separate analysis of patients undergoing endovascular treatment, patients treated with alteplase achieved more often major neurologic improvement (OR, 0.34 [95% CI, 0.12–0.93]; *P*=0.035) and experienced less often any ICH (OR, 1.70 [95% CI, 1.7–14.65]; *P*=0.003) (Table S3).

In the pooled population with moderate and severe stroke, the ITT analysis showed a trend toward higher rates of any ICH and sICH in patients treated with tenecteplase (OR, 1.53 [95% CI, 0.99–2.66]; *P*=0.051 and OR, 2.51 [95% CI, 0.98–6.44]; *P*=0.054, respectively). In the alteplase arm, ordinal shift analysis of mRS at 3 months showed better functional outcome (OR, 1.18 [95% CI, 1.18–2.18]; *P*=0.002) as well as better functional outcome at 3 months using mRS cutoff 0 to 2 (OR, 0.50 [95% CI, 0.33–0.78]; *P*=0.002). Major neurologic improvement at 24 hours, expressed by NIHSS score, was more common in the alteplase arm (OR, 0.77 [95% CI, 0.49–0.99]; *P*=0.05). Mortality at 3 months was more common in the tenecteplase arm (OR, 2.42 [95% CI, 1.28–4.59]; *P*=0.007) (Table 3).

In the tenecteplase arm, the ITT analysis showed that death within 90 days occurred in 35 patients. Among 22 patients with severe stroke, 12 patients died of the initially large ischemic stroke and malignant edema; 2 of sICH; 1 of renal insufficiency and pneumonia; 1 of herpes encephalitis; and 6 of unknown cause in nursing homes. Among 13 patients with moderate stroke, 2 patients died of sICH; 1 of lung embolism; 1 of myocardial infarction; 1 of cardiac failure; 1 of fatal recurrent major ischemic stroke; and 7 of unknown cause in nursing homes.

In the alteplase arm, death within 90 days occurred in 21 patients. Among 9 patients with severe stroke, 2 patients died of sICH; 4 of the initially large ischemic stroke and malignant edema; 1 of pneumonia; and 2 of unknown cause in nursing homes. Among 12 patients with moderate stroke, 3 patients died of sICH; 1 of myocardial infarction and cardiac failure; 1 of pneumonia; and 7 of unknown cause in nursing homes.

DISCUSSION

The pooled data analysis of both NOR-TEST trials confirms the conclusion of NOR-TEST 2A, stating that tenecteplase, 0.4 mg/kg, is not safe in patients with moderate and severe AIS. The pooled analysis was performed mainly to reduce potential bias. The pooled analysis contains, in contrast to NOR-TEST, almost 50% fewer stroke mimics.[13] Furthermore, the primary

Table 2. Primary and Secondary End Points in the Per-Protocol Analysis

End point	Per-protocol analysis			
	Tenecteplase (N=235)	Alteplase (N=248)	OR (95% CI)	*P* value
Primary end point				
mRS score 0 to 1 at 3 mo, N (%)*	96 (40.9)	112 (45.2)	0.79 (0.53–1.19)	0.26
Secondary end points				
mRS score 0 to 2 at 3 mo, N (%)*	128 (54.5)	164 (66.1)	0.52 (0.33–0.80)	0.003
Major neurologic improvement at 24 h expressed by NIHSS, N (%)*	132 (58.9)	154 (64.4)	0.74 (0.50–1.11)	0.14
Ordinal shift analysis of mRS at 3 mo, N (%)*	…	…	1.64 (1.17–2.28)	0.004
Any ICH, N (%)*	42 (17.9)	30 (12.1)	1.66 (0.97–2.82)	0.06
HI1, N (%)	8 (3.4)	6 (2.4)		0.52
HI2, N (%)	11 (4.7)	8 (3.2)		0.41
PH1, N (%)	6 (2.6)	7 (2.8)		0.86
PH2, N (%)	8 (3.4)	6 (2.4)		0.52
PHr, N (%)	6 (2.6)	3 (1.2)		0.33
IVH, N (%)	1 (0.4)	0		0.49
Symptomatic ICH, N (%)*	11 (4.7)	5 (2.0)	2.39 (0.79–7.24)	0.12
mRS score 5 to 6 at 3 mo, N (%)*	31 (13.2)	23 (9.3)	1.59 (0.85–2.97)	0.15
Mortality at 3 mo, N (%)*	28 (11.9)	15 (6.1)	2.48 (1.20–5.10)	0.01

HI indicates hemorrhagic infarction; ICH, intracranial hemorrhage; IVH, intraventricular hemorrhage; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; PH, parenchymal hemorrhage; and PHr, remote PH.

*Adjusted for age, pretreatment NIHSS score, premorbid mRS score, time from onset to intravenous thrombolysis, endovascular treatment, and source trial.

and secondary end points in the pooled analysis were analyzed, as in NOR-TEST 2A, excluding patients with mild stroke.[16] Both patients with mild stroke and stroke mimics have a significantly better prognosis and lower occurrence of sICH compared with moderate and severe stroke, which statistically obscures the true safety profile of the tested thrombolytics.[21,22]

NOR-TEST 2A was designed with a firm power calculation. The premature termination of the trial with significantly fewer patients than planned might bring a bias into the interpretation. There was also an imbalance in terms of older age and higher occurrence of prestroke disabilities in patients receiving tenecteplase.[16] These imbalances have been partly compensated by merging the subjects from both trials, achieving better balanced demographics along with a larger and more homogeneous cohort, thus yielding a higher statistical power.

The mortality at 3 months was higher in the tenecteplase arm in both ITT and PP analyses, which corresponds to the result of NOR-TEST 2A. Moreover, both analyses favor alteplase in terms of favorable outcome at 3 months using mRS ordinal shift analysis as well as mRS cutoff point 0 to 2. After stratification based on NIHSS score, higher mortality was observed only

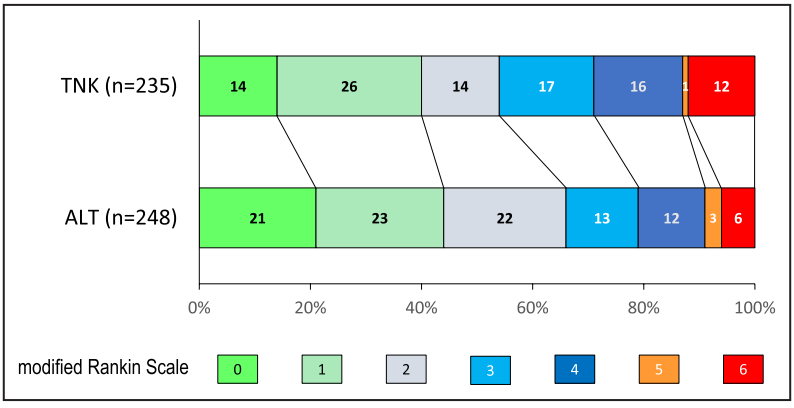

Figure 1. Distribution of modified Rankin Scale scores at 3 months in the per-protocol analysis.
ALT indicates alteplase; and TNK, tenecteplase.

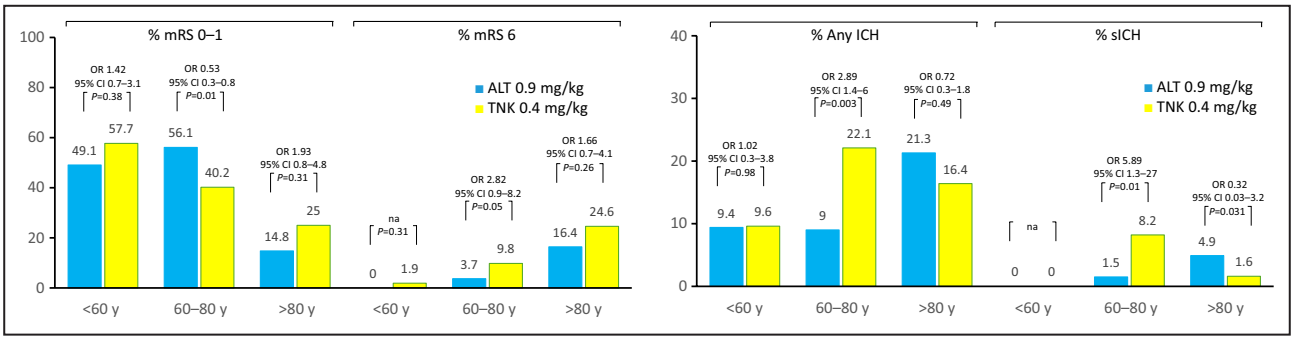

Figure 2. Distribution of outcome and hemorrhage based on age groups in the per-protocol analysis.
ALT indicates alteplase; ICH, intracranial hemorrhage; mRS, modified Rankin Scale; OR, odds ratio; sICH, symptomatic ICH; and TNK, tenecteplase.

in patients with severe stroke (Figure 3). A similar finding was observed in a previous subanalysis of NOR-TEST.[15] However, in NOR-TEST, the amount of any ICH and sICH was more balanced between the arms and sICH was the cause of death only in 1 patient treated with tenecteplase. The reason for the difference between the trials is not clear. We could not show that older age influences the safety of tenecteplase, 0.4 mg/kg (Figure 2). This corresponds to previous studies of alteplase in elderly individuals and to a previous subanalysis of NOR-TEST.[23,24] In the pooled analysis, any ICH and sICH were more common in the middle-aged group (Figure 2). This group's predominance in the trials gives statistically stronger results, and an overall negative safety profile of tenecteplase, 0.4 mg/kg, may be present independently of age. A by chance observation may, however, also explain the results, because the stratified cohorts, predominantly those aged ≤60 and ≥80 years, may be underpowered.

There was no significant change in primary and secondary outcome after exclusion of patients with unknown onset of stroke, indicating that these 2 populations may be similar for primary and secondary outcomes. Patients with unknown onset of stroke, however, represent a small portion; and it is therefore not possible to draw firm conclusions based on the results (Table S2).

Although there was a higher number of both any ICH and sICH in the tenecteplase arm, sICH was considered as direct cause of death only in 4 patients treated with tenecteplase and in 5 patients treated with alteplase. Many patients in the tenecteplase arm died as a consequence of an initial large ischemic stroke or malignant edema, but the cause of death was not attributed to tenecteplase as such.

The frequency of sICH was similar between the pooled analysis and the 0.4-mg/kg tenecteplase arm in EXTEND-IA TNK (Tenecteplase versus Alteplase before Endovascular Therapy for Ischemic Stroke) trial part 2.[25] However, these 2 studies are difficult to compare because only 20% of patients in the pooled analysis underwent EVT, and a high proportion of these patients had moderate stroke with lower NIHSS score on admission. Furthermore, the NOR-TEST trials contain some patients with large-vessel occlusion not undergoing EVT for various reasons (Table 1). One can

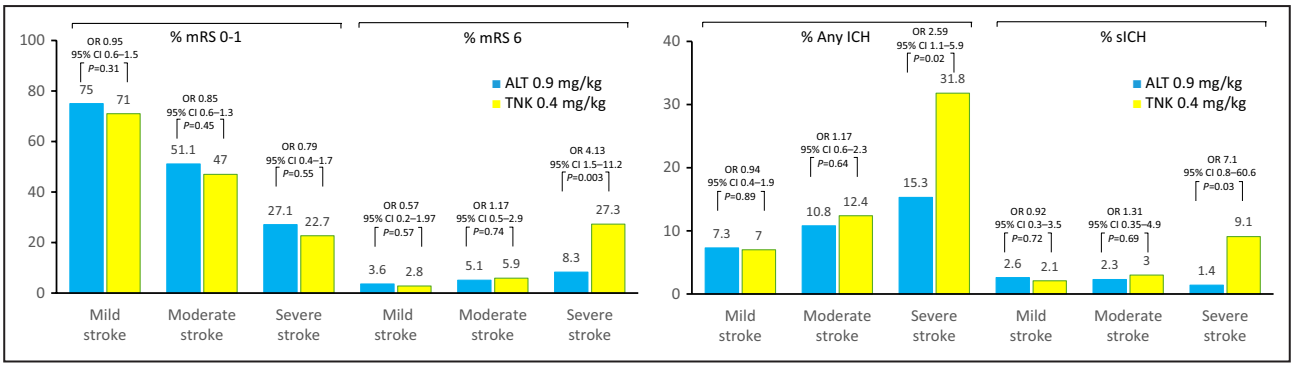

Figure 3. Distribution of outcome and hemorrhage based on severity of stroke on admission in the per-protocol analysis.
ALT indicates alteplase; ICH, intracranial hemorrhage; mild stroke, National Institutes of Health Stroke Scale (NIHSS) score ≤5; moderate stroke, NIHSS score 6 to 14; mRS, modified Rankin Scale; OR, odds ratio; severe stroke, NIHSS score ≥15; sICH, symptomatic ICH; and TNK, tenecteplase.

Table 3. Primary and Secondary End Points in the Intention-to-Treat Analysis

End point	Intention-to-treat analysis			
	Tenecteplase (N=287)	Alteplase (N=310)	OR (95% CI)	*P* value
Primary end point				
mRS score 0 to 1 at 3 mo, N (%)*	118 (42.9)	138 (45.9)	0.78 (0.53–1.15)	0.21
Secondary end points				
mRS score 0 to 2 at 3 mo, N (%)*	151 (54.9)	192 (63.8)	0.50 (0.33–0.78)	0.002
Major neurologic improvement at 24 h expressed by NIHSS, N (%)*	162 (59.1)	196 (65.3)	0.77 (0.49–0.99)	0.05
Ordinal shift analysis of mRS at 3 mo*	…	…	1.18 (1.18–2.18)	0.002
Any ICH, N (%)*	48 (16.7)*	36 (11.6)	1.53 (0.99–2.66)	0.05
HI1, N (%)	10 (3.5)	6 (1.9)		0.24
HI2, N (%)	11 (3.8)	9 (2.9)		0.53
PH1, N (%)	6 (2.1)	8 (2.6)		0.69
PH2, N (%)	9 (3.1)	7 (2.3)		0.51
PHr, N (%)	9 (3.1)	4 (1.3)		0.16
IVH, N (%)	1 (0.4)	0		0.48
Symptomatic ICH, N (%)*	15 (5.2)	7 (2.3)	2.51 (0.98–6.44)	0.054
mRS score 5 to 6 at 3 mo, N (%)*	39 (14.2)	30 (10.0)	1.49 (0.99–3.07)	0.06
Mortality at 3 mo, N (%)*	35 (12.7)	21 (7.0)	2.42 (1.28–4.59)	0.007

HI indicates hemorrhagic infarction; ICH, intracranial hemorrhage; IVH, intraventricular hemorrhage; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; PH, parenchymal hemorrhage; and PHr, remote PH.

*Adjusted for age, pretreatment NIHSS score, premorbid mRS score, time from onset to intravenous thrombolysis, endovascular treatment, and source trial.

hypothesize that patients with smaller clots not undergoing EVT may have delayed recanalization, increased blood-brain barrier damage, and thereby higher bleeding rates when treated with high-dose tenecteplase, 0.4 mg/kg. This higher bleeding rate might be comparable to the bleeding rate with EVT plus tenecteplase in patients with larger clots. In the NOR-TEST trials, patients undergoing EVT and receiving alteplase more often achieved major neurologic improvement and had a lower rate of any ICH (Table S3). There was, however, no significant difference in sICH and mortality between the arms. Interestingly, mortality was similar in patients undergoing EVT and receiving tenecteplase, 0.4 mg/kg, compared with the same treatment in EXTEND-IA TNK trial part 2 (17.8% versus 17%), whereas the occurrence of sICH was higher in the pooled analysis (8.9% versus 4.7%). The small population size in NOR-TEST may, however, make this result underpowered and thus uncertain.

The risk of sICH increases with stroke severity, but the treatment benefit of alteplase still outweighs the risk of adverse events independently of age.[26,27] Our findings emphasize that stroke severity plays a crucial role when it comes to safety of tenecteplase. In the pooled analysis, any ICH, sICH, and mortality at 90 days appeared to be more common in patients with severe stroke when treated with tenecteplase. Neither NOR-TEST 2A nor the pooled analysis could therefore prove that tenecteplase, 0.4 mg/kg, is noninferior to standard-dose alteplase for safety. On the basis of these results, we cannot recommend further trials testing the tenecteplase, 0.4 mg/kg, in AIS.

Patients with mild stroke or stroke mimics treated with alteplase have low occurrence of unfavorable outcome and ICH.[22,28] But although tenecteplase, 0.4 mg/kg, and standard dose-alteplase have similar safety profiles in these populations,[13,21] further testing of 0.4 mg/kg in these patients also does not seem justifiable.

The convenience of tenecteplase in clinical practice, and its pharmacologic superiority, makes tenecteplase a desirable thrombolytic drug in acute stroke therapy.[3] A lower tenecteplase dose may have a better safety profile but might also have lower efficacy. The ENCHANTED Study (Enhanced Control of Hypertension and Thrombolysis Stroke Study) did not show noninferiority of low-dose alteplase compared with standard-dose alteplase for death and disability at 90 days, but showed significantly fewer symptomatic intracerebral hemorrhages with low-dose alteplase.[29] However, in a general stroke population, the recently published alteplase compared to tenecteplase trial testing tenecteplase, 0.25 mg/kg, compared with standard-dose alteplase showed noninferiority in terms efficacy but a positive shift in the safety profile.[30] In patients with large-vessel occlusion treated with intravenous tenecteplase before EVT, the EXTEND-IA TNK part 2 trial suggests that tenecteplase, 0.40 mg/kg, does not confer an advantage over the 0.25-mg/kg dose.[25] Thus, tenecteplase. 0.25 mg/kg, seems to

be a reasonable alternative to alteplase for all patients presenting with AIS and meeting standard criteria for thrombolysis.

There are limitations of the presented study. The post hoc analysis may be misleading because of the different power estimates of the 2 trials and the non-randomized character of the study. The subgroup analyses included in the study, stratifying subjects by age and stroke severity, may be biased because of the smaller populations in each group. Type 1 error may lead to higher likelihood of by chance observation.

In conclusion, the pooled analysis of NOR-TEST and NOR-TEST 2A indicates a worse safety profile of tenecteplase, 0.4 mg/kg, compared with standard-dose alteplase in AIS within 4.5 hours after stroke onset, and predominantly so in patients with severe stroke.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S3
Figure S1

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