Stroke

CLINICAL TRIAL

Tenecteplase Treatment and Thrombus Characteristics Associated With Early Reperfusion: An EXTEND-IA TNK Trials Analysis

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BACKGROUND: Intracranial occlusion site, contrast permeability, and clot burden are thrombus characteristics that influence alteplase-associated reperfusion. In this study, we assessed the reperfusion efficacy of tenecteplase and alteplase in subgroups based on these characteristics in a pooled analysis of the EXTEND-IA TNK trial (Tenecteplase Versus Alteplase Before Endovascular Therapy for Ischemic Stroke).

METHODS: Patients with large vessel occlusion were randomized to treatment with tenecteplase (0.25 or 0.4 mg/kg) or alteplase before thrombectomy in hospitals across Australia and New Zealand (2015–2019). The primary outcome, early reperfusion, was defined as the absence of retrievable thrombus or >50% reperfusion on first-pass angiogram. We compared the effect of tenecteplase versus alteplase overall, and in subgroups, based on the following measured with computed tomography angiography: intracranial occlusion site, contrast permeability (measured via residual flow grades), and clot burden (measured via clot burden scores). We adjusted for covariates using mixed effects logistic regression models.

RESULTS: Tenecteplase was associated with higher odds of early reperfusion (75/369 [20%] versus alteplase: 9/96 [9%], adjusted odds ratio [aOR], 2.18 [95% CI, 1.03–4.63]). The difference between thrombolytics was notable in occlusions with low clot burden (tenecteplase: 66/261 [25%] versus alteplase: 5/67 [7%], aOR, 3.93 [95% CI, 1.50–10.33]) when compared to high clot burden lesions (tenecteplase: 9/108 [8%] versus alteplase: 4/29 [14%], aOR, 0.58 [95% CI, 0.16–2.06]; $P_{interaction}$=0.01). We did not observe an association between contrast permeability and tenecteplase treatment effect (permeability present: aOR, 2.83 [95% CI, 1.00–8.05] versus absent: aOR, 1.98 [95% CI, 0.65–6.03]; $P_{interaction}$=0.62). Tenecteplase treatment effect was superior with distal M1 or M2 occlusions (53/176 [30%] versus alteplase: 4/42 [10%], aOR, 3.73 [95% CI, 1.25–11.11]), but both thrombolytics had limited efficacy with internal carotid artery occlusions (tenecteplase 1/73 [1%] versus alteplase 1/19 [5%], aOR, 0.22 [95% CI, 0.01–3.83]; $P_{interaction}$=0.16).

CONCLUSIONS: Tenecteplase demonstrates superior early reperfusion versus alteplase in lesions with low clot burden. Reperfusion efficacy remains limited in internal carotid artery occlusions and lesions with high clot burden. Further innovation in thrombolytic therapies are required.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: carotid artery ■ reperfusion ■ tenecteplase ■ thrombus ■ tomography

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This manuscript was sent to Emmanuel Touzé, Guest Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/STROKEAHA.122.041061.

For Sources of Funding and Disclosures, see page 713.

Stroke is available at www.ahajournals.org/journal/str

Nonstandard Abbreviations and Acronyms

CT	computed tomography
ICA	internal carotid artery
LVO	large vessel occlusion

In patients with large vessel occlusion (LVO) stroke, achieving rapid reperfusion is critical in limiting disability and preserving functional independence.[1] In 10% to 30% of patients with LVO, early reperfusion can be achieved by bridging with an intravenous thrombolytic before the initiation of endovascular therapy.[1–4] Such early reperfusion is associated with improved clinical outcomes. In alteplase-treated patients, early reperfusion is associated with longer times from thrombolytic administration to postlytic imaging, site of vessel occlusion, the presence of residual flow through a thrombus, and reduced clot burden.[1,5–7] Thrombus migration has also been associated with alteplase administration and is linked to better functional outcomes but, paradoxically, decreased rates of complete reperfusion following endovascular thrombectomy.[8,9]

Clinical trials and observational studies comparing tenecteplase to alteplase have demonstrated increased rates of early reperfusion in tenecteplase-treated patients.[3,10,11] A recent analysis has shown that, similar to alteplase, reperfusion after tenecteplase is associated with longer times postlytic administration to imaging (reperfusion) assessment. However, the relationship between tenecteplase-associated reperfusion and thrombus characteristics has yet to be fully investigated. Also unknown is the effect of tenecteplase on inducing thrombus migration and partial reperfusion.

In this study, we pooled data from the EXTEND-IA TNK trial (Tenecteplase Versus Alteplase Before Endovascular Therapy for Ischemic Stroke) and performed an imaging analysis to evaluate the reperfusion effectiveness of tenecteplase and alteplase in the context of radiological thrombus features such as occlusion site, contrast permeability, and clot burden. Given the increased half-life of tenecteplase and resistance to plasminogen activator inhibitor, we hypothesized that tenecteplase would be more efficacious than alteplase, especially in thrombi with lower clot burden and contrast permeability.

METHODS

Data Availability Statement

The authors declare that all data and methodological detail are available within the article and the Supplemental Material. Access to EXTEND-IA TNK datasets can be obtained from study authors upon reasonable request.

Subjects

Subjects were participants enrolled in the EXTEND-IA TNK[3] trial, and the EXTEND-IA TNK Part 2[12] trial (Determining the Optimal Dose of Tenecteplase Before Endovascular Therapy for Ischemic Stroke). The EXTEND-IA TNK studies were multicenter, prospective, randomized controlled trials designed to determine the efficacy of tenecteplase in the context of LVO and endovascular therapy. Patients with computed tomography (CT) angiography-confirmed occlusions of the internal carotid (ICA), middle cerebral, or basilar artery were enrolled and treated with a thrombolytic within 4.5 hours of symptom onset.

In EXTEND-IA TNK, patients were randomized to tenecteplase 0.25 mg/kg or alteplase 0.90 mg/kg. In EXTEND-IA TNK Part 2, patients were randomized to tenecteplase 0.25 mg/kg or 0.40 mg/kg. Patients were enrolled from March 2015 to October 2017 (EXTEND-IA TNK) and December 2017 to July 2019 (EXTEND-IA TNK Part 2) in multiple hospitals across Australia and New Zealand. Exclusion criteria for both trials have been previously described.[3,12] In this analysis, patients with a basilar artery occlusion or isolated extracranial ICA occlusion were excluded as some of the variables of interest (eg, clot burden score) could not be evaluated.

Imaging Analysis and Variables of Interest

All patients received a noncontrast CT scan, CT perfusion, and CT angiography at baseline. Repeat imaging assessments were performed at the initial pass during cerebral angiography. In the minority of patients who did not undergo a formal digital subtraction angiogram, repeat CT perfusion and angiography data were utilized.

In this analysis, we chose to assess the following radiological thrombus features: Intracranial occlusion Site,[5] Clot Permeability, measured via Residual Flow Grades,[5] and Clot Burden, as evaluated through the Clot Burden Score.[13] Imaging assessments were performed by a stroke neurologist (V.Y., 8 years of experience) with oversight from a senior clinician with 15 years of experience (B.C.). All imaging assessments were performed in a blinded fashion using Horos Imaging Software (version 3.3.6).

Intracranial occlusion site, based on the position of the most proximal clot face, was identified on baseline CT angiogram (with confirmation using CT perfusion, where necessary) with the following categorizations: ICA (I, T, or L subtypes[14]), proximal M1, distal M1, or proximal M2. Proximal and distal M1 occlusions were differentiated by comparing with the contralateral M1 segment in the coronal plane and using the midpoint as a reference. Contrast permeability through the clot was evaluated with residual flow grading based on techniques previously described in the INTERRSeCT study (Identifying New Approaches to Optimize Thrombus Characterization for Predicting Early Recanalization and Reperfusion With IV Alteplase and Other Treatments Using Serial CT Angiography Study).[5] We used baseline CT angiogram source images (arterial phase) with 3-mm maximum intensity projections. Thrombi were categorized into 3 grades of residual flow. A grade 0 was assigned when no contrast could be observed permeating the thrombus. If contrast permeated diffusely through the thrombus, but was not well defined, a grade 1 was assigned. If a streak of well-defined contrast was observed within the thrombus, then a grade 2 was assigned (Figure S1). Clot burden was assessed via source CT angiogram images with the previously described clot burden score.[13] Ranging from

0-10, a 10-point score implied the absence of thrombus and normal vasculature. A point was deducted for each anterior circulation vessel region that was not visualized with contrast. A 0-point score represented the complete occlusion of the major ipsilateral anterior circulation vessels.

Imaging Outcomes

The primary outcome, early reperfusion, was defined as the absence of retrievable thrombus or >50% reperfusion on repeat imaging assessment. This corresponded to an expanded Thrombolysis in Cerebral Infarction 2b–3 or >50% reduction in the Tmax >6 s CT perfusion lesion volume on repeat imaging at the time angiography would otherwise have occurred.[15] We also assessed partial reperfusion, defined as thrombus dissolution or migration with a restoration of blood flow <50% of the involved territory (expanded Thrombolysis in Cerebral Infarction 2a) and clot debulking, defined as the presence of thrombus migration without a substantial restoration of distal blood flow (expanded Thrombolysis in Cerebral Infarction 1).

Clinical Assessment and Outcomes

Clinical outcomes evaluated in this study include disability level at 90 days via an ordinal analysis of the modified Rankin Scale, freedom from disability (defined as a modified Rankin Scale score of 0–1 or no change from baseline at 90 days), and functional independence (defined as modified Rankin Scale score of 0–2 or no change from baseline at 90 days). Clinical follow-up assessments of trial patients were performed centrally with evaluators being blinded to treatment allocation.

Statistical Analysis

Individual patient data were pooled across the 2 trials and across tenecteplase dose groups (0.25 and 0.40 mg/kg). Fisher exact test, Mann Whitney *U*, and ANOVA were used as appropriate when evaluating baseline patient characteristics. In assessing our imaging outcomes in the whole cohort, we compared the treatment effect of tenecteplase and alteplase while adjusting for intracranial occlusion site, time from thrombolytic administration to angiographic assessment, and study (as a random effect) using mixed effects logistic regression models (covariates selected a priori).

We then assessed subgroups based on intracranial occlusion site, the presence of contrast permeability, and clot burden, and compared tenecteplase to alteplase for our primary outcome while adjusting for relevant covariates in separate mixed effect models with interaction testing. Contrast permeability was defined as residual flow grades 1 or 2. Clot burden scores were grouped into high clot burden (0–4) and low clot burden (5–10). Due to the presence of zero events, we assessed differences between tenecteplase and alteplase and partial reperfusion via unadjusted Fisher tests. In a sensitivity analysis, we assessed early reperfusion rates between patients who received 0.25 mg/kg and 0.40 mg/kg doses of tenecteplase and patients who received 0.25 mg/kg tenecteplase and 0.90 mg/kg alteplase, via unadjusted χ^2 testing.

Finally, we compared the 90-day clinical outcomes of patients who achieved early reperfusion with a thrombolytic to all patients who did not achieve early reperfusion, using mixed effects logistic and proportional odds models with a priori adjustments for age, baseline clinical severity (National Institutes of Health Stroke Scale), time from symptom onset to puncture, and study (as a random effect). We also compared the long-term outcomes of patients who achieved partial reperfusion with an intravenous thrombolytic to patients who had no significant change in prethrombectomy reperfusion status. Variables, outcomes, and confounders for each model are outlined in the Supplemental Methods. Patients with missing data in regard to the variables and outcomes of interest were excluded from our analysis. All reported *P* values are 2-sided with $P<0.05$ regarded as significant. Statistical analysis was performed using SPSS v28.0 (IBM, Armonk, NY) and STATA v17 (StataCorp, College Station, TX).

Patient Consents and Reporting Guidelines

Local research ethics board approval was obtained at all EXTEND-IA TNK enrolling sites. Written informed consent was obtained from the participant or a legal representative before enrollment, except in jurisdictions allowing deferral of consent for emergency treatment, in which case consent was obtained at a later time point to continue participation. This study complies with Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

RESULTS

Of the 502 patients enrolled in the 2 randomized trials, 37 patients were excluded: 18 patients presented with basilar artery occlusions, 11 patients presented with isolated extracranial ICA occlusions, and 8 patients had poor quality or missing imaging data (Figure 1). Our primary analysis cohort, therefore, consisted of 465 patients: 369 (79%) were treated with tenecteplase (pooled 0.25 and 0.40 mg/kg doses) and 96 (21%) were treated with alteplase (0.90 mg/kg). Baseline patient characteristics are presented in Table 1. Imaging and time metrics were similar between the 2 treatment groups. A proximal occlusion (ICA or Proximal M1) was present in 247/465 (55%) of patients. Of the 92 (20%) patients presenting with an occlusion in the ICA, 8 presented with an I-lesion (9%), 72 with a T-lesion (78%), and 12 with an L-lesion (13%). Contrast permeability was observed in 208 out of 465 (44%) of the cohort, the majority presenting with residual grade 1 flow. Residual flow grades, stratified by intracranial occlusion site, are presented in Table S1.

Early reperfusion at repeat imaging assessment was observed in 84 out of 465 (18%) patients. Partial reperfusion and clot debulking were observed in 50 out of 465 (11%) and 12 out of 465 (3%) patients, respectively. Reperfusion status at repeat imaging assessment, stratified by thrombolytic treatment are presented in Figure 2. Tenecteplase was associated with a higher odds of early reperfusion (adjusted odds ratio [aOR], 2.18 [95% CI, 1.03–4.63]) and partial reperfusion (aOR, 15.63 [95% CI, 2.11–115.89]). No difference in clot debulking was observed between the 2 treatment groups (aOR, 0.79 [95% CI, 0.21–3.00]).

A comparison of tenecteplase and alteplase early reperfusion rates, in subgroups of intracranial occlusion site,

Stroke. 2023;54:706–714. DOI: 10.1161/STROKEAHA.122.041061

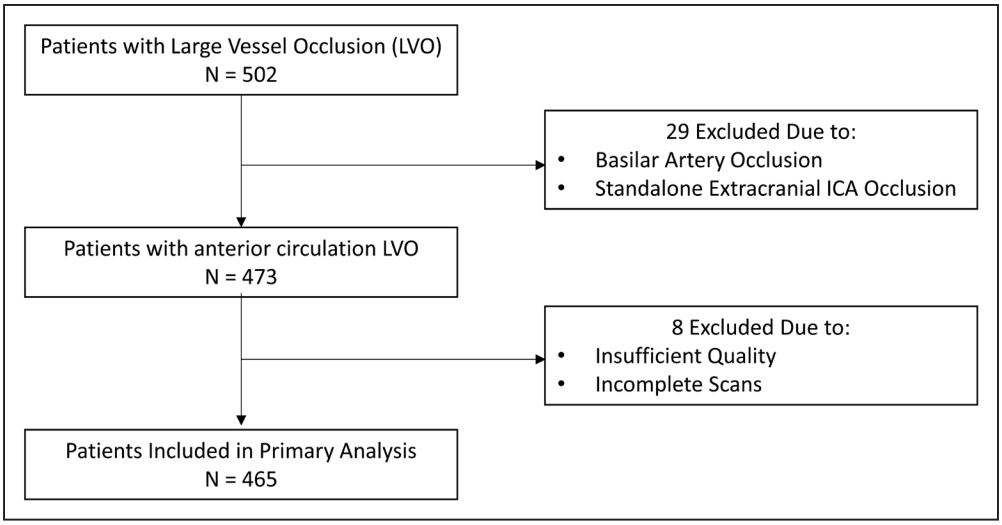

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) patient selection.
ICA indicates internal carotid artery; and LVO, large vessel occlusion.

clot permeability, and clot burden is presented in Table 2. Tenecteplase reperfusion rates were higher than alteplase in patients with distal M1 or M2 occlusions (aOR, 3.73 [95% CI, 1.25–11.11]). Early reperfusion rates did not differ significantly between the 2 lytic treatments in patients with proximal M1 occlusions (aOR, 2.09 [95% CI, 0.62–7.02]) and reperfusion rates were notably poor in patients with an ICA occlusion (tenecteplase 1% versus alteplase 5%, aOR, 0.22 [95% CI, 0.01–3.83]; $P_{interaction}$=0.16). Occlusions with low clot burden (defined as clot burden scores of 5–10) favored tenecteplase (aOR, 3.93 [95% CI, 1.50–10.33]) with a notable difference when compared with patients with high clot burden (defined as clot burden scores of 0–4; tenecteplase: 8% versus alteplase: 14%, aOR, 0.58 [95% CI, 0.16–2.06]; $P_{interaction}$=0.01). We did not observe an association between contrast permeability and the treatment effect of tenecteplase (permeability present: aOR, 2.83 [95% CI, 1.00–8.05] versus permeability absent: aOR, 1.98 [95% CI, 0.65–6.03]; $P_{interaction}$=0.62).

In a sensitivity analysis, no differences in early reperfusion were observed between patients treated with tenecteplase 0.25 mg/kg versus 0.40 mg/kg (Tables S3 and S4). In a comparison of tenecteplase 0.25 mg/kg and alteplase 0.90 mg/kg, early reperfusion occurred in 47 out of 230 (20%) tenecteplase patients, compared with 9 out of 96 (9%) alteplase patients (Table S5). Similar to the primary analysis, tenecteplase 0.25 mg/kg treatment effect was superior in patients with low clot burden (tenecteplase: 24% versus alteplase 8%, aOR, 3.47 [95% CI, 1.29–9.33]; $P_{interaction}$=0.06; Table S6).

Forty-nine instances of thrombus migration resulting in partial reperfusion occurred with tenecteplase use, compared to one case seen with alteplase (baseline ICA occlusion with a residual flow grade of 0 migrating to the proximal M1). Thrombus migration patterns and their relationship to reperfusion status are provided in Table 3. Thrombus movement from the ICA to the M1 (resulting in reperfusion of the anterior cerebral artery territory; Figure S2) and from the distal M1 to the M2 were the most frequently observed. Partial reperfusion rates in subgroups of intracranial occlusion site, clot permeability, and clot burden, are presented in Table S2. Among tenecteplase-treated patients, partial reperfusion in contrast permeable thrombi (residual flow grades 1 or 2) occurred at an unadjusted rate of 23% (28/121) compared with 12% (21/173) in thrombi with no appreciable permeability. Tenecteplase-associated partial reperfusion of the ICA occurred at a rate of 25% (18/72) compared to 6% (1/18) in alteplase-treated patients.

Adjusting for the relevant covariates, early reperfusion (tenecteplase and alteplase patients) was associated with improved modified Rankin Scale scores at 90 days, (adjusted common OR, 2.52 [95% CI, 1.62–3.94]) when compared with all patients who did not achieve early reperfusion. Patients who achieved early reperfusion with an intravenous thrombolytic had increased rates of freedom from disability (68% versus 46%, adjusted OR, 3.07 [95% CI, 1.74–5.41]) and functional independence (75% versus 56%, adjusted OR, 3.28 [95% CI, 1.75–6.13]). Partial reperfusion was not associated with a modified Rankin scale shift when compared to patients who had no significant change in reperfusion (Figure 3).

DISCUSSION

In a pooled individual patient data analysis of 2 randomized trials, we found that thrombolytic-induced reperfusion before thrombectomy favored tenecteplase over alteplase in patients with low clot burden. We observed higher rates of tenecteplase-induced reperfusion in distal LVO, but contrast permeability, as represented via residual flow grades, was not associated with tenecteplase treatment effect. One of the most notable findings of our analysis was the degree of thrombus change observed in those treated with tenecteplase. Up to a third of

Table 1. Baseline Patient Characteristics Stratified by Thrombolytic Treatment (All Patients, n=465)

	All patients (n=465)	Pooled tenecteplase (0.40 and 0.25 mg/kg, n=369)	Alteplase (0.90 mg/kg, n=96)	*P* value
Age, y; median (IQR)	74 (65–82)	74 (64–81)	75 (67–82)	0.54
Female sex	216 (47%)	169 (46%)	47 (49%)	0.58
Cause of stroke				
Cardioembolic occlusion	220 (47%)	167 (45%)	53 (55%)	0.28
Large artery occlusion	71 (15%)	57 (15%)	14 (15%)	
Undetermined/other	174 (37%)	145 (39%)	29 (30%)	
Medical history				
Hypertension	295 (63%)	236 (64%)	59 (62%)	0.65
Diabetes	79 (17%)	61 (17%)	18 (19%)	0.61
Dyslipidemia	182 (39%)	144 (39%)	38 (40%)	0.92
Prior stroke or TIA	69 (15%)	53 (14%)	16 (17%)	0.57
Antiplatelet Use	192/462 (41%)	155/366 (42%)	37 (39%)	0.50
Clinical and laboratory markers				
Glucose, mmol/L; median (IQR)*	6.4 (5.7–7.9)	6.4 (5.7–8.1)	6.5 (5.6–7.8)	0.56
NIHSS; median (IQR)	17 (11–21)	17 (11–21)	17 (13–22)	0.22
Imaging				
Site of vessel occlusion				
Internal carotid artery	92 (20%)	73 (20%)	19 (20%)	0.19
MCA (first segment, proximal)	155 (33%)	120 (33%)	35 (37%)	0.19
MCA (first segment, distal)	130 (28%)	99 (27%)	31 (32%)	0.19
MCA (second segment)	88 (19%)	77 (21%)	11 (12%)	0.19
Tandem lesion	69 (15%)	54 (15%)	15 (16%)	0.81
Clot burden score				
0–4	137 (30%)	108 (29%)	29 (30%)	0.81
5–7	165 (36%)	129 (35%)	36 (38%)	
8–10	163 (35%)	132 (36%)	31 (32%)	
Residual flow grade				
Grade 0	257 (55%)	209 (57%)	48 (50%)	0.44
Grade 1	183 (39%)	140 (38%)	43 (45%)	
Grade 2	25 (5%)	20 (5%)	5 (5%)	
Workflow processes				
Transferred for care	144/463 (31%)	121/367 (33%)	23 (24%)	0.09
Time from symptom onset to thrombolytic initiation, min; median (IQR)	130 (101–167)	129 (100–165)	133 (104–176)	0.51
Time from first hospital arrival to thrombolytic, min; median (IQR)†	55 (41–72)	54 (42–72)	56 (37–69)	0.45
Time from symptom onset to arterial puncture or repeat imaging, min; median (IQR)‡	179 (140–238)	175 (140–249)	189 (149–226)	0.94
Time from thrombolytic to initial angiographic assessment; median (IQR)‡	58 (36–85)	57 (33–87)	60 (41–81)	0.72

Results are (n,%) unless otherwise stated. IQR indicates interquartile range; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; and TIA, transient ischemic attack.

*Missing 96 patients.

†Missing 22 patients.

‡Missing 2 patients.

patients exhibited some degree of thrombus change with tenecteplase administration, compared to <15% of patients treated with alteplase (Figure 2).

Although the rates of prethrombectomy reperfusion in our analysis are similar to previously published observational studies,[16,17] our findings are in contrast to data from the recently published AcT trial (Alteplase Compared to Tenecteplase in Patients With Acute Ischemic Stroke).[18] In AcT, early reperfusion rates in patients with LVO (measured via the revised Arterial Occlusive Lesion score[5]) were around 10% and did not differ significantly between tenecteplase and alteplase treatment groups. The reasons for this difference are not immediately clear. Intracranial occlusion site distributions between the AcT

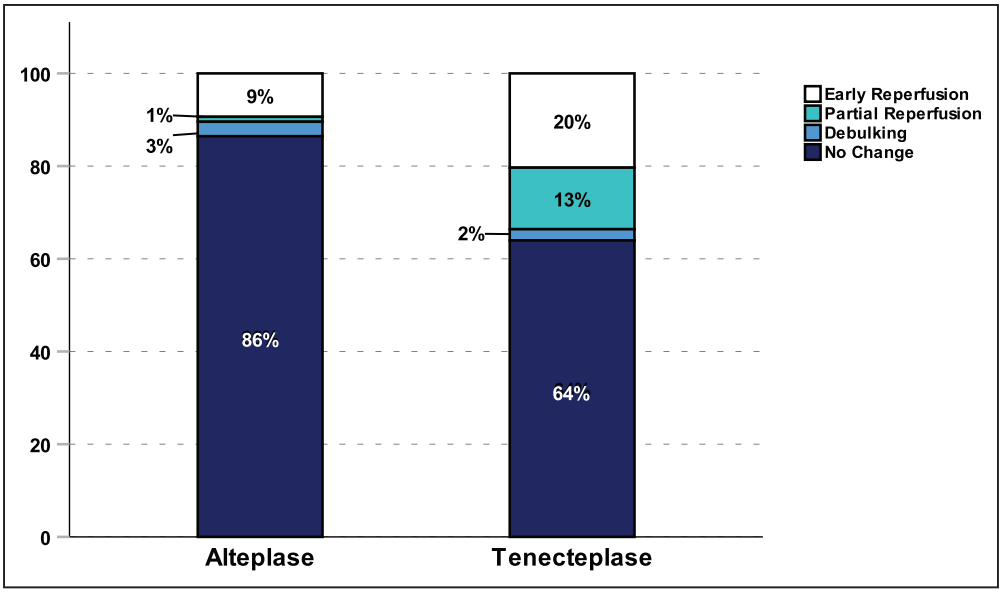

Figure 2. Reperfusion status at subsequent assessment (initial angiographic assessment or repeat computed tomography perfusion/angiography) stratified by thrombolytic treatment.
After adjusting for intracranial occlusion site, time from thrombolytic administration to angiographic assessment, and study (as a random effect), tenecteplase was associated with a higher incidence of early reperfusion (adjusted odds ratio [aOR], 2.18 [95% CI, 1.03–4.63]) and partial reperfusion (aOR, 15.63 [95% CI, 2.11–115.89]). No difference in clot debulking was observed between the 2 treatment groups (aOR, 0.79 [95% CI, 0.21–3.00]). Early reperfusion was defined as the restoration of blood flow to >50% of the involved territory or no retrievable intracranial thrombus at the initial angiogram and partial reperfusion was defined as thrombus dissolution or migration with a restoration of blood flow <50% of the involved territory. Clot debulking was defined as the presence of thrombus migration without a substantial restoration of blood flow.

and EXTEND-IA TNK cohorts were similar. Of note, the reported times of baseline CT to arterial puncture in the AcT trial (60 minutes [interquartile range, 43–88]) were similar to the lytic administration to angiographic assessment times observed in our analysis (58 minutes [interquartile range, 36–85]). As such, the time of lytic administration to angiographic assessment may have been shorter in AcT and this could partially explain the difference in findings. A similar pattern of short lytic to puncture times and lower than expected prethrombectomy reperfusion rates with thrombolytics has also been observed in the SWIFT-DIRECT trial (Solitaire With the Intention for Thrombectomy Plus Intravenous t-PA Versus DIRECT Solitaire Stent-Retriever Thrombectomy in Acute Anterior Circulation Stroke).[19] Ultimately, further analysis of the AcT trial may provide additional insights, and confirmation of our findings in ongoing tenecteplase studies (ETERNAL-LVO [Extending the Time Window for Tenecteplase by Effective Reperfusion in Patients With Large Vessel Occlusion; https://www.clinicaltrials.gov;

Table 2. Early Reperfusion Status and Intracranial Clot Characteristic Subgroup Analysis

	Tenecteplase (0.40 and 0.25 mg/kg pooled, n=369)	Alteplase (0.90 mg/kg, n=96)	Treatment effect aOR (95% CI)	$P_{interaction}$
Intracranial occlusion site				
Internal carotid artery*	1/73 (1%)	1/19 (5%)	0.22 (0.01–3.83)‡	0.16
MCA: proximal M1	21/120 (18%)	4/35 (11%)	2.09 (0.62–7.02)‡	
MCA: distal M1 or M2 segment	53/176 (30%)	4/42 (10%)	3.73 (1.25–11.11)‡	
Contrast permeability				
Contrast permeability present†	38/160 (24%)	5/48 (10%)	2.83 (1.00–8.05)§	0.62
Contrast permeability absent	37/209 (18%)	4/48 (8%)	1.98 (0.65–6.03)§	
Clot burden score				
5–10	66/261 (25%)	5/67 (7%)	3.93 (1.50–10.33)‡	0.01
0–4	9/108 (8%)	4/29 (14%)	0.58 (0.16–2.06)‡	

aOR indicates adjusted odds ratio; and MCA, middle cerebral artery.
*Includes I, T, and L occlusions.
†Defined as residual flow grades 1 or 2.
‡Adjusted for residual flow grade, time from thrombolytic administration to angiographic assessment, and study (as a random effect).
§Adjusted for intracranial occlusion site, time from thrombolytic administration to angiographic assessment, and study (as a random effect).

Table 3. Thrombus Migration Patterns and Reperfusion Status Achieved With Thrombolysis (Tenecteplase or Alteplase)

	Early reperfusion (n=84)	Partial reperfusion (n=50)	Clot debulking (n=12)
ICA → ICA (partially occlusive)	…	2 (4%)*	…
ICA → M1	…	16 (32%)	2 (17%)
ICA → M2	…	1 (2%)	…
Proximal M1 → distal m1	3 (4%)	2 (4%)	2 (17%)
Proximal M1 → M2	10 (12%)	1 (2%)	1 (8%)
Distal M1 → distal M1 (partially occlusive)	…	2 (4%)†	2 (17%)‡
Distal M1 → M2	14 (17%)	18 (36%)	3 (25%)
ICA → NRT or distal occlusion (M3 and beyond)	2 (2%)	…	…
M1 (proximal or distal) → NRT or distal occlusion (M3 and beyond)	27 (32%)	…	…
M2 → NRT or distal occlusion (distal M2, M3, and beyond)	28 (33%)	8 (16%)	2 (17%)

CT indicates computed tomography; ICA, internal carotid artery; M1, first segment of the middle cerebral artery; M2, second segment of the middle cerebral artery; M3, third segment of the middle cerebral artery; and NRT, no retrievable thrombus.

*In both cases, an ICA T-occlusion is identified on CT angiogram (A1 is filled retrograde). On initial digital subtraction angiography run, the T-occlusions persist but with residual anterograde flow into the A1 segment.

†In both cases, a distal M1 occlusion identified on CT angiogram. On initial digital subtraction angiography run, the distal M1 occlusion persists but with improved flow in the M2 areas.

‡In both cases a distal M1 occlusion identified on CT angiogram. On initial digital subtraction angiography run, the distal M1 occlusion persists but is still partially occlusive with only a slight improvement in residual flow.

Unique identifier: NCT04454788]; BRIDGE-TNK [Endovascular Treatment With Versus Without Intravenous rhTNK-tPA in Stroke; https://www.clinicaltrials.gov; Unique identifier: NCT04733742]; TEMPO-2 [A Randomized Controlled Trial of TNK-tPA Versus Standard of Care for Minor Ischemic Stroke With Proven Occlusion; Unique identifier: NCT02398656]) will be required.

In our analysis, we reported a median door-to-needle time of 55 minutes (41–72). Although this is less than the Australian average and comparable with treatment metrics from quality improvement registries,[20] stroke units worldwide continue to work on further streamlining their systems of care, shortening door-to-needle times in the process.[21,22] Most of these systems utilize alteplase and, therefore, require a system that can incorporate the initial bolus dose and subsequent infusion. The bolus dose of tenecteplase over 5 to 10 seconds has the potential to further streamline acute stroke treatment, as demonstrated in mobile stroke units that report reduced scene-to-needle times with tenecteplase.[10] Although the EXTEND-IA TNK trials used emergency treatment or short-form consent processes and did not require neurointerventional acceptance before randomization, it is likely that treatment in routine clinical practice with no trial-related procedures would be faster. It is, therefore,

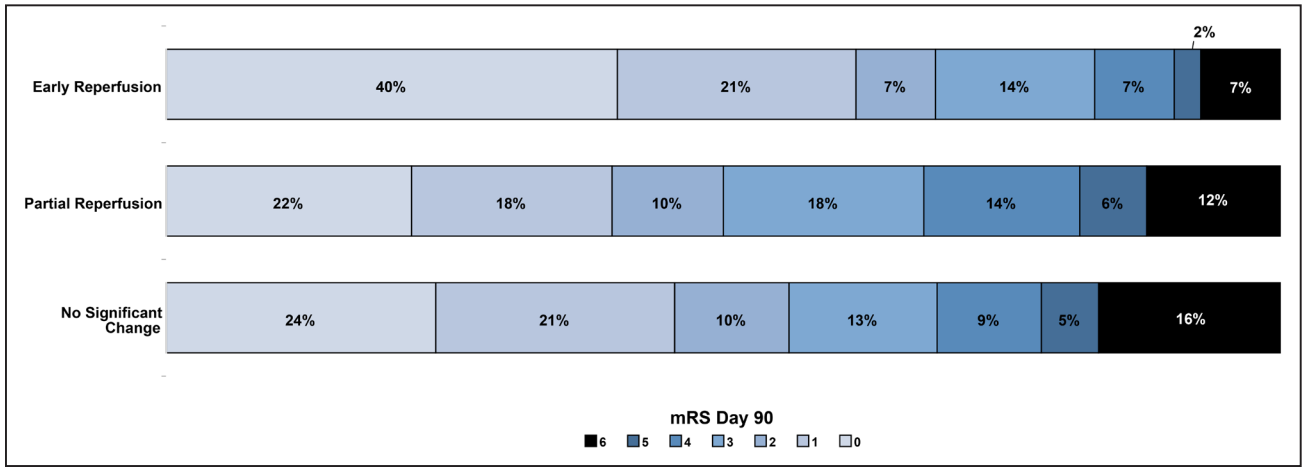

Figure 3. Modified Rankin Scale (mRS) scores at 90 d stratified by reperfusion status achieved with thrombolysis at subsequent assessment (initial angiographic assessment or repeat computed tomography perfusion/angiography).
Twelve cases of clot debulking were pooled into the no significant change arm. Early reperfusion (n=84) was associated with mRS shift, adjusting for baseline National Institutes of Health Stroke Scale, age, time from symptom onset to arterial puncture, and study (as a random effect), when compared with all patients who did not achieve early reperfusion (n=381; adjusted common odds ratio [acOR], 2.52 [95% CI, 1.62–3.94]). Partial reperfusion (n=50) was not associated with an mRS shift when compared to patients who had no significant change in reperfusion (n=331; acOR, 1.15 [95% CI, 0.68–1.95]).

possible that, as systems continue to adopt tenecteplase, shortened door-to-needle times, and potential improvements in early reperfusion rates, can result.

Both alteplase and tenecteplase were largely ineffective in achieving early reperfusion where patients had ICA occlusions or occlusions with a high clot burden (Table 2). As per Table S1, 63 out of 92 ICA occlusions exhibited some degree of clot permeability (flow grades 1 or 2). Even then, only 2 cases of early reperfusion were observed. It is important to note that ≈25% of tenecteplase-treated patients with ICA occlusion had thrombus migration from the ICA to the proximal M1, opening the A1 segment in the process (Table 3). Although patients who were able to achieve early reperfusion with either thrombolytic had reduced disability in the long term, we did not observe this same trend in those who exhibited partial reperfusion prethrombectomy (Figure 3). Clinical benefit with partial reperfusion was not detected but our sample size was limited. Our findings highlight the inherent limitations of the current generation of thrombolytics and provide further motivation for the study of potential adjunctive agents, such as argatroban and eptifibatide[23,24] (MOST trial [Multi-Arm Optimization of Stroke Thrombolysis; https://www.clinicaltrials.gov; Unique identifier: NCT03735979]), dornase alfa (EXTEND-IA DNase [Improving Early Reperfusion With Adjuvant Dornase Alfa in Large Vessel Ischemic Stroke; https://www.clinicaltrials.gov; Unique identifier: NCT05203224] and NETs-Target trials [Efficacy of Pulmozyme on Arterial Recanalization in Post-Thrombectomy Patients Managed for Ischemic Stroke; https://www.clinicaltrials.gov; Unique identifier: NCT04785066]) or agents targeting von Willebrand Factor.[25,26]

Our study has several limitations. To ensure adequate sample size for the analysis, we pooled the 0.25 mg/kg and 0.40 mg/kg tenecteplase dosing arms. Although 0.40 mg/kg dosing will not be used in routine care, given safety issues identified in recent studies,[27,28] there was no evidence of heterogeneity in reperfusion rates between the dosing arms in our sensitivity analyses (Tables S3 and S4). Furthermore, in a second sensitivity analysis comparing tenecteplase 0.25 mg/kg and alteplase 0.90 mg/kg, we observed consistency in our overall findings (Tables S5 and S6). In addition, thrombus characteristics such as clot length or alternate methods of measuring thrombus features (eg, thrombus attenuation increase for clot permeability) were not evaluated in our analysis. We specifically chose to assess clot permeability through residual flow grading and clot burden through the clot burden score because of their ability to be easily applied to patient care at the bedside. We do plan to evaluate clot length and alternate methods of clot permeability in future studies, and in particular, plan to investigate how these alternate methods may increase the accuracy of evaluating tenecteplase-associated reperfusion in large vessel occlusions.

CONCLUSIONS

Tenecteplase demonstrates early reperfusion superiority to alteplase in thrombi with low clot burden. Higher rates of tenecteplase-induced reperfusion were observed in patients with distal LVO. We did not observe an association between contrast permeability and tenecteplase treatment effect. Reperfusion efficacy remains limited in proximal lesions with large clot burden. There is a clear unmet need for improved intravenous thrombolytic treatments.

ARTICLE INFORMATION

Received August 23, 2022; final revision received October 2, 2022; accepted October 26 2022.

Presented in part at the International Stroke Conference, Dallas, TX, February 8–10, 2023.

The podcast and transcript are available at https://www.ahajournals.org/str/podcast.

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Sources of Funding

The EXTEND-IA TNK trial (Tenecteplase Versus Alteplase Before Endovascular Therapy for Ischemic Stroke) received funding from the National Health and Medical Research Council Australia (GNT1113352, GNT1111972). Dr Yogendrakumar is supported by the University of Melbourne, a Canadian Institutes of Health Research Fellowship Award, and a Detweiler Travelling Fellowship Award (Royal College of Physicians and Surgeons of Canada).

Disclosures

Dr Yogendrakumar reports grants from Melbourne Research, University of Melbourne and grants from Canadian Institutes of Health Research. Dr Mitchell reports compensation from Stryker Corporation for other services; compensation from Stryker Corporation for consultant services; and compensation from Medtronic USA, Inc, for other services. Dr Kleinig reports travel support from Boehringer Ingelheim. Dr Thijs reports compensation from Medtronic for consultant services; compensation from Pfizer for consultant services; compensation from Boehringer Ingelheim for consultant services; compensation from Bayer for consultant services; and compensation from Amgen for consultant services. Dr Dewey reports employment by Eastern Health. Dr Yan reports compensation from Royal Melbourne Hospital for consultant services. Dr Donnan reports compensation from Argenica Therapeutics Limited for consultant services; compensation from Amgen for consultant services; grants from National Health and Medical Research Council; and compensation from Boehringer Ingelheim for consultant services. Dr Davis reports compensation from Boehringer Ingelheim for other services; compensation from Amgen for other services; compensation from Medtronic for other services; and compensation

from Abbott Pharmaceuticals for other services. The other authors report no conflicts.

Supplemental Material

Expanded Methods
Figures S1–S2
Tables S1–S6

APPENDIX

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