RESEARCH ARTICLE

Tenecteplase Improves Reperfusion across Time in Large Vessel Stroke

Vignan Yogendrakumar, MD,[1] James Beharry, MBChB,[1,2] Leonid Churilov, PhD,[1] Khairunnisa Alidin, CNC,[1] Melissa Ugalde, CNC,[1] Lauren Pesavento, CNC,[1] Louise Weir, NP,[1] Peter J. Mitchell, MMed,[3] Timothy J. Kleinig, PhD,[4] Nawaf Yassi, PhD,[1,5] Vincent Thijs, PhD,[2,6] Teddy Y. Wu, PhD,[7] Darshan G. Shah, MBBS,[8] Helen M. Dewey, PhD,[9] Tissa Wijeratne, PhD,[10] Bernard Yan, DMedSc,[1,3] Patricia M. Desmond, MD,[3] Gagan Sharma, MCA,[1] Mark W. Parsons, PhD,[1,11] Geoffrey A. Donnan, MD,[1] Stephen M. Davis, MD,[1] and Bruce C. V. Campbell, PhD,[1] for the Royal Melbourne Stroke Registry and EXTEND-IA TNK Collaborators

Objective: Tenecteplase improves reperfusion compared to alteplase in patients with large vessel occlusions. To determine whether this improvement varies across the spectrum of thrombolytic agent to reperfusion assessment times, we performed a comparative analysis of tenecteplase and alteplase reperfusion rates.

Methods: Patients with large vessel occlusion and treatment with thrombolysis were pooled from the Melbourne Stroke Registry, and the EXTEND-IA and EXTEND-IA TNK trials. The primary outcome, thrombolytic-induced reperfusion, was defined as the absence of retrievable thrombus or >50% reperfusion at imaging reassessment. We compared the treatment effect of tenecteplase and alteplase, accounting for thrombolytic to assessment exposure times, via Poisson modeling. We compared 90-day outcomes of patients who achieved reperfusion with a thrombolytic to patients who achieved reperfusion via endovascular therapy using ordinal logistic regression.

Results: Among 893 patients included in the primary analysis, thrombolytic-induced reperfusion was observed in 184 (21%) patients. Tenecteplase was associated with higher rates of reperfusion (adjusted incidence rate ratio [aIRR] = 1.50, 95% confidence interval [CI] = 1.09–2.07, $p = 0.01$). Findings were consistent in patient subgroups with first segment (aIRR = 1.41, 95% CI = 0.93–2.14) and second segment (aIRR = 2.07, 95% CI = 0.98–4.37) middle cerebral artery occlusions. Increased thrombolytic to reperfusion assessment times were associated with reperfusion (tenecteplase: adjusted risk ratio [aRR] = 1.08 per 15 minutes, 95% CI = 1.04–1.13 vs alteplase: aRR = 1.06 per 15 minutes, 95% CI = 1.00–1.13). No significant treatment-by-time interaction was observed ($p = 0.87$). Reperfusion via thrombolysis was associated with improved 90-day modified Rankin Scale scores (adjusted common odds ratio = 2.15, 95% CI = 1.54–3.01) compared to patients who achieved reperfusion following endovascular therapy.

View this article online at wileyonlinelibrary.com. DOI: 10.1002/ana.26547

Received Jun 24, 2022, and in revised form Sep 17, 2022. Accepted for publication Nov 8, 2022.

Address correspondence to Dr Yogendrakumar, Department of Neurology, Royal Melbourne Hospital, 300 Grattan St, Parkville, VIC 3050, Australia. E-mail: vyogendrakum@student.unimelb.edu.au

From the [1]Department of Medicine and Neurology, Melbourne Brain Centre at the Royal Melbourne Hospital, University of Melbourne, Parkville, Victoria, Australia; [2]Department of Medicine, Austin Health, University of Melbourne, Heidelberg, Victoria, Australia; [3]Department of Radiology, Royal Melbourne Hospital, University of Melbourne, Parkville, Victoria, Australia; [4]Department of Neurology, Royal Adelaide Hospital, Adelaide, South Australia, Australia; [5]Population Health and Immunity Division, Walter and Eliza Hall Institute of Medical Research, Parkville, Victoria, Australia; [6]Florey Institute of Neuroscience and Mental Health, University of Melbourne, Parkville, Victoria, Australia; [7]Department of Neurology, Christchurch Hospital, Christchurch, New Zealand; [8]Department of Neurology, Princess Alexandra Hospital, Brisbane, Queensland, Australia; [9]Eastern Health and Eastern Health Clinical School, Department of Neurosciences, Monash University, Clayton, Victoria, Australia; [10]Melbourne Medical School, Department of Medicine and Neurology, University of Melbourne and Western Health, Sunshine Hospital, St Albans, Victoria, Australia; and [11]Department of Neurology, Liverpool Hospital, University of New South Wales, Sydney, New South Wales, Australia

Additional supporting information can be found in the online version of this article.

Interpretation: Tenecteplase, compared to alteplase, increases prethrombectomy reperfusion, regardless of the time from administration to reperfusion assessment. Prethrombectomy reperfusion is associated with better clinical outcomes.

ANN NEUROL 2023;93:489–499

Introduction

Achieving early reperfusion in an acute ischemic stroke strongly influences clinical outcomes.[1–4] In large vessel occlusion (LVO) patients treated with intravenous alteplase, the reported rates of thrombolytic agent-induced reperfusion prior to endovascular therapy ranges from 10 to 30%.[5–8] Alteplase-induced reperfusion is associated with several factors, including occlusion site, thrombus permeability, and the time from thrombolytic to subsequent imaging assessment.[7,9–11]

The influence of the time required for a thrombolytic to induce reperfusion has been demonstrated in prior studies, with higher rates of reperfusion associated with longer thrombolytic to imaging assessment time periods.[7] Tenecteplase improves prethrombectomy reperfusion compared to alteplase, specifically in LVO patients.[5,12–14] However, whether this relates to enhanced earlier reperfusion (compared to alteplase) is unclear. Past analysis[15] of patients transferred between hospitals for endovascular therapy have suggested that the difference in reperfusion rates between the two thrombolytic agents narrows in patients with longer time periods between lytic treatment and imaging reassessment. This past analysis only assessed reperfusion rates at a select time point, but the data suggest that the treatment effect of tenecteplase is primarily "frontloaded." Therefore, it may be concluded that the benefit of tenecteplase would be limited in patients who require long interhospital transfers for endovascular therapy. With differing costs between alteplase and tenecteplase, and evidence suggesting that prolonged thrombolysis to groin puncture times are associated with poorer outcomes and a lower likelihood of achieving successful reperfusion with endovascular therapy,[16] identifying the thrombolytic agent that is most likely to achieve early reperfusion, especially in patients who require transfer to endovascular capable centers, is critical.

To determine whether the differential rate of tenecteplase- versus alteplase-induced reperfusion persists across the spectrum of thrombolytic to reperfusion assessment times, we performed a comparative analysis of tenecteplase and alteplase reperfusion rates. We hypothesized that improved reperfusion rates with tenecteplase would be observed across the spectrum of thrombolytic to reperfusion assessment times.

Patients and Methods

Participants

Patients were participants enrolled in the Tenecteplase versus Alteplase before Endovascular Therapy for Ischemic Stroke (EXTEND-IA TNK) trial,[3] the Effect of Intravenous Tenecteplase Dose on Cerebral Reperfusion Before Thrombectomy in Patients with Large Vessel Occlusion Ischemic Stroke (EXTEND-IA TNK Part 2) trial,[17] the intervention arm from the Extending the Time for Thrombolysis in Emergency Neurological Deficits–Intra-Arterial (EXTEND-IA) trial,[18] and the Royal Melbourne Stroke Registry.

The EXTEND-IA TNK trials were multicenter, prospective, randomized trials. Patients with computed tomographic (CT) angiography-confirmed occlusions of the internal carotid artery (ICA), middle cerebral artery (MCA), or basilar artery were enrolled and treated with thrombolytic within 4.5 hours of symptom onset. In EXTEND-IA TNK, patients were randomized to open-label tenecteplase 0.25mg/kg or alteplase 0.90mg/kg, and in EXTEND-IA TNK Part 2, patients were randomized to open-label tenecteplase 0.25mg/kg or 0.40mg/kg. Exclusion criteria for both trials have been previously described.[3,10]

The EXTEND-IA trial was a multicenter, prospective, randomized trial assessing endovascular therapy plus thrombolytic (alteplase 0.90mg/kg) versus thrombolytic alone in patients with confirmed occlusions of the ICA or MCA. Study enrollment and treatment with thrombolysis took place within 4.5 hours of symptom onset, and endovascular therapy was started within 6 hours of symptom onset. Because patients in the thrombolytic-only arm did not receive an early reperfusion assessment, for this analysis we used data from the endovascular therapy plus thrombolytic arm only.

The Royal Melbourne Stroke Registry is an ongoing prospective observational cohort of consecutive patients admitted to the Royal Melbourne Hospital Comprehensive Stroke Centre (Melbourne, Victoria, Australia), which operates as a statewide referral center for endovascular therapy. Patients are either treated locally or transferred from other hospitals for ongoing care, and the registry is designed to collect data on all patients assessed or treated at the Royal Melbourne Hospital. The population of interest for our analysis consisted of patients with confirmed occlusions of the ICA, MCA, or basilar artery who were treated with a thrombolytic (alteplase 0.90mg/kg or tenecteplase 0.25mg/kg, clinician choice) prior to planned endovascular therapy. We performed an analysis of patients who were admitted from January 2017 to December 2020. Transfer patients include those who were assessed and provided a thrombolytic within a mobile

stroke unit, patients treated at primary stroke centers within the Greater Melbourne area (metropolitan), or patients assessed via telestroke from hospitals located within the surrounding regional areas outside the city (rural). We included patients who received a thrombolytic within 9 hours from symptom onset and endovascular therapy within 24 hours from symptom onset, as per EXTEND,[19] DAWN,[20] and DEFUSE-3[21] criteria, respectively. Patients with modified Rankin Scale (mRS) ≥ 4 were excluded. We excluded patients with lytic to assessment time > 4 hours.

Imaging and Clinical Assessments

All patients received noncontrast CT imaging, CT perfusion imaging, and a CT angiogram at baseline. The primary outcome, thrombolytic-induced reperfusion, was defined as the absence of retrievable thrombus or >50% reperfusion on repeat imaging assessment. Repeat imaging assessments were performed at the initial pass during cerebral angiography, and in patients who did not undergo a formal angiogram, through repeat CT perfusion and angiography. In patients who underwent catheter angiography, the expanded Thrombolysis in Cerebral Infarction (eTICI) score for the initial angiography run was centrally adjudicated by a neurointerventionist blinded to study treatment using the pretreatment CT angiogram and CT perfusion as the reference for initial site of occlusion and arterial territory at risk. eTICI = 2b/3 (>50% reperfusion) was regarded as substantial reperfusion. Patients who did not undergo catheter angiography had repeat CT perfusion with automated map production, and reperfusion was defined as >50% reduction in Tmax >6 seconds lesion volume when compared to the baseline perfusion images. No retrievable thrombus was centrally adjudicated by a neurointerventionist blinded to study treatment as the absence of occlusion in the ICA, first segment of the MCA (M1), or proximal second segment of the MCA (M2).

Clinical outcomes evaluated in this study include disability level at 90 days via an ordinal analysis of the mRS, freedom from disability (defined as mRS = 0–1 or no change from baseline at 90 days), functional independence (defined as mRS = 0–2 or no change from baseline at 90 days), and all-cause mortality. Clinical follow-up assessments of trial patients were blinded to treatment (centrally performed); however, assessment of patients within the registry were not blinded.

Statistical Analysis

Individual patient data were pooled across all 4 data sources and across tenecteplase dose groups (0.25mg/kg and 0.40mg/kg). Fisher exact test, analysis of variance, Mann–Whitney *U* test, and Kruskal–Wallis test were used as appropriate when evaluating baseline characteristics. In assessing our primary outcome, we compared the treatment effects of tenecteplase and alteplase (0.90mg/kg) using a Poisson regression model with thrombolytic to reperfusion assessment time as an offset (exposure) time. Treatment effect was adjusted for age, baseline National Institutes of Health Stroke Scale (NIHSS), occlusion site, time from symptom onset to thrombolytic, and study as fixed effects. This estimate was presented as an adjusted incidence rate ratio (aIRR) with respective 95% confidence interval (CI) using alteplase as the reference. In a second analysis, we evaluated the association of thrombolytic to assessment times and thrombolytic-induced reperfusion within each treatment arm, adjusting for the aforementioned variables via modified Poisson models with robust error estimation[22] and assessed for a potential treatment-by-time interaction. This estimate was presented as an adjusted risk ratio (aRR) with respective 95% CIs per 15 minutes of time from thrombolytic administration to reperfusion assessment. Using the final models, we plotted these relationships using the *marginsplot* module from Stata.

Exploratory analyses with the aforementioned methodology were performed in several patient subgroups: (1) patients with an M1 occlusion, (2) patients with an M2 occlusion, and (3) patients who were treated with thrombolysis and then transferred to a comprehensive stroke center for endovascular therapy. Due to the nonrandomized allocation of thrombolytic among patients in the registry cohort, we performed a sensitivity analysis using trial-only patients. Finally, we also assessed reperfusion rates of tenecteplase 0.25 and 0.40mg/kg dosing against alteplase, separately.

We compared the 90-day clinical outcomes of patients who achieved early reperfusion with a thrombolytic to patients who achieved successful reperfusion (eTICI = 2b-3) via endovascular therapy, using mixed effects logistic and proportional odds models with a priori adjustments to age, baseline clinical severity (NIHSS), time from symptom onset to puncture, and study as random effects. In patients with thrombolytic-induced reperfusion found on repeated CT perfusion imaging who did not proceed to endovascular therapy, the time of CT perfusion was used in place of the arterial puncture time as an adjustment covariable. Because mRS assessments were unblinded in the registry cohort, a sensitivity analysis of long-term clinical outcomes was performed using trial-only patients. Statistical analysis was performed using SPSS v28.0 (IBM, Armonk, NY) and Stata v17 (StataCorp, College Station, TX).

Standard Protocol Approvals, Registrations, and Patient Consents

Local research ethics board approval was obtained at all EXTEND-IA and EXTEND-IA TNK enrolling sites. Written informed consent was obtained from the participant or a legal representative before enrollment, except in jurisdictions where deferral of consent for emergency treatment was allowed, in which case consent was obtained at a later time point to continue participation. Local research ethics board approval was acquired for ongoing data collection into the Royal Melbourne Registry, and the requirement for consent was waived for use of deidentified data.

Results

Of the 572 patients enrolled among the 3 randomized trials, 39 patients were excluded; 1 patient lacked the primary outcome, 3 patients did not have lytic to reperfusion assessment times recorded, and 35 patients from the thrombolytic-only arm of the EXTEND-IA trial did not receive an early reperfusion assessment. Between January 2017 and December 2020, 6,284 patients were admitted to the Royal Melbourne Hospital Stroke Unit. Detailed patient selection is outlined in Supplement Figure S1 with 566 registry patients pooled with 533 trial patients. After excluding duplicate trial patient data that were captured in the registry and censoring patients with lytic to assessment times > 4 hours, 893 patients were included in the primary analysis.

Baseline patient characteristics, stratified by trial versus registry status are outlined in Supplemental Table S1. Patients within the registry had a higher proportion of MCA (M1) occlusions, were more likely to be transferred from rural regions, and had longer symptom onset to lytic/puncture and lytic to assessment times. Higher proportions of ICA and M2 occlusions were observed among trial patients. Of the 893 primary analysis patients, 492 (55%) were treated with tenecteplase and 401 (45%) were treated with alteplase. Eighty percent of patients receiving tenecteplase did so within the context of the 3 randomized trials. In contrast, only 33% of alteplase-treated patients received treatment within the trials, the majority receiving treatment within the registry. As such, differences in the baseline patient characteristics of tenecteplase and alteplase patients mirror those of trial versus registry cohorts (Table 1). Baseline comparisons of tenecteplase and alteplase patients within the trial and registry cohorts are outlined in Supplemental Tables S2 and S3, respectively.

Thrombolytic-induced reperfusion was observed in 184 (21%) patients (tenecteplase: 104/492 [21%], alteplase: 80/401 [19%]). In univariate analysis, early reperfusion was associated with occlusion site (greater with occlusion of the M1 and M2), increased age, lower clinical severity, and longer thrombolytic to reperfusion assessment time (Table 2). Time from thrombolytic to reperfusion assessment was longer in those who received alteplase compared to tenecteplase (median = 93 vs 63 minutes; see Table 1). Accounting for thrombolytic to assessment time, tenecteplase was associated with higher rates of thrombolytic-induced reperfusion (aIRR = 1.50, 95% CI = 1.09–2.07). The probability of thrombolytic-induced reperfusion over time from lytic initiation to subsequent assessment, stratified by tenecteplase or alteplase choice, is shown in Figure 1. In multivariate modified Poisson models, longer thrombolytic to reperfusion assessment time was associated with greater reperfusion in both tenecteplase-treated (aRR = 1.08 per 15 minutes, 95% CI = 1.04–1.13) and alteplase-treated (aRR = 1.06 per 15 minutes, 95% CI = 1.00–1.13, $p_{\text{interaction}} = 0.87$) cohorts.

With alteplase as the reference, in an exploratory analysis of M1 occlusions (n = 526), we report an aIRR of 1.41 (95% CI = 0.93–2.14). Similarly, we report an aIRR of 2.07 (95% CI = 0.98–4.37) in an analysis of M2 occlusions (n = 154). In patients who received a thrombolytic at a primary stroke center and were then subsequently transferred (n = 466), we report an aIRR of 1.40 (95% CI = 0.95–2.05). The probability of thrombolytic-induced reperfusion over time from lytic initiation to subsequent assessment for these 3 specific patient subgroups is shown in Figure 2. In a sensitivity analysis of trial-only patients (n = 525), we report an aIRR of 1.91 (95% CI = 0.95–3.95; Supplemental Fig S2). Finally, in a comparison of 0.25mg/kg and 0.40mg/kg tenecteplase dosing to alteplase, we report aIRRs of 1.47 (95% CI = 1.07–2.03) and 1.63 (95% CI = 0.85–3.16), respectively.

Successful reperfusion, either through early reperfusion with a thrombolytic or following endovascular therapy, was achieved in 764 patients (86%). Of these 764 patients, 90-day mRS was reported in 709 patients (93%). Adjusting for age, baseline clinical severity (NIHSS), and time from symptom onset to puncture (or repeat imaging), early reperfusion (prior to endovascular therapy) was associated with improved mRS scores at 90 days (adjusted common odds ratio [OR] = 2.15, 95% CI = 1.54–3.01) when compared to post-endovascular therapy reperfusion (Fig 3). Patients who achieved early reperfusion with thrombolysis had increased rates of freedom from disability (adjusted OR = 2.46, 95% CI = 1.64–3.68) and functional independence (adjusted OR = 2.85, 95% CI = 1.82–4.46), and reduced rates of mortality (adjusted OR = 0.43, 95%

TABLE 1. Baseline Patient Characteristics Stratified by Treatment (All Patients, n = 893)

Characteristic	Pooled tenecteplase, 0.40 and 0.25mg/kg, n = 492	Alteplase, 0.90mg/kg, n = 401	*p*
Age, yr, median (IQR)	73 (64–81)	71 (62–79)	0.02
Female sex	220 (45%)	180 (45%)	0.96
Cause of stroke			
Cardioembolic occlusion	215 (44%)	194 (48%)	0.10
Large artery occlusion	78 (16%)	73 (18%)	
Undetermined/other	199 (40%)	134 (33%)	
Study			
EXTEND IA	0 (0%)	32 (8%)	N/A
EXTEND IA-TNK	99 (20%)	101 (25%)	
EXTEND IA-TNK Part 2	293 (60%)	0 (0%)	
Royal Melbourne Registry	100 (20%)	268 (67%)	
Medical history			
Hypertension	324 (66%)	260 (65%)	0.75
Diabetes	80 (16%)	72 (18%)	0.50
Dyslipidemia	205 (42%)	174 (43%)	0.60
Prior stroke or TIA	71 (14%)	45 (11%)	0.16
Antiplatelet use	199/487 (41%)	139 (35%)	0.06
Clinical and laboratory markers			
Glucose, mmol/l, median (IQR)[a]	6.4 (5.8–8.2)	6.4 (5.7–7.9)	0.54
NIHSS, median (IQR)[b]	17 (11–21)	16 (11–20)	0.29
Imaging			
Site of vessel occlusion			
Internal carotid artery	94/487(19%)	69/399 (17%)	<0.01
MCA [first segment]	270/487 (55%)	256/399 (64%)	
MCA [second segment]	102/487 (21%)	52/399 (13%)	
Basilar artery	21/487 (4%)	22/399 (5%)	
Tandem occlusion	68 (14%)	62 (17%)	0.25
Workflow processes			
Location			
Metropolitan[c]	389 (79%)	268 (67%)	<0.01
Mobile stroke unit	37 (8%)	7 (2%)	
Rural	66 (13%)	126 (31%)	
Transferred for care	208 (42%)	258 (64%)	<0.01
Time from symptom onset to thrombolytic initiation, min, median (IQR)	134 (100–180)	145 (108–194)	<0.01
Time from first hospital arrival to thrombolytic, min, median (IQR)[d]	53 (41–72)	53 (30–67)	0.03
Time from symptom onset to arterial puncture or repeat imaging, min, median (IQR)[e]	190 (145–265)	250 (180–315)	<0.01
Time from thrombolytic to reperfusion assessment [initial angiographic assessment or repeat CT perfusion/angiography], median (IQR)	63 (40–100)	93 (65–144)	<0.01

Note: Results are given as n (%) unless otherwise stated.

[a]Missing 325 patients.

[b]Missing 19 patients.

[c]Defined as patients treated locally at the Royal Melbourne Hospital or transferred from primary stroke centers within the Greater Melbourne area.

[d]Missing 338 patients.

[e]Missing 1 patient.

Abbreviation: CT = computed tomography; IQR = interquartile range; MCA = middle cerebral artery; N/A = not applicable; NIHSS=National Institutes of Health Stroke Scale; TIA = transient ischemic attack.

TABLE 2. Factors Associated with Early Reperfusion (Whole Cohort, n = 893)

Factor	Thrombolytic-Induced Reperfusion, n = 184	No Thrombolytic-Induced Reperfusion, n = 709	*p*
Age, yr, median (IQR)	74 (66–82)	72 (62–80)	0.01
Female sex	91 (49%)	309 (44%)	0.15
Cause of stroke			
Cardioembolic occlusion	86 (47%)	323 (46%)	0.38
Large artery occlusion	25 (14%)	126 (18%)	
Undetermined/other	73 (40%)	260 (37%)	
Medical history			
Hypertension	124 (67%)	460 (65%)	0.52
Diabetes	31 (17%)	121 (17%)	0.94
Dyslipidemia	87 (47%)	292 (41%)	0.14
Prior stroke or TIA	32 (17%)	84 (12%)	0.05
Antiplatelet use	79 (43%)	259/704 (37%)	0.13
Clinical and laboratory markers			
Glucose, mmol/l, median (IQR)[a]	6.4 (5.7–8.4)	6.4 (5.7–7.9)	0.59
NIHSS, median (IQR)[b]	15 (8–19)	17 (12–21)	<0.01
Imaging			
Site of vessel occlusion			
Internal carotid artery	4/183 (2%)	159/703 (23%)	<0.01
MCA [first segment]	112/183 (61%)	414/703 (59%)	
MCA [second segment]	53/183 (29%)	101/703 (14%)	
Basilar artery	14/183 (8%)	29/703 (4%)	
Tandem occlusion	20/181 (11%)	110/680 (16%)	0.09
Workflow processes			
Location:			
Metropolitan[c]	111 (50%)	546 (77%)	<0.01
Mobile stroke unit	11 (6%)	33 (5%)	
Rural	62 (34%)	130 (18%)	
Transferred for care	117 (64%)	349 (49%)	<0.01
Time from stroke onset to thrombolytic initiation, min, median (IQR)	136 (99–180)	139 (106–188)	0.18
Time from first hospital arrival to thrombolytic, min, median (IQR)[d]	50 (35–69)	54 (40–70)	0.12
Time from stroke onset to arterial puncture or repeat imaging, min, median (IQR)[e]	230 (165–309)	213 (158–292)	0.04
Time from thrombolytic to reperfusion assessment [initial angiographic assessment or repeat CT perfusion/ angiography], median (IQR)	95 (62–151)	72 (45–1,115)	<0.01

Note: Results are given as n (%) unless otherwise stated.

[a]Missing 325 patients.

[b]Missing 19 patients.

[c]Defined as patients treated locally at the Royal Melbourne Hospital or transferred from primary stroke centers within the Greater Melbourne area.

[d]Missing 338 patients.

[e]Missing 1 patient.

Abbreviation: CT = computed tomography; IQR = interquartile range; MCA = middle cerebral artery; NIHSS = National Institutes of Health Stroke Scale; TIA = transient ischemic attack.

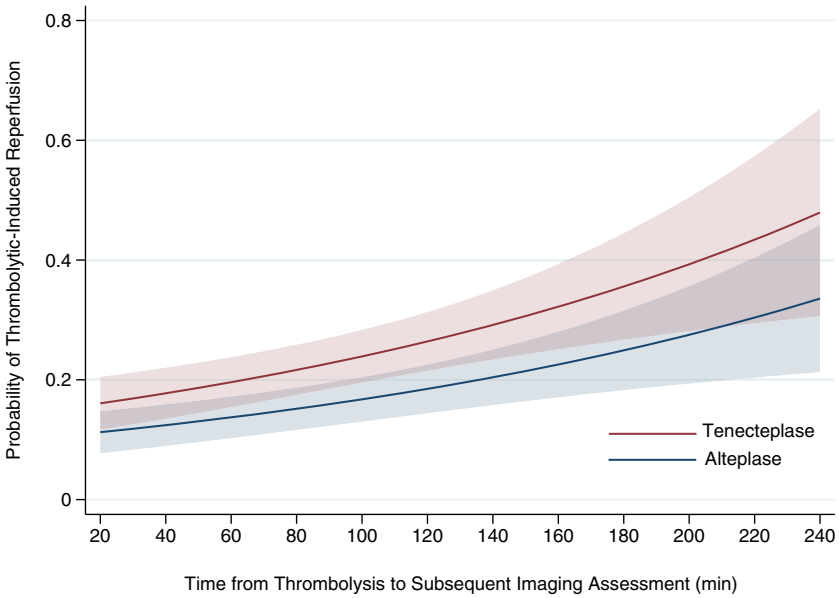

FIGURE 1: Probability of thrombolytic-induced reperfusion from the initiation of thrombolytic to subsequent assessment (initial angiographic assessment or repeat computed tomographic perfusion/angiography) stratified by thrombolytic treatment (n = 893). Thrombolytic to assessment time was significantly associated with reperfusion (tenecteplase: adjusted risk ratio [aRR] = 1.08 per 15 minutes, 95% confidence interval [CI] = 1.04–1.13 vs alteplase: aRR = 1.06 per 15 minutes, 95% CI = 1.00–1.13). No significant treatment by time interaction was observed (p = 0.87). The shaded areas indicate 95% CIs.

CI = 0.21–0.87; Table 3). These findings remained consistent when a sensitivity analysis of trial-only patients was performed (Supplementary Table S4).

Discussion

In a pooled individual patient data analysis of 3 randomized trials and a nonrandomized registry cohort, we found that thrombolytic-induced reperfusion prior to thrombectomy favored tenecteplase over alteplase along a spectrum of lytic to assessment times. Furthermore, large vessel occlusion patients who were able to achieve reperfusion with either thrombolytic prior to endovascular therapy had reduced disability in the long-term compared to patients who achieved successful reperfusion following endovascular therapy.

The findings of our comparative model are in contrast to past comparisons of tenecteplase- and alteplase-treated transfer patients, in whom the differences in reperfusion rates appeared to converge with longer lytic to assessment times (tenecteplase 21% vs alteplase 18% at a median 90 minutes postlysis).[15] However, our time–reperfusion models (see Fig 2) are similar to previous modeling presented by Menon and colleagues in the INTERRSeCT study,[7] and our analysis benefits from a larger sample size and the use of prospective multicenter data. It is important to note that the time when an imaging reassessment was performed does not tell us the exact time when reperfusion occurred. As such, we are not able to comment on the potential mechanism underlying the higher rates of thrombolytic-induced reperfusion with tenecteplase. Given the bolus nature of tenecteplase administration, the higher rates of reperfusion may reflect a faster onset of plasmin generation and therefore, the lytic effect of tenecteplase may be a "frontloaded" phenomenon.[23] However, the longer half-life of tenecteplase, in combination with an increased resistance to plasminogen activator inhibitor, may also extend the drug's ability to debulk large clots.[24] Further investigations with the use of real-time continuous Doppler ultrasound, as presented previously by Tsivgoulis and colleagues, may provide additional insights into these questions.[25] With an increased rate of reperfusion at longer lytic to assessment time points, and consistent findings in a subanalysis of patient transfers (see Fig 2C), our analysis is supportive of the use of tenecteplase in patients requiring transfer to endovascular-capable centers.

Our study has several limitations. First, there were several differences in baseline patient characteristics between tenecteplase- and alteplase-treated patients. Baseline medical differences between tenecteplase- and alteplase-treated patients were minimal between trial (Supplemental Table S2) and registry cohorts (Supplemental Table S3). Among trial participants, differences in workflow processes (eg, a higher number of patient transfers in the tenecteplase arm) were observed;

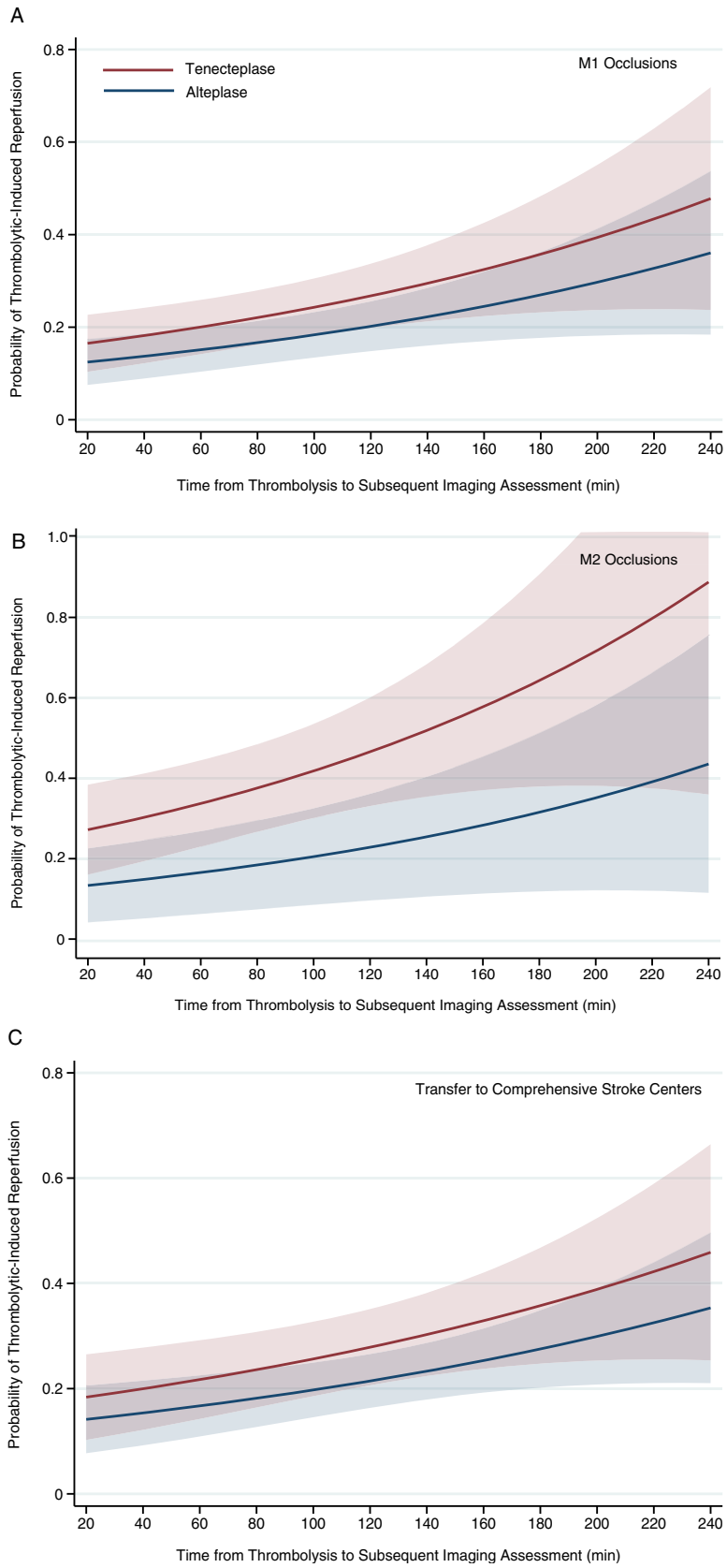

FIGURE 2: Probability of thrombolytic-induced reperfusion from the initiation of thrombolytic to subsequent assessment in specific subgroups. (A) First segment (M1) middle cerebral artery (MCA) occlusions (n = 526). (B) Second segment (M2) MCA occlusions (n = 154). (C) Patients transferred to a comprehensive stroke center (n = 466). The shaded areas indicate 95% confidence intervals.

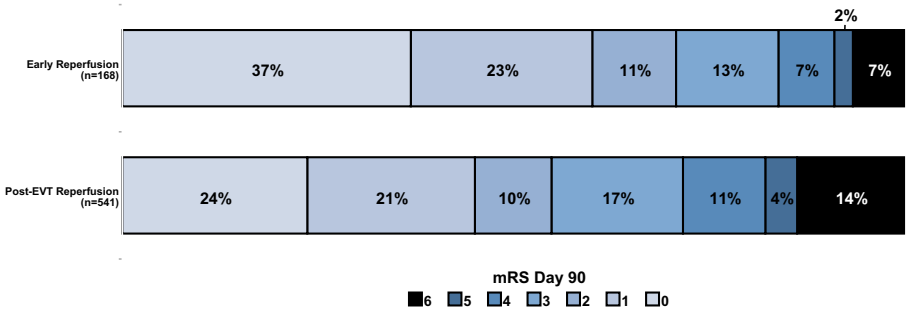

FIGURE 3: Modified Rankin Scale (mRS) scores at 90 days stratified by patients who achieved early reperfusion with thrombolysis (tenecteplase or alteplase) versus patients who achieved reperfusion following endovascular therapy. Early reperfusion was associated with mRS shift, adjusting for baseline National Institutes of Health Stroke Scale, age, and time from symptom onset to arterial puncture (or repeated computed tomographic perfusion in those who reperfused and did not proceed to thrombectomy) and study (as a random effect), when compared to patients who only achieved successful reperfusion (expanded Thrombolysis in Cerebral Infarction = 2b–3) after endovascular therapy (adjusted common odds ratio = 2.15, 95% confidence interval = 1.54–3.01). EVT = endovascular therapy.

TABLE 3. Clinical Outcomes Stratified by Patients Who Achieved Early Reperfusion with Thrombolysis (Tenecteplase or Alteplase) versus Patients Who Achieved Reperfusion following Endovascular Therapy

	Early Reperfusion, n = 168	Post-EVT Reperfusion, n = 541[a]	Effect Size
Ordinal analysis of mRS[b,c]	1 (0–3)	2 (1–4)	acOR = 2.15 (1.54–3.01)
Freedom from disability[c,d]	106 (63%)	248 (46%)	aOR = 2.46 (1.64–3.68)
Functional independence[c,e]	124 (74%)	300 (55%)	aOR = 2.85 (1.82–4.46)
Mortality[c]	11 (7%)	74 (14%)	aOR = 0.43 (0.21–0.87)

[a]Post-EVT successful reperfusion is defined as expanded Thrombolysis in Cerebral Infarction 2b–3.
[b]Data are represented as median (interquartile range).
[c]Adjusted for baseline National Institutes of Health Stroke Scale score, age, time from symptom onset to arterial puncture (or repeated computed tomographic perfusion in those who reperfused and did not proceed to thrombectomy), and study (as a random effect).
[d]Defined as mRS score of 0–1 or no change from baseline.
[e]Defined as mRS score of 0–2 or no change from baseline.
Abbreviations: acOR = adjusted common odds ratio; aOR = adjusted odds ratio; EVT = endovascular therapy; mRS = modified Rankin Scale.

this is due to an increased number of regional centers and rural transfers involved in EXTEND-IA TNK Part 2. Most notably, we observed differences in vessel occlusion site, onset to thrombolysis times, and lytic to assessment times. Our main findings were adjusted for these imbalances, and in an exploratory analysis of patient subgroups, we observed consistency in effect estimates between the selected subgroups and our main analysis. The widened CIs and lack of formal statistical significance among the reperfusion rates calculated for each subgroup are likely due to limitations with sample size. Furthermore, in a sensitivity analysis of trial-only patients and 0.25mg/kg tenecteplase versus alteplase comparisons, we continued to show consistency with our overall findings. Regardless, further validation in an independent cohort is recommended.

Second, our time–reperfusion model is limited to lytic to assessment times of <240 minutes. We made a conscious choice to censor data at the 240-minute mark, as we wanted to ensure that an adequate sample size was present at each time epoch to ensure model accuracy. Although this limits our understanding of thrombolytic-induced reperfusion differences between tenecteplase and alteplase in patients with prolonged lytic to reperfusion assessment times, prior workflow studies of interhospital transfers for endovascular therapy-eligible patients have largely reported transfer times ranging from 20 to 300 minutes.[26–28] As such, we feel that our model is representative of patients in clinical practice. In addition, change in NIHSS at the time of reperfusion assessment was not available for our analysis. We are therefore not

able to comment on the immediate changes in clinical improvement between tenecteplase and alteplase.

Third, we selected a dichotomous reperfusion outcome that had been previously used in both the EXTEND-IA and EXTEND-IA TNK trials. Although this approach allows for straightforward data pooling and is easy to interpret, it prevents us from being able to assess partial reperfusion and/or thrombus migration. The relationship between tenecteplase use and thrombus migration is not well understood and therefore warrants further investigation. Multiple grading systems that are designed to assess these concepts are available[29] but are predominantly designed for assessment of cerebral angiograms, making data pooling with perfusion and CT angiographic images difficult. As such, we elected to utilize a dichotomous approach that would work for both the catheter angiogram and CT setting.

Finally, the pooling of randomized and nonrandomized patients increased the risk of selection bias, particularly when assessing clinical outcomes. In conjunction with this, the mRS assessment of registry patients was unblinded, thereby also generating a risk of evaluation bias. It is with this in mind that we performed a sensitivity analysis of trial-only patients, the findings of which were consistent with our main analysis.

Conclusions

In large vessel occlusion patients with thrombolytic to reperfusion assessment times of up to 240 minutes, increased rates of early reperfusion with tenecteplase persisted across the time spectrum. Achieving reperfusion with an intravenous thrombolytic prior to endovascular therapy was strongly associated with improved clinical outcomes when compared to patients who achieved successful reperfusion only after endovascular therapy. Our findings provide further support for the use of tenecteplase as the preferred agent in drip-and-ship models of stroke care.

Acknowledgments

None. Open access publishing facilitated by The University of Melbourne, as part of the Wiley - The University of Melbourne agreement via the Council of Australian University Librarians.

Author Contributions

V.Y., L.C., and B.C.V.C. contributed to the conception and design of the study; J.B., K.A., M.U., L.P., L.W., and G.S. contributed to the acquisition and analysis of data; P.J.M., T.J.K., N.Y., V.T., T.Y.W., D.G.S., H.M.D., T.W., B.Y., P.M.D., M.W.P., G.A.D., and S.M.D. contributed to drafting the text or preparing the figures.

Potential Conflicts of Interest

T.J.K. receives educational meeting support from Boehringer Ingelheim. D.G.S. has received speaker's honoraria from Boehringer Ingelheim. M.W.P. is on the Global Metalyse Advisory Board for Boehringer Ingelheim. V.T. receives personal compensation from Boehringer Ingelheim. The remaining authors have nothing to report.

Data Availability Statement

The authors declare that supporting data and methodological details are available within the article and online-only supplement. The data that support the findings of this study can be obtained from the study authors upon reasonable request.

References

1. Arrarte Terreros N, Bruggeman AAE, Swijnenburg ISJ, et al. Early recanalization in large-vessel occlusion stroke patients transferred for endovascular treatment. J Neurointerv Surg 2022;14:480–484.
2. Czap AL, Parker S, Yamal J, et al. Immediate recanalization of large-vessel occlusions by tissue plasminogen activator occurs in 28% of patients treated in a Mobile stroke unit. Stroke Vasc Interv Neurol 2022;2:e000101.
3. Goyal M, Almekhlafi M, Dippel DW, et al. Rapid alteplase administration improves functional outcomes in patients with stroke due to large vessel occlusions. Stroke 2019;50:645–651.
4. Saver JL, Fonarow GC, Smith EE, et al. Time to treatment with intravenous tissue plasminogen activator and outcome from acute ischemic stroke. JAMA 2013;309:2480–2488.
5. Campbell BCV, Mitchell PJ, Churilov L, et al. Tenecteplase versus alteplase before thrombectomy for ischemic stroke. N Engl J Med 2018;378:1573–1582.
6. Seners P, Turc G, Naggara O, et al. Post-thrombolysis recanalization in stroke referrals for thrombectomy: incidence, predictors, and prediction scores. Stroke 2018;49:2975–2982.
7. Menon BK, Al-Ajlan FS, Najm M, et al. Association of Clinical, imaging, and thrombus characteristics with recanalization of visible intracranial occlusion in patients with acute ischemic stroke. JAMA 2018; 320:1017–1026.
8. Ospel JM, Singh N, Almekhlafi MA, et al. Early recanalization with alteplase in stroke because of large vessel occlusion in the ESCAPE trial. Stroke 2021;52:304–307.
9. Demchuk AM, Goyal M, Yeatts SD, et al. Recanalization and clinical outcome of occlusion sites at baseline CT angiography in the interventional Management of Stroke III trial. Radiology 2014;273: 202–210.
10. Mishra SM, Dykeman J, Sajobi TT, et al. Early reperfusion rates with IV tPA are determined by CTA clot characteristics. AJNR Am J Neuroradiol 2014;35:2265–2272.
11. Labiche LA, Malkoff M, Alexandrov AV. Residual flow signals predict complete recanalization in stroke patients treated with TPA. J Neuroimaging 2003;13:28–33.

12. Parsons M, Spratt N, Bivard A, et al. A randomized trial of tenecteplase versus alteplase for acute ischemic stroke. N Engl J Med 2012;366:1099–1107.

13. Bivard A, Huang X, Levi CR, et al. Tenecteplase in ischemic stroke offers improved recanalization: analysis of 2 trials. Neurology 2017; 89:62–67.

14. Bivard A, Zhao H, Churilov L, et al. Comparison of tenecteplase with alteplase for the early treatment of ischaemic stroke in the Melbourne Mobile stroke unit (TASTE-A): a phase 2, randomised, open-label trial. Lancet Neurol 2022;21:520–527.

15. Seners P, Caroff J, Chausson N, et al. Recanalization before thrombectomy in tenecteplase vs. alteplase-treated drip-and-ship patients. J stroke 2019;21:105–107.

16. Zhu F, Gauberti M, Marnat G, et al. Time from I.V. thrombolysis to thrombectomy and outcome in acute ischemic stroke. Ann Neurol 2021;89:511–519.

17. Campbell BCV, Mitchell PJ, Churilov L, et al. Effect of intravenous Tenecteplase dose on cerebral reperfusion before thrombectomy in patients with large vessel occlusion ischemic stroke: the EXTEND-IA TNK part 2 randomized clinical trial. JAMA 2020;323:1257–1265.

18. Campbell BCV, Mitchell PJ, Kleinig TJ, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med 2015;372:1009–1018.

19. Ma H, Campbell BCV, Parsons MW, et al. Thrombolysis guided by perfusion imaging up to 9 hours after onset of stroke. N Engl J Med 2019;380:1795–1803.

20. Nogueira RG, Jadhav AP, Haussen DC, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. N Engl J Med 2018;378:11–21.

21. Albers GW, Marks MP, Kemp S, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. N Engl J Med 2018;378:708–718.

22. Zou G. A modified poisson regression approach to prospective studies with binary data. Am J Epidemiol 2004;159:702–706.

23. Benedict CR, Refino CJ, Keyt BA, et al. New variant of human tissue plasminogen activator (TPA) with enhanced efficacy and lower incidence of bleeding compared with recombinant human TPA. Circulation 1995;92:3032–3040.

24. Logallo N, Kvistad CE, Thomassen L. Therapeutic potential of Tenecteplase in the Management of Acute Ischemic Stroke. CNS Drugs 2015;29:811–818.

25. Tsivgoulis G, Saqqur M, Sharma VK, et al. Timing of recanalization and functional recovery in acute ischemic stroke. J stroke 2020;22: 130–140.

26. Ng FC, Low E, Andrew E, et al. Deconstruction of Interhospital transfer workflow in large vessel occlusion. Stroke 2017;48:1976–1979.

27. Pérez de la Ossa N, Abilleira S, Jovin TG, et al. Effect of direct transportation to thrombectomy-capable center vs local stroke center on neurological outcomes in patients with suspected large-vessel occlusion stroke in nonurban areas: the RACECAT randomized clinical trial. JAMA 2022;327:1782–1794.

28. van Meenen LCC, Riedijk F, Stolp J, et al. Pre- and Interhospital workflow times for patients with large vessel occlusion stroke transferred for Endovasvular thrombectomy. Front Neurol 2021;12: 730250.

29. Zaidat OO, Lazzaro MA, Liebeskind DS, et al. Revascularization grading in endovascular acute ischemic stroke therapy. Neurology 2012; 79:S110–S116.