Real-world comparative safety and efficacy of tenecteplase *versus* alteplase in acute ischemic stroke patients with large vessel occlusion

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Abstract

Background and aims: Tenecteplase has recently emerged as an alternative thrombolytic agent in acute ischemic stroke (AIS) patients with large vessel occlusion (LVO), possibly superior in achieving early reperfusion compared with alteplase. We aimed to compare the safety and efficacy of intravenous tenecteplase with intravenous alteplase for AIS patients with LVO in everyday clinical practice settings.

Methods: We prospectively evaluated patients with AIS due to LVO, treated with intravenous thrombolysis (IVT) with or without mechanical thrombectomy in two tertiary stroke centers. Patients were treated with standard-dose alteplase (0.9 mg/kg) or 0.25 mg/kg tenecteplase. Safety outcomes included prevalence of symptomatic intracranial hemorrhage (sICH) and mortality. Efficacy outcomes included averted thrombectomy, major neurological improvement at 24 h (defined as decrease in baseline NIHSS score of 8 points or greater) and functional status on discharge and on 3 months assessed by modified Rankin Scale (mRS).

Results: Nineteen AIS patients with LVO received tenecteplase and 39 received alteplase. We observed a non-significant higher rate of averted thrombectomies (32% *versus* 18%, $p = 0.243$) and a non-significant higher rate of sICH (16% *versus* 5%, $p = 0.201$) in the tenecteplase group. The rate of 24 h major neurological improvement was higher in the tenecteplase group (64% *versus* 33%, $p = 0.046$) but this was marginally attenuated in multivariable analyses (adjusted OR 10.22, 95% CI: 0.73–142.98; $p = 0.084$). Discharge mRS, 3-months mRS, and 3-month functional independence (mRS scores of 0–2) did not differ ($p > 0.2$) between the two groups. The rates of 3-month mortality (11% *versus* 18%, $p = 0.703$) were similar in the two groups. No independent association between thrombolytic agent and safety or efficacy outcomes emerged in multivariable regression analyses.

Conclusion: The present pilot observational study highlights that AIS patients with LVO treated with 0.25 mg/kg bolus administration of tenecteplase had increased likelihood to achieve early neurological improvement compared with AIS patients treated with alteplase, but this association was attenuated after adjustment for potential confounders. There were no significant differences in 3-month functional or safety outcomes between the two groups. This preliminary real-world observation requires independent confirmation in larger, multicenter studies.

Keywords: alteplase, intravenous thrombolysis, large vessel occlusion, mechanical thrombectomy, stroke, tenecteplase

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Introduction

Intravenous thrombolysis (IVT) with alteplase in acute ischemic stroke (AIS) patients remains the only approved systemic reperfusion therapy, albeit with a relatively low potential to achieve complete recanalization in patients with large vessel occlusions (LVOs).[1] Tenecteplase is a genetically modified variant of alteplase, which exhibits some important pharmacological advantages:[2] higher fibrin specificity resulting in absence of fibrinogen depletion and lower incidence of systemic hemorrhage, increased resistance to plasminogen activator inhibitor-1, and longer serum half-life (up to 20 min) that favors bolus administration. Tenecteplase has been approved for systemic reperfusion of acute myocardial infarction and has recently been studied as an alternative thrombolytic agent in AIS.[3,4] In a recently published randomized controlled clinical trial (RCT) (EXTEND-IA TNK)[5] tenecteplase (0.25 mg/kg), showed increased rates of complete reperfusion in patients with AIS due to LVO, scheduled to undergo mechanical thrombectomy (MT), compared with standard-dose (0.9 mg/kg) alteplase; this resulted in better functional outcomes, quantified by modified Rankin Scale (mRS) scores at 3 months. In addition, the second part of the same trial, which was designed to clarify the optimal dosage of tenecteplase, did not show any significant advantage of the higher (0.4 mg/kg) compared with the lower dose (0.25 mg/kg).[6]

Aims

In view of the former considerations, we sought to compare in everyday clinical practice the safety and efficacy outcomes of intravenous tenecteplase and intravenous alteplase for AIS patients with LVO who are eligible for acute reperfusion therapies (IVT with or without MT) in two tertiary stroke centers.

Methods

We prospectively evaluated acute AIS patients due to LVO, treated with IVT with or without MT during a 4-year period (January 2016–March 2020) in two tertiary stroke centers in Greece (Department of Neurology, Attikon University Hospital, and Stroke Unit, Metropolitan Hospital) participating in SITS (Safe Implementation of Thrombolysis in Stroke) Registry.[7] Included patients were treated with alteplase between January 2016 and March 2018 and with tenecteplase after April 2018,

following the publication of EXTEND-IA TNK trial results.[5] The present study is a *post hoc* analysis of prospective registry data. Patients were included if they fulfilled the following criteria: (1) age over 18 years old, (2) clinically diagnosed AIS with a measurable neurologic deficit in the National Institute of Health Stroke Scale (NIHSS) presenting within the 4.5 h window from symptom onset (NIHSS score ⩾1), (3) LVO (internal carotid artery, first segment of middle cerebral artery, second segment of middle cerebral artery or basilar artery),[5] confirmed by computed tomography (CT) angiography, magnetic resonance (MR) angiography or transcranial Doppler and (4) eligibility for intravenous thrombolysis according to international recommendations,[8–10] (5) signed informed consent by the patient or his/her proxies for the off-label treatment with tenecteplase (April 2018–March 2020) or the on-label treatment with alteplase (January 2016–March 2018).

Decision for systemic reperfusion with IVT (alteplase 0.9 mg/kg or tenecteplase 0.25 mg/kg) was made based on AHA/ASA[8,9] or European Stroke Organisation (ESO) recommendations[10] and the judgment of the treating physician (fellowship-trained vascular neurologists). Patients who declined treatment with tenecteplase were still offered standard treatment with alteplase and were included in the final analysis.

The following parameters were prospectively recorded for all included patients: (1) Demographic characteristics (age, sex), (2) history of vascular risk factors (diabetes mellitus, hypertension, current smoking, hypercholesterolemia, coronary artery disease, congestive heart failure and valvular disease), (3) prior history of stroke, (4) laboratory test values on admission [international normalized ratio (INR), activated partial thromboplastin time (aPTT), total platelet count, glucose and low-density lipoprotein (LDL) levels], (5) admission systolic and diastolic blood pressures, measured using automated blood pressure cuffs. Stroke severity was assessed with NIHSS score at admission, 24 h post IVT, and at discharge. Safety outcomes included prevalence of symptomatic intracranial hemorrhage (sICH) and mortality; sICH was defined using standard SITS registry definitions.[7] The primary efficacy outcomes included averted thrombectomy. Secondary efficacy outcomes included major neurological improvement at 24 h, and functional status on discharge and on 3 months. Major neurological improvement at 24 h was

considered if there was a reduction in the baseline NIHSS score of at least 8 points, in accordance with the relevant definition in the AUSTRALIAN TNK trial.[4] Functional status on discharge and at 3 months was evaluated using mRS. Functional independence was defined as a mRS score of 0–2 at 3 months. Stroke severity and functional outcome (mRS) at discharge and at 3 months were assessed by certified vascular neurologists.[11]

CT and CT angiography were performed on 64-slices scanners. CT slice thickness was 1.25 mm with acquisitions in axial, sagittal and coronal planes, with three-dimensional reformations. We used a magnetic resonance imaging (MR) scanner of 1.5 Tesla (Siemens Avanto Magnetom). The stroke MRI protocol included axial diffusion weighted imaging, axial gradient echo T2*-weighted or susceptibility weighted imaging series, time-of-flight MR angiography (TOF) and fluid-attenuated inversion recovery sequences. CT/MR findings were interpreted and extracted in each participating institution independently by experienced neurologists or neuroradiologists that were blinded to clinical outcomes. The hyperdense vessel sign (HVS), a highly specific marker of arterial obstruction,[12] was identified on non-contrast CT if the lumen of any, non-calcified, intracranial artery appeared more dense than adjacent or equivalent contralateral arteries. Clot length was quantified using standard methodology.[13] Transcranial color-coded duplex (TCCD) or transcranial Doppler sonography were performed by certified in neurosonology vascular neurologists using a standardized, fast track insonation protocol for transcranial ultrasound examination.[14,15]

The study was approved by the local Ethics Committees of Attikon University Hospital (decision number EBΔ37) and Metropolitan Hospital (decision number 2829). All participants provided signed informed consent.

Statistical analysis

All binary variables were presented as percentages, while continuous variables were presented with their corresponding mean values and standard deviations (SDs), in cases of normal distributions, or as medians with interquartile ranges (IQRs) in cases of skewed distributions. Statistical comparisons between the two groups were performed using unpaired t-test, Mann–Whitney U-test, χ^2 test and Fisher exact test, as appropriate. The distribution of the 3-month mRS scores between patients treated with alteplase and tenecteplase was compared using the Cochran–Mantel–Haenszel test and univariable/multivariable ordinal logistic regression (shift analysis).

All efficacy and safety outcomes of interest were further assessed in multivariable binary and ordinal multivariable logistic regression models adjusting for the *a priori* defined confounders of age, baseline NIHSS score, and presence of proximal intracranial occlusion. The final variables that were independently associated in the multivariable logistic and ordinal regression analyses with the outcome of interest were selected using an alpha value of 0.05 and adjusted associations were provided as odds ratios (ORs) or common odds ratios (cORs), with their corresponding 95% confidence intervals (95% CI).

All statistical analyses were conducted with the Stata Statistical Software Release 13 (College Station, TX, StataCorp LP).

Results

Our final cohort comprised 58 AIS patients with LVO; 19 received tenecteplase (mean age 69 years, IQR 63–77) and 39 received alteplase (mean age 70, IQR 51–78). Baseline characteristics in the two treatment groups are summarized in Table 1. In general, there were no significant differences between the two groups. Median admission NIHSS scores were 19 points (IQR: 12–23) in the tenecteplase group and 16 points (IQR: 10–20) in the alteplase group, a difference that was not significant ($p = 0.340$). The prevalence of proximal occlusions (internal carotid artery, first segment of middle cerebral artery, basilar artery) was 90% in the tenecteplase group and 74% in the alteplase group; however, this difference did not reach statistical significance ($p = 0.182$). The onset-to-treatment times were almost identical [median 165 min (IQR 105–230) in tenecteplase *versus* 165 min (IQR: 130–220) in alteplase; $p = 0.486$] in both groups. Regarding the neuroimaging characteristics, thrombus length tended to be higher in the tenecteplase group (14.6 ± 9.0 mm *versus* 11.4 ± 6.7 mm, $p = 0.167$). Although not reaching statistical significance, HVS was also more prevalent in the tenecteplase group (69% *versus* 47%, $p = 0.107$).

Table 2 summarizes the efficacy and safety outcomes in each patient group. Averted MT

Table 1. Baseline characteristics in patients treated with tenectplase and alteplase.

	Tenecteplase (*n* = 19)	Alteplase (*n* = 39)	*p*-value
Age, years (median, IQR)	69 (51–78)	70 (63–77)	0.471
Male sex (%)	57.9%	35.8%	0.112
Weight, kg (median, IQR)	75 (66–97)	80 (74–90)	0.392
Smoking (%)	36.9%	28.2%	0.505
Hypertension (%)	78.9%	64.1%	0.251
Diabetes (%)	10.5%	33.3%	0.108
Hyperlipidemia (%)	47.3%	43.6%	0.786
Prior stroke (%)	15.8%	7.7%	0.382
Congestive heart failure (%)	10.5%	10.2%	>0.999
Valvular disease (%)	5.3%	12.8%	0.653
Coronary artery disease (%)	15.8%	38.5%	0.130
NIHSS score on admission, points (median, IQR)	19 (12–23)	16 (10–20)	0.340
Systolic BP on admission, mmHg (median, IQR)	140 (120–158)	150 (135–165)	0.169
Diastolic BP on admission, mmHg (median, IQR)	80 (62–90)	80 (71–90)	0.491
Platelet count on admission, $\times10^9$/l (median, IQR)	218 (196–282)	232 (200–295)	0.607
LDL on admission, mg/dL (median, IQR)	117 (85–136)	119 (103–145)	0.414
Hyperglycemia on admission (%)*	10.5%	33.3%	0.108
Onset-to-door time, min (median, IQR)	120 (60–161)	110 (75–150)	>0.999
Door-to-needle time, min (median, IQR)	40 (30–45)	50 (35–65)	0.065
Onset-to-treatment time (median, IQR)	165 (105–230)	165 (130–220)	0.486
Posterior circulation stroke (%)	15.8%	5.1%	0.318
Hyperdense vessel sign in CT (%)	47.4%	69.2%	0.107
Thrombus length, mm (mean ± SD)	14.6 ± 9.0	11.4 ± 6.7	0.167
Intracranial vessel occlusion (%)	ICA: 5.3% M1-MCA: 68.4% M2-MCA: 10.5% Basilar: 15.8%	7.7% 61.5% 25.6% 5.1%	0.348
Proximal occlusion (%)†	89.5%	74.3%	0.182
Duration of hospitalization, days (mean ± SD)	15.2 ± 14.8	14.6 ± 15.6	0.977

*admission glucose ≥144 mg/dL.
†ICA, M1-MCA, BA.
BA, basilar artery; BP, blood pressure; CT, computed tomography; ICA, internal carotid artery; IQR, interquartile range; LDL, low-density lipoprotein; MCA, middle cerebral artery; NIHSS, National Institute of Health Stroke Scale; SD, standard deviation.

Table 2. Outcomes in patients treated with tenecteplase and alteplase.

	Tenecteplase (*n* = 19)	Alteplase (*n* = 39)	*p*-value
Averted mechanical thrombectomy (%)	31.5%	17.9%	0.243
Any intracranial hemorrhage (%)	21.7%	7.7%	0.201
Symptomatic intracranial hemorrhage (%)	15.8%	5.1%	0.318
NIHSS score 24 h, points (median, IQR)	7 (2–10)	9 (3–15)	0.440
DNIHSS 24 h, % (median, IQR)	65% (46–75)	41% (0–65)	0.222
Major neurological improvement at 24 h* (%)	64.2%	33.3%	0.046
Discharge mRS score, points (median, IQR)	3 (1–5)	3 (1–5)	0.707
3-month mRS score, points (median, IQR)	2 (1–4)	3 (1–5)	0.466
3-month Functional Independence (%)†	57.9%	48.7%	0.512
3-month Mortality (%)	10.5%	17.9%	0.703

DNIHSS: relative decrease in NIHSS score at 24 h compared with admission NIHSS score.
*NIHSS score decrease ⩾8 points (AUSTRALIAN TNK definition),
†mRS scores of 0–2.
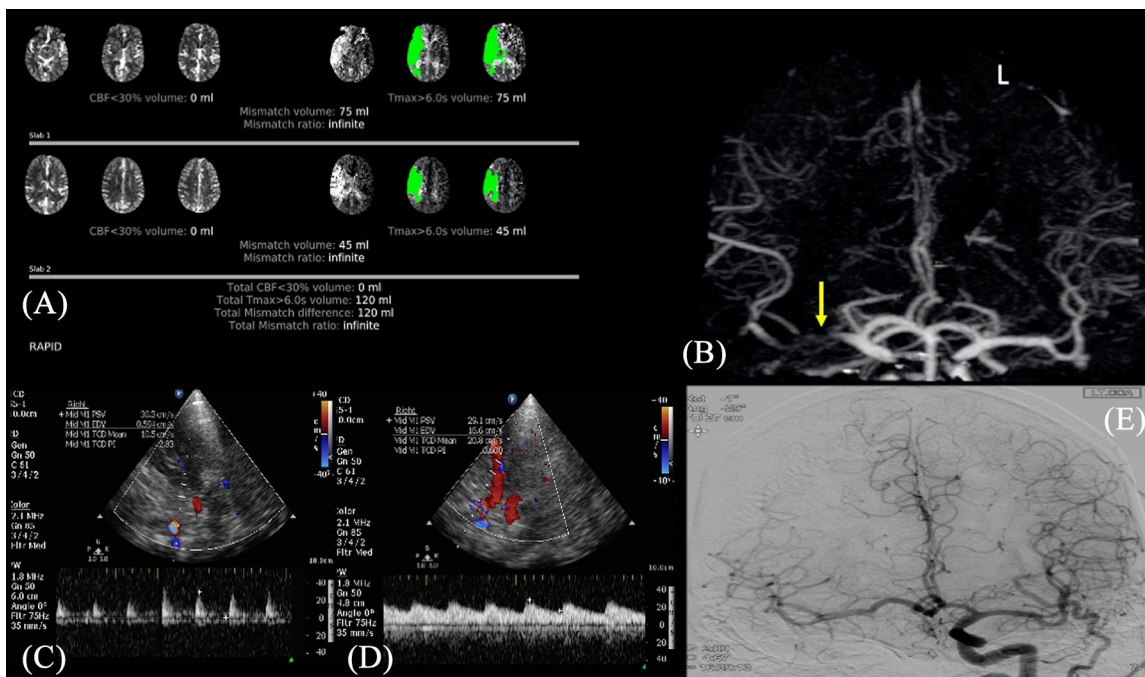IQR, interquartile range; NIHSS, National Institute of Health Stroke Scale; mRS, modified Rankin Scale.

Figure 1. Example of averted mechanical thrombectomy in a patient with acute ischemic stroke due to right middle cerebral artery occlusion. (A) CT-perfusion mismatch-map with RAPID software (IschemaView, Menlo Park, CA) demonstrated a critically hypoperfused region of 120 ml in the middle cerebral artery territory (shown in green) and no area of <30% reduced cerebral bloodflow compared with non-ischemic brain areas, resulting in a 120 ml mismatch difference (infinite mismatch ratio). (B) CT angiogram revealed a right middle cerebral artery occlusion (arrow). (C) TCCD recordings showing the presence of minimal flow signals [thrombolysis in brain ischemia (TIBI I)] on the proximal middle cerebral artery segment. (D) Complete reperfusion of the middle cerebral artery following tenecteplase infusion (TIBI V) was confirmed on digital subtraction angiography (E), which also demonstrated the occlusion of right internal carotid artery due to dissection.
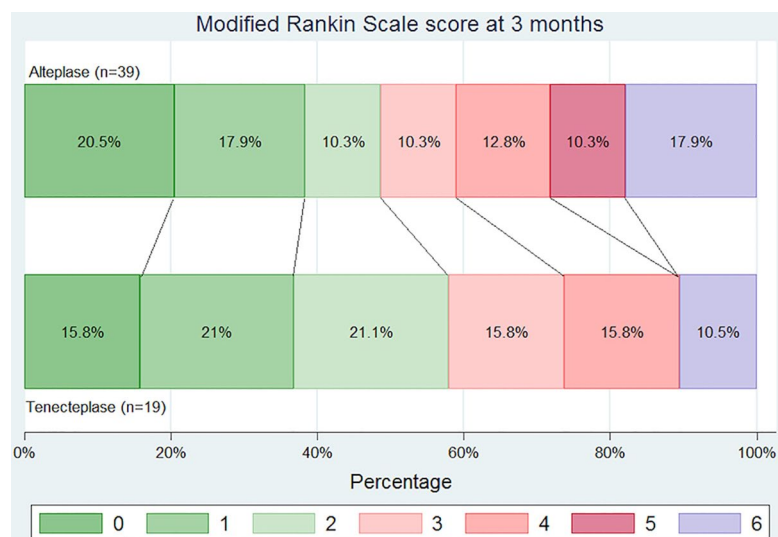
Figure 2. Distribution of modified Rankin Scale scores at three months (Grotta bars) in the two treatment groups. Statistical comparison was conducted using Cochran–Mantel–Haenszel test ($p = 0.466$).

(Figure 1) was achieved in 32% and 18% of patients treated with tenecteplase and alteplase, respectively, but this difference was not significant ($p = 0.243$). Major neurological improvement assessed at 24h was significantly more frequent in the tenecteplase group (64% *versus* 33%, $p = 0.046$). There were no missing 3-month follow-up evaluations in both treatment groups.

Discharge mRS, 3-month mRS (Figure 2), and 3-month functional independence did not differ between the two groups. Rates of sICH were numerically higher in tenecteplase-treated patients (16% *versus* 5%, $p = 0.318$). In the group treated with tenecteplase, sICH occurred only in patients receiving bridging therapy (3/14; 21%), while there was no case of symptomatic intracranial bleeding among patients treated with IVT monotherapy using tenecteplase ($n = 5$). Rates of 3-month mortality were 11% and 18% with tenecteplase and alteplase, respectively, and this difference was not significant ($p = 0.703$).

Table 3 shows the univariable and multivariable associations of the thrombolytic agent with safety and efficacy outcomes in multivariable logistic regression models adjusting for age, baseline NIHSS score, and presence of proximal intracranial occlusion. No statistically significant independent association emerged in regression analyses regarding averted MT (adjusted OR: 2.75, 95% CI: 0.70–10.70; $p = 0.145$), sICH (adjusted OR 4.25, 95% CI: 0.51–35.07; $p = 0.179$), any ICH (adjusted OR 3.60, 95% CI: 0.66–19.70; $p = 0.139$), and functional improvement at 3 months (shift analysis, adjusted cOR 1.47, 95% CI: 0.53–4.00; $p = 0.464$), functional independence at 3 months (adjusted OR 1.50, 95% CI: 0.48–4.71; $p = 0.489$) and 3-month mortality

Table 3. Univariable and multivariable binary and ordinal logistic regression analyses evaluating the association of thrombolytic agent (tenecteplase *versus* alteplase) with outcomes.

	Crude OR/cOR (95% CI)	*p*-value	Adjusted OR/cOR (95% CI)	*p*-value
Averted thrombectomy	2.11 (0.59, 7.49)	0.248	2.75 (0.70, 10.70)	0.145
Any ICH	3.20 (0.64, 16.10)	0.158	3.60 (0.66, 19.70)	0.139
sICH	3.47 (0.53, 22.80)	0.195	4.25 (0.51, 35.07)	0.179
Major neurological improvement at 24 h	3.60 (0.99, 13.13)	0.052	10.22 (0.73, 142.98)	0.084
Discharge modified Rankin Scale	1.20 (0.32, 2.15)	0.699	1.49 (0.53, 4.17)	0.442
3-month modified Rankin Scale	1.31 (0.51, 3.33)	0.574	1.47 (0.53, 4.00)	0.464
Functional independence	1.45 (0.48, 4.37)	0.512	1.50 (0.48, 4.71)	0.489
Mortality	0.54 (0.10, 2.88)	0.469	0.40 (0.06, 2.46)	0.315

CI, confidence interval; cOR, common odds ratio; ICH, intracranial hemorrhage OR, odds ratio; sICH, symptomatic intracranial hemorrhage.

(adjusted OR 0.40, 95% CI:0.06–2.46; $p=0.315$). The initial univariable association (crude OR 3.60, 95% CI: 0.99–13.13; $p=0.052$) between tenecteplase treatment and higher likelihood of major neurological improvement at 24h was marginally attenuated in multivariable analyses (adjusted OR 10.22, 95% CI: 0.73–142.98; $p=0.084$).

Discussion

Our observational pilot study showed that IVT with tenecteplase or alteplase had similar safety and efficacy in AIS patients with LVO. Our preliminary data point to the same direction with the results of a recently published RCT (EXTEND-IA TNK). We documented a non-significant increase in the rates of averted thrombectomy with tenecteplase (32%) compared with alteplase (18%), which is numerically close to the 12% increase (22% *versus* 10%) that was documented in the EXTEND-IA TNK trial.[5,16] Similarly, a pooled analysis of two phase II RCTs comparing tenecteplase with alteplase showed that IVT with tenecteplase was associated with higher rates of successful recanalization at 24h (71%) compared with alteplase (43%, $p<0.001$) in AIS patients with LVO.[16] Notably, the higher recanalization rates of tenecteplase translated into improved clinical outcomes at 24h and 3 months in the former studies. In our cohort, we also documented higher rates of major neurological improvement at 24h with tenecteplase (64% *versus* 33%); however, this association did not retain its significance in adjusted analyses. Averted MT is possibly a more robust criterion for the comparative efficacy of tenecteplase *versus* alteplase, since endovascular reperfusion procedures may obscure potential differences in the effect on clinical outcomes of each thrombolytic agent used for IVT. On the other hand, tenecteplase offers the advantage of bolus administration, which in turn may lead to an acceleration of the endovascular procedure, facilitating swift groin puncture.[2] Workflow efficiencies and ease of use in the emergency department have made tenecteplase the preferred thrombolytic agent during the COVID-19 pandemic,[17] by reducing risk of exposure and transmission.

In our cohort, the higher reperfusion rates in the tenecteplase group came along with a non-significant increase in the rates of sICH. In all prior randomized RCTs of tenecteplase *versus* alteplase[3,4,18,19] including a network metaanalysis,[20] no safety issues have been reported in terms of increased rates of sICH. Therefore, our result should be treated with caution, given the large confidence interval ranges due to our small study sample, and the fact that the rates of sICH in tenecteplase-treated patients did not translate into increased 3-month mortality (11% *versus* 18% with alteplase) or functional dependence (42% *versus* 51% with alteplase) rates. Another possible explanation for the increased sICH rates in the tenecteplase-treated patients could be the higher clot burden (more proximal occlusions and greater thrombus length)[21] and the higher baseline stroke severity (higher admission NIHSS scores) in the tenecteplase subgroup.

Even in current era of endovascular therapies for LVO, there is still intense interest for the improvement of outcomes of systemic thrombolysis using more potent thrombolytic agents.[22] Recent ESO/European Society for Minimally Invasive Neurological Therapy (ESMINT) recommendations suggest the use of tenecteplase over alteplase in AIS patients with confirmed LVO who are scheduled to undergo MT (based on expert opinion).[6] Moreover, the updated American Heart Association/American Stroke Association (AHA/ASA) guidelines for the early management of AIS have also issued a similar recommendation (IIb-class of recommendation).[5] Real-world observational studies like ours can provide further data and lend support to the generalizability of the major RCT results into everyday clinical practice.[23]

Certain limitations of the present pilot study need to be acknowledged including the observational *post hoc* design, the small sample size, the absence of propensity score matching, the lack of randomization and blinding in the evaluation of clinical outcomes. Sample size was not predetermined, whereas study duration was determined *a priori* for 2 years and patient recruitment was slower than originally expected. The small sample size, the wide 95%CI and the imbalances between the two groups indicate that the present findings do not allow for definitive conclusions and may serve only for hypothesis generation and sample size estimation of future RCTs and prospective multicenter studies. Furthermore, the small number of events regarding both efficacy and safety outcomes may render inappropriate the adjustment for covariates. Nevertheless, we decided to present crude as well as adjusted analysis because the statistical analysis plan was prespecified in our study protocol and both crude and adjusted associations

point to the same direction. In addition, a major limitation is the comparison of data from different time periods and the inherent selection bias of a "real world" study, which is also reflected at the substantial (but not significant) higher percentage of male patients in the tenecteplase group. We also note the heterogenous neuroimaging criteria (CT, MR and ultrasound) that were applied for the confirmation of LVO at the baseline evaluation of AIS patients. However, our findings represent our preliminary experience in everyday clinical practice of two tertiary stroke centers using a more pragmatic approach in the clinical settings, where CT or MR angiography are not always available (patients with renal failure, agitated patients with suboptimal iv lines) and the need for timely applied acute reperfusion therapies is critical. In the small number of patients who did not undergo CT angiography or MR angiography (n = 4), TCCD confirmed the LVO by a standardized[14,15] and well validated (compared with digital substraction angiography)[24] protocol. Similarly, perfusion imaging was not included in the selection criteria, even though it has been reported that tenecteplase has more pronounced clinical benefit in patients with targeted mismatch.[4]

In conclusion, the present pilot observational study highlights that AIS patients with LVO treated with 0.25 mg/kg bolus administration of tenecteplase had increased likelihood to achieve early neurological improvement compared with AIS patients treated with alteplase, but this association was attenuated after adjustment for potential confounders. There were no significant differences in 3-month functional or safety outcomes between the two groups. Further validation of these preliminary real-world observations is required in larger multicenter real-world evidence settings and ongoing RCTs like TEMPO-2[25] and TIMELESS.[26]

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