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Comparison of the safety and efficacy of dual antiplatelet therapy versus tenecteplase in patients with minor nondisabling acute ischemic stroke

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To evaluate the safety and efficacy of dual antiplatelet therapy (DAPT) versus tenecteplase in minor non-disabling acute ischemic stroke. This retrospective observational study utilized data from our stroke database. All consecutive patients with minor non-disabling acute ischemic stroke treated with either DAPT or tenecteplase between January 2020 and June 2023 were included in the analysis. Of the 62 patients included in the analysis, the median (IQR) age was 66 (58–76) years, and 21 patients (34%) were female. Compared with patients receiving DAPT, those treated with tenecteplase were had higher NIHSS score at treatment (median [IQR], 4 [2–5] vs. 1 [1–2]; *P* = 0.01). At 90 days, 74.2% of patients (23/31) in the DAPT group and 71.0% (22/31) in the tenecteplase group had an excellent functional outcome (*P* = 0.78). Lower proportion of patients with minor bleeding events in DAPT group than tenecteplase group (3.2% [1/31] vs. 25.8% [8/31], *P* = 0.01). The findings in this study show that patients presenting with minor nondisabling acute ischemic stroke within 4.5 h of symptom onset, dual antiplatelet treatment was similar to intravenous tenecteplase with regard to excellent functional outcome at 90 days. However, more proportion of patients with bleeding events treated with tenecteplase.

Keywords Tenecteplase, Dual antiplatelet therapy, Minor nondisabling acute ischemic stroke, Stroke, Neurology

Abbreviations

DAPT	Dual antiplatelet therapy
NIHSS	National Institutes of Health Stroke Scale
mRS	Modified Rankin Scale
IVT	Intravenous thrombolysis
sICH	Symptomatic intracerebral hemorrhage
EVT	Endovascular therapy

Current guidelines recommend intravenous alteplase is the standard of care for the treatment of acute ischemic stroke (AIS) within 4.5 h of symptom onset[1–3]. Approximately 50% of AIS cases are classified as minor stroke, defined by a National Institutes of Health Stroke Scale (NIHSS) score of ≤ 5[4,5]. However, recent study have demonstrated that dual antiplatelet therapy (DAPT) may be noninferior to intravenous alteplase in terms of excellent functional outcome at 90 days for patients with minor stroke, but early neurological deterioration and bleeding incident occurred in the alteplase group were high than DAPT[6].

Tenecteplase is a genetically modified version of alteplase with higher fibrin specificity, greater resistance to inactivation of fibrinogen activator inhibitor-1, and longer half-life that permits quick bolus delivery. Currently, It has already become the standard intravenous thrombolysis for eligible patients with ST-elevation

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myocardial infarction and has shown promising results in AIS[7–9]. Authors of several cohort studies have showed a higher incidence of reperfusion at 24 h and better clinical outcomes with tenecteplase than with alteplase in AIS patients[10,11]. Therefore, American Heart Association/American Stroke Association, the European Stroke Organization, and the Australian and New Zealand Living Stroke Guidelines have endorsed tenecteplase as an alternative to alteplase for AIS[2,8,12]. Furthermore, a large-scale prospective observational study also found that tenecteplase was associated with a lower risk of systemic bleeding complications compared to alteplase[8].

In this study, we aim to assess the risk of systemic bleeding complications associated with tenecteplase compared to DAPT for patients with minor nondisabling AIS. We hypothesized that Tenecteplase will be associated with lower risk of systemic bleeding complications than DAPT in this patient population.

Methods

Patient and study design

The data were obtained from the prospective registry of our stroke database. All consecutive patients with minor nondisabling AIS who treated by DAPT or tenecteplase between January 2020 and June 2023 were enrolled if meeting these inclusion criteria: (1) age ≥ 18 years; (2) National Institutes of Health Stroke Scale (NIHSS)(range, 0 to 42; higher scores indicate greater stroke severity) score ≤ 5, with less than or equal to 1 point on single-item scores, such as vision, language, neglect, or single limb weakness, and a score of 0 in the consciousness item; (3) computed tomography(CT) or magnetic resonance imaging (MRI) was performed on admission to identify ischemic stroke; and (4) receiving study treatment within 4.5 h of stroke symptoms. Exclusion criteria included: (1) pre- stroke disability (modified Rankin Scale [mRS] score (range, 0 [no symptoms] to 6 [death]),) ≥ 2; (2) history of intracerebral hemorrhage; (3) definite indication for anticoagulation.

The following data were also collected: patient's demographics, comorbidities, risk factors of stroke, symptom onset of stroke, NIHSS, mRS, treated with intravenous thrombolysis (IVT) or DAPT, time from onset-to-needle (OTN), time from door-to-needle (DTN), clinical outcomes such as mRS after 90 days, symptomatic intracerebral hemorrhage (sICH), and any bleeding events.

The study adhered to the ethical guidelines of the Declaration of Helsinki and received approval from the Ethics Committee of Zhejiang Provincial People's Hospital (Approval No. KY2017019). Due to the study's retrospective nature, the Ethics Committee of Zhejiang Provincial People's Hospital waived the requirement to obtain informed consent.

Outcomes

The primary outcome was an excellent functional outcome, defined as a modified Rankin Scale (mRS) score of 0 to 1 at 90 days. Secondary outcomes were included a favorable functional outcome (mRS score of 0 to 2) at 90 days and length of hospital stay. Safety outcomes included symptomatic intracerebral hemorrhage (sICH) and any bleeding events during the study period. sICH was defined as the presence of hemorrhage on a head CT scan, accompanied by neurological deterioration (≥ 4-point increase in NIHSS). Major bleeding was defined as the need for a transfusion of two or more units of blood or a decrease in hemoglobin of ≥ 2 g/dL and without life-threatening. Other cases of bleeding were classified as minor, such as gingival bleeding, etc[13].

Statistical analysis

Baseline characteristics and clinical outcomes were compared hierarchically based on 'Tenecteplase' or 'DAPT' thrombus surface phenotype. The results were presented as frequency, mean ± standard deviation (SD), or median (interquartile range, IQR). The overall sample used Pearson's χ^2-test or Fisher's exact test for categorical variables. In contrast, the Student's *t*-test or Mann Whitney *U* test (for non-Gaussian distributions) is used for continuous variables comparison. $P < 0.05$ was considered statistically significant. All statistical analyses were conducted using SPSS Statistics (Version 25), and graphical presentations were created using GraphPad Prism 8 (GraphPad Software, San Diego, CA, USA).

Results

Demographics and clinical characteristics

Between January 2020 and June 2023, a total of 156 patients were screened, and 62 patients were enrolled into this study. Patient selection process is shown in Fig. 1. Baseline characteristics of patients were shown in Table 1. We categorized the patients into DAPT group and tenecteplase group. The median (IQR) age was 66 years (IQR 58–76), and 21 patients (34%) were female. Thirty-one patients (50%) received tenecteplase, and 31 (50%) were treated with DAPT. Compared to the DAPT group, patients treated with tenecteplase were lower rates of hypertension (19/31 [61.3%] vs. 26/31 [83.9%], $P = 0.04$), had lower INR at treatment (median [IQR], 0.97 [0.92–1.00] vs. 1.01 [0.98–1.07]; $P = 0.01$), had lower systolic blood pressure at treatment (median [IQR], 159 [128–189] vs. 167 [144–193]; $P = 0.03$), had higher NIHSS score at treatment (median [IQR], 4 [2–5] vs. 1 [1–2]; $P = 0.01$).

Primary and secondary outcomes

For the primary outcome, the proportion of patients with mRS scores of 0 or 1 at 90d was 74.2% (23/31) in the DAPT group and 71.0% (22/31) in the tenecteplase group. There were no differences in the rate of mRS score 0–1 at 90d between DAPT group and tenecteplase group ($P = 0.78$). No significant differences were observed between the groups for the secondary outcomes, including mRS scores of 0–2 at 90 days (96.8% [30/31] vs. 90.3% [28/31], $P = 0.31$) and length of hospital stay (median [IQR], 7 [6–10] vs. 8 [6–12], $P = 0.7$) (Table 2; Fig. 2).

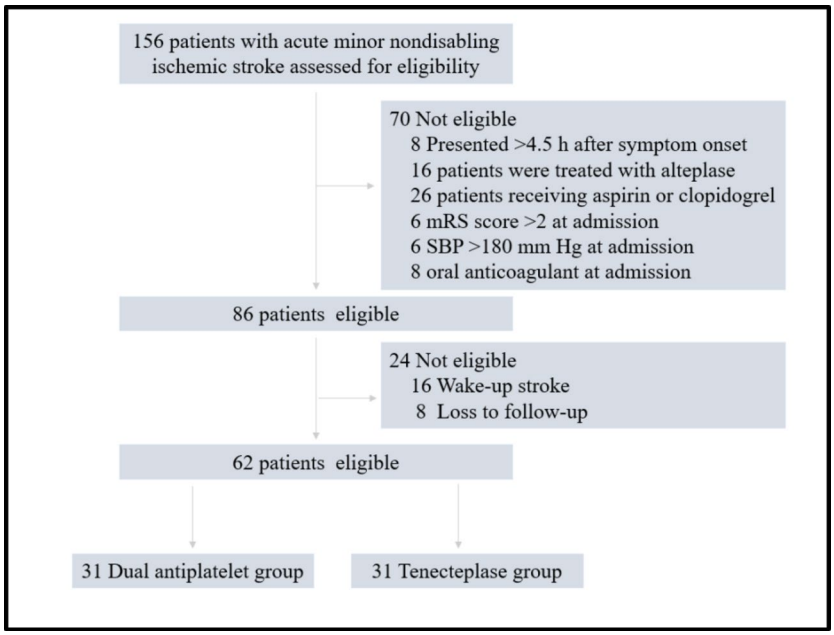

Fig. 1. Flow chart of patient selection.

Baseline characteristics	DAPT ($n=31$)	Tenecteplase ($n=31$)	P
Age (years) (mean (SD))	66 (56–76)	65 (54–73)	0.43
Sex (male)	18 (58.1)	23 (74.2)	0.18
Current smoking[#]	9 (29.0)	12 (38.7)	0.42
Current drinking[#]	5 (16.1)	7 (22.6)	0.52
Medical history			
Hypertension	26 (83.9)	19 (61.3)	0.04
Diabetes	9 (29.0)	12 (38.7)	0.42
Atrial fibrillation	2 (6.5)	4 (12.9)	0.39
Time from onset of symptoms to receipt of assigned treatment, median (IQR), h	1.5 (1.0–3.5)	2.0 (1.0–2.5)	0.66
INR at treatment, median (IQR), s	1.01 (0.98–1.07)	0.97 (0.92–1.00)	0.01
Systolic blood pressure at treatment, median (IQR), mmHg	167 (144–193)	159 (128–189)	0.03
Diastolic blood at treatment, median (IQR), mmHg	95 (73–105)	86 (71–105)	0.72
Blood glucose level at treatment, median (IQR), mmol/L	7.07 (6.29–10.70)	8.58 (6.71–10.28)	0.30
NIHSS score at treatment, median (IQR)[$]	1.0 (1.0–2.0)	4.0 (2.0–5.0)	0.01
Onset-to-needle (OTN), median (IQR), min%	NA	149.1 (98.0–179.0)	
Door-to-needle (DTN), median (IQR), min^	NA	44.7 (36.0–45.0)	
Presumed stroke cause*			0.46
Large artery atherosclerosis	9 (29)	11 (35.5)	
Small artery occlusion	4 (13.0)	6 (19.4)	
Cardioembolic	13 (41.9)	10 (32.3)	
Others	5 (16.1)	4 (12.9)	

Table 1. Characteristics of study participants. [#]Current smoking was consuming more than 1 cigarette per day within 1 year before the onset of the disease. Current drinking defined as consuming alcohol more than once a week within 1 year before the onset of the disease. [$]Patients with NIHSS ≤ 5 were eligible for this study; NIHSS scores range from 0 to 42, with higher scores indicating more severe neurological deficit. *NA* not applicable. [%]Onset-to-needle, Time from onset of symptoms to needle. ^Door-to-needle, Time from patient arrival at hospital to treatment. *The presumed stroke cause was classified according to the Trial of Org 10,172 in the Acute Stroke Treatment (TOAST) classification system. Others were including undetermined causes and other.

	DAPT ($n=31$)	Tenecteplase ($n=31$)	P
Primary outcome			
mRS score 0–1 at 90d	23 (74.2)	22 (71.0)	0.78
Secondary outcomes			
mRS score 0–2 at 90 d	30 (96.8)	28 (90.3)	0.31
Length of hospital stay, median (IQR)	7.0 (6.0–10.0)	8.0 (6.0–12.0)	0.70
Safety outcomes			
Symptomatic intracerebral hemorrhage (sICH)	0	1 (3.2)	0.12
Any bleeding events			0.01
Major	0	0	
Minor	11 (3.2)	8 (25.8)	

Table 2. Clinic outcomes of included patients.

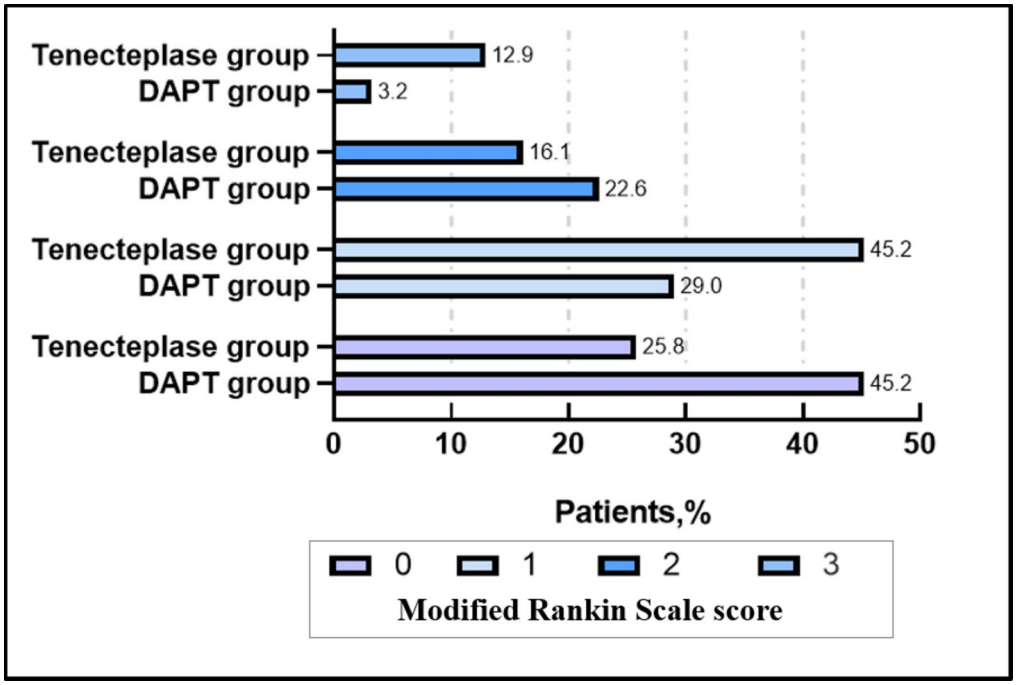

Fig. 2. Distribution of Modified Rankin Scale Scores at 90 days.

Safety outcomes

In the tenecteplase group, one patient experienced sICH, and eight experienced other bleeding events, while none in the DAPT group had sICH, and only one patient experienced a minor bleeding event. Neither group of patients had major bleeding events. There were differences in the rate of the minor bleeding events between DAPT group and tenecteplase group (3.2% [1/31] vs. 25.8% [8/31], $P=0.01$) (Table 2; Fig. 3).

Discussion

In this study, we found that among patients with minor nondisabling acute ischemic stroke (AIS) treated within 4.5 h of symptom onset, intravenous tenecteplase was comparable to dual antiplatelet therapy (DAPT) in achieving excellent functional outcomes (modified Rankin Scale [mRS] 0–1) at 90 days. Secondary outcomes, including favorable functional outcomes (mRS 0–2) and hospital length of stay, also showed no statistically significant differences between the two treatment groups. However, patients receiving tenecteplase experienced a higher incidence of bleeding events compared to those on DAPT.

Tenecteplase is a genetically modified alteplase. Three variants of the alteplase molecule enhance its specificity to fibronectin 15-fold, resistance to fibrinogen activator inhibitors 80-fold, and prolonged its half-life[9]. Authors of several cohort studies have reported that tenecteplase, as an intravenous thrombolytic agent, at a dose of 0.25 mg/kg was similar to alteplase in all patients with AIS within 4.5 h of symptom onset[14,15]. Additionally, Bala et al. showed that in patients presenting with LVO who were candidates for endovascular therapy (EVT), tenecteplase also showed similar safety and efficacy compared to alteplase[16]. The CERTAIN trial further highlighted that tenecteplase was associated with a lower risk of sICH than alteplase[8].

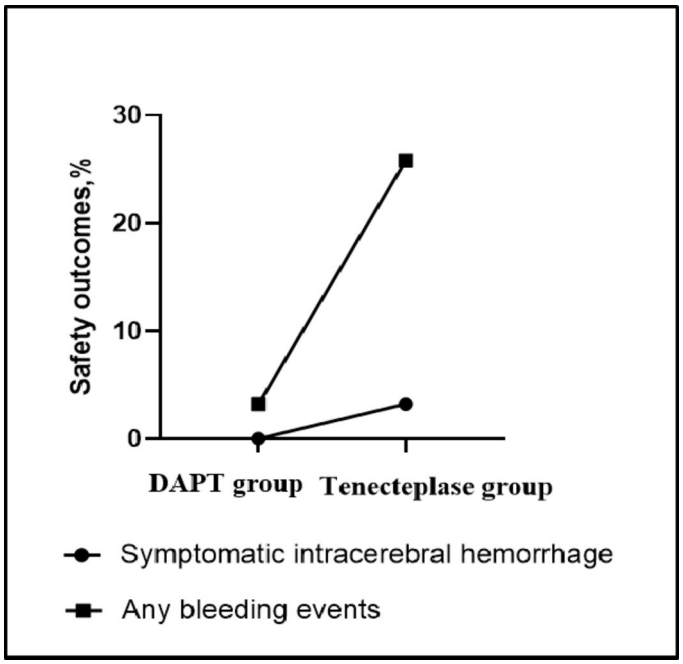

Fig. 3. Rates of symptomatic intracerebral hemorrhage and any bleeding events.

Our findings align with but also differ from previous clinical trials that explored the role of intravenous thrombolysis in minor stroke. The PRISMS trial, which compared alteplase with single antiplatelet therapy in patients with acute minor ischemic stroke, concluded that alteplase did not provide additional benefit over antiplatelet therapy and raised concerns about bleeding risks[17]. But IST-3 randomized trial showed that the superiority of intravenous alteplase compared with standard medical therapy for patients with minor ischemic stroke[18]. Therefore, it may be challenging for stroke physicians to decide whether to treat intravenous alteplase in patients with minor nondisabling stroke within 4.5 h of symptom onset. For addressing this challenge, the ARAMIS study was designed with a strategy that differed from that of the PRISMS study. Aspirin plus clopidogrel (300 mg loading dose) was administered for 12 ± 2 days, followed by guideline-based antiplatelet treatment until 90 days in ARAMIS study. The strategy of DAPT was based on the CHANCE and POINT studies, which found the superiority of DAPT to aspirin alone in minor acute stroke[19,20]. But there was more early neurological deterioration (9.1%), more risk of sICH and bleeding events in the alteplase group compared with DAPT[6].

This trail was the first study to attempt to address how to choose DAPT and tenecteplase for patients with acute minor nondisabling AIS within 4.5 h of symptom onset. While the proportion of patients achieving excellent functional outcome (78.2% vs. 71.0%) was lower than that achieved in the ARAMIS study (91.5% vs. 93.7%), which might partially be attributed to differing comorbidities, or vascular risk factor profile. However, the percentage of patients with good functional outcome (96.8% vs. 90.3%) was similar to ARAMIS study (95.9% vs. 95.4%).

In terms of safety, our results indicate a higher risk of sICH and a significantly greater number of bleeding events in the tenecteplase group compared to DAPT. These findings emphasize the importance of weighing the benefits of thrombolysis with tenecteplase against the potential bleeding risks, particularly in patients with minor nondisabling AIS.

Limitations

This study had several limitations. (1) The retrospective nature of the study and the relatively small number of patients is one of the most important aspects limiting the clinical significance of the current results. Therefore, the results should be interpreted with caution. (2) Our study was performed at a single Asian institution, and the population-specific experience may not be generalizable globally. (3) Only patients treated within 4.5 h from stroke symptom onset were included, so our results may not be generalizable to patients treated outside this window.

Conclusions

In summary, the findings in this study showed that patients presenting with minor nondisabling AIS within 4.5 h of symptom onset, dual antiplatelet treatment was similar to intravenous tenecteplase with regard to excellent functional outcome at 90 days. However, more proportion of patients with bleeding events treated with tenecteplase.

Data availability

Raw data supporting the conclusions of this paper can be obtained by contacting Xinzhao Jiang (jiangxz19@mails.jlu.edu.cn).

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Author contributions

Xinzhao Jiang study concept and acquisition of data.; Ruozhen Yuan, study concept and acquisition of data.; Jiawei Ye, acquisition of data; Xu Wang acquisition of data. Zongjie Shi, study design and critical revision of the manuscript; Shunyuan Guo, study design and critical revision of the manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

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