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Dual Antiplatelet Therapy vs Alteplase in Adult Patients with Acute Minor Ischemic Stroke: A Systematic Review and Meta-Analysis

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Abstract

The efficacy and safety of dual antiplatelet therapy (DAPT) relative to intravenous (IV) alteplase in patients with acute minor ischemic stroke are insufficiently established. Therefore, we aimed to perform a meta-analysis to compare DAPT with IV alteplase in patients with acute minor stroke. MEDLINE, Embase, and Cochrane were searched for studies comparing DAPT with IV alteplase in patients with minor stroke. Functional and safety outcomes in 90 days were analyzed. Statistical analysis was performed using Rstudio 4.3.1. Subanalyses were performed restricted to non-disabling minor strokes and NIHSS score ≤ 3. PROSPERO (CRD42023440986). We included five studies with a total of 6,340 patients, of whom 4,050 (63.9%) received DAPT. The follow-up period for all included studies was 90 days. There was no significant difference for individual outcomes of mRS 0–1 (OR 1.26; 95% CI 0.85–1.89; p = 0.25), mRS 0–2 (OR 0.99; 95% CI 0.69–1.43; p = 0.97), or all-cause mortality (OR 0.80; 95% CI 0.20–3.13; p = 0.75) between groups. Symptomatic intracranial hemorrhage (sICH) was significantly lower (OR 0.11; 95% CI 0.003–0.36; p < 0.001) in patients treated with DAPT compared with IV alteplase. In terms of mRS 0–1 and mRS 0–2, we found no significant difference in both subgroup analyses. We found no statistically significant difference between DAPT and IV alteplase regarding functional outcome (mRS scores of 0–1 and 0–2) or all-cause mortality at 90 days in patients with minor ischemic stroke. Additionally, DAPT was associated with a significantly lower rate of sICH.

Keywords Minor ischemic stroke · Dual anti-platelet therapy · Tissue plasminogen activator · Meta-analysis

Highlights

- Efficacy and safety of Dual Antiplatelet Therapy (DAPT) versus intravenous (IV) alteplase in minor ischemic stroke patients admitted within 4.5 hours of symptom onset.
- No statistically significant differences were found between DAPT and IV alteplase in terms of modified Rankin Scale (mRS) scores of 0–1 and 0–2 and all-cause mortality rates at 90 days.
- DAPT was associated with significantly lower rates of symptomatic intracranial hemorrhage when compared to IV alteplase.

Introduction

Stroke stands as the second leading cause of death on a global scale [1, 2]. A significant 85% of all strokes are ischemic [3], with over half of these categorized as minor stroke, despite the absence of a widely accepted definition[4, 5]. The definition of minor ischemic stroke often hinges on a National Institutes of Health Stroke Scale (NIHSS) score

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of ≤ 5 or ≤ 3. However, a consensus definition is lacking[6]. The treatment of acute minor strokes introduces a nuanced challenge; while the decision to treat with IV thrombolysis involves various considerations, such as the onset of substantial disability, approximately 30% of untreated patients with minor strokes still experience disability after 90 days [7].

Current guidelines advocate for reperfusion therapy, specifically with intravenous (IV) alteplase, for patients enduring a minor but disabling ischemic stroke, assuming their last well-known status was within the preceding 4.5 h [8, 9]. Recent research exploring the extension of this treatment window through advanced neuroimaging introduces questions regarding safety and applicability [10–12]. Notably, the term "disabling" leans heavily on professional interpretation. Despite ongoing efforts to pinpoint early predictors of neurological deterioration in patients presenting with minor strokes [13, 14], the efficacy of reperfusion therapies for minor, non-disabling strokes is yet to be decisively determined [8, 9].

Recent clinical trials spotlighted the efficacy of Dual Antiplatelet Therapy (DAPT)—comprising clopidogrel and aspirin—in reducing the risk of recurrent stroke within 90 days after a minor stroke – or high-risk TIA [8, 9]. These insights have been integrated into the American Heart Association/American Stroke Association (AHA/ASA) guidelines, establishing an IA recommendation for the initial management of patients with minor noncardioembolic ischemic strokes (NIHSS score ≤ 3) who have not received IV alteplase. This involves commencement within 24 h post-symptom onset and continuation for 21 days [15]. Furthermore, emergent data suggest that the 90-day outcomes for patients with minor non-disabling ischemic strokes treated with DAPT in the acute phase (within 4.5 h from onset) are not inferior to those treated with IV alteplase [16].

In our systematic review and meta-analysis, we compared DAPT with IV alteplase in the acute phase for patients diagnosed with minor ischemic stroke, providing a comprehensive assessment of DAPT's efficacy and safety.

Methods

Search strategy

The present systematic review and meta-analysis were performed according to *Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-Analysis* (PRISMA) guidelines[17]. The research protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) under the protocol number CRD42023440986. MEDLINE, Embase, and Cochrane Library were systematically searched from inception to August 7, 2023, with the following search strategy: ("minor stroke" OR "mild stroke" OR TIA OR "transient ischemic attack") AND (alteplase OR IVT OR tPA OR "t-PA" OR rtPA OR "rt-PA" OR thrombolysis) AND ("dual antiplatelet" OR DAPT OR clopidogrel OR ticagrelor OR "P2Y12 inhibitors").

Selection criteria

Inclusion criteria were: (1) randomized controlled trials (RCTs) or observational cohorts; (2) comprising patients diagnosed with minor stroke – defined as those presenting with an acute ischemic stroke and an NIHSS score of ≤ 5 – within 4.5 h from onset; (3) comparing DAPT initiated within 24 h after onset with IV alteplase initiated within 4.5 h after onset; and (4) reporting at least one outcome of interest. We excluded studies with (1) overlapping populations or (2) with cross-over design. There were no restrictions regarding the publication date or language. Two reviewers (J.H.R. and T.D.D.C.) independently selected the studies. Any discrepancies were resolved by consensus and arbitration by a third author (P.V.).

Data extraction

The following information about each study was collected: (1) study characteristics, including study design, time of follow-up, and sample size; (2) patient baseline characteristics, such as age (years), sex, prior stroke, or transient ischemic attack (TIA), baseline NIHSS score, TOAST classification at the time of admission, comorbidities; and (3) outcomes of interest.

Outcomes

We analyzed the following outcomes: functional outcomes – (1) modified Rankin Scale (mRS) score of 0 to 1, and (2) mRS score of 0 to 2 at 90 days; and safety outcomes – (3) all-cause mortality at 90 days and (4) symptomatic intracranial hemorrhage (sICH).

Statistical analysis

Statistical analysis was conducted using RStudio Software version 4.3.1 [18]. Binary endpoints were analyzed using odds ratios (OR) with 95% confidence intervals. Statistical significance was defined as p-value < 0.05. Heterogeneity was assessed using I^2 statistics, and it was considered significant when $I^2 > 25\%$. The Mantel–Haenszel random-effects model was applied for all outcomes. Additionally, we conducted a leave-one-out analysis to assess the impact of each study on the overall results. We also performed a subgroup analysis for patients with non-disabling minor stroke and an NIHSS ≤ 3. The statistical analysis was conducted by three (P.V., J.E.P, and A.M.A) authors.

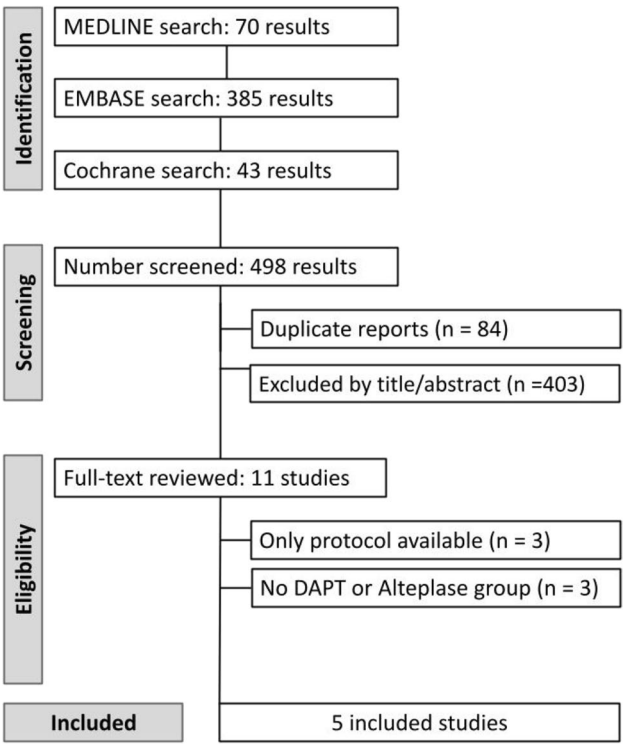

Fig. 1 PRISMA flow diagram of study screening and selection

Quality assessment

The risk of bias analysis for each study was conducted using the Cochrane Risk of Bias tool for RCTs (RoB 2) and Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) for non-randomized studies[19, 20]. Three independent authors (P.V., J.E.P., and M.Z.P.) evaluated the risk of bias for each study, and disagreements were resolved through consensus.

Results

Study selection and characteristics

Our systematic search identified 498 articles, as demonstrated in Fig. 1. After screening for duplicate reports and studies that met our inclusion criteria, 11 remained and were thoroughly assessed. Finally, five studies were included with a total of 6,340 patients, of whom 4,050 (63.9%) received DAPT treatment, and 4,110 (64.8%) were male [16, 21–24]. The follow-up period for all included studies was 90 days. Among studies that reported the TOAST classification, 2,035 (35.5%) were classified as having a small artery occlusion (SAO), 1,742 (30.3%)

Table 1 Characteristics of Included Studies

	Chen et al., 2023 [16] DAPT/Alteplase	Duan et al., 2023 [21] DAPT/Alteplase	Lan et al., 2019 [22] DAPT/Alteplase	Sykora et al., 2023 [23] DAPT/Alteplase	Wang et al., 2021 [24] DAPT/Alteplase
Type of study	RCT	Prospective	Retrospective	Retrospective	Post hoc
Patients	369/350	722/251	119/109	2,625/1,195	215/385
Age (y)	65(57–71)/64(56–71)	63(56–70)/62(55–68)	64(32–86)/67(33–89)	71(19–99)/68(21–98)*	64(55–71)/61(54–69)
Male	256(69.5)/240(68.6)	510(70.6)/178(70.9)	86(72.3)/74(67.9)	1,609(61.3)/751(62.8)	149(69.3)/257(66.8)
Prior TIA	4(1.1)/2(0.6)	25(3.5)/3(1.2)	NA	NA	7(3.3)/14(3.6)
Prior stroke	82(22.2)/77(22.0)	169(23.4)/44(17.5)	22(18.5)/18(16.5)	588(22.4))/192(16.1)	42(19.5)/65(16.9)
Baseline NIHSS	2(1–3)/2(1–3)	2.0(1–4)/3.0(2–4)	2.5(0–5)/4(1–5)	1(0,3–2)/2(0–3.2)	2(1–3)/2(1–3)
Hypertension	211(57.2)/169(48.3)	468(64.8)/166(66.1)	86(72.3)/80(73.4)	2,193(83.5)/870(72.8)	135(62.8)/252(65.5)
Diabetes	101(27.4)/86(24.6)	211(29.2)/52(20.7)	34(28.6)/19(17.4)	757(28.8)/227(19)	52(24.2)/77(20)
Smoking	122(33.1)/118(33.7)	246(34.1)/89(35.5)	44(37.0)/18(16.5)	709(27)/257(21.5)	87(40.5)/157(40.8)
TOAST					
LAA	54(14.6)/46(13.1)	357(49.4)/119(47.4)	32(26.9)/19(17.4)	661(25.2)/190(15.9)	NA
CE	1(0.3)/1(0.3)	21(2.9)/17(6.8)	0/0	0/0	NA
SAO	87(23.6)/79(22.6)	120(16.6)/41(16.3)	85(71.4)/90(82.6)	1,091(41.6)/442(36.9)	NA
SOE	2(0.5)/3(0.9)	20(2.8)/6(2.4)	0/0	102(3.9)/60(5.0)	NA
SUE	225(61.0)/221(63.1)	204(28.3)/68(27.1)	2(1.7)/0	634(24.2)/388(32.5)	NA

Values are presented as median (interquartile range) or as No. (%). *Value expressed as mean (range, SD)

CE cardioembolic, *DAPT* dual antiplatelet treatment, *LAA* large-artery atherosclerosis, *NA* not available, *NIHSS* National Institutes of Health Stroke Scale, *RCT* randomized controlled trial, *SAO* small-artery occlusion, *SOE* stroke of other determined etiology, *SUE* stroke of undetermined etiology, *TIA* transient ischemic attack, *TOAST* trial of Org10172 in acute stroke treatment

undetermined etiology, and 1,478 (25.7%) large artery atherosclerosis (LAA). The IV alteplase dose was 0.9 mg/kg to a maximum dose of 90 mg. The initial dose of aspirin ranged between 75 and 300 mg, followed by 100 mg/day, while the initial dose of clopidogrel ranged from 75 to 600 mg, followed by 75 mg/day. Details of the study characteristics are reported in Table 1.

Pooled analysis of included studies

Concerning the assessed outcomes, mRS 0–1 (84% DAPT vs. 84% IV Alteplase; OR 1.26; 95% CI 0.85–1.89; p = 0.25; I^2 = 70%; Fig. 2a), mRS 0–2 (94% DAPT vs. 94% IV Alteplase; OR 0.99 IV Alteplase; 95% CI 0.69–1.43; p = 0.97; I^2 = 32%; Fig. 2b), and all-cause mortality (0.46% DAPT vs. 0.51% IV Alteplase; OR 0.80; 95% CI 0.20–3.13; p = 0.75; I^2 = 0%; Fig. 3), did not show any statistical difference between groups. Additionally, there was a significantly lower rate of sICH in the DAPT group (0.13% DAPT vs. 1.3% IV alteplase; OR 0.11; 95% CI 0.03–0.36; p < 0.001; I^2 = 70%; Fig. 4). Therefore, a leave-one-out sensitivity analysis was made to understand the impact of each study on the overall results for mRS 0–1 (OR 1.26; 95% CI 0.85–1.89; I^2 = 70%; Supplementary Fig. 1) and mRS 0–2 (OR 0.99; 95% CI 0.69–1.43; I^2 = 32%; Supplementary Fig. 2) there was no statistically significant difference between groups.

Furthermore, a subgroup analysis of patients with non-disabling minor stroke was made, mRS 0–1 (88% DAPT vs. 91% IV Alteplase; OR 0.95; 95% CI 0.45–2.02; p = 0.89; I^2 = 74%; Supplementary Fig. 3A) and mRS 0–2 (95% DAPT vs. 96% IV Alteplase; OR 0.81; 95% CI 0.39–1.69; p = 0.57; I^2 = 40%; Supplementary Fig. 3B) without statistical differences between groups. Similarly, in a subgroup analysis of patients with NIHSS ≤ 3 no statistical differences were found between groups for mRS 0–1 (85% DAPT vs. 84% IV Alteplase; OR 1.25; 95% CI 0.95–1.65; p = 0.11; I^2 = 30%; Supplementary Fig. 4).

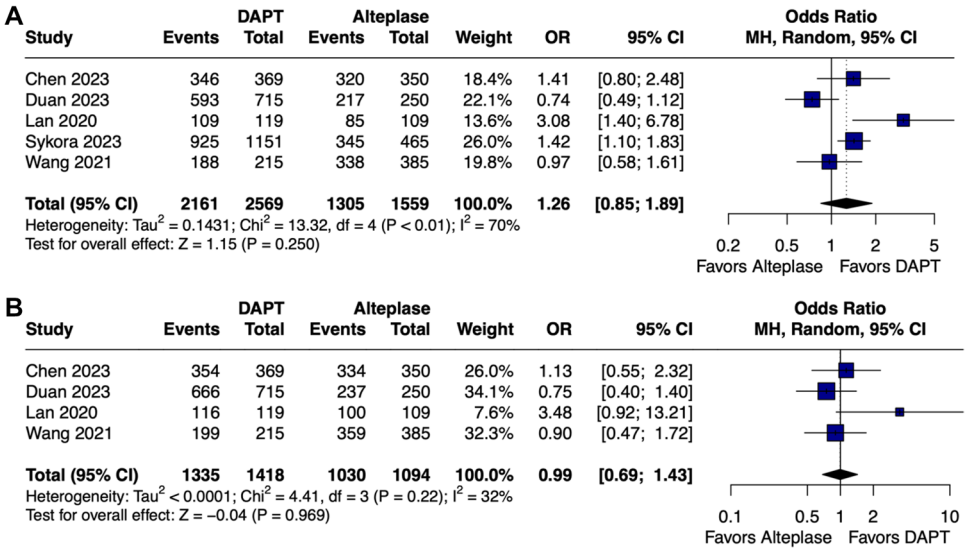

Fig. 2 **A**: There was no significant difference for mRS 0–1 at 90 days between DAPT and IV Alteplase groups. **B**: There was no significant difference for mRS 0–2 at 90 days between DAPT and the IV alteplase groups

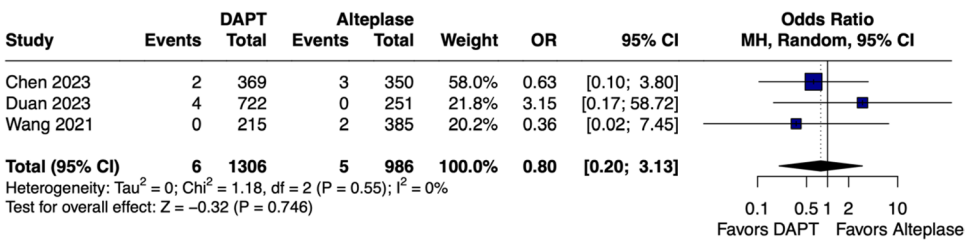

Fig. 3 There was no significant difference in mortality at 90 days between DAPT and the IV alteplase groups

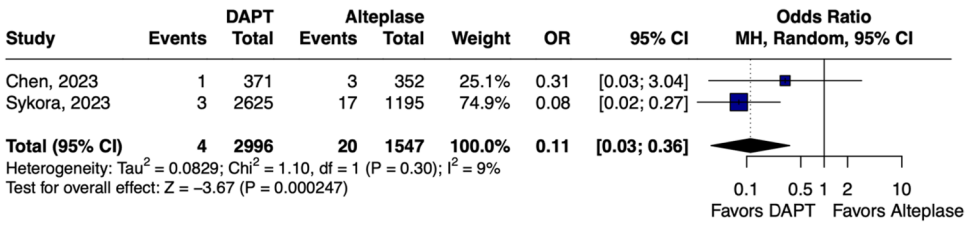

Fig. 4 There was a significantly lower rate of sICH in the DAPT group compared with the IV alteplase group

Quality assessment

Our systematic review and meta-analysis included five studies, one RCT, and four observational. The randomized trial was evaluated using the RoB-2 tool, resulting in a low risk of bias (Supplementary Table 1) [19]. Similarly, in the observational studies assessed using the ROBINS-I tool, all articles were rated as having a moderate risk of bias (Supplementary Table 2) [20].

Discussion

Our systematic review and meta-analysis evaluated five studies with a total of 6,340 patients to compare the efficacy and safety of DAPT versus IV alteplase in patients with minor ischemic stroke admitted within 4.5 h of symptom onset. Our pooled analyses showed no statistically significant difference between groups when considering mRS scores 0–1, mRS 0–2, or all-cause mortality rates at 90 days. Nonetheless, there was a lower rate of sICH in the DAPT group when compared with IV alteplase. Furthermore, no difference was seen in 90-day functional outcomes (mRS scores of 0–1 and mRS scores of 0–2) in a subgroup analysis of non-disabling stroke patients and patients with an NIHSS score ≤ 3.

Many variables must be considered when selecting the treatment of choice, or even whether to treat a minor stroke patient. This lack of consensus on the recommended treatment can be partly due to the dependence on the NIHSS for minor stroke definition, which has no widely accepted definition, with some studies using the cutoff of NIHSS scores ≤ 3 and others using NIHSS ≤ 5. [4, 5] Nonetheless. this scale may neglect essential aspects such as stroke volume and location, and type of disability, and can often underestimate the severity of posterior circulation and non-dominant anterior circulation strokes. There is a significant observation that approximately 30% of minor stroke patients who do not undergo thrombolytic therapy experience disability 90 days post-event[9], perhaps indicating a gap in the current assessment and treatment strategy. Therefore, future research should integrate these variables into patient randomization protocols. In this context, employing advanced neuroimaging techniques in the initial evaluation may provide more detailed insights into stroke characteristics, potentially enhancing treatment choice and patient outcomes.

The treatment for patients in the acute phase (≤ 4.5 h from onset) remains similar to what it was years ago, with the severity of disability being the main determinant of whether to treat with IV alteplase or not. Prior attempts to establish the efficacy of IV alteplase in non-disabling minor stroke patients have been challenged due to early study termination [25]. Consequently, current guidelines do not recommend using IV alteplase for this subgroup[7, 15]. The ARAMIS study was the first RCT addressing DAPT versus IV alteplase for non-disabling minor acute ischemic stroke[16]. They found that DAPT was non-inferior to IV alteplase regarding mRS scores of 0–1 at 90 days when administered in patients treated within 4.5 h from the last time seen well while observed fewer hemorrhagic events and early deterioration in patients treated with DAPT when compared to those treated with IV alteplase. Our meta-analysis aimed to assess this specific subgroup; however, we could only include two studies in our analysis due to limited individual study data[16, 21]. Despite these constraints, we observed no significant differences in functional outcomes between the two treatments among patients with non-disabling minor strokes. Accordingly, our findings suggest that within our analyzed data set, there is no apparent advantage of one treatment over the other for this subgroup.

There is also growing concern about the early identification of patients who, despite initially presenting with a minor stroke in the emergency room, may later deteriorate with higher NIHSS scores, such as those who present with a large vessel occlusion (LVO) minor stroke. Previous studies have developed scores to predict deterioration in targeted subgroups, considering variables like occlusion site and thrombus length[14], emphasizing the importance of considering diverse variables when determining the most appropriate intervention for these patients[13]. While the evidence supports the efficacy of IV thrombolysis in patients with LVO, its benefits remain unclear for other groups. Our results, which included a leave-one-out analysis excluding Duan et. al., that exclusively evaluated LVO stroke minors, revealed no conclusive preference favoring DAPT. Notably, as the presence of LVO was not discriminated in all studies, we were unable to assess this specific subgroup. Therefore, future randomized clinical trials with stratified data considering the presence of LVO, independent of the TOAST classification, are essential to elucidate the optimal treatment strategy for this subgroup.

Since no significant difference was found between the functional outcomes or all-cause mortality, and IV alteplase was associated with higher odds of sICH, a cost-effectiveness analysis should be considered. The cost of IV alteplase increased by about $> 100\%$ over a decade, but the base payment for hospitals only increased by 8%. Besides that, the less intensive monitoring, easier administration, and lower cost of DAPT reinforce the preference for its use.

Our study has limitations. Firstly, four of the five included studies were non-randomized, potentially associated with confounding factors that could influence the findings. Consequently, there might be a selection bias since the treatment was chosen based on the physician's judgment of the best

treatment for a given patient. It is reasonable to assume that many patients with disabling minor ischemic stroke might have been allocated to the IV alteplase treatment group, potentially biasing the results. Secondly, our primary outcome exhibited significant heterogeneity. We addressed this issue by conducting a leave-one-out analysis to assess the impact of each study on the overall results. Lastly, due to limited data availability, only two studies were included in the subgroup assessment of non-disabling strokes, and we could not assess a subgroup restricted to patients with LVO.

Our data suggest a preference for the use of DAPT in patients with minor strokes. However, due to the limitations mentioned above, we should interpret these findings with caution, particularly considering whether the stroke is disabling or non-disabling and whether there is evidence of LVO. Probably DAPT might benefit more patients with non-disabling minor strokes who do not present with LVO upon admission, but further investigation is warranted to establish conclusive insights into whether DAPT is superior, non-inferior, or inferior to IV alteplase.

Conclusion

Our meta-analysis, focusing on patients admitted within 4.5 h from the onset of minor ischemic stroke, found no statistically significant difference between DAPT and IV alteplase regarding functional outcome (mRS 0–1 and 0–2) and all-cause mortality at 90 days. Additionally, DAPT was associated with significantly lower odds of symptomatic intracranial hemorrhage. To solidify these findings, conducting further research on a larger scale is crucial. We suggest stratification of data considering the presence of disability, as well as the presence of large vessel occlusion at admission. This could add new insights into specific subgroups that might benefit more from one treatment. Ultimately, a robust body of evidence is essential for informed clinical decision-making.

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Data availability Data supporting the findings of this article is included within the article and its supplementary material.

Declarations

Competing Interests The authors have no relevant financial interests to disclose.

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