Systematic Review/Meta-Analysis

INTERNATIONAL JOURNAL OF SURGERY

OPEN

Efficacy and safety of intra-arterial thrombolysis after endovascular reperfusion for acute ischemic stroke: a systematic review and meta-analysis of randomized trials

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Objective: This pooled analysis aims to evaluate the efficacy and safety of intra-arterial thrombolysis (IAT) following near-complete to complete reperfusion by endovascular thrombectomy (EVT) in patients with acute ischemic stroke due to large vessel occlusion (AIS-LVO).

Methods: We conducted a search of PubMed, Embase, and Cochrane databases to identify randomized controlled trials (RCTs) investigating the adjunct benefit of IAT in patients with AIS-LVO who had achieved a score on the Thrombolysis In Cerebral Infarction (TICI) scale of 2b-3 after EVT. Efficacy outcomes encompassed excellent functional outcome, defined as a modified Rankin Scale (mRS) score of 0–1 at 90 days, and functional independence (mRS 0–2). Safety outcomes included symptomatic intracranial hemorrhage (sICH) and mortality at 90 days. A network meta-analysis (NMA) was performed to evaluate the effects of different types of intra-arterial thrombolytic agents on mRS 0–1.

Results: A total of 7 RCTs were included in the analysis, involving 2128 patients. Relative risks (RR) and 95% confidence intervals (CI) were pooled using a random-effects model. The pooled results indicated that adjunctive IAT did not significantly improve the rate of functional independence (RR 1.04, 95% CI 0.96-1.13, $P = 0.29$). However, there was a significant increase in excellent functional outcome with adjunctive IAT (RR 1.23, 95% CI 1.11-1.36, $P < 0.001$). The pooled analysis did not demonstrate any differences between EVT + IAT and EVT only in rates of sICH (RR 1.23, 95% CI 0.81-1.85, $P = 0.33$) or 90-day mortality (RR: 0.98, 95% CI: 0.82-1.18; $P = 0.86$). The NMA found no significant difference in achieving mRS 0–1 among arterial adjunctive alteplase, tenecteplase, and urokinase following successful reperfusion.

Conclusions: IAT as an adjunct to successful EVT appears to enhance excellent functional outcome in patients with AIS-LVO without a significant increase in sICH and mortality.

Keywords: endovascular thrombectomy, functional outcome, intra-arterial thrombolysis, ischemic stroke

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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International Journal of Surgery (2025) 111:4002–4008

Received 24 January 2025; Accepted 2 April 2025

Supplemental Digital Content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's website, www.lww.com/international-journal-of-surgery

Published online 25 April 2025

http://dx.doi.org/10.1097/JS9.0000000000002404

HIGHLIGHTS

- This study evaluates the safety and effectiveness of intra-arterial thrombolysis (IAT) after thrombectomy.
- Meta-analysis combines data from four randomized trials involving 2,128 stroke patients.
- Adjunctive IAT improves functional recovery in patients with large vessel stroke.
- Results highlight gender-specific benefits, with female patients deriving greater advantages.

Background

Acute ischemic stroke (AIS) is a primary cause of disability in adults[1]. Endovascular thrombectomy (EVT) has established itself as the standard of care for AIS resulting from large vessel occlusion (LVO), markedly improving patients' 90-day functional outcomes[2]. However, clinical challenges persist; although approximately 71% of patients achieve vessel recanalization, only 27% achieve disability-free survival at 90 days[3]. This discrepancy highlights that reperfusion alone may not resolve critical pathological factors, and microcirculatory dysfunction

could be one of the contributing causes[4]. In response to these challenges, intra-arterial thrombolysis (IAT) has been suggested as an adjunctive therapy to decrease microthrombus burden and enhance microvascular perfusion[5,6].

Previous research indicated that nearly half of interventional physicians empirically use IAT during EVT[7]. However, previous randomized controlled trials (RCTs) evaluating the efficacy and safety of IAT after EVT have reported inconsistent findings.[8-14] Furthermore, the American Stroke Association/American Heart Association (ASA/AHA) guidelines, based on limited evidence, have designated it merely as a "reasonable adjunctive therapy."[15] The CHOICE trial showed promising outcomes, with a higher proportion of patients achieving 90-day modified Rankin Scale (mRS) score of 0–1 with IAT versus placebo (59.0% vs. 40.4%), but was terminated prematurely due to enrollment issues. Subsequent high-quality RCTs, including ATTENTION-IA, POST-UK, and POST-TNK, failed to replicate these findings, with POST-TNK even reporting a higher risk of intracranial hemorrhage in the IAT group[9,10,12]. These discrepancies may stem from study design variations, statistical power limitations, and endpoint assessment differences.

To resolve these controversies, we conducted a meta-analysis incorporating the latest RCTs, examining the efficacy and safety of adjunctive IAT post-EVT in LVO-AIS patients. We also used trial sequential analysis (TSA) to assess the conclusiveness of the efficacy evidence and analyzed the impact of clinical characteristics, such as thrombolytic agent type, preceding intravenous thrombolysis, and occlusion site, on treatment efficacy. Additionally, we conducted a network meta-analysis to indirectly compare the efficacy of different intra-arterial thrombolytic agents. Our work aims to provide additional evidence to aid clinicians in selecting optimal post-EVT treatment strategies.

Methods

This study strictly complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and A Measurement Tool to Assess systematic Reviews 2 (AMSTAR 2) guidelines[16,17]. This study was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the unique identifier (CRD420251015702).

Eligibility criteria

Comparative studies published in English in peer-reviewed journals were considered eligible if they adhered to the Population, Intervention, Comparison, Outcome, and Study Design (PICOS) framework.

Population: Adult patients with AIS-LVO who achieved successful EVT, defined as Thrombolysis In Cerebral Infarction (TICI) 2b-3. Intervention: Adjunctive IAT administered following successful EVT. Comparison: EVT procedures completed without adjunctive IAT. Outcomes: The primary outcome was an excellent functional outcome, defined as an mRS score of 0–1 at 90 days. Secondary outcomes included functional independence (mRS 0–2), incidence of symptomatic intracranial hemorrhage (sICH), and all-cause mortality at 90 days. Study Design: Only RCTs were included.

Search strategy

We systematically searched PubMed, Embase, and the Cochrane Central Register of Controlled Trials for studies published between 1 January 2015 and 10 February 2025. The search strategy included the following terms: "Acute Ischemic Stroke," "Large Vessel Occlusion," "Mechanical Thrombectomy" or "Endovascular Therapy," and "Intra-Arterial Thrombolysis." The full search strategy was provided in Supplemental Digital Content, Table 1 (available at: http://links.lww.com/JS9/E93). Additionally, we manually screened the reference lists of relevant reviews and searched conference abstracts published by the International Stroke Group, the European Stroke Organisation, and the Chinese Stroke Association to identify and include relevant studies.

Data extraction

All search results were managed using EndNote software. Two independent reviewers screened studies based on predefined eligibility criteria, classifying them as eligible, ineligible, or uncertain. Exclusion criteria followed the PICOS framework, beginning with a title and abstract review[18]. If a study could not be excluded based on these alone, it would be considered potentially relevant and proceed to full-text review. Studies were included only if both reviewers agree on their eligibility. Any disagreements were resolved through discussion, and if necessary, a third reviewer served as an arbitrator.

Extracted data included study characteristics, baseline patient information, and outcomes of interest. Study characteristics encompassed the trial name, year of publication, country of origin, and sample size. Outcomes of interest included the mRS score at 90 days and sICH. If disagreements arised and could not be resolved through discussion, a third reviewer would mediate to ensure consensus.

Risk of bias assessment

The Cochrane Risk of Bias Tool were used to evaluate the risk of bias in the included studies, considering factors such as sequence generation, allocation concealment, blinding, and other potential biases[19]. The overall risk of bias was determined by its highest-risk rating across all assessed domains. For instance, if any domain was classified as having a high risk of bias, the study would be rated as having a high overall risk. Any disagreements between reviewers were thoroughly discussed until consensus is reached.

Quality of evidence

Two reviewers evaluated the quality of evidence using the Grading of Recommendations, Assessment, Development, and Evaluation system (GRADE)[20], considering factors such as risk of bias, inconsistency, indirectness, imprecision, and publication bias. The evidence was then classified into four levels: very low, low, moderate, or high. Any disagreements were resolved through discussion with a third reviewer.

Statistical analysis

Statistical analysis was performed using Review Manager 5.4. Categorical outcomes were summarized as risk ratios (RRs) with

95% confidence intervals (CIs). Due to clinical and methodological heterogeneity, a random-effects model was used for pooled analysis[21]. Statistical heterogeneity was assessed using the Cochran Q test (P <0.1 indicating significance) and quantified with the I^2 statistic, where I^2 > 50% indicated substantial heterogeneity[22]. For the primary efficacy outcome, we used TSA to assess the risk of random errors caused by repeated testing[23]. This method established diversity-adjusted required information sizes and trial sequential monitoring boundaries, applying a 5% type I error threshold and 80% statistical power to ensure analytical rigor and reduce spurious conclusions. Sensitivity analyses were conducted for all outcomes using the leave-one-out method and excluding unpublished trials. Subgroup analyses for the primary outcome were conducted based on type of thrombolytic agent, bridging intravenous thrombolysis, site of occlusion, and degree of reperfusion. A network meta-analysis (NMA) will then be conducted to compare the effects of different intra-arterial thrombolytic agents on the primary efficacy outcomes using the netmeta package. Given the limited number of studies (<10), an Egger regression test for publication bias was not feasible. Statistical significance was set at P <0.05.

Results

Trial selection and characteristics

A total of seven trials met the inclusion criteria (Fig. 1). The ATTENTION-IA trial focused on participants with acute posterior circulation stroke. The CHOICE trial included participants with both anterior and posterior circulation strokes, while the other five trials investigated acute anterior circulation stroke. The sample sizes of the included trials ranged from 52 to 271 participants. The CHOICE trial[13] was conducted in Spain, whereas the remaining trials were conducted in China. The CHOICE trial[13] used alteplase at a dose of 0.225 mg/kg, the POST-UK trial[12] used urokinase (100 000 IU), the POST-TNK and ATTENTION-IA trials[9,10] administered tenecteplase at a dose of 0.0625 mg/kg, and the ANGEL-TNK trial[11] used tenecteplase at a dose of 0.125 mg/kg. In the DATE trial[8], participants were assigned to receive either 0.0625 mg/kg or 0.03125 mg/kg of tenecteplase. The ATTENTION-IA, CHOICE, and PEARL trials[9,13,14] permitted bridging IVT before EVT for eligible participants, whereas the other trials[8,10-12] did not allow bridging IVT before EVT. Table 1 summarizes the characteristics of the included RCTs.

Risk of bias

The risk of bias analysis indicated a low risk for the ATTENTION-IA, POST-TNK, and POST-UK trials.[8-12,14] The ANGEL-TNK, DATE, and PEARL trials have not yet been published and were considered to have a moderate risk of bias based on their protocols[8,11,14]. The CHOICE trial had a small sample size and was prematurely terminated, resulting in a moderate risk of bias[13]. Detailed risk of bias assessments are provided in Supplemental Digital Content, Figure 1 (available at: http://links.lww.com/JS9/E93).

Efficacy outcomes

Rates of excellent functional outcome (mRS score 0–1) at 90 days between EVT + IAT and EVT only among 2128 patients were compared across all 7 studies included.[8-14] The rate of mRS score 0–1 in the EVT + IAT group (485 of 1082 [44.8%]) was observed to be higher compared with the EVT only group (378 of 1046 [36.1%]), resulting in a calculated RR of 1.23 (95% CI, 1.11-1.36; P < 0.001) (Fig. 2), indicating a statistically significant difference between both groups. There was no observed heterogeneity among the included studies, as indicated by I^2 = 0 and P = 0.42. TSA indicated that the cumulative Z-curve crossed both the conventional boundary and the trial sequential monitoring boundary, entering the benefit area, suggesting sufficient evidence (Supplemental Digital Content, Figure 2, available at: http://links.lww.com/JS9/E93).

Data on the functional independence (mRS score 0–2) at 90 days was provided by all 7 studies,[8-14] encompassing a total of 2128 patients. In the EVT + IAT group, the mRS score 0–2 was found to be higher (586 of 1082 [54.2%]) than in the EVT only group (543 of 1046 [51.9%]). However, the calculated RR was 1.04 (95% CI, 0.96-1.13; P = 0.29) (Supplemental Digital Content, Figure 3A, available at: http://links.lww.com/JS9/E93), indicating no significant difference between the 2 groups. There was no observed heterogeneity among the included studies, as evidenced by I^2 = 0 and P = 0.98.

Table 1

Baseline characteristics of included trials

Trial	CHOICE	POST-TNK	POST-UK	ATTENTON-IA	ANGEL-TNK	DATE	PEARL
Year	2022	2025	2025	2025	2025	2025	2025
Country	Spain	China	China	China	China	China	China
Occlusion site	ICA, M1, M2 or PCA	ICA, M1, or M2	ICA, M1, or M2	Basilar, vertebral, or P1	ICA, M1, or M2	ICA, M1, or M2	ICA, M1, or M2
Thrombolytic agent	Alteplase (0.225 mg/kg)	Tenecteplase (0.0625 mg/kg)	Urokinase (100 000 IU)	Tenecteplase (0.0625 mg/kg)	Tenecteplase (0.125 mg/kg)	Tenecteplase (0.0625/ 0.03125 mg/kg)	Alteplase (0.225 mg/kg)
Participations EVT + IAT vs EVT (n)	62 vs 52	269 vs 271	267 vs 267	104 vs 104	126 vs 129	92 vs 65	164 vs 160
Time from onset to randomisation	24 hours	24 hours	24 hours	24 hours	4.5–24 hours	24 hours	24 hours
eTICI score	2b50-3	2c-3	2c-3	2b50-3	2b50-3	2b50-3	2b50-3
IVT before EVT	With or without	Without	Without	With or without	Without	Without	With or without

EVT = endovascular thrombectomy; eTICI = extended thrombolysis in cerebral infarction; IAT = intra-arterial thrombolysis; ICA = internal carotid artery; IU = international units; IVT = intravenous thrombolysis; M1 = main trunk of the middle cerebral artery; M2 = first-order branch of the main trunk of the middle cerebral artery; PCA = posterior cerebral artery; P1 = first segment of the posterior cerebral artery.

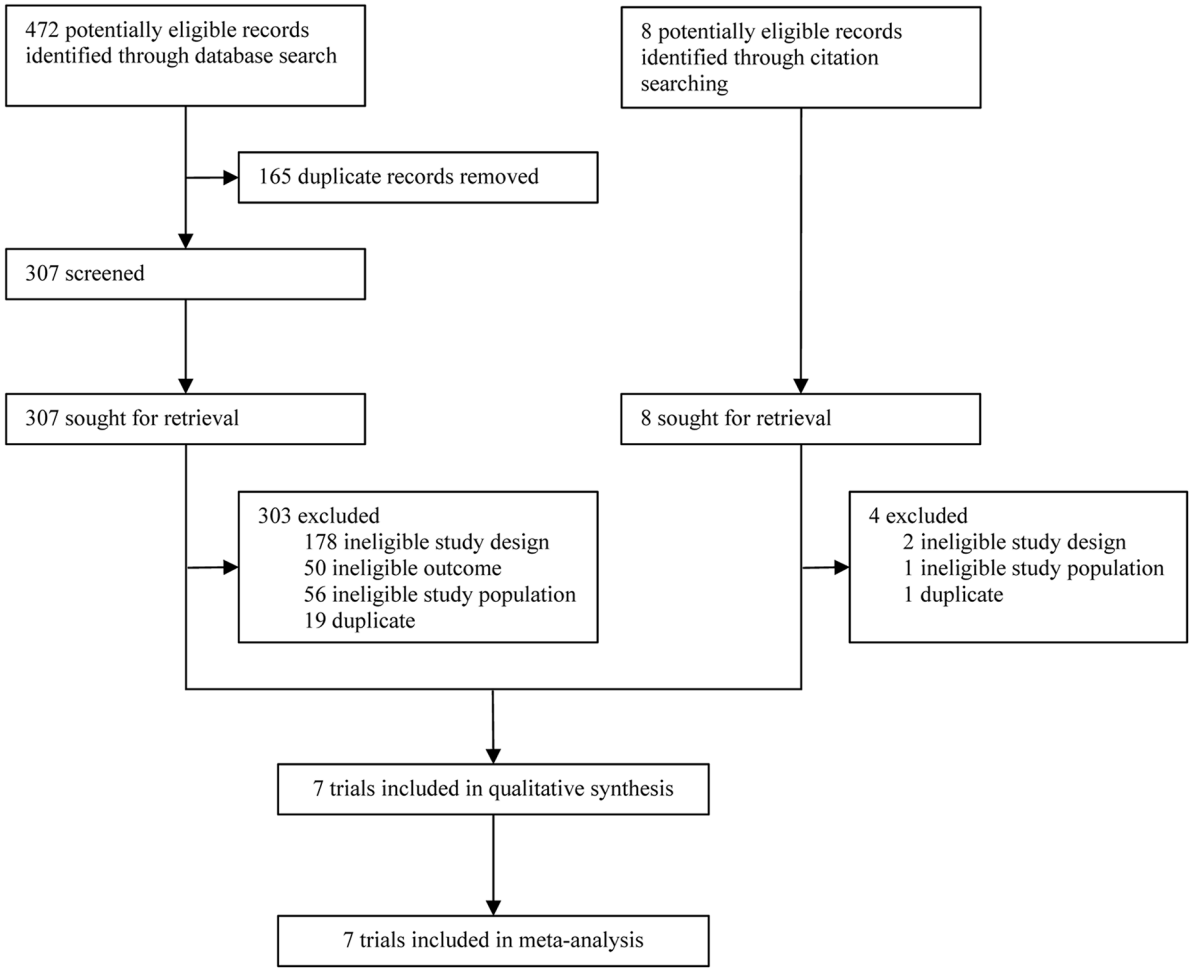

Figure 1. Study flow diagram.

Safety outcomes

Results from 6 studies[9-14] involving 1956 patients indicated that the group with EVT + IAT (50 of 981 [5.1%]) had a higher occurrence of symptomatic ICH compared with the EVT only group (41 of 975 [4.2%]). However, the calculated RR of 1.23 (95% CI, 0.81-1.85; P = 0.33) (Supplemental Digital Content, Figure 3B, available at: http://links.lww.com/JS9/E93) did not reach statistical significance. Importantly, there was no observed heterogeneity among the studies included, as indicated by $I^2 = 0$ and $P = 0.56$.

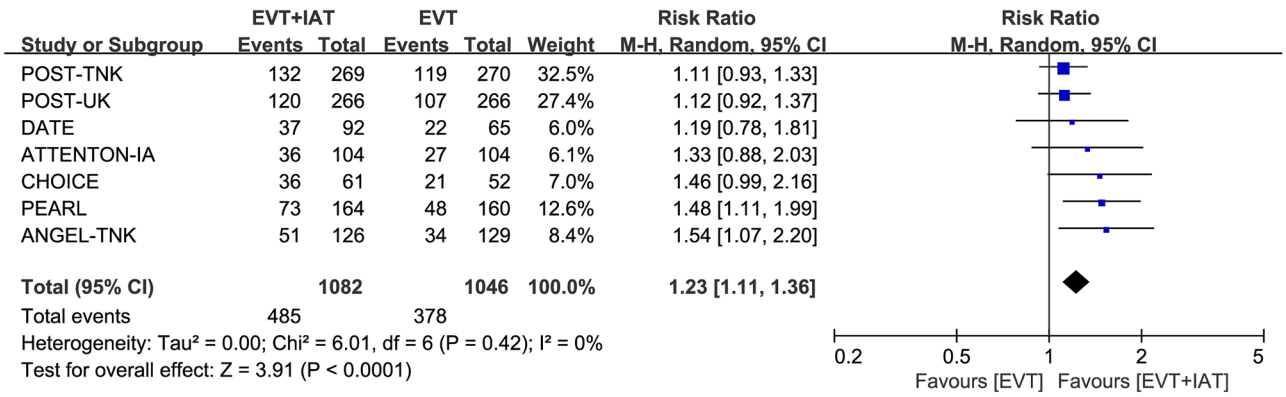

Figure 2. Forest plots for the modified Rankin Scale Score of 0–1 at 90 days.

The conducted analysis comparing the 3-month mortality rates between patients receiving EVT + IAT and EVT only included 2128 patients from all 7 studies.[8-14] In the EVT + IAT group (197 of 1082 [18.2%]), mortality at 90 days was found to be lower compared with the EVT only group (194 of 1046 [18.5%]). The calculated RR of 0.98 (95% CI, 0.82-1.18; $P = 0.86$) (Supplemental Digital Content, Figure 3C, available at: http://links.lww.com/JS9/E93) did not demonstrate statistical significance. No heterogeneity was found among the included studies, as evidenced by $I^2 = 0$ and $P = 0.53$.

Sensitivity analyses

Exclusion of individual trials demonstrated no substantial impact on statistical significance or heterogeneity across all outcome measures (Supplemental Digital Content, Figure 4, available at: http://links.lww.com/JS9/E93). A sensitivity analysis excluding unpublished trials confirmed the robustness of all outcomes (Supplemental Digital Content, Figure 5, available at: http://links.lww.com/JS9/E93).

Subgroup analyses

The subgroup analyses of the primary efficacy outcome were presented in Supplemental Digital Content, Figure 6 (available at: http://links.lww.com/JS9/E93). The results were generally consistent with the main analysis. The proportion of patients achieving mRS 0–1 may be higher in the TICI 2b50-3 subgroup than in the TICI 2c-3 subgroup ($P = 0.03$).

Network meta-analysis

Our NMA found that, compared to the EVT only group, the proportion of patients achieving an mRS score of 0–1 was higher in the EVT + IAT group with alteplase and tenecteplase, while no significant difference was observed with urokinase (Supplemental Digital Content, Figure 7, available at: http://links.lww.com/JS9/E93). Furthermore, no significant difference was found among the alteplase, tenecteplase, and urokinase groups.

Quality of evidence

The quality of evidence was rated as moderate for all outcomes. Detailed assessment information is outlined in Supplemental Digital Content, Table 2 (available at: http://links.lww.com/JS9/E93).

Discussion

Main findings

We conducted a systematic review and meta-analysis of seven RCTs to evaluate the efficacy and safety of IAT as an adjunctive therapy to EVT in patients with AIS-LVO. The results demonstrated that adjunctive IAT following successful reperfusion increased the proportion of patients achieving a mRS 0–1. TSA indicated that additional RCTs are unlikely to change the direction of the effect on mRS 0–1. Furthermore, no significant differences were found in the outcomes of mRS 0–2, sICH, or mortality.

Comparison with previous studies

A recent meta-analysis of several observational studies evaluated the efficacy of adjunctive IAT in improving functional outcomes following successful EVT, but the results were contradictory.[24-26] The findings from observational studies may be influenced by confounding factors, and there are substantial differences in patient population characteristics. To further explore the impact of adjunctive IAT following successful reperfusion in AIS-LVO patients, a recent comment of three RCTs found no significant improvement in functional outcomes[27]. However, the authors noted that while the efficacy outcomes did not reach statistical significance, the potential benefit of adjunctive IAT cannot be excluded, as the CIs for the effect estimate encompassed clinically meaningful benefits. Furthermore, regarding safety outcomes, only the POST-TNK trial suggested a potential risk of intracranial hemorrhage associated with adjunctive IAT[10], whereas the safety outcomes for sICH and mortality risk were consistently validated. It is noteworthy that the three trials had different inclusion criteria and procedural protocols. For example, the CHOICE trial allowed bridging IVT before EVT[13], whereas the POST-UK and POST-TNK trials did not[10,12]. Moreover, the trials employed different intra-arterial thrombolytic agents: alteplase, urokinase, and tenecteplase, respectively. Given the inconsistencies in study design and the limited number of pooled studies, we conducted a meta-analysis incorporating the latest RCTs. This analysis aimed to determine whether adjunctive IAT following successful EVT could increase the proportion of mRS score 0–1 without elevating the risk of sICH or mortality.

Potential implications for clinical practice

The evidence regarding the efficacy of adjunctive IAT in improving excellent functional outcomes after successful reperfusion in patients with AIS-LVO remains inconsistent, as indicated by previous meta-analyses of observational studies and recent RCTs. The 2019 ASA/AHA guidelines, the 2023 edition of the Clinical National Guideline for Stroke for the United Kingdom and Ireland, and the 2024 Chinese Stroke Association guidelines on reperfusion therapy for acute ischemic stroke have not provided explicit recommendations for adjunctive IAT[15,28,29]. The current evidence remains insufficient to support its routine implementation in clinical practice. Our meta-analysis integrates all available high-quality RCTs on adjunctive IAT, offering additional evidence that it may improve the proportion of patients achieving an mRS score 0–1. We further utilized TSA to assess the conclusiveness of the evidence supporting the effect of adjunctive IAT in increasing the proportion of patients achieving an mRS score of 0–1. The evidence of GRADE reinforced the efficacy of adjunctive IAT following successful EVT, with safety outcomes aligning with previous findings[24]. Prior comments of three RCTs have raised concerns regarding inconsistencies in study characteristics, particularly in the selection of intra-arterial thrombolytic agents and the inclusion of bridging intravenous thrombolysis[27]. Our subgroup analyses, stratified by clinical characteristics, provide a comprehensive evaluation of the efficacy of adjunctive IAT in improving excellent functional outcomes. Subgroup analysis based on the degree of reperfusion further suggests that the efficacy of continuous IAT may exhibit a "threshold effect." The proportion of patients achieving mRS 0–1 was significantly higher in the TICI 2b50-3 subgroup than in the TICI 2c-3 subgroup. This phenomenon

may result from the synergistic effect of adjunctive IAT in a partially recanalized state. In TICI 2b50-3 patients, the residual thrombus burden is higher, and the degree of large vessel reperfusion is moderate, allowing thrombolytic agents to further dissolve emboli in the microcirculation and improve perfusion. The NMA found no significant difference in achieving mRS 0–1 among arterial adjunctive alteplase, tenecteplase, and urokinase following successful reperfusion. Considering the existing body of evidence, our findings support the efficacy and safety of adjunctive IAT in patients with AIS-LVO undergoing successful EVT. However, the clinical relevance of this benefit must be cautiously balanced with safety considerations, as the risks of sICH did not demonstrate a statistically significant increase. Although our findings indicate that ICH risk did not hinder patients in the adjunctive IAT group from attaining outstanding functional recovery, this highlights the critical need for careful patient selection. The importance of individualized treatment strategies should be emphasized. Future trial should further investigate the outcomes in stratified patient populations with different characteristics to balance the benefits and risks of reperfusion[6,30]. These results offer valuable insights into the potential adoption of adjunctive IAT as part of post-reperfusion management in patients with AIS-LVO.

Study strengths and limitations

The strength of this meta-analysis lies in its comprehensive evaluation of the efficacy and safety of adjunctive IAT following successful EVT. Additionally, the robustness of the findings was validated through predefined subgroup and sensitivity analyses, further enhancing their reliability. Moreover, the certainty provided by TSA and GRADE assessments reinforces the clinical relevance of these results. Finally, the NMA evaluated that different types of adjunctive intra-arterial thrombolytic agents may have no significant difference in primary efficacy outcomes for patients.

This study has several limitations. First, there is variability in patient characteristics across the trials. Although subgroup analyses were conducted to mitigate the impact of these confounding factors, the limited number of studies, particularly the single RCT on posterior circulation infarction and the single RCT investigating intra-arterial urokinase thrombolysis, restricted the statistical power required to draw definitive conclusions. Second, there are constraints in selecting the most effective thrombolytic agent, whether alteplase, urokinase, or tenecteplase. Third, most RCTs were conducted in China, introducing geographical limitations that may hinder the generalizability of adjunctive IAT to patients in other regions. Additionally, the outcomes of the ANGEL-TNK, DATE, and PEARL trials were extracted from international stroke conferences and remain unpublished, making baseline data inaccessible. However, we additionally conducted a sensitivity analysis excluding three grey trials to confirm the stability of the outcomes. Finally, the lack of baseline data and the unavailability of patient-level data prevented a more detailed analysis of study design, procedures, and baseline characteristics. In summary, these limitations highlight the necessity for further research.

Conclusions

The findings of this systemic review and meta-analysis suggest that EVT + IAT appears to be safe in patients with LVO stroke, and adjunctive IAT result in a greater likelihood of excellent functional outcome. Clinical practice guidelines may consider including the recommendation to perform routine use of IAT in patients undergoing EVT.

Ethical approval

The ethical review form is not applicable, as the methodology of our article is meta-analysis.

Consent

The informed consent from patients or volunteers is not applicable, as the methodology of our article is meta-analysis.

Sources of funding

None.

Author contributions

W.M.L., Y.G., and G.Y.: study conception and design; W.M.L., Q.J.B., and H.Z.Z.: manuscript drafting; all authors: acquisition, analysis, and interpretation of data, critical revision for important intellectual content, final approval of the manuscript. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflicts of interest disclosure

The authors declare that they have no competing interests.

Research registration unique identifying number (UIN)

This study strictly complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and A Measurement Tool to Assess Systematic Reviews 2 (AMSTAR 2) guidelines. This study was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the unique identifier (CRD420251015702).

Guarantor

Corresponding author Wenmiao Luo is willing to take full responsibility for the article, including the accuracy and appropriateness of the reference list.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Data availability statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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