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Antiplatelet therapy versus intravenous thrombolysis for mild acute ischaemic stroke: a living systematic review and meta-analysis

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ABSTRACT

Background Previous studies have shown contradictory results between early application of antiplatelet therapy and intravenous thrombolysis (IVT) for mild acute ischaemic stroke (AIS), with National Institutes of Health Stroke Scale score 0–5.

Objective To compare the benefits and risks of antiplatelet therapy and IVT in patients with mild AIS.

Methods A systematic search of MEDLINE, Embase and Cochrane Library was conducted from database inception until July 2023, without language restriction. Randomised clinical trials (RCTs) or observational studies were selected. The primary outcomes were 90-day functional outcomes, measured by the modified Rankin Scale (mRS) score. The protocol has been registered before data collection.

Results Two RCTs and four observational studies with relatively low risk of bias that enrolled 3975 patients were analysed (2454 in antiplatelet therapy and 1521 in IVT therapy). There were no significant differences between antiplatelet therapy and IVT in 90-day functional outcomes (mRS 0–1, OR 1.08 (95% CI 0.73 to 1.58); mRS 0–2, OR, 1.04 (95% CI 0.63 to 1.73)), death (OR, 0.64 (95% CI 0.19 to 2.13)) and stroke recurrence (OR, 0.71 (95% CI 0.28 to 1.79)). Antiplatelet therapy was associated with a reduced risk of symptomatic intracranial haemorrhage (sICH) compared with IVT (OR, 0.20 (95% CI 0.06 to 0.69)).

Conclusions Among patients with mild AIS, compared with IVT, early application of antiplatelet therapy was not significantly associated with improved functional outcomes, reduced death or stroke recurrence, but was significantly associated with a reduced risk of sICH.

PROSPERO registration number CRD42023447862.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ For patients with mild acute ischaemic stroke (defined as National Institutes of Health Stroke Scale score 0–5), intravenous thrombolysis (IVT) is not recommended in clinical practice with low level of evidence based on the current guidelines.

WHAT THIS STUDY ADDS

⇒ This study revealed that compared with IVT, early application of antiplatelet therapy was not significantly associated with improved functional outcomes, reduced death and stroke recurrence, but was significantly associated with lower risk of symptomatic intracranial haemorrhage among patients with mild acute ischaemic stroke. Through this study, the level of evidence was upgraded.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Based on the current evidence, early application of antiplatelet therapy rather than IVT is recommended in clinical practice for mild acute ischaemic stroke. Additionally, this study helps to upgrade the level of evidence of the corresponding guidelines. When relevant researches are released, it will be updated to ensure that the best available evidence is provided.

INTRODUCTION

Mild acute ischaemic stroke (AIS), defined as a National Institutes of Health Stroke Scale (NIHSS) score of 0 to 5, accounts for approximately 60% of all cases of ischaemic stroke.[1] Nearly 30% of these patients are disabled at 90 days,[2] and more than 50% require health assistance or die when discharged.[3] Previous studies have shown that antiplatelet therapy and intravenous thrombolysis (IVT) can both improve functional outcomes in mild AIS,[4 5] but the benefits and risks between the two treatments still remain controversial. It contributed to a dilemma in clinical decision-making, and relatively weak recommendations in 2019 American Heart Association/American Stroke Association (AHA/ASA) guidelines and 2021 European Stroke Organisation (ESO) guidelines for the early management of AIS.[1 6]

Although these treatments can reduce disability, they both have corresponding clinical application limitations. For instance, antiplatelet agents may cause drug intolerance and increase the risk of peptic ulcers, while thrombolytic agents are time dependent, expensive and have a high risk of

haemorrhagic complications.[7 8] To evaluate the benefits and risks, some randomised clinical trials (RCTs) and observational studies have been conducted recently for head-to-head comparisons.[9–14] However, it is worth noticing that some studies have reached inconsistent conclusions due to different treatment plans or statistical analysis methods, which causes confusion in making clinical decisions and updating guidelines.

To address this issue, we first performed a living systematic review (LSR) and meta-analysis to synthesise existing evidence, as well as compare clinical outcomes and adverse events of antiplatelet therapy versus IVT among patients with mild AIS.

METHODS

Search strategy and study selection

This study was registered in the International Prospective Register of Systematic Reviews (PROSPERO) and conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)[15] and the Meta-analysis of Observational Studies in Epidemiology[16] reporting guidelines.

The MEDLINE, Embase and Cochrane Library databases were comprehensively searched without language restrictions from their inception until July 2023 using the terms 'mild stroke', 'antiplatelet therapy' and 'IVT' (details shown in online supplemental table S1). The inclusion criteria were patients with a NIHSS score 0 to 5 in AIS, defined by 2019 AHA/ASA guidelines,[1] receiving IVT within 4.5 hours of onset versus antiplatelet therapy (including single antiplatelet therapy and dual antiplatelet therapy); and RCTs or observational studies. The exclusion criteria were no head-to-head comparisons of antiplatelet therapy and IVT; and cross-sectional analysis, case reports, case series, comments and editorials.

Based on the same criteria, we will conduct automatic and manual searches and screen the upcoming studies regularly to ensure that the findings of this systematic review remain up-to-date. When the study results become stable, or no longer an issue that affects clinical decision-making and guideline revision, the LSR will not be updated.[17]

Data extraction

Two authors independently screened abstracts and titles followed by full texts to check eligibility for inclusion, with any disagreements resolved through consensus from a third author. Using predetermined data extraction forms, relevant data were independently extracted by two reviewers, including study characteristics (titles, authors, publication year, study design, origin and enrolment period); patient characteristics (age, gender, baseline NIHSS, onset time and sample size); treatment regimens (medication name, dosage and duration) and outcome data (functional outcomes, death, stroke recurrence and bleeding events).

Risk of bias assessment

Risk of bias for included studies was assessed independently by two authors, using the Cochrane Risk of Bias 2 (RoB 2) for RCTs, and the Newcastle Ottawa quality assessment scale (NOS) for observational studies. Any discrepancies were settled by consensus from a third author. The RoB2 tool consists of five components: the randomisation process, deviations from the intended interventions, missing outcome data, measurement of the outcome and selection of the reported result. Risk of bias from RoB2 is rated as low risk of bias, some concerns and high risk of bias. The NOS consists of three domains, including selection, comparability and outcome. It is a nine-star rating scale, with more stars indicating low risk of bias. The certainty of evidence of each outcome was evaluated based on the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) method, rating as very low, low, moderate and high.

Statistical analysis

The primary outcome was excellent functional outcome defined as a modified Rankin Scale (mRS) score of 0 to 1 at 90 days. Secondary outcomes were favourable functional outcome defined as an mRS score of 0 to 2 at 90 days, all-cause death within 90 days, recurrent stroke within 90 days, and symptomatic intracranial haemorrhage (sICH) according to SITS-MOST, ECASS-II or ECASS-III criteria.

In the analysis, a pooled OR of clinical outcomes and adverse events between antiplatelet therapy versus IVT were estimated, with 95% CI for each outcome. Heterogeneity across studies was assessed using I^2 value. If an I^2 was 50% or greater, the random-effects model was used; whereas the fixed-effects model was used if an I^2 was less than 50%. Sensitivity analyses and subgroup analyses were conducted to explore the sources of heterogeneity. Potential publication bias was investigated by Egger regression test.

For all analyses, a two-sided $p<0.05$ was considered statistically significant. Statistical analyses were performed using the Review Manager Software Package (RevMan V.5.3; Cochrane Collaboration) and Stata V.16.0 (Stata Corp).

RESULTS

The search identified 456 articles, and after removing duplicates, 406 were screened by titles and abstracts. Successively, 21 studies were subjected to a full-text review, and 15 ineligible studies were excluded for the following reasons: ineligible intervention or exposure (n=9), full-text articles not found (n=3), ineligible outcomes (n=2) and ineligible study design (n=1). Six studies met the eligibility criteria for extraction, including two RCTs and four observational studies. The PRISMA flow diagram is shown in figure 1.

In total, the included studies had 3975 patients (1032 in RCTs and 2943 in observational studies; 2454 in antiplatelet therapy and 1521 in IVT therapy), with a mean

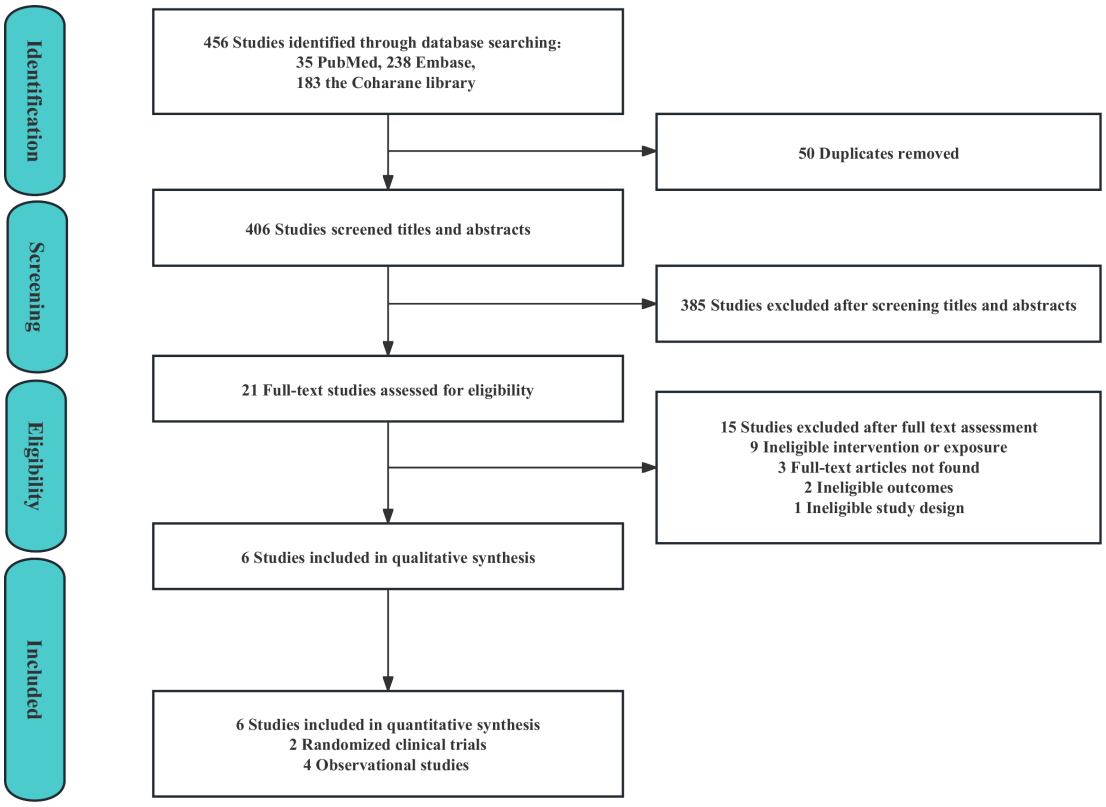

Figure 1 Flow diagram.

age ranging from 62 to 64 years. The studies were published between 2018 and 2023. Enrolled patients were from the United States, China and Austria. Baseline characteristics of the included studies are summarised in table 1. The risk of bias of RCTs and observational studies are shown in online supplemental figure S1 and S2 and online supplemental table S2, respectively. Most of the included studies were of good quality, with only one study was considered as some concerns in deviations from intended interventions. The certainty of evidence for each outcome in RCTs was moderate to high, while low to moderate in observational studies assessed by GRADE (online supplemental figure S3).

90-day functional outcomes

Pooling the results from the random-effects model showed that no significant differences were found between antiplatelet therapy and IVT in the excellent functional

Table 1 Characteristics of included studies

Study	Study design	Origin	Definition	Symptom onset, hour	Sample size	Antiplatelet therapy	IVT therapy	Outcome
Chen 2023	RCT	China	NIHSS≤5	< 4.5 hour	719	DAPT	Alteplase	①②③④
Duan 2023	Cohort study	China	NIHSS≤5	< 4.5 hour	1177	DAPT/aspirin alone	Intravenous thrombolysis	①②③
Sykora 2023	Cohort study	Austria	NIHSS≤3	NA	718	DAPT	Intravenous thrombolysis	①④
Wang 2021	Cohort study	China	NIHSS≤3	< 4.5 hour	830	DAPT/aspirin alone	Intravenous thrombolysis	①②
Lan 2020	Cohort study	China	NIHSS≤5	NA	218	DAPT	Alteplase	①②③④
Khatri 2018	RCT	United States	NIHSS≤5	< 3 hour	313	Aspirin alone	Alteplase	①②③④

①Long-term functional outcomes; ②death; ③stroke or other vascular events; ④symptomatic intracranial haemorrhage.
DAPT, dual antiplatelet therapy; IVT, intravenous thrombolysis; NA, not applicable; NIHSS, National Institutes of Health Stroke Scale; RCT, randomised clinical trial.

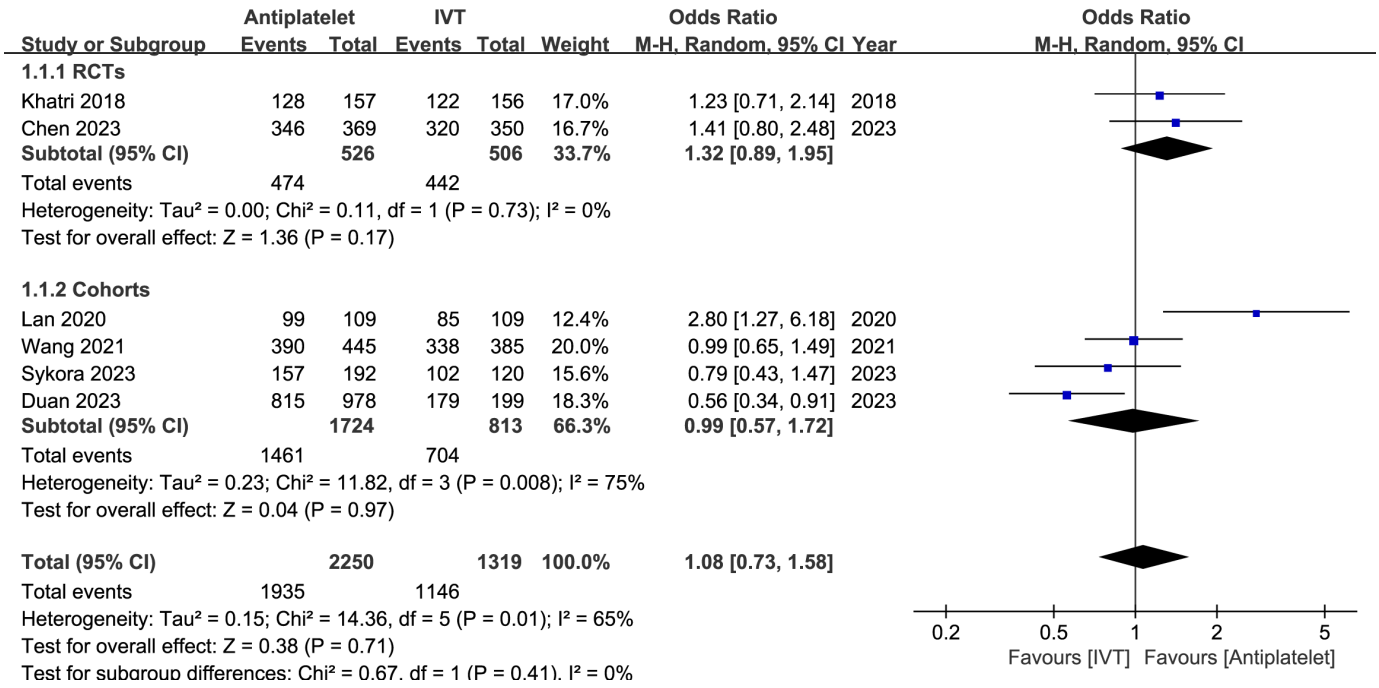

Figure 2 Forest plot of antiplatelet therapy versus IVT on excellent functional outcome at 90 days. IVT, intravenous thrombolysis; RCT, randomised clinical trial; M-H, Mantel-Haenszel.

outcome at 90 days (OR, 1.08 (95% CI 0.73 to 1.58); figure 2), and in the favourable functional outcome at 90 days (OR, 1.04 (95% CI 0.63 to 1.73); online supplemental figure S4). The certainty of evidence was found to be moderate in RCTs and low in observational studies.

To explore the source of heterogeneity, we conducted subgroup analyses by the time of administration, various antiplatelet therapies and aetiologies. In terms of the time of administration, the pooled 90-day functional outcome showed no significant difference in the treatment initiated within 3 hours (mRS 0–1, OR, 1.23 (95% CI 0.71 to 2.14); mRS 0–2, OR, 1.52 (95% CI 0.68 to 3.38)) and within 4.5 hours (mRS 0–1, OR, 0.91 (95% CI 0.55 to 1.50); mRS 0–2, OR, 0.78 (95% CI 0.54 to 1.14)) (online supplemental figures S5 and S6). Stratifying the analysis by various antiplatelet therapies, there were no significant differences in either the aspirin monotherapy (mRS 0–1, OR, 0.82 (95% CI 0.44 to 1.50); mRS 0–2, OR, 0.76 (95% CI 0.32 to 1.80)) or the dual antiplatelet therapy (DAPT) (mRS 0–1, OR, 1.09 (95% CI 0.70 to 1.68); mRS 0–2, OR, 1.00 (95% CI 0.58 to 1.73)) (online supplemental figure S7 and S8). For the aetiologies classified by Trial of ORG 10172 in Acute Stroke Treatment (TOAST), antiplatelet agents were associated with better functional outcomes measured by 90-day mRS 0 to 1 in small artery occlusion (SAO) patients (OR, 3.17 (95% CI 1.39 to 7.22)), while no significant differences were found in other TOAST classifications (large artery atherosclerosis, OR, 1.37 (95% CI 0.52 to 3.63); cardioembolic, not applicable; other determined cause, not applicable; undetermined cause, OR, 1.13 (95% CI 0.55 to 2.33)) (online supplemental figure S9). In addition, statistical heterogeneity in 90-day functional outcomes was reduced after performing leave-one-out sensitivity analysis, but there was still no significant difference between the two groups (mRS 0–1, OR, 1.19 (95% CI 0.93 to 1.51); mRS 0–2, OR, 1.18 (95% CI 0.83 to 1.69)) (online supplemental figure S10 and S11).

All-cause death

Pooling the results from the fixed-effects model showed that no significant difference was found in all-cause death within 90 days among participants receiving antiplatelet therapy versus IVT (OR, 0.64 (95% CI 0.19 to 2.13)) (figure 3). The certainty of evidence was found to be moderate in RCTs, and low in observational studies.

Stroke recurrence

Pooling the results from the fixed-effects model showed that there was no significant difference in stroke recurrence within 90 days between two groups (OR, 0.71 (95% CI 0.28 to 1.79)) (online supplemental figure S12). The certainty of evidence was found to be moderate in RCTs, and low in an observational study.

Symptomatic intracranial haemorrhage

Antiplatelet therapy was associated with a lower risk of sICH compared with IVT (OR, 0.20 (95% CI 0.06 to 0.69)) (figure 4). The certainty of evidence was found to be high in RCTs, and moderate in observational studies.

Publication bias

There was no publication bias regarding the 90-day functional outcomes (Egger regression test, p>0.05). Additionally, the publication bias of other outcomes could not be measured for the insufficient included studies.

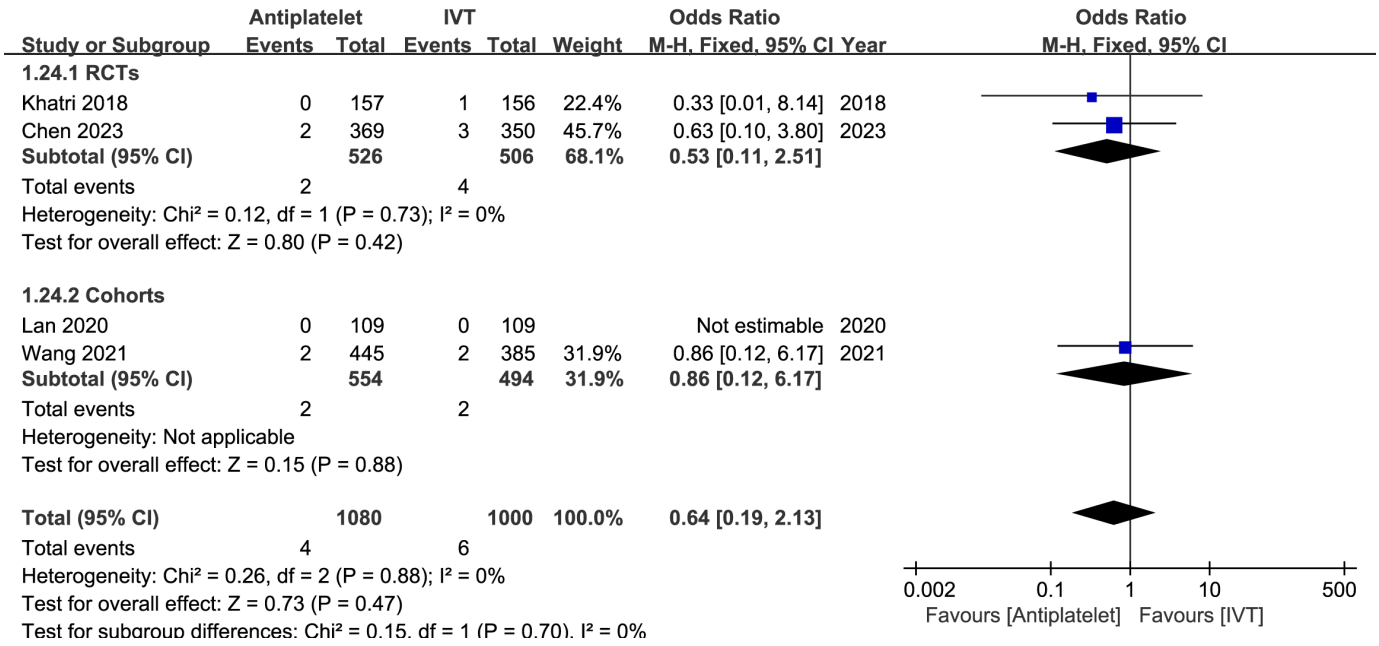

Figure 3 Forest plot of antiplatelet therapy versus IVT on death within 90 days. IVT, intravenous thrombolysis; RCT, randomised clinical trial; M-H, Mantel-Haenszel.

DISCUSSION

This is the first LSR and meta-analysis revealing that early application of antiplatelet therapy appears to be equivalent to IVT in 90-day functional outcome, all-cause death and stroke recurrence for mild AIS, despite an 80% decrease in the odds of sICH. Our results were in agreement with the current AHA/ASA and ESO guidelines,[1] which do not recommend the use of IVT in patients with mild AIS within 3 hours or 3–4.5 hours of onset, but upgraded the level of evidence.

In recent years, large-sample clinical registration data from various countries have been successively reported, and it has been found that mild AIS has a high risk of disability, recurrence and impairment of cognitive function.[3 18] Moreover, it has gradually been realised that mild stroke is not mild, but it leads to considerable disease burden.[19] Following the release

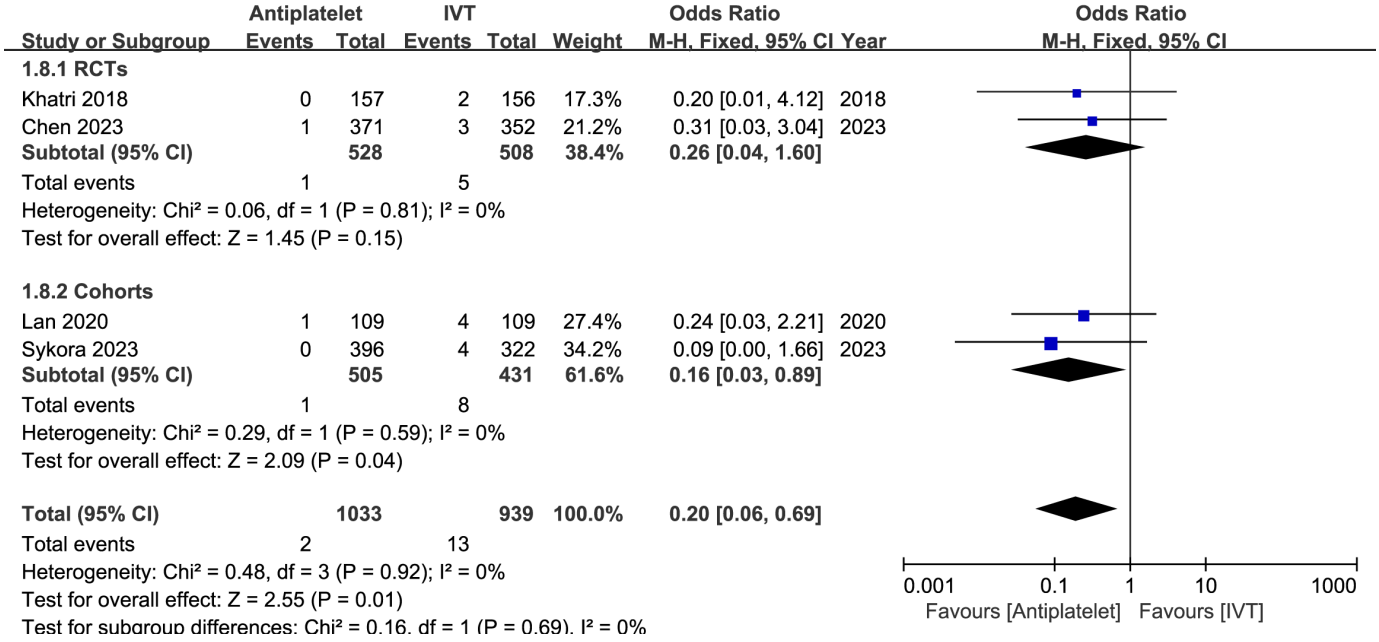

Figure 4 Forest plot of antiplatelet therapy versus IVT on sICH within 90 days. IVT, intravenous thrombolysis; RCT, randomised clinical trial; sICH, symptomatic intracranial haemorrhage; M-H, Mantel-Haenszel.

of a series of trials of antiplatelet drugs for secondary prevention, the AHA/ASA guidelines recommended the use of antiplatelet agents in patients with minor non-cardioembolic AIS to reduce the risk of recurrent stroke.[1] With the continuous optimisation of antiplatelet treatment regimens, stroke recurrence within 90 days has decreased to 6.0%.[20–22] For nearly one-third of these patients at risk of being disabled, reducing disability at an early stage has become the most pressing issue. Notably, a recent meta-analysis synthesised five RCTs revealed that antiplatelet agents could also improve the proportion of functional independence.[23] Likewise, IVT therapy improved functional outcomes in these patients, but simultaneously increased the risk of sICH.[24] Over the last few years, there has been a marked increase in the use of IVT therapy, with 4 out of 10 patients receiving recombinant tissue plasminogen activator (r-tPA) following minor stroke.[3]

To evaluate the benefits and risks of the two treatment options, relevant studies have been published recently. In 2018, a randomised, double-blind, double-placebo clinical trial, the effect of alteplase versus aspirin on functional outcome for patients with AIS and minor non-disabling neurologic deficits (PRISMS),[11] showed that IVT did not improve 90-day functional outcome but increased the risk of sICH. Unfortunately, as the trial was terminated, the conclusion should be interpreted with caution. Subsequently, in 2023, a multicentre, blinded endpoint, non-inferiority RCT, dual antiplatelet therapy versus alteplase for patients with minor non-disabling AIS (ARAMIS),[9] enrolled 760 patients who were randomly assigned to the DAPT and r-tPA groups. The results showed that clopidogrel combined with aspirin was non-inferior to alteplase in improving the excellent functional outcome at 90 days, with a similar risk of sICH in both groups. Several observational studies have compared the two treatments in larger populations and real clinical settings, but they have drawn inconsistent conclusions.[10 12–14] Therefore, it is necessary to conduct a systematic review of various types of previous studies at this point, considering the internal and external authenticities, to help clinical decision-making and guideline revision more comprehensively.

Accumulating studies have revealed the association between IVT and functional outcomes in patients with mild AIS.[5 24] However, these studies all compared IVT with no IVT, so we could not draw the conclusion of IVT and antiplatelet therapy in reducing disability. The reason for clarifying this point is that application of antiplatelet drug to specific patients with mild AIS is strongly recommended by current guidelines, whereas the other treatments (such as anticoagulation and statins) are not. To compile the best current evidence, studies that did not clearly describe antiplatelet drug regimens were excluded. A previous meta-analysis that included seven observational studies showed that the proportion of patients in the IVT group with excellent functional outcome at 90 days was 74.8%, and the proportion of patients with sICH was 1.9%.[24] In our study, the proportion of mRS 0–1 at 90 days was slightly higher (86.4%), whereas the proportion of sICH was close (1.4%). This discrepancy may be because the previous study included participants with baseline NIHSS score 0–6, but the population in our study had lower NIHSS scores. Besides, it is noteworthy that two RCTs were included in our study, which reduced the impact of relevant confounding factors on the results.

Moreover, subgroup and sensitivity analyses were performed in our study to explore the source of heterogeneity. Regarding the 90-day functional outcomes measured by mRS 0 to 1, antiplatelet agents were more effective in SAO patients compared with IVT. It was reported that more than half of SAO patients who received IVT would experience early neurological deterioration, leading to poor functional outcomes.[25] The optimal treatment for mild ischaemic stroke varies among different aetiologies, and further explanation of the mechanism is needed in the future. Also, the heterogeneity was significantly decreased after excluding one study, meaning that study led to high heterogeneity.[10] After reviewing the literature, we found that the possible reason was that the patients all combined with large vessel occlusion, which was in line with previous studies showing that such patients were more likely to benefit from IVT.[26] In addition, this study showed that IVT was only superior to single antiplatelet therapy, but not better than DAPT, which needs to be verified in future studies.

Recently, in June 2024, a prospective, randomised, open-label with blinded endpoint assessment, controlled trial, tenecteplase versus standard of care for minor ischaemic stroke with proven occlusion (TEMPO-2) was published. The results showed that in patients with mild ischaemic stroke with intracranial occlusion within 12 hours of onset, tenecteplase were not beneficial for preventing disability, but they were associated with more sICH and death compared with the non-thrombolytic standard of care.[27] Besides, another ongoing study will bring novel evidence after completion. A randomised, open-label, blind endpoint controlled trial, PUMICE (Recombinant Human Prourokinase for Injection vs Standard Medical Treatment for Acute Mild Ischemic Stroke within 4.5 Hours After Symptom Onset; NCT 05507645), is comparing the benefits and risks between intravenous urokinase and standard medical treatment in patients with mild AIS. In addition, future studies can apply advanced imaging technology to better identify the risk of haemorrhage and neurological deterioration in patients with mild AIS, helping to better evaluate individualised treatment options and benefit patients to the utmost extent.[28]

Given that the lack of evidence leading to weak recommendation in current guidelines as well as

conflict findings of published studies, there is an urgent need to synthesise the current evidence to guide clinical decision-making and guideline revision. In addition, some ongoing researches will be published in the future. Based on the current situation, LSR was chosen as the most appropriate method in our study. Compared with traditional systematic review that cannot be updated in a timely manner, LSR can more effectively provide the updated recommendations as soon as the latest relevant evidence becomes available.[17]

Limitation

This study has some limitations. First, we conducted a meta-analysis for both RCTs and observational studies, leading to potential confounding bias. However, all of the included studies had a relatively low risk of bias with restrict study design. The main source of bias was that one of the RCTs was open-labelled,[9] and another cohort study was biased because the exposed and non-exposed groups were selected from different populations.[14] Additionally, based on the GRADE method,[29] the estimated effect of the meta-analysis was ranked as moderate to high quality of evidence in RCTs and low to moderate in observational studies, which strengthened our confidence in interpreting the results. Second, one of the included studies, PRISMS,[11] was terminated due to the participant recruitment being below target; therefore, the results may be interpreted with caution. However, a post hoc analysis performed by that investigators revealed that it was unlikely that the early termination accounted for the failure to explore the benefit of alteplase.[30] Furthermore, this study applied a double-blind, double-placebo design, which was beneficial in avoiding selection bias and reporting bias during the trial. Third, due to the limited data, we were unable to conduct further subgroup analysis in other aspects, such as combined with large vessel occlusion and different IVT drugs (such as urokinase). More details need to be reported in subsequent researches, so that other valuable conclusions can be drawn in the future. Fourth, the definition of sICH was varied due to different study period, but the differences were not substantial, resulting in little impact on overall results of the meta-analysis. Fifth, taking into account two-thirds of the studies were conducted in China, large-scale, well-designed studies in other countries are needed to confirm our conclusion.

CONCLUSION

The result of this LSR and meta-analysis revealed that no significantly differences were found between early application of antiplatelet therapy and IVT in terms of 90-day functional outcomes, death or stroke recurrence in patients with mild AIS. In addition, antiplatelet agents were associated with a lower risk of sICH. Our results support the current guidelines that IVT is not recommended for patients with mild stroke symptoms within 4.5 hours of onset based on the available evidence,[1] contributing to upgrade the level of evidence for this recommendation in updating guidelines.

Contributors Conceptualisation: MQ, LF, CZhang, YG. Data curation: TLiu, TLi, ZC, CZhou, MZ. Formal analysis: MQ, XS. Methodology: SC, CZhang. Software: XS, ZC. Supervision: LF, TLi, QJ, CZhang, YG. Validation: MQ, TLiu, XS. Visualisation: XS, ZC. Writing—original draft: MQ, TLiu, XS, SC. Writing—review and editing: LF, CZhang, YG. All the authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

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