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Comparative Efficacy and Safety of Thrombolytic Agents, Mechanical Thrombectomy, and Their Combination in Acute Ischemic Stroke: A Network Meta-Analysis of Randomized Controlled Trials

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ADMINISTRATIVE INFORMATION

Support - This study was supported by National Key Research and Development Program of China (No. 2022YFC3501101).

Review Stage at time of this submission - Piloting of the study selection process.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202560011

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 3 June 2025 and was last updated on 3 June 2025.

INTRODUCTION

Review question / Objective The objective of this network meta-analysis is to compare the efficacy and safety of thrombolytic agents, mechanical thrombectomy, and their combination in the treatment of acute ischemic stroke (AIS). The specific research questions are:
Efficacy outcomes:
What are the comparative effects of thrombolytic agents, mechanical thrombectomy, and their combination on functional outcomes at 90 days, as measured by the modified Rankin Scale (mRS)?
How do these interventions compare in terms of achieving successful recanalization of occluded cerebral vessels?
Safety outcomes:
What is the relative risk of treatment-related symptomatic intracranial hemorrhage (sICH) associated with these interventions?
Overall comparison and ranking:
What are the relative rankings of these interventions in terms of their efficacy and safety profiles for the treatment of acute ischemic stroke?
The analysis will include data from randomized controlled trials (RCTs) to ensure a high level of evidence, and the results will provide evidence-based guidance for clinical decision-making in the management of acute ischemic stroke.

Condition being studied Acute ischemic stroke (AIS) is a neurological emergency caused by the sudden occlusion of a cerebral artery, most commonly due to a thrombus or embolus. This results in reduced blood flow to brain tissue, leading to ischemia and, if untreated, irreversible neuronal damage. AIS is a leading cause of death and long-term disability worldwide, with significant socioeconomic and healthcare burdens.

Timely and effective reperfusion therapies, such as thrombolytic agents (e.g., intravenous alteplase) and mechanical thrombectomy, are critical for

restoring blood flow, minimizing brain injury, and improving functional outcomes. However, these interventions carry risks, including symptomatic intracranial hemorrhage (sICH), which may offset their benefits in certain patients.

This network meta-analysis focuses on evaluating the efficacy (functional outcomes at 90 days and successful recanalization) and safety (risk of sICH) of different reperfusion strategies, including thrombolytic agents, mechanical thrombectomy, and their combination, to provide evidence-based insights for optimizing the management of AIS.

METHODS

Search strategy For example
pubmed: ("Ischemic Strokes" OR "Stroke, Ischemic" OR "Ischaemic Stroke" OR "Ischaemic Strokes" OR "Stroke, Ischaemic" OR "Acute Ischemic Stroke" OR "Acute Ischemic Strokes" OR "Ischemic Stroke, Acute" OR "Stroke, Acute Ischemic" OR "Cryptogenic Ischemic Stroke" OR "Cryptogenic Ischemic Strokes" OR "Ischemic Stroke, Cryptogenic" OR "Stroke, Cryptogenic Ischemic" OR "Cryptogenic Embolism Stroke" OR "Cryptogenic Embolism Strokes" OR "Embolism Stroke, Cryptogenic" OR "Stroke, Cryptogenic Embolism" OR "Cryptogenic Stroke" OR "Cryptogenic Strokes" OR "Stroke, Cryptogenic" OR "Wake-up Stroke" OR "Stroke, Wake-up" OR "Wake up Stroke" OR "Wake-up Strokes") AND ("Thrombolysis" OR "rt-PA" OR "Tissue Plasminogen Activator" OR "Tirofiban") AND ("Mechanical Thrombectomy" OR "Endovascular Therapy" OR "Solitaire" OR "Trevo") AND ("Randomized Controlled Trial" OR "RCT").

Participant or population This review will include participants diagnosed with acute ischemic stroke (AIS).

Intervention Thrombolytic agents, mechanical thrombectomy, and their combination.

Comparator The comparators will depend on the specific interventions assessed in each included randomized controlled trial.

Study designs to be included Randomized controlled trials (RCTs).

Eligibility criteria None.

Information sources
Electronic databases:
PubMed
Embase
Cochrane library
Web of Science
ClinicalTrials.gov
Trial registers:
WHO International Clinical Trials Registry Platform (ICTRP)
EU Clinical Trials Register
Grey literature:
Searches will be conducted in the OpenGrey database to identify unpublished studies or conference proceedings.
Contact with study authors:
When necessary, corresponding authors of included studies will be contacted to clarify study details, obtain missing data, or access unpublished results.
Manual searching:
Reference lists of included studies and relevant systematic reviews will be manually screened to identify additional eligible trials.
Language restrictions:
Only studies published in English or with full English translations will be included.
All sources will be searched from inception to the date of the final search to ensure comprehensive coverage of the relevant literature.

Main outcome(s) To evaluate the comparative efficacy of these treatments in terms of:
Functional outcomes at 90 days, as measured by the modified Rankin Scale (mRS).
Rates of successful recanalization of occluded cerebral vessels.
To assess the safety of these interventions by analyzing the incidence of treatment-related symptomatic intracranial hemorrhage (sICH).

Quality assessment / Risk of bias analysis The quality of the included randomized controlled trials (RCTs) will be assessed using the Cochrane Risk of Bias (RoB) 2.0 tool, which evaluates the following domains:
1.Bias arising from the randomization process:
Adequacy of random sequence generation.
Allocation concealment.
2.Bias due to deviations from intended interventions:
Whether participants and personnel were blinded to the intervention.
3.Bias due to missing outcome data:
Completeness of outcome data and strategies for handling missing data.
4.Bias in measurement of the outcome:
Blinding of outcome assessors and objectivity of outcome measurements.
5.Bias in selection of the reported result:
Selective outcome reporting.

Each domain will be assessed as having a low risk of bias, some concerns, or high risk of bias, based on the criteria provided in the RoB 2.0 manual.
The overall risk of bias for each study will be categorized as:
Low risk of bias: All domains are judged as low risk of bias.
Some concerns: At least one domain raises some concerns, but no domains are judged as high risk.
High risk of bias: At least one domain is judged as high risk, or there are multiple domains with some concerns that substantially lower the confidence in the results.
Two independent reviewers will conduct the risk of bias assessment. Discrepancies will be resolved by discussion or, if necessary, consultation with a third reviewer.

Strategy of data synthesis This network meta-analysis (NMA) will be conducted to compare the efficacy and safety of thrombolytic agents, mechanical thrombectomy, and their combination in the treatment of acute ischemic stroke (AIS). The analysis will follow the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions and the PRISMA-NMA statement.
1. Effect measures
For all dichotomous outcomes (90-day mRS scores , successful recanalization, and symptomatic intracranial hemorrhage [sICH]), the results will be expressed as odds ratios (ORs) with 95% confidence intervals (CIs).
2. Data synthesis methods
The network meta-analysis will combine direct and indirect evidence.
A random-effects model will be applied to account for potential heterogeneity across studies.
3. Statistical methodology
(1)Network structure: A network diagram will be created to illustrate the relationships between the included interventions and the availability of direct and indirect comparisons.
(2)Consistency assessment: The consistency of the network will be evaluated by comparing direct and indirect evidence. If inconsistency is detected, subgroup or sensitivity analyses will be performed.
(3)Ranking of interventions: The relative ranking of interventions will be determined using the surface under the cumulative ranking (SUCRA) curve.
4. Heterogeneity assessment
Statistical heterogeneity will be assessed by estimating the between-study variance.
5. Assessment of publication bias
Potential publication bias will be assessed using funnel plot.

Subgroup analysis If heterogeneity is detected, the following subgroup analyses will be performed:
Type of thrombolytic agent:
Subgroup comparisons will be conducted based on different thrombolytic agents to evaluate whether the specific agent used impacts efficacy or safety outcomes.

Sensitivity analysis To assess the robustness and reliability of the findings from the network meta-analysis, the following sensitivity analyses will be conducted:
Fixed-effects model analysis:
The network meta-analysis will be repeated using a fixed-effects model to compare the results with those obtained from the random-effects model.

Country(ies) involved China.

Keywords Acute ischemic stroke, thrombolytic agents, mechanical thrombectomy,Network Meta-Analysis.

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