ONLINE SUPPLEMENT

The efficacy and safety of intravenous recombinant tissue plasminogen activator among mid ischemic stroke: a Meta-analysis

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1. PRISMA checklist
2. Comprehensive search strategy
3. Supplemental Table 1. Quality assessment of the included studies
4. Supplemental Figure 1. Funnel plot for publication bias for sICH
5. Supplemental Figure 2. Funnel plot for publication bias for mortality

1. PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5-6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5

Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6-7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6-7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6-7
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7-8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7-8

Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7-8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	7-8
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9-11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11-12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	12

2. Comprehensive search strategy

1. cerebrovascular disorders/ or basal ganglia cerebrovascular disease/ or brain ischemia/ or exp brain infarction/ or hypoxia-ischemia,brain/ or carotid artery diseases/ or carotid artery thrombosis/ or carotid artery, internal, dissection/ or intracranial arterial diseases/ orcerebral arterial diseases/ or infarction, anterior cerebral artery/ or infarction, middle cerebral artery/ or infarction, posterior cerebralartery/ or exp "Intracranial Embolism and Thrombosis"/ or exp stroke/ or vertebral artery dissection/
2. (isch?emi$ adj6 (stroke$ or apoplex$ or cerebral vasc$ or cerebrovasc$ or cva or attack$)).tw.
3. 1 or 2
4. (minor or mini or mild or warning).tw.
5. 3 and 4
6. thrombolytic therapy/
7. fibrinolytic agents/ or plasmin/ or plasminogen/ or tissue plasminogen activator/ or exp plasminogen activators/ or urokinase-type/ or plasminogen activator/
8. fibrinolysis/
9. (thromboly$ or fibrinoly$ or recanalis$ or recanaliz$).tw.
10. ((clot$ or thrombus) adj5 (lyse or lysis or dissolve$ or dissolution)).tw.
11. (tPA or t-PA or rtPA or rt-PA or plasminogen or plasmin or alteplase or actilyse).tw.
12. (anistreplase or streptodornase or streptokinase or urokinase or pro?urokinase or rpro?uk or lumbrokinase or duteplase or lanoteplase or pamiteplase or reteplase or saruplase or staphylokinase or streptase or tenecteplase or desmoteplase or retevase).tw.
13. 6 or 7 or 8 or 9 or 10 or 11 or 12
14. 5 and 13

CINAHL

Stroke

1. Cerebrovascular Disorders OR (MH “Basal Ganglia Cerebrovascular Disease+”) OR (MH “Carotid Artery Diseases+”) OR (MH “Cerebral Ischemia+”) OR (MH "Arteriovenous Malformations+") OR (MH “Cerebral Vasospasm”) OR (MH “Intracranial Arterial Diseases+”) OR (MH "Intracranial Embolism and Thrombosis+") OR (MH “Intracranial Hemorrhage+”) OR (MH “Stroke+”) OR (MH “Vertebral Artery Dissections”)or (MH “Stroke Patients”) OR (MH “Stroke Units”)
2. (TI (brain or cerebr* or cerebell* or intracran* or intracerebral) or AB (brain or cerebr* or cerebell* or intracran* or intracerebral)) and (TI (ischemi* or ischaemi* or infarct* or thrombo* or emboli* or occlus*) or AB (ischemi* or ischaemi* or infarct* or thrombo* or emboli* or occlus*))
3. 1 or 2
4. TI (minor or mini or mild or warning) or AB (minor or mini or mild or warning)
5. 3 and 4
6. TI (thrombolytic therapy) or AB (thrombolytic therapy)
7. (MH "Plasminogen Activators+") or TI (fibrinolytic agents or plasmin or plasminogen or tissue plasminogen activator or urokinase-type or plasminogen

activator) or AB (fibrinolytic agents or plasmin or plasminogen or tissue plasminogen activator or urokinase-type or plasminogen activator)

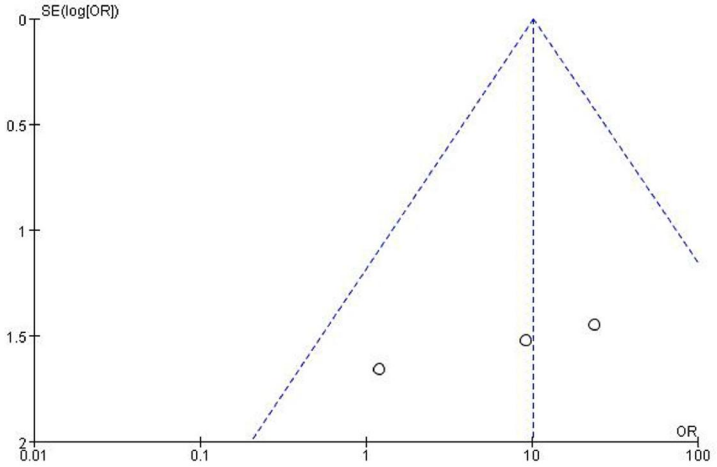
8. TI (fibrinolysis) or AB (fibrinolysis)
9. TI (thromboly* or fibrinoly* or recanalis* or recanaliz*) or AB (thromboly* or fibrinoly* or recanalis* or recanaliz*)
10. TI ((clot* or thrombus) N5 (lyse or lysis or dissolve* or dissolution)) or AB ((clot* or thrombus) N5 (lyse or lysis or dissolve* or dissolution))
11. TI (tPA or t-PA or rtPA or rt-PA or plasminogen or plasmin or alteplase or actilyse) or AB (tPA or t-PA or rtPA or rt-PA or plasminogen or plasmin or alteplase or actilyse)
12. TI (anistreplase or streptodornase or streptokinase or urokinase or prourokinaseor pro-urokinaseor rpro-ukor rprouk or lumbrokinase or duteplase or lanoteplase or pamiteplase or reteplase or saruplase or staphylokinase or streptase or tenecteplaseor desmoteplase or retevase) or AB (anistreplase or streptodornase or streptokinase or urokinase or prourokinaseor pro-urokinaseor rpro-ukor rprouk or lumbrokinase or duteplase or lanoteplase or pamiteplase or reteplase or saruplase or staphylokinase or streptase or tenecteplaseor desmoteplase or retevase)
13. 6 or 7 or 8 or 9 or 10 or 11 or 12

14. 5 and 13

3. Supplemental Table 1. Quality assessment of the included studies

Publications	Selection				Comparability	Outcome		
Observational studies	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure to implants	Demonstration that outcome of interest was not present at start of study		Assessment of outcome	Follow-up long enough for outcomes	Adequacy of follow up of cohorts
Khatri, et al 2010[21]	1	1	1	1	2	1	1	1
Huisa, et al 2012[18]	1	1	1	1	1	1	1	1
Urra, et al 2013[12]	1	1	1	1	1	1	1	1
Greisenegger, et al 2014[11]	1	1	1	1	2	1	1	1
Nesi, et al 2014[13]	1	1	1	1	1	1	1	1
Khatri, et al 2015[14]	1	1	1	1	2	1	1	1
Ng, et al 2016[16]	0	0	1	1	1	1	1	1

4. Supplemental Figure 1. Funnel plot for publication bias for sICH



5. Supplemental Figure 2. Funnel plot for publication bias for mortality