



Should Routine Intravenous Thrombolysis Be Considered in Patients Receiving Endovascular Thrombectomy for Acute Ischemic Stroke With Large Vessel Occlusions?

TAKE-HOME MESSAGE

Intravenous thrombolysis in patients with acute ischemic stroke from large vessel occlusions undergoing endovascular thrombectomy demonstrates higher frequencies of reperfusion, but it is not associated with significant improvements in function or mortality when compared with endovascular thrombectomy alone.

METHODS

DATA SOURCES

In November 2023, the authors queried 7 electronic databases (CENTRAL, Cochrane Database of Systematic Reviews, MEDLINE, Embase, Scopus, LILACS, and Google Scholar), clinical trial registries for ongoing trials (US National Institutes of Health Ongoing Trials Register, WHO ICTRP), and reference lists screened from review articles. One year later they queried Ovid and Scopus databases to assess for postpublication concerns (eg, retractions, errata, letters, and corrigenda).

STUDY SELECTION

The authors included randomized control trials of adult patients with acute ischemic stroke receiving endovascular therapy within 24 hours of onset.¹ They focused on intravenous therapy and excluded studies of intra-arterial thrombolysis. Meta-analysis studies randomized patients to control (ie, endovascular therapy monotherapy) versus endovascular therapy with intravenous

EBEM Commentators

Paul Kim, DO
Joshua Easter, MD, MSc
Brit Long, MD
*Department of Emergency Medicine
University of Virginia Medical School
Charlottesville, VA*

Jestin N. Carlson, MD, MS, Alan Jones, MD, and Michael Gottlieb, MD, serve as editors of the SRS series.

Editor's Note: This is a clinical synopsis, a regular feature of the *Annals'* Systematic Review Snapshot (SRS) series. The source for this systematic review snapshot is: **Gottlieb M, Carlson JN, Westrick J, et al. Endovascular thrombectomy with versus without intravenous thrombolysis for acute ischaemic stroke. *Cochrane Database Syst Rev.* 2025;4:CD015721. doi:10.1002/14651858.CD015721.pub2**

Results

Table. Comparison of outcomes in patients receiving EVT with IVT versus EVT alone.

Outcomes*	Patients (RCTs)	RR (95% CI)	Heterogeneity (I^2) (%)	Certainty
Functional independence (mRS score <3)	2,336 (6)	1.03 (0.92-1.14)	67	Moderate [†]
Successful revascularization (TICI grades 2b-3)	2,326 (6)	1.04 (1.01-1.08)	0	High
Complete revascularization (TICI grade 3 only)	2,037 (5)	1.14 (1.02-1.28)	0	High
Mortality	2,336 (6)	0.94 (0.78-1.14)	0	High
Asymptomatic ICH	2,334 (6)	1.13 (1.00-1.29)	0	High
Symptomatic ICH	2,336 (6)	1.20 (0.84-1.70)	0	Moderate [‡]
Excellent functional outcome (mRS score <2)	2,336 (6)	0.99 (0.92-1.05)	0	High

AIS, Acute ischemic stroke; CI, confidence interval; EVT, endovascular thrombectomy; ICH, intracranial hemorrhage; IVT, intravenous thrombolysis; mRS, modified Rankin scale; RCT, randomized controlled trial; RR, relative risk.

*All outcomes were observed within a 90-day time period.

[†]Downgraded for inconsistency: large I^2 value, indicating heterogeneity may be substantial.

[‡]Downgraded for imprecision: 95% CI (0.94-1.70) fails to exclude important benefit or harm.

thrombolysis within 4.5 hours of stroke onset. Eligible studies needed to also include at least one of the following designated outcomes observed within a 90-day period: functional independence (modified Rankin scale <3), excellent functional outcome (modified Rankin scale <2), mortality, asymptomatic intracranial hemorrhage, symptomatic intracranial hemorrhage, and successful revascularization, or complete revascularization.² The degree of revascularization was based on the thrombolysis in cerebral infarction (TICI) grade.³ TICI grades 2b to 3 signified successful revascularization, whereas complete revascularization was characterized by a TICI grade 3 only. All types of intravenous thrombolysis (eg, alteplase [tPA] and tenecteplase) and endovascular therapy techniques (eg, angioplasty aspiration and laser recanalization) were included. Two review authors (MG, JNC) independently read through reports and selected those that met inclusion criteria with a third reviewer (GDP) adjudicating disagreements.

DATA EXTRACTION AND SYNTHESIS

Two review authors (MG, JNC) extracted and categorized data by study methods (eg, design, country, and publication type), participant characteristics, intervention details, outcomes, and other factors (eg, funding source, conflicts of interest, and participants lost to follow-up).^{1,4} Risk-of-bias assessment was conducted using 2 review authors (MG, JNC) based on the Cochrane Handbook for Systematic Reviews of Interventions and Risk-of-Bias 2 tool.^{5,6} A third reviewer (GDP) settled any disagreements between the 2 reviewers. Intravenous

Authors identified 9,382 articles and ultimately included 6 randomized control trials.¹ Of the total 2,336 participants included in these studies, 1,170 received both endovascular therapy and intravenous thrombolysis, whereas the other 1,166 received endovascular therapy monotherapy. The mean age was 71 years. Men represented the majority (55.7%). Mean National Institutes of Health Stroke Scale scores were 17 for patients receiving endovascular therapy monotherapy and 16 for the endovascular therapy and intravenous thrombolysis dual therapy. All studies had participants with vessel occlusion of either the middle cerebral artery or intracranial internal carotid artery, and one study also included those with basilar artery occlusion. Four studies used tPA 0.9 mg/kg, one study used tPA 0.6 mg/kg, and one study used either tPA 0.9 mg/kg or tenecteplase 0.25 mg/kg. The authors designated functional independence (modified Rankin scale score <3) as the only “critical” outcome, which was improved in patients receiving endovascular therapy with intravenous thrombolysis (Table). Successful revascularization (TICI grades 2b-3) and complete revascularization (TICI grade 3 only) were more common with endovascular therapy with intravenous thrombolysis compared with endovascular therapy alone. The remainder of outcomes (ie, excellent functional outcome (modified Rankin scale score <2), mortality, and asymptomatic or symptomatic intracranial hemorrhage) showed no significant difference between either groups.

Commentary

Cerebrovascular disease is the fourth leading cause of overall

mortality in the United States based on a 2023 report by the National Center for Statistics.⁸ According to the American Heart Association and American Stroke Association guidelines for acute ischemic stroke management, intravenous tPA is recommended for patients presenting within 3 hours of symptom onset or from their last known baseline state (Class of Recommendation I, Level of Evidence A).⁹ This treatment window may be extended to 4.5 hours for select patients, retaining a Class of Recommendation I designation, although the level of evidence is downgraded to B-R. For mechanical thrombectomy, the recommended time window is within 6 to 16 hours from the last known normal (Class of Recommendation I, Level of Evidence A). This window may be extended up to 24 hours in select patients, although with a lower strength of recommendation (Class of Recommendation IIa, Level of Evidence B-R).⁹

This meta-analysis reviewed the efficacy and safety of intravenous thrombolysis administration in conjunction with endovascular therapy, finding improved functional independence (modified Rankin scale score <3) and revascularization with endovascular therapy plus intravenous thrombolysis versus endovascular therapy alone.¹ Authors found no statistically significant difference in excellent functional outcome (modified Rankin scale score <2), mortality, and asymptomatic or symptomatic intracranial hemorrhage. Although the point estimate for intracranial hemorrhage was slightly higher in the group receiving intravenous thrombolysis, this difference was not

thrombolysis included tPA or tenecteplase, whereas different endovascular therapy techniques were combined, thereby allowing for a single pairwise comparison. Risk ratios were calculated to measure treatment effects. When multiple outcome assessments were listed, the time points furthest from the intervention were used. Intention-to-treat data were used to mitigate the effect of missing information. The authors employed random-effects models to observe for clinical differences not already accounted for by their evaluation of statistical heterogeneity. Data not amenable to meta-analysis were represented by forest plots, providing visual demonstration of statistical heterogeneity based on direction and magnitude of effects. Chi-square tests and I^2 statistics were applied to determine statistically significant heterogeneity ($P < .10$). Certainty of evidence was assessed using the GRADE system as well as guidelines provided in the Cochrane Handbook for Systematic Reviews of Interventions.⁷ The authors forewent sensitivity analysis on the basis that all included studies were deemed low risk for bias, as all studies used modified Rankin scale within 90 days and designated thrombectomy monotherapy as the control group.

statistically significant when analyzing 2,334 patients receiving endovascular therapy. These findings are noteworthy given that the aforementioned American Heart Association/American Stroke Association guidelines recommend intravenous thrombolysis for eligible patients, even when endovascular therapy is being considered (Class of Recommendation I, Level of Evidence A).⁹ These guidelines

cite multiple randomized controlled trials demonstrating improved functional outcomes with mechanical thrombectomy performed in conjunction with tPA.⁹

This meta-analysis does have notable limitations. First, there were a limited total number of studies eligible for inclusion, and there were insufficient randomized control trials to conduct potentially illuminating planned subgroup analyses based on stroke severity, location of the large vessel occlusion, type of endovascular therapy, and choice of intravenous thrombolysis agent. These subgroup analyses may have demonstrated different results. Second, there were significant differences in inclusion and exclusion criteria among studies as well as variance in the interventions themselves.¹ Third, although most studies used tPA dosed at 0.9 mg/kg, one study used a lower dose (0.6 mg/kg), and another study used either tPA or tenecteplase. No studies observed the exclusive use of tenecteplase, which may be superior to tPA regarding functional outcomes and reduced disability at 3 months, as well as equivocal safety profiles.¹⁰ Finally, there was potential conflict of interest from the included randomized control trials, with multiple study authors reporting receiving funding or fees from pharmaceutical companies.

Future studies will likely have more frequent inclusion of tenecteplase, which received Food and Drug Administration approval in 2025 for acute ischemic stroke management; it will be interesting to see how this change impacts

the results from this analysis.^{11,12} Further studies should also investigate the potential benefits of the observed improvements in revascularization rates from endovascular therapy and intravenous thrombolysis; improved revascularization might improve unmeasured outcomes such as predisposition to additional strokes, severity of subsequent strokes, and recrudescence of stroke symptoms. Finally, additional studies may allow further analysis of subgroups, which may demonstrate the groups most likely to benefit from therapy.

1. Gottlieb M, Carlson JN, Westrick J, et al. Endovascular thrombectomy with versus without intravenous thrombolysis for acute ischaemic stroke. *Cochrane Database Syst Rev.* 2025;4:CD015721.
2. Banks JL, Marotta CA. Outcomes validity and reliability of the modified Rankin scale: implications for stroke clinical trials: a literature review and synthesis. *Stroke.* 2007;38:1091-1096.
3. Fugate JE, Klunder AM, Kallmes DF. What is meant by "TICI"? *AJNR Am J Neuroradiol.* 2013;34:1792-1797.
4. Review Manager (RevMan). Version 8.15. The Cochrane Collaboration. 2024. Accessed August 2, 2025. revman.cochrane.org
5. Higgins JPT, Savović J, Page MJ, et al. Assessing risk of bias in a randomized trial [updated October 2019]. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, eds. *Cochrane Handbook for Systematic Reviews of Interventions.* 2024. Cochrane Version 6.5. Accessed August 2, 2025. www.training.cochrane.org/handbook
6. Sterne JA, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ.* 2019;366:l4898.
7. Schünemann H, Brozek J, Guyatt G, et al. Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach [updated October 2013]. GRADE Working Group. Accessed August 2, 2025. <https://gdt.guidelinedevelopment.org/app/handbook/handbook.html>
8. Murphy SL, Kochanek KD, Xu JQ, et al. *Mortality in the United States, 2023. NCHS Data Brief.* Hyattsville, MD: National Center for Health Statistics; 2024:521.

9. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2019;50:e344-e418.
10. Palaodimou L, Katsanos AH, Turc G, et al. Tenecteplase vs alteplase in acute ischemic stroke within 4.5 hours: a systematic review and meta-analysis of randomized trials. *Neurology*. 2024;103:e209903.
11. U.S. Food and Drug Administration. *FDA roundup: March 4, 2025*. FDA News Releases; March 4, 2025. Accessed June 14, 2025. <http://www.fda.gov/news-events/press-announcements/fda-roundup-march-4-2025>
12. Wang DZ, Rose JA, Honings DS, et al. Treating acute stroke patients with intravenous tPA: the OSF stroke network experience. *Stroke*. 2000;31:77-81.