Endovascular Thrombectomy for Acute Ischemic Stroke
A Meta-analysis

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IMPORTANCE Endovascular intervention for acute ischemic stroke improves revascularization. But trials examining endovascular therapy yielded variable functional outcomes, and the effect of endovascular intervention among subgroups needs better definition.

OBJECTIVE To examine the association between endovascular mechanical thrombectomy and clinical outcomes among patients with acute ischemic stroke.

DATA SOURCES We systematically searched MEDLINE, EMBASE, CINAHL, Google Scholar, and the Cochrane Library without language restriction through August 2015.

STUDY SELECTION Eligible studies were randomized clinical trials of endovascular therapy with mechanical thrombectomy vs standard medical care, which includes the use of intravenous tissue plasminogen activator (tPA).

DATA EXTRACTION AND SYNTHESIS Independent reviewers evaluated the quality of studies and abstracted the data. We calculated odds ratios (ORs) and 95% CIs for all outcomes using random-effects meta-analyses and performed subgroup and sensitivity analyses to examine whether certain imaging, patient, treatment, or study characteristics were associated with improved functional outcome. The strength of the evidence was examined for all outcomes using the GRADE method.

MAIN OUTCOMES AND MEASURES Ordinal improvement across modified Rankin scale (mRS) scores at 90 days, functional independence (mRS score, 0-2), angiographic revascularization at 24 hours, symptomatic intracranial hemorrhage within 90 days, and all-cause mortality at 90 days.

RESULTS Data were included from 8 trials involving 2423 patients (mean [SD] age, 67.4 [14.4] years; 1131 [46.7%] women), including 1313 who underwent endovascular thrombectomy and 1110 who received standard medical care with tPA. In a meta-analysis of these trials, endovascular therapy was associated with a significant proportional treatment benefit across mRS scores (OR, 1.56; 95% CI, 1.14–2.13; P = .005). Functional independence at 90 days (mRS score, 0-2) occurred among 557 of 1293 patients (44.6%; 95% CI, 36.6%-52.8%) in the endovascular therapy group vs 351 of 1094 patients (31.8%; 95% CI, 24.6%-40.0%) in the standard medical care group (risk difference, 12%; 95% CI, 3.8%-20.3%; OR, 1.71; 95% CI, 1.18-2.49; P = .005). Compared with standard medical care, endovascular thrombectomy was associated with significantly higher rates of angiographic revascularization at 24 hours (75.8% vs 34.1%; OR, 6.49; 95% CI, 4.79-8.79; P < .001) but no significant difference in rates of symptomatic intracranial hemorrhage within 90 days (70 events [5.7%] vs 53 events [5.1%]; OR, 1.12; 95% CI, 0.77-1.63; P = .56) or all-cause mortality at 90 days (218 deaths [15.8%] vs 201 deaths [17.8%]; OR, 0.87; 95% CI, 0.68-1.12; P = .27).

CONCLUSIONS AND RELEVANCE Among patients with acute ischemic stroke, endovascular therapy with mechanical thrombectomy vs standard medical care with tPA was associated with improved functional outcomes and higher rates of angiographic revascularization, but no significant difference in symptomatic intracranial hemorrhage or all-cause mortality at 90 days.


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Endovascular therapy for acute ischemic stroke, in particular Intra-arterial Versus Systemic Thrombolyis for Acute Ischemic Stroke (SYNTHESIS),26 Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE),27 and Interventional Management of Stroke III (IMS III),28 failed to show a significant benefit of endovascular strategies. However, these trials had several well-recognized limitations, including inconsistent use of vascular imaging to confirm vessel occlusion prior to randomization, variable use of intravenous tPA in the endovascular therapy group, and reliance on less effective and older-generation mechanical devices.20,37,38 These factors were important contributors to heterogeneity in our meta-analysis. These limitations of early trials were addressed in the more recent trials, beginning with Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN).29 The results of MR CLEAN,29 favoring endovascular intervention, prompted interim analyses of the Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (ESCAPE).30 Extending the Time for Thrombolysis in Emergency Neurological Deficit—Intra-Arterial (EXTEND-IA),31 and Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment (SWIFT-PRIME)32 trials. The Randomized Trial of Revascularization with Solitaire FR Device versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting within Eight Hours of Symptom Onset (REVASCAT)33 trial was stopped for a preplanned interim analysis. These 4 trials were subsequently halted due to observed benefits in the endovascular therapy group.

In our analysis, the relative benefit associated with endovascular therapy was increased by concomitant use of intravenous tPA. Evidence in support of this combination therapy is present in the current literature with several possible explanations.39,40 A combination approach takes advantage of the speed of intravenous tPA administration and the greater recanalization potential of endovascular therapy. In addition, early initiation of treatment with intravenous tPA may reduce clot burden, restore a critical amount of blood flow, and facilitate subsequent arterial recanalization by endovascular mechanical thrombectomy.41,42 However, patients who receive tPA and those who do not receive tPA can be different populations. Patients who did not receive intravenous tPA may have had contraindications or late presentation. These may have contributed to the relatively smaller treatment effect reported with mechanical thrombectomy among patients not receiving intravenous tPA that we observed in our study.

In our study, the improvement in functional outcomes associated with endovascular therapy was significantly greater when computed tomography angiography or magnetic resonance angiography were used to confirm proximal arterial occlusion prior to trial enrolment. This is intuitive because the absence of preprocedural vascular imaging may lead to the catheterization of patients without a proximal occlusive clot, and therefore patients who are unlikely to benefit from neurointerventional treatment.

In the context of acute ischemic stroke, endovascular therapy is often considered, and evaluated as, a single treatment modality. However, a high degree of variability exists in the inherent nature of this therapy, and in reality, endovascular intervention may include a number of different but related strategies, some of which may be more effective than others. Endovascular strategies include chemical clot dissolution with local delivery of tPA, or recanalization of arterial occlusion by clot disruption, aspiration, or retrieval using a microcatheter or one of many mechanical devices. The Merci retriever was the first thrombectomy device to receive US Food and Drug Administration approval in 200443 and was widely used in early trials evaluating endovascular treatments for acute ischemic stroke, including SYNTHESIS,26 MR RESCUE,27 and IMS III.28 Nevertheless, high-quality evidence exists from 2 trials in support of the improved efficacy of newer retrievable stent devices, including the Solitaire Flow Restoration device and Trevo retriever, compared with older devices, such as the Merci retriever.44,45 Thrombectomy therapy was achieved by stent retriever devices in the majority of patients in the MR CLEAN29 and ESCAPE30 trials and in all patients in the EXTEND-IA,31 SWIFT-PRIME,32 and REVASCAT33 trials. In our meta-analysis, the use of stent retrievers for mechanical thrombectomy was a significant source of heterogeneity related to treatment outcomes and significantly affected the relative benefit associated with endovascular therapy compared to optimal medical treatment.

The limitations of our meta-analysis include variability in the design and reporting of included trials that we investigated using prespecified subgroup and sensitivity analyses. However, we could not evaluate some factors due to lack of reported data (eg, general vs local anesthesia, time to treatment, use of intra-arterial thrombolytic agents). Of these, time to treatment may have an important effect on the efficacy of endovascular therapy. Delays of even less than 30 minutes can significantly reduce the probability of functional independence after endovascular therapy.41,42 However, endovascular intervention for stroke is not universally available, and therefore, some of these patients may require transfer to a regional stroke center with neurointerventional capabilities. For this reason and others, it would be prudent to define a precise maximal time window after which treatment is considered relatively futile, similar to what exists for intravenous tPA (<4.5 hours). Previous clinical studies evaluating the importance of time to endovascular therapy have provided mixed results.46-48 with current included trials using a variable therapeutic time window, ranging from 5 to 12 hours. Most eligible studies used a time window up to 6 hours from stroke onset. Although REVASCAT33 included a 6- to 8-hour group and ESCAPE30 enrolled 49 patients at 6 to 12 hours, a definitive positive treatment effect has not been demonstrated in these subgroups.20 However, trials evaluating treatment windows extending beyond 6 hours and up to 24 hours are under way, including the Trevo and Medical Management Versus Medical Management Alone in Wake Up and Late Presenting Strokes (DAWN, ClinicalTrials.gov NCT02142283) and Perfusion Imaging Selection of Ischemic Stroke Patients for Endovascular Therapy (POSITIVE, ClinicalTrials.gov NCT01852201) trials.
Furthermore, the type of mechanical device used for endovascular thrombectomy may have a significant influence on revascularization and functional outcomes. Although newer retrievable stent devices were available for use in more recently published trials, the exact outcomes of all types of devices were not recorded in all studies, particularly older trials, preventing a complete comparison of outcomes stratified by the device type. In our sensitivity analyses, stent retrievers were associated with more favorable outcomes than other devices, although results according to the exact device type (eg, Solitaire Flow Restoration device vs Trevo retriever) were not reported. Moreover, some of the subgroup analyses in the present study were limited by relatively smaller sample size and by virtue of patient selection among included trials. For example, age, NIHSS score, and ASPECTS may be associated with the relative benefit of endovascular over standard therapy. However, many of the trials excluded patients with low ASPECTS (ie, <6) and older patients (ie, >80 years) or patients without premorbid independent function, limiting the ability of our meta-analysis to detect differences in treatment benefit related to these variables. These are important considerations because many patients with ischemic stroke are elderly and many present with evidence of advanced ischemia and infarction. Future trials will need to delineate upper age limits and clinical and radiological indicators of utility or futility of endovascular treatment.

This meta-analysis synthesizes evidence from multicenter randomized clinical trials, and may help inform the design and execution of future studies examining the efficacy of endovascular therapy for acute ischemic stroke. Additional trials are needed to systematically study the relationship of patient-, disease-, and treatment-related variables with outcomes following mechanical thrombectomy, and to identify the ideal patient to undergo endovascular therapy. Limits on age, ASPECTS, NIHSS score, and, perhaps most importantly, time to treatment, need to be explored. In addition to optimizing patient selection, trials should explore and define the optimal endovascular therapy with respect to technique, device, regional vs general anesthesia, and dosage of intracerebral thrombolytic, if any. The relationship of these variables to safety outcomes, such as mortality and morbidity, should also be studied. The results of such studies could inform the development of clinical practice guidelines. Moreover, studies are needed to evaluate the cost-effectiveness of endovascular therapy for the treatment of ischemic stroke. In addition, it may be beneficial for medical personnel involved in the early care of patients with acute ischemic stroke, such as paramedics and emergency physicians, to be trained to identify candidate patients who may benefit from endovascular therapy, and for communication to appropriate neurointerventional staff to be streamlined to mobilize neurointerventional resources and reduce the time from stroke onset to recanalization and reperfusion.

Conclusions
Among patients with acute ischemic stroke, endovascular therapy with mechanical thrombectomy compared with standard medical care with tPA was associated with improved functional outcomes and higher rates of angiographic revascularization but no significant difference in occurrence of symptomatic intracranial hemorrhage or all-cause mortality at 90 days.