Mechanical Thrombectomy Trials in Acute Ischemic Stroke

An overview of the new class I evidence supporting intra-arterial treatment for acute ischemic stroke.

BY FRANK J. ATTenELLO, MD, AND WILLIAM J. MACK, MD

The stroke neurology and endovascular neurointerventional communities have historically relied heavily upon a strong evidence base to guide decision making. However, definitive class I evidence in acute stroke treatment has been limited. Intravenous alteplase was initially regarded as the only proven therapy to restore perfusion within 4.5 hours of ischemic stroke, despite a narrow therapeutic window and recanalization in only one-third of patients.\(^1,2\) Endovascular therapy subsequently became the subject of numerous randomized trials over the last 2 decades, but results were inconclusive. Early trials employed intra-arterial urokinase and prourokinase alone without mechanical thrombectomy,\(^3,4\) whereas more recent studies focusing on mechanical thrombectomy resulted in neutral findings.\(^6-8\)

Although neurointerventionists regularly observed recanalization and clinical recovery after mechanical thrombectomy, a lack of definitive support for treatment from randomized trials proved frustrating. However, many suggested these neutral results were a function of delays in reperfusion and poor treatment candidate selection prior to recent advances.\(^9\) Evolving endovascular treatments have remedied this, allowing improved imaging to identify salvageable hypoperfused penumbra, setting the stage for a new set of trials.\(^10-12\)

In 2015, The New England Journal of Medicine released the results of five separate multicenter, prospective, randomized trials between January and September 2015.\(^9,13-16\) Each trial supports the efficacy and safety of mechanical thrombectomy in the treatment of acute ischemic stroke. The results of these trials—MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands),\(^13\) EXTEND-IA (Extending the Time for Thrombolysis in Emergency Neurological Deficits–Intra-Arterial),\(^9\) ESCAPE (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times),\(^14\) SWIFT PRIME (Solitaire FR With the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke),\(^15\) and REVASCAT (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 8 Hours of Symptom Onset)\(^16\)—are summarized in Table 1.\(^9,13-16\)
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<th>TABLE 1. SUMMARY OF NEW CLASS I STUDIES EVALUATING MECHANICAL THROMBECTOMY IN ACUTE ISCHEMIC STROKE</th>
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<td><strong>MR CLEAN</strong></td>
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**MR CLEAN**

The MR CLEAN trial randomized 500 patients, with 233 assigned to intra-arterial treatment plus usual care and 267 to usual care alone. Patients were eligible if they had proximal anterior circulation occlusions that could be intra-arterially treated within 6 hours of symptom onset. Mechanical treatment with a retrievable stent was used in the majority of cases, with an intra-arterial thrombolytic agent used as monotherapy in one case. Results showed a significant difference in outcome, with the intervention group demonstrating a significantly higher proportion of functionally independent patients (modified Rankin Scale [mRS] score of 0–2) compared with the control group at 90 days (32.6% vs 19.1%). Radiographic analysis at 24 hours noted no evidence of remaining vessel occlusion in 75.4% of patients in the intervention group versus 32.9% in the control group. In terms of safety, there were no significant differences in mortality or symptomatic intracerebral hemorrhage (ICH) between groups. However, in the intervention group, 1.7% had vessel dissection, 0.9% had vessel perforation, and 5.6% had new ischemic stroke in a different vascular territory. Of note, subgroup analysis showed a consistent treatment effect in subgroups of age, National Institutes of Health Stroke Scale (NIHSS), and Alberta Stroke Program Early CT Score (ASPECTS).

**EXTEND-IA**

The EXTEND-IA trial evaluated treatment outcomes in patients with salvageable ischemic penumbra (time to maximum delay > 6 seconds) and an irreversibly damaged ischemic core of < 70 mL on screening CT perfusion. Patients required intravenous alteplase within 4.5 hours of stroke onset and were divided into those treated via mechanical thrombectomy with the Solitaire FR (flow restoration) stent retriever (Medtronic, Inc.) or intravenous alteplase alone. Again, positive results required early termination of the trial after 70 patients, with functional independence (mRS, 0–2) achieved in 71% of patients in the treatment group versus 41% in the control group at 90 days (P = .01). Reperfusion at 24 hours was also greater in the treatment group compared to the control group (100% vs 37%; P < .001). Symptomatic ICH occurred in two patients in the control group. In the treatment group, there were two parenchymal hematomas, and embolization into a different vascular region was noted in 6%. No significant differences were found in mortality. Of note, 25% of eligible patients were excluded based on imaging criteria. The authors assert that the CT perfusion requirements and shorter times to therapy account for noted improvements in functional outcomes and reperfusion compared to the MR CLEAN trial.

**ESCAPE**

The ESCAPE trial also employed imaging criteria with CT and CT angiography to select treatment patients, selecting 316 patients with small infarct core (ASPECTS, 6–10) and moderate-to-good collateral circulation (filling ≥ 50% middle cerebral artery [MCA] pial arterial circulation). Notably, a 12-hour window after symptom onset was permitted for patients with a proximal occlusion in the anterior circulation. Similar to the EXTEND-IA trial, ESCAPE was stopped early. Both trial terminations were due to early, unplanned interim analyses prompted by the release of results of the MR CLEAN trial. Results again showed a significantly higher rate of functional independence (mRS, 0–2) in the intervention group compared to the control group (53% vs 29.3%; P < .001). Reperfusion was achieved (via thrombolysis in cerebral infarction score 2b/3) in 72% of the intervention group. Among the controls, recanalization was noted in 31%. Patients in the intervention group had a reduced mortality rate of 10% versus 19% in the control group. Finally, there were no differences in occurrence of ICH between the groups. Of note, subgroup analysis showed an effect (odds ratio ≥ 1-point increase in mRS at 90 days) across subgroups defined by age, sex, baseline NIHSS and ASPECTS, occlusion region, and previous alteplase treatment. However, among 49 patients who were randomized ≥ 6 hours after stroke onset, there was no significance in difference in functional outcome between the groups.

**SWIFT PRIME**

Results from SWIFT PRIME were published in the June 2015 issue of *The New England Journal of Medicine*. The study was conducted at 39 centers, primarily in the United States and Europe. The trial enrolled 196 patients aged 18 to 80 years with intracranial internal carotid artery (ICA) or proximal MCA occlusions within 6 hours of symptom onset and 1.5 hours of imaging. The first 71 patients were assessed with Rapid software (iSchemiaView, Inc.) to quantify core infarct/penumbral mismatch. Ultimately, the investigators changed to a small-to-moderate core infarct strategy to accommodate centers without perfusion imaging capabilities. Patients received intravenous tissue plasminogen activator (tPA; medical management group) or treatment with tPA and thrombectomy using Solitaire retrievable stents (endovascular treatment group). The trial was halted early due to efficacy. Good outcomes (mRS, 0–2) were achieved in 60% of patients in the endovascular treatment group and 35% in the medical management group. Symptomatic
ICH rates of 0% and 3% were noted at 27 hours in the endovascular treatment group and medical management group, respectively. There was no significant difference in 90-day mortality between the medical management (12%) and endovascular treatment groups (9%).

**REVASCAT**

The REVASCAT trial was conducted in four centers in Catalonia, Spain. Patients were aged 18 to 80 years and had anterior circulation large vessel occlusions that could be treated within 8 hours of symptom onset. Study sites were certified stroke centers that treated more than 500 patients with acute stroke and performed > 60 mechanical thrombectomies annually (with operators who performed ≥ 20 thrombectomies with the Solitaire device). ASPECTS > 6 on CT or > 5 on MRI were used to determine eligibility. The study criteria were changed to include patients up to aged 85 years with ASPECTS > 8 after 160 patients were enrolled. Patients were randomized to treatment with medical therapy (including intravenous alteplase when eligible) and mechanical thrombectomy with the Solitaire stent retriever device or medical therapy alone. Study recruitment was terminated after the first planned interim analysis (25% patients completed 90-day follow-up) due to loss of equipoise. The study demonstrated that in patients with acute stroke secondary to large vessel proximal occlusions and an absence of large infarct on baseline scan, mechanical thrombectomy with the Solitaire stent retriever device was safe and led to improved clinical outcomes compared to medical therapy alone.

**THERAPY TRIAL**

The THERAPY trial assessed the effectiveness of the Penumbra aspiration system (Penumbra, Inc.) in patients with acute ischemic stroke from large vessel occlusions. Although the final results of the study are yet to be published, data were presented at the European Stroke Organisation Conference in April 2015 in Glasgow, Scotland. The trial was stopped early after 108 of the planned 692 patients had been enrolled because of favorable data on endovascular treatment from other recently reported trials. Thirty-eight percent of mechanical thrombectomy patients achieved good outcomes (mRS, 1–2 at 90 days), whereas only 30% of medically treated patients had good outcomes.

**CONCLUSION**

The current class I evidence for mechanical thrombectomy is encouraging, providing much-needed data supporting a vital endovascular treatment in a recoverable population. These studies further highlight the ability to select patients based on the size of the penumbra and ischemic core. Treatment and referral centers should embrace these data and continue to increase referrals for endovascular treatments of acute ischemic stroke.

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