



Endovascular Treatment for Acute Ischemic Stroke

The evidence shines a light on the need for stroke education for both clinicians and the public.

By Neil Majmundar, MD and Priyank Khandelwal, MD



Introduction

Acute ischemic stroke (AIS) affects over 800,000 people in the US annually, making it a leading cause of morbidity and mortality.¹ An estimated

8% to 22% of these patients are candidates for endovascular treatment (EVT), which can result in a significant improvement in patient outcome if performed successfully in a timely fashion.² Treatment modalities for patients presenting with AIS are geared toward reperusing the affected vascular territory and minimizing complications. Treatment with intravenous recombinant tissue plasminogen activator (IV-rtPA) alone has benefit for some patients who present within 4.5 hours of symptom onset, but has shown limited benefit in patients presenting with large vessel occlusion (LVO).²⁻⁴

Although increased awareness of stroke symptoms, streamlined protocols for first responders and emergency department physicians, and prompt administration of IV-rtPA have all been effective in improving stroke outcomes, EVT provides another modality for achieving goals of reperfusion, minimal complications, and improved outcomes, especially in patients with the most severe strokes.

Early Trials 1999-2004

The early belief was that direct intra-arterial (IA) thrombolytic administration to the occluded vessel would provide improved rates of recanalization superior to that of IV-rtPA. Although efficacy of IA prourokinase (IA-r-proUK) for thrombolysis was demonstrated for patients with middle cerebral artery (MCA) occlusion in a randomized controlled trial,⁵ the bleeding rate was substantial, resulting in diminished enthusiasm for the next phase of trials of EVT for AIS.

Second-Generation Trials 2005-2012

The mechanical embolus removal in cerebral ischemia (Merci) device (Stryker, Kalamazoo, MI) was the first endovascular clot retrieval device investigated in a new era of mechanical thrombectomy, and recanalization was achieved in 48% of patients treated.⁶ Neurologic improvement, measured as an increase of ≥ 10 points on the National Institutes for Health Stroke Scale (NIHSS), was seen in approximately 32% of patients, and the symptomatic intracranial hemorrhage rate was low (7.8%).⁶ Endovascular clot removal with the second-generation Merci device resulted in a recanalization rate of 69.5% when combined with IA-rtPA.⁷

Another early thrombectomy device from the Penumbra corporation (Alameda, CA) was developed to aspirate clots in occluded vessels. Treatment with the Penumbra system of patients with LVO refractory to IV-rtPA resulted in thrombolysis in myocardial infarction (TIMI) scores of grade 2 or 3 in 81.6% of the treated arteries with low rates of symptomatic intracranial hemorrhage and acceptable rates of functional independence.⁸

Although the Merci and Penumbra results demonstrated adequate rates of revascularization and showed promise for EVT in AIS, 3 major studies brought the efficacy of EVT into question because no significant improvement from treatment with EVT versus standard medical management was seen.⁹⁻¹¹ It is worth mentioning that these 3 studies did not require confirmation of LVO before enrolling a patient into the treatment arm.

Next-Generation Trials 2015

The next generation of trials demonstrated the clear efficacy of EVT combined with IV-rtPA versus IV-rtPA alone. The MR CLEAN^a trial showed clear benefit in outcomes for patients who had EVT.¹² Second-generation thrombec-

a. Multicenter randomized clinical trial of endovascular treatment for acute ischemic stroke. (ISRCTN10888758)



tomy devices—stent retrievers (also called *stentriever*s)—were used in the majority of patients undergoing EVT. There was no upper-limit age cutoff for enrollees, who were all required to undergo noninvasive vascular imaging to confirm the presence of an anterior circulation LVO. Patients treated with EVT and conventional medical management (CMM) had a higher rate of achieving functional independence (32%, defined as a score of 0-2 on the modified Rankin Scale [mRS]) compared to those treated with standard medical management alone (19%).¹²

After MR CLEAN results were released, the ESCAPE^b trial ended early; interim analysis showed 53% of patients treated with EVT achieved functional independence versus 29% of those treated with CMM.¹³ This trial was geared toward streamlining the care of stroke patients, encouraging the use of CT angiography (CTA) versus MRI, setting the door-to-puncture time of less than 60 minutes, and door-to-recanalization time of less than 90 minutes.¹³

The SWIFT PRIME^c trial also prioritized noninvasive vascular imaging to identify LVO and encouraged all centers to use postprocessing software for target-mismatch penumbra. Similar to MR CLEAN and the ESCAPE trial, SWIFT PRIME also showed high rates of reperfusion (thrombolysis in cerebral infarction [TICI] score 2b/3) in 88% of patients and better functional independence outcomes in the intervention arm compared to CMM.¹⁴ The EXTEND-IA^d and REVASCAT^e also showed that mechanical clot removal using stent retrievers improved patient outcomes compared to CMM.^{15,16}

Authors from these trials pooled patient-level data from MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, and

EXTEND IA in the HERMES collaboration and demonstrated that endovascular clot removal with stentriever significantly improved patients' functional outcomes at 90 days.¹⁷ The number needed to treat (NNT) was 2.6 (Figure).¹⁷ These landmark trials clearly demonstrated the efficacy of EVT or mechanical thrombectomy in the treatment of emergent LVO. In addition to the clear benefits for patients, these trials promoted the role of advanced imaging to identify patients with adequate collateral circulation who may present outside the treatment window and still benefit from EVT.

Role of Imaging in Patient Selection

Initial imaging for patients presenting with suspected LVO typically includes a noncontrast head CT and a head and neck CTA. These studies provide adequate information to identify patients who would benefit most from EVT within 6 hours of symptom onset. The Alberta stroke program early CT (ASPECT) score, a 10-point grading system used to detect early ischemic changes on head CT, is often used to help determine whether a patient is a candidate for EVT.¹⁸ Many studies have shown that an ASPECT score of 7 or more leads to better outcomes.¹⁹ The ESCAPE, SWIFT PRIME, and REVASCAT all used an ASPECT score of less than 6 as part of the exclusion criteria, which partly explains the superior results.

The role of perfusion-weighted imaging has been explored for determining which patients may benefit most from mechanical thrombectomy. The DEFUSE-2^f trial demonstrated that patients with target-tissue mismatch (core volume < 70 mL and penumbra-to-core mismatch ratio ≤ 1.8) had better 90-day outcomes after mechani-

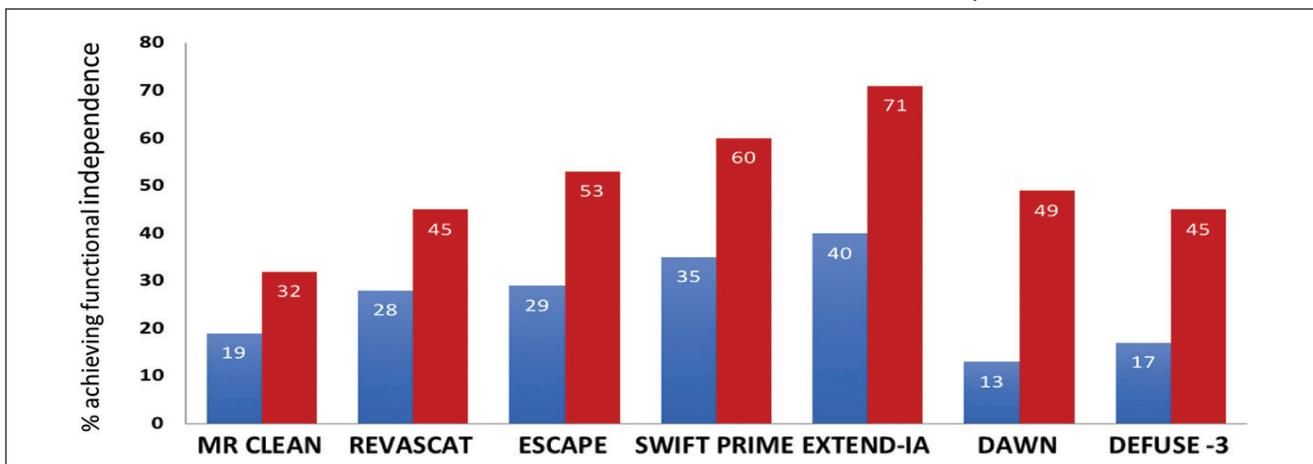


Figure. Percentage of patients treated with EVT achieving functional independence (red) compared to the percentage of control subjects achieving functional independence (blue) in recent trials. See footnotes for full trial names and NCT identifiers.

b. Endovascular treatment for small core and anterior circulation proximal occlusion with emphasis on minimizing CT to recanalization times. (NCT01778335)

c. Solitaire with the intention for thrombectomy as primary endovascular treatment for acute ischemic stroke (NCT 01657461)

d. Extending the time for thrombolysis in emergency neurological deficits-intraarterial. (NCT01492725)

e. Endovascular revascularization with solitaire device versus best medical therapy in anterior circulation stroke within 8 Hours. (NCT01692379)

f. Diffusion weighted imaging evaluation for understanding stroke evolution study-2. (NCT01349946)



cal thrombectomy with successful recanalization.²⁰ This trial was also pivotal in demonstrating that patients with salvageable tissue on perfusion imaging would still benefit from reperfusion outside the time window of 6 hours for mechanical thrombectomy used at many centers.²⁰

Recent Trials Extend Time Window for Intervention

The DAWN[®] trial demonstrated an increased rate of functional independence in patients treated with thrombectomy plus CMM (49%) compared to CMM alone (13%).²¹ The DEFUSE 3^h trial was terminated early because on interim analysis it showed improved functional outcomes with thrombectomy plus CMM alone when treatment occurred from 6 to 16 hours after ischemic stroke.²²

Both of these trials used a postprocessing-perfusion software (Rapid; IschemaView, Inc, Menlo Park, CA) for determining the dead tissue (ie, core) volume versus salvageable tissue (ie, penumbra). Although the trials allowed patients with core volumes of ≤ 30 mL in DAWN and ≤ 70 mL in DEFUSE 3 to be considered for mechanical thrombectomy, the final average core volume for patients enrolled these trials was 7 to 10 mL. This meant that patients who benefited from the trials were those with small cores and large penumbras. These trials still provided enough evidence that treatment of stroke should be based on physiological response of brain tissue after ischemia, rather than time from symptom onset alone.

Recommendations

There has been a revolution in treatment of AIS in recent years extending the treatment window to 24 hours and beyond. When done in a timely fashion and for the right patient population, mechanical thrombectomy is a highly effective therapy. Now that the effective treatment for AIS in patients with LVO has been established, we need effective protocols to ensure patients are brought, in timely fashion, to comprehensive stroke centers and thrombectomy-ready centers. It will also be necessary to have sufficient numbers of well-trained hospital staff including stroke neurologists and endovascular experts to deal with an increase in patients with stroke who require screening and treatment. Systems of care for people who have had a stroke need to be adapted so that optimal treatments are available to all patients. It is of paramount importance that we educate not only our colleagues, but also the general population, about the advancement and treatment options for patients with stroke so they can receive the treatment they deserve. ■

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g. Diffusion weighted imaging (DWI) or computerized tomography perfusion (CTP) assessment with clinical mismatch in the triage of wake up and late presenting strokes undergoing neurointervention. (NCT02142283)

h. Endovascular therapy following imaging evaluation for ischemic stroke 3. (NCT02586415)

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