Mechanical Thrombectomy for Acute Ischemic Stroke

Results of the DAWN trial expand the beneficial role of stent retrieval therapy for acute ischemic stroke beyond the conventional time window.

By Ashutosh P. Jadhav, MD, PhD

On October 25, 2014, the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) investigators presented results of their randomized controlled trial of patients with acute ischemic stroke presenting within 6 hours of stroke undergoing medical therapy versus mechanical thrombectomy in the setting of anterior circulation large vessel occlusion (internal carotid artery [ICA], middle cerebral artery segment 1 [M1]). Notably, they found that intra-arterial therapy was safe and effective and led to higher rates of functional independence with smaller final infarct volume. These results initiated a domino effect in which multiple subsequent trials were either prematurely halted due to loss of clinical equipoise or assessed at prespecified endpoints with benefit observed across trials using predominantly stent retriever technology.

The results of six total endovascular trials (MR CLEAN, Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke [ESCAPE], Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours [REVASCAT], Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke [SWIFT PRIME], Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial [EXTEND-IA], Trial and Cost Effectiveness Evaluation of Intra-arterial Thrombectomy in Acute Ischemic Stroke [THRACE]) contrasted sharply with the results of three prior clinical trials (Interventional Management of Stroke Trial [IMS3], Local Versus Systemic Thrombolysis for Acute Ischemic Stroke [SYNTHESIS], Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy [MR RESCUE]) that were presented back-to-back at the International Stroke Conference in 2013. The 2013 trials also investigated the benefit of intra-arterial therapy over medical therapy but showed neutral results. The discrepancy between these first-generation mechanical thrombectomy trials versus the second-generation trials is likely multifactorial, including differences in patient selection, work flow, and clot retrieval technology. Specifically, the second-generation trials focused on selecting patients with smaller baseline infarct volume with confirmed proximal large vessel occlusion. Fast work flow was emphasized to minimize the symptom onset to recanalization time. Most of the patients were treated with stent retriever devices with significantly higher rates of complete or near-complete recanalization compared to older technologies.

This confluence of these factors was likely contributory and accordingly, the 2015 American Heart Association/American Stroke Association guidelines interpreted the new trial results as supportive of a class I, level of evidence A recommendation for stent retriever thrombectomy in a carefully defined population of patients: namely, patients with National Institutes of Health Stroke Scale (NIHSS) score of 6 or higher in the setting of a documented proximal anterior circulation large vessel occlusion and small baseline core infarct. Because most patients were treated in the early time window (within 6 hours of symptom onset), the benefit of treatment initiated beyond 6 hours of symptom onset was believed to be uncertain, and additional randomized trial data were recommended.

The DAWN Trial

To address this area of clinical uncertainly, the Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention With Trevo (DAWN) trial investigators sought to test the benefit of
mechanical clot retrieval in patients presenting in the late time window (6–24 hours). Like the second-generation trials, there was emphasis on selecting patients presenting with small established infarct in the setting of a proximal anterior circulation large vessel occlusion (ICA, M1). To ensure high rates of recanalization, the treatment arm was limited to use of the stent retriever thrombectomy device (Trevo device; Stryker Neurovascular). Unique to the study design was the selection of patients based on clinical–core mismatch. Specifically, patients were believed to be potential beneficiaries of recanalization if there was a significant clinical deficit disproportionately severe compared to the already established infarct. Infarct volume was measured using automated software on CT perfusion maps or MRI–diffusion-weighted imaging (RAPID software; iSchema-View). Patients were considered eligible if they met one of the following criteria: group A: age ≥80 years, NIHSS ≥10, core infarct <21 mL; group B: age <80 years, NIHSS ≥10, infarct <31 mL; group C: age <80 years, NIHSS ≥20, infarct 31–<51 mL.

From September 2014 to February 2017, the DAWN trial enrolled a total of 206 patients, 107 of whom were randomized to the thrombectomy arm and 99 to the medical arm. The median NIHSS was 17 in both groups, with comparable baseline median infarct volume (7.6 mL vs 8.9 mL). Immediate reperfusion was achieved in 84% of patients in the treatment arm with median time from last seen well to reperfusion time of 13.6 hours. There were no differences between the two groups in terms of safety outcomes (mortality or symptomatic hemorrhage). The rate of functional independence at 90 days (as measured by modified Rankin Scale score of 0–2) was 49% in the thrombectomy group and 13% in the control group. For every 2.8 patients who underwent thrombectomy, one additional patient had functional independence at 90 days. Benefit with thrombectomy was consistent across age, stroke severity, site of occlusion, and mode of presentation (wake-up stroke vs witnessed onset versus unwitnessed onset).

**Implications of DAWN for the Future of Stroke**

Although previous case series and smaller datasets had suggested the possibility of extending thrombectomy to later time windows, the DAWN trial is the first randomized controlled trial to successfully demonstrate the benefit of mechanical thrombectomy up to 24 hours of symptom onset in select patients with anterior circulation occlusions. Selection based on imaging and evidence of a small core, rather than a purely time-based paradigm, allows enrichment for patients with favorable compensatory mechanisms in the setting of ischemia. Clearly, not all patients have such compensatory mechanisms, and emphasis will continue to be placed on fast treatment times. However, for the approximately 40% of large vessel occlusions that present beyond 6 hours of symptom onset, the possibility of continued benefit has now been established.

These results will likely significantly affect the ability to improve outcomes in a population with an otherwise dismal prognosis in the absence of reperfusion therapy. As guidelines begin to incorporate these findings, there will be critical implications in identifying opportunities to intervene on patients who may have been considered to be outside of the therapeutic time window. Large scale efforts to increase patient and health care provider awareness will be essential to ensuring that all disabling symptoms developing within 24 hours of last seen well are brought to timely medical attention. Systems of care will need to be realigned to appropriately triage and identify all potential thrombectomy candidates.

The results of the DAWN trial have initiated a paradigm shift in which the therapeutic time window has been significantly expanded. The next steps as a community will be to identify these patients quickly and direct them to the appropriate level of care.