

## EDITORIAL



## Improved Prospects for Thrombectomy in Large Ischemic Stroke

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Mechanical endovascular thrombectomy, when performed within 24 hours after the onset of symptoms in patients with small-to-moderate acute ischemic strokes that are due to proximal occlusion of a large cerebral vessel, has been shown to result in rates of recanalization of 70 to 80% and to significantly improve functional independence at 90 days.<sup>1,2</sup> Thrombectomy represents one of the most effective treatments in medicine: the number needed to treat to prevent disability in one patient with stroke is 2.3. These results, however, do not apply to patients with large strokes, who have been mostly excluded from clinical trials of thrombectomy. Treatment guidelines for thrombectomy recommend that the procedure be performed only in the populations in the published positive trials, which have largely included patients with ischemic-core volumes of less than 50 ml.<sup>3</sup> The concerns that have limited the use of thrombectomy to smaller strokes arise from potential reperfusion injury in necrotic brain tissue, resulting in an increased risk of hemorrhage, edema, disability, and death.

Various methods have been used in clinical trials to identify large strokes. The Alberta Stroke Program Early Computed Tomography Score (ASPECTS) is calculated on the basis of the number of regions of the brain displaying early ischemic changes on computed tomography (CT); values range from 0 to 10, with lower values indicating larger infarction.<sup>4</sup> ASPECTS values of 5 or less have been considered to be large strokes. Alternatively, the ischemic-core volume can be measured with the use of CT or perfusion magnetic resonance imaging (MRI), with a large stroke considered to be an ischemic-core volume

of 50 ml or greater. The method of quantifying outcomes after stroke has also been somewhat fluid across trials. The modified Rankin scale assesses disability on a scale from 0 (no disability) to 6 (death). Because of the extent of brain damage in large strokes, “good outcomes” have generally included scores on the modified Rankin scale of 0 to 3 (with a score of 3 indicating moderate disability, but patients are able to walk without assistance).<sup>5</sup>

A trial conducted in Japan, the results of which were recently published in the *Journal*,<sup>6</sup> was among the first to enroll patients with large strokes and proximal vessel occlusion and randomly assign them to undergo endovascular thrombectomy and receive medical care or to receive medical care alone. A total of 203 patients were enrolled, and 202 were included in the analysis; thrombectomy resulted in significantly better functional outcomes than medical care. Surprisingly, the incidence of symptomatic intracranial hemorrhage was not significantly higher in the endovascular-therapy group than in the medical-care group, but the incidence of any intracranial hemorrhage was higher in the endovascular-therapy group. In addition, the incidences of edema, hemicraniectomy, and death were not higher with endovascular therapy than with medical care. Concerns about the wider applicability of these results have been raised, including that the trial was performed in an exclusively Japanese cohort, the use in Japan of a lower thrombolytic dose of alteplase before thrombectomy than is typical in some other countries, and the selection of patients on the basis of MRI, which is more sensitive than CT. The results of

two additional trials of thrombectomy for large strokes, now published in the *Journal*, confirm the benefits shown in the Japanese trial, but in international and Chinese populations.

A Randomized Controlled Trial to Optimize Patient's Selection for Endovascular Treatment in Acute Ischemic Stroke (SELECT2),<sup>7</sup> which enrolled 352 patients from the United States, Canada, Europe, Australia, and New Zealand, randomly assigned patients to undergo endovascular thrombectomy and receive standard medical care or to receive standard medical care alone within 24 hours after the onset of stroke (i.e., the time the patient was last known to be well). While SELECT2 was still recruiting patients, the positive results of the Japanese trial prompted an interim analysis by the data and safety monitoring board. On the basis of the results of this analysis, the board recommended that recruitment in SELECT2 be stopped. The results of the primary outcome (the score on the modified Rankin scale) favored thrombectomy. The number of patients in the thrombectomy group who had functional independence (a score on the modified Rankin scale of 0 to 2) and independent ambulation (a score on the modified Rankin scale of 0 to 3), which were secondary outcomes, was more than double that in the medical-care group. Symptomatic intracranial hemorrhage was infrequent, and the incidence was similar in the two groups. The incidence of death was also similar in the two groups, but neurologic worsening was more frequent in the thrombectomy group than in the medical-care group and was associated with worse outcomes.

The Endovascular Therapy in Acute Anterior Circulation Large Vessel Occlusive Patients with a Large Infarct Core (ANGEL-ASPECT) trial<sup>8</sup> enrolled 456 Chinese patients within 24 hours after the onset of stroke. This trial was also stopped early because a planned interim analysis showed “good outcomes” in 47.0% of the patients in the endovascular-thrombectomy group, as compared with 33.3% of the patients in the medical-management group. The incidences of symptomatic intracranial hemorrhage, any intracranial hemorrhage, and hemicraniectomy were higher with thrombectomy than with medical management.

All three trials, despite differences in design, patient selection, thrombolytic treatment and dose, geographic location, and imaging criteria, showed remarkably similar results. The benefits of throm-

bectomy were consistent across age, degree of neurologic deficit, imaging characteristics, time of treatment, and geographic location. Despite concerns about assessing the potential benefit of thrombectomy on the basis of a shift in outcome categories (thrombectomy could prevent death, but survival may be associated with severe disability after the procedure),<sup>9</sup> the results of all three trials showed that mortality was similar between the trial groups, but that a shift from worse to better outcomes had occurred across all other outcome categories among patients who underwent thrombectomy. Together, the trials provide reassuring information from more than a thousand patients with large ischemic strokes in different medical systems that will probably lead to changes in patterns of care delivery. It is reasonable to suggest that endovascular thrombectomy be offered to patients with large strokes (which represent about 20% of all ischemic strokes due to proximal occlusion of a cerebral vessel) if they arrive in a timely fashion at a center that is capable of performing the procedure and if the patients have an ASPECTS value of 3 to 5 or an ischemic-core volume of 50 ml or greater. Higher rates of “good outcomes” may be anticipated if this treatment is performed, despite increased risks of symptomatic hemorrhage, edema, neurologic worsening, and hemicraniectomy. Patients and families should be made aware of the limitations of treatment and the anticipated residual neurologic deficits resulting from the large infarction. The improved chance of independent walking and the ability to perform other daily activities in patients with the most severe strokes is welcome news for patients and for the field of stroke treatment.

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