

EDITORIALS



Endovascular Therapy for Stroke — It's about Time

Anthony J. Furlan, M.D.

Although many stroke centers worldwide have performed endovascular stroke therapy since the results of the Prolyse in Acute Cerebral Thrombolism (PROACT) II trial were published in 1999,¹ lingering uncertainties about efficacy and the selection of patients created an uneasy equipoise. Especially nettlesome was the uncertain benefit of endovascular therapy as compared with intravenous tissue plasminogen activator (t-PA). The controversy over endovascular therapy was heightened in 2013 when the results of the Interventional Management of Stroke (IMS) III,² Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE),³ and Local versus Systemic Thrombolysis for Acute Ischemic Stroke (SYNTHESIS Expansion)⁴ clinical trials suggested that endovascular therapy was no more effective than intravenous t-PA alone.

Now, in resounding fashion, five randomized clinical trials — the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN),⁵ the Extending the Time for Thrombolysis in Emergency Deficits — Intra-Arterial (EXTEND-IA) trial,⁶ the Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (ESCAPE) trial,⁷ the Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment (SWIFT PRIME) trial,⁸ and the Randomized Trial of Revascularization with Solitaire FR Device versus Best Medical Therapy in the Treatment of Acute Stroke Due to an Anterior Circulation Large Vessel Occlusion Presenting within Eight Hours of Symptom Onset (REVASCAT),⁹ the results of the latter two now being published in the *Journal* — have shown that endovascular therapy is highly beneficial,

as compared with intravenous t-PA alone, in patients with occlusions of the intracranial internal carotid artery or middle cerebral artery up to 6 hours after stroke onset. The absolute benefit of endovascular therapy, as compared with intravenous t-PA alone, with regard to an outcome of functional independence at 90 days (defined as a modified Rankin scale score of ≤ 2 , on a scale from 0 [no symptoms] to 6 [death]) ranged from 13.5 to 31 percentage points. This translates into a number needed to treat for benefit as low as three patients and no more than seven patients. There was no significant increase in the rate of symptomatic brain hemorrhage with endovascular therapy in any of the trials.

What caused this sea change since the three negative endovascular trials appeared in 2013? Technology has changed. Stent-retriever device technology results in faster, more complete recanalization as defined by significantly higher rates of Thrombolysis in Cerebral Infarction angiographic scores of 2b (indicating successful reperfusion of $\geq 50\%$) or 3 (complete reperfusion), as compared with intravenous t-PA alone or earlier-generation thrombectomy devices.

In addition, a heightened awareness of the importance of time has changed. An emergency department door-to-groin puncture time of 90 minutes was achieved in the SWIFT PRIME trial. This goal requires stroke-workflow efficiencies not yet in place in many hospitals.

A third change has been neuroimaging criteria for the selection of patients. The rapid demonstration of large-vessel occlusion must now become part of the standard evaluation of acute stroke. To minimize hemorrhage risk and to reduce futile recanalization, the selection of patients may also require the determination of the volume

of irreversibly infarcted brain tissue, which reflects the adequacy of collateral blood flow. Here, there is no consensus on the best method. Penumbra mismatch (i.e., the ratio of ischemic tissue at risk to irreversibly infarcted brain) was used in the EXTEND-IA trial with a minimum requirement of 20%, whereas the SWIFT PRIME trial required an 80% mismatch.

More recently, core-infarct volume has replaced mismatch as the favored neuroimaging selection criterion. The EXTEND-IA trial excluded patients with a core-infarct volume of more than 70 ml; in the SWIFT PRIME trial, the cutoff point for core volume was 50 ml. Most sites used computed tomography (CT) for the determination of vascular occlusion and core infarct; magnetic resonance imaging (MRI) is more sensitive than CT for core-volume assessment but is not available on an emergency basis in many hospitals. Automated MRI and CT analysis software (RAPID, Stanford University) improves the speed and accuracy of core-volume determination.

However, perhaps neither core nor mismatch neuroimaging is essential, because at some point time trumps physiology. MR CLEAN (a pragmatic trial) required only vessel imaging, whereas the ESCAPE trial and REVASCAT used the Alberta Stroke Program Early CT Score (ASPECTS)¹⁰ as a measure of infarct core and excluded patients with an ASPECTS of less than 6. Although quick and easy to perform, it is unclear whether an ASPECTS alone is sufficient for predicting endovascular outcome because it only approximates core volume. How far the time window for endovascular treatment can be extended with the use of imaging selection criteria is also unclear. Regardless, earlier is always better, because time is brain. Pending the resolution of this issue, it is probably best to avoid initiating endovascular therapy in patients with large (>50 to 70 ml) infarct cores as assessed by means of CT or MRI or an ASPECTS of 4 or less, beyond 6 hours from stroke onset.

Reminiscent of the paradigm shift in stroke therapy that was introduced by intravenous t-PA, endovascular stroke therapy has major implications for systems of stroke care. However, as opposed to (and thanks to) the introduction of intravenous t-PA into practice, a stroke infrastructure is already in place in many countries, and in the United States there are Joint Commission–certified comprehensive stroke centers and

primary stroke centers. Stroke infrastructure must now adapt to endovascular therapy. As with intravenous t-PA, only a small percentage of patients with stroke will require endovascular therapy (estimates are 10%), but this small percentage will drive the reorganization of systems of stroke care.

Not every hospital can or should perform endovascular stroke therapy. Thus, endovascular stroke therapy has major implications for triaging decisions by emergency medical services, since in cities or regions with both comprehensive stroke centers and primary stroke centers, candidates for endovascular therapy should now be directly transported to a comprehensive stroke center as rapidly as possible. Transport decisions will be facilitated by the development of algorithms for endovascular therapy. For example, patients with large-vessel occlusions will usually have a baseline National Institutes of Health Stroke Scale score of 10 or more (on a scale of 0 to 42, with higher scores indicating greater severity), which might become a trigger for transfer by emergency medical services to a comprehensive stroke center. Mobile stroke transport units (also known as “strokemobiles”), which allow intravenous t-PA to be started in the field and may also allow CT angiography to screen for large-vessel occlusion, are being evaluated.¹¹ Health care systems can also shave off many minutes with the use of workflow efficiencies, such as “telestroke” and streamlined emergency-department and neuroimaging throughput.

Many stroke centers were already performing endovascular therapy even before this definitive new data appeared. Now, even skeptics of endovascular therapy will be convinced. The real winners are our patients with devastating strokes. Endovascular equipoise no longer exists. It's about time.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

From University Hospitals Case Medical Center, Case Western Reserve University, Cleveland.

This article was published on April 17, 2015, at NEJM.org.

1. Furlan A, Higashida R, Wechsler L, et al. Intra-arterial prokinase for acute ischemic stroke — the PROACT II study: a randomized controlled trial. *JAMA* 1999;282:2003-11.
2. Broderick JP, Palesch YY, Demchuk AM, et al. Endovascular therapy after intravenous t-PA versus t-PA alone for stroke. *N Engl J Med* 2013;368:893-903.
3. Kidwell CS, Jahan R, Gornbein J, et al. A trial of imaging

selection and endovascular treatment for ischemic stroke. *N Engl J Med* 2013;368:914-23.

4. Ciccone A, Valvassori L, Nichelatti M, et al. Endovascular treatment for acute ischemic stroke. *N Engl J Med* 2013;368:904-13.

5. Berkhemer OA, Fransen PSS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med* 2015;372:11-20.

6. Campbell BCV, Mitchell PJ, Kleinig TJ, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med* 2015;372:1009-18.

7. Goyal M, Demchuk AM, Menon BK, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med* 2015;372:1019-30.

8. Saver JL, Goyal M, Bonafe A, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. *N Engl J Med* 2015;2285-95.

9. Jovin TG, Chamorro A, Cobo E, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N Engl J Med* 2015;2296-306.

10. Puetz V, Dzialowski I, Hill MD, Demchuk AM. The Alberta Stroke Program Early CT Score in clinical practice: what have we learned? *Int J Stroke* 2009;4:354-64.

11. Warach S. Prehospital thrombolysis for stroke: an idea whose golden hour has arrived. *JAMA Neurol* 2015;72:9-10.

DOI: 10.1056/NEJMe1503217

Copyright © 2015 Massachusetts Medical Society.

Bystander-Initiated CPR by Design, Not by Chance

Comilla Sasson, M.D., Ph.D., and David J. Magid, M.D., M.P.H.

Every hour in the United States, 38 people have an out-of-hospital cardiac arrest, and fewer than 1 of 10 survive.¹ Increasing data show that timely provision of cardiopulmonary resuscitation (CPR) saves lives, and tens of millions of people have been trained to perform it. Yet, less than half of persons with cardiac arrest in the United States receive bystander-initiated CPR,¹ and there are significant disparities in its provision.² Factors that affect these disparities include a person's neighborhood and his or her race or ethnic group. In two well-designed studies in this issue of the *Journal*, Hasselqvist-Ax and colleagues examine the association of bystander-initiated CPR with survival,³ and Ringh and colleagues evaluate a new mobile-phone intervention to improve rates of bystander-initiated CPR.⁴

The study by Hasselqvist-Ax et al. assessed the association between bystander-initiated CPR and 30-day survival among persons with out-of-hospital cardiac arrest recorded in the Swedish Cardiac Arrest Registry. Bystander-initiated CPR was performed in 51% of more than 30,000 patients with cardiac arrest. Thirty-day survival was significantly higher when CPR was performed before arrival of emergency medical services (EMS) than when it was not performed before EMS arrival (10.5% vs. 4.0%), even though EMS response times and times from cardiac arrest to defibrillation were longer in patients who received bystander-initiated CPR. Increased survival among patients who received bystander-initiated CPR persisted after propensity-score adjustment and was noted in all subgroups. As with all observational studies, unmeasured confounding could have influenced

the results. However, this study is among the largest to examine bystander-initiated CPR, and the finding of improved survival with CPR is consistent with most prior studies.⁵

The findings of Hasselqvist-Ax and colleagues reinforce the conclusion that there is a critical need for interventions to increase the use of bystander-initiated CPR. Interventions such as chest-compression-only CPR, emergency dispatchers providing instructions for performing CPR, targeted training in black and Latino neighborhoods, and large-scale public education campaigns have increased rates of bystander-initiated CPR to some degree, but there is plenty of room for improvement. New approaches to sending people who are trained in CPR to the right place at the right time — so they can perform what they have been trained to do — are needed.

The study by Ringh et al. involves such a new approach. The authors used a randomized-trial design to evaluate a mobile phone–supported intervention to improve rates of bystander-initiated CPR in Stockholm. Overall, 9828 adult lay volunteers who were trained in CPR and who provided their cell-phone numbers agreed to be dispatched to assist persons nearby who were in out-of-hospital cardiac arrest. Calls to a central emergency dispatch center regarding a suspected cardiac arrest were randomly assigned to the control or intervention group. In both groups, an ambulance with first responders was dispatched and instructions over the telephone for the administration of CPR were provided. In the intervention group, in addition to these measures, volunteers within 500 m who were trained in CPR received