### Endovascular Therapy for Acute Ischemic Stroke

**Joseph P. Broderick, MD**

**Background and Purpose**—To review advances in endovascular therapy for acute ischemic stroke.

**Methods**—Data from primate studies, randomized studies of intravenous recombinant tissue-type plasminogen activator, and nonrandomized and randomized studies of endovascular therapy were reviewed.

**Results**—Clinical trial data demonstrate the superiority of endovascular treatment with thrombolytic medication or mechanical methods to reopen arteries compared with control patients from the PROACT II Trial treated with heparin alone. However, these same clinical trials, as well as preclinical primate models, indicate that recanalization, whether by endovascular approaches or standard-dose recombinant tissue-type plasminogen activator, is unlikely to improve clinical outcome after a certain time point. Although the threshold beyond which reperfusion has no or little benefit has yet to be conclusively defined, accumulated data to this point indicate an overall threshold of \( \approx 6 \) to 7 hours. In addition, although the risk of symptomatic intracerebral hemorrhage is similar in trials of intravenous lytics and endovascular approaches, endovascular approaches have distinctive risk profiles that can impact outcome.

**Conclusions**—The treatment of acute ischemic stroke is evolving with new tools to reopen arteries and salvage the ischemic brain. Ongoing randomized trials of these new approaches are prerequisite next steps to demonstrate whether reperfusion translates into clinical effectiveness. Physiologic time to reperfusion will remain critical no matter which tools prove most effective and safest. (**Stroke. 2009;40[suppl 1]:S103-S106**.)

**Key Words:** intra-arterial therapy ■ tissue-type plasminogen activator ■ Concentric Retriever ■ EKOS Microinfusion Catheter ■ acute ischemic stroke ■ controlled clinical trials

---

**Timing of Reperfusion and Clinical Outcome**

In primate models of focal acute ischemic stroke, timing of reperfusion of the occluded middle cerebral artery is strongly correlated with preservation of brain tissue.\(^8,9\) Reperfusion of the middle cerebral artery is associated with minimal damage when it occurs within 20 minutes from onset.\(^8\) Approximately 50% of the brain is spared with reperfusion within 90 minutes, but there is no sparing of brain tissue when reperfusion occurs at 400 minutes (\( \approx 6 \) to 7 hours) or longer after onset.\(^8,10\)

These findings in primates mirror the time-dependent clinical effectiveness of intravenous (IV) recombinant tissue-type plasminogen activator (rt-PA) in humans. In a pooled analysis of all randomized, acute stroke trials of rt-PA administered within 6 hours from onset, rt-PA given within 90 minutes was associated with a 2.8-fold greater likelihood of an excellent functional outcome compared with placebo.\(^11\) This decreased to 1.6-fold for subjects treated within 90 to 180 minutes and to 1.4-fold for those treated within 180 to 270 minutes. There was no significant benefit, and greater mortality, for those subjects treated beyond 270 minutes. With the assumption that recanalization with IV rt-PA occurs over 1 to 2 hours after initiation, these data also indicate a maximum threshold of \( \approx 6 \) to 7 hours for clinically effective reperfusion. However, the location of the thrombus and the timing of reperfusion were not imaged in these IV rt-PA trials.

Recent data from the IMS I and IMS II trials support the findings from primate models.\(^12\) In IMS I and IMS II, subjects received IV rt-PA begun within 3 hours of onset.\(^13,14\) Subjects were then taken immediately to angiography, where additional IA therapy with rt-PA was given via standard micro-
catheters or the EKOS MicroLysUS catheter. For those individuals with an occluded internal carotid artery or occluded M1 or M2 divisions of the middle cerebral artery at angiography, there was a strong relation between the timing of reperfusion and a favorable clinical outcome. Those subjects who had reperfusion of occluded vessels beyond 5½ hours had outcomes similar to those subjects who did not reperfuse after IA therapy. In summary, physiologic time to reperfusion is just as important for endovascular approaches as for intravenous lytics.

A maximum threshold of 6 to 7 hours for clinically effective reperfusion is at odds with a commonly expressed view that endovascular recanalization in acute stroke patients is always desirable and equates with clinical effectiveness. The only randomized endovascular trial in which significantly improved recanalization and a favorable clinical outcome were linked is PROACT II, in which subjects were randomized within 6 hours to IA prourokinase and heparin compared with heparin alone. The median time to start of IA therapy in PROACT II was >5 hours, but randomization had to occur within 6 hours.

The nonrandomized MERCI, Multi-MERCI, and PENUMBRA Trials allowed initiation of IA treatment to 8 hours. In these nonrandomized trials, subjects who recanalized had better outcomes than those who did not. These trials used historical controls from the PROACT Study as the comparison group, and subjects in these nonrandomized trials who recanalized did better than these historical controls. Thus, the underlying logic for the common view can be summarized as follows: Device that opens arteries better than medical therapy (historical controls from PROACT II) = device that is effective in opening arteries = device that is effective for acute ischemic stroke. Given this logic and an assumed similar safety profile, devices with a higher recanalization rate should result in a clinically more effective therapy.

There are fundamental difficulties with the view that equates recanalization with clinical effectiveness. First, recanalizers may be fundamentally different in key baseline variables that are associated with long-term outcome compared with nonrecanalizers, such as age, site of occlusion collateral flow, etc. Second, nonrecanalizers may be harmed by intervention(s). A number of subjects in the nonrandomized trials who did not recanalize were subjected to additional reperfusion therapies (other drugs, devices, etc). Finally, historical controls, though helpful for screening of potential therapies, carry substantial biases when included for evaluation of the clinical effectiveness of new therapies. Examples of biases include differences in patient populations; changes in standard medical, neurocritical, or neurointerventional care over time; and changes in the use of do-not-resuscitate orders.

**Comparison of Endovascular Trials**

The rate of successful recanalization in endovascular trials has not always mirrored the rate of good clinical outcomes. For example, subjects in the MERCI Trial had a mean baseline National Institutes of Health Stroke Scale (NIHSS) score of 20, and their groin puncture occurred at a median of 4.3 hours after onset, with a mean procedure duration of 2.1 hours. The overall TIMI II–III reperfusion rate at the end of the procedure was 48%. However, the overall mortality rate at 90 days was 44%, and only 28% had a good functional outcome as measured by a Rankin Scale score of 0 to 2. The subsequent Multi-MERCI Trial also included 29% of subjects initially treated with IV rt-PA. Subjects had a median baseline NIHSS score of 19, a mean time to groin puncture of 4.3 hours, and a mean procedure duration of 1.6 hours. The overall TIMI II–III rate with the Concentric Retriever alone was 57%, and the rate with additional adjuvant therapy was 69%. The 90-day mortality was 34%, and 36% of subjects had a Rankin Scale score of 0 to 2.

In the randomized PROACT Trial, which has been used as the primary comparison trial for nonrandomized endovascular trials, subjects with a middle cerebral artery occlusion (baseline NIHSS score of 17) were randomized to IA prourokinase plus heparin or heparin only within 6 hours of onset. The recanalization rate at the end of prourokinase infusion was 66%. The mortality at 90 days was 25%, and 40% of subjects had a Rankin Scale score of 0 to 2.

In the IMS II Trial, subjects ages 18 to 80 years with a baseline NIHSS score ≥10 had IV rt-PA (0.6 mg/kg over 30 minutes) started within 3 hours of onset. The baseline median NIHSS score was 19. For subjects with an arterial occlusion at angiography, additional rt-PA was administered via the EKOS microinfusion catheter or a standard microcatheter at the site of the thrombus up to a total dose of 22 mg over 2 hours of infusion or until thrombolysis had been achieved. Overall, all IMS II subjects treated with IA rt-PA via EKOS or standard microcatheters had a 4% (2/55) TICI/TIMI III and 60% (33/55) TICI/TIMI II and III reperfusion grade flow after completion of the IA procedure. The 3-month mortality in IMS II subjects was 16%, and 46% of subjects had a Rankin Scale score of 0 to 2.

Results from the nonrandomized PENUMBRA Trial were presented at the International Stroke Conference in February 2008 but have yet to be published. The reported reperfusion rates after completion of the procedure were higher than all prior studies, but the rate of Rankin Scale score of 0 to 2 at 90 days was lower than the rates in the MERCI, Multi-MERCI, and IMS trials.

By comparison, subjects in the CLOT-BUST Trial, who had occlusions of the middle cerebral artery as demonstrated by transcranial Doppler and a median baseline NIHSS score of 16, were treated within 3 hours of stroke onset with standard-dose IV rt-PA over 1 hour and transcranial ultrasound. The sustained recanalization rate at 2 hours as measured by transcranial Doppler was only 38%, yet 51% had a Rankin Scale score of 0 to 2 at 90 days.

The discrepancy between recanalization rates and clinical outcomes detailed here can largely be explained by differences in the time from stroke onset to start of therapy. The proportion of subjects who achieved a Rankin Scale score of 0 to 2 in these trials is well correlated with time to treatment. All subjects in the IMS I and II and CLOT-BUST Trials had treatment with IV rt-PA begun within 3 hours and had the best reported overall outcomes at 90 days. PROACT II, in which subjects were randomized within 6 hours, had the next best functional outcome. Subjects treated in the MERCI, Multi-MERCI, and PENUMBRA Trials, despite good recan-
eralization rates, had the lowest proportions of good outcomes but also had the longest time windows from stroke onset to initiation of therapy.

These clinical trial data indicate that recanalization, whether by standard-dose rt-PA or endovascular approaches, is unlikely to improve clinical outcome after a certain time point. Although the threshold beyond which reperfusion has no or little benefit has yet to be conclusively defined, accumulated data to this point indicate an overall threshold of ≈6 to 7 hours. The use of imaging to define later or even earlier thresholds of viability in individual patients remains a very active area of study.

**Risks of Endovascular Approaches Compared With Intravenous Lytics**

Although the risk of symptomatic intracerebral hemorrhage is similar in trials of IV lytics and endovascular approaches, endovascular approaches have distinctive risk profiles that can impact outcome. Puncture of the femoral arteries can be associated with severe hemorrhagic complications, although this occurs in only 1% to 3% of subjects. Devices and the angiographic procedure itself can also damage arteries, produce arterial spasm, and cause fragmentation of the clot. Devices can fracture and may be unable to be retrieved. Also, recent data from the IMS I and II Trials presented at the 2008 International Stroke Meeting in New Orleans illustrate the potential risks of intubation and heavy sedation that are frequently used in a standard fashion at some institutions and could be potentially associated with pulmonary or other complications. Finally, even frequent microcatheter contrast agent injections have been associated with increased risk of hemorrhagic change.

**What is Needed**

Endovascular treatment for acute stroke is promising but, except for the PROACT II Study, its clinical effectiveness has yet to be proven. In addition, the superiority of endovascular approaches to standard IV rt-PA within 3 hours of onset has yet to be proven.

Two National Institute of Neurological Disorders and Stroke–funded randomized clinical trials are addressing the clinical effectiveness of endovascular therapy. The IMS III Trial is a randomized trial of subjects with moderate to severe acute ischemic stroke (NIHSS score ≥10) who are treated with IV rt-PA within 3 hours of onset. A projected 900 subjects between the ages of 18 to 80 years will be enrolled during the next 5 years at >60 centers in the United States, Canada, and Australia. Both approaches must have IV treatment initiated within 3 hours of stroke onset. Subjects will be randomized in a 2:1 ratio with more subjects enrolled in the combined IV/IA group. The IV rt-PA-alone group will receive the standard full dose (0.9 mg/kg, 90 mg maximum [10% as bolus]) of IV rt-PA over 1 hour. The combined IV/IA group will receive a lower dose of IV rt-PA (∼0.6 mg/kg, 60 mg maximum) over 40 minutes followed by immediate angiography. If a treatable thrombus cannot be demonstrated, no IA therapy will be administered. If an appropriate thrombus is identified, treatment will continue with either the Concentric Merci thrombus-removal device, infusion of rt-PA, and delivery of low-intensity ultrasound at the site of the occlusion via the EKOS Micro-Infusion Catheter, or infusion of rt-PA via a standard microcatheter. The choice of IA strategy is to be made by the treating neurointerventionalist. IA treatment must begin within 5 hours and be completed within 7 hours of stroke onset. As of July 12, 2009, 179 subjects have been randomized.

**Randomized MR and REcanalization of Stroke Clots by Embolectomy**

The MR-Rescue Trial is designed to test the effectiveness of embolectomy compared with standard medical management in 120 subjects at 30 centers who are either ineligible for IV rt-PA or who are able to have endovascular therapy initiated within 8 hours from stroke onset. All subjects, ages 18 to 85 years, must have an occlusion of the internal carotid or middle cerebral artery as demonstrated by magnetic resonance angiography and an NIHSS score of 6 or more. Subjects are also stratified by a magnetic resonance penumbral pattern (penumbral versus nonpenumbral). Embolectomy is performed with the various approved Merci Retriever catheters. Subjects are able to be treated with adjunctive rt-PA after use of the Retriever has been completed. Additional modifications in the MR-Rescue Trial are ongoing. In summary, the treatment of acute ischemic stroke is evolving with new tools to reopen arteries and salvage the ischemic brain. Randomized trials of these new approaches are the prerequisite next steps to demonstrate clinical effectiveness. Physiologic time to reperfusion will remain critical no matter which tools prove most effective and safest.

**Disclosures**

Dr Broderick has received catheters for the ongoing National Institute of Neurological Disorders and Stroke-funded IMS III study from Concentric Inc, EKOS Corp, and Johnson and Johnson Co and study medication from Genentech. He has also acted as consultant for Genentech and Johnson and Johnson.

**References**


