A Matter of Time: An Update on Intervventional Stroke Research

New advancements suggest enhanced opportunities to improve outcomes and save lives.

Experts weigh in.

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Interventional stroke treatment is care that uses catheters or microcatheters to unblock a blood vessel in the brain soon after a stroke occurs. Also known as intra-arterial stroke therapy, this treatment administers clot-busting medication to the site in the brain where the blockage is positioned. The goal of interventional stroke therapy is to restore blood flow to brain tissue as quickly as possible to prevent brain damage.1

Stroke remains a major cause of death and disability. Acute thrombolytic therapy offers the potential to achieve early recanalization, save tissues, and improve outcome. Currently, intravenous treatment (IV) tPA is the only approved acute stroke therapy. IV tPA is an effective therapy for acute ischemic stroke but has substantial limitations when used alone to open blocked arteries.

Circumstances that exclude patients from interventional stroke therapy include:
- Hemorrhagic stroke;
- A stroke or head trauma within the past three months;
- Major surgery within the last two weeks;
- Uncontrollable high blood pressure;
- Internal bleeding;
- Seizure; and
- Blood clotting problems or taking anticoagulant medications.

One study that gave neurologists a lot of excitement was the Interventional Management of Stroke trials. The IMS I trial suggested that combination therapy with IV-rtPA and an intra-arterial (IA) approach was safe and may be clinically useful in AIS treatment.2 This was further supported by the IMS II trial, a single-arm pilot study showing preliminary estimates of efficacy and safety of combination IV and IA therapy.

The latest iteration, the Interventional Management of Stroke Trial (IMS III), sought to compare two different strategies for restoring blood flow to the brain in patients who have had a severe ischemic stroke. Trial participants were randomized to receive either the standard FDA-approved IV of the clot-dissolving drug tPA alone or a combination approach that provides both standard IV tPA and an IA therapy using either tPA delivered into the artery directly at the site of the clot or an FDA-approved device to remove the blood clot in the brain. Therapy
published sooner. The analysis will help determine the best next steps to improve outcomes in patients with acute ischemic stroke, as will other trials, according to Dr. Broderick.

But instead of getting a spot-on interventional stroke treatment’s marquee, the curtains were drawn. Upon the recommendation of the Data and Safety Monitoring Board (DSMB), National Institute of Neurological Disorders and Stroke (NINDS) stopped enrollment for the IMS III trial. “Under the experimental conditions in the trial, the data collected to date showed no difference in clinical outcome for those patients treated with IV tPA alone versus those treated with IV tPA plus an FDA cleared intra-arterial (IA) device therapy and/or additional intra-arterial tPA,” the NINDS said in a statement regarding its sponsored study. It did note there were no significant safety concerns.

That decision came down on May 2, 2012 after a preplanned interim analysis was reviewed by the trial’s independent DSMB on April 18, 2012. The data showed that the study had a very low likelihood of demonstrating the pre-specified, clinically significant difference in benefit between the treatment arms of the study. The DSMB’s decision was based upon the primary outcome in the study, the Modified Rankin Score at three months, meeting the threshold for futility. This analysis included data from 587 participants enrolled at over 50 sites worldwide.

Completion of ongoing follow-up of all 656 enrolled patients and analysis of complete data are forthcoming, according to Joseph Broderick, MD at the University of Cincinnati, who conducted the clinical leadership of the study. “IMS III will be presented at the [International Stroke Conference] in Honolulu in February and will provide important information about where we are and how to go forward,” he told Practical Neurology. We hope to have results published sooner. The analysis will help determine the best next steps to improve outcomes in patients with acute ischemic stroke, as will other trials, according to Dr. Broderick.

“The recently completed randomized trials (IMS III, SYNTHESIS, and MR Rescue), all of which should be published in the next six to nine months, will provide important data about the relationship between clinical outcomes and angiographic reperfusion, he said. The field will need to reflect on these results to determine best next steps.”

SYNTHESIS
The SYNTHESIS Expansion trial (Local Versus Systemic Thrombolysis for Acute Ischemic Stroke) sought to compare the immediate endovascular approach versus intravenous alteplase, which is different to the combined intravenous-endovascular approach that is being tested by the IMS-III study, two study authors, Alfonso Ciccone and Roberto Sterzi, noted in a Lancet Neurology piece.

SYNTHESIS is a completed pragmatic multicenter randomized controlled trial (RCT), open-label, with blinded follow-up aiming to determine whether loco-regional IA with recombinant tissue-plasminogen activator (rt-PA) and/or mechanical devices, as compared with systemic IV infusion of rt-PA within three hours of ischemic stroke, increases the proportion of independent survivors at three months, according to StrokeCenter.org.

The 350 eligible patients were randomized to receive either 0.9mg/kg (max 90mg) IV rt-PA (control arm) or up to 0.9mg/Kg IA rt-PA (max 90mg) over 60 minutes into the thrombus, eventually associated with clot mechanical disaggregation/dislocation or retraction/aspiration. The procedural choices of the interventional neuroradiologist were dependant on the type of occlusion, circumstances, and experience. The study authors are attempting to detect or disprove (alpha=5 percent and power probability=80 percent) a 15 percent absolute difference between the treatment groups in the percentage of patients with a favorable outcome (Modified Rankin Scale Score = 0-1). The neurological deficit was scored using the NIH Stroke Scale at day 7 or day of discharge, whichever occurred first. A patient’s clinical condition was again evaluated by a telephone call after 90 days.

The authors note their study was pragmatically based on the ‘uncertainty principle’ between endovascular treatment and systemic intravenous thrombolysis for patients eligible for intravenous alteplase. There were no prespecified clinical or instrumental criteria to further select a patient, although investigators were left free to use them.

“Both the single and combined approaches have advantages and disadvantages and need to be tested in randomised controlled trials and not in prospective single-centre cohort studies. Cohort studies should follow, not precede, randomised controlled trials, as was the case with intravenous thrombolysis,” the study authors write.

MR RESCUE
The Magnetic Resonance and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) study is a Phase II study...
that is evaluating whether mechanical embolectomy with the MERCI or Penumbra device is superior to standard medical management of acute ischemic stroke presenting within eight hours of stroke onset.\(^5\) Patients treated with IV t-PA up to 4.5 hours from symptom onset with persistent vessel occlusion on post-treatment MRI may also be included. The NIH funded trial study has set sights on identifying patients who may benefit from intervention using MRI perfusion imaging.

A total of 120 participants from approximately 30 different medical centers are enrolled the study. Participants will be randomized to either receive treatment by mechanical embolectomy with the Merci Retriever or Penumbra System and standard medical care or treatment with standard medical care alone.\(^6\)

Participants who undergo the Merci Retriever or Penumbra System route will have a cerebral arteriogram with pictures taken with dye prior to the procedure to determine the location of the blockage, and following the procedure to determine if blood supply has been restored. The total mechanical embolectomy procedure with either device will take approximately one to two hours. Participants will have brief neurological exams several times during this time to monitor changes in their neurological condition.\(^6\)

Previous testing has determined that the use of the Merci Retriever is successful in opening up blocked blood vessels in approximately half of the individuals in whom it is used, and the Penumbra System is successful in opening up blocked blood vessels in approximately 80 percent of the individuals in whom it is used.\(^5\)

### THE INTERVENTIONAL MANAGEMENT OF STROKE (IMS) II STUDY

The IMS I trial suggested that combination therapy with IV rt-PA and an IA approach was safe and could be clinically useful in AIS treatment. This was advanced further by the IMS II trial, the single-arm pilot study that showed preliminary estimates of efficacy and safety of combination IV and IA therapy.

The preceding Phase II study sought participants between ages 18 to 80, with a baseline NIHSS ≥ 10 had rt-PA started (0.6 mg/kg over 30 minutes) within three hours of onset.\(^1\) The 81 subjects researchers found had a median baseline NIHSS score of 19. The median time to initiation of intravenous rt-PA was 142 minutes as compared with 108 minutes for placebo and 90 minutes for rt-PA–treated subjects in the NINDS rt-PA Stroke Trial (P<0.0001). The three-month mortality in IMS II subjects was 16 percent as compared with the mortality of placebo (24 percent) and rt-PA–treated subjects (21 percent) in the NINDS rt-PA Stroke Trial. The rate of symptomatic intracerebral hemorrhage in IMS II subjects (9.9 percent) was not significantly different than that for rt-PA treated subjects in the NINDS t-PA Stroke Trial (6.6 percent). IMS II subjects had significantly better outcomes at three months than NINDS placebo-treated subjects for all end points (OR ≥ 2.7) and better outcomes than NINDS rt-PA–treated subjects as measured by the Barthel Index and Global Test Statistic.

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 two hours of infusion or until thrombolysis.