Introducing a new era of ischemic stroke care

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Three years ago, the trial results of the Interventional Management of Stroke (IMS) III, Magnetic Resonance and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE), and SYNTHESIS Expansion were simultaneously published in 2013 in the New England Journal of Medicine, and their results demonstrated futility in the use of endovascular thrombectomy when combined with intravenous (IV) tissue plasminogen activator (tPA) for the treatment of large cerebral artery occlusions.2,4,12 These results sent ripples and then waves through the stroke community, having repercussions for medical reimbursement and casting considerable doubt that endovascular reperfusion could ever be a clinically effective strategy.

Today that doubt has been erased by not 1, but 5 studies published in 2015 in the New England Journal of Medicine.1,3,6,10,16 Two further groups have presented preliminary analyses of their studies but remain unpublished. Despite these studies taking place across different countries, occurring within various health care systems, and having various inclusion criteria, all demonstrated efficacy for endovascular therapy in the setting of large-vessel occlusion with convincing improvements in independent outcome (modified Rankin Scale [mRS] scores of 0–2) at 90 days and numbers needed to treat (NNTs) of between 3 and 7 (Table 1).

So, what changed between 3 years ago and today? What do we know now that we did not know then? The development, ease, and widespread use of more effective devices such as the stent retriever have greatly affected reperfusion times for large-vessel occlusion. Because device use is only effective with the necessary prerequisites of image-based patient selection and fast treatment para-

digs, an increased emphasis on imaging and on system efficiencies for the streamlining of workflow were critical enabling factors.

Image-Based Patient Selection

Although the time window for the treatment of patients in these recent trials was variable, they all used image-based criteria to assist with patient selection. An important shared theme of their imaging-based patient selection was the exclusion of patients with a large core (where a large proportion of the tissue at risk has already infarcted), most commonly using the Alberta Stroke Program Early CT score (ASPECTS). While not overtly stipulated in the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN), very few patients with low ASPECTS were randomized in the trial. Another common theme was the documentation of proximal intracranial occlusion, i.e., the M1 segment of the middle cerebral artery (MCA) with or without occlusion of the intracranial internal carotid artery (ICA). Some trials used additional imaging strategies to exclude patients with large cores, e.g., collateral evaluation in the Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (ESCAPE) trial, and CT perfusion imaging in the Extending the Time for Thrombolysis in Emergency Neurological Deficits—IntraArterial (EXTEND-IA) trial, and in most patients in the Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment (SWIFT PRIME) trial. In IMS III, 14% of patients with low ASPECTS (4 or less) were included in the trial, 8% of 306 patients with a baseline CT angiogram (CTA) did not have any vessel occlusion, and another 20% did not have a proximal vessel occlusion (M1 segment of the MCA ± ICA; an additional 350 participants in the trial had no baseline CTA).2,9 These values were much smaller in the current trials, and all patients had pre-randomization documentation of proximal vessel occlusion. Some of the trials had extensive education and quality improvement initiatives to hold the image-based criteria to the highest standards and to ensure the selection of appropriate patients.
The Need for Speed

We also now know that having a system in place to achieve fast reperfusion times is crucial for treating large vessel occlusion. The most important interval times in patients who were selected for randomization were the imaging-to-groin-puncture and the imaging-to-reperfusion times. SWIFT PRIME was able to achieve a qualifying image-to-groin-puncture time of 57 minutes, and in ESCAPE, the median time from the start of imaging to groin puncture was 51 minutes. The ESCAPE study had a rigorous target of achieving a CT-to-reperfusion time of less than 90 minutes, and the median CT-to-reperfusion time actually achieved in the study was 84 minutes. By comparison, the IMS III study had an approximate median CT-to-reperfusion time of 230 minutes. The message is clear: once patients are selected based on the clinical and imaging criteria, then fast reperfusion is both possible and necessary to salvage brain at risk for infarction.

Thrombectomy Devices

Empirically, stent retrievers are the dominant thrombectomy device and have made a major impact on the ability of the interventionalist to reperfuse large cerebral vessels in a short period of time. In IMS III, the majority of patients in the endovascular arm received intraarterial tPA or underwent thrombectomy with older generation devices, while stent retrievers were used in only 4 of 434 patients. All the recent studies showed a benefit of endovascular interventions with a high rate of stent retriever use. In ESCAPE and MR CLEAN, stent retrieval accounted for more than 80% of the interventional procedures performed, and the endovascular interventions in EXTEND-IA, SWIFT PRIME, and the Randomized Trial of Recanalization with Solitaire FR Device versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting within Eight Hours of Symptom Onset (REVASCAT) exclusively mandated stent retrieval. Stent retrievers have previously demonstrated significant increases in reperfusion rates compared with older-generation devices, and reperfusion according to the strict definition of Thrombolysis in Cerebral Infarction classification 2b or 3 was achieved in as many as 86% of patients in the recent trials compared with only 41% of patients in IMS III. Addition-ally, the benefit of the stent retriever strategy may lie in the shorter time it takes to achieve reperfusion. Initial deployment of the stent across the occluded segment often leads to immediate reperfusion (the “bypass effect”), until the thrombus can be physically removed during stent withdrawal. The recent studies further demonstrated that stent retrievers are safer than other thrombectomy procedures, because symptomatic intracerebral hemorrhage rates were much lower than in IMS III: 3.6% in ESCAPE, 0% in SWIFT PRIME, 1.9% in REVASCAT, and 0% in EXTEND-IA, compared with 6.2% in IMS III.

Suction-aspiration catheter systems were used in a small minority of instances in the ESCAPE and MR CLEAN trials. Prior data have shown excellent recanalization rates using these systems. More empirical information will be forthcoming from The Randomized, Concurrent Controlled Trial to Assess the Penumbra System's Safety and Effectiveness in the Treatment of Acute Stroke (THERAPY) study.

Important Subgroups

We have also learned in these new studies that endovascular thrombus retrieval is particularly suited for certain groups of patients. Those with tandem cervical carotid and intracranial occlusions, for example, accounted for 13%, 16%, and 29% of those enrolled in the ESCAPE, REVASCAT, and MR CLEAN studies, respectively. Traditionally, with medical treatment alone these patients have a dismal prognosis. Endovascular therapy in this population led to dramatically improved outcomes: in REVASCAT, an odds ratio of 4.3 in patients with extracranial carotid occlusion favoring intervention, and in ESCAPE, an odds ratio of 3.9. Although patients with ipsilateral cervical carotid artery occlusion have the poorest prognosis, they show the largest effect size with endovascular therapy.

Older patients also demonstrated a significant benefit from endovascular intervention. In SWIFT PRIME, similar benefits were shown in patients less than 70 years of age as well as those 70 or older, with odds ratios favoring intervention of 1.67 and 1.78, respectively. The odds ratio favoring intervention for patients in the ESCAPE trial was 2.7 in patients 80 years old or less and 3.0 in patients over the age of 80. We note that these patients represent the relatively healthy elderly, living independently in the community prior to stroke onset. Hence, advanced age should not by itself be used to exclude patients from receiving endovascular treatment for large-vessel occlusion.

We also learned that patients with large-vessel occlusions benefit from endovascular intervention regardless of whether IV tPA was administered or, in patients who received IV tPA, whether the endovascular procedure began

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Trial</th>
<th>Comparison</th>
<th>No. of Patients</th>
<th>Absolute Difference in mRS Score 0–2 at 90 Days (95% CI)</th>
<th>NNT (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berkhemer et al., 2015</td>
<td>MR CLEAN</td>
<td>IA ± IV vs usual care alone</td>
<td>267 233</td>
<td>13.5% (5.9–21.2)</td>
<td>7 (4–17)</td>
</tr>
<tr>
<td>Campbell et al., 2015</td>
<td>EXTEND-IA</td>
<td>IA + IV vs IV alone</td>
<td>35 35</td>
<td>31.4% (9.4–53.5)</td>
<td>3 (1–11)</td>
</tr>
<tr>
<td>Goyal et al., 2015</td>
<td>ESCAPE</td>
<td>IA ± IV vs usual care alone</td>
<td>150 165</td>
<td>23.8% (13.2–34.4)</td>
<td>4 (3–8)</td>
</tr>
<tr>
<td>Jovin et al., 2015</td>
<td>REVASCAT</td>
<td>IA ± IV vs usual care alone</td>
<td>103 103</td>
<td>15.5% (2.6–28.5)</td>
<td>6 (4–38)</td>
</tr>
<tr>
<td>Saver et al., 2015</td>
<td>SWIFT PRIME</td>
<td>IA + IV vs IV alone</td>
<td>98 98</td>
<td>24.7% (10.9–38.4)</td>
<td>4 (3–9)</td>
</tr>
</tbody>
</table>

IA = intraarterial.
* All outcomes favored intervention.
before the infusion had ended. Hence, there is no reason to consider endovascular treatment as rescue therapy only to be considered after IV tPA has “failed”; instead, both treatments should be applied in parallel by beginning the endovascular procedure during the tPA infusion. Intravenous tPA, among eligible candidates, remains the standard of care and first-line acute therapy.

Furthermore, accordant with case series data showing that general anesthetic use is associated with increased procedural times and poorer outcomes, the recent trials reported a low rate of general anesthetic use in the endovascular group (9.1% in ESCAPE and 6.7% in REVASCAT) providing evidence of proof of concept that endovascular treatment can be performed safely and with good outcomes, without general anesthesia. Given the benefits of using conscious sedation or even no sedation only—no loss of the neurological examination, reduced risk of ventilator-associated pneumonia, faster early recovery, and mobilization and reduced resource use—we believe that conscious sedation should be favored over general anesthesia. A randomized assessment of routine general anesthesia compared with conscious sedation is desirable, given the widely varying opinions on this issue in the endovascular community. General anesthesia will continue to have an important role in specific situations of the uncooperative or impaired consciousness patient.

**Implication of Results on Systems of Care**

The biggest challenge ahead is getting the correct patient to the correct hospital as fast as possible. Implementation of these positive trial results will require a major effort on the part of paramedics, physicians, nurses, health care personnel, and administrators that influence each stage of the workflow: from the periphery to the appropriate emergency room, from the emergency room to the CT scanner, and from the CT scanner to the angiography suite. Triage and emergency staff will require training to recognize a possible stroke. Transportation systems will need to be refined such that these patients are taken directly to stroke centers equipped for endovascular treatment. Finally, a team approach to multitasking and division of labor is critical to expedite the time from imaging to endovascular treatment, with multiple actions proceeding in parallel (such as image interpretation and obtaining consent) while the angiography suite is being prepared.

**Future Opportunities**

Despite marked improvement in clinical outcomes with mechanical thrombectomy in each one of these recent studies, dependency or death (an mRS score of 3–6) continued to be noted in as many of 67% of patients in the endovascular group, which equates to a huge margin for potential further improvement.

These trial results pose other important questions that will need to be explored: what are the outer time limits for endovascular therapy; what imaging strategies allow selection of the most appropriate patient for treatment; what are the determinants for iatrogenic harm from endovascular therapy; and can these trial results be extrapolated to the distal carotid or posterior circulations? There will likely be further innovation in device technology and endovascular techniques, and these innovations will need to be evaluated rigorously. Patient-level meta-analyses are being planned from the current trials, and some of these questions may get answered in the near future.

These recent trials mark the beginning of an exciting new era for the neuroendovascular interventionalist. At last there is a large body of irrefutable evidence showing we can substantially reduce the morbidity and mortality that stroke patients would otherwise suffer. What a difference 2 years can make.

**References**


Disclosures
Dr. Hill has received clinical or research support for a study from Medtronic. Dr. Goyal has served as a consultant to Covidien and has a licensing agreement with GE Healthcare for the development of new systems of stroke diagnosis.