Emerging Therapy Critiques

Joseph P. Broderick, MD; Gerhard Schroth, MD

What the SWIFT and TREVO II Trials Tell Us About the Role of Endovascular Therapy for Acute Stroke

The Solitaire With the Intention for Thrombectomy (SWIFT) trial¹ and the TREVO II trial,² published online in *Lancet* in August 2012, are important trials in the history of endovascular therapy for acute ischemic stroke for several reasons. First, both randomized trials compared a new technology, 2 versions of a stent-retriever, with a previously Food and Drug Administration-cleared technology, the Merci Retriever. The latest iteration of the Merci Retriever, which had been cleared for use since 2005, is a flexible nitinol wire with distal corkscrew-shaped coil loops with attached filaments. Stent-retriever technology is based on self-expanding stents that can be fully deployed and then retrieved about 5 minutes later, after migration of the thrombus through the stent struts.³

Retrievable stents were introduced in 2010 in experienced, high-volume comprehensive European stroke centers with increased rates of recanalization in a shorter time compared with intra-arterial thrombolysis.⁴ The Merci Retriever and retrievable stents are distal thrombectomy devices that require navigation of the device through and beyond the site of occlusion without image-guidance of a high-resolution biplane or 3D roadmap. In contrast, proximal thrombectomy devices allow a safe, image-guided approach to the site of occlusion and aspiration of the thrombus.

These 2 randomized trials broke the trend of single-arm trials comparing a new technology with the intravenous heparin arm of the randomized PROACT II trial study, which was completed in 1998.⁵ The goal of past single-arm trials, used for both the Merci Retriever⁶,⁷ and Penumbra Aspiration System,⁸ was to obtain 510k clearance by the FDA, or regulatory approval in other countries, for thrombectomy in acute ischemic stroke. However, no randomized trial of these devices has demonstrated improved clinical outcome by a thrombectomy device compared with standard therapy, whether intravenous tissue-type plasminogen activator (tPA) within 3 and subsequently 4.5 hours, or no reperfusion therapy ≥4.5 hours.

Second, both trials demonstrated superiority with regards to the primary study end point compared with the Merci Retriever. The primary end point in the SWIFT trial was thrombolysis in myocardial ischemia scale 2 or 3 flow in all treatable vessels⁹ without symptomatic intracranial hemorrhage after ≤3 passes of the assigned device, as assessed by an independent core laboratory that was masked to study assignment. The primary end point in the TREVO II trial was a thrombolysis in cerebral infarction scale 2 or 3 flow,⁹ with the assigned device alone as assessed by an unmasked central imaging core. The use of different scoring scales, differences in masking of study assignment, and lack of information on reperfusion by location of vessel occlusion complicates comparison between reperfusion rates for the 2 stent retrievers. But both stent retrievers were clearly superior to the Merci Retriever with regards to reperfusion within these 2 small trials, as well as compared with other just-published endovascular trials that used the Merci Retriever (Table 1).⁹,¹⁰,¹¹ Future trials going forward should use the thrombolysis in cerebral infarction scoring and a central core imaging laboratory and report data per site of vascular occlusion to enable more consistent comparisons between endovascular approaches.

Both trials also demonstrated superior clinical outcomes for the respective stent-retriever with regard to their predefined secondary clinical end point. The end point for clinical outcome of the SWIFT trial was defined as modified Rankin Scale (mRS) of ≤2, or equal to the prestroke mRS if the prestroke mRS was >2, or National Institutes of Health Stroke Scale score improvement of ≥10 points. Using this definition, the Solitaire retriever group had superior outcomes, 58% versus 33% for the Merci Retriever group; difference 25% (6–43), odds ratio (OR), 2.78 (1.25–6.22); P value noninferiority=0.0001, P value superiority=0.02. However, the rate of mRS of 0 to 2 at 90 days for the Solitaire group (37%) was not significantly different from that of the Merci group (29%; P=0.53), and outcomes between the 2 groups were nearly identical for subjects treated with intravenous tPA before endovascular therapy. The secondary clinical end point of the TREVO trial was an mRS ≤2 at 90 days. Using this definition, the TREVO stent-retriever group (40%) had superior outcomes compared with the Merci Retriever group (22%; OR, 2.39 [1.16–4.95]; P=0.0130).

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1. Received March 2, 2013; accepted April 11, 2013.
2. From the Department of Neurology and Rehabilitation Medicine, University of Cincinnati Neuroscience Institute, Cincinnati, OH (J.P.B.); and Institute of Diagnostic and Interventional Neuroradiology, University of Bern—Inselspital, Bern, Switzerland (G.S.).
3. Correspondence to Joseph P. Broderick, MD, Department of Neurology and Rehabilitation Medicine, University of Cincinnati Neuroscience Institute, 260 Stetson St, Suite 2300, PO Box 670525, Cincinnati, OH 45267-0525. E-mail joseph.broderick@uc.edu
4. © 2013 American Heart Association, Inc.
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Safety is where there is substantial divergence between the 2 trials. SWIFT reported a lower 90-day mortality rate in the Solitaire group than the Merci group (17% versus 38%; OR, 0.34 [0.14–0.81]) and lower rates of symptomatic intracerebral hemorrhage (ICH; Solitaire 2% versus Merci 11%; OR, 0.14 [0.02–1.23]). In the TREVO II trial, the 90-day mortality rates (stent-retriever 33% versus Merci 24%; OR, 1.61 [0.83–3.13]) and symptomatic ICH rates (stent-retriever 7% versus Merci 9%; OR, 0.75 [0.25–2.26]) were not significantly different. Symptomatic ICH in both trials used the European Cooperative Acute Stroke Study III criteria.12 The higher rates of mortality and symptomatic ICH in the Merci group compared with the Solitaire group in the SWIFT trial are likely attributable not only to improved reperfusion with the stent-retriever but also to differences in rates of intravenous tPA between the treatment arms and particularly the use of additional mechanical devices used after the Merci Retriever. These additional attempts at revascularization after failure with the Merci Retriever may have led to additional complications associated with intracranial hemorrhage and even death. In contrast, the Merci group in the TREVO II trial had a trend toward lower 90-day mortality rate compared with the stent-retriever group, despite much better overall outcomes with regard to mRS of 0 to 2 in the stent-retriever group. These variances in mortality between the trials speak to the limitations of smaller randomized trials, in which more extreme differences between groups can be observed because of imbalances in important prognostic variables, other treatments, or simply chance.

Both of these trials indicate that the stent-retriever devices, as used in these trials, are preferable to the Merci Retriever when endovascular therapy is considered. The larger issue is whether these 2 trials provide sufficient evidence that the use of the stent-retriever devices should be the standard of care for subjects with acute ischemic stroke, either with or without preceding tPA within 4.5 hours or out to the 8-hour window as in the current trials. Table 3 shows the 90-day mRS ≤2 for the SWIFT, TREVO II, Interventional Management of Stroke (IMS III), and Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) trials.1,2,10,11 The 90-day mRS outcome in the intravenous tPA-only group in the IMS III trial who had an intracranial internal carotid artery, middle cerebral artery trunk (M1), or basilar artery occlusion on pretreatment computed tomography angiography is quite similar to the outcomes for the stent-retriever groups in SWIFT and TREVO II, which include internal carotid artery, M1, M2, and vertebral-basilar occlusions. The endovascular group in the IMS III trial, which included treatment with intra-arterial tPA, the Merci Retriever, the Penumbra Aspiration system, and only a handful of Solitaire devices, had similar outcomes in subjects who had internal carotid artery, M1, and M2, and vertebral-basilar occlusions at angiography after treatment with intravenous tPA compared with subjects treated with stent retrievers in the SWIFT and TREVO II trials. A key comparison between

### Table 1. Reperfusion Rates in Recent Randomized Endovascular Trials

<table>
<thead>
<tr>
<th>Study Groups</th>
<th>No. of Patients</th>
<th>Intravenous tPA, %</th>
<th>TICI or TIMI 2–3, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWIFT Solitaire stent-retriever</td>
<td>58</td>
<td>33</td>
<td>89</td>
</tr>
<tr>
<td>SWIFT Merci Retriever</td>
<td>55</td>
<td>47</td>
<td>67†</td>
</tr>
<tr>
<td>TREVO II stent-retriever</td>
<td>88</td>
<td>58</td>
<td>92†</td>
</tr>
<tr>
<td>TREVO II Merci Retriever</td>
<td>90</td>
<td>50</td>
<td>77†</td>
</tr>
<tr>
<td>IMS III Merci Retriever</td>
<td>77</td>
<td>100</td>
<td>73‡</td>
</tr>
<tr>
<td>MR Rescue embolectomy/penumbral</td>
<td>34</td>
<td>47</td>
<td>59§</td>
</tr>
<tr>
<td>MR Rescue embolectomy/nonpenumbral</td>
<td>30</td>
<td>40</td>
<td>77§</td>
</tr>
</tbody>
</table>

IMS III indicates Intervventional Management of Stroke III; MR; SWIFT, solitaire with the intention for thrombectomy; TICI, thrombolysis in cerebral infarction; TIMI, thrombolysis in myocardial infarction; tPA, tissue-type plasminogen activator; and TREVO II.

*TIMI 2 or 3 score as assessed at site at completion of procedure (reperfusion after completion of procedure reported only by site review in SWIFT trial—ICA, M1, M2, and vertebral basilar arteries).
§TICI 2 or 3 score as assessed by core laboratory at completion of procedure (ICA, M1, M2, or vertebral-basilar arteries).
†TICI 2 or 3 score as assessed by core laboratory at completion of procedure. Includes only intracranial ICA and M1 occlusions.
‡TICI 2 or 3 score as assessed by core laboratory at completion of procedure. Endovascular approach included primarily Merci Retriever and smaller number of Penumbra devices.

### Table 2. Safety End Points and Use of Adjunctive Therapies in SWIFT and TREVO II Trials

<table>
<thead>
<tr>
<th>Study Groups</th>
<th>No. of Patients</th>
<th>Intravenous tPA, %</th>
<th>Symptomatic ICH, %</th>
<th>90-Day Mortality, %</th>
<th>Add-On IA Therapy, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWIFT solitaire</td>
<td>58</td>
<td>33</td>
<td>2</td>
<td>17</td>
<td>21†</td>
</tr>
<tr>
<td>SWIFT Merci</td>
<td>55</td>
<td>47</td>
<td>11</td>
<td>38</td>
<td>44†</td>
</tr>
<tr>
<td>TREVO II Retriever</td>
<td>88</td>
<td>58</td>
<td>7</td>
<td>33</td>
<td>2†</td>
</tr>
<tr>
<td>TREVO II Merci</td>
<td>90</td>
<td>50</td>
<td>9</td>
<td>24</td>
<td>7†</td>
</tr>
</tbody>
</table>

IA indicates intra-arterial; ICH: SWIFT, solitaire with the intention for thrombectomy; tPA, tissue-type plasminogen activator; and TREVO II.

*Only 1 treated with IA tPA alone, in remainder another mechanical device was used alone (n=17) or with IA tPA (n=6). Devices included Penumbra, stent placement, additional Merci devices, or other devices.
†Only adjunctive intra-arterial tPA.
the trials is the percentage of terminal internal carotid artery occlusions at the time of angiography, which are associated with lower rates of recanalization and poorer outcomes compared with M1 and M2 occlusions and are numerically lowest in the TREVO II stent-retriever arm and several treatment arms of MR Rescue. The only major differences between the trials are the greater frequency of intravenous tPA use and the shorter time from stroke onset to groin puncture in the IMS III trial. Thus, there is clear equipoise for randomized trials comparing intravenous tPA alone to endovascular approaches with or without preceding tPA.

From the neuroradiological point of view, there may be several reasons why the rates of good clinical outcome in SWIFT and TREVO II were not as impressive as expected. Recent developments in stroke imaging, which were not applied in these studies, may improve the efficacy and safety of the interventional approach. Modern computed tomography technology visualizes the extent of the thrombus and provides information about the vessels distal to the thrombus. This information can also be obtained from modern MRI (eg, susceptibility weighted imaging) or 3D or 4D flat panel techniques in the angiography suite. Blind navigation through and distal to the thrombus may result in deployment of the device, retrievable stents as well as the Merci device, in the thrombus itself, or in nonoccluded branches, which may serve as collaterals for the penumbra. Embolization into these distal nonoccluded vessels is a potential risk. On the basis of the advanced computed tomography, mechanical retrieval, or flat panel 3D and 4D images, optimal devices and techniques can be adapted to the individual angioarchitecture of the occluded vessel and balanced with the risk to the patient. In patients with difficult anatomy proximal and distal to the site of occlusion, it might be better to avoid endovascular treatment with stent retrievers and to use other techniques, such as proximal thrombectomy and thrombo-aspiration, with recently available high-flow distal access catheters or intra-arterial thrombolysis. One additional limitation of SWIFT and TREVO II is that training in the use of the new devices before the randomized trial was limited to a few cases or by use of a bench model of the human cerebrovasculature.

There is compelling evidence that a good clinical outcome is strongly correlated with time from stroke onset to reperfusion, no matter what device or approach is used. The rate of a good clinical outcome using endovascular therapy approaches the rate in those subjects without any reperfusion in prior single-arm studies of IMS I, IMS II, and the Recanalyzer trials when the time to reperfusion is >6 hours. Although the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution Study 2 trial has provided data about the potential usefulness of image selection for endovascular therapy in later time windows, the MR Rescue trial demonstrates the potential limitations of penumbral imaging as a predictor of response to endovascular therapy compared with standard therapy. The presence of a penumbra on brain imaging before treatment in the MR Rescue trial did predict a good clinical outcome in both treatment groups. Similarly, the Alberta Stroke Program Early CT Score on baseline computed tomography is an excellent predictor of outcome in clinical trials and clinical practice but has not worked well as a predictor of response to therapy in a randomized trial. Once again, there is clear equipoise for randomization between endovascular therapy and standard therapy outside of the window for intravenous tPA, with or without the use of penumbral imaging.

**Conclusion**

SWIFT and TREVO II trials represent milestones in the history of treatment of acute ischemic stroke. They emphasize the importance of randomized trials and the advances in the technology to reopen occluded intracranial arteries. However, they do not demonstrate that patients’ outcomes are improved with stent-retriever technology compared with intravenous tPA within 4.5 hours or compared with no reperfusion therapy after 4.5 hours. Ongoing and future randomized trials that focus on minimization of time from onset to endovascular...
therapy are critical to determine the best use of this promising technology in patients with acute ischemic stroke.

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