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

Joseph P. Broderick, MD[1] and **Gerhard Schroth, MD**[2]

[1]Department of Neurology and Rehabilitation Medicine, University of Cincinnati Neuroscience Institute, Cincinnati, Ohio [2]Institute of Diagnostic and Interventional Neuroradiology, University of Bern – Inselspital. Switzerland

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The Solitaire With the Intention For Thrombectomy (SWIFT) trial[1] and the TREVO II Trial,[2] published online in Lancet 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, two versions of a stent retriever, with a previously FDA 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 five 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 as compared to 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 3-D roadmap. In contrast, proximal thrombectomy devices allow a safe, image-guided approach to the site of occlusion and aspiration of the thrombus.

These two randomized trials broke the trend of single arm trials comparing a new technology to 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 Retriever[6, 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 as compared to standard therapy, whether intravenous t-PA within three and subsequently 4 ½ hours, or no reperfusion therapy beyond 4 ½ hours.

Corresponding Author: 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, or at joseph.broderick@uc.edu.

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Second, both trials demonstrated superiority with regards to the primary study endpoint as compared to the Merci Retriever. The primary endpoint in the SWIFT Trial was Thrombolysis In Myocardial Ischemia (TIMI) scale 2 or 3 flow in all treatable vessels[9] without symptomatic intracranial hemorrhage after up to three passes of the assigned device, as assessed by an independent core laboratory which was masked to study assignment. The primary endpoint in the TREVO II Trial was a Thrombolysis in Cerebral Ischemia (TICI) 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 regarding reperfusion by location of vessel occlusion complicates comparison between reperfusion rates for the two stent-retrievers. But both stent retrievers were clearly superior to the Merci Retriever with regards to reperfusion within these two small trials, as well as compared to other just published endovascular trials that used the Merci retriever (Table 1).[10, 11] Future trials going forward should use the TICI 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 regards to their predefined secondary clinical endpoint. The SWIFT Trial's endpoint for clinical outcome was defined as modified Rankin Score (mRS) of 2 or less, or equal to the prestroke mRS if the prestroke mRS was greater than 2, or NIHSS score improvement of 10 points or more. Using this definition, the Solitaire retriever group had superior outcomes, 58% vs. 33% for the Merci Retriever group; difference 25% [6–43], OR 2·78 [1·25–6·22]; p value non-inferiority=0·0001, p value superiority=0·02). However, the rate of mRS of 0–2 at 90 days for the Solitaire group (37%) was not significantly different than that of the Merci group (29%, p = 0.53) and outcomes between the two groups were nearly identical for subjects treated with IV t-PA prior to endovascular therapy. The TREVO 2 Trial's secondary clinical endpoint was a mRS ≤ 2 at 90 days. Using this definition, the TREVO stent retriever group (40%) had superior outcomes as compared to the Merci retriever group (22%) [OR − 2.39 (1.16–4.95), p value 0.0130].

Safety is where there is substantial divergence between the two trials. SWIFT reported a lower 90-day mortality rate in the Solitaire group than the Merci group (17% vs. 38%; OR 0·34 [0·14–0·81] as well as lower rates of symptomatic intracerebral hemorrhage (Solitaire 2% vs. Merci 11%, OR 0.14 (0.02–1.23). In the TREVO 2 Trial, the 90-day mortality rates (stent retriever 33% vs. Merci 24%, OR 1.61 (0.83 – 3.13) and symptomatic ICH rates (stent retriever 7% vs. Merci 9%, OR 0.75 (0.25–2.26) were not significantly different. Symptomatic ICH in both trials used the ECASS III criteria.[12] The higher rates of mortality and symptomatic ICH in the Merci group as compared to the Solitaire group in the SWIFT Trial are likely due not only to improved reperfusion with the stent-retriever but also to differences in rates of IV t-PA between the treatment arms and particularly the use of additional mechanical thrombectomy devices in the Merci group in the SWIFT Trial (Table 2). In the SWIFT Trial, 44% of the Merci group had additional endovascular treatment with various 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 2 Trial had a trend toward lower 90-day mortality as compared to the stent retriever group, despite much better overall outcomes with regards to mRS of 0–2 in the stent retriever group. These variances in mortality between the trials speak to the limitations of smaller randomized trials where 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 two 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 t-PA within 4 ½ 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 2, IMS III, and MR Rescue Trials.[1, 2, 10, 11] The 90-day mRS outcome in the IV t-PA only group in the IMS III Trial who had an intracranial internal carotid artery (ICA), middle cerebral artery trunk (M1), or basilar artery occlusion on pre-treatment CT angiography, is quite similar to the outcomes for the stent retriever groups in SWIFT and TREVO 2 which include ICA, M1, M2 and vertebral-basilar occlusions. The endovascular group in the IMS III Trial, which included treatment with intra-arterial t-PA, the Merci retriever, the Penumbra Aspiration system, and only a handful of Solitaire devices, had similar outcomes in subjects who had ICA, M1, M2, and vertebral-basilar occlusions at angiography after treatment with IV t-PA as compared to subjects treated with stent retrievers in the SWIFT and TREVO II trials. A key comparison between the trials is the percentage of terminal ICA occlusions at the time of angiography which are associated with lower rates of recanalization and poorer outcomes as compared to M1 and M2 occlusions and which are numerically lowest in the Trevo 2 stent retriever arm and several treatment arms of MR Rescue. The only major differences between the trials are the greater frequency of IV t-PA 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 IV t-PA alone to endovascular approaches with or without preceding t-PA.

From the neuroradiological point of view, there may be several reasons why the rates of good clinical outcome in SWIFT and TREVO 2 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 CT 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 (e.g., Susceptibility Weighted Imaging [SWI]) 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 well as the Merci device, in the thrombus itself, or in non-occluded branches, which may serve as collaterals for the penumbra. Embolization into these distal non-occluded vessels is a potential risk. Based on advanced CT, MR or flat panel 3D and 4D images, optimal devices and techniques can be adapted to the individual angio-architecture of the occluded vessel and balanced with the risk to the patient. In patients with difficult anatomy proximal and/or 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 2 is that training in the use of the new devices prior to 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 Recanalyze Trials when the time to reperfusion goes beyond 6 hours.[13, 14] While the DEFUSE II Trial has provided data about the potential usefulness of image selection for endovascular therapy in later time windows,[15] the MR RESCUE Trial[11] demonstrates the potential limitations of penumbral imaging as a predictor of response to endovascular therapy as compared to standard therapy. The presence of a “penumbra” on brain imaging prior to treatment in the MR RESCUE Trial did predict a good clinical outcome in both treatment groups. Similarly,

the ASPECTS score on baseline CT 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.[16] Once again, there is clear equipoise for randomization between endovascular therapy and standard therapy outside of the window for IV t-PA, with or without the use of penumbral imaging.

Conclusion

SWIFT and TREVO 2 Trials represent milestones in the history of treatment of acute ischemic stroke. They emphasize the importance of randomized trials as well as the advances in the technology to reopen occluded intracranial arteries. However, they do not demonstrate that patients' outcomes are improved with stent retriever technology as compared to intravenous t-PA within 4 ½ hours or compared to no reperfusion therapy after 4 ½ 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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Table 1

Reperfusion Rates in Recent Randomized Endovascular Trials

Study Groups	No. of patients	IV t-PA	TICI or TIMI 2–3
SWIFT Solitaire stent retriever	58	33%	89%*
SWIFT Merci retriever	55	47%	67%*
TREVO II stent retriever	88	58%	92%†
TREVO II Merci retriever	90	50%	77%†
IMS III Merci retriever	77	100%	73%‡
MR Rescue Embolectomy/Penumbral	34	47%	59%§
MR Rescue Embolectomy/Non-Penumbral	30	40%	77%§

*Thrombolysis in Myocardial Infarction (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)

†Thrombolysis in Cerebral Infarction (TICI) 2 or 3 score as assesses by core laboratory at completion of procedure (ICA, M1, or 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 Endpoints and Use of Adjunctive Therapies in SWIFT and TREVO 2 Trials

Study Groups	No. of patients	IV t-PA	Symptomatic ICH (%)	90-day Mortality	Add-on IA therapy
SWIFT Solitaire	58	33%	2%	17%	21%*
SWIFT Merci	55	47%	11%	38%	44%*
TREVO 2 Retriever	88	58%	7%	33%	2%†
TREVO 2 Merci	90	50%	9%	24%	7%†

*Only one treated with intra-arterial (IA) t-PA alone, in remainder another mechanical device was used alone (N = 17) or with IA t-PA (N=6). Devices included Penumbra, stent placement, additional Merci devices or other devices

†Only adjunctive IA t-PA

Table 3

Comparison of 90-day Modified Rankin Score ≤ 2 in Randomized Endovascular Trials

Study Groups	No. of patients	% ICA occlusions	IV t-PA	Time to groin puncture (mean, minutes)	mRS ≤ 2 at 90 days
SWIFT Solitaire (ICA, M1, M2, vertebral-basilar)	58	21%	33%	294	37%
SWIFT Merci (ICA, M1, M2, vertebral-basilar)	55	25%	47%	320	29%
TREVO II Retriever (ICA, M1, M2, vertebral-basilar)	88	16%	58%	276	40%
TREVO II Merci (ICA, M1, M2, vertebral-basilar)	90	19%	50%	270	22%
IMS III Endovascular Arm at angiography *and after IV t-PA* (ICA, M1, M2, vertebral-basilar)	294	24%	100%	205	33% *
IMS III t-PA only arm who had ICA, M1, or basilar occlusions *on pre-treatment CTA*	71	32%	100%	NA	38%
MR Rescue Embolectomy/Penumbral † (ICA, M1, M2)	34	18%	47%	381 †	21%
MR Rescue Standard Rx./Penumbral †(ICA, M1, M2)	34	15%	26%	381 †	26%
MR Rescue Embolectomy/Non-Penumbral † (ICA, M1, M2)	30	23%	40%	381 †	17%
MR Rescue Standard Rx/Non-Penumbral † (ICA, M1, M2)	20	10%	35%	381 †	10%

* For those with ICA, M1, or basilar on *pre-treatment CTA*, 41% mRS 0–2

† Penumbral pattern defined as substantial salvageable tissue and small infarct core. 381 minutes represents mean time for entire trial

CTA – CT angiography

NA – not applicable