Endovascular treatment of acute ischemic stroke: the end or just the beginning?

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Various endovascular intraarterial approaches are available for treating patients with acute ischemic stroke who present with severe neurological deficits. Three recent randomized trials—Interventional Management of Stroke (IMS) III, Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE), and Synthesis Expansion: A Randomized Controlled Trial on Intra-Arterial Versus Intravenous Thrombolysis in Acute Ischemic Stroke (SYNTHESIS Expansion)—evaluated the efficacy of endovascular treatment of acute ischemic stroke and, after failing to demonstrate any significant clinical benefit of endovascular therapies, raised concerns and questions in the medical community regarding the future of endovascular treatment for acute ischemic stroke. In this paper, the authors review the evolution of endovascular treatment strategies for the treatment of acute stroke and provide their interpretation of findings and potential limitations of the three recently published randomized trials. The authors discuss the advantage of stent-retriever technology over earlier endovascular approaches and review the current status and future directions of endovascular acute stroke studies based on lessons learned from previous trials. (<http://thejns.org/doi/abs/10.3171/2013.10.FOCUS13374>)

KEY WORDS • acute ischemic stroke • endovascular procedure • large-vessel occlusion • mechanical thrombectomy • neuroimaging • stent retriever

Abbreviations used in this paper: CTA = CT angiography; ECASS = European Cooperative Acute Stroke Study; ICA = internal carotid artery; IMS = Interventional Management of Stroke; MCA = middle cerebral artery; MERCI = Mechanical Embolus Removal in Cerebral Ischemia; MR RESCUE = Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy; MRA = MR angiography; NIHSS = National Institutes of Health Stroke Scale; PROACT = Prolyse in Acute Cerebral Thromboembolism; rtPA = recombinant tPA; SARIS = Stent-Assisted Recanalization in acute Ischemic Stroke; SWIFT = SOLITAIRE With the Intention For Thrombectomy; tPA = tissue plasminogen activator; TREVO 2 = Thrombectomy Revascularization of Large Vessel Occlusions in Acute ischemic stroke; SYNTHESIS Expansion = Synthesis Expansion: A Randomized Controlled Trial on Intra-Arterial Versus Intravenous Thrombolysis in Acute Ischemic Stroke; TICI = Thrombolysis in Cerebral Infarction; TIMI = Thrombolysis in Myocardial Infarction.

OVER the last decade, various endovascular intraarterial approaches have been developed for treating patients with acute ischemic stroke presenting with severe neurological deficits. Single-arm prospective studies showed higher recanalization rates for large-vessel occlusion stroke with intraarterial approaches than with intravenous recombinant tissue plasminogen activator (rtPA).

Three long-anticipated trials (MR RESCUE,¹⁵ IMS III,¹ and SYNTHESIS Expansion³) evaluating safety and efficacy of endovascular treatment of acute ischemic stroke were published earlier this year. All three trials failed to demonstrate any significant clinical benefit of endovascular therapies. These studies immediately raised concerns and questions in the medical community regarding the fu-

ture of endovascular treatment for acute ischemic stroke, which were reflected in electronic media and medical journals.^{2,13} In this paper, we review the evolution of systemic intravenous and intraarterial endovascular treatment strategies for the treatment of acute stroke, and we provide our interpretation of the findings and potential limitations of the recently published trials.^{1,3,15} Additionally, we discuss the current status of and future directions for endovascular acute stroke studies on the basis of lessons learned from previous trials.

Intravenous Thrombolysis in Acute Ischemic Stroke

Stroke remains the leading cause of long-term disability in the US, and approximately 795,000 people suffer from stroke each year.⁷ The global burden of stroke is also severe; stroke remains the second leading cause of death worldwide, showing its greatest impact in low-income countries.^{14,17}

In 1996, intravenous thrombolysis with rtPA received FDA approval for treatment of acute ischemic stroke within the first 3 hours of symptom onset, based on the results of the landmark National Institute of Neurological Disorders and Stroke rtPA stroke trial.²³ The trial demonstrated overall greater ability of rtPA in achieving long-term favorable outcomes (assessed by functional examinations—modified Rankin scale and Barthel index—administered during a 3-month follow-up period) compared with placebo treatment, with no improvement in mortality at 3 months.

The European Cooperative Acute Stroke Study (ECASS) III was a randomized study that compared intravenous rtPA with placebo and further demonstrated the benefit of rtPA when administered within 3–4.5 hours; 52% of patients had a favorable outcome after thrombolysis compared with 45% with placebo.⁸ Intravenous thrombolysis performed within a 3- to 4.5-hour window in a carefully selected group of patients (excluding patients > 80 years, those with severity of stroke symptoms according to National Institutes of Health Stroke Scale [NIHSS] score > 25, those with previous oral anticoagulation therapy, and those with history of stroke and diabetes, which were associated with higher risk for intracranial hemorrhage in ECASS III [although recent data suggest that intravenous thrombolysis might be beneficial even in some of these high-risk patients²¹]) is currently recommended by the American Heart Association (considered Class I, Level of Evidence B).¹⁰ However, despite the American Heart Association recommendation and positive results in ECASS III, expansion of the treatment window to 4.5 hours was not approved by the FDA. Therefore, intravenous thrombolysis within the first 3 hours of stroke symptom onset remains the only FDA-approved systemic intravenous treatment in the US.

The main advantages of intravenous thrombolysis over intraarterial endovascular treatment include low cost and simplicity and ease of administration; a stroke team can administer rtPA rapidly in the emergency department after completion of basic laboratory testing and exclusion of hemorrhage on noncontrast CT scanning of the head,

without the need for an angiography suite and involvement of multiple personnel. Despite an increase in the number of acute stroke cases treated with intravenous rtPA, most patients are still excluded from receiving thrombolysis, due to delayed presentation or numerous contraindications for systemic administration of rtPA. A recent analysis of intravenous rtPA utilization in acute stroke showed a steady increase in cases from 1.2% in 2004 to 3.4% in 2009.⁹ Still, although that study demonstrated an almost 3-fold increase in intravenous rtPA utilization over a 5-year period, it shows that a staggering 7% of acute stroke patients do not receive the FDA-recommended treatment despite meeting the inclusion criteria.

Intravenous Thrombolysis and Large-Vessel Occlusion

Analyses have demonstrated that the clinical efficacy of intravenous thrombolysis and its ability to achieve successful recanalization are limited in patients presenting with acute stroke due to large-vessel occlusion. This commonly includes occlusions of the following arteries: internal carotid artery (ICA), proximal middle cerebral artery (MCA) segments, vertebral artery, and basilar artery. Transcranial Doppler ultrasonography performed immediately after systemic rtPA administration showed a strong relationship between early response to thrombolysis, dramatic recovery, and occlusion site.³¹ Occlusion of the ICA terminus was least likely to achieve recanalization (successful in only 6%). Conversely, smaller, more distal occlusions had a much greater chance for successful revascularization, which increased to an impressive 44% of cases when thrombus was present within the M₂ segment, whereas more proximally located MCA occlusions had successful recanalization with rtPA in only 30%. A strong relationship was found between occlusion site (that is, distal MCA occlusion) and ability to achieve early dramatic neurological recovery. Computed tomography angiography (CTA) has also shown a strong impact of clot location on long-term outcomes following intravenous thrombolysis: more than 80% of treated stroke patients with a more distally located clot had good neurological outcome at 3 months.³⁴ Proximal MCA occlusion was associated with only a 22% chance of good outcome, and none of the patients with occlusion located in the most distal segment of the ICA experienced good recovery.³⁴

Large-Vessel Occlusion as a Target for Endovascular Therapy

Enthusiasm for endovascular catheter-assisted interventions for acute stroke was in part triggered by observations of limited recanalization rates achieved with systemic thrombolysis in patients with large-vessel occlusion. In trials of intraarterial therapies conducted in the 1990s, investigators relied on clinical evaluation alone for screening of cases in which large-vessel occlusion was suspected, because noninvasive imaging modalities (such as CTA or magnetic MR angiography [MRA]) were not widely available. Even at this early stage of emergency

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stroke treatment it was recognized that such an approach was a poor predictor for identifying patients with large-vessel occlusion.

The Prolyse in Acute Cerebral Thromboembolism (PROACT) II trial evaluated intraarterial thrombolysis with the pharmacological agent prourokinase in patients with suspected MCA occlusion.⁶ Clinically eligible patients ($n = 474$) were required to undergo screening catheter angiography. Of those, only a minority ($n = 180$) qualified for trial enrollment and randomization, whereas most patients ($n = 294$) were excluded simply because the suspected occlusion was not confirmed by the angiogram or was present but in a different anatomical location than originally suspected. Such a high number of patients excluded from enrollment can be explained by the relatively mild symptoms required to qualify for angiography in the trial. The minimum NIHSS score to qualify for trial enrollment in PROACT II was set at 4.

Subsequent studies have generated concerns regarding the suboptimal predictive value of the NIHSS score in identifying patients with large-vessel occlusion, especially those who present after a longer interval from symptom onset to clinical evaluation.^{25,39} In a prospective cohort study of 699 patients with symptoms consistent with acute ischemic stroke, CTA demonstrated significant overlap in the range of stroke severity (measured by NIHSS score) in patients with and without occlusion of a proximal vessel, confirming that NIHSS score alone is an unreliable predictor for larger vessel occlusion when selecting patients for endovascular interventions.¹⁸ The study investigators estimated that the NIHSS score threshold of 10 would result in almost equal numbers of patients with and without large-vessel occlusion (meaning that almost 50% of patients with an NIHSS score of 10 would not have large-vessel occlusion but instead have stroke from other causes). Only higher NIHSS score was a reliable predictor: large-vessel occlusion was found in 90% of cases with an initial NIHSS score ≥ 16 , and an NIHSS score of 27 was 100% predictive of a proximally located occlusive lesion amenable to endovascular intervention.

Evolution of Endovascular Stroke Technology

A review of prospective trials of intraarterial stroke therapies since 1999 demonstrated a significant improvement in recanalization rates over the last 2 decades.⁴ The most recent trials, which included the use of stent-retriever technology, reported successful recanalization in approximately 85% of cases, compared with recanalization rates of only 50% with earlier technologies (such as pharmacological thrombolysis or mechanical thrombectomy with the Merci retriever [Stryker]). Figure 1 illustrates different endovascular approaches to stroke treatment.

Several grading systems have been developed to describe revascularization during neurointervention on the basis of cerebral angiography findings.^{38,41} The two most commonly used are Thrombolysis in Myocardial Infarction (TIMI) and Thrombolysis in Cerebral Infarction (TICI). The TIMI grading system was originally developed to assess the degree of cardiac reperfusion during interventions for acute myocardial infarction and subse-

quently was applied to neurointerventions.³⁷ The TICI grading system was a modification of the TIMI scale developed specifically for the intracranial circulation.¹⁰ Grades in both systems range from 0 (no recanalization/reperfusion) to 3 (complete recanalization/reperfusion), but TICI allows more detailed description of partial recanalization and a greater reperfusion range: none to minimal limited to the parent artery (TICI Grade 0 or 1), partial reperfusion beyond the occlusion site (TICI Grade 2a), near-complete or more than 50% reperfusion beyond the occlusion site (TICI Grade 2b), or complete (TICI Grade 3). Figure 2 provides examples of cerebral angiographic runs corresponding to different degrees of the TICI scale.

Pharmacological intraarterial thrombolysis was the first endovascular strategy that was extensively studied for acute ischemic stroke treatment (Fig. 1A). In PROACT II, partial or complete recanalization occurred in 66% of cases of acute MCA occlusion treated with this approach.⁶ However, complete recanalization (TIMI Grade 3, which is strongly associated with the best clinical outcomes) was observed in only 19% of patients, indicating the overall poor efficacy of intraarterial pharmacological thrombolysis for these lesions. Occlusions within the ICA terminus segment (which are most resistant to treatment with intravenous thrombolysis³⁴) were excluded from this study.

Mechanical thrombectomy with the Merci retriever truly revolutionized endovascular treatment of acute stroke (Fig. 1C). This device was prospectively evaluated in the Mechanical Embolus Removal in Cerebral Ischemia (MERCi) and in multi-MERCi trials in patients with intracranial occlusion of the anterior or posterior circulation, including the most challenging ICA terminus and basilar occlusions.^{35,36} The trials showed a strong correlation between good clinical outcome and successful recanalization. Because these studies were single arm in design, they did not directly compare outcomes of thrombectomy with the Merci retriever with other endovascular approaches.

In 2008, the FDA granted approval for a second endovascular device—the Penumbra aspiration system (Penumbra, Inc.)—which is based on the principle of clot aspiration through a reperfusion catheter coupled with mechanical breakdown of the clot with separators of various sizes (Fig. 1D). Similar to studies evaluating the Merci device, the Penumbra system was evaluated only in a single-arm prospective study, the Penumbra Pivotal Stroke trial.²⁷ The Merci retriever and the Penumbra aspiration system were the main tools in the arsenal of stroke neurointerventionists until recently, when newer devices called stent retrievers showed superiority over earlier technology and instantly became the dominant device in the neurointerventional suite.

Stent retrievers work by temporarily deploying a stent that captures the thrombus and at the same time instantly restores blood flow to the affected brain territory by displacing the clot peripherally against the artery wall, a concept called “temporary endovascular bypass” (Fig. 1E). The ability to obtain rapid recanalization in the setting of acute stroke was first demonstrated with permanently deployed intracranial stents in the Stent-Assisted

FIG. 1. Illustration of different approaches to intraarterial (IA) treatment of patients with acute stroke due to large-vessel occlusion. An intracranial vessel with occlusive thrombus is shown. **A:** Intraarterial pharmacological thrombolysis is done by injecting a thrombolytic agent through a microcatheter directly into the clot. **B:** Microwire manipulation breaks down the clot into smaller particles. **C:** Mechanical thrombectomy with the Merci retriever works by wrapping around and capturing the clot. **D:** Aspiration thrombectomy using the Penumbra aspirator and separator breaks down the clot under constant negative pressure. **E:** A stent retriever (Solitaire or Trevo) allows capture of the thrombus and instant restoration of blood flow. Both the stent and clot are then retrieved together. Copyright University at Buffalo Neurosurgery. Published with permission.

Recanalization in acute Ischemic Stroke (SARIS) trial, in which the median time from procedure onset to successful recanalization was only 45 minutes.¹⁶ With stent retrievers, both the thrombus and stent are retrieved after flow restoration, thus eliminating the need for the dual antiplatelet therapy that is typically required with intracranial stent implantation.

Two randomized trials comparing the Merci retriever with the Solitaire FR (Covidien) (SOLITAIRE With the Intention For Thrombectomy [SWIFT] trial) and the Trevo (Stryker) (Thrombectomy Revascularization of Large Vessel Occlusions in Acute ischemic stroke [TREVO 2] trial) stent retrievers in patients treated within 8 hours of symptom onset demonstrated higher recanalization rates and significantly improved clinical outcomes in patients treated with the stent retrievers (Table 1).^{24,33} In the SWIFT trial, a remarkable 58% of patients achieved good neurological outcome at 3 months, compared with only 33% of patients in the Merci group, an almost 2-fold magnitude of difference.³³ At the same time, mortality rates were lower in the Solitaire group than in the Merci group

(17% and 38%, respectively). On the basis of these results, the FDA granted approval of the Solitaire FR and Trevo stent-retriever devices for treatment of stroke due to large-vessel occlusion.

IMS III Trial

The IMS III trial tested the hypothesis that a combined intravenous-intraarterial approach (“bridging”) to recanalization of acute stroke is superior to intravenous thrombolysis alone (Table 1).¹ Intravenous rtPA had to be administered within 3 hours of stroke symptom onset. This is the largest randomized stroke trial conducted so far, with an enrollment of 900 subjects planned to demonstrate the superiority of the combined approach.

After the first 656 participants had been enrolled, the study was halted because an interim analysis demonstrated futility, that is, a low likelihood of finding a significant difference between the two treatment groups. The main finding of the trial was similar (3-month clinical outcomes in the two groups). There were no major safety

FIG. 2. Examples of the TICl score in a case of proximal MCA occlusion. From left to right: TICl 0 shows no recanalization/reperfusion of the primary occluded vessel (arrow). TICl 1 shows partial reperfusion beyond the initial occlusion but not filling of distal MCA branches. TICl 2a and TICl 2b correspond to partial (< 50%) and near-complete (> 50% but less than full) reperfusion beyond the occlusion site, respectively. TICl 3 indicates complete reperfusion of the entire MCA territory.

concerns; the rates of symptomatic intracranial hemorrhage (the most feared complication of revascularization in acute ischemic stroke) and death were similar between the groups.

Documentation of large-vessel occlusion on noninvasive imaging was not incorporated in the original IMS III protocol, and an NIHSS score of 10 or higher was used for screening purposes. Only after 284 patients had been enrolled did a protocol modification allow CTA so that the investigators could exclude patients with severe neurological deficits in the absence of a target lesion amenable to endovascular intervention. As discussed earlier, the NIHSS score alone is not an accurate enough predictor of large-vessel occlusion, allowing patients without large-vessel occlusion (meaning those without a target for intraarterial therapy) to mistakenly enter the trial. This resulted in 20% of patients enrolled in the endovascular arm having no large-vessel occlusion on angiography and therefore not receiving any endovascular therapy, yet those patients were considered in the endovascular treatment arm for trial purposes. In a subgroup analysis of patients with confirmed large-vessel occlusion, intravenous rtPA plus endovascular therapy was significantly better in terms of recanalization and outcomes than intravenous rtPA alone ($p = 0.01$) (AM Demchuk, presented at the International Stroke Conference, 2013).

Despite the investigators' attempts to stay abreast of rapidly evolving endovascular stroke technology by incorporating new-generation devices as FDA clearance was obtained, of the 334 patients randomized to and receiving endovascular therapy, only 5 were treated with stent retrievers, that is, the technology associated with the highest reperfusion rates. Most patients in the endovascular arm received pharmacological intraarterial thrombolysis or thrombectomy with the Merci retriever, 2 approaches that are currently considered antiquated for endovascular stroke intervention.

The IMS III trial also suffered from a significant delay of more than 2 hours between initiation of intravenous

rtPA and intraarterial therapies, which was longer than in the earlier IMS I and IMS II trials and potentially diminished the clinical effect of intraarterial interventions. As expected, the shorter time from the administration of intravenous rtPA to the beginning of intervention was associated with a direction of effect toward better outcomes in IMS III. These issues raise serious concerns regarding relevance of the trial to endovascular stroke treatment as practiced today.

SYNTHESIS Expansion Trial

In the randomized SYNTHESIS Expansion trial, endovascular therapy for ischemic stroke performed within 4.5 hours of symptom onset was compared with intravenous thrombolysis alone (Table 1).³ However, unlike the IMS III trial, patients who were randomized into the endovascular arm of this trial were directly treated with intraarterial therapies (no previous "bridging" protocol). Similar to the results of IMS III, there were no significant differences in safety (rates of intracranial hemorrhage and death) or long-term outcomes between the two treatment approaches.

Again, the trial protocol did not include confirmation of large-vessel occlusion by noninvasive imaging (such as CTA or MRA) before randomization, allowing patients with strokes due to other mechanisms (such as lacunar strokes) to mistakenly enter the trial. Moreover, a minimal NIHSS threshold for study enrollment was not defined in the trial protocol.

More concerning is that intraarterial thrombolysis was allowed even in cases in which angiography showed no occlusion; rtPA was injected into the vascular territory that was presumably affected. This practice would inevitably include patients with strokes due to small-vessel disease. This population responds better to intravenous rtPA and is not considered appropriate for intraarterial therapy by most practitioners. Unfortunately, angiographic assessment of perfusion deficit pre- and postintervention

TABLE 1: Recently published randomized trials of acute stroke therapies*

Trial	Trial Arms	Key Selection Criteria	Types of Endovascular Therapy	Conclusions
IMS III	1) IV rtPA; 2) IV rtPA+endovascular	NIHSS score ≥ 10 in patients w/o CTA/ MRA & NIHSS ≥ 8 in patients w/ CTA/ MRA showing anterior/posterior large-vessel occlusion	IA rtPA, MicroSonic SV infusion system, Merci retriever, Penumbra System, Solitaire FR stent retriever	no difference in good neurological outcome (mRS score 0–2), symptomatic ICH, or mortality
MR RESCUE	1) good penumbral pattern & thrombectomy; 2) no penumbral pattern & thrombectomy; 3) good penumbral pattern & medical therapy (antiplatelet); 4) no penumbral pattern & medical therapy (antiplatelet)	stroke onset ≤ 8 hrs, NIHSS score 6–29, anterior circulation large-vessel occlusion on MRA/CTA, infarct core on perfusion imaging ≤ 90 ml, & penumbral mismatch $\leq 70\%$	Merci retriever, Penumbra system	no difference in good neurological outcome (mRS score 0–2) among all 4 groups; smaller final infarct vol in good penumbral pattern groups
SYNTHESIS Expansion	1) IV rtPA; 2) endovascular	no defined NIHSS threshold/cutoff; confirmation of large-vessel occlusion before intervention was not required	wire manipulation, IA rtPA, Merci retriever, Penumbra system, stent retrievers; if no large-vessel occlusion on angiography, IA rtPA could still be administered	no difference in good neurological outcome (mRS score 0–2), symptomatic ICH, or mortality
SWIFT	1) stent-retriever thrombectomy; 2) mechanical thrombectomy	NIHSS score 8–29 & stroke onset ≤ 8 hrs w/ anterior/posterior large-vessel occlusion	Solitaire FR device (stent-retriever arm); Merci Retrieval system (mechanical thrombectomy arm)	improved good neurological outcome (mRS score 0–2 or NIHSS improvement by ≥ 10 points), recanalization, & lower mortality w/ Solitaire FR
TREVO 2	1) stent-retriever thrombectomy; 2) mechanical thrombectomy	NIHSS score 8–29 & stroke onset ≤ 8 hrs w/ anterior/posterior large-vessel occlusion	Trevo Retriever (stent-retriever arm), Merci Retrieval system (mechanical thrombectomy arm)	improved good neurological outcome (mRS score 0–2) & recanalization w/ Trevo; similar mortality rates

* FR = flow restoration; IA = intraarterial; ICH = intracranial hemorrhage; IMS = Interventional Management of Stroke; IV = intravenous; MR RESCUE = Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy; mRS = modified Rankin scale; NIHSS = National Institutes of Health Stroke Scale.

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tion was not provided in the trial. Of 181 patients in the endovascular arm, stent retrievers were used in only 23 patients (13%); most patients in this arm were treated with wire manipulation and local thrombolysis—treatment that is no longer considered the standard for endovascular stroke interventions.

MR RESCUE Trial

The MR RESCUE trial tested the hypothesis that a favorable neuroimaging (“penumbral”) pattern can identify patients likely to achieve greater benefit from endovascular treatment of acute stroke (Table 1).¹⁵ Patients with confirmed large-vessel occlusion were randomized to receive endovascular treatment or standard medical treatment within 8 hours of ischemic stroke symptom onset on the basis of the presence of a favorable penumbral pattern. A favorable penumbral pattern was defined as a difference between predicted brain tissue at risk (perfusion defect) and infarcted core with irreversible damage constituting up to 70% of at-risk area (diffusion defect). The final results showed similar outcomes in the two groups, arguing against the “penumbra” hypothesis in patient selection for endovascular therapies.

Randomization of patients with an infarct core volume as large as 90 ml was permitted. Such high volumes of infarcted core are associated with poor outcomes following revascularization, which raises the argument that the design of the MR RESCUE trial allowed the inclusion of cases that potentially would not have benefited from revascularization, even if they were technically successful.^{30,40}

The study randomized patients into 4 groups based on perfusion results (penumbral vs nonpenumbral) and type of treatment (standard medical vs endovascular), with 20–34 patients in each group. Such a small number of patients in each group likely underpowered this trial, which should also be considered when interpreting the data.

It should be noted that stent retrievers were not included in the endovascular arm. An angiographically successful outcome was defined as TICI Grade 2a or 3 revascularization. A TICI Grade 2a corresponded to only partial reperfusion of the affected territory (Fig. 2). Only 27% of patients were able to achieve a TICI Grade 2b or 3 (perfusion over two-thirds of the affected territory or full perfusion, respectively), which would indicate more robust reperfusion, arguing that effective recanalization was not achieved in most patients in the endovascular group, regardless of a penumbral imaging pattern. Distinguishing between these degrees of recanalization is clinically important. For example, partial (TICI Grade 2a) versus near-complete (TICI Grade 2b or 3) intraarterial reperfusion has significant implications for both infarct volumes and clinical outcomes; better reperfusion rates directly correlate with smaller final infarct volume and improved clinical outcomes.¹²

Lessons Learned

What have we learned from these latest three trials of endovascular treatment of acute stroke? The trials confirmed a strong association between the degree of successful revascularization and improved clinical out-

comes, which was demonstrated earlier by a meta-analysis of acute stroke trials that included various intravenous and intraarterial therapies.²⁸ They confirmed the importance of achieving rapid reperfusion and that minimizing delays from symptom onset to reperfusion time can lead to better patient outcomes. Finally, the trials demonstrated similar safety profiles of intravenous and intraarterial reperfusion therapies, including intracranial hemorrhage rates, which were thought to be much higher with endovascular approaches in the past.

However, these three trials do not demonstrate failure of endovascular therapy for acute stroke. They do not reflect modern standards of intraarterial revascularization in patients with acute stroke. Evaluation for large-vessel occlusion with noninvasive imaging is currently recommended by many practitioners for all patients with acute stroke considered for emergency endovascular interventions,¹¹ yet the IMS III¹ and SYNTHESIS Expansion³ trials did not require such screening prior to enrollment and randomization.

A subgroup analysis of the IMS III trial that included only patients with confirmed large-vessel occlusion showed a benefit of endovascular therapy over intravenous rtPA alone.³ Although consideration of acute stroke patients for intraarterial therapies based on NIHSS score and noncontrast brain CT results alone might have a benefit of minimizing timing from symptom onset to reperfusion, it cannot be an acceptable standard in clinical trials. Randomized controlled trials can be considered the benchmark when comparing safety and efficacy of therapeutic interventions only when the treatment groups are appropriately selected to ensure the trial’s validity and accuracy. Moreover, with modern imaging technology, CTA can be rapidly performed at the time of the first noncontrast CT scan without further delays and with a relatively low radiation and contrast dose. Current acute stroke management guidelines support the use of CT or perfusion MRI along with diffusion-weighted MRI for estimation of the size of irreversibly infarcted area and ischemic penumbra, especially when considering patients for endovascular therapies beyond the standard time window for intravenous thrombolysis.¹¹

The three trials in question also underscore practical issues encountered when evaluating rapidly evolving technology. Stent retrievers have been shown to be more effective in achieving revascularization than previous mechanical and pharmacological devices. Nevertheless, the proportion of patients treated with stent retrievers in the recent three trials was so small that it would be deceptive to interpret the results of those trials as a reflection of modern practice. In combining these three trials together, only 28 (5%) of 579 patients treated with various endovascular approaches were treated with stent retrievers. At the most recent American Academy of Neurology annual meeting, results from the North American Solitaire acute stroke registry were presented, specifically focusing on cases of acute stroke treated with intravenous thrombolysis followed by Solitaire FR stent retrieval (OO Zaidat, presented at the American Academy of Neurology Annual Meeting, 2013). Outcomes from this IMS III–like cohort were compared with results from the intravenous

thrombolysis—only group in the IMS III trial, and better clinical outcomes were found in patients treated with a combination of intravenous rtPA and stent retrievers. Although comparison of these two studies has limitations and should be interpreted with caution, it suggests that recent technology—which was not adequately studied in the trials in question—may play a critical role in acute stroke endovascular therapy.

The current uncertainty regarding the role of endovascular therapy in acute stroke is reminiscent of the evolution of percutaneous cardiac interventional procedures for myocardial infarction; after numerous trials and tribulations, it was not until newer-generation devices became available that the interventional approach became the accepted treatment of acute myocardial infarction. Although coronary and cerebral reperfusion therapies share common patterns, cerebral reperfusion therapies are advancing at a slower pace.²⁶ The use of stent-retriever technology is the first treatment capable of showing higher and more complete reperfusion rates, comparable to coronary interventions for myocardial infarction.³²

What lessons have we learned to ensure that future stroke trials will definitively answer the questions regarding the value of intraarterial stroke therapies? To ensure appropriate selection of patients, all potential candidates should undergo a baseline CTA or MRA evaluation to document the presence and extent of large-vessel occlusion. Clot characteristics, including length and composition, are important indicators of recanalization after intravenous thrombolysis and can be used as biomarkers in selecting patients with a higher likelihood of benefit from the intraarterial approach.^{22,29} All attempts should be made to minimize delays from stroke symptom onset to achievement of successful reperfusion. Stent retrievers should be the first-line treatment device used in clinical trials, given their clear benefit in achieving faster, more robust reperfusion and improved clinical outcomes. Newer-generation devices such as large-bore catheters delivered intracranially with direct clot aspiration through direct carotid artery puncture techniques may further enhance clot retrieval speed and efficacy. Finally, advances in imaging technology involving perfusion analyses using CT or MR methodologies with more reasonable “favorable penumbral patterns” are constantly improving our ability to identify those patients who are more likely to benefit from acute stroke interventions.⁵

Several ongoing clinical trials have incorporated such key selection points in their design. For example, The Randomized, Concurrent Controlled Trial to Assess the Penumbra System’s Safety and Effectiveness in the Treatment of Acute Stroke (THERAPY) is evaluating the efficacy of the Penumbra System as adjunctive therapy to intravenous thrombolysis in the setting of arterial occlusion with a large clot burden (clot length > 8 mm) to identify patients who are unlikely to respond to intravenous thrombolysis alone (ClinicalTrials.gov identifier NCT01429350). The Solitaire FR With the Intention For Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke (SWIFT-PRIME) trial is examining whether combining Solitaire FR stent-retriever thrombectomy with intravenous thrombolysis improves clinical

outcomes (ClinicalTrials.gov identifier NCT01657461). Patients with a favorable imaging pattern based on an MR or a CT perfusion study are selected for this trial, and the protocol is designed to minimize the time interval between imaging and angiography.

The PerfusiOn Imaging Selection of Ischemic STroke Patients for EndoVascular Therapy (POSITIVE) trial will be launched soon (ClinicalTrials.gov identifier NCT01852201). Instead of testing a specific endovascular device, it will allow utilization of multiple endovascular approaches, including stent retrievers. Device use alone or in combination with other devices will be determined by the treating interventionist on a case-by-case basis and will be compared with standard medical therapy with antithrombotic agents in patients with acute stroke due to large-vessel occlusion. The trial will include patients with a favorable perfusion pattern within 12 hours of stroke onset, significantly extending the time window for patient enrollment in comparison with previous trials. Treatment of strokes with unknown time of onset or so-called “wake-up” stroke is another promising direction of endovascular stroke therapy. Emerging data suggest that intravenous thrombolysis in carefully selected wake-up stroke patients might be safe and effective.^{19,20} Such patients, most of whom are excluded from intravenous thrombolysis in daily clinical practice, may prove to be excellent candidates for future endovascular stroke trials.

We encourage investigators from all involved fields to join efforts in developing more effective strategies for the treatment of acute stroke. Endovascular approaches to stroke treatment will continue to evolve and so will continue to improve our capabilities to help patients suffering from this devastating condition.

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