

## Endovascular Therapy in Acute Ischemic Stroke Challenges and Transition From Trials to Bedside

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**R**apid and effective revascularization is the mainstay of acute ischemic stroke treatment. Until recently, intravenous recombinant tissue-type plasminogen activator (r-tPA) was the only established therapeutic option. Five recently published trials have now proven the benefit of endovascular treatment, changing dramatically the evaluation and treatment of acute ischemic stroke.<sup>1-5</sup> Thrombectomy with stent retrievers is now recommended as the standard of care for acute ischemic strokes with a proximal large vessel occlusion in the anterior circulation.<sup>6,7</sup> In this article, we review the current evidence on endovascular therapy in acute ischemic stroke and discuss the major challenges in the implementation of this therapy. We address the challenges of the generalizability of trial results to different patient populations, implementation of endovascular therapy in the acute setting for large populations within various geographical contexts, and approaches to evaluating future innovations in the field of neuroendovascular care.

### Lessons From Current Evidence

The 4 pillars of successful revascularization with endovascular therapy to achieve a good clinical outcome are the following:

1. Rapid neurovascular imaging is critical to identify the eligible patient. All 5 positive randomized controlled trials used varying imaging selection criteria, including a minimum of a noncontrast computed tomography (CT)

head to identify a small core using the Alberta Stroke Program Early CT score (ASPECTS) score and a computed tomography (CT) angiography of the head and neck to ascertain a proximal vessel occlusion.<sup>8</sup> Vascular imaging also serves the interventionalist for planning the endovascular procedure.

2. Retrievable stents are safe and effective. Retrievable stents were used in the large majority of patients in all 5 trials with reported number needed to treat of 2.5 to 7 for an independent outcome at 90 days across the trials. Moreover, patient safety was preserved with very low overall procedural complication rates.
3. Time is brain. Analogous to the onset-to-treatment time lessons with intravenous r-tPA, time to endovascular treatment is critical. Much has been learned about workflow from the previously published endovascular trials.<sup>9-11</sup> Improved clinical outcomes are observed with decreased time to reperfusion.<sup>12</sup> The recent 5 positive trials had broad inclusion criteria, randomizing patients  $\leq 12$  hours after stroke onset, but the median stroke onset to groin puncture time was  $<4.5$  hours in all trials, and time to recanalization was  $<6$  hours.
4. Intravenous r-tPA remains the standard of care. All eligible patients in the trials received intravenous r-tPA with a percentage ranging from 73% to 100%. The combination of intravenous and endovascular therapy for revascularization did not raise any safety concerns. However,

Received September 10, 2015; final revision received November 23, 2015; accepted November 25, 2015.

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The opinions expressed in the article are not necessarily those of the editors or of the American Heart Association.

Guest Editor for this article was Emmanuel Touzé, PhD.

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(*Stroke*. 2016;47:548-553. DOI: 10.1161/STROKEAHA.115.011426.)

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*Stroke* is available at <http://stroke.ahajournals.org>

DOI: 10.1161/STROKEAHA.115.011426

intravenous r-tPA has limited efficacy for early recanalization in the context of large vessel occlusion (31% showed recanalization on CT angiography performed at 2–8 hours within the Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times (ESCAPE) trial and only 7% before angiography in the intervention group).<sup>2,13</sup> Although it remains relevant and important to give intravenous r-tPA to obtain early reperfusion, parallel processing to avoid delays in endovascular therapy is critical. The crucial metric is time from neuroimaging to reperfusion.<sup>14</sup>

## Exploring the Edges of Evidence and Special Populations

As in other fields of medicine, randomized controlled trials results need to be judiciously applied to individual patients. Although some cases represent natural extrapolation of the evidence, other situations are more distinct (Table). We discuss 4 situations where the evidence is not entirely clear.

### The Very Young and the Very Old

Generalizing a trial result to patients at the extremes of age is challenging. Subgroup analysis of the very elderly patients ( $\geq 80$  years) in the recent trials did not reveal any heterogeneity of the treatment effect. In one trial, a large mortality benefit was seen in this subgroup (24% reduction in 90-day mortality in ESCAPE). Despite the inherent limitations of subgroup analysis, this suggests that older age alone should not be an exclusion criterion. Rather, a more holistic evaluation of the patient and their pre-morbid status is desired. At the other extreme, almost no evidence exists concerning the efficacy of endovascular therapy in stroke in the very young population. Stroke is a disabling cause of acute neurological deficits in the pediatric population. A recent publication highlights the long-term disability after stroke, arguing that the preconceived notion that children have a better recovery after stroke because of brain plasticity may not hold true, at least compared with other young adults.<sup>15</sup> A few recently published observational studies with a small number of patients suggest that endovascular therapy may be a reasonable therapeutic approach in well-selected cases of stroke in the very young.<sup>16,17</sup> Moreover, special consideration must be given to the underlying pathophysiology, often dissimilar to adult stroke. These include inherited thrombophilia and metabolic disorders, local vasculitis, congenital heart disease, and other acquired conditions (malignancy-associated hypercoagulable state or dissection). Finally, because of body size, endovascular treatment of a 1-year-old baby will require a different set of skills than treating a 15-year-old teenager.

### Eligibility by Time and by Imaging

Mechanical thrombectomy  $\leq 6$  hours after symptom onset is the new standard of care. However, when faced with the scenario of a patient presenting at 10 hours after symptom onset who fulfills the imaging and clinical criteria, should this patient be offered endovascular treatment? Does time of onset or neuroimaging determine patient eligibility for endovascular treatment?

**Table. Scenarios for Thrombectomy Where Evidence Is Sparse**

The extremes of ages (pediatric and very elderly population)
Mild stroke
Stroke with delayed presentation or unknown onset
Ischemic stroke with distal occlusions
Ischemic stroke of the posterior circulation
Conscious sedation versus general anesthesia
Optimal approach to tandem intracranial and extracranial occlusions
Periprocedural blood pressure and antiplatelet management

The best answer would be a combination of both features. The ischemic tissue core grows with time. Based on this principle, all 5 recent trials expanded their inclusion criteria beyond the 4.5 hour intravenous r-tPA window.<sup>1–5</sup> ESCAPE was the only trial that included a sizeable number of patients beyond 6 hours,  $\leq 12$  hours from last seen normal based on imaging criteria of CT head showing small- to moderate-sized core (ASPECT $>5$ ) and good collateral circulation on preferably multiphase CT angiogram.<sup>18</sup> Forty-nine participants were randomized beyond 6 hours. There was a trend towards benefit with endovascular treatment in the 6- to 12-hour window (common odds ratio [cOR] 2.3 95% confidence interval [0.8–6.8]) without an increase in adverse effects, but the trial was not powered to assess statistical significance in this subgroup.<sup>2</sup> The exclusion of patients with poor collaterals and large ischemic cores from the trials makes it difficult to make firm conclusions about the interaction of neuroimaging findings with treatment effect. Newer trials that use imaging selection in the extended time windows, such as the Trevo and Medical Management Versus Medical Management Alone in Wake Up and Late Presenting Strokes (DAWN trial, Clinical Trials Identifier NCT02142283) may answer the question of whether stroke patients should be treated based on a time versus tissue window paradigm.

### Tandem Extracranial and Intracranial Lesions

One interesting finding is that patients with cervical carotid artery occlusive lesion in addition to the intracranial occlusion showed a dramatic treatment effect. The ESCAPE trial and the Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours (REVASCAT) trial showed, respectively, cOR 9.6, 95% confidence interval [2.6–35.5] and cOR 4.3, 95% confidence interval [1.5–12.5] in favor of the endovascular treatment arm in this subgroup ( $n=40$ ).<sup>2,5</sup> Despite this remarkable benefit from intracranial thrombectomy, the optimal management of the cervical carotid artery occlusion is still unclear. Essentially, there are 3 different approaches, including (1) bypassing the lesion and conducting a formal assessment for revascularization by carotid endarterectomy or carotid artery stenting at a later time, or (2) immediate angioplasty and stenting of the lesion before attending the intracranial occlusion, or again (3) recanalization of the intracranial lesion first followed by angioplasty and stenting of the cervical carotid lesion before ending the procedure. The efficacy and safety of periprocedural antiplatelet management of patients with carotid artery

stents is also uncertain. It is possible that a meta-analysis of the trials may answer this question. A randomized clinical trial with several treatment arms may be needed to determine the ideal management for this subgroup.

### Mild Strokes, Distal Occlusions, and Posterior Circulation

The management of patients with proximal vessel occlusion and very low National Institutes of Health Stroke Scale (NIHSS) score has not yet been definitively answered by the current trials.<sup>1-5</sup> This is an extremely challenging clinical scenario in acute stroke therapy. Most enrolled patients had moderate to severe strokes based on clinical assessment (NIHSS score >5). The Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) trial had a more pragmatic approach and included patients with NIHSS score  $\geq 2$ . To add another layer of complexity, the NIHSS may not capture all clinically meaningful deficits.<sup>19</sup> For instance, the NIHSS is biased to score left hemisphere strokes higher compared with the right hemisphere. Yet, the effect on functional outcomes at 90 days may be greater with right hemisphere lesions.<sup>20</sup> Indeed, minor strokes have been shown to be disabling, with one in 4 patients being unable to return home and one in 10 requiring nursing home.<sup>21,22</sup> Pathophysiologically, the mismatch between clinically mild symptoms and a proximal occlusion can be explained by cerebral perfusion through collaterals or through forward flow through a permeable thrombus. However,  $\leq 20\%$  of these patients will suffer recurrence or progression of symptoms, whether it is because of clot propagation, inadequate collateral circulation, or hemodynamic fluctuations.<sup>23,24</sup> From a practical perspective, patients with large-vessel occlusions, such as the proximal middle cerebral artery, and mild symptoms are not common. Currently, the evidence is indeterminate. Rigid, threshold-based decision-making on the NIHSS should be eschewed in favor of case-by-case decision of the clinical team based on age, imaging factors, eloquence of brain involved, ease of access, skill, and comfort of the interventionist. The Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial (EXTEND IA) and Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment (SWIFT PRIME) trials used CT perfusion to identify a small infarction core.<sup>3,4</sup> Patients with mild symptoms may particularly benefit from such imaging to further understand the perfusion mismatch to guide therapy.

Similarly, there is limited evidence for endovascular therapy with distal occlusions beyond the proximal M1 segment of the middle cerebral artery. These represent a heterogeneous group of situations because of variable arterial anatomy: the affected brain territory and clinical deficits will have high variance. Moreover, distal occlusions are typically associated with smaller clots with a higher chance of response to intravenous r-tPA.<sup>25,26</sup> Some cases of M2 occlusions can be associated with high stroke severity. Patients with M2 occlusions with high NIHSS would seem a more appropriate endovascular candidate than those with milder symptoms.<sup>27</sup> Moreover, the current generation of endovascular devices are adapted for proximal M1 occlusion, allowing for concomitant proximal occlusion and suction. Necessarily, they

may have a different safety and efficacy profile for the distal occlusions. A significant number of M2 occlusions were enrolled among the published endovascular trials. Pooled analysis may shed light into the benefit of thrombectomy in this population. Improvement in technology is also likely to make distal occlusions more amenable to safe thrombectomy.

Finally, definitive evidence is still lacking for treatment of posterior circulation occlusions. Acute treatment of basilar artery occlusions is a delicate situation because the brain stem is such an eloquent part of the central nervous system that a small volume of infarct can have devastating clinical repercussions. Moreover, basilar thrombus may have a better chance to respond to intravenous r-tPA because the thrombolytic can act on both ends of the clot. Nevertheless, data from the International Multicenter Registry for Mechanical Recanalization Procedures in Acute Stroke (ENDOSTROKE) study group, a 148-patient multicenter registry, suggest that the use of a retrievable stent is a predictor of good outcome.<sup>28</sup> Recruitment is still ongoing in the phase III randomized controlled trial addressing this issue.<sup>29</sup>

### Quality of Recanalization/Reperfusion

In the current trials, reperfusion results were presented in a dichotomous fashion merging the modified Thrombolysis in Cerebral Infarction (mTICI) scale 2B, defined as partial filling visualized in  $\geq 50\%$  of the vascular territory and mTICI 3, representing complete reperfusion with normal filling. Technically, this is a very wide range of recanalization. We have previously proposed mTICI 2C as an additional stratum of recanalization for cases with near-complete perfusion except for slow flow in a few distal cortical vessels or small distal cortical emboli.<sup>30</sup> Patients with mTICI 2C have better clinical outcome compared with mTICI 2B.<sup>31</sup> The problem of what represents good recanalization remains. What is the interventionist's endpoint? During an intense emergency procedure, perfection can be the enemy of good. Aiming for perfect reperfusion may increase the chance of complications. There are aspects of good reperfusion which are likely to be related to presence of an occlusion that is amenable to further improvement by achieving recanalization, whereas there are likely other aspects, such as absence of salvageable brain in the area supplied by the vessel, that may result in poor perfusion irrespective of whether vessel occlusion is present or not.

### Implementation of the Current Evidence

We are faced with multiple implementation challenges.<sup>32</sup> First, effectively organized systems of care are essential to provide this treatment to eligible stroke patients as quickly as possible. Second, future technological innovations will affect the evolution of care. Third, analogous to other areas of medicine, there will be a tendency to use endovascular treatment beyond the current indications (eg, A2, M2 occlusion, beyond 6 hours from onset, etc). The optimal solution to manage this, whether through further randomized controlled trials or through well-implemented registries, remains uncertain. Fourth, the access and affordability of the treatment, which can be particularly relevant to the developing parts of the world, must be addressed.



National and international guidelines should be quickly adapted to the current developments and should be evidence-based. Good examples of a quick response are the updated American Heart Association and Canadian Best Practice guidelines.<sup>6,7</sup> We encourage the establishment of registries to capture the real-world application of endovascular treatment. Registration of patients undergoing interventions, their outcomes and complications, will assist in determining whether the treatment is as effective and safe in clinical practice as in trials. These registries should be national or international and independent of manufacturers. Initiatives are ongoing in the Netherlands and Europe (MR CLEAN and Safe Implementation of Treatments in Stroke [SITS] registries). New treatment approaches and indications should be tried, but should be well documented. Evidence-based guidelines will also help to indicate the boundaries of our knowledge and inference and, in this way, will help to define where new clinical trials are most helpful.

### Creating Effective Systems of Care

Acute stroke treatment in the era of endovascular therapy is a team sport with the players being, broadly speaking, coming from 4 distinct areas of expertise: (1) medical management, usually provided concurrently by the emergency department physician and a stroke team, occasionally requiring anesthesiology expertise, (2) clinical stroke and neurocritical care expertise, (3) imaging expertise, and (4) endovascular expertise. Parallel workflow, teamwork, and trust will allow for the speed to achieve target door to reperfusion times.<sup>14</sup> It is likely, as in other areas of medicine, that there will be a volume-by-outcome relationship. The minimal number of cases per center needed for good outcomes, as well as standard complication rates, need to be determined. Because of the expected volume-by-outcome relationship, we strongly feel that centralization of endovascular stroke care with 24×7 availability of a well-trained staff is necessary for excellence of care.

Another significant challenge to the creation of centralized endovascular centers is the prehospital identification of eligible patients. Paramedics involvement and training is crucial. Several prehospital screening scoring systems for stroke diagnosis and severity exist.<sup>33</sup> These need adaptation to the new clinical reality, which needs a quick and accurate assessment of the likelihood of an intracranial large artery occlusion. Current mobile stroke ambulance technology can also be adapted to include neurovascular imaging ability or to involve a trained physician at the scene through videoconferencing with the appropriate patient confidentiality standards. Because acute stroke presentations may in fact be nonvascular mimics, the best methods for prehospital identification of eligible patients remain to be determined for both optimal sensitivity and specificity.

Local geography, as well as variability, in population density also impact implementation of endovascular therapy. There is some evidence to suggest that making the diagnosis of a proximal large-vessel occlusion at the local stroke center and starting intravenous r-tPA before transfer to an endovascular center (drip and ship paradigm) produces revascularization delays compared with patients directly transferred to an endovascular center before neurovascular imaging (mothership

paradigm).<sup>2,34</sup> However, if transportation times to the endovascular center are prolonged, patients may benefit from stopping at the regional hospital for neurovascular imaging to avoid significant delays to intravenous r-tPA and to determine endovascular eligibility. The decision to go directly to the endovascular-capable center versus stop at the primary one depends on the likelihood of an intracranial occlusion, distance to regional hospital and intervention center, and the relationship between time and treatment effect. Established metrics, such as door to needle times, can help determine what diversion is appropriate. If an endovascular center is 30 minutes farther for the patient than the primary stroke center, but has a median door to needle time that is 30 minutes shorter, a strong case can be made to divert directly to the endovascular center without any intravenous r-tPA delays expected. Metrics should be established to monitor primary stroke centers. Cardiology uses the term door-in-door-out time to monitor this in acute myocardial infarction.<sup>35</sup> A door-in-door-out time ≤30 minutes may be required to make the drip-and-ship paradigm effective. Overall, we will need to regularly assess our treatment times and clinical outcome. This can be under the form of a registry or other innovative tools. Electronic visualization tools have been shown to improve door-to-needle and picture-to-puncture times.<sup>36</sup>

Financial issues arise with the establishment of preferential transportation paradigms. These are complex and require a political solution. Any time a patient goes directly to a tertiary center, the primary stroke center loses an opportunity to treat a patient. This can lead to financial and workload issues, affect ability to maintain case volumes and skill sets, and affect ability to attract qualified staff. Primary centers may be motivated to provide an endovascular stroke service. This can potentially lead to many relatively inexperienced low-volume centers, which will not be as effective in replicating the results of the trials. Because of the low volumes, they would struggle to maintain good workflow and efficiency, especially after hours, because a critical volume of patients is required to allow a sustainable call schedule. A potential solution to this issue is to establish collaborative networks on a regional basis. A shared-care model, such as drip and ship and ship back, acute interventional care could be offered at a single tertiary center with preestablished repatriation arrangements. This approach shares the cost and hospital income. In addition, it avoids overloading the tertiary center with stroke unit care and allows optimization of the use of stroke beds throughout a region.

### Innovation in the Endovascular Field

The field of endovascular therapy is ripe for innovation. We foresee further improvements in imaging with faster and higher quality CT head and CT angiography or emergence of a semi-automated computer-aided detection of large core and proximal vessel occlusion. Similarly for the endovascular procedure, there will likely be development of better simulation technologies to train interventionists on various anatomical scenarios. We look forward to further development in conscious sedation for procedure-related discomfort. General anesthesia has been associated with worse clinical outcome, whether secondary to revascularization delays or blood pressure fluctuations.<sup>37,38</sup> We support ongoing randomized

controlled trials, such as the Sedation Versus Intubation for Endovascular Stroke Treatment (SIESTA) trial, aiming specifically to answer the question on sedation in acute ischemic stroke patients.<sup>39</sup>

Ongoing innovations in endovascular technologies create new challenges. How do we effectively monitor new technologies against old ones? Is the fact that a particular new device got approval to sell (by using the 510K process by the Food and Drug Administration) sufficient for there to be open endorsement for the new device? How do we distinguish between minor modification (we call these version 1.1) and completely new devices (version 2.0)? Importantly, newer may not necessarily be better. These challenges of the assessment incremental technological evolution are not new and involve multiple stakeholders, including the treating physicians and teams, industry, regulatory authorities, payers, and patients. We, in the stroke community, will have an important role to play in determining the acceptable standard and answers to the questions above by designing appropriate studies or establishing registries.

In conclusion, in light of the recent positive trials making endovascular therapy the standard of care for acute ischemic stroke secondary to large vessel occlusion, we present 3 major challenges that need to be addressed. First, effective implementation of trial results across large populations; second, monitoring, encouraging, and approving only the new innovative therapies that result in further improvement in patient outcomes; and third, creating a framework to allow extrapolation of trial results to patient populations that were not tested in the trials. Finally, last but not the least, we wish to stimulate future discussions on increasing accessibility to endovascular therapy in developing nations. We call upon our colleagues in the field to take a proactive and innovative stance in providing guidance and influencing policy through creation of registries or active visualization, allowing feedback for reevaluation of target goals of outcomes.

### Disclosures

Dr Goyal has received research grants from Covidien for design and conduct of SWIFT PRIME trial. Also, Covidien provided partial funding of the ESCAPE trial to the University of Calgary. Dr Goyal has received honoraria from Covidien (significant) and Stryker (modest) for speaking engagements. Dr Goyal has a licensing agreement with GE Healthcare for further development of systems of stroke diagnosis (significant). Dr Davis has received honoraria from Boehringer Ingelheim (modest), BMS Pfizer (modest), and Covidien (modest). He has also served as a consultant for Boehringer Ingelheim (modest), BMS Pfizer (modest). Dr Hacke has received a research grant from Boehringer Ingelheim (significant). He has also received funds for speaking engagements from Boehringer Ingelheim (modest). He has also received honoraria from Covidien as Steering Committee fees (modest). He is a consultant to Neuravi (modest). Dr Hill has received research grant from Medtronic for the ESCAPE trial (grant given to University of Calgary; significant). He is a consultant to Merck for clinical trials (modest). Dr Yavagal has received honoraria from Covidien for participating in the SWIFT PRIME steering committee (modest). Dr Saver is an employee of the University of California. The University of California has patent rights in retrieval devices for stroke. Dr Saver has served as an unpaid site investigator in multicenter trials sponsored by Medtronic and Stryker for which the UC Regents received payments on the basis of clinical trial contracts for the number of subjects enrolled. Dr Saver received

stock options for services as a scientific consultant regarding trial design and conduct to Cognition Medical. Dr Saver receives funding for services as a scientific consultant regarding trial design and conduct to Medtronic/Covidien, Stryker, Neuravi, and Boehringer Ingelheim (prevention only). Dr Saver serves as an unpaid consultant to Genentech advising on the design and conduct of the PRISMS trial; neither the University of California nor Dr Saver received any payments for this voluntary service. Dr Murayama has received research grant from Stryker (significant). He is also a consultant from Stryker (significant). Dr Turjman is a consultant for Medtronic and Stryker. Dr Yoshimura received Speakers' Bureau/Honoraria from Tanabe-Mitsubishi, Sanofi, Boehringer Ingelheim, Bayer, and Otsuka Pharmaceutical Co. The University of California has patent rights in retrieval devices for stroke. Dr Demchuk received honoraria for continuing medical education and unrestricted grant to support the ESCAPE trial from Covidien. The other authors report no conflicts.

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KEY WORDS: acute ischemic stroke ■ endovascular therapy ■ stent ■ stent retriever ■ thrombectomy

## Endovascular Therapy in Acute Ischemic Stroke: Challenges and Transition From Trials to Bedside

Mayank Goyal, Amy Y.X. Yu, Bijoy K. Menon, Diederik W.J. Dippel, Werner Hacke, Stephen M. Davis, Marc Fisher, Dileep R. Yavagal, Francis Turjman, Jeffrey Ross, Shinichi Yoshimura, Zhongrong Miao, Rohit Bhatia, Mohammed Almekhlafi, Yuichi Murayama, Sung-Il Sohn, Jeffrey L. Saver, Andrew M. Demchuk and Michael D. Hill

*Stroke*. 2016;47:548-553; originally published online January 7, 2016;  
doi: 10.1161/STROKEAHA.115.011426

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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