Guest Editorial: Endovascular Treatment of Acute Ischemic Stroke: What's Next?

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Stroke remains the leading cause of long-term disability in the United States.[1] Strokes resulting from large-vessel occlusion are especially associated with poor prognosis and neurological outcomes. Currently, <1% of all stroke cases are treated with endovascular therapies. Intravenous thrombolysis is the only US Food and Drug Administration-approved treatment for acute ischemic stroke in the United States.

Compared with other areas of neuroendovascular therapies such as the treatment of aneurysms or vascular malformations, endovascular treatment of acute ischemic stroke is still at its inception. Within a very short period (only over the course of the last 10 years), we have witnessed a robust technical revolution in the design and principles of stroke thrombectomy approaches. What started with a set of limited tools that were often borrowed from other interventional laboratories such as cardiac or peripheral vascular interventional radiology suites has quickly led to the birth of a new field with specific devices designed explicitly for manipulations within the intracranial vessels such as highly trackable aspiration catheters and stent retrievers.

Randomized trials have now become the gold standard for evaluating the safety and efficacy of a particular drug or an intervention for subsequent US Food and Drug Administration approval in clinical practice. No clinical benefit of intra-arterial therapies was demonstrated by the 3 randomized trials of endovascular stroke therapies published in 2013 (Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy [MR RESCUE],[2] Interventional Management of Stroke [IMS] III,[3] and Synthesis Expansion: A Randomized Controlled Trial on Intra-Arterial vs Intravenous Thrombolysis in Acute Ischemic Stroke [SYNTHESIS Expansion][4]), which led some to question the future of such interventions. The limitations of these trials such as the lack of proper patient selection, the use of outdated devices resulting in incomplete recanalization and reperfusion, and significant delays to the initiation of intra-arterial therapy have been the subject of heated discussions among professional societies and clinicians.

Therefore, the outcomes of endovascular stroke trials relying on modern thrombectomy technology have been long anticipated. The first glimpse at the emerging data came from the 9th World Stroke Congress at which the preliminary results of the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) were announced (D. Dippel, "Results of the MR CLEAN Trial"; oral presentation given at the 9th World Stroke Conference; October 25, 2014; Istanbul, Turkey; http://www.controlled-trials.com/ISRCTN10888758). This trial compared outcomes in patients with large-vessel stroke treated with endovascular therapy (mostly stent retrievers) with outcomes in those treated with medical therapy, including patients treated with intravenous thrombolysis. Patients treated with intra-arterial interventions developed smaller strokes on follow-up imaging and demonstrated better functional outcomes at 90 days than patients treated with medical therapy alone.

Release of these exciting results had an explosive effect on the other ongoing endovascular stroke trials. Immediately after the release of the preliminary MR CLEAN results, the Data and Safety Monitoring Board (DSMB) of the Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke (ESCAPE) trial (another randomized trial comparing intra-arterial stroke therapy with medical management alone; http://clinicaltrials.gov/show/NCT01778335) performed an interim analysis of the available clinical data and decided to halt the study. At the time this article was being prepared for publication, the findings of the ESCAPE trial had not been released; thus, we can only speculate that the DSMB decision to stop further enrollment in the trial could have been due to the evidence of superiority of

endovascular therapy because there was no longer evidence of equipoise between the treatment efficacies.

The US-based trial Solitaire FR With the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke (SWIFT PRIME; http://clinicaltrials.gov/show/NCT01657461) has also been halted by the DSMB in light of the MR CLEAN results. A similar response is expected from the DSMBs of several other ongoing stroke trials in the United States. We are witnessing a fascinating domino effect in which outcomes of merely a single trial are affecting the entire neurointerventional and stroke communities worldwide, and we are anxiously awaiting the official results of the other trials. The significance of demonstrating that endovascular therapy saves lives and reduces disability cannot be underestimated. In the current financial climate of decreased reimbursements and escalating control of the healthcare system by insurance companies and the government, validation of the cost-effectiveness of endovascular stroke treatment is of critical importance. Changing the status of endovascular stroke therapy from experimental to recommended would also have profound implications for the organization of acute stroke care networks on both the national and local levels because comprehensive stroke centers further assume a leadership position in providing care for thrombectomy-eligible patients.

We can reliably conclude that current thrombectomy devices are faster and better than their predecessors in capturing and removing clots and opening intracranial vessels. With the use of modern stroke thrombectomy devices, successful recanalization and reperfusion rates now approach an impressive 80% to 95%.[5] As a result, good neurological outcomes are seen more frequently in patients treated with modern devices than early-generation devices, which was convincingly shown in the Thrombectomy Revascularization of Large Vessel Occlusions in Acute Ischemic Stroke (TREVO 2) and SOLITAIRE With the Intention for Thrombectomy (SWIFT) trials,[6,7] in which the Trevo (Stryker, Kalamazoo, Michigan) and Solitaire (Covidien, Irvine, California) stent retrievers were used. The current state of neurointerventional stroke therapies is reminiscent of the evolution of cardiac interventions for myocardial infarction. After a period of initial trials questioning the efficacy of percutaneous interventions, primary stenting emerged as an effective way of providing complete cardiac reperfusion, becoming the recommended treatment of myocardial infarction.

Although some neurointerventionists argued whether randomizing patients with acute stroke to receive noninterventional therapies was ethical or even technically achievable given the complexity of those cases and multiple confounding factors (eg, location and extent of occlusion and variations in collateral supply), until now, with lack of solid data supporting the clinical equipoise of catheter-based interventions with standard available treatments, we could continue enrollment in trials, informing the patients and their families that the experimental treatment may or may not be better than the standard. Although we certainly need to wait for the final results of MR CLEAN, ESCAPE, SWIFT PRIME, and other ongoing endovascular stroke trials that have stopped enrollment and are currently analyzing the outcomes of enrolled patients, considering the strong emerging evidence in support of the mechanical thrombectomy approach, we need to accept that clinical equipoise no longer exists. This will have a profound effect on the design and direction of future stroke trials.

Along with the therapeutic approach, the definition of what represents successful recanalization has evolved, becoming more rigorous once we learned that complete or near-complete reperfusion of the entire affected brain territory was required to

achieve clinical improvement.[8] The Thrombolysis in Cerebral Infarction (TICI) grading system, which ranges from 0 (no recanalization or reperfusion) to 3 (complete recanalization or reperfusion; Figure), was developed specifically for the assessment of thrombolysis success in the intracranial circulation.[9] For example, in-hospital mortality, disability rates, and final infarct volumes vary significantly between only partial (TICI 2a) and near-complete (TICI 2b or 3) reperfusion achieved in patients treated with endovascular stroke therapy.[10]

Establishing vessel recanalization and brain reperfusion is strongly associated with good neurological outcomes.[11] And yet, the rates of favorable outcomes even with modern devices still are approximately twice as low as the rates of successful recanalization that we are able to achieve. Why is that? To answer this question, we need to approach and think of the management and treatment of acute stroke from multiple angles.

According to American Heart Association guidelines, the intravenous thrombolysis treatment, when indicated, needs to be initiated within the first 60 minutes of a patient's arrival at the hospital because its treatment efficacy is strongly time-dependent.[12] The Joint Commission and other organizations use this essential metric as a part of the stroke certification processes for hospitals. In contrast to the guidelines for intravenous therapy, for those patients who are potential candidates for endovascular stroke interventions, there is tremendous variability in the entire process of hospital care preceding the patient's arrival at the interventional suite and the start of the intervention. Initial clinical and imaging evaluations and interactions between emergency department personnel and stroke neurology and neurointerventional teams differ greatly with respect to the determination of potential candidates for intra-arterial interventions. Involving emergency medical services personnel in the recognition of stroke patients who are potential candidates for intra-arterial interventions, developing acute stroke protocols for emergency room personnel, and mobilizing the neurointerventional team early are some promising ways of reducing time to initiation of intra-arterial reperfusion therapies.[13,14]

Delaying time to angiographic reperfusion results in worse clinical outcomes. This has again been recently demonstrated in an analysis of the IMS III trial in which every 30-minute delay to reperfusion was associated with a decreased likelihood of favorable clinical outcome (adjusted relative risk, 0.88; 95% confidence interval, 0.80-0.98).[15] Modern endovascular stroke trial protocols (eg, SWIFT PRIME and Perfusion Imaging Selection of Ischemic Stroke Patients for Endovascular Therapy [POSITIVE; http://clinicaltrials.gov/show/NCT01852201]) mandated strict time limits between baseline neuroimaging and femoral artery puncture to ensure the randomization of appropriate patients for catheter-based interventions and the initiation of such interventions without delay. The same principle should apply to strokes treated outside of clinical trials. Similarly, time from femoral artery puncture to reperfusion should be minimized, which is best achieved by using the latest-generation thrombectomy tools.

Reperfusing dead brain is futile. In fact, it might be harmful. Therefore, it is critically important to ensure that we judiciously select those patients who are likely to show clinical improvement with resolution of neurological deficits once flow is restored within the occluded intracranial vessel. Whether this is achieved best by using noncontrast brain computed tomography, measuring diffusion-weighted imaging volume with magnetic resonance, or

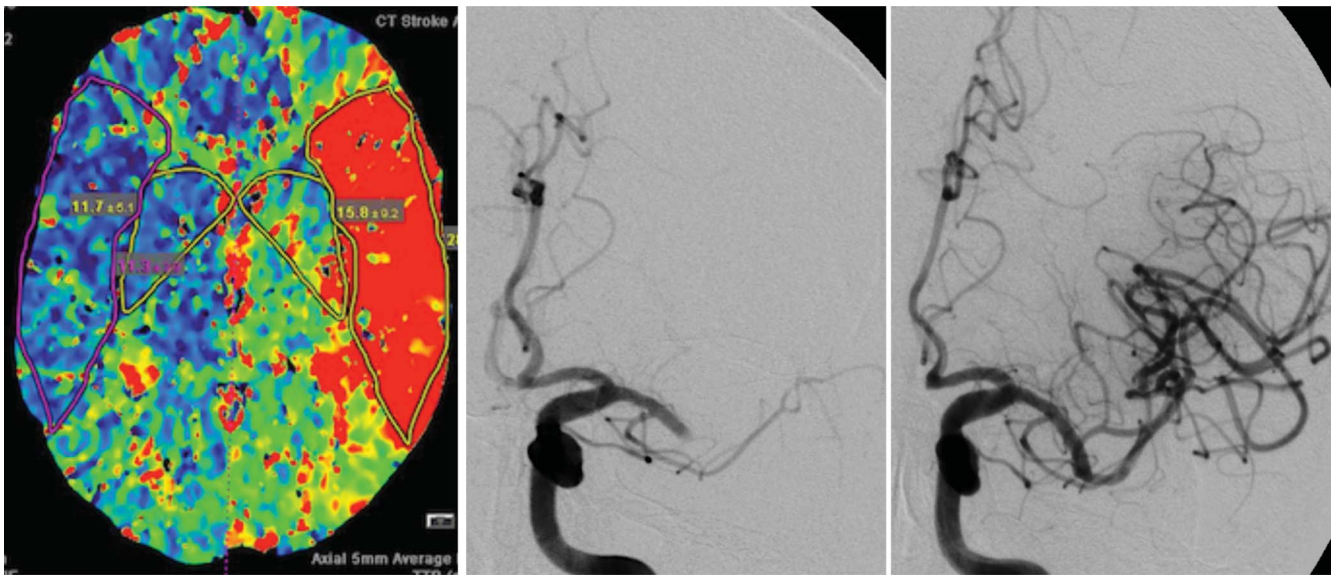

FIGURE. *A case of acute stroke from the left middle cerebral artery occlusion.* **Left**, *computed tomographic perfusion image demonstrates a perfusion deficit within the left hemisphere.* **Middle**, *baseline angiography shows a cutoff within the M1 middle cerebral artery segment, indicating the site of the occlusion.* **Right**, *after successful thrombectomy with a stent retriever, complete recanalization and reperfusion of the left middle cerebral artery territory are achieved, corresponding to a Thrombolysis in Cerebral Infarction score of 3.*

using advanced brain perfusion imaging showing a mismatch between penumbral and infarct core brain tissue is a subject of ongoing research. The degree of collateral flow, which can be assessed rapidly with computed tomographic angiography, is another potentially promising tool for patient selection that is used at some institutions.

Neuroprotection might provide the solution to extend the window for successful reperfusion and thus to increase the number of patients eligible for thrombectomy therapies. The key to demonstrating clinical success of neuroprotective trials will rely on our ability to initiate neuroprotection immediately after the onset of stroke symptoms, be that by means of pharmacological agents or hypothermia. This will likely require the initiation of such therapies even before the patient's arrival at the emergency department, similar to current neuroprotective protocols in patients with cardiac arrest. The Field Administration of Stroke Therapy-Magnesium (FAST-MAG) trial of intravenous magnesium showed that as a result of excellent team work involving paramedics, stroke physicians, and emergency department personnel, neuroprotective treatment was initiated in 74% of patients within the first hour of stroke symptom onset.[16] This is an excellent example that, through joint effort, we can design and carry out trials of endovascular therapies in which neuroprotection can be started ultra-early.

This is an extremely exciting time for those of us who perform endovascular interventions. Very soon, we will be entering a new era of stroke trials, designing faster and more efficient ways of identifying those patients who would benefit from catheter-based interventions and developing protocols tailored to patients with large-vessel occlusion. For the neuroendovascular specialty, for which newer devices and treatment protocols appear every few months, this is a challenging task that requires concerted effort.

Disclosures

Dr Levy has had shareholder/ownership interests in Intratech Medical Ltd and Blockade Medical LLC; has been a principal investigator for the Covidien US SWIFT PRIME trials; and has received compensation from Abbott for carotid training for physicians. Dr Mokin has received an educational grant from Toshiba.

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