

# Interventional Stroke Trials: What's Needed, What's Next?

Recent favorable data have added to our stroke management understanding and capabilities but also have presented new key questions to address.

**BY READE A. DE LEACY, MBBS, AND J MOCCO, MD, MS**

**B**efore December 2014, the only proven therapy to treat acute ischemic stroke within 4.5 hours of symptom onset was recombinant tissue plasminogen activator (rtPA). The last 18 months have seen a dramatic alteration in the landscape of neuroendovascular surgery and stroke neurology as a result of the recent overwhelming evidence in favor of mechanical thrombectomy for emergent large vessel occlusion (ELVO) in acute stroke.<sup>1-5</sup> However, each of the positive trials was carried out in hospitals and health systems that had well-defined patient selection criteria and well-established systems of care in place to provide rapid clinicoradiologic assessment and endovascular therapy by highly trained and experienced neurointerventionists, stroke neurologists, and emergency physicians. It is important to understand that in order to replicate the results of these trials, the clinical conditions and expertise under which the patients were selected and the interventions were performed would likely need to be replicated.

The recently published data have not only changed the way this condition is treated across the globe, but they have also raised the question of how we can create and implement the critical systems of care needed to provide this new service. As we move beyond the era of debate over medical versus endovascular therapy for ELVO, there are now further challenges for the neuroendovascular and stroke community. In addition to the continued refinement of acute stroke intervention systems of care throughout the various health systems across the globe, other issues must be addressed, including clarification as to whether a specific endovascular approach should be used in preference (eg, stent retriever use with or without novel protection devices or direct aspiration techniques) and the development of

a guide for the appropriateness of endovascular therapy for patients with “wake-up” strokes or those who present beyond 6 hours after symptom onset. Coexistent with addressing the last point is the need to develop and define robust evidence-based criteria for assessing the physiological reserve of an individual’s brain with novel or advanced multimodality imaging techniques, thus moving from the traditional “time is brain” paradigm to what may be the more appropriate “physiology is brain” philosophy.

## NEW DIRECTIONS FOR ADDRESSING ONGOING CHALLENGES

With modern endovascular devices and recent data from the positive endovascular stroke trials, it is now possible to achieve reliably high rates of TICI 2b/3 recanalization (57%–88%).<sup>6</sup> Although device technology will continue to develop and improve, greater gains in patient outcomes will most likely come through the accelerated initiation of therapy, be it intravenous rtPA or endovascular clot removal, and via the implementation of streamlined and efficient systems of care. Intravenous thrombolytic therapy is well known to be most effective when administered in the first or “golden” hour after the onset of symptoms.<sup>7</sup> However, therapy can rarely be administered within this time window with the acute health care model as it stands. Recent times have seen the incorporation of telemedicine and the advent of the mobile stroke treatment unit (MSTU) in order to address the need to decrease both door-to-needle and door-to-clot times. The use of MSTUs, in addition to the reorganization of emergency and radiology departments to implement streamlined clinical and imaging protocols, have been shown to decrease the time to definitive care.<sup>8-11</sup> These units serve

as a mobile point of care for both clinical and radiologic assessment, as well as for the initiation of treatment under the guidance of stroke physicians and radiologists using wireless network capability.

In reality, populations outside of major metropolitan regions and in developing countries are unlikely to benefit from the implementation of MSTUs and the development of close-by comprehensive stroke centers in the foreseeable future. Early initiation of adjunctive neuroprotective therapies may help in further extending the time available to safe recanalization or reperfusion therapy by slowing down the conversion of ischemic penumbra to infarct core in a process that is also known as “penumbral freezing.” To this point, numerous treatments have shown that robust protection in rodents has unfortunately failed to translate into significant benefits in human clinical trials.<sup>12</sup> However, certain neuroprotective strategies have shown promise in human stroke patients (induced hypothermia, minocycline, cerebrolysin, and ginsenoside Rd). Potential physiologic and pharmacologic targets for the development of novel neuroprotective agents include preventing ischemic inflammation and oxidative stress, repairing the disruption of the blood–brain barrier, and diminishing the adverse effects of ischemic neuronal excitotoxicity, apoptosis, and autophagy.

Wake-up strokes and patients presenting outside the currently accepted 6-hour time frame for endovascular intervention remain a clinical dilemma. Studies have estimated that between 8% to 28% of all strokes present as wake-up strokes.<sup>13</sup> Historically, treatment has been withheld from this group of patients due to the increased incidence of reperfusion hemorrhage following recanalization. There are currently several trials underway seeking to determine the role of intravenous rtPA and/or endovascular mechanical thrombectomy in patients who present with wake-up strokes or those who present outside of the 3-hour time window since last known normal. Trials such as EXTEND (NCT01580839), POSITIVE (NCT01852201), and DAWN (NCT02142283) incorporate advanced imaging techniques including CT perfusion and MR perfusion with diffusion-weighted imaging into patient selection to determine the size of the infarct core versus the total territory at risk or penumbra.

The results of these trials may provide a framework for regulatory authorities to guide clinicians on the use of intravenous or endovascular therapy for this subgroup of stroke patients. Additionally, if neuroprotective therapy can be shown to preserve the ischemic penumbra and delay progression to completed infarct (under the direction of validated multimodality advanced imaging), the number of patients who may qualify for and be successfully treated by endovascular therapy will inevitably rise.

Although reperfusion and recanalization in ELVO for acute stroke is associated with improved outcomes, it also puts the brain at risk of reperfusion injury. Before the widespread use of intravenous thrombolysis and modern thrombectomy devices, this form of injury was relatively uncommon. In the new era of acute stroke therapy, adjunctive agents or techniques aimed at decreasing the likelihood of reperfusion injury are needed. As the field moves forward, drugs targeting the inflammatory response or the scavenging of oxidative free radicals may find a place in intravenous or intra-arterial catheter-directed therapy for patients with TICI 2b/3 recanalization.<sup>14</sup>

The 2015 AHA/ASA update to the 2013 guidelines for the early management of patients with acute ischemic stroke regarding endovascular treatment accurately reports that the majority of patients in MR CLEAN and ESCAPE and all patients enrolled in EXTEND-IA, SWIFT PRIME, and REVASCAT who underwent endovascular therapy were treated with stent retrievers.<sup>15</sup> From this, a new recommendation (class I, level of evidence A) was made, which states that patients should undergo endovascular treatment with a stent retriever if they meet the criteria for intervention out to 6 hours from symptom onset. However, questions remain as to the optimal endovascular equipment and technique to be used for clot removal, particularly as it is unclear which patients in the aforementioned trials also had concomitant direct aspiration during stent retrieval. Therefore, the relative contribution of stent retrieval or direct aspiration is unknown. The chosen method of revascularization by either direct catheter aspiration (ADAPT), the use of a stent retriever with or without a balloon guide catheter, or the Solitaire technique, which uses a stent retriever with direct catheter aspiration, remains largely based on operator preference and previous experience. Recent in vivo and retrospective nonrandomized in vitro studies have shown conflicting evidence as to the clinical and cost-effectiveness benefit of each approach.<sup>16,17</sup> The COMPASS trial (NCT02466893), which is currently underway, compares direct aspiration as a first-line approach versus the use of a stent retriever, with primary outcome measures of 90-day global disability as determined by the modified Rankin Scale and secondary outcome measures of cost-effectiveness for either technique.

## CONCLUSION

The last 12 to 18 months have seen a dramatic change in the way acute stroke is managed. Endovascular therapy now forms the crucial therapeutic component in the treatment of acute stroke from a large vessel occlusion. Attention now needs to be directed toward how to best develop, integrate, and improve these new systems of stroke therapy into exist-

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ing regional, national, and global health systems. The COMPASS trial will attempt to clarify the most clinically successful and cost-effective endovascular approach for recanalization. Further clinical trials (DAWN, POSITIVE, and EXTEND) are designed to determine the appropriateness of and develop selection criteria for intervention for patients with delayed presentation from symptom onset and for the roughly one in five stroke patients with wake-up strokes. With advanced imaging techniques being more and more likely to play a crucial role in patient selection beyond 6 hours since last known normal, further validation of these novel imaging techniques will be required. A more widespread implementation of mobile stroke units and the further discovery and refinement of therapeutic targets for neuroprotection and neurorestoration both before and after recanalization will undoubtedly increase the number of patients who will qualify for recanalization therapy as time moves forward. ■

*Reade A. De Leacy, MBBS, is Assistant Professor, Department of Neurosurgery, Cerebrovascular Center, Mount Sinai Health System in New York, New York. He has stated that he has no financial interests related to this article.*

*J Mocco, MD, MS, is Professor and Vice Chair, Department of Neurosurgery, and Director of the Cerebrovascular Center, Mount Sinai Health System in New York, New York. He has disclosed that he is a consultant for Pulsar Vascular; Cerebrotech Medical; TSP, Inc.; an investor in Blockade Medical and TSP, Inc.; and receives research funding from Medtronic, Inc.; Stryker Corporation; Penumbra, Inc.; and Codman Neurovascular, Inc. Dr. Mocco may be reached at (212) 241-3400; j.mocco@mountsinai.org.*

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