Emerging Therapy Critiques

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Endovascular Treatment for Ischemic Strokes
With Large Vessel Occlusion
Proven Therapy and Bright Future

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Intravenous tissue-type plasminogen activator (tPA) has been the mainstay and only therapy with proven clinical benefit in patients with acute ischemic stroke for the nearly 20 years. Patients harboring a large vessel occlusions (LVOs) seemed to be recalcitrant to intravenous thrombolysis that portended a poor neurological recovery. Catheter-based treatments offered a promise of higher recanalization rates and better outcomes. Over 2 decades, there has been increasing operator experience and advances in technology allowing for efficient and effective removal of the offending thrombus. Three randomized controlled trials published in February 2013 failed to demonstrate the benefit of intra-arterial therapy (IAT) but had slow rates of recruitment, absence of mandating the presence of an LVO, prolonged times to IAT and use of older generation thrombectomy devices. This led to an initial dampening of enthusiasm followed by a resolve of the stroke community to press forward with clinical trials.

The Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands (MR CLEAN) addressed several of the weaknesses of previous trials by enrolling only patients with a proven LVO in the anterior circulation, enrolling a high proportion of patients with more proximal occlusions of the carotid terminus and M1 MCA (91%) and achieving higher TICI 2b or 3 reperfusion rates as compared with recent studies. With 500 enrolled patients, 233 in the intervention (IAT) arm and 267 in the control (medical management only, resulting in a 13.5% absolute difference in rates of functional independency (modified Rankin scale, 0–2). Endovascular therapy was found to lead to better outcomes across all prespecified secondary outcome measures without an increase in symptomatic hemorrhages. The study, however, had few limitations in the design and execution. First, the study did not capture all screen failures, thereby raising the question of selection bias. Second, the protocol stated that selection of patients for randomization follows the gray area principle, thereby potentially limiting the generalizability of the results because of the lack of equipoise for all patients. Third, the time from IV tPA to randomization exceeded the specified time in the protocol which raises concerns about the reasons behind that delay. This delay although may also reflect patients who were recalcitrant to IV tPA and have a persistent vascular occlusion. Also, there have been criticisms about the low overall rates of good outcome in the IV tPA group only compared with other studies, but MR CLEAN is the first trial to study patients with a confirmed vascular occlusion where the natural history of such patients may portend a worse outcome than previously noted. Furthermore, the nature of the study design and stroke centers distribution in the Netherlands included patients presenting to outside hospitals then transferred to endovascular capable centers as well as those presenting primarily to the endovascular centers creating a heterogeneous sample that is different from other trials populations. Finally, the study incorporated patients with tandem occlusions which have traditionally been excluded from other endovascular trials. A total of 30 patients (12.9%) received a carotid intervention simultaneous to the thrombectomy procedure. These limitations not only may affect the generalizability of the results but also may be more reflective of the current endovascular practice and probably making this study more applicable to the real world treatment of the disease.

Nonetheless, MR CLEAN is the first positive study since PROACT II showing benefit from IAT in acute ischemic stroke patients with LVO. It showed the benefit of adjunctive IAT to IV tPA in patients with a definitive LVO treated with effective thrombectomy devices. It is important to note that of the 195 patients treated with mechanical intervention, 190 (97.4%) were treated with stent retrievers. The uniformity of using a technology with consistent results that has replaced previous iterations used in the Interventional Management of Stroke (IMS) III trial probably led to higher rates of reperfusion compared with previous studies.

MR CLEAN has brought a much needed energy and excitement to the field of stroke that has been mired with negative trials. The positive results along with the recently published results of ESCAPE (Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke) and EXTEND-IA (Extending the Time for Thrombolysis in Emergency Neurological
Deficits—Intra-Arterial)\(^9\) along with the presentation of SWIFT PRIME (Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment)\(^10\) all showing overwhelming efficacy of endovascular therapy with a stunning number needed to treat 1 in 3 or 4 should solidify the role of IAT as an effective treatment option for patients with LVO <6 hours from symptom onset. These data should erase previous doubts concerning the effectiveness of IAT in patients with LVO in the anterior circulation. There is no longer equipoise to randomize patients to medical therapy in comparison to IAT, and thus future trials should assess strategies to enhance clinical outcomes and optimization of patient selection.\(^11\)

The field now must embrace the treatment paradigm and consolidate its efforts to disseminate the information to treating clinicians. Importantly and if endovascular therapy becomes a Food and Drug Administration approved therapy, which is expected based on the overwhelming positive results of 4 randomized controlled trials, then a shift toward enhancing outcomes through improved pre-IAT screening tools and improving systems of care to reduce times to reperfusion may allow for cutting edge trials forthcoming. Efforts now should concentrate on improving patients’ access to centers equipped to offer the treatment especially with the current construct of stroke centers being designated as primary and comprehensive stroke centers may lead to challenges for patients harboring larger neurological deficits. In many European countries and Canada, patients are taken to a handful of centers where care is delivered in an expeditious manner. The crucial question for system optimization is if patients with larger clinical deficits should bypass primary stroke centers and be taken directly to a comprehensive stroke center at the expense of time to receive IV tPA but at the gain of reducing time to IAT.\(^12\) This crucial question is similar to what has already been addressed in the treatment algorithm to what has already been addressed in the treatment algorithm to what has already been addressed in the treatment algorithm to what has already been addressed in the treatment algorithm to what has already been addressed in the treatment algorithm for patients with ST-segment—elevation myocardial infarction with the DANAMI-2 (Danish Multicenter Randomized Study of Invasive Versus Conservatie Treatment in Patients With Inducible Ischemia After Thrombolysis in Myocardial Infarction) trial where primary angioplasty was superior to the combination of thrombolysis and angioplasty.\(^13\) The absence of a prehospital screening tool as effective as an electrocardiogram for ST-segment—elevation myocardial infarction may not exist, but surrogates such as hemiplegia with gaze preference or the Los Angeles Motors Score\(^14\) offers an opportunity to address this crucial question. Furthermore, expanding telemedicine networks and implementing more fluid and effective transfer processes for patients with LVO can offer a good solution in cases where these patients present to distant centers.

MR CLEAN showed that with determination and government supporting policies, a smaller country can conclude a well-designed trial enrolling more patients in less than half the time that took the United States to do with IMS III. We tip our hats to the investigators and their government and hope that we all as investigators would learn from the Dutch lesson to improve our execution of future trials so answers can be found in a more expeditious manner.

The long awaited positive results from MR CLEAN shows without a doubt that IAT for acute strokes with LVO is a valuable treatment option that should be considered to enhance neurological recovery. The exciting results of MR CLEAN will allow patients to receive cutting edge treatment for an extremely devastating disease and the promise of more advances forthcoming. MR CLEAN is just the beginning and the future seems brighter.

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**References**


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