

**Mini-Review**

# Endovascular Treatment for Acute Ischemic Stroke: Updates and Future Implications

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**Key Words**

Acute ischemic stroke · Endovascular treatment · Thrombectomy

**Abstract**

Stroke constitutes the primary cause of acquired disability in adults and is a second leading cause of death worldwide. The low recanalization rate after intravenous thrombolysis calls for an alternate therapy for acute ischemic stroke. The methodology for endovascular treatment has evolved greatly over the past two decades. The past 6 months have seen great progress in this area, with several randomized clinical trials all proving the efficacy and safety of endovascular treatment. Three key factors are important for good functional outcome after endovascular treatment: fast imaging to prove proximal occlusion and to exclude large infarct core, using mainly the stent retriever thrombectomy devices and establishing an efficient workflow to achieve fast reperfusion. Although positive results of RCTs are encouraging and bring what is urgently needed in the field, transforming these positive results into clinical practice will be both a challenge and opportunity of the next 5 years. It will need hard work, leadership and cooperation of all members involved in the chain of treating a stroke patient. In the wake of these positive trials, hospitals and professional organizations are working together to save every minute when fighting against this devastating disease.

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Stroke constitutes the primary cause of acquired disability in adults and is the second leading cause of death worldwide [1, 2]. High rates of death and disability despite management with intravenous rt-PA call for alternative therapies. Since the PROACT II study [3], the methodology for endovascular treatment of ischemic stroke has evolved greatly over the past two decades. Meanwhile, unremitting efforts have also been made in this area to investigate the

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effectiveness of endovascular treatment. In 2013, 3 randomized trials, the Interventional Management of Stroke III [4], MR RESCUE [5] and SYNTHESIS Expansion [6], all failed to show the superiority of endovascular therapy over medical treatment alone. The neutral findings of these 3 trials led to a dampening of enthusiasm in the field.

### Lessons from Previous Negative Trials in 2013

Although well designed, those three trials had some limitations that possibly led to the neutral results. They included a relatively low recanalization rate with older generation of thrombectomy devices, delays in the workflow to achieve fast reperfusion and lack of applying fast and effective imaging to screen for proximal occlusion and to exclude those with a large infarct core [7]. Given the lessons learned from the negative results, new trials have started with varying principles, selection criteria and new generation devices, trying to overcome the limitations of previous trials.

### Positive Randomized Trials in 2015

The MR CLEAN study (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) is the first randomized controlled trial that proved the efficacy of mechanical thrombectomy [8]. MR CLEAN avoided the drawbacks of previous trials by only including proven large artery occlusion within 6 h of anterior stroke, obtaining a highly fluent workflow to achieve fast recanalization and mainly use of the stent retriever technology [retrievable stents were used in 190 of the 233 patients assigned to intra-arterial treatment (IAT)]. The trial enrolled 500 patients in 16 medical centers in the Netherlands, of whom 445 patients (89.0%) received intravenous rt-PA before randomization. 233 patients were assigned to IAT, and the other 267 patients were treated with usual care alone. The results showed a 13.5% absolute difference of functional independence in favor of the intervention, with an adjusted common odds ratio of 1.67 by shifting analysis. No significant differences of mortality and symptomatic intracerebral hemorrhage (sICH) could be found between the two groups. These results indicated that endovascular treatment is both safe and effective and for patients with acute anterior intracranial large arterial occlusion within 6 h of onset.

MR CLEAN brought heated discussion once published and lit again the enthusiasm of neurointerventionists in the field. Subsequent to the MR CLEAN trial, several randomized clinical trials performed unplanned interim analyses and were all stopped because of the efficacy of endovascular treatment [2, 7, 9, 10]. These trials applied varying principles and selection criteria for randomization. Nevertheless, they all have something in common: proven large vessel occlusion before inclusion, intensive and efficient workflow and using mainly the stent retriever devices.

The ESCAPE (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times) trial [7] included 316 participants in 22 centers worldwide. Compared with MR CLEAN and prior trials, the ESCAPE trial presented with a shorter time interval (median time from first NCCT slide to reperfusion, 84 min) and a low rate of general anesthesia, and using CT angiography to evaluate collateral circulation and exclude large infarct core. The result showed that the rate of a 90-day good outcome was higher in the intervention group (53.0 vs. 29.3%;  $p < 0.001$ ), with a common odds ratio of 2.6 (95% CI 1.7–3.8;  $p < 0.001$ ) in favor of intervention. A lower mortality rate was observed in the intervention group (10.4 vs. 19.0%;  $p = 0.04$ ). There was no significant difference in the rates of sICH (3.6 vs. 2.7%;  $p = 0.75$ ). ESCAPE provides evidence of rapid

endovascular treatment plus standard care in proximal intracranial arterial occlusion with a small infarct core and moderate-to-good collateral circulation.

The EXTEND-IA trial [9] (Extending the Time for Thrombolysis in Emergency Neurological Deficits – Intra-Arterial) obtained advanced perfusion-imaging criteria to select patients suitable for endovascular treatment. Patients eligible for randomization had to present with acute anterior proximal occlusion within 4.5 h and evidence of salvageable tissue and small infarct core (<70 ml) on CT perfusion. The trial was halted after assigning 70 patients because of efficacy. The reperfusion rate at 24 h was higher in the endovascular group than in the control group (100 vs. 37%;  $p < 0.001$ ). Endovascular therapy also showed greater early neurological improvement at 3 days (80 vs. 37%;  $p = 0.002$ ) and also higher functional independence at 90 days (71 vs. 40%;  $p = 0.01$ ). No differences in mortality and sICH were observed.

The REVASCAT trial [10] (Endovascular Revascularization with Solitaire Device versus Best Medical Therapy in Anterior Circulation Stroke within 8 Hours) was another trial halted early because of efficacy towards endovascular treatment. The trial enrolled 206 anterior proximal occlusion patients within 8 h of symptom onset at 4 centers in Spain to receive either medical therapy alone or endovascular therapy (with stent retriever) plus medical therapy. Endovascular therapy showed a common odds ratio for 90-day mRS improvement of 1.7 (95% CI 1.05–2.8) compared with the control group. Further, an externally regulated registry kept a detailed log of all screening patients in the trial, which found that only 8 patients eligible for randomization were treated outside the trial.

The SWIFT PRIME study [2] (Solitaire™ with the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke) incorporated lessons from previous trials with earlier generation of endovascular devices that showed neutral results. It used the Solitaire stent retriever to achieve a higher recanalization rate. SWIFT PRIME has shorter median time from imaging to groin puncture (57 min in the intervention group) than earlier neutral clinical trials. At 39 centers, the trial enrolled 196 patients with occlusions in the anterior proximal intracranial circulation and an absence of large ischemic core lesions with CT angiography or MRA imaging before randomization. Among them, 98 patients received medical therapy and endovascular therapy, and the other 98 patients had medical therapy alone, with both groups accepting full-dose rt-PA. A reduced disability rate at 90 days and a higher rate of functional independence were observed in the intervention group (60 vs. 35%,  $p < 0.001$ ). The two groups had no significant differences in 90-day mortality (9 vs. 12%;  $p = 0.50$ ) or sICH (0 vs. 3%;  $p = 0.12$ ).

Two more trials, the THERAPY [11] and THRACE [12] were first presented at the 2015 European Stroke Organization Conference and will be published soon.

### Future Implications: Challenges and Opportunities

The positive results are encouraging and bring what is urgently needed in the field. With the publishing of these 7 trials, a new era of early management of acute ischemic stroke has already begun. It is foreseeable that endovascular treatment will be guideline-recommended treatment in the near future.

However, this does not mean that IAT will soon be widely performed and replace intravenous thrombolysis to be the standard treatment of acute ischemic stroke. Most patients in these RCTs are treated in large comprehensive stroke centers. The time from stroke onset to the initiation of the endovascular procedure was significantly shorter than the similar interval in the previous trials, especially the time targets used in ESCAPE trial [7], which may have contributed to the substantially higher proportion of patients with independent functional

outcomes observed in these positive studies. However, for those in primary hospitals, access to early IAT treatment is still limited, which is attributed to equipment and interventionist shortage. In addition, both pre- and in-hospital time delay is also challenging the treatment outcomes in clinical practice.

### **Time Is Always Brain: Learning from the Cardiologist**

The MR CLEAN, ESCAPE and SWIFT-PRIME trials have shown that a picture-to-puncture time of <60 min and a picture-to-perfusion time of <90 min is achievable with an efficient workflow [2, 7, 8].

Although achieving this goal in clinical practice may seem hard at the moment, we should be encouraged when we look at the history of percutaneous coronary intervention for acute coronary syndrome [13–15]. Ten years ago, the median door-to-balloon time for percutaneous coronary intervention in the US was 96 min, and only 27.3% of patients reached the ‘D2B <75 min’ goal. In 2006, the American College of Cardiology launched the D2B Alliance, a national campaign to improve D2B times to reduce in-hospital delays. In 2010, the median D2B time declined from 96 to 64 min, and 70.4% patients reached the ‘D2B <75 min’ goal.

In 2009, the AHA/ASA promoted the Target: Stroke Initiative campaign for intravenous thrombolysis, resulting in a huge improvement in the rate of door-to-needle time <60 min in the US [16]. A similar campaign may also be needed in endovascular treatment. There still remains a long way to go for hospitals to achieve the picture-to-perfusion time of <90 min in practice. Minimizing delays between the time of arrival and reperfusion needs rigorous efforts in management efficiency and intensive quality improvement, training and feedback during the treatment practice.

### **More Neurointerventionists Are Needed**

Another problem we are facing now is that the number of interventionists who perform IAT did not change much in the past decade. It is reported that <30% of Get With The Guidelines-Stroke hospitals provide IAT [17]. One solution is transferring all patients into a comprehensive stroke center where IAT can be performed. But this costs time and may be a burden to the ‘gold 6-hour’ window. More importantly, it will not solve all the problems. With public education emphasizing early arrival and efficient prehospital triage, we can expect more patients presenting within the recommended time window. Ultimately, if IAT were to become the standard treatment in the next few years, we must implement systemic training of more neurointerventionists to meet the target.

Rapid and complete reperfusion is the key to functional independence of acute stroke patients. To reach this goal, hard work, leadership and cooperation of all members involved in the chain of treating stroke patients will be needed. Hospitals, interventionists and professional organizations have to work together to do everything they can to save each minute during the whole procedure. In the wake of these positive trials, the first class has been taught, and neurologists now have a different option for fighting against this devastating disease.

### **Disclosure Statement**

The authors have no conflict of interest to disclose.

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