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EDITORIAL

# Endovascular Therapy Proven for Stroke – Finally!

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Cardiologists often remark that the field of ischaemic stroke follows in the footsteps of cardiology, just one to two decades later. In the case of endovascular reperfusion therapies this certainly seems to have been the case but there are now multiple positive randomised trials establishing the benefit of mechanical thrombectomy over and above standard care, which included intravenous alteplase in most cases. We will outline the new evidence, contrast the recent trials with the earlier negative studies and discuss some important differences between acute myocardial infarction and ischaemic stroke and the techniques required to treat them.

**Keywords** Ischaemic stroke • Endovascular thrombectomy • Computed tomography perfusion imaging • Thrombolysis

## The Latest Data

The first positive trial was released at the World Stroke Congress in October 2014 to a standing ovation and subsequently published in the New England Journal of Medicine [1]. This Dutch trial called ''MR CLEAN'' randomised 500 patients within six hours of stroke onset and was able to demonstrate significantly improved functional outcome at three months in a severe stroke population with 33% of endovascular patients returning to independent function versus 19% of standard care patients (89% of whom received intravenous alteplase). This led to a data safety monitoring committee review of several other trials which were stopped early for efficacy.

The Australian/New Zealand EXTEND-IA study [2] and Canadian ESCAPE study [3] were presented and concurrently published in February along with the presentation of initial results from the Covidien/Medtronic-sponsored SWIFT-PRIME study [4]. EXTEND-IA was able to demonstrate significant benefits in reduced disability with only 70 patients – 71% of patients treated with alteplase plus endovascular thrombectomy returned to independence compared with 40% of patients who received alteplase alone [2]. In SWIFT-PRIME (n=196), 60% of alteplase plus endovascular versus 36% of alteplase-only patients were independent at three months [3]. ESCAPE (n=316) allowed recruitment to 12 hours and included alteplase-ineligible patients [3]. Despite this, 84% were treated <6 h and 72% received alteplase. At three months, 53% were independent in the endovascular group versus 29% in the standard care arm. All of these trials were highly statistically and clinically significant with a number needed to treat three to four patients to achieve an extra independent outcome. In ESCAPE and EXTEND-IA there was an approximately 50% reduction in mortality which was statistically significant in ESCAPE. These two trials included a substantial proportion of patients

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aged over 80 who have higher mortality risk with standard care and patients with internal carotid artery occlusion, which carries a higher mortality than middle cerebral artery occlusion (32% vs 15% in the ESCAPE standard care group). However, the relative reduction in mortality with endovascular therapy was the same regardless of site of arterial occlusion [3]. Subsequently three further trials have been reported showing similar results, including publication of the REVASCAT trial [5]. This 206 patient study achieved functional independence in 44% of the endovascular group treated within 8h of stroke onset versus 28% of standard care patients.

The concern in stroke treatment, in distinction to AMI, is haemorrhagic transformation of the infarct which can be lethal. There were no safety concerns in these trials. Symptomatic haemorrhagic transformation of the infarct was no more frequent in the endovascular arm and in EXTEND-IA and SWIFT-PRIME the trends were towards lower intracerebral haemorrhage which could relate to faster reperfusion before severe blood-brain barrier damage has developed. Inexperienced proceduralists also have substantial risk of causing wire perforation of cerebral vessels. However, in the hands of the trial interventionists who had to fulfill strict credentialling requirements, perforation was uncommon.

These trials are small by cardiac standards and the robust statistical significance illustrates the power of disability-based outcomes in stroke. The differences in modified Rankin Scale, which measures functional independence, are highly clinically and economically significant. Importantly, there was no heterogeneity in treatment effect based on age or stroke severity. As a result, the European Stroke Organisation has already released new guidelines giving a Level 1a recommendation for endovascular thrombectomy within six hours of stroke onset [6] and the US guidelines are expected to follow shortly.

## The Previous Negative Trials

It is only two years since the publication of three negative trials in the same edition of the New England Journal of Medicine. The IMS-3 [7], SYNTHESIS [8] and MR-RESCUE [9] trials all failed to show the benefit of various intra-arterial approaches over standard care. There were, in retrospect, major flaws in design which have been thoroughly dissected in the literature [10–13] and informed the recent successful trials. A major problem was that the rates of successful revascularisation with early generation devices were uninspiring – in the range of 27-40%. There was also no imaging to ensure a blocked blood vessel from which to retrieve clot. All the recent studies used CT angiography to prove vessel occlusion and most added extra selection to exclude patients with large areas of irreversibly injured ischaemic brain. Time to reperfusion is clearly also important and there has been a progressive reduction in treatment delay over time. The substantially improved outcomes in EXTEND-IA and SWIFT-PRIME compared to MR-CLEAN probably relate to a combination of a) increased successful revascularisation from 58% to 86-88%, b) faster treatment with no delays to assess potential response to intravenous thrombolysis and c) the exclusion of patients with large areas of dead brain at baseline using CT perfusion imaging (in 100% of EXTEND-IA and 83% of SWIFT-PRIME patients).

Another challenge in the negative trials was consecutive recruitment as many proceduralists had limited equipoise and treated the most favourable candidates open label. The pessimism that flourished following the negative trials and refusal of some US insurance agencies to pay for the procedure drove renewed equipoise and greatly assisted the subsequent trials. In MR-CLEAN, government funding was only available for endovascular procedures performed within the trial - an excellent strategy to promote consecutive recruitment [1].

## Stent Retrieval versus Angioplasty and Stenting

A major difference in stroke versus acute myocardial infarction is that most intracranial occlusions are embolic from large artery or cardiac sources. The vessel is therefore usually normal at the site of occlusion and this means that thrombectomy is sufficient to restore flow without concern about reocclusion. Intra-cranial stenting, with the accompanying requirement for dual antiplatelets and heparin, increases the risk of haemorrhagic transformation (even without Gp-2b3a inhibitors) and is avoided wherever possible. A proportion of patients (10% in EXTEND-IA) require stenting of the cervical carotid to obtain access to intracranial thrombus. The optimal antithrombotic regimen for these patients has not been determined but aspirin alone for the first 24 hours was often used. There are now a number of available stent retriever devices and other methods such as suction thrombectomy are also marketed. However, given the high rates of revascularisation achieved with the Solitaire device, the onus is on the manufacturers of competitor devices to demonstrate equivalent efficacy and safety.

## "Bridging" Intravenous Thrombolysis versus Direct Endovascular Therapy

The current approach in stroke is to give intravenous thrombolysis to all eligible patients and then take selected patients with large vessel occlusions amenable to thrombectomy for the endovascular treatment. It appears that this approach does not increase the risk of symptomatic intracerebral haemorrhage [1–3,7] and the use of groin closure devices effectively prevents haematoma formation. This is similar to the pharmacoinvasive strategy applied in myocardial infarction when percutaneous coronary intervention is not immediately available [14] as currently relatively few centres have

on-site neurointervention and fewer still are able to achieve door to groin puncture times <90 min.

## Implementation

Whilst the centres involved in these trials have immediately made stent-thrombectomy the standard of care, there are a number of challenges in extending access to this therapy in many countries. In Australia and New Zealand the number of neurointerventionists and the comprehensive training required confines treatment to a small number of high volume centres in each state. The requirements for recognition of training in neurointervention involve at least two years of dedicated interventional neuroradiology training after completion of radiology, neurosurgery or neurology training and an ongoing case-load of at least 100 intra-cranial interventions per annum (including aneurysms, arteriovenous malformations and stroke). The equipment is also specialised with a requirement for biplane angiography suites. There is a need to centralise neurointerventional services to maintain procedural volume which, as in all specialities, is directly related to outcomes. It also makes economic sense not to staff and equip multiple 24/7 units within close proximity. Although stroke is more common than AMI, the proportion of patients eligible for thrombectomy is probably ~10% which translates to a much smaller number of endovascular procedures than in cardiology. Nonetheless these patients form a critically important group that is responsible for much of the disability burden of stroke and the number needed to treat for mortality benefit in ESCAPE and EXTEND-IA is half that of percutaneous coronary intervention (PCI) versus fibrinolysis in acute myocardial infarction (NNT 10 vs 20) [15].

## Conclusion

The evidence for stent-thrombectomy is now overwhelming and promises to transform outcomes for the most severe cohort of stroke patients. Faster, more effective reperfusion has delivered outcomes previously unheard of with patients discharged directly home just a few days after a stroke that would previously have led to either devastating disability or death. There are issues to resolve around the best method to select patients using brain imaging and the best use of intravenous thrombolysis. However, for now alteplase remains the initial treatment for all eligible patients. The challenge is to reorganise our systems and overcome geographical challenges to provide access to as many stroke patients as possible.

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