Endovascular stent thrombectomy: the new standard of care for large vessel ischaemic stroke

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Summary

Background **Results of initial randomised trials of endovascular treatment for ischaemic stroke, published in 2013, were neutral but limited by the selection criteria used, early-generation devices with modest efficacy, non-consecutive enrolment, and treatment delays.**

Recent developments **In the past year, six positive trials of endovascular thrombectomy for ischaemic stroke have provided level 1 evidence for improved patient outcome compared with standard care. In most patients, thrombectomy was performed in addition to thrombolysis with intravenous alteplase, but benefits were also reported in patients ineligible for alteplase treatment. Despite differences in the details of eligibility requirements, all these trials required proof of major vessel occlusion on non-invasive imaging and most used some imaging technique to exclude patients with a large area of irreversibly injured brain tissue. The results indicate that modern thrombectomy devices achieve faster and more complete reperfusion than do older devices, leading to improved clinical outcomes compared with intravenous alteplase alone. The number needed to treat to achieve one additional patient with independent functional outcome was in the range of 3·2–7·1 and, in most patients, was in addition to the substantial efficacy of intravenous alteplase. No major safety concerns were noted, with low rates of procedural complications and no increase in symptomatic intracerebral haemorrhage.**

Where next? **Thrombectomy benefits patients across a range of ages and levels of clinical severity. A planned meta-analysis of individual patient data might clarify effects in under-represented subgroups, such as those with mild initial stroke severity or elderly patients. Imaging-based selection, used in some of the recent trials to exclude patients with large areas of irreversible brain injury, probably contributed to the proportion of patients with favourable outcomes. The challenge is how best to implement imaging in clinical practice to maximise benefit for the entire population and to avoid exclusion of patients with smaller yet clinically important potential to benefit. Although favourable imaging identifies patients who might benefit despite long delays from symptom onset to treatment, the proportion of patients with favourable imaging decreases with time. Health systems therefore need to be reorganised to deliver treatment as quickly as possible to maximise benefits. On the basis of available trial data, intravenous alteplase remains the initial treatment for all eligible patients within 4·5 h of stroke symptom onset. Those patients with major vessel occlusion should, in parallel, proceed to endovascular thrombectomy immediately rather than waiting for an assessment of response to alteplase, because minimising time to reperfusion is the ultimate aim of treatment.**

Introduction

In view of the strongly positive results of recent trials of endovascular thrombectomy for ischaemic stroke,[1–6] it seems remarkable that only 2 years ago, the reporting of three neutral endovascular trials[7–9] led to widespread pessimism in the neurological community about the value of endovascular treatment. Although these early trials were state of the art when designed, in retrospect they had clear limitations: early-generation devices were relatively ineffective in achieving recanalisation; initiation of endovascular treatment was often delayed; non-consecutive enrolment occurred owing to lack of clinical equipoise, leading to open-label treatment for patients deemed to be good candidates, boosted by remuneration incentives for open-label therapy; and basic imaging selection to confirm major vessel occlusion was not routinely done.[10–12] Some US insurance agencies stopped funding the procedure after these initial reports,[7–9] and concerns were raised that the proliferation of new endovascular trials would fragment recruitment and delay results. Fortunately for patients with ischaemic stroke, this predicted outcome did not unfold. Indeed, neutral studies facilitated the recruitment of participants into subsequent trials by resetting the level of investigator equipoise.

Five positive randomised trials have now been published,[1–5] which used predominantly stent retrievers in patients with occlusions in anterior circulation vessels only, and two more have reported interim outright positive results[6] or a trend to positive results[13] in the form of abstracts. The MR CLEAN study (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands)[1] was the first to be completed. Investigators recruited rapidly, possibly in part because reimbursement for the procedure in the Netherlands was restricted to trial participants, which encouraged consecutive recruitment—an admirable model for the investigation of unproven treatments. Release of the MR CLEAN trial results[1] at the 9th World Stroke Congress in October, 2014, prompted review of the ongoing trials. EXTEND-IA (Extending the Time for

Thrombolysis in Emergency Neurological Deficits—Intra-Arterial),[2] ESCAPE (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times),[3] and SWIFT PRIME (Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment)[4] were stopped by data safety monitoring committees after interim analyses crossed pre-specified efficacy boundaries. REVASCAT (Randomized Trial of Revascularization with Solitaire FR Device versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting within Eight Hours of Symptom Onset)[5] was halted at a pre-planned interim analysis because of loss of equipoise in the trial population and because the intervention was associated with significantly improved functional outcome. The THRACE (Trial and Cost Effectiveness Evaluation of Intra-arterial Thrombectomy in Acute Ischemic Stroke) study[6] ran to completion and has reported positive interim results, whereas the THERAPY (Assess the Penumbra System in the Treatment of Acute Stroke) trial,[13] which used aspiration catheters, was terminated early, showing a trend to benefit. In this Rapid Review, we summarise the results of the latest trials and discuss the implications for stroke management.

Lessons learned from variation between trials

Although the recent endovascular trials[1–6,13] differed in inclusion criteria, therapeutic time window, and the precise intervention used, great consistency can be seen in the clinical populations enrolled and the overall results (table, figure 1). All trials have shown a substantial reduction in disability at 90 days after treatment. The effect size in these trials is one of the largest across disciplines of medicine, with a number needed to treat (NNT) to achieve an additional patient with independent functional outcome in the range of 3·2–7·1.

Age

Age has been a common and increasingly controversial exclusion criterion in stroke trials. Upper age limits were applied in the SWIFT PRIME,[4] REVASCAT,[5] THRACE,[6] and THERAPY[13] trials (table); by contrast, MR CLEAN,[1] EXTEND-IA,[2] and ESCAPE[3] had no upper age limit but, as in all the trials, required independent pre-morbid function. Available subgroup analyses suggest no heterogeneity in treatment effect between younger and older patients. Elderly patients with large strokes who do not achieve early reperfusion have high mortality, partly due to frequent use of a palliative treatment approach. In ESCAPE,[3] the absolute risk difference in mortality in patients aged older than 80 years was 24% (17 of 39 patients [44%] in standard care *vs* 9 of 46 endovascular-treated patients [20%]). In view of the data available at present, as is the case for intravenous thrombolysis,[14] exclusion of patients from endovascular treatment on the basis of age alone is not justified.

Clinical severity

Clinical severity at baseline, assessed by use of the National Institutes of Health Stroke Scale (NIHSS) score, was the key determinant of entry to the IMS III (Interventional Management of Stroke III) trial,[7] which did not use non-invasive imaging to prove vessel occlusion. Post-hoc analysis suggested treatment benefit in the subset of participants with evidence from CT angiography of large artery occlusion in this overall neutral trial.[15] The latest trials[1–6,13] used CT or MR angiography to establish eligibility of participants on the basis of vessel occlusion and some used less restrictive NIHSS criteria (table). Although subgroup analysis of the MR CLEAN[1] and ESCAPE[3] trials showed no heterogeneity in treatment effect across the range of baseline NIHSS scores, few patients had very mild strokes. Patients with major vessel occlusion and mild clinical deficit at presentation have a substantial risk of subsequent deterioration.[16,17] Data therefore strongly support intervention in patients with disabling stroke and acute proximal vessel occlusion in the anterior circulation; however, some uncertainty remains in the case of patients with very mild stroke.

Site of vessel occlusion

Intracranial large vessel occlusions of the internal carotid artery are termed either T occlusion (if they include the terminal internal carotid artery and initial segments of both the anterior cerebral artery and the middle cerebral artery) or L occlusion (if they include only the terminal internal carotid artery and the proximal middle cerebral artery). The initial horizontal segment of the middle cerebral artery before bifurcation and the Sylvian fissure is termed M1, and the post-bifurcation segment in the Sylvian fissure is termed M2. All the recent trials included T occlusions and L occlusions of the internal carotid artery and M1 occlusions of the middle cerebral artery. Patients with these lesions clearly benefited from endovascular treatment, including those with tandem extracranial internal carotid stenosis or occlusion and middle cerebral artery occlusion. Many questions remain unanswered regarding the optimum management of extracranial carotid stenosis in patients with angioplasty or stenting. Patients with stents require antiplatelet drugs, which might increase haemorrhage risk. MR CLEAN[1] and EXTEND-IA[2] included more distal (M2) occlusions of the middle cerebral artery, and the other trials inadvertently included some patients with M2 occlusion. However, these M2 occlusions are less common and more variable in the territory supplied and in their geometry than other occlusion sites, affecting patient suitability for thrombectomy. Meta-analysis of individual patient data might clarify effectiveness for M2 occlusions. In the interim, patients with significant clinical deficits and accessible M2 geometry should be considered for endovascular thrombectomy. No evidence has been reported of heterogeneity of effect on

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For more about the **National Institutes of Health Stroke Scale score** see http://www.nihstrokescale.org/