Stroke in 2015: the year of endovascular treatment

Patients with acute ischaemic stroke caused by large artery occlusions, those affecting the terminal parts of the internal carotid artery and the main stem of the middle cerebral artery, have long been recognised to have poor outcomes despite optimum medical care; this is true even when intravenous thrombolysis is used, with up to 25% of patients dying and about 50% left with permanent disability. The need for better treatment for this substantial group of severely affected patients has been answered conclusively and dramatically over the past 12 months by a series of landmark clinical trials that will shape the future of acute stroke care and stroke services worldwide. Other trial results have been less dramatic, but are equally important in clarifying appropriate management of most hospitalised stroke patients.

Endovascular devices for clot disruption or retrieval, initially arising from the needs of interventional neuroradiologists tackling intracranial aneurysms or arteriovenous malformations, have been approved for clinical practice since the early 2000s, and were increasingly used in acute stroke after decisions to reimburse their use in various health-care systems were made, despite the absence of evidence of clinical benefit. A series of clinical trials in 2013 (IMS-3, MR RESCUE, and SYNTHESIS), in which no significant differences were found between intervention and control, were disappointing, but the deficiencies of these trials—including late intervention, predominant use of older devices with higher complication rates, and inconsistent and infrequent use of advanced imaging for patient selection—were addressed and avoided in a subsequent series of clinical trials. The presentation of the Dutch MR CLEAN[1] trial in October, 2014 was pivotal; the trial was applauded both figuratively and literally. In this trial, 500 patients were randomised to either best medical care (including intravenous thrombolysis, if indicated) or medical care with additional intra-arterial thrombectomy (IAT) and results showed a significant benefit of IAT. This treatment was mostly delivered as an adjunct to intravenous thrombolysis and using stent-retrievers—the newest generation of devices, which offer high rates of recanalisation, short procedure times, and low complication rates.

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Results from the MR CLEAN trial caused a domino effect among other ongoing trials; each study in turn was terminated ahead of schedule by their data monitoring committees because of the overwhelming benefit of IAT shown in interim analyses. Findings from four further trials have been published (ESCAPE,[2] EXTEND-IA,[3] SWIFT-Prime,[4] and REVASCAT[5]), two more have been presented at conferences (THRACE and THERAPY), and the results from the UK-based Pragmatic Ischaemic Thrombectomy Evaluation (PISTE) trial are expected shortly. Broadly speaking, all trials included patients with occlusions of the internal carotid artery or middle cerebral artery; more than 85% were treated with intravenous thrombolysis initiated soon after symptom onset (median of 85–127 min), and with brain and vascular imaging features that suggested small areas of irreversibly damaged tissue (ischaemic core). High proportions of patients achieved complete or near-complete tissue reperfusion with IAT, predominantly with stent-retrievers, and most patients were treated (and indeed reperfused) within 6 h of symptom onset. The highly significant benefits, translating into numbers needed to treat of four to eight for recovery to independence, and unprecedented reductions in mortality in several studies, represent unequivocal proofs of concept for the use of these devices in the treatment of stroke.

Thrombectomy will continue to have a high profile as secondary analyses from individual trials and pooled analyses proceed. The substantial treatment effects mean that statistically significant findings are obtained from what appear to be modest sample sizes, disconcertingly so for anyone accustomed to cardiovascular trials. With fewer than 2000 patients in all completed thrombectomy trials, few subgroup analyses will have statistical validity, so many questions will probably remain unanswered. Because it seems unlikely that randomisation to best medical therapy alone within the first 6 h after stroke onset will be feasible in any future trial, the current dataset might be all of the randomised data that we will ever have, and questions around generalisability could persist—a situation reminiscent of that after the first positive trials of intravenous thrombolysis for stroke 20 years ago.

Service-level reorganisation to deliver rapid intravenous thrombolysis has been shown to be beneficial in the treatment of stroke,[6] and could be used as a model for the implementation of thrombectomy. Implementation could be hindered by major shortages of neurointerventionalists and diagnostic neuroradiology services, and a greater need for optimisation of in-hospital protocols than that needed for intravenous thrombolysis for maximum benefit.

Development of thrombolytic therapy continued in 2015, with extensions of the use of alteplase and potentially better thrombolytic agents to patient groups not eligible for treatment (such as those with unknown time of symptom onset) under investigation. Extension of the use of thrombolytic therapy occurred despite disappointing findings for vampire-bat-derived desmoteplase,[7] which might have been caused by the late intervention window used and use of a variety of imaging selection modalities.

Findings from the AVERT trial,[8] which involved as many patients as all of the endovascular trials combined, overturned an established (if suboptimally evidence-based) guideline by showing that very early mobilisation within 24 h of stroke onset was associated with a reduced likelihood of favourable outcome after stroke. This finding was unexpectedly counterintuitive, but very important for organisation of stroke-unit care, which has implemented early mobilisation since it was suggested to contribute to improved outcome in the Trondheim stroke unit trials[9] over a decade ago. The two groups of the AVERT trial differed little in time at which mobilisation of patients began (18·5 h [very early mobilisation group] *vs* 22·4 h [usual care group]), but the early mobilisation group received markedly more frequent and more prolonged efforts to mobilise than the usual care group. Perhaps a useful reminder that speed is not universally optimal in stroke care.

In all, it has been a year that introduced major changes in stroke care. In the early stages, speed is of the essence in seeking reperfusion as rapidly and completely as can be achieved. The increasingly complex needs for the management of the most severely affected stroke patients have acquired a weight of evidence that will drive system change; but once the dust has settled, a pause and a gentler pursuit of rehabilitation therapies might be appropriate. Advances come from trials both large and small, and both positive and negative.

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