DECADE IN REVIEW—STROKE

Progress in acute ischaemic stroke treatment and prevention

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Recent decades have seen a dramatic reduction in age-adjusted stroke-related mortality, presumably owing to better control of vascular risk factors, use of antithrombotic agents and improvements in acute stroke care. Here, we highlight a few developments in stroke prevention and acute care that have particularly influenced the care of patients.

Treatment of acute ischaemic stroke has advanced at a remarkable pace in the past 10 years. One important advance was the broadening of the therapeutic window for intravenous recombinant tissue plasminogen activator (rtPA) in acute ischaemic stroke. Two important trials expanded the original eligibility criteria (initiating treatment within 3 h from symptom onset) for intravenous thrombolytic agents. The European Cooperative Acute Stroke Study III evaluated the efficacy of thrombolysis conducted 3–4.5 h after the onset of symptoms.[1] A favourable outcome of no disability (modified Rankin Scale [mRS] score 0–1) was achieved in 52.4% of patients who were treated with rtPA, in comparison with 45.2% in the placebo arm of the study, yielding a significant odds ratio of 1.34 for the primary outcome of no disability.[1] The third International Stroke Trial demonstrated that individuals older than 80 years derived benefits similar to those seen in younger patients.[2] Recent meta-analysis of individual patient data from 9 randomized controlled trials of intravenous rtPA demonstrated better outcomes for patients treated within 4.5 h of symptom onset than for those given no rtTPA, irrespective of stroke severity and age. The benefit was greater with earlier thrombolysis (for mRS 0–1, OR 1.75 at <3 h versus OR 1.26 at >3 to <4.5 h from symptom onset).[3]

Despite these expanded indications, thrombolytics are of benefit for only a minority of patients with stroke, largely because of the delay in recognizing symptoms and the short therapeutic time window. Early enthusiasm for endovascular recanalization was dampened by three trials published in 2013 that failed to show improvements in clinical outcomes, highlighting the need for earlier recanalization, more-effective devices and appropriate patient selection. Five randomized controlled trials that incorporated these lessons and were published in 2015 showed substantial benefits of mechanical endovascular recanalization (MER). These studies enrolled patients with anterior circulation strokes and large vessel occlusion (most of whom were treated with intravenous rtPA) and employed new-generation stent retrievers. Meta-analysis of the 2015 trials showed that MER after intravenous rtPA was associated with an increased likelihood of excellent outcomes at 90 days (mRS 0–1 OR 2.59, 95% CI 1.92–3.48) and functional outcomes (mRS 0-2 OR 2.48, 95% CI 1.95–3.15), with no difference in mortality or symptomatic intracerebral haemorrhage.[4]

The key differences between the new endovascular trials and earlier studies were a major decrease in the time to vessel recanalization and tissue perfusion (Figure 1), use of next-generation devices, and improved selection of patients with large vessel occlusion.[5] Other imaging selection criteria have been applied in individual trials, including estimation of the infarct core by diffusion MRI or Alberta Stroke Program Early CT Score (ASPECTS), assessment of perfusion mismatch with CT or MRI techniques, and detection of adequate collaterals by multiphase CT angiography. Whether implementation of these imaging modalities results in better outcomes or extension of the recanalization window is being investigated.

In light of the current data, the American Heart Association/American Stroke Association has updated the guidelines for acute stroke management, providing a strong recommendation (Class I, level of evidence A) for MER with stent retrievers for patients aged ≥18 years who were previously independent, were treated with intravenous rtPA within 4.5 hours of stroke onset, had an NIH Stroke Scale score >6, had internal carotid or middle cerebral artery M1 segment occlusion and had anASPECTS >6, as long as endovascular treatment can be initiated within 6 h of symptom onset.[6] To realize the benefits of intravenous and endovascular therapy for acute ischaemic stroke, reductions in the time to recanalization are required; these reductions could be achieved through improvements to processes, including prehospital transport policies and in-hospital workflows, facilitated by data-driven quality performance improvement programmes.

In contrast to the recent success of endovascular devices in acute stroke treatment, endovascular approaches for stroke prevention have been less successful. Trials have not demonstrated superiority of patent foramen ovale closure or stenting of recently symptomatic intracranial atherosclerotic disease over usual care, thus emphasizing the importance of medical management. Moreover,

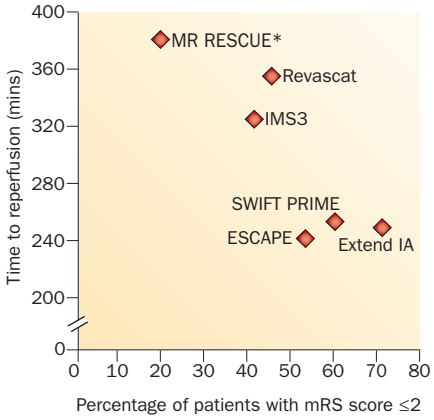

Figure 1 | Association between time to recanalization and clinical outcomes in trials of mechanical endovascular recanalization. Across six trials, the mean time from symptom onset to recanalization* therapy correlated with the likelihood of low disability (mRS score ≤2; little or no disability) at 90 days. *In the MR RESCUE study, the time range used was from the latest time point at which the individual was known to be well to the groin puncture. Abbreviation: mRS, modified Rankin Scale.

> “In the coming decade, research and health policy for stroke should focus on promoting healthy lifestyles...”

gaps in the evidence persist regarding the choice between extracranial carotid artery stenting, carotid endarterectomy, and medical management for symptomatic and asymptomatic carotid stenosis.

Medical prevention of stroke that results from atrial fibrillation has advanced dramatically. For many decades, warfarin was the only effective strategy in this context, but was under-utilized because warfarin has a narrow therapeutic range and multiple interactions with medications and foods making frequent testing and dose adjustment necessary. New non-vitamin-K oral anticoagulants (NOAC) do not require dose adjustment or monitoring. Currently available agents for non-valvular atrial fibrillation include a direct thrombin inhibitor (dabigatran) and three factor Xa inhibitors (rivaroxaban, apixaban and edoxaban). Multiple large international randomized trials of these drugs have confirmed their prespecified primary hypotheses. Meta-analysis has confirmed that the available NOACs reduce stroke or systemic embolism by 19% when compared with warfarin (RR 0.81, 95% CI 0.73–0.91) and reduce major haemorrhagic events by 14% (RR 0.86, 95% CI 0.73–1.00).[7] The benefits are similar for those with and without previous cerebral ischaemic events. Based on the available evidence, NOACs are recommended in guidelines for patients with non-valvular atrial fibrillation who are at risk of stroke.[8] Ongoing studies are attempting to develop ways to rapidly detect and reverse the anticoagulant effects of NOACs.

Approximately 30% of ischaemic strokes are classified as cryptogenic, and are usually treated with antiplatelet agents. Prolonged electrocardiographic monitoring reveals atrial fibrillation in a proportion of cryptogenic strokes, though the diagnostic yield varies with the thoroughness of causative evaluation and the frequency and modality of monitoring. The Cryptogenic Stroke and Underlying Atrial Fibrillation study addressed these concerns; patients with cryptogenic cerebral ischaemic events within 90 days of extensive diagnostic testing were randomly assigned to receive an insertable cardiac monitor or a conventional Holter monitor.[9] Among the 441 enrolled patients, the rate of atrial fibrillation detection with continuous monitoring was 8.9%, 12.4% and 30% at 6, 12 and 36 months, respectively, compared with 1.4%, 2% and 3% with conventional follow-up. Atrial fibrillation was defined as lasting >30 s, but 92.3% of patients had at least one episode of longer than 6 min. These findings support the recommendation of extended cardiac rhythm monitoring for appropriately selected patients with cryptogenic stroke, because such monitoring could indicate the need for a change in therapy. Despite extensive evaluations, including prolonged cardiac monitoring, some patients with cryptogenic ischaemic stroke could be reclassified as having an embolic stroke of undetermined source. Ongoing trials are investigating the use of NOACs versus aspirin for secondary stroke prevention in this subgroup.

Despite a reduction in age-adjusted mortality in recent decades, the global burden of stroke prevalence and disability is increasing, with a disproportional effect on low-income countries and minorities.[10] With an ageing population and growing prevalences of obesity, physical inactivity and diabetes mellitus, the prevalence of stroke is expected to increase, at a substantial cost to society. In the coming decade, research and health policy for stroke should focus on promoting healthy lifestyles, improving the control of hypertension and diabetes, expanding access to health care, enhancing systems of care to provide timely and effective care, exploring better rehabilitative measures, and reducing health disparities. The many successes of the last decade for stroke prevention and treatment should provide a solid foundation for continued progress, but many challenges are still ahead.

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