**Introduction to the ACNR Stroke Series**

In the next installment of our ACNR stroke series, we tackle the question of how to manage extracranial and intracranial arterial stenosis, an increasingly common challenge within and outside the stroke field. Many trials have emerged in recent years, requiring clinicians to make sense of a large amount of complex data. A key question is when should revascularisation be used in preference to modern medical prevention. In this excellent article, Fiona Kennedy and colleagues present a clear and concise summary of the evidence needed to make clinical decisions, and also outline areas of uncertainty requiring further research.

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**What to do about Extracranial and Intracranial Stenosis**

**Summary**

- Medical therapy for stroke prevention has improved in the last 20 years, including widespread use of statins
- Optimised medical management should be implemented in all patients with extracranial or intracranial stenosis
- Patients with stenosis should be evaluated on an individual basis in order to decide on the best management
- Up to date clinical trials are required to determine the efficacy of modern medical therapy for the treatment of atherosclerotic stenosis compared with revascularisation

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**Introduction**

Stroke is a major cause of morbidity and mortality in the UK with around 11,000 strokes occurring in England every year! An important cause of stroke is atherosclerosis of the extracranial and intracranial arteries supplying the brain. Atherosclerosis is commonly found at sites of arterial branching, with the major sites of relevance to stroke being the origins of the internal carotid and vertebral arteries. Atherosclerotic stenosis can also be asymptomatic and patients may be identified during investigations for contralateral ischaemia, cardiac surgery and peripheral vascular disease. Challenges arise when faced with the decisions of how to treat patients with symptomatic and asymptomatic stenosis, whether extracranial or intracranial. Controversy exists regarding whether medical treatment is superior to recanalisation, and certainly physicians and surgeons may have different views. In this review we aim to summarise the existing evidence for the treatment of intracranial and extracranial stenosis providing arguments for and against different strategies.

**Extracranial carotid artery disease**

Approximately 20% of ischaemic strokes can be attributed to atherosclerosis at the carotid bifurcations, causing ipsilateral carotid artery territory ischaemia. The management of carotid stenosis focuses on revascularisation and optimising medical treatment. Carotid endarterectomy (CEA), which was first performed in the 1950s, can reduce the risk of recurrent stroke. The European Carotid Surgery Trial (ECST) and the North American Symptomatic Carotid Endarterectomy Trial (NASCET) both showed a benefit in reducing the overall risk of stroke in patients with recently symptomatic carotid artery stenosis greater than 70%. As a consequence of these reports CEA is
recommended to all patients with similar characteristics to the trial patients. In 2004 Rothwell et al developed a risk model using ECST data that predicted the future risk of stroke in patients managed with medical treatment only. This model was validated in the NASCET dataset and showed that only patients with a high-predicted five-year risk of stroke (>20%) were likely to benefit from endarterectomy. Rothwell showed that surgery was not beneficial, and may even be harmful, in certain patients with a lower risk of recurrent stroke. Surgery itself is not without risk. The 30-day risk of stroke and death following endarterectomy was 7% in ECST but has improved in the last 30 years with a reported perioperative rate of stroke and death of 3.4% in the surgical arm of the International Carotid Stenting Study (ICSS) (see Figure 1). The Asymptomatic Carotid Surgery Trial (ACST) randomised asymptomatic patients found to have 60-99% carotid artery stenosis, between CEA and medical therapy. Over 10 years follow-up, the risk of stroke or perioperative death was reduced in those allocated CEA compared to those allocated deferral of any carotid procedure, but the absolute risks were low (13.4% vs. 17.9%) with a net gain over 10 years of only 4.6% (95% CI 1.2 to 7.9).

Carotid artery stenting (CAS) may be an alternative to endarterectomy (Figures 2 and 3). Trials comparing CEA and CAS in symptomatic patients have been published. The largest of these trials, the International Carotid Stenting Study (ICSS) included 1713 patients. The 30-day per protocol analysis showed a higher risk of stroke, death or procedural myocardial infarction in the stenting group compared with the CEA group (relative risk 1.83, 95% CI 1.21, 2.77, p<0.001) but the long-term results did not show any difference in disabling or fatal stroke between both revascularisation techniques over a median of four years follow up. A recent analysis looking at modified Rankin score in both groups of patients also did not show any significant difference. EVA-3S, which also compared stenting and endarterectomy was prematurely stopped due to safety concerns. The 30-day incidence of any stroke or death was 3.9% after endarterectomy and 9.6% after stenting (relative risk 2.59% CI 1.25-1.7, p=0.01). Similar to ICSS, SPACE and CREST did not report a difference between treatment groups in relation to their end-points.

Medical therapy for the secondary prevention of stroke has improved dramatically since the initial carotid trials. During ECST and NASCET statins for lowering cholesterol were not widely available. It was not until the mid-1990s that statins were used to lower cholesterol and were shown to reduce the risk of myocardial infarction. Only 17% of patients in ACST were taking statins. Even in the more recent trials like CREST and ICSS, only approximately ¾ of patients were taking statins for secondary prevention. Observational studies have shown that patients who take statins have a 30-50% risk reduction in recurrent stroke rate. Combined with improvements in the management of blood pressure and newer anti-platelet agents, the validity of the older trials might be questioned. New trials investigating the effect of modern medical therapy on patients with carotid stenosis are ongoing. The Second European Carotid Surgery Trial (ECST2) is currently randomising patients with asymptomatic or symptomatic carotid stenosis who have a low to intermediate risk of stroke between modern optimal medical therapy (OMT) alone and immediate revascularisation plus OMT. OMT includes targets for blood pressure and cholesterol and modifying lifestyle factors like smoking.

Vertebrobasilar artery stenosis

Intracranial artery stenosis causes approximately 8-10% of strokes and is more common in the Asian and Afro-Caribbean populations. Patients with severe intracranial stenosis (70-99%) are at high risk of recurrent events, therefore it is important to define treatment strategies to prevent these events. Historically these patients have been treated medically but the high recurrent stroke rate on medical therapy has led to an interest in revascularisation. Revascularisation has been proven successful in certain patients with extracranial disease, therefore studies and trials have been designed to test the safety and efficacy of angioplasty and stenting in the patient population with ath erosclerotic intracranial disease. However the long-term effect of such treatments have not been well established.
A meta-analysis of 31 suitable intracranial stenting studies by Groshel et al concluded that intracranial angioplasty and stenting is feasible and has a high initial success rate, however highlighted the associated procedural risks and high restenosis rates. However, this analysis pre-dated SAMMPRIS and there was limited randomised data comparing stenting to medical therapy. Most of the evidence-based medicine in this area comes from small registries that conclude stenting is feasible and can be safely performed.

The Stenting and Aggressive Medical Management for Preventing Recurrent stroke In Intracranial Stenosis (SAMMPRIS) trial is the first RCT in patients with atherosclerotic intracranial stenosis. SAMMPRIS compared revascularisation using the Wingspan stent with aggressive medical management. SAMMPRIS was stopped after enrolling only 451 patients because there was a high-observed risk of stroke and death in the stenting group. In January 2014 the final results from SAMMPRIS were published in The Lancet. Patients were followed up for a median of 32.4 months and results supported the use of aggressive medical management in high-risk patients with atherosclerotic intracranial stenosis over percutaneous transluminal angioplasty and stenting (PTAS) with the Wingspan system.

SAMMPRIS and several published studies have suggested that medical therapy for high-risk patients with intracranial stenosis is superior to stenting. Other studies however have reported lower perioperative risks associated with angioplasty and stenting. The contradiction that exists in terms of success rates and adverse events may reflect differences in the perioperative management of patients and also the risk associated with individual patients. Tight risk factor control, especially blood pressure, can help reduce the risk associated with revascularisation procedures in any arterial territory.

Different revascularisation techniques have been used in these trials and studies including different types of stents. The stents that are used in these situations are often not specifically designed for the intracranial circulation and are modifications of cardiac stents. Patient risk profiles also differ amongst studies. In order to eliminate these biases further studies are needed to investigate which stents should be used, optimised risk factor management and patient selection for the procedures.

Conclusion
Understanding the risks and benefits of different treatments in specific patient groups with atherosclerotic stenosis is the key to making the correct decisions. More evidence is required from randomised trials, especially more detailed assessment of risk factors and the composition of the atherosclerotic plaque. Medical treatment for the prevention of stroke has evolved over the last 20-30 years and in some cases requires re-evaluating the results from older trials. In intracranial stenosis there is very little evidence to help physicians make an informed decision but with ongoing trials we can hope that more answers are on their way. Patients should be evaluated on an individual basis and the correct treatment decided. In intracranial and vertebral disease the focus has shifted towards revascularisation whereas in extra cranial carotid disease optimised medical management may be the way forward for patients at lower risk of recurrent stroke. It is important to develop a way of risk-scoring individuals, which can help identify those at high risk who may require a more aggressive approach. Aggressive medical management should be implemented in all patients where it is safe to do so, including BP control and lipid lowering therapy. good diabetics management and cessation of hazardous lifestyle habits, most importantly smoking. This type of medical management will not only reduce the risk of stroke associated with the stenosis but also the perioperative risk of stroke and death that is too often quoted for revascularisation procedures.

REFERENCES

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