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The latest skirmishes in the long-term battle between carotid endarterectomy and stenting

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The first descriptions of carotid angioplasty appeared more than 30 years ago, but it is only now that we have good evidence to support endovascular treatment of carotid disease. Endovascular treatments were originally proposed as less invasive than carotid endarterectomy. This concept was challenged by those who argued that endovascular procedures were likely to dislodge clot or atheromatous debris into the brain. There was also concern that endovascular treatments did not remove the underlying pathology and would have a high incidence of recurrent symptoms. In part, this led to the development of stents designed to hold the artery open and prevent plaque rupture. However, laboratory studies suggested that the lengthening of stents during deployment sheared off

atheromatous debris into the distal vessel. It was only after the introduction of protection devices, such as filters placed distal to the stenosis, that carotid stenting became regarded as suitable for mainstream use. This concept was sufficiently promising for several large randomised trials to begin to compare stenting with endarterectomy.

Debate concerning the periprocedural risks has distracted attention from the main aim of carotid revascularisation, the long-term prevention of ipsilateral stroke. The majority of stented patients, around 95%, survive the procedure without major complications. Thus the important question for these patients is whether stenting is durable in terms of preventing stroke. The publication of long-term results from the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) provides reassuring data that addresses this question.¹ CREST included 1607 patients with carotid stenosis who consented to long-term follow up. The rate of post-procedural stroke over a median follow-up of 7.4 years was 6.9% in the stenting group and 5.6% in the endarterectomy group (hazard ratio [HR] 0.99, 95% confidence interval [CI] 0.64 to 1.52). These results add to similar findings reported from the European-based trials. For example, the International Carotid Stenting Study (ICSS) followed 1710 patients for up to 10 years after randomisation and reported that beyond 30 days after treatment, there was no difference in ipsilateral stroke rates (4.7% vs. 3.4%, HR 1.29, CI 0.74-2.24, p=0.36).² Another recent trial, the Asymptomatic Carotid Trial (ACT I), comparing stenting with endarterectomy in 1453 patients also showed similar long-term outcomes with rates of ipsilateral stroke from 30 days to 5 years after the procedure of 2.2% and 2.7% respectively.³

One can therefore conclude that stenting is as effective as endarterectomy in preventing long-term stroke after successful revascularisation once the periprocedural period is over, but questions remain about which patients should have endarterectomy rather than stenting, and which patients would be better off not having revascularisation. There are consistent data showing that in symptomatic patients, the rate of periprocedural stroke is higher in stented patients. In a pooled analysis of three European-based trials, the 30-day rate of stroke or death in patients allocated stenting was 7.7% versus 4.4% after endarterectomy (risk ratio 1.74, 95%CI 1.32 to 2.30).⁴ In CREST, the procedural rate of stroke or death in symptomatic patients was similar at 6.0 vs 3.2% respectively (HR 1.89, 95%CI 1.11 to 3.21).⁵

The increased rate of stroke associated with stenting has to be balanced against an increased risk of myocardial infarction (MI) with endarterectomy. Surgery also risks cranial nerve palsy, which is rarely disabling, and a greater rate of wound infection and hematoma. When all these outcome events are combined, there is little difference in the total number of periprocedural events between stenting and surgery. Nevertheless, there has been a tendency for neurologists to assume that stroke is a worse outcome event than MI or cranial nerve palsy. Although microembolism is very frequently detected by transcranial Doppler during carotid stenting, this is usually asymptomatic (figure). Moreover, the excess procedural strokes associated with stenting are minor and most seem to recover completely.² In ICCS, despite an excess of minor procedural stroke in the stenting group, there was no long-term difference in functional status measured by the modified Rankin scale at one year, five years or the end of follow up between stenting and endarterectomy.²

Similarly, health-related quality of life scores were not significantly different between the two treatments in CREST and ICSS beyond the early treatment period.^{6,7}

Before deciding that the treatments can be considered equivalent, it is worth examining factors that increase the risk of stenting. The most important of these is the age of the patient. In a pooled analysis of all four trials within the Carotid Stenosis Trialists Collaboration, Howard et al reported a very strong correlation between age and periprocedural risk of stroke or death of stenting, that was not seen for endarterectomy.⁸ This risk was no different in patients aged <60, but by the age of 70 to 74, the stenting risk was twice that of carotid endarterectomy (HR 2.09, 95%CI 1.32 to 3.32). These findings suggest that carotid stenting should not be recommended for patients aged over 70 if they can be safely treated by endarterectomy. Irrespective of age, extensive white matter disease on brain imaging also predicts an increased stenting risk.⁹ Technical factors also influence risk. For example, closed cell stent designs appear safer than open cell designs.¹⁰ CREST mandated the use of protection devices, but in the European-based trials, protection device use was not associated with a reduced rate of stroke, neither was the experience of the investigators, but a higher annual volume of procedures was an important indicator of safer stenting.^{10,11}

The topical question is whether all patients currently treated by stenting or endarterectomy need revascularisation at all. There is increasing evidence that intensive medical therapy is highly effective at preventing stroke in low risk patients, particularly those with asymptomatic stenosis, who have stroke rates around 0.5%/year.^{12,13} Over half the patients in CREST were asymptomatic and in ACT I all had asymptomatic stenosis. In CREST, the

periprocedural stroke and death rate in the asymptomatic patients was 2.5% with stenting and 1.4% with endarterectomy.⁵ This difference was not statistically different, but the HR (1.88, 95% CI 0.79 to 4.42) was virtually identical to that found in symptomatic patients, suggesting the difference is likely to be real. In ACT I, the 30-day rates of stroke or death were 2.9% in the stenting group and 1.7% in the endarterectomy group, with 5-year rates of stroke-free survival of 93.1% and 84.7% respectively.³ All these rates are higher than the expected rates of stroke in asymptomatic patients treated with intensive medical therapy alone. The fact that neither CREST nor ACT I recruited the planned number of asymptomatic patients might be fortunate.

The concern that revascularisation for asymptomatic carotid stenosis is still considered appropriate by many clinicians has led to two large on-going trials recruiting patients with asymptomatic stenosis, namely CREST-2 in North America (<https://clinicaltrials.gov/ct2/show/NCT02089217>) and ECST-2 (www.ecst2.com) based in Europe. Both randomize patients between revascularisation, allowing the choice of stenting or endarterectomy, and intensive medical therapy alone. ECST-2 also includes lower risk symptomatic patients. The results of these trials should provide much needed information on the relative risks and benefits of all three treatments in current use. There is a need for the trials to develop algorithms incorporating imaging and clinical features to identify patients who warrant revascularization, as well as those who have an unacceptable risk from revascularization e.g. from comorbid conditions.¹⁴ Asymptomatic patients at a risk high enough to warrant intervention (perhaps 10-15% of cases) might be identified by transcranial Doppler embolus detection and other methods in development, including plaque imaging.¹⁵ To further timely recruitment into these trials and spare patients the risk

of inappropriate intervention, it would be prudent to respect a moratorium on intervention outside these trials for low-risk patients with asymptomatic or symptomatic stenosis, until the trials are completed.

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Legend to figure

Transcranial Doppler recording from the middle cerebral artery showing showers of microemboli during carotid stenting. Showers of emboli commonly (even usually) occur during carotid stenting. Panel A shows microemboli while crossing the aortic arch during stenting of a common carotid; Panel B shows microemboli during stenting of an internal carotid artery. Reproduced by permission from Spence JD (2016).¹³

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