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SYMPTOMATIC CAROTID ARTERY STENOSIS IS BEST TREATED BY CAROTID ENDARTERECTOMY

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Introduction

Ask a dysphasic patient who has received a carotid artery stent if he or she would instead have rather had a troponin enzyme leak or minor myocardial infarction (MI). Although the answer is clear to most of us, there are many interventionalists and clinicians who have inappropriately interpreted recent data from the CREST trial to conclude that carotid artery stenting (CAS) is equivalent to carotid endarterectomy (CEA).

Almost 30 years ago, the North American Symptomatic Carotid Endarterectomy Trial (NASCET) indicated that symptomatic, high-grade carotid artery stenosis results in stroke rates greater than 20% at 1 year if not treated by CEA.[1] Although a great debate currently exists as to whether or not most asymptomatic carotid artery stenoses warrant intervention, most physicians still believe that symptomatic disease should be treated by some invasive intervention. However, there is presently considerable controversy over the question of whether or not CAS should replace CEA in a few or many patients. Ethics, economics, skill levels, physician preference, and patient preference all play a role in deciding between CEA versus CAS for the treatment of symptomatic carotid stenosis.

Today there exists a great deal of information relating to the treatment of carotid disease. Level-one evidence founded on properly conducted, prospective, randomized trials helps guide us in treating our patients. Studies such as EVA-3S (Endarterectomy Versus Angioplasty in Patients with Severe Symptomatic Stenosis), SPACE I (Stent Protected Angioplasty Versus Carotid Endarterectomy), and ICSS (International Carotid Stenting Study) have all recruited exclusively symptomatic patients.[2-4] EVA-3S was stopped prematurely for safety concerns regarding CAS after enrolling 527 patients. The periprocedural stroke rate was 8.8% after CAS vs. 2.7% after CEA (RR 3.3, 95% CI 1.4–7.5, P = .004). This represented more than a three-fold increase in stroke incidence in the stenting group. After randomization and treatment, the SPACE trial reported on 573 CAS patients and 563 CEA patients. The major stroke rate for SPACE was 4.2% for CAS and 2.5% for CEA (RR 1.68, 95% CI 0.89–3.19). ICSS randomized 855 patients to CAS and 858 patients to CEA. The interim 120-day stroke rate was 7.7% for CAS and 4.1% for CEA (RR 1.92, 95% CI 1.27–2.89, P = .002). A recently published substudy of ICSS looked at magnetic resonance imaging (MRI) to assess for new diffusion-weighted lesions. Compared to pre-procedure imaging, CAS was found to have a three-fold increase in new cerebral lesions based on diffusion-weighted MRI compared to CEA.[5] Although some have questioned the skill levels of the CAS operators in each of these trials, all of them favor CEA when considering the incidence of periprocedural stroke, the very endpoint that the procedure in question is supposed to prevent.

The Carotid Revascularization Endarterectomy versus Stent Trial (CREST) was deemed an important and well-conducted trial, randomizing both asymptomatic and symptomatic patients into CAS versus CEA groups (CAS: n = 1262; CEA: n = 1240).[6] Many interventionalists and others have expressed the opinion that CREST has finally answered the decade-long debate regarding the safety and efficacy of CAS and its equivalence to CEA in the treatment of both symptomatic and asymptomatic carotid stenosis. Unfortunately, this is just not true.

Just as with the previously mentioned randomized trials, there are several intrinsic limitations to CREST.[7] The interpretation of the CREST data is further compounded by physicians bringing their own set of biases to the analysis. With a nonsignificant p value of 0.51, CREST concluded that the composite primary endpoint of stroke, MI, or death from any cause over the 4-year follow-up

Endpoint	CAS n = 1262 # of patients (%)	CEA n = 1240 # of patients (%)	*P* Value
Primary endpoint ≤4 years (stroke, death, MI)	85 (7.2%)	76 (6.8%)	0.51
Primary endpoint 30-day (stroke, death, MI)	66 (5.2%)	56 (4.5%)	0.38
Any periprocedural stroke	52 (4.1%)	29 (2.3%)	0.01
Periprocedural major ipsilateral stroke	11 (0.9%)	4 (0.3%)	0.09
Periprocedural MI	14 (1.1%)	28 (2.3%)	0.03
Death	9 (0.7%)	4 (0.3%)	0.18

Table 1. CREST data. CAS: carotid artery stenting; CEA: carotid endarterectomy; MI: myocardial infarction.[6]

period was 7.2% for CAS and 6.8% for CEA, suggesting equivalence of the two procedures. However, when the endpoints were analyzed separately, CAS had an almost two-fold increased risk for periprocedural stroke when compared to CEA (4.1% vs. 2.3%, P = .01). Conversely, the incidence of myocardial infarction was 1.1% for CAS vs. 2.3% for CEA (P = .03). When these very different endpoints were combined together to form a "composite" endpoint between stroke, MI, and death, the procedures appeared to be equivalent. This has led many to believe that the issue of comparability is resolved, that no further trials comparing CAS to CEA are needed, and that CREST justifies the widespread and increased use of CAS to treat asymptomatic and symptomatic patients.

CREST is indeed a well-conducted and exemplary study, but some important flaws in the trial should be noted.[7] First, CREST bundled asymptomatic and symptomatic patients. Most clinicians should recognize that these represent two distinct disease processes with a very different natural history and periprocedural complication rate. In addition, the inclusion of asymptomatic patients dilutes the power and significance of the trial in such a way that the incidence of death or major stroke appear to be insignificant, even though the individual stroke/death results are quite different (Table 1). Second, as mentioned above, the combined endpoint of stroke, MI, and death is misleading. A minor stroke is very different from a minor MI since the stroke patients may be left with permanent changes in mood, affect, intelligence, and memory. This is indicated by the greater degree of impaired health observed after strokes than after MIs in CREST.[6] Third, the lower incidence of MI in the CAS group may be attributed to the more intensive antiplatelet regimen that these patients received. Lastly, the CREST operators were expert vetted interventionalists, and the question remains if the CREST results can be extrapolated to CAS operators at large in the community setting. This question is underscored by the fact that all population-based studies have demonstrated worse outcomes for CAS than CEA.[8-10]

Despite all these points, we believe that CAS outcomes will improve as better techniques are introduced and that it will have an important role in the treatment of symptomatic carotid stenosis, although future trials are needed. Recent and expected improvements in CAS include: 1) improved embolic protection, with flow cessation and reversal;[11, 12] 2) better stent technology with membrane or mesh-covered stents;[13] 3) better patient selection; and 4) more experienced and skilled operators.

How best to manage the large number of patients with asymptomatic carotid stenosis remains an area of great controversy. Improved medical therapy (BMT) with the optimal use of statins, beta blockers, ACE inhibitors, antiplatelet agents, and other drugs has made great strides in the last 2 decades. As a result of this and possibly other factors, recent meta-analyses and prospective population-based studies on asymptomatic carotid stenosis suggest low annual stroke rates of ≤1% and even as low as 0.34% with high-dose statin therapy and dual antiplatelet regimens.[14-16] Therefore, the so-called landmark trials justifying the use of invasive therapy (CEA) for asymptomatic carotid stenosis are now obsolete. Most asymptomatic carotid stenosis patients are probably best treated medically, sparing them the costs and risks of either CEA or CAS. Of course, randomized trials will be needed to prove this, and several such trials comparing CEA, CAS, and BMT are under way or under consideration. There is also a great need for methods to identify asymptomatic carotid plaques — which increase the risk of stroke even after BMT — so that patients with these high-risk plaques receive aggressive treatment. There is some promise that such techniques will be available in the future.[17-19]

While there exists a plethora of data with regard to carotid artery disease, one would be short-sighted and close-minded to stop the pursuit of answers that may be just over the horizon. More work will have to be done and more trials conducted before we can definitively recommend one mode of therapy over another in most patients with carotid artery stenosis.

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