Treatment for routine symptomatic carotid bulb atherosclerosis

Carotid endarterectomy is better than stenting

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Symptomatic internal carotid artery (ICA) stenosis is a common cause of ischemic stroke. The goal of management is to decrease the risk of stroke. This objective can be reached with a combination of medical therapy and revascularization with either carotid endarterectomy (CEA) or carotid artery stenting (CAS). At this time, evidence-based medicine provides guidance for our decision regarding which revascularization procedure is the most appropriate for the patient with routine, symptomatic carotid stenosis, i.e., with no clinical or radiographic exclusions for either procedure. The choice of treatment for revascularization comes down to 3 questions: 1) If the goal is to reduce stroke, which treatment option provides the best short and long-term outcomes? 2) Which treatment is cost-effective? 3) Which treatment provides the best patient-centered outcomes?

Two recent trials evaluating the difference between CEA and CAS are the Carotid Revascularization Endarterectomy vs Stent Trial (CREST)¹ and the International Carotid Stenting Study (ICSS).² In CREST, the primary composite endpoint of any stroke, myocardial infar-

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tion (MI), or death within 30 days following treatment plus any ipsilateral stroke during long-term follow-up (median 2.5 years) was similar for CAS and CEA (7.2% vs 6.8%, hazard ratio [HR] 1.1, 95% confidence interval [CI] 0.8–1.5). There was no differential treatment effect according to symptomatic status. In contrast, the ICSS interim safety analysis evaluating the 120-day rate of stroke, death, or procedural MI reported that more patients in the CAS group reached the combined endpoint of stroke, MI, or death than the CEA group (8.5% vs 5.2%, HR 1.69, 95% CI 1.16–2.45, $p = 0.006$).² In addition, a subanalysis of 231 patients in ICSS underwent MRI and demonstrated more ischemic brain lesions on diffusion-weighted imaging after treatment with CAS than with CEA (50% vs 17%, odds ratio [OR] 5.2, 95% CI 2.8–9.8).³ Considering the data in context, recent meta-analyses report consistent findings. Economopoulos et al.⁴ included data abstracted from publications including CREST and confirmed the short-term risk for stroke in the CAS group (OR 1.53, 95% CI 1.23–1.91; $p < 0.001$). The authors noted that when MI is included as an outcome, the differences become nonsignificant between CAS and CEA. The authors also evaluated long-term outcomes and found that CAS was associated with a higher rate of stroke (pooled OR, 1.37; 95% CI 1.13–1.65; $p = 0.001$) and stroke or death (pooled OR, 1.25; 95% CI 1.06–1.48; $p = 0.01$). Bangalore et al.⁵ evaluated death, MI, or stroke and reported CAS was associated with an increased risk of both periprocedural and intermediate to long-term outcomes. The available clinical data from the 2 largest trials comparing CEA vs CAS seem to have differing composite outcomes of stroke, myocardial infarction, and death. However, individuals undergoing CAS appear to have a greater risk of the outcome of stroke.

When one considers the totality of data, it is fair to say that CAS demonstrates a consistently higher periprocedural risk of stroke both in individual trials and in meta-analyses. Long-term risks of CAS remain unclear. CREST, the largest randomized controlled trial to date, demonstrated similar outcomes between CAS and CEA¹; however, the largest meta-analysis to date demonstrated increased intermediate and long-term risks with CAS.⁵ It is also fair to say that CEA carries its own risks, namely MI and cranial nerve injury. CREST provided evidence that the consequences of periprocedural stroke and MI are perceived differently by patients, with stroke significantly affecting health status at 1 year.¹ When patients had a stroke or MI during the periprocedural period, stroke (even minor stroke) affected health status more than MI. As clinicians, we interpret the available data and come to a conclusion that the risk of a procedure is worth the expected outcome for an individual patient. Patient preferences also need to be part of this equation.

At this time, the best evidence demonstrates a consistently higher periprocedural risk of stroke with CAS. The reasons for this increased risk need to be sorted out and are likely to be multifactorial. This is underscored by a possible differential response to CAS and CEA in particular subgroups. For instance, patients >70 years have been reported to have more events with CAS.^{1,4} In addition, the preplanned subgroup analysis of CREST designed to assess whether men and women have a difference in risk between CAS and CEA revealed that women had a higher risk of periprocedural events with CAS, which was driven by a higher risk of stroke.⁶ With the caveat that subgroup analyses should be interpreted as hypothesis generating, these data warrant further evaluation.

As with CEA, the benefit of CAS is dependent upon the periprocedural morbidity and mortality of the interventionalist. In CREST, there was a rigorous certification process and only a single device system was used. Each interventionalist submitted information on 10 to 30 CAS procedures for review by a multispecialty review committee before approval to participate in CREST. Then, during the lead-in phase, each approved interventionalist performed CAS procedures using the study devices in as many as 20 patients.⁷ The use of a lead-in phase and a single device system may not reflect a real-world scenario and may be essential in decreasing the risk of periprocedural stroke. A prospective Italian study compared the experience of interventionalists dichotomized into 2 separate 3-year intervals. Comparing the first with the second interval of the study period, the 30-day major stroke and death rate decreased

from 3.1% to 0.9% ($p = 0.047$), and the 30-day any stroke and death rate decreased from 8.2% to 2.7% ($p = 0.005$).⁸ Currently there is no public database that a patient can access to ensure that the physician performing CAS or CEA has had significant experience with the procedure. This issue becomes particularly relevant when one considers treatment within a health care system where CAS is not routinely performed due to restrictions of stent availability or affordability, and in centers where case volume may be low.

When considering 2 treatments for the same disease, the issue of cost comes into question. Young et al.⁹ conducted a Markov analysis of the 2 procedures using direct Medicare costs (2007 USD), and characteristics of a symptomatic 70-year-old cohort over a lifetime. In the base case analysis, CAS produced 8.97 quality-adjusted life-years (QALYs), compared with 9.64 QALYs for CEA. CEA also had a greater benefit than CAS, with lower direct costs. When one considers the uninsured population in the United States as well as countries where there is no medical insurance and the burden of medical care cost is placed on the individual, the question of cost is critical. For example, in India, the cost of CEA compared to CAS derived from an average of 2 major government medical centers was \$135 USD for CEA and \$1,135 USD for CAS.^{10,11} The higher cost becomes prohibitive and results in fewer CAS procedures being performed, therefore decreasing the experience needed to ensure optimal effectiveness and safety of CAS.

The choice between CAS and CEA in symptomatic patients remains an individualized decision which takes into account risks of treatment, patient comorbidities and preferences, and complication rates of the treating physician. If the primary objective is to decrease the risk of stroke, then existing data support CEA as the treatment of choice, especially when one considers the recent evidence of even minor periprocedural stroke significantly impacting health status long-term. There is overwhelming evidence that older patients do better with CEA. There is emerging evidence that women may fare better with CEA, which needs further evaluation. From a global perspective, lack of access, center experience, and higher cost of CAS at this time favor CEA.

CAS is a relatively new treatment modality compared with CEA for symptomatic extracranial carotid stenosis for patients with conventional risk. There are still questions remaining regarding the procedure itself (e.g., the use of embolic protection devices), and the possibility that certain patient populations may respond differently to CAS. In time, as the CAS procedure is improved and standardized and the differential response of certain patient populations is clarified, it is likely that the periprocedural risk of stroke with CAS will decrease. Until this goal is achieved, CEA remains the cost-effective treatment of choice to decrease the risk of stroke in patients with symptomatic extracranial carotid artery stenosis.

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DISCLOSURES

Dr. Sangha and Dr. Singh report no disclosures. Dr. Gonzales serves on the editorial board of *Stroke*; receives research support from the NIH and the American Heart Association; and is the local site PI at UT Health for the Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST).

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