Evidence-based treatment of carotid stenosis: is the evidence strong enough?

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Young et al.12 present a timely review of evidence-based treatment of carotid artery disease. With the publication of the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST)2 and the release of preliminary International Carotid Stenting Study (ICSS)7 data, the management of carotid stenosis has gained a substantial amount of recent attention. Since the advent of the carotid angioplasty and stenting (CAS) procedure, there has been significant debate as to what is, or what will ultimately be, the most effective and safe treatment modality for atherosclerotic carotid artery disease.

As Davis and Donnan3 noted in a recent editorial in the New England Journal of Medicine, trends in the evolution of stroke treatment have consistently followed those developed for the management of myocardial infarction. Effective preventive strategies such as blood pressure modification and antiplatelet regimens were successfully translated from cardiac disease to stroke. The application of thrombolytic therapy for acute cerebral revascularization was adopted from the cardiac catheterization labs. Many of the translational neuroprotective strategies proposed today were first presented in the cardiac and vascular biology literature. The medical community and the general public continuously seek to embrace less invasive therapies. It is not unreasonable to surmise, then, that carotid endarterectomy (CEA) surgeries may one day be displaced by CAS techniques (or the indications may be significantly narrowed), much like coronary artery bypass graft procedures. The question is whether we have yet reached that point. Young et al. argue that we have not.

The treatment of carotid artery stenosis has historically been guided by evidence-based practice and large clinical studies.1,4–6 Relatively few neurosurgical procedures have been assessed with such rigor, or with a comparable breadth of trials. Years ago, indications appeared to be fairly clear; a safe and effective surgical procedure (CEA) was performed to treat a potentially devastating disease. Over time, however, endovascular techniques and best medical therapies have improved significantly. Symptomatic and asymptomatic lesions clearly have dissimilar natural history patterns. The current data on the treatment of carotid artery disease is inconsistent and appears to be inconclusive. Meta-analyses and pooled studies are difficult to interpret due to variations in techniques, device utilization, and operator experience. Proponents of each treatment modality interpret results of carotid revascularization studies in very different ways. This lack of consensus highlights the uncertainty with respect to an optimal treatment algorithm.

Rather than simply reviewing the existing literature, the authors present a manuscript that focuses on trial design and statistical interpretation with respect to the relevant randomized and population-based studies. Their review not only evaluates the current data, but the models used for its generation and interpretation.

The section of this paper addressing methods of statistical analysis illustrates an important concept. Whereas the initial CEA studies were designed to assess for superiority, many of the recent trials comparing CEA and CAS use a noninferiority design.8,9,11 The CREST study assessed for superiority, but did not demonstrate a statistically significant difference in the primary outcome end point. These data are summarized in Fig. 1 of Young et al.’s manuscript. Pertinent results must be interpreted within the scope of the study design.

Based on the CREST data,2 the US FDA’s Circulatory System Devices Advisory Panel has recommended expanding the availability of the CAS procedure to patients at standard risk for adverse events while undergoing surgery.10 A critical issue is whether the Centers for Medicare and Medicaid Services (CMS) will approve reimbursement for CAS in standard-risk patients. It is important to realize that the qualifications of “safe and effective” used by the FDA are quite different from the standards of “reasonable and necessary” used by the CMS.

Do the existing study designs (and resultant data) address the necessity of the procedure(s)? As the authors remark, several of the investigations (Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy [SAPPHIRE], Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis [EVA-3S], and Stent-Protected Percutaneous Angioplasty of the Carotid artery versus Endarterectomy [SPACE]) were initiated to demonstrate noninferiority rather than superiority.8,9,11,12 As opposed to an equivalence trial, a noninferiority design retains the capacity to claim superiority. Results from these investigations, however, were somewhat inconsistent (SAPPHIRE favored stent treatment, whereas EVA-3S favored endarterectomy) due to varying inclusion criteria and diverse patient populations. Two investigations were terminated early.8,9

See the corresponding article in this issue (E2).
Positive primary outcome results from a large, randomized superiority trial would be compelling. The CREST study, however, does not demonstrate superiority with regard to the primary end point for either CEA or CAS. Each procedure exhibited benefit with respect to alternate end points (decreased number of myocardial infarctions in the stent-treated group, decreased number of strokes in the endarterectomy group) and according to patient age (stent placement procedures for younger patients, endarterectomy for older patients).

In the setting of perceived clinical equipoise, factors such as cost effectiveness, complications, and ease of administration were evaluated. It remains unclear whether either procedure provides clear secondary advantages. An argument can be made that, as technology evolves, the efficacy of CAS procedures may continue to improve. Supporters assert that this trajectory warrants consideration when evaluating clinical practice patterns.

In an age of radical health care transformation designed to promote cost-effective medicine, it will be interesting to see whether the CMS approves CAS coverage for asymptomatic patients, asymptomatic patients, both, or neither. Proponents and detractors can probably find arguments and evidence to support or dispute any decision.

The approval of the CAS procedure in standard-risk patients would be likely to have broad implications for the quantity of procedures undertaken and the allocation of the 2 treatment modalities. The number of specialties that train members to perform angioplasty and stenting procedures (radiology, neurology, neurosurgery, cardiology, vascular surgery) is far greater and the operator volume is larger than in those that train physicians to perform CEA. Practice standards appear to shift with the publication of each new clinical trial. Decisions by the FDA and CMS can be assumed to have a more far-reaching impact.

The authors’ conclusions are logical based on the evidence to date. There do not appear to be enough existing data to favor CEA or CAS procedures uniformly. The paper serves as a comprehensive review of the existing literature. Furthermore, it reminds us of the impact of trial design and statistical analysis on the results of an investigation. Utilization trends will reflect individual physician’s interpretation of the studies within the scope of guidelines determined by the FDA and CMS. Until clear and convincing data demonstrate the superiority of one procedure or the other, appropriate patient selection should remain the guiding principle in treatment allocation. (DOI: 10.3171/2011.3.FOCUS1186)

Disclosure
The author reports no conflict of interest.

References