Remaining Carotid Questions

Perspectives on the progress and shortcomings of current carotid revascularization methods and concerns that must be answered before the medical community can unite on standards of care.

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The landscape of asymptomatic carotid artery disease is complex because several significant trends affect the way practitioners view patients who present with this condition. The driving force of this issue is dread of stroke. Stroke is the most feared of cardiovascular events by patients, likely because of the perceived risk of disability. Many patients both with and without stroke would rather die than live with severe disability,[1] and the risk of death is not minimal. In the Framingham Heart Study, patients alive at 60 years without myocardial infarction (MI) or stroke live an average of 20 more years, whereas those with an MI live 11 more years, and, worst of all, those with stroke lived 8 more years.[2] Finally, the cost of stroke to both the patient and health care system is enormous. For example, it is estimated that stroke care represents 5% of all medical care in the United Kingdom.[3] Thus, everyone involved in stroke prevention and care, from patient to clinician, fears this event and its consequences.

The last several decades have seen remarkable improvements in primary and secondary prevention of atherosclerotic disease. The incidence of MI, stroke, and amputation has all declined significantly.[4-6] There has been a groundswell of support for the concept that there is an appreciable change in stroke rates as a result of internal carotid artery disease over the last 3 decades. The support for this contention largely derives from retrospective analyses of outcomes in disparate trials or observations from small populations.[7,8] There are many possible explanations for this change over time. Demographic changes include the increased use of antiplatelet therapy, the decrease in coronary heart disease, the decrease in cigarette smoking, and the decrease in atrial fibrillation—all of which may have contributed to the change. In addition, new effective medical therapies have become commonplace, such as the hydroxymethylglutaryl-co-enzyme A inhibitors (statins) and antagonists of the renin-angiotensin system. Each of these agents reduces the rate of overall stroke in high-risk patients. These therapies, however, have not yet been proven in patients with severe carotid stenosis.[9,10] The improvement in medical therapy has been associated temporally with reduced incidence of MI and severity of MI when it occurs,[11] and it seems likely to be the same for stroke. Although stroke remains a feared event with significant morbidity and mortality, the rate of developing a stroke from

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asymptomatic internal carotid artery disease appears to be diminishing both by preventing the development of severe carotid stenoses in the first place, as well as stabilizing severe plaques that do develop. This rate will likely decrease further as asymptomatic carotid artery disease becomes classified as a coronary heart disease-risk-equivalent, prompting more uniform aggressive therapy in the population.

However much the epidemiological and observational data may provide evidence of a reduction in carotid–associated stroke, definitive statements that medical therapy is now the treatment of choice for this condition are largely presumed rather than proven. This is because the only direct comparative data available found that surgical revascularization was more effective in preventing stroke than deferred surgery. Two large randomized surgical clinical trials were performed evaluating carotid endarterectomy (CEA), the Asymptomatic Carotid Artery Surgery study (ACAS) and the Asymptomatic Carotid Surgery trial (ACST),[12,13] and both showed a reduction in ipsilateral stroke compared with initial observation and medical therapy (aspirin). There were several caveats: the benefit did not manifest for a couple of years; most of the stroke reduction was in small stroke and transient ischemic attack—not major stroke; women did not benefit as much as men; and little data concerning patients in their 80s and older were obtained.[14] Despite these limitations, there was a dramatic increase in the use of surgical therapy.[15] Outcomes from CEA have improved over time as well.

More recently, the carotid landscape has been marked by the advent of percutaneous revascularization. Two major innovations in this field since the first reported balloon angioplasty in the early 1980s include the use of stents and embolic protection devices. Use of embolic protection devices made clear that embolization of atherosclerotic debris was common and likely occurs in more than half of patients undergoing endovascular repair.[16,17] Although no clinical trials of endo-

vascular repair and medical therapy compared with medical therapy alone have been performed, two trials of endovascular repair with embolic protection compared with CEA have been performed in patients with asymptomatic carotid artery disease. In the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial, 334 high-risk patients with either symptomatic or asymptomatic carotid artery disease were enrolled and randomized to CEA or carotid artery stenting (CAS).[18] Results showed a reduction in the primary endpoint of death, MI, and stroke in the stent arm. The Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST) studied 2,502 patients with both symptomatic and asymptomatic internal carotid artery disease, comparing endovascular and surgical revascularization.[19] CREST is the most important study comparing the two revascularization modalities in asymptomatic disease. In the asymptomatic cohort, there was no difference between the CEA and CAS arms in the primary endpoint (death, stroke, and/or MI).[20] Three other randomized trials in standard surgical-risk asymptomatic patients are in progress. The US ACT I study randomizes between CAS and CEA in 1,700 patients and is currently nearing completion. The global UK-based ACST-2 study is randomizing between CAS and CEA in 5,000 patients and is approaching 1,000 patients enrolled. Last, the SPACE-2 study is assessing revascularization (CEA or CAS) versus medical therapy in Germany.

Currently, there are a variety of opinions in the medical community concerning the state of the field. These range from those who advocate medical therapy only[21] to those who think CEA is valuable and the best choice therapy[22] to those who think that CAS is an alternative to CEA.[23] Based on the wide diversity of opinion, the lack of a revascularization trial with standard use of current medical therapy, and the better understanding of suitable anatomy for both CEA and CAS, a clinical trial evaluating these issues is needed. We must answer the following question: Does referral for best revascularization improve outcomes in patients with asymptomatic carotid stenosis beyond optimal medical therapy? North American-based CREST-2 is designed to address this question and is currently in the application process for funding by the NIH. Until such a trial is complete, it will be hard to unify medical community opinion concerning the proper framework of care for these patients. ■

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