

EDITORIAL COMMENT

Carotid Endarterectomy Versus Carotid Artery Stenting

Case Closed... Now What!?!*

Robert D. Safian, MD

Royal Oak, Michigan

The answer to the question “What is the optimal management of patients with carotid artery disease?” remains hotly debated and contentious. In the 1990s, the elements of this debate were focused on the relative merits of carotid endarterectomy (CEA) versus medical therapy (basically, aspirin), which most physicians considered settled by 4 randomized clinical trials in patients with symptomatic (1,2) and asymptomatic (3,4) carotid stenosis. Taken together, these trials formed the base of evidence that supported the recommendations for CEA in symptomatic

See page 163

carotid stenosis >50% and in asymptomatic carotid stenosis >70%. In the last 15 years, the findings of these studies have been challenged on the basis of 2 important therapeutic innovations: one in pharmacological approaches to coronary, peripheral, and cerebrovascular atherosclerosis, and the other in the development of minimally invasive techniques for carotid revascularization relying on carotid artery stenting (CAS) and embolic protection devices (EPDs). From a clinical trials perspective alone, more than \$100 million have been devoted to studies of the *technique* of carotid revascularization, whereas there are no large-scale clinical trials of optimal medical therapy for stroke prevention in patients with severe carotid stenosis.

In this issue of *JACC Cardiovascular Interventions*, Brooks et al. (5) report the culmination of 10 years of follow-up in 189 patients randomized to CEA versus CAS in the “Kentucky trial”; in-hospital outcomes and vessel patency at 2 years were previously reported in symptomatic (6) and asymptomatic (7) patients. The principle findings of this study are that at 10 years, there was no difference in the risk

of death or ipsilateral stroke for patients assigned to CEA or CAS, and the risk of late myocardial infarction (MI) was highest among patients who presented initially with symptomatic carotid stenosis (hazard ratio: 2.32, 95% confidence interval: 1.30 to 4.15; $p = 0.005$) and who were assigned to CEA (hazard ratio: 2.27, 95% confidence interval: 1.35 to 3.81; $p = 0.002$). The authors conclude that CEA and CAS provide equal protection for prevention of ipsilateral stroke, and that CAS may be superior to CEA for preserving long-term event-free survival. The strengths of the study are the long duration of follow-up (10 years), the randomized allocation of treatment, independent neurological evaluation, and the interdisciplinary collaboration between neurosurgeons, cardiologists, and neurologists. The weaknesses of the study are the small number of randomized patients ($n = 189$) and patients eligible for follow-up ($n = 173$), single-center enrollment, performance of CAS without EPDs, lack of information about the risk profile of the patients, and the exceedingly high late mortality (50.2%).

Although proponents of CAS may cheer this study, I find it somewhat enigmatic in some respects and compelling in others. First, the original cohort of 189 patients consisted of 104 symptomatic patients (55%) and 85 asymptomatic patients (45%); the risk of periprocedural stroke was zero (6,7). These are remarkably excellent results, particularly in symptomatic patients. For comparative purposes, the risk of periprocedural stroke was 4.4% in high-risk CAS patients (with EPDs) in the BEACH (Boston Scientific Embolic Protection Carotid Stenting Trial for High-Risk Surgical Patients) (8) (using the same stent that was used in the Kentucky trial), 6.2% (after CAS) and 7.9% (after CEA) in the randomized SAPHIRE (Stenting and Angioplasty With Protection in Patients at High Risk for Endarterectomy) trial (9); and 4.1% (after CAS) and 2.3% (after CEA) in the CREST (Carotid Revascularization Endarterectomy Versus Stenting Trial) in standard-risk patients (10). Although it is possible that EPDs contributed to the risk of periprocedural stroke after CAS, this position would be difficult to defend in the context of the declining risk of stroke with contemporary proximal and distal EPDs, and also defies the current national coverage determination policy mandating the use of EPDs in the United States. Second, the 10-year mortality of 50.2% contrasts sharply with the 5% risk of death/stroke at 4 years in the CREST trial (10), and with the 20% to 24.2% risk of death at 3 years in the SAPHIRE trial (9), and suggests that carotid revascularization trials might need to be extended to 5 to 10 years of follow-up. Finally, Figure 2 of Brooks et al. (5) is very compelling; it also supports the need for follow-up beyond 4 years, at which time both survival curves begin to diverge. More importantly, Figure 2 appears to link symptomatic carotid stenosis with subsequent acute MI, suggesting that unstable plaque in the carotid arteries may be a marker for

*Editorials published in *JACC: Cardiovascular Interventions* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Interventions* or the American College of Cardiology.

From the Department of Cardiovascular Medicine and the Oakland University William Beaumont School of Medicine, Beaumont Health System, Royal Oak, Michigan. Dr. Safian has reported that he has no relationships relevant to the contents of this paper to disclose.

vulnerable plaque in the coronary arteries, and that the period of vulnerability may last for several years.

On considering the Kentucky trial and the universe of CAS trials, I believe that CAS and CEA have reached clinical equipoise as strategies for carotid revascularization...case closed! Our mission now should turn to study of medical therapies for carotid artery disease, and to noninvasive and invasive imaging tools to allow us to characterize plaque in the carotid circulation (and elsewhere). We know that many patients have unstable carotid plaque and may be at risk for stroke, even in the absence of severe stenosis or symptoms (11,12). Important studies in the coronary (13) and renal (14) circulation have helped define optimal medical therapy for preventing major cardiovascular events, so it is appropriate to consider such therapies in future clinical trials to define the role of optimal medical therapy and revascularization for patients with carotid artery disease; hopefully, the CREST-2 trial will acquire funding to do so. Although revascularization will play an important role in alleviating stenosis and passivating plaque in the carotid arteries, systemic therapies will clearly be important, particularly for stabilizing plaque locally and in remote vascular beds.

Reprint requests and correspondence: Dr. Robert D. Safian, Center for Innovation and Research in Cardiovascular Diseases (CIRC), Beaumont Health System, Oakland University William Beaumont School of Medicine, Royal Oak, Michigan 48073. E-mail: rsafian@beaumont.edu.

REFERENCES

1. North American Symptomatic Carotid Endarterectomy Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med* 1991;325:445-53.
2. European Carotid Surgery Trialists' Collaborative Group. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). *Lancet* 1998;351:1379-87.
3. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic carotid artery stenosis. *JAMA* 1995;273:1421-8.
4. Halliday A, Mansfield A, Marro J, et al. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomized controlled trial. *Lancet* 2004;363:1491-502.
5. Brooks WH, Jones MR, Gisler P, et al. Carotid angioplasty with stenting versus endarterectomy: 10-year randomized trial in a community hospital. *J Am Coll Cardiol Intv* 2014;7:163-8.
6. Brooks WH, McClure RR, Jones MR, Coleman TC, Breathitt L. Carotid angioplasty and stenting versus carotid endarterectomy: randomized trial in a community hospital. *J Am Coll Cardiol* 2001;38:1589-95.
7. Brooks WH, McClure RR, Jones MR, Coleman TC, Breathitt L. Carotid angioplasty and stenting versus carotid endarterectomy for treatment of asymptomatic carotid stenosis: a randomized trial in a community hospital. *Neurosurgery* 2004;54:318-25.
8. White CJ, Iyer SS, Hopkins LN, Katzen BT, Russell ME, BEACH Trial Investigators. Carotid stenting with distal protection in high surgical risk patients: the BEACH trial 30 day results. *Catheter Cardiovasc Interv* 2006;67:503-12.
9. Gurm HS, Yadav JS, Fayad P, et al. Long-term results of carotid stenting versus endarterectomy in high-risk patients. *N Engl J Med* 2008;358:1572-9.
10. Brott TG, Hobson RW, Howard G, et al. Stenting versus endarterectomy for treatment of carotid stenosis. *N Engl J Med* 2010;363:11-23.
11. Freilinger TM, Schindler A, Schmidt C, et al. Prevalence of non-stenosing, complicated atherosclerotic plaques in cryptogenic stroke. *J Am Coll Cardiol Img* 2012;5:397-405.
12. Lindsay AC, Biasioli L, Lee JMS, et al. Plaque features associated with increased cerebral infarction after minor stroke and TIA: a prospective, case-control, 3-T carotid artery MR imaging study. *J Am Coll Cardiol Img* 2012;5:388-96.
13. Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med* 2007;356:1503-16.
14. Cooper CJ, Murphy TP, Cutlip DE, et al., the CORAL Investigators. Stenting and medical therapy for atherosclerotic renal-artery stenosis. *N Engl J Med* 2014;370:13-22.

Key Words: carotid endarterectomy ■ carotid stenosis ■ carotid stenting.