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Cervical Carotid Revascularization: Indications From an Endovascular Perspective

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The benefit of prophylactic treatment of extracranial carotid bifurcation disease with surgical endarterectomy was established for symptomatic and asymptomatic stenosis in the 1990s in several landmark trials. More recently, the results of the Asymptomatic Carotid Atherosclerosis Study (ACAS) have been confirmed by a much larger trial demonstrating the effectiveness of endarterectomy in asymptomatic patients versus maximum modern medical therapy [1]. In an understandable effort to eliminate confounding variables, however, these trials excluded patients with significant medical and surgical comorbidities; in the North American Symptomatic Carotid Endarterectomy Trial (NASCET), two of three patients screened were ineligible for the study on the basis of one or more high-risk qualities [2]. In fact, these patients comprise between 20% and 50% of the population in whom endarterectomy would otherwise be considered appropriate therapy in clinical practice [3,4]. Moreover, in surveys performed after the NASCET and ACAS, the 30-day mortality rate at high-volume nontrial hospitals was greater than twice that at NASCET centers and almost three times that at low-volume nontrial hospitals [2], suggesting a patient selection issue or operator and/or facility issue.

In several subsequent nonrandomized analyses, the high-risk features excluded in the NASCET and ACAS have been associated with a significant increase in adverse outcomes. Specifically, death, stroke, and myocardial infarction (MI) at 30 days ranged between 7.8% and 9.9% for patients older than 75 years of age [5,6]. The risk of stroke and death alone is typically more than twice that seen in the ACAS and NASCET in patients with congestive heart failure (8.6%) [5], the presence of angina pectoris or coexistent coronary disease necessitating bypass surgery (9.9%–18.7%) [5,6], prior carotid endarterectomy (CEA) with recurrent stenosis (7.6%–10.9%) [7,8], contralateral occlusion (14.3%) [9], and renal insufficiency (8.2%–13%) [10,11]. In a retrospective study performed by the Cleveland Clinic on more than 3000 patients undergoing CEA in a 10-year period, patients with coronary artery disease, chronic obstructive pulmonary disease, and chronic renal insufficiency (creatinine level >3.0 mg/dL) were found to have three times the in-hospital stroke and death rate compared with patients in a normal risk category [3]. Although there are also data relating outcomes to operator and/or center volumes, most observers believe that the extrapolation of the NASCET and ACAS results to these high-risk patients has resulted in these less than favorable outcomes, which are significantly worse than those reported in the original trials.

At about the same time that the role of endarterectomy was being clarified in the United States, an evolution in device technology with the advent of self-expanding stents allowed the consideration of an endovascular alternative to surgery to address its apparent deficiencies in the high-risk patient. Although early work with carotid angioplasty in Europe dates back to the 1980s, the results were suboptimal, and carotid stenting did not start in earnest in the United States until the early to mid-1990s. Those early reports demonstrated the potential of this new technology in high-risk patients, even if the stroke and death rates ranged between 7% and 11% [12,13]. After these single-center reports, the first

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attempt at a randomized trial versus endarterectomy was the Wallstent Carotid Trial (1997–1999), which enrolled largely standard-risk patients [14]. The trial was halted prematurely after approximately 200 patients were enrolled, because it seemed as though the noninferiority end points would not be satisfied. Although there were no significant differences between the treatment groups, there was a trend favoring endarterectomy. Critique of this early trial focused on several key issues: the lack of a dedicated stent (the original Wallstent [Boston Scientific, Natick, Massachusetts] was a tracheobronchial device; it has since been modified for carotid application), the lack of cerebral embolic protection, the inexperienced nature of most operators, the absence of a phase I feasibility trial, and trial design (eg, end point definitions, statistical underpinnings).

Armed with the lessons of this trial and with a better understanding of device, operator, and trial requirements, technology evolved to include dedicated, low-profile, and nitinol stents as well as embolic protection devices and an expanded pool of experienced operators, and the concept of initiating trials in high-risk surgical patients evolved. Although not entirely exclusive, the overlap between a surgical high-risk feature and an endovascular approach to carotid treatment is generally quite limited. Accordingly, the next phase of study involved the high-risk patients in whom endarterectomy was proving difficult. Importantly, those investigating carotid stenting also recognized the importance of independent neurologic auditing of results [15], and it was incorporated into those trials going forward.

The first multicenter randomized control trial ever to examine outcomes of surgery in patients with high-risk features, the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) study, was conducted as a pivotal trial for device approval (Precise nitinol stent [Cordis Endovascular; Johnson & Johnson, New Brunswick, New Jersey] and Angioguard filter embolic protection device [Johnson & Johnson]) for Cordis Endovascular/Johnson & Johnson [16]. Patients with severe carotid stenosis (>50% in symptomatic patients and >80% in asymptomatic patients) and high-risk features were randomized to endarterectomy or carotid stenting after agreement as to their appropriateness among a team consisting of an experienced surgeon, an experienced interventionist, and a neurologist at each site. High-risk comorbidities were defined in two broad categories: anatomic and medical. The anatomic inclusions were contralateral carotid occlusion or laryngeal nerve palsy, prior neck irradiation, prior endarterectomy with recurrent stenosis, difficult surgical access, and tandem lesions. Medical inclusion criteria were severe left ventricular dysfunction (ejection fraction <30%) or New York Heart Association class III/IV heart failure, open heart surgery within 6 weeks, easily provoked angina or an acute coronary syndrome, severe pulmonary disease, and age greater than 80 years. In addition to the 334 patients randomized (310 treated), 407 patients considered to be at excessive surgical risk were entered into a stent registry and 7 patients in whom stenting was considered prohibitive were entered into an endarterectomy registry. The randomized phase of the trial was halted before completion because of lack of enrollment once other nonrandomized registries were in place as preferred alternatives for patients and treating physicians. The 360-day primary end point of all death, all stroke (to 30 days) and ipsilateral stroke (to 360 days), and MI (to 30 days) was 12.2% for the stent arm and 20.1% for endarterectomy ($P = 0.053$), fulfilling the prespecified end point of noninferiority. The risk of stroke out to 2 years was not different for the two treatments, 5.9% for stenting and 5.8% for surgery, and the low 1-year clinically driven target lesion revascularization rates, 0.6% and 3.6%, respectively, demonstrated durability of the initial results in both arms. Subsequent analysis revealed that the ipsilateral stroke rate in both treatment arms was comparable to those in the NASCET and ACAS trials. Based on the results of this randomized control trial, on April 21, 2004, the device advisory panel to the US Food and Drug Administration (FDA) recommended approval of the Precise stent and Angioguard embolic protection system for patients in whom carotid revascularization was indicated and who had high-risk surgical features as defined in the trial.

Several other pivotal device trials followed the SAPPHIRE study but in registry rather than randomized formats according to agreements with the FDA. In these studies, a weighted historical control is used as the comparator to the stent results and is constructed based on a continuously updated review of the literature for outcomes specific to the proportion of each high-risk inclusion group in the trial. The inclusion criteria in these later studies were similar to those of the SAPPHIRE trial, as were the end points, with the

notable exception that the SAPPHIRE study included all death to 1 year, whereas these studies only included death to 30 days as one of the primary measures of procedural safety along with stroke and MI. The ACCULINK for the Revascularization of Carotids in High Risk Patients (ARCHeR), Registry to Evaluate the NeuroShield Bare Wire Cerebral Protection System and Xact Stent in Patients at High Risk for Carotid Endarterectomy (SECuRITY), and Boston Scientific EPI: A Carotid Stenting Trial for High-Risk Surgical Patients (BEACH) studies have all reported 30-day data [17–19], and the ARCHeR trial has reported 1-year primary end point results [20]. The 30-day stroke, death, and MI rates in those trials ranged between 5.4% and 7.8%, and the 1-year freedom from death, ipsilateral stroke, and MI in the ARCHeR study was 90%, statistically better than the historical surgical control. These trial results are remarkable for their low rates of major complications (especially when compared with surgery), their consistency across devices and operators, and their durability in stroke prevention, and they solidify the indication for carotid stenting with embolic protection in the high surgical risk patient.

Carotid stenting with embolic protection is now moving into the standard-risk patient cohorts with the Carotid Revascularization Endarterectomy versus Stent Trial (CREST), sponsored by the National Institute of Neurological Disorders and Stroke (NINDS) of the National Institutes of Health (NIH), in which symptomatic patients are being randomized to receive surgery or stenting. An enrollment of approximately 2500 patients at 70 sites is anticipated over the next several years. In addition, randomized trials in standard-risk asymptomatic patients are being contemplated and should address the role of stenting in the most common cohort currently undergoing CEA in this country.

References

[1] Asymptomatic Carotid Surgery Trial. Lancet 2004.

[2] Wennberg DE, Lucas FL, Birkmeyer JD, et al. Variation in carotid endarterectomy mortality in the Medicare population: trial hospitals, volume, and patient characteristics. JAMA 1998;279:1278–81.

[3] Ouriel K, Hertzer NR, Beven EG, et al. Preprocedural risk stratification: identifying an appropriate population for carotid stenting. J Vasc Surg 2001; 33:728–32.

[4] Lepore MR Jr, Sternbergh WC III, Salartash K, et al. Influence of NASCET/ACAS trial eligibility on outcome after carotid endarterectomy. J Vasc Surg 2001;34:581–6.

[5] Goldstein LB, Samsa GP, Matchar DB, et al. Multicenter review of preoperative risk factors for endarterectomy for asymptomatic carotid artery stenosis. Stroke 1998;29:750–3.

[6] McCrory DC, Goldstein LB, Samsa GP, et al. Predicting complications of carotid endarterectomy. Stroke 1993;24:1285–91.

[7] Das MB, Hertzer NR, Ratliff NB, et al. Recurrent carotid stenosis. A five-year series of 65 reoperations. Ann Surg 1985;202:28–35.

[8] Meyer FB, et al. Recurrent carotid stenosis. In: Sundt's occlusive cerebrovascular disease. 2nd edition. Philadelphia: WB Saunders; 1994. p. 310–21.

[9] Gasecki AP, Eliasziw M, Ferguson GG, et al. Long-term prognosis and effect of endarterectomy in patients with symptomatic severe carotid stenosis and contralateral carotid stenosis or occlusion: results from NASCET. North American Symptomatic Carotid Endarterectomy Trial (NASCET) Group. J Neurosurg 1995;83:778–82.

[10] Wong JH, Findlay JM, Suarez-Almazor ME. Regional performance of carotid endarterectomy. Appropriateness, outcomes, and risk factors for complications. Stroke 1997;28(5):891–8.

[11] Hamdan AD, Pomposelli FB Jr, Gibbons GW, et al. Renal insufficiency and altered postoperative risk in carotid endarterectomy. J Vasc Surg 1999;29: 1006–11.

[12] Diethrich E, Ndiaye M, Reid DB. Stenting in the carotid artery: initial experience in 110 patients. J Endovasc Surg 1996;3:42–62.

[13] Yadav JS, Roubin GS, Iyer S, et al. Elective stenting of the extracranial carotid arteries. Circulation 1997; 95:376–81.

[14] Gray WA, et al. Presented at the American Stroke Association National Meeting. February 2001.

[15] Rothwell, Slattery J, Warlow CP. A systematic review of the risks of stroke and death due to endarterectomy for symptomatic carotid stenosis. Stroke 1996;27:260–5.

[16] Yadav J. Presented at the American Heart Association Meeting. 2002.

[17] Wholey M. Presented at the American College of Cardiology Annual Sessions. 2003.

[18] Whitlow P. Presented at the American Heart Association National Meeting. 2003.

[19] White C. Presented at All That Jazz Meeting. April 2004.

[20] Gray W. Presented at the American College of Cardiology National Meeting. March 2004.