The Cart and The Horse
The Advancing Technology of Carotid Artery Stenting
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Endarterectomy is recommended in current clinical guidelines for selected patients with a significant symptomatic or asymptomatic extracranial carotid artery stenosis, provided that the operation can be performed with acceptable safety.1–3 These recommendations are based on the results of several controlled trials in which those randomized to have the operation had better clinical outcomes compared with those who did not, on a background of what at the time was considered to constitute best medical therapy. The advent of angioplasty/stenting offers the promise of a less invasive means of directly treating carotid artery stenotic disease compared with endarterectomy. Unlike surgical procedures, however, pharmaceuticals, biologicals, and devices are subject to regulatory approval in the United States by the Food and Drug Administration. Placement of a carotid artery stent system was first approved by the Food and Drug Administration in 2004 for the treatment of patients deemed “at high risk for adverse events from carotid endarterectomy who require carotid revascularization [who have] neurological symptoms and ≥50% stenosis of the common or internal carotid artery by ultrasound or angiogram, or in patients without neurological symptoms and ≥80% stenosis of the common or internal carotid artery by ultrasound or angiogram” (http://www.fda.gov/cdrh/pdf4/p040012a.pdf).

Registries were developed to help assess the safety of stent systems as used in larger populations, in part to help identify risks that might not have been apparent based on the smaller numbers of subjects included in the randomized trial that compared stenting with endarterectomy in patients at high risk of postendarterectomy complications.4 In that trial, the 30-day stroke, myocardial infarction, or death was 2.1% with stenting versus 9.3% with endarterectomy (P=0.18) for symptomatic patients; for those with an asymptomatic carotid artery stenosis, the periprocedural rates were 5.4% versus 10.2% (P=0.20), respectively. A 2008 review noted that the 30-day postprocedure event rates (stroke, myocardial infarction, or death) in carotid-stenting registries ranged from 2.1% to 8.3%.5 A more recent registry reported a 4.4% periprocedural stenting complication rate in patients at high endarterectomy complication risk (3.2% stroke, 0.7% myocardial infarction, 1.1% death).6 In this issue of Circulation: Cardiovascular Interventions, Gray et al7 report on the combined final results of another high-risk registry and the interim results of a second. The combined 30-day stroke and death rate for stenting was 5.3% (95% CI, 3.6% to 7.4%) for those with symptomatic disease and 2.9% (95% CI, 2.4% to 3.4%) for those with an asymptomatic stenosis; the rates were 1.7% (95% CI, 0% to 8.9%) and 2.7% (95% CI, 1.3% to 4.9%) for symptomatic and asymptomatic patients with anatomic features unfavorable for surgery (ie, prior endarterectomy, prior radical neck surgery or radiation therapy, surgically inaccessible stenosis, neck tumors, spine immobility, tracheostomy, and contralateral laryngeal nerve palsy). The complication rates found in these more recent registry studies, therefore, seem reassuring in that they generally compare favorably with those of the high carotid endarterectomy risk randomized trial, seem to reflect further temporal improvements as experience with the technique has increased (at least in those with asymptomatic disease) and tend to support the use of stenting in selected symptomatic patients who cannot have an endarterectomy because of anatomic features unfavorable for surgery.

Gray et al also note that the complication rates with carotid artery stenting that they report are within American Heart Association–recommended standards for endarterectomy as performed in average-risk patients (ie, <6% for symptomatic lesions and <3% for asymptomatic lesions).2,3 The direct application of these standards to the more recent carotid stenting data, however, may not be appropriate. The guideline recommendations are based on randomized trials with contemporaneous controls and are internally consistent. Acceptable complication rate thresholds might, however, be lower and absolute numbers of patients needed to treat to prevent a stroke increased if the event rates with medical therapy declined compared with when the trials were done. The results of the randomized trials of endarterectomy for high-grade symptomatic carotid artery stenosis were published almost 2 decades ago,8–10 with reports of trials for patients with a moderate symptomatic stenosis now more than 10 years old.11,12 Unlike these largely contemporaneous trials of endarterectomy for symptomatic stenosis, nearly a decade passed between the reports of the two, large randomized trials of endarterectomy for patients with a 60% to 99% asymptomatic carotid artery stenosis. The results of the Asymptomatic Carotid Atherosclerosis Study (ACAS) were published in 1995 and those of the Medical Research Council (MRC) Asymptomatic Carotid Surgery Trial (ACST) were published...
Any major stroke or perioperative death

Any stroke or any perioperative death

Major ipsilateral stroke or any perioperative major stroke or death

Ipsilateral stroke, any perioperative stroke or death

Any major stroke or death

Any stroke or death

in 2004.13,14 ACAS found that the 5-year risk of the primary outcome (ipsilateral stroke, any periproductive stroke, or death) was reduced from 11.0% for patients treated only medically to 5.1% for those who also had surgery (P=0.004).

The ACST supported the conclusion of ACAS, finding a 5-year risk of 11.8% with medical therapy versus 6.4% for surgery (P<0.0001). This benefit, however, was for any stroke or periproductive death rather than for the ACAS primary outcome. The Table compares the results of ACAS with those of the ACST based on the ACAS primary and secondary end points with the results of the ACST tabulated based on data provided in the trial report. The Table also gives calculated relative risk reductions for each ACAS end point for each trial. As can be seen, the results of the 2 trials are not completely comparable with the rates of nonvascular death higher in the ACST. Focusing just on fatal and nonfatal stroke in patients not having endarterectomy (ie, the outcome of stroke or “perioperative” death in nonsurgical subjects), the rate in ACST was 8.4% compared with 17.5% in ACAS.

Although indirect comparisons are fraught with potential biases, medical therapy evolved in the interval between the 2 trials and may have contributed to the relatively lower stroke rate in patients treated medically without endarterectomy in the ACST. This not only points out the potential hazards of using historical controls to support the efficacy of an intervention but also suggests that the complication thresholds derived from past clinical trials, at least for patients with an asymptomatic carotid artery stenosis, may no longer be appropriate.

It is also important to reiterate that the comparability of carotid artery stenting and endarterectomy in patients at average risk of complications with endarterectomy has not been established. Three meta-analyses comparing carotid angioplasty (with or without stenting and with or without distal protection devices) with endarterectomy were published in 2008. Owing to differences in the trials that were included in each analysis, as well as variation in study end points and in the types of statistical analyses conducted, 1 meta-analysis concluded that there is no difference between stenting and endarterectomy in patients with symptomatic stenosis15 and 2 concluded that carotid artery stenting is neither safer nor as safe as endarterectomy.16,17 A 2009 Cochrane Systematic Review concluded that, “the data are difficult to interpret because the trials are heterogeneous [with] 5 stopped early, perhaps leading to an overestimate of the risks of endovascular treatment,” and that “the results do not support a change in clinical practice away from recommending carotid endarterectomy as the treatment of choice for suitable carotid artery stenosis.”18 Yet, carotid endarterectomy is being performed less frequently and carotid artery stenting more frequently, at least among Medicare beneficiaries. Between 1998 and 2004, the rate of carotid endarterectomy decreased by 17% (P<0.01), whereas the rate of stenting increased by 149% (P<0.01).19 Analysis of the complication rates of 254 044 carotid endarterectomies and 14 035 stenting procedures from the US Nationwide Inpatient Sample from 2003 to 2004 found that, compared with endarterectomy, carotid artery stenting was associated with higher rates of both periproductive stroke (2.1% versus 0.9%, P<0.0001) and death (1.3% versus 0.4%, P<0.0001).20 After adjustment for confounders, carotid artery stenting was still associated with higher postprocedural odds of postprocedural stroke (odds ratio, 2.49; 95% CI, 1.91 to 3.25) and death in both symptomatic (odds ratio, 2.64; 95% CI, 1.89 to 3.69) and asymptomatic (odds ratio, 2.37; 95% CI, 1.46 to 3.84) patients.

The results of yet to be reported randomized trials comparing stenting with endarterectomy in average-risk patients, including the Carotid Revascularization Endarterectomy versus Stent Trial and the International Carotid Stenting Study, are desperately needed to help further inform clinical decision making. Even after these results become available, rigorous case selection and a realistic view of the comparable potential risks and benefits of the intervention need to be carefully assessed when considering whether to offer carotid revascularization to a particular patient, and if revascularization is appropriate, which procedure to recommend.

Disclosures

Dr Goldstein is the site investigator for CREST (National Institutes of Health), is a consultant for Johnson & Johnson, and serves on the Site Oversight Committee for ACT-1 (Abbott).

References


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