Circulation: Fire in the Hole: Carotid Stenting Versus Endarterectomy
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Carotid artery stenting has weathered a withering attack during the past year. Comparisons of the 3 recent randomized trials from Europe comparing carotid stenting with endarterectomy in symptomatic patients lead many to favor endarterectomy. The other 2 trials from North America included a mix of symptomatic and asymptomatic patients with carotid stenosis, and suggest more muted differences, pointing to equivalence or at least equipoise between the 2 modes of revascularization. This transatlantic tug-of-war is particularly focused on the importance of adequate training and experience in stenting among operators, the different end points between these trials, and patient selection.

Operator Experience and Skill
As with carotid endarterectomy, adequate operator training, credentialing, and auditing are important aspects of carotid stenting. Credentialing to select surgeons with low complication rates was a major feature of the randomized trials of endarterectomy in comparison with medical therapy 2 decades ago. The minimization of periprocedural stroke and death permitted an assessment of the maximum efficacy of endarterectomy in symptomatic and asymptomatic patients. However, this principle was applied selectively in the recent major trials of carotid stenting compared with carotid endarterectomy. Whereas carotid endarterectomy required specific criteria for demonstrating volume and low procedural complications in all trials, relatively inexperienced operators could do carotid stenting in some European studies. Embolic protection devices, often considered an essential tool to prevent periprocedural stroke, were used variably in the European studies, and could be a marker of operator experience or carotid plaque with a perceived higher risk of embolization in these trials. Notably, the absolute difference in periprocedural stroke between endarterectomy and stenting was lower in the North American trials, where credentialing for stenting by case review of 20 or more carotid stent cases was a prerequisite for operators. Because the differences in outcomes are much less in the periprocedural period, operator skill and other factors related to low periprocedural adverse events will determine the long-term value and widespread applicability of either mode of revascularization.

Periprocedural End Points
Recent reviews criticize the inclusion of periprocedural myocardial infarction as an end point in Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) and Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST). They claim that this loads the dice in favor of stenting, in particular, when general anesthesia and vascular surgery have higher risks of periprocedural myocardial infarction. This argument is supported by the analysis of quality of life at 1 year in CREST. In these post hoc analyses, periprocedural major and minor stroke, but not myocardial infarction, significantly lowered physical and mental component scales. Although the declines with major stroke were consistent across scales, the declines with minor stroke were smaller, and similar in magnitude to, patients experiencing periprocedural myocardial infarction. The CREST trial did not report the quality-of-life differences between endarterectomy and stenting, in contrast to the SAPPHIRE trial, where there were no differences in quality of life between the 2 modes of intervention at 1 year. Nevertheless, the CREST results propagated a view by prominent neurologists that stroke was a more important periprocedural adverse event than myocardial infarction.

Mechanistic versus Patient-Orientated End Points
The end points of clinical trials in the treatment of carotid disease to prevent stroke also require more thought. Arguably, there are 2 important perspectives to consider (Table). These include a more mechanistic question of whether...
endarterectomy, stenting, or medical therapy alone can reduce stroke caused by a significant carotid stenosis. The efficacy end points most suitable for this question are the long-term risk of ipsilateral stroke and cerebrovascular death (including periprocedural events). Because asymptomatic disease generally requires 3 years for benefit over medical therapy, a 4- to 5-year time frame for this end point is appropriate; whereas, in symptomatic patients, a shorter time frame of 1 to 2 years may be adequate.

The second perspective is that of the patient. To the patient, the important goal is to prevent any stroke (ipsilateral or contralateral), death from any cause, and myocardial infarction over a similar time frame. Secondary efficacy end points could be the softer ones of cognitive function, independence in activities of daily living, and quality of life (perhaps more difficult to measure, but end points many patients would value more highly).

The primary safety end points concern those immediately related to the procedures, such as periprocedural stroke, death, or myocardial infarction (within 30 days). The CREST report in the current issue of Circulation makes a strong case for the inclusion of periprocedural myocardial infarction, because it is an important predictor of death. Had CREST systematically ascertained myocardial infarction and contralateral stroke after the periprocedural period, we might be more informed on the relative importance of periprocedural myocardial infarction and stroke on these patient-orientated outcomes. Secondary safety end points could include periprocedural silent myocardial infarction (as justified in this CREST report), or silent cerebral emboli identified by magnetic resonance imaging providing this latter end point relates to subsequent stroke, death, or functional outcomes.

### Risks and Benefits of Revascularization

Most carotid endarterectomy and stenting is for asymptomatic disease. Even among patients with carotid territorial transient ischemic attack or minor stroke, the risk of subsequent stroke rapidly declines to asymptomatic levels with medical therapy. In the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and European Carotid Surgery Trial (ECST) studies, the risk of any periprocedural stroke or death, or ipsilateral stroke over 5 years, was 13% among patients with a significant stenosis whose time from last transient ischemic attack or stroke was 3 or more months. This risk is similar to the 5-year risk of any stroke or perioperative death in medically treated asymptomatic subjects in the Asymptomatic Carotid Surgery Trial (ACST) study (11%). When presented as event-free risks, some patients balk at carotid revascularization when told it will increase their 5-year event-free risk from 89% to 93%. Thus, the identification of patients at low periprocedural risk for cardiovascular events and higher than average long-term stroke risk is a crucial component of strategies assessing overall benefit from carotid revascularization.

The CREST report in this issue of Circulation and other studies identify risk factors for perioperative cardiovascular events that are shared between endarterectomy and stenting (eg, age >75 years, operator/surgical experience and skill, mild cognitive defects or dementia, recent acute coronary syndromes, and prior cardiovascular disease). Other risk factors are more relevant for increasing the risk with stenting (heavily calcified lesions and excessive tortuosity of the internal carotid), and some risk factors are specific to endarterectomy (congestive heart failure, very high or very low lesions, prior radiotherapy, prior ipsilateral carotid endarterectomy, and contralateral occlusion). However, contemporary studies of carotid revascularization make assumptions of benefit based on antique medical therapy.
Optimal Medical Therapy: An Untested Treatment

This highlights the major deficiency in our knowledge on the management of carotid disease for stroke prevention. Contemporary optimal medical therapy directed against atherosclerosis and platelet activity potently prevents stroke in populations at high cardiovascular risk. For example, in the randomized trials of coronary disease prevention, statins lowered the risk of ischemic stroke by 20% to 50%. In the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study, which enrolled patients with transient ischemic attack or minor stroke, intensive statin therapy lowered the 5-year rate of fatal or nonfatal stroke risk by an absolute difference of 1.9% (relative reduction of 16%). Although these studies did not specifically enroll patients with significant carotid stenoses, similar magnitudes of effect were observed in the ACST study among patients receiving lipid lowering of varying intensity. Optimal medical therapy attacks the biological processes of plaque instability and inflammation (fire in the hole) responsible for ischemic stroke in patients with carotid disease. Thus, contemporary optimal medical therapy is likely to erode the potential incremental benefit from carotid revascularization.

Current Practice

The wide variation in periprocedural adverse events between the stent versus endarterectomy trials points to a measured approach when deciding on any carotid revascularization or the mode of revascularization. When the risk of stroke without revascularization is high, carotid stenting will be favored in patients with higher periprocedural surgical risk and endarterectomy will be favored in patients at high periprocedural risk from stenting. Both modes of revascularization require operators who are adequately trained, credentialed, and audited for low periprocedural adverse events. The relative merits of stent versus surgery for patients at average periprocedural risk are less concerning with good operator experience than the more pressing issue of improving our ability to define patients who really obtain benefit from revascularization beyond optimal medical therapy.

Importantly, antiatherosclerotic (statins, antihypertensives, nonsmoking, and weight reduction) and antiplatelet (aspirin and thienopyridines) therapy are not placebo treatment, and may be the preferred alternative in patients with characteristics that portend high periprocedural risk from either stenting or surgery (inexperienced operator/surgeon, patients with extreme age, cognitive deficits or dementia, or recent acute coronary syndromes). In clinical practice, the balance of risks may require true grit on the part of operators and surgeons to refer to other specialties or decline revascularization in favor of optimal medical therapy alone. As a profession, the future of carotid revascularization depends on our courage to test optimal medical therapy with and without revascularization in randomized trials against mechanistic and patient-orientated outcomes.

Disclosures

None.

References


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