Angioplasty and Stenting Should Be Performed Only in the Setting of a Clinical Trial

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Dr. Roubin cites exciting observational data supporting carotid artery stenting as treatment for focal carotid artery disease. Unfortunately, observational studies cannot substitute for randomized trials. The design is not experimental. The treatment for each patient is chosen by the interventionalist, and so selection bias cannot be avoided. Assessment of outcomes is vulnerable to investigator ascertainment bias and in some cases conflict of interest. Full reporting cannot be ensured, nor can publication bias be avoided. Comparison to historical controls is not valid because the competing medical and surgical treatments have advanced.

For surgical therapy, randomized trials have shown that absolute risk reduction may be high as 5% per year for symptomatic patients with stenosis ≥70%, approximately 1% per year for symptomatic patients with stenosis ≥50% to 69%, and up to 1% per year in asymptomatic patients with stenosis ≥60%, when surgical results are optimal. Benefits for asymptomatic women following CEA have not been established, and CEA has not been compared with medical treatments as currently recommended (eg, antihypertensive therapy for blood pressure ≥135 mm Hg systolic, ≥85 mm Hg diastolic; lipid-lowering therapy for diet-resistant LDL >100 mg/dL; alternative antiplatelet therapy for aspirin failure).

For carotid stenting, safety and efficacy (and durability) as first-choice treatment have not been established for low-risk patients. For such patients, those who would have been eligible for NASCET or ACAS, carotid stenting must be considered experimental. CEA is the standard of care. Accordingly, carotid stenting should be done in the context of a clinical trial protocol, patient informed consent, and oversight of institutional review boards. Interventionalist-reported case series cannot justify stenting for low-risk patients, even those reporting outstanding results. The more generalizable prospective, multicenter trial experience as of 2002 does not suggest low morbidity and mortality. In CAVATAS, stroke lasting more than 7 days, intracerebral hemorrhage, or death within 30 days occurred in 6 patients among the 55 who were treated with carotid stenting. In the WALLSTENT trial, stroke or death occurred within 30 days in 12%.

For high-risk symptomatic patients, stenting has the potential advantage of being less invasive. In addition, patients with high cervical stenoses, radiation-induced stenoses, and post-CEA stenoses are technically more challenging for the surgeon. Nonetheless, observational data are not sufficient to proceed with stenting as first-choice treatment. Studies of CEA for high-risk patients, those who would not have qualified for NASCET, have reported perioperative stroke and death rates equivalent to those reported for stenting. A safety advantage for carotid stenting compared with CEA has not been shown for any high-risk comorbidity.

High-risk asymptomatic patients are better off with medical therapy until proven otherwise (ie, in a randomized clinical trial). A “need” for carotid revascularization has not been empirically established in these patients. Perioperative risk is 3% to 5% in the best of hands. No evidence exists to suggest that carotid stenting is superior to 2002 medical therapy, eg, for the asymptomatic 82-year-old diabetic male, the 72-year-old asymptomatic female with cardiomyopathy, or the asymptomatic patient with restenosis.

What, then, are the indications for carotid stenting outside a clinical trial? A positive evidence-based recommendation cannot be sustained. But, much of what we do in medicine is not supported by evidence from randomized clinical trials. For some of the special cases mentioned above (symptomatic patients with postirradiation stenosis, post-CEA stenosis, high cervical stenosis, stenosis with contralateral occlusion, or stenosis with need for coronary revascularization), randomized trials may not be feasible. Carotid stenting may be considered—for symptomatic patients—by centers with unassailable excellent results.

Is it ethical to study carotid stenting in clinical trials, or are the patients of 2002 being used as guinea pigs to benefit the patients of 2012? The success of coronary artery stenting and the observational evidence Dr. Roubin cites do offer the rationale and the ethical support for randomized clinical trials. However, these trials must protect patients by including only interventionalists with demonstrated low morbidity and mortality, comparable to that of the surgeons. Once under way, these trials must be monitored frequently to ensure that the low rates of morbidity and mortality are reproduced within the scrutiny of the trial. In addition, investigators should have mechanisms in place for evaluating new technology, such as the distal embolization capture devices now...
being touted, or new drugs, such as the GPIIb/IIIa platelet aggregation receptor antagonists.

References

Angioplasty and Stenting Should Not Be Restricted to Clinical Trials

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Excellence in clinical practice necessitates the application of evidence-based medical decision-making in determining patient management. The evidence comes from many sources, including prospective randomized trials and prospective cohort studies with rigorous outcomes assessment. Prospective multicenter, randomized studies may provide a sense of generalization of results to the community at large but lack specificity for individual patients. Alternatively, individual operator results are highly specific in determining efficacy of carotid stenting. Arguments against restricting the performance of carotid stenting to the setting of a clinical trial center on the issues of individual operator expertise and the narrow eligibility criteria used in randomized trials. Even if widespread application of carotid stenting were to await the completion of prospective randomized trials, “level 1 scientific evidence” would be available for only a small subset of patients with carotid stenoses. The hypocrisy of vascular surgeons who advocate the restriction of carotid stenting lies first in the decades of carotid endarterectomy (CEA) procedures before availability of “level 1 evidence” of its benefit, and second and more importantly, the widespread application of CEA to large subsets of patients (eg, elderly and females) never satisfactorily studied in prospective randomized trials.

An argument is often forwarded that allowing patients and physicians to choose a preferred therapy unduly impedes recruitment into ongoing randomized trials. Examination of the contemporary development of cardiovascular and cerebrovascular therapies does not support such arguments. The NIH-sponsored Coronary Artery Surgery Study (CASS), Bypass versus Angioplasty Revascularization Investigation (BARI), North American Symptomatic Carotid Endarterectomy Trial (NASCET), and Asymptomatic Carotid Atherosclerosis Study (ACAS) were all completed in a clinical environment in which these medical, interventional, and surgical therapies were freely and widely practiced in the community. It might reasonably be argued that widespread utilization and expertise in coronary bypass surgery, coronary...
angioplasty, and CEA enabled the success of these trials. The same is true for carotid stenting.

Carotid stenting has now been in use for almost a decade. Immediate outcomes in terms of periprocedural neurological events have improved markedly as expertise in the community has grown and embolic protection technology has become available. Restricted application of the therapy is currently more a function of FDA and HCFA intervention than the absence of sound clinical results. Questions have been raised about the influence of surgical societies on these agencies and political and financial motivation to restrict a technique, regardless of its merit, that might decrease the role of carotid endarterectomy.

Operator expertise is pivotal in determining the success of carotid stenting. Unlike the usual pharmaceutical intervention, efficacy of stenting mostly depends on its application to the patient. This has 2 important implications. The first is that proceeding with a clinical trial without establishing operator expertise would be similar to starting a drug trial without any idea of the formulation, potency, or dose of the agent to be tested. It follows that before proceeding with expensive and time-consuming randomized trials, we must allow operators to develop expertise. Technical expertise can to some extent be taught, but ultimately it only comes with experience in performing a larger number of cases. On average, NASCET and ACAS surgeons had many years of experience and had performed hundreds of cases before CEA was compared with medical therapy in a randomized trial. In the Carotid Revascularization Endarterectomy versus Stenting (CREST) trial, stent operators are being rigorously credentialed before they can proceed in the randomized trial. Progress is being impeded precisely because most of the operators have very limited experience and cannot gain experience with the technique given FDA, HCFA, and local medical and political restrictions.

The second important point concerning operator expertise is that in the case of carotid stenting, it is easy to measure. Objective performance criteria can be defined and preprocedural and postprocedural neurological examination can precisely document adverse events. Given that late events have been rare, vigorous procedural outcomes assessment (periprocedural stroke and death) can provide an accurate measure of efficacy and basis for local decision-making. Vascular surgeons must of course be held to the same standards. In symptomatic patients, a ≤5% 30-day complication rate is acceptable. For asymptomatic patients meeting ACAS criteria (eg, <80 years of age), a ≤3% 30-day complication rate is acceptable.

Can these outcomes be achieved by individual experienced operators and groups? The current evidence strongly suggests it can be achieved and documented. Current acceptable results need to be examined in the context of routine use of embolic protection devices. Theron at al10 first reported low complication rates with embolic protection. Henry et al confirmed this work with a now commercially available distal balloon occlusion, embolic protection system. In a consecutive series of 150 patients, they observed 1.3% nondisabling strokes and 1.6% disabling strokes (including 1 fatality) at 30 days. Parodi et al in 46 consecutive procedures—23 with a variety of embolic protection devices—showed a 9.5% complication rate in the unprotected cohort and 0% in the protected patients. Reimers et al10 reported 84 consecutive patients using 3 embolic protection systems with 1.2% nondisabling and 0% disabling strokes at 30 days. Al-Mubarak et al reported a multicenter, consecutive 162-patient experience with a single embolic filter with 1.5% nondisabling and 0% disabling stroke at 30 days. Numerous reports confirm that competent and experienced operators can perform carotid stenting with very low complication rates.12–15 In our own experience with 5 different embolic protection systems, 370 cases have been completed (all with neurological audit) with a 2% nondisabling stroke risk and 0.3% disabling stroke risk.16

In addition, late outcome data are now available. Angiographic restenosis rates, need for repeat intervention, and ipsilateral stroke rates have been extremely low. Freedom from ipsilateral stroke or neurological death after 30 days was 99% at 3 years in 1 large study. Only 3% of patients required any additional intervention on the stented vessel.6 In the prospective, randomized, multicenter Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS), 3-year clinical outcomes were identical for angioplasty/stenting and CEA.17

Undoubtedly, from a patient’s perspective, carotid stenting has some distinct advantages. There is no operative incision on the neck; no general anesthesia, operative risk, or risk of cranial nerve damage; and potential for a day case procedure.18 These undeniable advantages of stenting over CEA are additional reasons that carotid stenting should not be limited to clinical trials. Carotid stenting should be restricted to operators who submit their outcomes to independent peer review and demonstrate efficacious results.

Clinical trials must be undertaken to rigorously validate the methods used in carotid stenting. Comparison to CEA is only 1 issue. More important studies are needed to compare different methods of embolic protection, other adjunctive devices, and pharmacological agents that may further enhance patient care. However, the practice of carotid stenting should not be restricted to randomized trials! In the final analysis, is the lack of prospective randomized trials the real issue? Or is this simply a “smoke screen” conveniently used by the surgical community to hide the “wagons they have circled around” their coveted CEA procedure?

References

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Key Words: carotid endarterectomy ■ clinical trials ■ outcome ■ stents

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**Carotid Stenting Is Unproven: Randomization Is a Must**

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Mr Smith is a 72-year-old man who has a transient episode of dysphasia and is found to have an 80% left internal carotid artery stenosis. In 2002, should he be treated with carotid endarterectomy (CEA), or should he be offered carotid stenting? If one practices evidence-based medicine, we believe he should only be offered a carotid stent in the context of a randomized controlled trial, given the proven benefits of endarterectomy in skilled surgical hands.1,2 Dr Roubin rightly indicates that there were huge numbers of endarterectomy procedures performed before the technique was validated in the pivotal North American and European trials in the 1990s, but it is also fair to note that there was no proven alternative treatments at that time. He points out that vested interests are also relevant in the vehemency of the arguments being mounted, but these concerns must be balanced against the frequency of carotid disease in Caucasian populations (often asymptomatic) and the risks of widespread introduction of stenting, without validation against the gold-standard procedure. Medical advances in stroke prevention are also relevant, including angiotensin-converting enzyme inhibitors, statins, and alternative antiplatelet strategies in aspirin failures and need to be incorporated in trial designs.

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head-to-head trials of endarterectomy versus stenting are needed to determine whether stenting is equivalent or superior to endarterectomy. However, we believe that Mr Smith should currently be advised to have a CEA performed by an experienced surgeon, unless he consents to be randomized in a controlled trial.

References

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