The Role of Stents in Patients with Carotid Disease

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Carotid endarterectomy, the most commonly performed peripheral vascular surgical procedure, is associated with substantial clinical benefit when performed in patients with significant carotid bifurcation stenotic disease. The rate of morbidity and mortality, however, is significant when performed in patients with medical comorbidities or challenging surgical anatomy. Carotid stenting has emerged as a less invasive alternative to traditional endarterectomy. A large number of clinical trials, both randomized and registry-based, are ongoing. Initial results suggest that the outcome of carotid stenting may be identical to that of endarterectomy in most patients and may also offer additional clinical benefit in patients at high risk from an open surgical approach.
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No vascular surgical procedure has been subject to such extreme scrutiny as carotid endarterectomy. Since the first carotid repair for symptomatic disease performed by the Argentineans Carrea, Molins, and Murphy in 1951,[1] the procedure has been investigated in a wide array of well-designed and well-executed clinical trials. In fact, a multicenter trial comparing the surgical and medical management of carotid disease was organized within a decade of Carrea's report, and the results of a randomized comparison of more than 1200 patients, known collectively as the Joint Study of Extracranial Occlusion, appeared in a series of publications in the late 1960s and early 1970s.[2] The articles

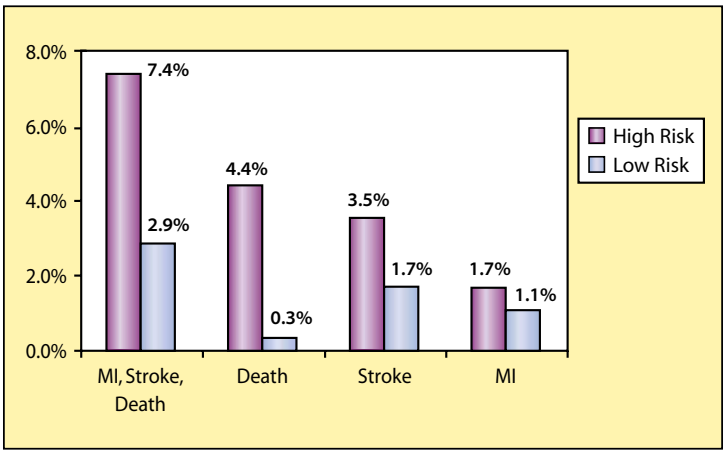

Figure 1. *The risk of stroke, myocardial infarction, and death as a composite end point and separately in 3061 high- and low-risk patients undergoing carotid endarterectomy at the Cleveland Clinic. Data from Ouriel et al.*[6]

from the study documented benefit from surgical revascularization over medical management in particular subgroups of patients. Noting the findings of this study, W. S. Fields suggested that any patient with localized, symptomatic carotid disease is best treated by carotid endarterectomy, with marked reduction in the frequency of recurrent neurologic events.[2]

Potential Limitations of Standard Therapy for Carotid Disease

Carotid endarterectomy is a well-proven intervention for carotid disease. The results of numerous clinical trials have documented its safety and efficacy; hence, it remains the standard of care for patients with severely stenotic extracranial lesions, whether the patient is symptomatic or not.[3-5] Nevertheless, the excellent results achieved with the procedure appear to be dependent on the baseline medical status of the patient. Relatively healthy patients do very well with open surgical repair of carotid lesions. The treatment of medically compromised patients, however, is associated with a much greater risk of complications, as illustrated in a review of more than 3000 patients undergoing carotid endarterectomy at the Cleveland Clinic Foundation between 1988 and 1998.[6] In this analysis of a consecutive series of patients, the risk of the composite end point of stroke, myocardial infarction, or death was quite satisfactory in patients who did not manifest one of four classes of baseline comorbidity (coronary artery disease requiring intervention, congestive heart failure, chronic lung disease, and renal insufficiency). The risk of perioperative morbidity and mortality was substantial, however, when patients exhibited one or more baseline comorbid conditions (Figure 1). Specifically, the risk of perioperative death was elevated by a factor of more than 5, stroke or myocardial infarction each by a factor of 2, and the composite end point of death, stroke, or myocardial infarction by a factor of almost 3.

The treatment of medically compromised patients, however, is associated with a much greater risk of complications, as illustrated in a review of more than 3000 patients undergoing carotid endarterectomy at the Cleveland Clinic Foundation between 1988 and 1998.

The interpretation of the Cleveland Clinic data is that, in most cases, carotid endarterectomy is a procedure with an extremely low rate of complications. In studies that specifically exclude high-risk patients from eligibility, for example, the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the Asymptomatic Carotid Atherosclerosis Study (ACAS), the rate of periprocedural complications can be expected to be extremely low.[7] Casual review of these trials is fraught with the grave error of assuming that the results of carotid endarterectomy are analogous in the unselected patients undergoing carotid repair at a wide range of hospitals and by practitioners with a broad spectrum of experience. On the contrary, there exist data suggesting that the results of the trials cannot even be generalized to patients undergoing endarterectomy at the hospitals that participated in the studies. In a study of 113,000 Medicare patients who underwent carotid endarterectomy during patient acquisition for the NASCET and ACAS trials (1992–1993), Wennberg and colleagues noted that the perioperative mortality rate was 1.4% in hospitals participating in the trials and 1.7% in hospitals that did not participate in the trials.[8] The rate of perioperative death rose to 2.5% in low-volume nontrial hospitals where fewer than seven carotid endarterectomies were performed annually. These relatively high complication rates are in direct contrast to the much lower mortality rates observed in the patients entered into the trials (0.1% in ACAS and 0.6% in NASCET). These findings suggest that eligibility criteria were sufficiently strict that patients in the NASCET and ACAS trials represented a small subset of the total

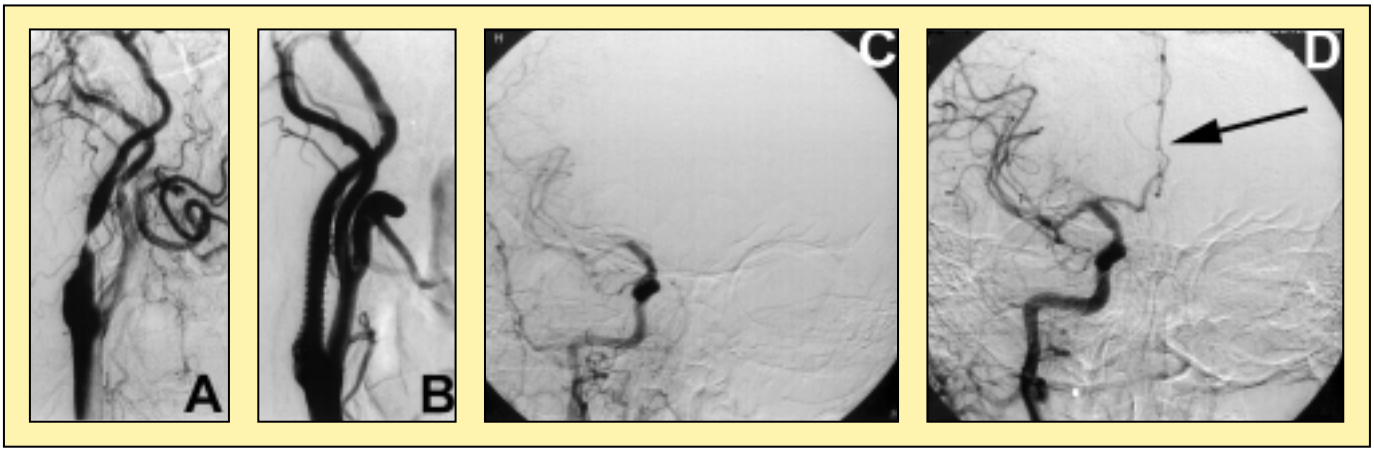

Figure 2. *Carotid stenting in a patient with a symptomatic right internal carotid lesion.* **(A)** *The preintervention angiogram, demonstrating a critical stenosis.* **(B)** *Postintervention, without residual stenosis.* **(C)** *The preintervention baseline intracranial angiogram demonstrating poor filling of the anterior cerebral vessels from the right-sided injection.* **(D)** *After stenting, the anterior cerebral circulation is now well visualized (arrow).*

population of patients undergoing carotid endarterectomy—a subgroup with the lowest frequency of baseline comorbid conditions and likely the lowest rate of perioperative adverse events.

The data from the Cleveland Clinic registry offer an explanation for the Wennberg findings. Patients in the multicenter trials of carotid endarterectomy were similar to the low-risk group of patients undergoing carotid repair at the Cleveland Clinic. In fact, the mortality rate of 0.2% in more than 1500 "low-risk" asymptomatic patients treated with carotid endarterectomy is remarkably similar to the ACAS mortality rate of 0.1%. Similarly, the mortality rate was 0.5% in 925 symptomatic patients undergoing carotid endarterectomy at the Cleveland Clinic, almost identical to the 0.6% mortality rate observed in the NASCET trial.

In addition to baseline comorbidities, there exists a variety of anatomic features that are also associated with poor outcome. These include such variables as contralateral carotid occlusion,[3] recurrent carotid lesions,[6] and a history of radiation therapy to the neck. These factors may be quite important in determining the outcome of open carotid procedures, with regard to perioperative stroke, myocardial infarction, and death as well as softer end points such as wound complications and cranial nerve injury. These anatomic features should also be taken into account in the differentiation between high- and low-risk patients. Complications that are associated with the invasive nature of open surgery would be likely to occur at a lower frequency in the stented subgroup. As such, both clinical and anatomic baseline variables should be addressed when delineating a high-risk patient population suitable for an initial investigation of endarterectomy versus stenting.

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Categories of Disease Appropriate for Carotid Stenting

The etiology of carotid bifurcation disease can be categorized into atherosclerotic and nonatherosclerotic processes, the former presenting much more frequently than the latter in clinical practice. The nonatherosclerotic causes of carotid bifurcation disease may be further subdivided into inflammatory problems, such as early postendarterectomy restenosis, Takaysu's arteritis, postendarterectomy intimal hyperplasia, and carotid

Figure 3. *The AngioGuard filter removed after stenting of the patient depicted in Figure 2. Note the large particle of debris within the stent (at 12 o'clock), as well as smaller, more gelatinaceous material.*

Table 1
Clinical Trials of Carotid Stenting

Trial	Sponsor	Design	Stent	Protection Device
ARCHeR	Guidant	Registry, high-risk	AccuLink	AccuNet
BEACH	Boston Scientific	Registry, high-risk	Wallstent, Monorail	FilterWire EX
CABERNET	Boston Scientific, EndoTex	Registry, high-risk	NexStent	EPI Filter
CARESS	ISIS	Registry, stent and endarterectomy	Originally Wallstent, now not specified	Originally PercuSurge, now not specified
CREST	Guidant, NIH, NINDS	Randomized, lower risk	AccuLink	AccuNet
ICSS (CAVATAS-2)	UK Stroke Association	Randomized	Not specified	Not specified
MAVErIC	Medtronic	Registry, high-risk	Medtronic/AVE Self-Expanding Carotid Stent	PercuSurge GuardWire Plus
SAPPHIRE	Cordis	Randomized and registry, high-risk	Precise	AngioGuard
SECURITY	Abbott	Registry, high-risk	X.act Stent	Formerly MedNova NeuroShield, now "Emboshield" rapid exchange version
SHELTER	Boston Scientific	Registry, high-risk	Wallstent, Monorail	PercuSurge GuardWire Plus
SPACE	German government, Boston Scientific, Guidant	Randomized, stent vs endarterectomy	Not specified	Not specified

stenosis occurring as a result of spontaneous dissections. It is attractive to hypothesize that the short-term results of carotid stenting would be best in nonatherosclerotic disease, especially early recurrent lesions after endarterectomy, because the lesions are, by and large, smooth.[9] As such, the potential for embolization is theoretically lower than that associated with complex atherosclerotic lesions. Clearly, the treatment of patients with the more esoteric causes of carotid stenosis is complicated, based on little more than anecdotal experience and, as such, should involve consultative input from a broad spectrum of specialists, including rheumatologists, hematologists, and vascular medicine practitioners. In patients with atherosclerotic disease, the risk of carotid stenting is correlated with the extent of the atherosclerotic process. Patients with diffuse disease involving the aortic arch and common carotid vessels should be viewed with caution, as should patients with significant intracranial disease. The heavily calcified, tortuous vessel is one fraught with difficulty, and the use of alternate treatment modalities should be strongly entertained. Of great importance is that patients with displacement of the arch vessels to the right side of the chest comprise a group for which technical difficulties should be expected.

With the demonstration of the efficacy of coronary angioplasty and stenting, there is presently great interest in percutaneous treatment for carotid disease (Figure 2). The large number of patients with suitable carotid lesions sparked interest on the part of industry, and, despite a national "noncoverage" policy for carotid angioplasty by the Health Care Financing Administration (now Center for Medicare and Medicaid Services), carotid stenting became one of the most widely discussed and hotly debated topics of the late 1990s. Interventional cardiologists, well versed in percutaneous angioplasty, were quick to embrace the new technology. Vascular surgeons, by contrast, viewed carotid angioplasty as a rather crude and as yet unproved threat to the meticulous procedure of carotid endarterectomy, one of the mainstays of contemporary peripheral vascular surgical practice. With neurologists and neurosurgeons in the middle, a conflict ensued, the resolution of which could be achieved only through the completion of well-controlled comparisons of the two treatment modalities.

Results of Trials of Carotid Stenting

The performance of well-designed clinical trials is the only pathway to gather objective long-term data on which clinical decisions may be based. Ultimately, comparative outcome analysis will resolve issues of safety and efficacy of carotid stenting versus carotid endarterectomy. A broad spectrum of carotid stenting trials exists (Table 1). Most have been registry-type analyses, involving prospective entry of a series of consecutively treated patients without a comparison group. These trials include single-center studies, in which the investigator served as the sponsor, as well as a variety of corporate-sponsored trials with such diverse acronyms as ACCULINK for Revascularization of Carotids in High-Risk Patients (ARCHeR); Boston Scientific/ EPI: A Carotid Stenting Trial for High-Risk Surgical Patients (BEACH); Carotid Artery Revascularization Using the Boston Scientific EPI FilterWire EX and the EndoTex NexStent (CABERNET); Evaluation of the Medtronic AVE Self-Expanding Carotid Stent System with Distal Protection in the Treatment of Carotid Stenosis (MAVErIC); and Stenting of High risk patients Extracranial Lesions Trial with Emboli Removal (SHELTER). Most of these registries were designed to evaluate patients thought to be at high risk for standard carotid endarterectomy and organized in an effort to gain approval for the stent and/or embolic protection device. The U.S. Food and Drug Administration (FDA) has demonstrated some flexibility in the consideration of device approval based on high-risk registries rather than randomized studies.

Clearly, the largest carotid stent registry is the global registry organized by Mark and Michael Wholey. At the time of the latest publication from this registry, more than 5000 patients had been entered from 36 centers worldwide.[10] Although the data suffer from the limitations inherent in any registry based on unmonitored, investigator-completed questionnaires and nonstandardized follow-up protocols, the results were truly exceptional. Within 30 days of the procedure, transient ischemic attacks occurred in 2.8% of the patients and minor and major stroke in 4.2%. The 30-day mortality rate was 0.9%, with a combined stroke/death rate of 5.1%. The rate of restenosis was extremely low, being evident in only 3.5% of patients at one year, and only 1.4% of patients experienced neurologic symptoms 1–12 months following the procedure.

There have been several randomized trials of carotid stenting versus endarterectomy. Various studies are ongoing in Europe and will not be discussed in this review. A study sponsored by Schneider (now part of Boston Scientific Corporation, Natick, MA) compared placement of the Wallstent without cerebral embolic protection with carotid endarterectomy. To date, the results have been presented orally but not published. The results of stenting in this trial, if anything, were worse than those with endarterectomy. However, a number of sites had little stenting experience at the time of their participation in the study. A subgroup analysis documented poor results in these low-volume centers.

The Carotid Revascularization Endarterectomy versus Stent Trial (CREST) is designed to compare the outcome of carotid stenting with that of endarterectomy in a patient population similar to that of the NASCET trial—in other words, in patients at relatively low risk for complications after carotid darterectomy.[11] The trial employs the AccuLink™ stent and the AccuNet™ filter (Guidant Corporation, Menlo Park, CA). The goal is to randomize approximately 2500 patients in this NIH- and Guidant-sponsored trial.

The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial has been completed, and results were reported at the 2002 American Heart Association Meeting.[12] SAPPHIRE, composed of a randomized portion and a registry portion, was actually two studies in one. Patients deemed suitable for either stenting or endarterectomy were randomized. Patients who were thought unsuitable for endarterectomy on the basis of severe medical comorbidities or anatomic considerations were entered into a stenting registry. Lastly, a small number of patients who were considered to be unsuitable for stenting, usually on the basis of anatomic criteria, were entered into a surgical registry. The study, which was sponsored by Cordis/Johnson and Johnson, utilized the Precise™ stent and AngioGuard filter (Cordis, Johnson and Johnson, Warren, NJ) (Figure 3).

Although the final results of the SAPPHIRE study are not yet available, the 30-day outcomes data in the randomized portion of the study demonstrated significant benefit of stenting over endarterectomy for the composite end point of stroke, myocardial infarction, or death. Although not assured, it is expected that this finding will persist beyond the 30-day time point. If so, SAPPHIRE will be the study that gains FDA approval for the procedure of carotid stenting in general and the Precise/AngioGuard system in particular for the subgroup of patients at high risk for standard carotid endarterectomy.

Use of Embolic Protection Devices

Atherosclerotic plaques in general and high-grade carotid plaques in particular are laden with lipid and calcium. The luminal surface may be covered with a carpet of aggregated platelets and fibrin. Such a situation, of course, is a set-up for distal embolization with percutaneous carotid interventions. In vivo studies have demonstrated a large number of emboli released during angioplasty and stenting of the carotid bifurcation,[13] and these data have been corroborated in the clinical setting using transcranial Doppler during stent procedures.[14] For this reason, a variety of "embolic protection devices" have been developed. Although none has gained approval for use in the cerebral circulation, at least one, PercuSurge® (Medtronic/AVE, Santa Rosa, CA), is approved for saphenous vein graft indications.

In vivo studies have demonstrated a large number of emboli released during angioplasty and stenting of the carotid bifurcation, and these data have been corroborated in the clinical setting using transcranial Doppler during stent procedures.

Embolic protection devices can be grouped into three categories. First are those that function as "nets" or "filters" placed distally in the internal carotid artery at the time of angioplasty and stenting. This group includes the AngioGuard filter, the AccuNet™ filter, the FilterWire EX™ embolic protection device (Boston Scientific, Natick, MA), and the MedNova NeuroShield™ device (MedNova Inc., Galway, Ireland). Second are devices that arrest blood flow in the internal carotid artery, allowing aspiration of the static column of blood that potentially contains atheroembolic debris. Foremost in this category is the PercuSurge device, which is associated with an obligate period of internal carotid flow arrest lasting approximately 10 minutes.[15] Third are devices that function with a balloon at the end of a sheath, allowing the operator to reverse flow in the internal carotid artery and extract potential emboli through the sheath. In the case of the Parodi Anti-Emboli System (ArteriA Medical Science, Inc, San Francisco, CA), the outflow channel of the sheath can be connected to the femoral vein, allowing any emboli to flow, presumably harmlessly, into the pulmonary circulation.[16] This class of devices has some theoretical attraction because they avoid the need to cross the carotid lesion; however, a mandatory period of absent or even reversed flow in the internal carotid artery is a potential shortcoming.

Despite the logic in using embolic protection devices, they are not without problems and complications. For instance, the filters must cross the lesion to be placed distally beyond the lesion. The profile of the devices, although small, still accounts for a small risk of embolization when crossing the lesion. In addition, the filters may become filled with debris, arresting flow in the internal carotid artery. Although the absence of flow is not in itself a serious problem (only a small minority of patients will experience mental status changes), the function of the filters depends on flow. Once there is no flow, emboli are no longer trapped in the filter but rather will reside within the static column of

Main Points

- Numerous clinical trials have documented the safety and efficacy of carotid endarterectomy; hence it remains the standard of care for patients with severely stenotic extracranial lesions.
- Relatively healthy patients do very well with open surgical repair of carotid lesions, but the treatment of medically compromised patients holds a much greater risk of complications.
- Although the final results of the SAPPHIRE study are not yet available, the 30-day outcomes data in the randomized portion of the study demonstrated significant benefit of stenting over endarterectomy for the composite end point of stroke, myocardial infarction, or death.
- With advances in stents, delivery systems, antiembolic devices and, most important, the technical expertise of the operators, it is likely that carotid stenting will become the treatment of choice for patients with significant carotid disease.
- Research into embolic protection devices is under way to reduce the risk of damage from the large number of emboli released during angioplasty and stenting of the carotid bifurcation.

blood between the carotid lesion and the filter. Unless this blood is vigorously aspirated—for example, through a 5F catheter placed just proximal to the filter—recapture of the filter will result in restitution of antegrade internal carotid blood flow and cerebral embolization of debris.

Summary

In conclusion, definitive treatment of extracranial carotid disease is well entrenched for patients with both symptomatic and asymptomatic severely stenotic lesions. The gold standard remains open surgical endarterectomy, but there is intense interest in carotid stenting from the clinical and investigative perspective. Initial results of stenting appear to be quite reasonable, challenging traditional endarterectomy in low-risk patients and probably surpassing endarterectomy in higher-risk subgroups. With advances in stents, delivery systems, antiembolic devices and, most important, the technical expertise of the operators, it is likely that carotid stenting will become the treatment of choice for patients with significant carotid disease. ■

Dr. Ouriel serves as a consultant to Cordis Corporation, a Johnson & Johnson company.

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