Carotid Artery Stenting: Current Status and Future Directions

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Carotid endarterectomy has been the mainstay of therapy for carotid occlusive disease in stroke prevention. Recent advances in endovascular technology has made carotid angioplasty and stenting a therapeutic modality in the treatment of carotid occlusive disease. The enthusiasm for this minimally invasive carotid intervention is hampered by the possibility of stent-related cerebral embolization, which can result in neurologic complications. Although current available data indicate that the results regarding success and complication rates are similar between carotid stenting and endarterectomy, numerous prospective clinical trials are currently underway to evaluate the efficacy of carotid artery stenting using various forms of cerebral protection devices. This article reviews the current status of carotid stenting, including recent clinical studies and ongoing prospective trials. Strategies relating to cerebral embolization protection are also discussed.

Introduction

The efficacy of carotid endarterectomy (CEA) in stroke and death prevention has been proven in numerous clinical trials.1-3 As a result, it has emerged as the standard treatment in patients with critical extracranial carotid stenosis. In view of the clinical study outcome, the American Heart Association (AHA) has established guidelines for the performance of CEA. Based on AHA recommended guidelines, CEA should only be performed if the combined rate of perioperative stroke and death rate is less than 3% in asymptomatic patients and 6% in symptomatic patients with high-grade extracranial carotid stenoses.3

Recent advances in endovascular technologies have brought enthusiasm in the realm of extracranial carotid disease therapy. Several experienced physicians have reported not only the safety of carotid artery stenting, but also satisfactory stroke and death rates when compared to the extrapolated AHA recommended guidelines.4-6 Despite the optimistic reports by few experienced physicians, neurologic events due to cerebral embolization during carotid stenting procedures remain a concern that must be overcome before widespread acceptance of this treatment modality. The purpose of this article is to describe carotid artery stenting and review the current status of carotid artery stenting including various cerebral embolization protection strategies. Results of recent carotid stenting studies and ongoing clinical trials will also be discussed.
Technique of Carotid Artery Stenting

While carotid artery stenting can be performed successfully using a variety of catheter-based techniques, we describe a technical protocol routinely used in our clinical practice.

The patient is given bivalirudin (Angiomax 1 mg/kg IV bolus) at the onset of the procedure and aspirin (81 mg/day) beginning 3 days before the intervention. The carotid stenting procedure is performed either in an angiosuite (Multi-Star Siemens) or an operating room using a mobile C-arm unit (OEC model 9800). Intravenous antibiotic (cephazolin, 1 g) is given 30 minutes before the procedure. Local anesthesia with 1% lidocaine is used to anesthetize the groin region followed by percutaneous cannulation of the common femoral artery. Following the placement of a 6F introducer sheath, an aortic arch angiogram in the left anterior oblique (LAO) projection using a pigtail catheter with power injection is performed. Selective cannulation of the carotid artery is performed using a 5F diagnostic catheter (SIM2, JB2, H1 or vertebral catheter) followed by advancement of a 0.035-inch Bentson guidewire into the proximal common carotid artery. Carotid angiography is performed to assess the carotid anatomy. Table I lists certain unfavorable radiographic features that may carry a higher risk of complications for carotid artery stenting.

Once the decision to perform stenting is confirmed based on the carotid angiogram, intravenous bivalirudin (2.5 mg/kg/hr) is maintained throughout the procedure. A guidewire exchange is performed with a 0.035-inch Amplatz Superstiff guidewire placement in the common carotid artery without traversing the carotid stenosis. The groin introducer sheath and diagnostic catheter are removed, followed by a 7F, 90-cm shuttle sheath placement in the distal common carotid artery by tracking over the Amplatz guidewire. The tracking of the shuttle sheath over the guidewire in the common carotid artery may be facilitated by positioning the guidewire in the external carotid artery.

Selective digital carotid angiography is performed via the sideport of the shuttle sheath to delineate the anatomy of the common, internal, and external carotid arteries. Biplanar intracranial injections are also performed to document cerebral vasculature. The Amplatz guidewire is next replaced with a 0.018-inch guidewire system with distal embolization device, which is used to cross the internal carotid lesion. Following the activation of the embolization device, a coaxial 4-mm × 4-cm angioplasty balloon is used to predilate the carotid lesion.

We prefer to use the self-expanding stent (monorail Wallstent by Boston Scientific, or ACCULINK nitinol stent by Guidant), which is deployed across the internal carotid stenosis with proximal attachment in the distal common carotid artery. Post-stenting balloon angioplasty may be performed using either a 5-mm or 6-mm diameter angioplasty balloon depending on the appearance of the completion angiogram. Completion angiography includes biplanar carotid and cerebral views to document vascular anatomy and exclude cerebral thromboembolism. The cerebral embolization protection device is deactivated, and the guidewire along with the shuttle sheath is removed. The groin puncture site is closed with a 6F femoral closure device (Perclose). The patient is to continue with oral clopidogrel for 3 months and aspirin therapy indefinitely.

Cerebral Embolization during Carotid Artery Stenting

Despite reports of the relative safety of the carotid artery stenting procedure,7-10 general concerns

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<tr>
<th>Table I. Unfavorable carotid angiographic appearance in which carotid stenting should be avoided.</th>
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<tr>
<td>• Extensive carotid calcification</td>
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<td>• Polypoid or globular carotid lesions</td>
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<td>• Severe tortuosity of the common carotid artery</td>
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<td>• Long segment stenoses (&gt; 2 cm in length)</td>
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<td>• Carotid artery occlusion</td>
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<td>• Severe intraluminal thrombus (angiographic defects)</td>
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<td>• Extensive middle cerebral artery atherosclerosis</td>
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exist regarding the potential for neurologic deficit as a result of embolic particles released from the carotid plaque during the carotid balloon angioplasty and stenting procedure. A study by Ohki and colleagues confirmed this phenomenon using an ex vivo model with human carotid plaques collected from carotid endarterectomy procedures. The authors demonstrated that embolic particles were consistently produced from all plaques following stent placement.

In a transcranial Doppler study that evaluated signals of cerebral embolization, Jordan and colleagues noted a mean of 7.4 emboli per stenosis with 4 neurologic events among 40 patients undergoing carotid stenting procedure (10%). In contrast, patients undergoing carotid endarterectomy had a mean of 8.8 emboli per stenosis with one neurologic deficit among 75 patients (1.3%). The mean number of cerebral emboli was 56.8 in patients with neurologic deficit and 31.2 in those without (p < 0.02). The authors concluded that cerebral embolization was the predominant cause of acute neurologic complications associated with carotid stenting.

The risk of cerebral embolization due to carotid intervention was underscored in The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS), which was a prospective, randomized trial comparing the safety and efficacy of carotid endarterectomy with carotid balloon angioplasty, with and without stenting. The study reported that a mean of 202 ± 119 high-intensity embolization signals were produced during the carotid balloon angioplasty procedure, in contrast to a mean of 52 ± 64 high-intensity embolization signals produced during a carotid endarterectomy (p < 0.05). The Leicester trial, which was another prospective randomized multicenter trial that compared the efficacy of carotid stenting versus endarterectomy, similarly reported that more cerebral embolization events occurred following carotid stenting than endarterectomy. This trial was halted because of the unacceptably high stroke death rate following carotid stenting (71%) compared with endarterectomy (0%) following the enrollment of only 17 patients.

The neurologic events due to stent-related cerebral embolization was illustrated by a recent study in which patients underwent diffusion-weighted magnetic resonance imaging (DW-MRI), and found new ipsilateral ischemic lesions that occurred after stent implantation in 29% of patients (n = 20). This study further underscored the clinical presence of cerebral embolization due to carotid intervention.

The abundance of clinical evidence regarding the risk of neurologic complication due to catheter-based carotid intervention has prompted many physicians to advocate routine use of distal protection devices to prevent cerebral embolization. Early studies have confirmed that significant amounts of embolic particles were routinely captured by the distal protection devices during carotid stenting. In a carotid stenting study that utilized the PercuSurge GuardWire system (Medtronic, Minneapolis, MN) to prevent cerebral embolization, the number of embolic particles retrieved per patient ranged from 22 to 667 and a mean particle diameter was 203 ± 256 µm.

Although no clinical study currently exists that proves embolization protection devices definitively reduces neurologic sequelae due to carotid stenting, its benefit in improving clinical outcome in coronary intervention was recently highlighted in the Saphenous Vein Graft Angioplasty Free of Emboli Randomized Trial (SAFER). This was a prospective randomized study that evaluated 550 patients with stenotic saphenous vein graft following CABG to either PercuSurge GuardWire-protected percutaneous transluminal coronary angioplasty (PTCA) or unprotected coronary intervention. The 30-day myocardial ischemic rate was 8.4% in the PercuSurge-protected group, in contrast to the 16.5% in the unprotected control group (p < 0.01). As the result of the clinical benefit demonstrated in the trial, the distal protection device is currently considered the standard of care in patients undergoing PTCA for high-grade coronary saphenous vein graft stenosis.

Cerebral Protection Devices for Carotid Artery Stenting

A variety of designs for cerebral protection devices currently exists in an effort to reduce distal embolization during carotid stenting procedure. Regardless of the device configuration, these devices can be grouped into 3 categories based on mechanisms by which the device prevents distal cerebral embolization, and they include 1) prox-
Clinical Results of Carotid Artery Stenting

With a rapid growth in the number of physicians who perform carotid artery stenting on a routine basis, an abundance of literature has emerged relating to the outcome of carotid artery stenting. Wholey and colleagues reported the first large scale registry regarding carotid artery stenting from hospitals in Europe, Asia, North and South America. The survey reported an overall restenosis rate of approximately 4.8%. This study was subsequently updated in 2000 in a worldwide carotid stenting registry that enrolled more than 8,600 patients from 42 centers in the United States, Europe, and South America. The technical success in the study was 98.5%. The 30-day minor and major stroke rates were 2.82% and 1.49%, respectively. The study reported a 30-day stroke and death rate of 5.8%, 1.02% of which was non-procedure-related mortality. Restenosis rates of carotid stenting were 1.99% and 3.46% at 6 and 12 months, respectively. The rate of neurologic events after carotid stenting was 1.42% at 12-month follow-up. The first large series single center experience in carotid stenting was reported by Yadav and colleagues who performed 126 carotid interventions in 107 patients. The authors reported a major stroke and mortality rate of 1.6%. Over 70% of patients in their study group were classified as high risk (by NASCET criteria) and would have been excluded from participating in either the NASCET or ACAS trial. Of the carotid procedures in this series, 74 were performed in symptomatic cases and there was no statistical difference in the complication rates between asymptomatic and symptomatic patients. Six month clinical follow-up was available on all patients. Eighty-one patients (76%) had either follow-up angiography (71 patients) or ultrasound (10 patients). The mean angiographic stenosis at 6 months was 18 ±16% with a range of –21% to 57%. In total, recurrent stenosis occurred in 4.9% of patients; all of whom remained asymptomatic.

The recently completed CAVATAS trial (Carotid and Vertebral Artery Transluminal Angioplasty Study) randomized 504 patients with high grade carotid stenosis (>70%) to either endovascular group (n = 251) or endarterectomy group (n = 253). The patients from both groups received identical medical treatment and were followed for a total of 3 years. A total of 6.4% of
patients in the endovascular group versus 5.9% of patients in the endarterectomy group (p = NS) had a disabling stroke or death at 30 days. The overall minor or major stroke rates in the endovascular and surgical groups were similar, which were 10.0% and 9.9%, respectively. However, local complications were greater in the endarterectomy group when compared to the endovascular group: cranial nerve palsy (8.7% vs 0%; p < 0.05) and hematoma requiring surgery or prolonged hospitalization (6.7% vs 1.2%; p < 0.05). In summary, endovascular and endarterectomy groups had similar stroke and death rates, but local complications were significantly greater in patients who underwent carotid endarterectomy.

A multicenter study was performed that analyzed 338 patients from 14 centers in the United States regarding the outcome of carotid stenting for restenosis following carotid endarterectomy.24 The average duration from the initial carotid endarterectomy was 5.5 ± 7.3 years, and 61% of the patients were asymptomatic. The overall 30-day stroke and death rate was 7.4% (n = 43). After the 30-day period, the incidence of fatal and nonfatal stroke was 3.2% (n = 31). The 3-year freedom from ipsilateral or fatal stroke based on Kaplan-Meier analysis was 92 ± 1%. The authors reported that age greater than 80 years was an independent predictor of 30-day stroke and death.

Physicians from the Cleveland Clinic recently reported their experience of 162 patients undergoing carotid stenting for high-grade stenosis (mean diameter stenosis, 83%).25 The overall success rate was 99%. Patients were given aspirin plus either clopidogrel or ticlopidine post-procedurally. The overall neurologic complication rate is 3.5%. The cumulative 30-day rate of death, patients in the endovascular group versus 5.9% of patients in the endarterectomy group (p = NS) had a disabling stroke or death at 30 days. The overall minor or major stroke rates in the endovascular and surgical groups were similar, which were 10.0% and 9.9%, respectively. However, local complications were greater in the endarterectomy group when compared to the endovascular group: cranial nerve palsy (8.7% vs 0%; p < 0.05) and hematoma requiring surgery or prolonged hospitalization (6.7% vs 1.2%; p < 0.05). In summary, endovascular and endarterectomy groups had similar stroke and death rates, but local complications were significantly greater in patients who underwent carotid endarterectomy.

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stroke, transient ischemic attack, and myocardial infarction was 5.6%. Specifically, those who received ticlopidine (n = 23) had a higher major adverse event rate 3%, in contrast to 4.3% in the patients who received clopidogrel (n = 139) (p = 0.01). The findings support both the efficacy of carotid stenting and the use of dual antiplatelet strategy of clopidogrel plus aspirin for patients undergoing carotid artery stenting.

Current Status of Prospective Randomized Carotid Stenting Trials

Numerous prospective randomized clinical trials or registries comparing carotid stenting and carotid endarterectomy are currently underway. A variety of cerebral embolization protection strategies are used in the stenting group in an effort to reduce procedural-related neurologic complications. Table III summarizes the current status of prospective randomized trials on carotid stenting using various types of cerebral embolization protection devices.

The SAPPHIRE trial (Study of Angioplasty with Protection in Patients at High Risk for Endarterectomy) is a prospective, randomized multicenter trial of carotid endarterectomy versus carotid artery stenting in high surgical risk patients. The study, which employed the SMART nitinol stent (Johnson & Johnson, Cordis, Warren, NJ) and the AngioGuard (Johnson & Johnson, Cordis, Warren, NJ) emboli protection device, enrolled 307 patients from 29 hospitals who were either asymptomatic with greater than 80% carotid stenosis or symptomatic with greater than 70% stenosis. All patients met high-risk criteria, which included chronic heart failure, chronic obstructive pulmonary disease, previous carotid endarterectomy, severe coronary artery disease, radical neck surgery, or radiation therapy. The initial results, which were reported in November 2002, noted the study randomized 156 patients to stenting and 151 patients to the endarterectomy arm. Patients who were treated with carotid stenting using the AngioGuard filter had a post-procedural major adverse event of 5.8% compared to 12.6% for patients randomized to surgery (p < 0.05). In a parallel stenting and endarterectomy registries for patients who could not be randomized in the trial, 409 patients were turned down for endarterectomy and were enrolled in a stent registry. The 30-day major adverse cardiac event rate was 7.8% in the stent group, in contrast to 14.3% for the 7 patients who declined stenting and were enrolled in the endarterectomy registry.

Another major randomized study is the CREST trial (Carotid Revascularization Endarterectomy Versus Stent Trial), which is jointly

Table III. Summary of current prospective trials of carotid stenting with cerebral protection devices.

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<th>Clinical Study</th>
<th>Sponsor</th>
<th>Stent</th>
<th>Embolization Device</th>
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<td>NexStent</td>
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<td>SHELTER</td>
<td>Boston Scientific</td>
<td>Wallstent</td>
<td>Percusurge</td>
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sponsored by Guidant Corporation (Indianapolis, IN) and the National Institute of Health. The study will randomize patients with symptoms who are at low surgical risk to either stenting or endarterectomy. The inclusion criteria are similar to those in the NASCET study. This study utilizes the AccuLink nitinol stent (Guidant, Ternacula, CA) as well as the AccuNet emboli prevention device (Guidant). The primary outcome events will include: 1) any stroke, myocardial infarction, or death during the 30 day perioperative or peri-procedural period; or 2) ipsilateral stroke after 30 days. The trial is expected to enroll 2,500 patients and be completed by 2007.

The Future of Carotid Artery Stenting

Many available published studies comparing carotid stenting and endarterectomy have demonstrated comparable post-procedural stroke and death rates between the two treatment groups. Moreover, the initial report of the SAPPHIRE trial noted a significantly improved short-term outcome in high-risk patients who underwent carotid stenting than carotid endarterectomy. With continual refinement and innovation, cerebral protection devices will likely continue to improve the results of carotid stenting. With all current ongoing carotid stenting trials incorporating varying cerebral protection strategies, it is becoming apparent that cerebral protection will be the standard of care in future carotid stenting. Until more clinical evidence becomes available from prospective trials, carotid stenting presently should be reserved to certain patient groups that included those with severe synchronous carotid and coronary artery disease, previous neck operation or irradiation, post-endarterectomy restenosis, high distal lesions, and preexisting cranial nerve palsy.

Many interventionists, including cardiologists and radiologists, are eager to incorporate carotid artery stenting in their respective clinical practice. With their catheter-based skills and access to imaging suites, they are certainly well positioned to offer such a treatment to patients when opportunity arises. Vascular surgeons must become engaged in endovascular practice and acquire necessary catheter-based skills so that they remain an important participant in future carotid disease management.

REFERENCES


