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Cervical Carotid Revascularization: The Role of Angioplasty with Stenting

Ricardo A. Hanel, MD, Elad I. Levy, MD,
Lee R. Guterman, PhD, MD, L. Nelson Hopkins, MD, FACS*

Department of Neurosurgery, Radiology, and Toshiba Stroke Research Center, School of Medicine and Biomedical Sciences, State University of New York at Buffalo, 3 Gates Circle, Buffalo, NY 14209–1194, USA

Stroke is the third largest cause of death after heart diseases and cancer and is the leading cause of permanent disability and disability-adjusted loss of independent life-years in Western countries [1–3]. Approximately 700,000 people in the United States experience a stroke annually, which results in an estimated $53.6 billion in direct and indirect costs [1]. By the year 2050, an estimated 1 million persons will suffer from stroke every year because of aging in the population and changes in the ethnic distribution [4].

Approximately 25% of the strokes occurring annually are attributable to ischemic events related to occlusive disease of the cervical internal carotid artery (ICA) [5]. Carotid stenosis caused by atherosclerotic disease increases the risk of ischemic stroke by acting as an embolic source or by causing hypoperfusion of the ipsilateral cerebral hemisphere. Introduced in the early 1950s [6], carotid endarterectomy (CEA) involves the performance of an arteriotomy of the cervical carotid artery with subsequent removal of the atherosclerotic plaque. Historically, CEA gained widespread acceptance [7] and was validated by the performance of several randomized trials, including the North American Symptomatic Carotid Endarterectomy Trial (NASCET) [8] and the Asymptomatic Carotid Atherosclerosis Study (ACAS) [9]. With some limitations, these studies have shown that CEA substantially reduces the stroke risk and increases the survival rate for patients with symptomatic carotid stenosis greater than 50% and asymptomatic stenosis greater than 60% [8–10]. During the past few years, carotid angioplasty with stenting (CAS) has evolved as an alternative to CEA, particularly for those patients in whom CEA is associated with a higher risk of complications [11–13]. The aim of this article is to review the relative indications and limitations for CEA and CAS and to describe the technique and results for CAS.

Carotid endarterectomy

Several randomized, multicenter, prospective trials have demonstrated evidence of the safety and efficacy of CEA in patients with symptomatic and asymptomatic carotid stenosis. Since the publication of the NASCET results in 1991 [8], CEA has been the standard of care for the revascularization of extracranial carotid stenosis [11]. In the preamble to this article, Snell and Loftus have reviewed the indications for cervical carotid revascularization from a surgical perspective. It is being increasingly recognized that certain patients who undergo CEA have a high risk of perioperative complications with increased mortality and morbidity, however [11].

Major carotid endarterectomy trials

One should keep in mind that selection criteria in the major CEA trials were restrictively defined. Exclusion criteria in the NASCET included a previous ipsilateral endarterectomy; an intracranial lesion that was more severe than the surgically accessible lesion; no angiographic depiction of the

* Corresponding author.

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carotid arteries and their intracranial branches; and organ failure of the lung, liver, or kidney. Temporary exclusion criteria included uncontrolled hypertension, diabetes mellitus, or unstable angina pectoris; myocardial infarction (MI) within the previous 6 months; contralateral CEA within the previous 4 months; signs of progressive neurologic dysfunction; and a major surgical procedure within the previous 30 days. These patients could be included in the trial if the disorder responsible for their ineligibility resolved within 120 days of their qualifying cerebrovascular event. Similar restrictive inclusion and exclusion criteria were used in the European Carotid Surgery Trial (ECST) [10], ACAS [10], and Asymptomatic Carotid Surgery Trial [14]. In effect, the stringent criteria used to select patients in the major CEA trials excluded those with the highest risk of complications (ie, the group in whom the benefits of CEA might not have been evident).

Moreover, the benefits of carotid revascularization surgery demonstrated by the NASCET [8,15], ACAS [9], and ECST [16] are lost if the 30-day rate of perioperative stroke or death exceeds 6% for patients with symptomatic carotid stenosis or 3% for those with asymptomatic carotid stenosis.

Clinical practice versus clinical trials

Substantial evidence in the literature shows that the complication rates in clinical practice often exceed those in clinical trials. Wennberg et al [17], when comparing the perioperative mortality among 113,300 Medicare patients undergoing CEA during 1992 and 1993 at NASCET and ACAS hospitals and at nontrial hospitals, found that the mortality rate was almost two times greater at nontrial hospitals (2.5% at nontrial hospitals versus 1.4% at trial hospitals). In a similar study, Hsia et al [18] reported that the 30-day mortality rate among Medicare beneficiaries undergoing CEA was 2.5%, a rate much higher than the 1.0% mortality rate described in the clinical trials. Chaturvedi et al [19] reported 30-day combined rates of major stroke and death of 11.1% for symptomatic patients and 5.6% for asymptomatic patients in a prospective small series of patients undergoing operations and routine neurological examinations at an academic center, suggesting an underestimation of complication rates on the basis of those obtained in clinical trials.

Operator experience is probably an important factor contributing to this significant difference in complication rates. Careful patient selection has been found to be the key determinant in maintaining a low perioperative complication rate, however. Certain patient groups have been found to have a higher risk for perioperative complications with CEA [11,20–22]. CAS is an alternative modality for carotid revascularization that could benefit these high-risk patients.

High-risk surgical candidates

The risk of CEA associated with medical comorbidities has been well documented in the literature with respect to neurologic complications, such as stroke, as well as nonneurologic complications, such as MI [23]. In an analysis of the NASCET results, CEA was approximately 1.5 times more likely to be associated with medical complications in patients with a previous history of MI, angina, or hypertension [22]. Because patients with other significant coexistent diseases were excluded from the major CEA trials, the indications for and the results of surgery in this subgroup of patients have not been established. Factors that increase the risk of perioperative morbidity and mortality are reviewed here.

Age

Older patients seem to have a higher rate of perioperative complications with CEA. When assessing perioperative mortality of 113,300 Medicare patients, Wennberg et al [17] found that patients 85 years of age or older were three times more likely to die than those younger than 70 years of age. In a multicenter review of 1160 CEA procedures, Goldstein et al [20,21] reported a postoperative stroke or death rate of 7.5% in asymptomatic patients 75 years of age or older versus a rate of 1.8% in patients younger than 75 years. Similarly, the risk of postoperative MI associated with CEA was 6.6% in symptomatic patients 75 years of age or older versus 2.3% in patients younger than 75 years [20,21]. A NASCET subgroup analysis performed by Alamowitch et al [24] found that patients aged 75 years or older actually derived a greater benefit from CEA than those in younger age groups, however. The absolute risk reduction was 28.9% for patients aged 75 years or older (n = 71), 15.1% for those between 65 and 74 years (n = 285), and 9.7% for patients younger than 65 years of age (n = 303). Hence, although CEA definitely seems to benefit older individuals, it is reasonable to ask the question whether CAS could achieve similar benefits with a lower perioperative complication rate in older patients [20,25].

Congestive heart failure

Patients with congestive heart failure have a higher rate of perioperative stroke or death with CEA. In a multicenter review of patients undergoing CEA, Goldstein et al [20,21] found a perioperative stroke or death rate of 8.6% in patients with congestive heart failure as opposed to 2.3% in patients without this condition. CAS might be considered an alternative to CEA for this patient population.

Severe coronary artery disease

Coronary artery disease is one of the most important factors to consider when evaluating the perioperative risk of CEA. The coexistence of severe carotid artery stenosis and symptomatic coronary artery disease presents the physician with a management dilemma [22,26]. The surgical repair of one condition cannot be accomplished without a substantial risk of complication from the other. In an analysis of the NASCET results, a history of treatment of coronary artery disease was associated with a lower CEA complication rate when compared with previously undiagnosed coronary artery disease [27]. This incongruity may be the result of improved cardiac and general medical care in patients undergoing treatment for coronary artery disease, many of whom may not have previously received regular long-term medical care.

Adjunct to coronary bypass surgery

Significant carotid artery disease places patients who are undergoing coronary artery bypass grafting (CABG) at an increased risk for stroke, embolization (air or atheromatous), or both. Faggioli et al [28] reported on a series of 539 patients who underwent noninvasive evaluation (with carotid Doppler ultrasonography and ocular pneumoplethysmography) for the detection of carotid artery occlusive disease before undergoing CABG. They found that greater than 75% carotid artery stenosis was an independent predictor of stroke risk (odds ratio = 9.9) during CABG.

For patients with significant coexistent disease of the carotid and coronary arteries, there is little debate that revascularization is appropriate for both conditions; however, controversy exists regarding the timing of the procedures. Surgical options include the performance of a simultaneous procedure or a staged approach in which one procedure is performed several days after the other. Reports of combined CEA and CABG suggest that the risk of stroke or death ranges from 7.4% to 9.4%, which is roughly 1.5 to 2.0 times the independent risk of each operation [22]. In a multicenter review, the composite risk of stroke and death was higher in patients who had CEA performed in conjunction with CABG (18.7%) than in those who had CEA alone (2.1%) [21].

Conversely, patients who undergo CEA before CABG also have a higher risk of perioperative complications [26,29]. In this high-risk subgroup, avoiding a major operation or general anesthesia by performing angioplasty with stenting may represent a valid alternative to CEA [30]. The CEA guidelines published by the American Heart Association report a composite incidence of stroke, MI, and death of 16.4% for combined carotid and coronary operations, 26.2% for CEA proceeded by CABG, and 16.4% for CABG proceeded by CEA [31]. These high rates of complications would clearly offset the long-term benefit from secondary stroke prevention. At our center, revascularization with CAS was performed before planned CABG in 49 patients with concomitant coronary artery and carotid artery diseases (carotid artery stenosis >70%) [30]. The 30-day mortality rate for the combined procedure was 8%, and the stroke rate for the same period was 2%. These complication rates seem to be substantially lower than those associated with combined CABG and CEA or with CABG followed by CEA. In addition, no clinically significant recurrent stenosis was noted during a mean follow-up interval of 27 months. Although the numbers in this report are small, the data support the consideration of CAS as a valid alternative to CEA in patients with coexistent clinically significant coronary artery disease when CABG is needed (Fig. 1).

Anatomic features and tandem lesions

Anatomic variations may increase the technical difficulty of CEA and adversely affect the results. A high carotid bifurcation near the skull base, especially in a patient with a short or thick neck, or a long carotid artery stenosis that extends to the skull base can be difficult to expose surgically. Surgical dissection of the carotid artery in these cases can be difficult and, at times, extremely traumatic. These patients could be candidates for CAS (Fig. 2).

The presence of tandem lesions, where the distal lesion is more severe than the proximal lesion, was an exclusion criterion for the NASCET [8]. Among symptomatic patients with ipsilateral carotid siphon stenosis, the risk of postoperative stroke or death associated with CEA in a multicenter review of 1160 procedures was 13.9% versus

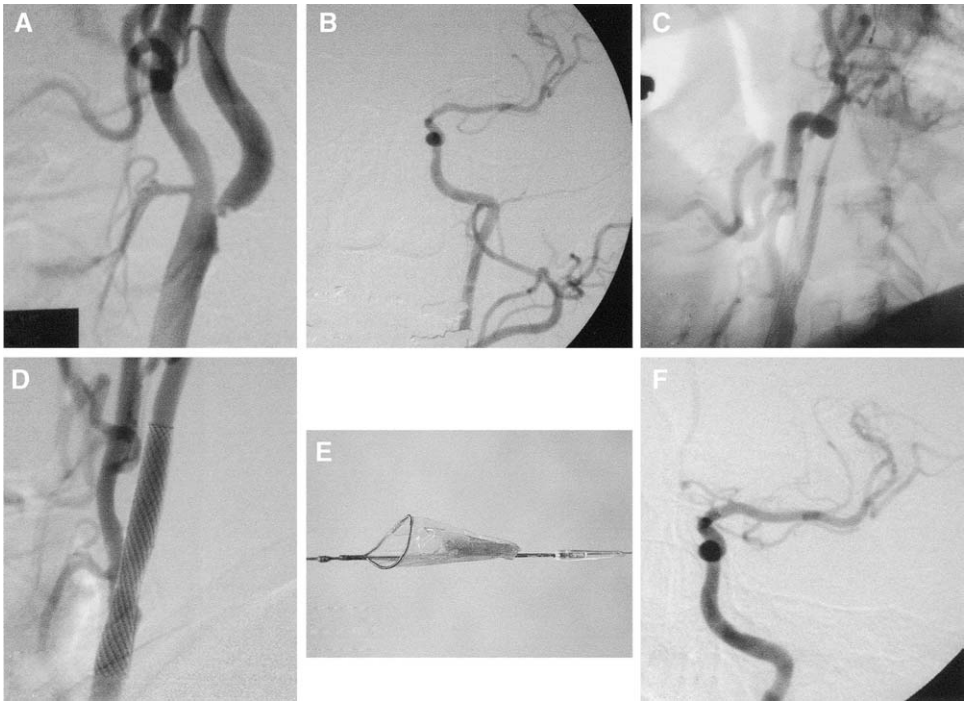

Fig. 1. This 58-year-old man presented with stable angina. Preoperative carotid Doppler ultrasound imaging demonstrated increased systolic velocities in the right carotid artery (419 cm/s). (*A*) Cerebral angiogram demonstrating the presence of severe stenosis involving the origin of the right internal carotid artery (ICA). (*B*) Intracranial image, frontal view, revealing lack of filling of the anterior cerebral artery, which suggests a flow-limiting effect of the cervical lesion or hypoplastic A1 segment of the anterior cerebral artery. Right carotid angioplasty with stenting was performed using a combination of an EPI FilterWire (Boston Scientific, Natick, Massachusetts) and a Wallstent (Boston Scientific). (*C*) After the poststent deployment angioplasty was performed, slowing of filling of the right ICA was noticed. This finding was attributed to the presence of debris in the filter. (*D*) After filter retrieval, normal flow was re-established in the right ICA. (*E*) Inspection of the filter demonstrated the presence of a large piece of plaque. (*F*) Intracranial image after cervical revascularization demonstrated flow augmentation with filling of the anterior cerebral artery territory in spite of the presence of a hypoplastic A1 segment.

7.9% in patients without distal stenosis [20]. Angioplasty was performed with and without stent placement in 11 patients with tandem lesions at our center [32]. The proximal lesion was considered to be the flow-limiting lesion and was the only lesion treated in 10 of these patients. In the remaining patient, both lesions were treated. No perioperative stroke or cardiac event or deaths occurred in this series. Hence, angioplasty with or without stenting could be considered a safe and viable alternative to CEA for patients with surgically inaccessible tandem carotid artery lesions.

Ipsilateral intraluminal thrombus

In a multicenter review of 1160 procedures, the risk of postoperative stroke or death with CEA was found to be 17.9% in symptomatic patients with ipsilateral intraluminal thrombus versus 8.1% in those without thrombus [20]. In a subgroup analysis of 53 patients enrolled in the NASCET who had intraluminal clot superimposed on atherosclerotic plaque identified by angiographic procedures, the 30-day risk of stroke was 10.7% in those randomly assigned to receive medical treatment and 12% in those who underwent CEA [33]. The high morbidity rate in this subgroup is related to the presence of fresh clot and the substantial risk of emboli dislodgment during surgical dissection of the carotid artery. Theoretically, CAS is an attractive alternative for these patients.

Contralateral occlusion

Patients with recent symptoms referable to severe carotid artery stenosis and coexistent contralateral carotid artery occlusion have a

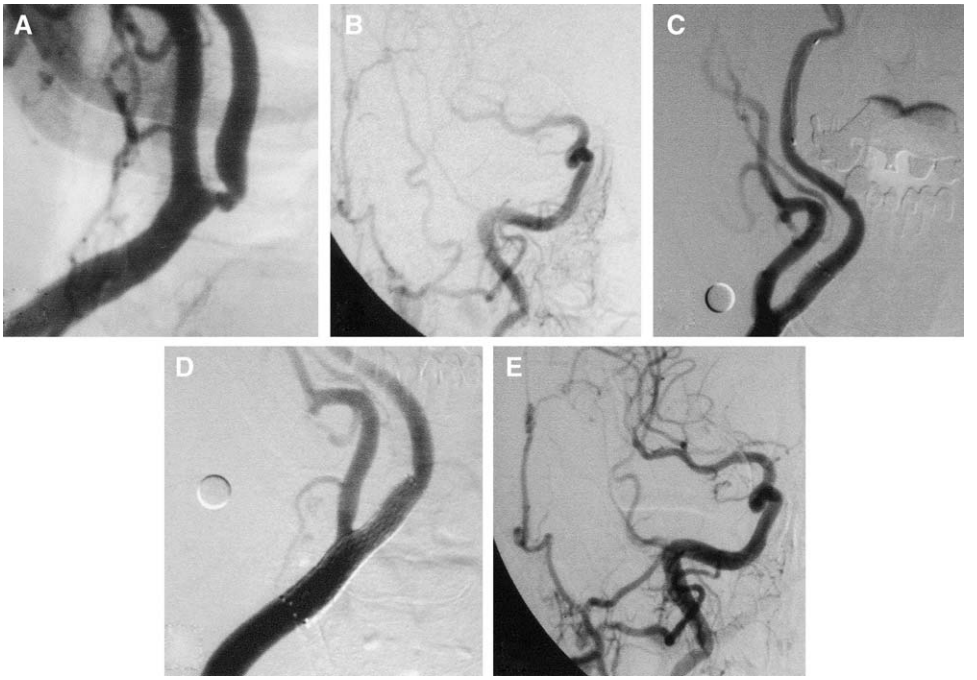

Fig. 2. This 86-year-old woman presented with progressively increasing Doppler ultrasound velocities in the right carotid artery. (*A*) Cerebral angiogram demonstrating the presence of a severe stenosis involving the origin of the right internal carotid artery (ICA). Because of her age (>80 years) and the fact that the lesion extended up to the body of C2, she was enrolled in the Carotid Revascularization with ev3 Arterial Technology Evolution (CREATE), a high-risk population carotid revascularization registry. (*B*) Intracranial image, frontal view, revealing delayed filling of ICA branches (when compared with the external carotid artery) as well as lack of filling of the anterior cerebral artery territory. (*C*) Right carotid artery stenting was performed using a combination of a Spider distal embolic protection device (ev3; Plymouth, Minnesota) and a Protégé Stent (ev3). Angiographic image after stenting demonstrates excellent revascularization of the vessel (*D*), with improvement of flow to the intracranial circulation (distal ICA branches filling before distal external carotid artery branches; anterior cerebral artery filling) (*E*).

high risk of ipsilateral ischemic stroke [34]. In the NASCET, the risk of ipsilateral stroke in medically treated patients with severe stenosis of the symptomatic carotid artery and occlusion of the contralateral carotid artery was 69.4% at 2 years [34]. Although CEA led to a significant reduction in stroke risk in this group, the perioperative risk of stroke or death in the presence of contralateral carotid artery occlusion was a high 14.3%. This increased risk may be related to the use of carotid artery shunting during CEA for patients with contralateral occlusions in up to 83% of cases [34]. In this subgroup, CAS represents a valid alternative to CEA, obviating the need for temporary occlusion in the presence of an already reduced cerebrovascular reserve. The preliminary combined results for phases 1 and 2 of the three-phase Acculink for Revascularization of Carotids in High Risk Patients (ARCHeR) trial showed a 30-day composite rate of stroke, MI, and death of 4.5% for the 66 patients with contralateral carotid occlusion included in this study [35].

Restenosis after carotid endarterectomy

Recurrent carotid artery stenosis is a potential problem after CEA (Fig. 3) [36]. Technically, a repeat operation is far more challenging than the initial procedure because of scarring around the arteries, friability of the recurrent plaque, and the necessity for more complex anastomosis techniques. Among 82 patients undergoing operations for recurrent carotid stenosis at the Mayo Clinic, the composite rate of major morbidity and mortality was 10.8%, a rate that was five times the risk associated with primary CEA at the same institution [36]. AbuRahma et al [37] found an increased risk of cerebral ischemic events associated with CEA for recurrent stenosis. The 30-day rates of

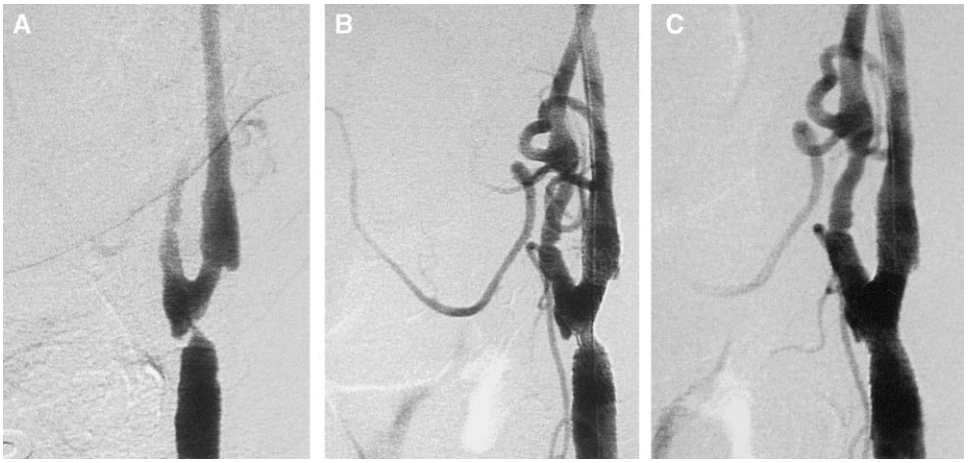

Fig. 3. This 57-year-old man presented with symptomatic recurrent stenosis of the left cervical carotid artery 2 years after endarterectomy. (*A*) Diagnostic cerebral angiogram demonstrating the presence of severe stenosis involving the distal segment of the left common carotid artery just proximal to the bifurcation. Left carotid artery stent placement with adjunctive distal embolic protection (EPI FilterWire; Boston Scientific Embolic Protection, San Carlos, California) was successfully performed. (*B*) Position of the filter after deployment of the stent (Precise Rx; Cordis, Miami Lakes, Florida). (*C*) Improvement in vessel diameter after poststent deployment angioplasty.

perioperative stroke and transient ischemic attacks (TIAs) were 4.8% and 4%, respectively, in the reoperation group, as compared with 0.8% and 1%, respectively, in the primary endarterectomy group. They also found a high rate (17%) of cranial nerve palsy with reoperation. In a review of the results of CAS performed at our center in a similar group of 18 patients with postendarterectomy recurrent carotid stenosis, only a single case of TIA and no perioperative stroke were identified [38]. The preliminary combined results of the ARCHeR 1 and 2 trials suggest that CAS is a technically feasible alternative to surgical re-exploration for patients with recurrent carotid artery stenosis [35]. The 30-day composite rate of stroke, MI, and death for the 141 patients receiving treatment with CAS for postendarterectomy recurrent stenosis in this study was 0.7%.

Radiation-induced carotid stenosis

Accelerated radiation-induced carotid stenosis is another factor that increases the risk of perioperative complications, primarily because of the technical pitfalls associated with a surgical approach. The presence of a long lesion, lack of well-defined dissection planes, and scarring around the vessels make the surgery more difficult [39,40], exposing these patients to a higher risk of wound infections and cranial nerve palsies. Carotid angioplasty and stent placement could provide a more effective method for treatment of carotid stenosis associated with radiation.

Carotid angioplasty and stenting

Background and preliminary results

Two major issues compelled the development of CAS: the need for a better therapeutic option for high-risk patients (as described previously) and the wave of minimally invasive surgery. After its introduction approximately 20 years ago by such pioneers as Kerber et al [41], Mathias et al [42], and Mullan et al [43], the field of endovascular treatment of carotid occlusive disease remained stationary, whereas the field of coronary and peripheral percutaneous transluminal angioplasty was developing at a rapid pace. In a review of the literature published up to 1996, Kachel [44] found only 523 carotid angioplasty procedures performed from 1980 to 1995.

Publication of the results obtained with stent-assisted balloon angioplasty in the coronary literature undoubtedly provided a new impetus for endovascular treatment of carotid artery occlusive disease [45] and prompted the performance of studies in which carotid angioplasty with or without stenting and CEA were compared. The purported advantages of stent placement over simple angioplasty included avoidance of plaque

dislodgment, intimal dissection, and late recurrent stenosis as well as diminution of vessel recoil.

The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS), the results of which were published in 2001, was the first randomized comparison of endovascular versus surgical treatment in patients with carotid artery stenosis [46]. Between March 1992 and July 1997, patients from 22 centers in Europe, Australia, and Canada were randomly assigned to endovascular treatment (n = 251) or CEA (n = 253). Stents suitable for use in the carotid arteries were developed during the course of the study. Despite the fact that the use of a stent in this trial was approved from 1994 onward, only 55 (26%) of the patients in the endovascular treatment group received a stent (the remainder received balloon angioplasty alone). Similar rates of stroke and death were reported for endovascular and surgical treatment. The number of recurrent strokes, with a mean follow-up period of approximately 2 years, was also similar in both groups. The 8-year follow-up report, which was presented in 2002, showed equivalent efficacy in stroke prevention for both therapeutic options [47].

Several other groups have reported on the effectiveness, safety, and durability of CAS. Roubin et al [12], in a review of their 5-year experience with a series of 528 consecutive patients undergoing CAS, described a 30-day major stroke or death rate of 2.6%. In 1996, Gil-Peralta et al [48] reported a series of 85 patients who underwent percutaneous angioplasty for symptomatic carotid artery stenosis over the course of a 4-year period. No deaths occurred within 30 days after the procedure, and the major morbidity rate at 30 days was 4.9%. Our group [49] has reported a 30-day major stroke or death rate of 5% in 80 high-risk patients who were considered ineligible for the NASCET according to the exclusion criteria of that study.

Distal embolic protection (DEP), initially introduced by Theron et al [50], is considered to be an important advance in the endovascular treatment of carotid occlusive disease. The rationale for using this technique is based on the concept that an embolic shower released from carotid plaque during CAS causes neurologic deficits in the periprocedural period [50]. Preliminary studies have demonstrated the potential benefit of DEP. Jaeger et al [51] reported the occurrence of cerebral ischemia (detected by diffusion-weighted MRI) in 29% (20 of 70) of patients undergoing CAS without cerebral embolic protection. This rate decreased to 7.1% with the use of embolic protection devices [52]. Whitlow et al [53] reported a multicenter experience in which a balloon device (PercuSurge GuardWire; PercuSurge, Sunnyvale, California) was used during CAS. Among the 75 patients treated with this device, no single case of periprocedural death or major stroke was noted.

The Carotid Revascularization Using Endarterectomy or Stent Systems (CARESS) Trial is a multicenter, prospective, nonrandomized clinical trial sponsored by the International Society for Endovascular Specialists (ISES) in collaboration with industry, the US Food and Drug Administration (FDA), and the Centers for Medicare and Medical Services [54]. This trial was designed as an equivalence cohort study to determine whether the rate of stroke or death after CAS with DEP is comparable with that for CEA. Patients with 50% or greater symptomatic carotid stenosis or 75% or greater asymptomatic carotid stenosis were enrolled in this trial. The population represented a broad-risk population typical of those treated in a general vascular practice. The CEA/CAS enrollment ratio at each clinical site was designed to be 2:1. The primary end point for comparison was the 30-day death and stroke rate. In phase 1 of this trial, 439 patients were enrolled from 14 clinical sites (254 CEA patients and 143 CAS patients; ratio of 1.8:1). Overall, 68% of the patients treated were asymptomatic, with a similar distribution in each group. The medical history before treatment was similar in both groups, with the exception of a more frequent history of previous CEA in the CAS group (30% versus 11% in the CEA group). The MI, stroke, and death rates were 0.8%, 2.4%, and 0.4%, respectively, in the CEA group and 0%, 2.1%, and 0%, respectively, in the CAS group. Statistically, the results of this study represented equivalence between the two revascularization modalities.

The Stent and Angioplasty with Protection for Patients at High Risk for Endarterectomy (SAPPHIRE) trial also demonstrated the benefit of DEP [55]. Patients from 29 centers in the United States were enrolled in this trial. Eligible study patients were those who were asymptomatic with greater than 80% stenosis (by Doppler ultrasound) or symptomatic with greater than 50% stenosis plus at least one feature that would place them at high risk for CEA (older than 80 years of age, congestive heart failure, severe chronic obstructive pulmonary disease, postendarterectomy recurrent carotid stenosis, previous radiation therapy, or previous radical neck surgery). Eligible patients

were then screened by a team that included a vascular surgeon, an interventionist, and a neurologist. Consensus that patients were good candidates for either procedure was required before randomization; those rejected as candidates for surgery underwent stenting and were included in a stent registry, whereas those rejected for stenting had surgery and were included in a surgical registry. At the end of the enrollment period in June 2002, 409 patients had been included in the stenting registry (CEA risk considered excessively high) and 7 patients in the surgical registry (CAS risk deemed excessive). A total of 307 patients were randomized: 156 to CAS and 151 to CEA. The devices used for CAS in this trial were the PRECISE nitinol stent (Johnson & Johnson, Warren, New Jersey) and the AngioGuard (Johnson & Johnson) distal protection device. The preliminary results have been presented but not published [56,57]. The 30-day composite stroke and death rate was similar for both groups (4.5% for CAS group versus 6.6% for CEA group). When the rate of MI was taken into consideration, the CAS group did better, with a major adverse cardiovascular event (MACE) rate of 5.8%, compared with a 12.6% MACE rate in the CEA group. The 1-year follow-up data for this study demonstrated overall MACE rates of 11.9% for the CAS group and 19.9% for the CEA group. At 1 year of follow-up, the incidence of major ipsilateral stroke was significantly higher in the CEA group (3.3%) versus the CAS group (0%). Regarding ipsilateral minor stroke, there was a trend toward more minor strokes in the CAS group (3.8% in the CAS group versus 2% in the CEA group; $P = 0.5$) [57].

The 30-day results of all three phases of the ARCHeR trial were presented as well as the 1-year follow-up data for phases 1 and 2 of the ARCHeR trial [35]. This trial included a total enrollment of 581 patients at 48 sites in the Unite States, Europe, and South America. Eligibility criteria included carotid artery stenosis that was asymptomatic and greater than 80% (by angiography) or symptomatic and greater than 50%. High-risk factors established for inclusion in this trial were the presence of two or more of the following criteria: (1) two or more coronary vessels with 70% or greater stenosis, (2) MI within 30 days, (3) CABG or valve surgery within 30 days, (4) unstable angina, and (5) contralateral carotid occlusion as well as one or more of the following criteria: (1) ejection fraction less than 30% or New York Heart Association functional class III or greater, (2) forced expiratory volume in the first second (FEV_1) less than 30% (predicted), (3) dialysis-dependent renal failure, (4) uncontrolled diabetes, (5) postendarterectomy recurrent stenosis, (6) history of radical neck surgery or radiation therapy, (7) surgically inaccessible lesion, (8) spinal immobility, (9) tracheostomy stoma, and (10) contralateral laryngeal nerve paralysis. Eligible patients were assessed by an independent neurologist before enrollment and throughout the CAS follow-up period. Enrollment in the trial included 158, 278, and 145 patients in phases 1, 2, and 3 of the trial, respectively. In phase 1 of the ARCHeR trial, patients were treated with use of the Acculink Stent (Guidant/Advanced Cardiovascular Systems, Menlo Park, California) alone. In phase 2 of the ARCHeR trial, patients were treated with a combination of the stent and the AccunetFilter (Guidant) for DEP. In phase 3 of the ARCHeR trial, next-generation rapid-exchange versions of the filter and stent were used. The ARCHeR trial results are summarized in Table 1 [58]. Further data analysis will be possible after the results of the study have been published.

The 30-day results of the Boston Scientific EPI: A Carotid Stenting Trial for High-Risk Surgical Patients (BEACH) were also recently presented and are provided in Table 1. In this trial, devices used were the EPI FilterWire EZ (Boston Scientific, Fremont, California) as DEP and the monorail Wallstent (Boston Scientific). The BEACH is a single-arm, prospective, nonrandomized trial in which 747 patients from 47 sites across the United States were enrolled. The high-risk inclusion criteria for the study population were similar to those described previously for the SAPPHIRE and ARCHeR studies.

Several other carotid stent registries are being maintained in the United States (Table 2). One randomized controlled trial currently under way is the Carotid Revascularization Endarterectomy versus Stent Trial (CREST), which is jointly sponsored by the National Institutes of Health and Guidant Corporation (Indianapolis, Indiana). The results of CREST and other carotid stent studies are expected to provide the level I evidence necessary for FDA approval for CAS as an optimal technique for carotid revascularization.

Endovascular management protocol and procedural technique

The technique of CAS varies slightly for each case depending on the clinical situation. The following is a description of the management

Table 1
Summary of single-arm registry results already presented

	ARCHeR 1 (n = 158)	ARCHeR 2 (n = 278)	ARCHeR 3 (n = 145)	BEACH
Major stroke at 30 days	1.9%	1.4%	1.4%	1%
Minor stroke at 30 days	2.5%	4.3%	4.8%	2.5% (1.9% ipsilateral)
MI at 30 days	2.5%	2.9%	0.7%	0.8%
Stroke-related death at 30 days	0.6%	0.7%	0	1.5% (all deaths)
Non–stroke-related death at 30 days	1.9%	1.4%	1.4%	
Major stroke from day 31 to 1 year	0	0.3%	N/A	Spring 2005
Minor ipsilateral stroke from day 31 to 1 year	0.6%	1%	N/A	Spring 2005
Stroke-related death from day 31 to 1 year	0	0	N/A	Spring 2005

Abbreviations: ARCHeR, Acculink for Revascularization of Carotids in High Risk Patients; ARCHeR 1, stent alone; ARCHeR 2, stent plus distal embolic protection; ARCHeR 3, rapid exchange version of stent and filter; BEACH, Boston Scientific EPI: A Carotid Stenting Trial for High Risk Surgical Patients; MI myocardial infarction; N/A, not available.

protocol and procedural technique used for most patients at our center.

Medical management

Endovascular procedures carry an inherent risk of intimal injury and subsequent thrombosis and vessel occlusion. Moreover, all stents are thrombogenic [59]. Therefore, patient preparation for stenting hinges on adequate administration of antiplatelet and anticoagulation therapies. Consideration must be given not only to the selection and dosing of antithrombotic medications but to minimizing the potential for associated hemorrhagic complications. Most information about treatment with these medications must be obtained from the cardiac literature, because clinical data in the neurosurgical literature are limited. Aspirin is a cyclooxygenase-1 inhibitor that irreversibly inhibits platelet aggregation but does not impede platelet adhesion or platelet-activated mitogenic activity. Clopidogrel is a thienopyridine derivative with potent antiplatelet action that inhibits adenosine phosphate–induced platelet aggregation. This drug works synergistically with aspirin, and evidence from the cardiac literature supports the use of combination antiplatelet regimens [60]. Clopidogrel, in combination with aspirin, has become the standard treatment for patients undergoing coronary angioplasty and stenting. When possible, patients are pretreated with aspirin (325 mg daily) and clopidogrel (75 mg daily) for at least 3 days before CAS or are given a loading dose of clopidogrel (300–600 mg) early on the day of the procedure.

For most stenting procedures, an intravenous bolus dose of heparin (50–75 U/kg) is administered after catheterization of the common carotid artery (CCA). Saline solutions used for irrigation of the catheters are prepared with heparin (1 U/mL), and catheter systems are flushed continuously with this solution. The activated coagulation time (ACT) is maintained in the range of 250 to 300 seconds for the duration of the procedure.

The use of platelet glycoprotein (GP) IIb-IIIa inhibitors (eg, abciximab, eptifibatide) in conjunction with CAS is controversial. These agents block the final common pathway of platelet aggregation by preventing the binding of fibrinogen to platelets and are the most potent of the antiplatelet drugs [61]. Our preliminary experience suggests that the administration of GP IIb-IIIa inhibitors places patients with chronic cerebral ischemia at an elevated risk of intracranial hemorrhage; therefore, such agents should be reserved for patients who experience thromboembolic complications during or soon after the procedure [61]. Abciximab can be given as an initial loading dose at 0.25 mg/kg immediately before the procedure is performed, followed by a 12-hour intravenous infusion at a rate of 10 μg/min. Eptifibatide may be administered as a loading dose at 180 μg/kg, followed by a 20- to 24-hour infusion at 0.5 to 2 mcg/kg. When the use of GP IIb-IIIa inhibition is recommended after the procedure, we suggest obtaining a CT scan before beginning the infusion to check for intracerebral hemorrhage, which would contraindicate the administration of these agents. In our daily practice, the use of such agents is reserved for the treatment of thromboembolic complications; we do not recommend the routine periprocedural administration of these agents.

Bradycardia occurs occasionally during angioplasty, particularly when the plaque involves the

Table 2
Carotid angioplasty and stenting trials

Study (manufacturer or sponsor)	Design	Clinical characteristics and percentage of stenosis	Stent	Distal protection device
ARCHeR 3 (Guidant)	Prospective single-arm registry (1-year follow-up results to be presented)	High risk Asymptomatic >80% Symptomatic >50%	Acculink RX	Accunet RX
BEACH (Boston Scientific)	Prospective single-arm registry (1-year follow-up results to be presented)	High risk Asymptomatic >80% Symptomatic >50%	Monorail Wallstent	EPI FilterWire EZ
CABERNET (Boston Scientific and EndoTex)	Prospective single-arm registry	High risk Asymptomatic >60% Symptomatic >50%	NexStent	EPI FilterWire
CARESS (NIH) (excludes CREST patients)	Prospective double-arm registry, physician chooses treatment, 2:1 CEA to CAS ratio	Asymptomatic >75% Symptomatic >50%	Physician's choice	Physician's choice
CREST (NIH, Guidant)	Randomized trial	Symptomatic >50%	Acculink	Accunet
MAVErIC 2 (Medtronic AVE)	Prospective single-arm registry	High risk Asymptomatic >80% Symptomatic >50%	Medtronic AVE Self-Expanding Stent System	PercuSurge
SECURITY (Perclose)	Prospective single-arm registry	High risk Asymptomatic >80% Symptomatic >50%	X-Act	NeuroShield
CREATE (ev3)	Prospective single-arm registry	High risk Asymptomatic >70% Symptomatic >50%	Protégé	Spider

Abbreviations: ARCHeR 3, Acculink for Revascularization of Carotids in High Risk Patients; BEACH, Boston Scientific EPI: A Carotid Stent for High Risk Surgical Patients; CAS, carotid artery angioplasty with stenting; CABERNET, Carotid Artery Revascularization Using Boston Scientific EPI FilterWire and EndoTex Stent; CARESS, Carotid Revascularization with Endarterectomy or Stenting Systems; CEA, carotid endarterectomy; CREATE, Carotid Revascularization with ev3 Arterial Technology Evolution; CREST, Carotid Revascularization Endarterectomy versus. Stent Trial; MAVErIC 2, Evaluation of the Medtronic AVE Self-Expanding Carotid Stent System with Distal Protection in the Treatment of Carotid Stenosis; NIH, National Institutes of Health; SECURITY, Study to Evaluate the Neuroshield Bare Wire Cerebral Protection System and X-Act Stent in Patients at High Risk for Carotid Endarterectomy.

Adapted from Levy EI, Kim SH, Bendok BR, Boulos AS, Xavier AR, Yahia AM, et al. Interventional neuroradiologic therapy. In: Mohr JP, Choi DW, Grotta JC, Weir B, Wolf PA, editors. Stroke: pathophysiology, diagnosis, and management. 4th edition. New York: Churchill Livingston; 2004. p. 1497; with permission.

carotid sinus. Atropine and a prepared dopamine solution are kept available should significant bradycardia and hypotension occur. Medical management of bradycardia during angioplasty is usually sufficient.

After stent placement, heparin therapy is generally discontinued but not reversed with protamine. In some situations, such as when an angiographically documented dissection or thrombosis is present, continued infusion of heparin is appropriate to maintain the activated prothrombin time 1.5 to 2.3 times the baseline value. Aspirin (325 mg daily) and clopidogrel (75 mg daily) are administered for at least 4 weeks after the procedure to allow for complete endothelialization of the stent [62]. Aspirin is continued indefinitely.

Preparation for the procedure

The procedure is performed in an angiography suite with biplane digital subtraction and fluoroscopic imaging capabilities. The patient is kept awake, with local anesthesia and sedatives administered to permit continuous neurologic assessment. Dorsalis pedis and posterior tibialis pulses are assessed and marked for later reference, a practice that is particularly important in patients with

coexistent peripheral vascular disease. A Foley catheter and two peripheral intravenous lines are placed. Oxygen saturation, cardiac rhythm, and blood pressure are monitored throughout the procedure.

Diagnostic angiogram

A 5-French sheath is placed in the right femoral artery, and a three-vessel diagnostic angiogram is obtained (if not previously performed) using a 5-French Simmons-2 or angled glide catheter. An intracranial angiogram with the injection of contrast material into the ipsilateral CCA is necessary for later comparison should intracranial thromboembolism be suspected after angioplasty. After a working projection image of the target vessel has been obtained, measurements are made of the vessel diameter proximal and distal to the lesion, the length of the lesion, and the severity of the stenosis (using the NASCET method [8]).

Vascular access

As previously mentioned, the loading dose of heparin is administered before the guide catheter is placed within the CCA. When the ACT reaches at least 250 seconds, the diagnostic catheter is positioned in the CCA and is used to advance a 0.035 in, 300 cm long stiff glide wire into the distal external carotid artery (ECA). In the setting of stenosis or occlusion of the ECA, an Amplatz exchange "J" wire (Cook, Bloomington, Indiana) is placed in the distal CCA and used to provide support for the guide sheath. With the stiff wire in position, the diagnostic catheter is removed as well as the femoral artery sheath. A 6-French, 90 cm guide sheath (Cook) is then advanced over the wire and placed just proximal to the carotid bifurcation. For those patients who have undergone complete diagnostic cerebral angiography, a combination of a 6-French, 90 cm shuttle select catheter (Cook) and a 6.5-French, head-hunter, 125 cm shuttle slip-catheter (Cook) is used. In these cases, the shuttle is introduced primarily in the femoral artery over a 0.035 in wire (this wire can be regular, stiff, or superstiff) and parked in the descending aorta. The inner obturator and wire are removed. The head-hunter shuttle slip-catheter is then advanced into the system, and the target vessel is catheterized. At this point, the wire (a 035 in, 300 cm long stiff glide or an Amplatz exchange "J" wire, depending on the status of the ECA) is advanced, followed by the slip-catheter and shuttle. The position and integrity of the target vessel as well as those of the distal ECA territory after manipulation with the exchange wire are assessed by angiography.

Carotid angioplasty with stenting procedure

Once the guide catheter is in place, we proceed with the following steps of the CAS procedure. First, the DEP device is positioned. If necessary, prestent deployment angioplasty is performed to enlarge the stenotic region sufficiently to permit passage of the stent. The stent is then deployed, after which time, poststent deployment angioplasty is done to remodel and expand the stent fully. Finally, the DEP is retrieved. After each step, high-resolution biplanar angiograms are obtained and neurologic examinations are performed to allow for prompt recognition of any changes from the patient's baseline status.

Distal embolic protection device placement. There are three classes of devices used for DEP: filtration, balloon occlusion, and flow reversal. Retrievable filters designed to collect debris during CAS are placed distal to the stenotic region without interrupting flow within the ICA. Examples of filtration devices include the EPI FilterWire (Boston Scientific Embolic Protection, San Carlos, California), Accunet (Guidant Corp.), AngioGuard (Cordis, Miami Lakes, Florida), Mednova (Abbott Laboratories, Abbott Park, Illinois), and Spider (ev3, Plymouth, Minnesota). Balloon occlusion techniques involve inflation of a balloon and interruption of flow in the ICA distal to the stenosis for the duration of the stenting procedure. An example of a balloon occlusion DEP device is the PercuSurge balloon. The flow-reversal technique involves the placement of balloons in the ECA and CCA to interrupt flow in these vessels and to cause retrograde flow in the ICA to prevent embolization into the intracranial circulation [63].

After the guide catheter is positioned, a DEP device (the authors' preference is to use a retrievable filter) mounted on a 0.014 in microguidewire is carefully guided across the stenotic region using a biplanar road-mapping technique. When crossing the lesion, the combination of turning and slightly pushing the device is preferred rather than simply pushing it. Ideally, the device should be placed in a relatively straight segment of the distal ICA and then deployed. Once the DEP device is deployed, the operator should assess the apposition of the device to the vessel wall to obtain more effective embolic containment.

Predilation angioplasty. With lower grade lesions, predilation angioplasty may not be necessary. The selection of a predilation angioplasty balloon is based on the dimensions of the lesion. The balloon must be long enough to cover the entire length of the lesion. The inflation diameter should be undersized to avoid overinflation and to open the artery just enough to allow passage of the stent. After an angiogram of the cervical carotid artery is obtained with the DEP device in place, the angioplasty balloon is advanced and centered on the lesion. The balloon is inflated to the manufacturer's recommended nominal pressure for several seconds and then deflated. The blood pressure cuff is set at a continuous mode during angioplasty to allow rapid sequential measurement of blood pressure should bradycardia and hypotension occur.

Stent placement. Most stents currently in use for CAS are self-expanding stents, such as the Wallstent, Acculink stent, and Precise stent (Cordis). The Wallstent is composed of stainless steel, and the Acculink and Precise stents are made of nitinol, a nickel and titanium alloy. Selection of the stent is determined by the length of the lesion and the normal diameter of the CCA. The stent should be oversized 1 to 2 mm more than the normal arterial caliber and should cover the lesion completely. At diameters less than full expansion, nitinol stents exert a chronic outward radial force that serves to maintain apposition of the stent to the vessel wall after deployment. Often, the stent extends from the CCA into the ICA, crossing the bifurcation and origin of the ECA; in these cases, the stent should be sized according to the larger caliber of the CCA. Although rare, when dealing with cases of contralateral ECA occlusion, one should be prepared for the potential need for revascularization of the ipsilateral ECA if occlusion occurs after stent deployment and poststent angioplasty.

When using a retrievable filter for distal protection, the position of the stent should be angiographically verified before the stent is deployed. The use of distal balloon occlusion precludes vessel assessment. In each case, anatomic landmarks should be carefully analyzed before the stent is deployed to ensure precise positioning of the stent.

Postdilation angioplasty. After the stent is in place, poststent deployment angioplasty is performed. Balloon selection is based on the diameter of the ICA. The balloon should be kept within the segment of stented artery during the angioplasty to avoid the risk of vessel dissection, especially at the distal ICA. Slow balloon inflation can be used on those patients with known overresponsive carotid baroreceptors.

Distal embolic protection device retrieval. After completing the poststent deployment angioplasty, cervical and intracranial images are obtained to assess target vessel patency and to exclude evidence of any major intracranial vessel occlusion. Once this is done, the DEP device is withdrawn, and a final series of cervical carotid and intracranial circulation angiograms are obtained.

The course of the DEP retrieval sheath through the segment of stented vessel should be carefully observed. The retrieval catheter can get caught on the stent struts protruding into the vessel lumen. This is especially important when using stents with an open-cell design. If this occurs, several options are available. Bringing the guide sheath closer to the stent may provide enough support to allow the stent to be crossed with the retrieval sheath. An angled, 4-French, 100 cm long diagnostic catheter can be used. Substituting the retrieval sheath for this catheter may allow the operator to navigate its tip around the difficult stent segment. Another option is the use of an angioplasty balloon with a 0.035 in compatible inner lumen, which would allow capture of the DEP device. Advancing the balloon into the difficult segment with partial inflation pushes the stent struts against the vessel wall, permitting further advancement of the balloon and subsequent retrieval of the device.

When distal balloon occlusion is used for DEP, 60 mL of blood is aspirated before the balloon is deflated. The aspiration is accomplished by use of an export catheter placed just proximal to the balloon.

Access site closure

After obtaining an angiogram of the femoral entry vessel, the decision to proceed with percutaneous closure is made. If the entry point of the sheath is above the bifurcation of the common femoral artery and the vessel is free of major atherosclerotic disease, the catheter systems and femoral sheath are removed, and a percutaneous closure device, such as the Perclose (Redwood City, California) or AngioSeal (St. Jude Medical, Minnetonka, Minnesota), is used. Otherwise, the guide sheath is exchanged for a 7-French, 15 cm sheath, which is left in place and removed when the ACT has normalized.

Periprocedural management and discharge plan

After the procedure, the patient is admitted to the intensive care unit for monitoring overnight. Hourly neurologic assessments and close surveillance of hemodynamic parameters are important. A systolic blood pressure of 110 to 160 mm Hg is maintained. A baseline carotid Doppler ultrasound study is obtained within 24 hours of the procedure to assess vessel patency and to provide a reference for further Doppler ultrasound evaluations. Most patients are discharged to home on the day after the procedure. As previously mentioned, aspirin and clopidogrel are prescribed.

Limitations of carotid angioplasty with stenting

Several anatomic features can make CAS difficult to undertake. Endovascular access to the carotid system can be problematic in patients with severe peripheral vascular disease that affects the iliac or femoral arteries and in those with a bovine configuration to the aortic arch, a tortuous aortic arch, or an ectatic CCA. Near-complete occlusion of the carotid artery (string sign) can impair safe passage of a DEP device, and a tortuous distal cervical ICA can make deployment of the device difficult. Also, because antiplatelet therapy is strongly recommended, an inability to tolerate these agents might be considered a relative contraindication to carotid stent placement.

Two major concerns exist regarding the durability of carotid revascularization with CAS: the efficacy of CAS in preventing long-term recurrence of ischemic events and the occurrence of in-stent stenosis after CAS. As previously mentioned, the 8-year follow-up results of the CAVATAS trial showed 90.8% of patients with no clinical ipsilateral ischemic events [47]. Few accounts exist of the restenosis rates after stenting. In the CAVATAS trial, severe (70%–90%) restenosis was found in 14% of patients treated with angioplasty with or without stenting (only 26% of patients in the endovascular group in that study received stents versus 4% of those receiving surgery) [46]. In a recent retrospective report of 183 patients, Doppler ultrasound results of greater than 80% recurrent stenosis (confirmed by angiographic evidence) after stent placement were found in 5.2% of the lesions stented, with restenosis after CEA representing the main risk factor for in-stent stenosis [64]. Similarly, we found a 5% rate of significant (symptomatic or >80%) in-stent stenosis (by digital subtraction angiography) in our series of 141 patients [65]. To determine the rate of hemodynamically significant recurrent carotid stenosis after stent-assisted angioplasty (in-stent stenosis) for carotid occlusive disease, we analyzed Doppler ultrasound data that had been prospectively collected from October 1998 to September 2002 for patients enrolled in carotid stent trials at our center. Patients included in this analysis were those with at least 6 months of follow-up with serial Doppler studies or elevated in-stent velocities (> 300 cm/s) demonstrated on postprocedural Doppler imaging. Hemodynamically significant recurrent stenosis (≥80%) was determined using the following Doppler ultrasound criteria: peak in-stent systolic velocity greater than or equal to 330 cm/s, peak in-stent diastolic velocity greater than or equal to 130 cm/s, and peak ICA-to-CCA velocity ratio greater than or equal to 3.8. Follow-up studies were obtained at approximate fixed intervals of 1 day, 1 month, 6 months, and yearly. Angiography was performed for patients with recurrent symptoms, Doppler ultrasound evidence of hemodynamically significant stenosis, or both. Retreatment was performed in patients who were symptomatic, had angiographic evidence of severe (≥80%) recurrent stenosis, or both. In our study, stents were implanted in 142 vessels in 138 patients (all but 5 were considered to be high-risk surgical candidates); 25 patients were subsequently lost to follow-up. For the remaining 112 patients (117 vessels), the mean Doppler follow-up duration was 16.42 ± 10.58 months (range: 4–49 months). Using one or more of the Doppler ultrasound criteria, greater than or equal to 80% in-stent stenosis was detected in 6 (5%) patients. Eight patients underwent repeat angiography. Six patients (3 of whom were symptomatic) required repeat intervention (4 required angioplasty alone, 1 required conventional angioplasty plus Cutting-Balloon [Boston Scientific Internventional Technologies, San Diego, California] angioplasty, and 1 required stent-assisted angioplasty). Thus, we showed that in a subset of primarily high-risk surgical candidates treated with stent-assisted angioplasty, hemodynamically significant restenosis rates are comparable with published rates of restenosis after surgery and that the treatment of recurrent stenosis in this limited number of patients incurred no periprocedural neurologic morbidity.

In reports evaluating recurrent carotid stenosis after angioplasty alone, Kachel [44,66] found no restenosis in his series of 57 patients, whereas Higashida et al [67] found a 5.5% incidence of restenosis in a series of 100 carotid angioplasties (follow-up period: 3 months to 7 years). In a report

by Yadav et al [13] describing patients treated with stent-assisted angioplasty for postoperative restenosis, no stenosis recurred in 8 of 22 patients who returned for follow-up angiography at 6 months. Perhaps the largest collection of patients from whom restenosis rates are available includes the global carotid stent registry of 12,392 procedures [68]. In this registry, the restenosis rates after carotid stenting were 2.7%, 2.6%, and 2.4% at 1, 2, and 3 years, respectively.

Summary

Carotid angioplasty with stent placement seems to be safer than CEA for some patients in the high-risk population. Studies are underway to assess the efficacy and long-term durability of this procedure (with distal protection) in NASCET- and ACAS-eligible populations.

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