Safety and Efficacy of Elective Carotid Artery Stenting in High-Risk Patients

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OBJECTIVES

We sought to evaluate the safety and efficacy of carotid artery stenting (CAS) in high-risk patients.

BACKGROUND

Carotid endarterectomy (CE) has been shown to be more effective than medical therapy, but it has limitations. Carotid artery stenting may be a reasonable alternative, particularly in high-risk patients.

METHODS

We prospectively evaluated the safety and efficacy of CAS in 170 consecutive patients who underwent the procedure in 192 carotid arteries. Of the patients enrolled, 129 (76%) would have been excluded from the major trials of CE and 54 (32%) were referred by vascular surgeons. This series represents a very high-risk group that included patients with unstable angina, previous ipsilateral CE, contralateral carotid artery occlusion and other severe comorbid illnesses. Only 25 (24%) of 104 symptomatic patients would have met the North American Symptomatic Carotid Endarterectomy Trial (NASCET) entry criteria. The patients’ mean age was 73 ± 8 years (95% confidence interval [CI] 57 to 89), and 42 patients (25%) were ≥80 years old. Patients had an independent neurologic examination before and after the procedure.

RESULTS

The procedural success rate was 99%, including 73 patients who had a coronary intervention. Mean carotid artery stenosis was 78 ± 10% before (95% CI 58 to 98) and 2 ± 3% after the procedure (95% CI 4 to 8). During the initial hospital period and 30 days after CAS, there was one major and two category 2 minor strokes, as well as two category 1 minor strokes (total 30-day stroke rate was 2.9% for treated patients or 2.6% for treated arteries). There were no myocardial infarctions or deaths during or within 30 days of CAS. None of the NASCET-eligible patients had a stroke. At a mean follow-up of 19 ± 11 months, three patients (2%) had asymptomatic restenosis. No other major strokes or neurologic deaths occurred.

CONCLUSIONS

Carotid artery stenting is feasible, can be performed even in high-risk patients and is associated with a low restenosis rate. (J Am Coll Cardiol 2000;35:1721–8) © 2000 by the American College of Cardiology

Cerebrovascular accidents (CVAs) occur each year in 500,000 Americans and result in 150,000 deaths and in substantial morbidity (1). Although antiplatelet agents have a continuing role in reducing CVA risk, randomized, controlled trials have shown that a reduction in carotid artery stenosis by carotid endarterectomy (CE) is superior to that of medical therapy alone (2–4).

Carotid endarterectomy, however, has certain limitations. In the North American Symptomatic Carotid Endarterectomy Trial (NASCET), 5.8% of patients had perioperative stroke or death (2). In the Asymptomatic Carotid Atherosclerosis Study (ACAS), the perioperative stroke rate was 2.8% (4). In higher-risk patients, particularly those with severe CAD, perioperative morbidity and mortality have been reported in up to 18% of patients (1,5–14). Cranial nerve palsies have been reported in up to 27% of patients (1,10). Also, restenosis occurs in 5% to 19% of patients, and scarring from the initial operation can make repeat CE difficult (9,15). Independent predictors of adverse outcome include contralateral occlusion, previous ipsilateral CE and combined coronary and carotid artery disease (CAD) (2,5–14). Further, CE is limited to the cervical portion of the carotid artery.

Recent studies suggest that carotid artery stenting (CAS) is feasible in the treatment of carotid artery stenosis (16–21). This procedure may prove to be safer, less traumatic and more cost-effective. Moreover, the risk/benefit ratio...
Patients were required to be enrolled in a protocol approved by the Institutional Review Board. Those with ≥60% stenosis in the common or internal carotid artery, or both, were entered into the study. June 1998 were studied. Symptomatic patients with documented CAD, or its suggestive symptoms, had coronary angiography first. In patients who had coronary artery bypass graft surgery (CABG) planned, CAS was performed first and then CABG was performed four weeks later.

Coronary artery stenting was performed using coaxial catheterization techniques adopted from coronary and other endovascular interventions. A 9F arterial sheath was inserted into the femoral artery, and an 8F sheath was inserted into the femoral vein for the placement of a temporary pacing catheter. Heparin was given intravenously, beginning with a bolus of 5,000 IU, as necessary, to maintain an activated clotting time >250 s. When CAS and coronary intervention were combined, the activated clotting time was maintained at ≥300 s. A 5F carotid diagnostic catheter (Mani, Cordis, Johnson & Johnson, The Netherlands) was used to engage the carotid artery over an 0.038-in. (0.096-cm) Terumo Glide wire. Then the catheter was advanced into a branch of the external carotid artery. This served as an exchange catheter for placement of an 0.038-in., Amplatz Extra Stiff guide wire. After removal of the diagnostic catheter, a 9F modified multipurpose guide catheter with a 0.096-in. (0.24-cm) internal diameter was advanced over the extra stiff exchange wire to a position just proximal to the carotid lesion. Initially, a 0.014-in. (0.035-cm) steerable guide wire was used to cross the lesion and was then exchanged for a 0.014-in. extra-support guide wire (Advanced Cardiovascular Systems, Inc., Guidant, Temecula, California). Predilation was performed using a low profile 4.0-mm coronary balloon. Thereafter, in 162 patients, balloon-expandable, stainless-steel, medium sized (10 to 15 mm in length) Palmaz biliary stents (Johnson & Johnson Interventional Systems Co., Warren, New Jersey) were used. In eight patients, self-expandable stents (Integra, Scimed, Boston Scientific, Watertown, Massachusetts) were used. The biliary stents were mounted, crimped and then delivered on a noncompliant peripheral balloon of the appropriate size (balloon/artery ratio 1:1). Stents were deployed with a single balloon inflation and then dilated with the same balloon or with a larger balloon using a higher pressure (10 to 12 atm). For a self-expanding stent, balloon dilation was done using a slightly undersized balloon with a low pressure (6 to 8 atm) inflation. In some cases, multiple overlapping Palmaz stents were used. All patients were given atropine sulfate (0.5 to 1.0 mg) before balloon inflation. In patients with hypotension, metaraminol bitartrate (100 to 200 μg) was also given. Neurologic status was continuously monitored both during and after CAS by simple contralateral hand-gripping maneuvers. The introducer sheaths were removed after the procedure when the activated clotting time was ≤180 s and no further anticoagulation was given. Patients were usually discharged the day after the procedure. All patients were treated with aspirin, 325 mg/day, indefinitely and ticlopidine, 250 mg twice daily, for at least three weeks.

**Clinical protocol.** A complete neurologic examination, including the National Institutes of Health (NIH) stroke scale or a modified stroke scale, was performed by a
neurologist before CAS. Computed tomography of the head and complete diagnostic cerebral angiography, including assessment of the intracranial collateral circulation were performed in all patients. The neurologic examination was repeated at 24 h, 30 days, six months and one year after CAS. Any change in neurologic status after CAS required repeat computed tomography of the head. A carotid artery ultrasound was performed at 30 days, six months and one year after CAS. Follow-up angiography was recommended for all patients at six months. Quantitative angiography was performed before, immediately after and six months after the procedure. Quantitative analysis was performed by an independent observer who did not know the patient outcome, using the ARTREK System (Imagecom, Mountain View, California). The percent diameter stenosis was obtained using the NASCET criteria, with the distal, nontapering portion of the internal carotid artery serving as the reference segment. The primary clinical end points assessed included death, any major or minor stroke and myocardial infarction (MI) within the first 30 days. Procedural success was defined as a reduction in the stenosis to ≥30% and absence of major stroke, MI or death.

Data collection and statistical methods. Clinical, angiographic and procedural data were prospectively recorded on a standardized form. The clinical and demographic variables collected included age, gender, symptoms, severity of CAD, presence or absence of diabetes mellitus, hypertension, hyperlipidemia, history of smoking, bilateral carotid artery stenosis or occlusion and whether the patient was randomizable into NASCET or ACAS. For calculation of stroke rates, the internal carotid plus ipsilateral common carotid arteries were considered as a single vessel, whereas the left internal carotid plus contralateral right internal carotid arteries were considered as two vessels. All data are expressed as the mean value ± SD; categoric variables are expressed as percentages. Cumulative frequency distributions were constructed for minimal lumen diameter and percent stenosis. Survival curves were drawn on an actuarial basis using the Kaplan-Meier technique. Statistical analysis was performed by using the chi-square test for discrete variables. A p value <0.05 was considered significant.

Definitions. MYOCARDIAL INFARCTION: Development of new Q waves on the electrocardiogram (ECG) and/or a creatine kinase elevation to at least twice the normal level, accompanied by above-normal elevation of the MB band.

CATEGORY 1 MINOR STROKE: A new neurologic deficit that changed the NIH stroke scale by 1 point and persisted for >24 h, but completely resolved or returned to baseline within seven days.

CATEGORY 2 MINOR STROKE: A new neurologic deficit that either resolved completely or returned to baseline within 30 days or that changed the NIH stroke scale by 2 or 3 points. By definition, both categories of minor stroke are nondisabling neurologic events.

| Table 1. Baseline Clinical and Demographic Characteristics (n = 170) |
|-----------------|-----------------|
| Male            | 100 (59%)       |
| Age (years)     | 73 ± 8          |
| Male            | 50–89           |
| Angina (NYHA functional class III or IV) | 74 (44%) |
| Myocardial infarction (recent) | 10 (6%) |
| LVEF ≤30%       | 44 (26%)        |
| Symptomatic     | 51 (30%)        |
| TIA             | 53 (31%)        |
| Asymptomatic    | 66 (39%)        |
| Previous ipsilateral CE | 16 (9%) |
| Contralateral carotid artery occlusion | 14 (8%) |
| Radical neck with radiation angitis | 4 (2%) |
| Cervical spine fixation | 1 (0.6%) |
| Diabetes mellitus | 61 (36%) |
| Hypertension    | 159 (94%)       |
| Chronic obstructive pulmonary disease | 35 (21%) |
| Chronic renal insufficiency | 33 (19%) |
| Current smokers | 50 (29%)        |
| Hyperlipidemia  | 117 (69%)       |

Data, except for age, are presented as the number (%) of patients. CE = carotid endarterectomy; CVA = cerebrovascular accident; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association functional class; TIA = transient ischemic attack.

MAJOR STROKE: A new neurologic deficit that persisted after 30 days and that changed the NIH stroke scale by ≥4 points.

RESULTS

Patient characteristics. The demographic and clinical characteristics of the 170 patients are shown in Table 1. The majority of patients in this study were men, and 25% were >80 years old. Almost one-half of them had Canadian Cardiovascular Society class III or IV angina. A history of CVA or TIA was present in >60% of patients. One hundred twenty-nine patients (76%) would have been excluded from NASCET and ACAS (Table 2), and 54 (31%) were referred for CAS by vascular surgeons.

Ninety-two percent (156 of 170) of the patients had CAD, as demonstrated by angiography. With respect to carotid anatomy, 84% of the lesions were eccentric, 25% had calcium present on fluoroscopy, 56% were of moderate to severe tortuosity and 24% were surgically inaccessible among symptomatic patients because of their location above the “Blesdale line.” Among 104 symptomatic patients, 79 met NASCET exclusion criteria, as shown in Table 2. Thirty-two of 51 patients with a recent CVA were anticoagulated with warfarin before CAS because angiography suggested the presence of thrombus. Three patients with a critical lesion and suggestion of thrombus on initial angiography did not require CAS, because of a decrease in the
severity of stenosis to <60% at follow-up angiography after warfarin therapy.

Procedural results and complications. Procedural data are shown in Table 3. A total of 192 carotid arteries in 170 patients were stented in a total of 183 procedures. A total of 265 stents (P104, n = 130; P154, n = 123; P204, n = 4; self-expanding, n = 8) were deployed. The procedural success rate was 99%. Most patients (64%) experienced significant bradycardia with balloon inflation, and hypotension requiring metaraminol occurred at least four weeks apart. The mean stenosis before the procedure was 78 ± 10% and 2 ± 3% after stenting. A typical example of angiographic results is shown in Figure 1. The reference diameter of the stented arteries was 5.66 ± 0.77 mm (95% confidence interval [CI] 4.12 to 7.2), and the balloon/artery ratio was 1:1. The cumulative frequency distribution of the minimal lumen diameter before (95% CI 0.44 to 1.4) and after CAS (95% CI 3.73 to 7.2) and at six-month follow-up (95% CI 3.34 to 6.34) in 108 patients is shown in Figure 2.

Late follow-up. Kaplan-Meier curves for survival free of death, MI, any stroke or any event are shown in Figure 4. Three non–Q wave MIs occurred during the 19-month follow-up. There were nine deaths during this time, none of which were attributed to a neurologic cause. Three patients had minor strokes, both category 2 (ipsilateral in two and contralateral in one patient). No major strokes occurred during the follow-up period. Two of the three patients with minor strokes had a MI and one had documented left ventricular thrombus. One hundred fifty-four patients were eligible for six-month duplex ultrasound and angiographic follow-up. Carotid artery duplex ultrasonography was done in 152 patients, and 108 (70%) had angiographic follow-up as well. Three patients had asymptomatic restenosis, and one had a mild degree of stent deformity. All three patients with restenosis (stenosis ≥60%) were successfully redilated.

DISCUSSION

This study demonstrates that CAS is both feasible and safe in high-risk patients. In the 170 patients reported herein, there were no procedural deaths or MIs and only one major stroke. These results were achieved despite the fact that 76% of the patients in this series would have been excluded from NASCET and ACAS (2,4). Also, in this series, 73 of the 170 patients underwent both CAS and a coronary intervention as a combined or staged procedure. These data suggest that CAS may be an appropriate substitute for CE, at least in patients at high risk for the latter procedure.

The resolution of obstruction to <60% with anticoagulation in almost 10% of patients with a recent stroke and carotid artery thrombus on the arteriogram suggests that it
may be appropriate to delay CAS in such patients until they complete a course of anticoagulation.

Comparison with previous studies. The NASCET and ACAS studies have demonstrated that when CE is performed by a highly skilled surgeon, operation is superior to medical therapy in preventing CVA, both in symptomatic and asymptomatic patients with high-grade carotid artery stenosis (2,4). In NASCET, the risk of stroke or death was 5.8%, and in ACAS, it was 2.8% (2,4). Although 76% of the patients would have been excluded from ACAS and NASCET, our complication rate was comparable. By limiting exclusion criteria to those that would make CAS inappropriate, we were able to include a group that is representative of the general population with cerebrovascular disease. This included 43% with symptomatic CAD who underwent CAS and a coronary intervention as a combined or staged procedure without major complications. Data suggest that combined or staged CE and CABG is associated with stroke rates of 4.5% to 7.1% and mortality rates of ~5.5% (5,6,12–14).

Other investigators (17–21) have reported CAS in a series of patients similar to ours. Of the 107 patients reported (20), 77% would have been excluded from NASCET or ACAS because of high risk. Four of the patients experienced restenosis, consistent with our finding of a low restenosis rate. Mathur et al. (17) studied the use of

Figure 1. An 82-year-old woman with a previous anterior MI (LVEF 25%) presented with unstable angina due to a critical left circumflex coronary artery stenosis. After a successful coronary intervention, carotid angiography showed critical, tandem (arrows) right carotid lesions (A) with an occluded contralateral internal carotid artery. Two (15-mm) Johnson & Johnson biliary stents were placed, with the proximal stent covering the distal common carotid artery (B), with excellent angiographic results. Intracerebral angiography showed excellent collateral filling (C) from the right carotid to the left anterior cerebral and middle cerebral arteries. (D) Follow-up duplex ultrasound at six months showed a widely patent stent. RT ICA = right internal carotid artery.
CAS in 231 patients with risk similar to that of our patients. They experienced a major CVA rate of 0.7% and a minor CVA rate of 6.2%. The authors identified advanced age and long or multiple lesions as being independently predictive of procedural CVA. These risk factors are different from those reported for procedural complications of CE, specifically contralateral carotid artery occlusion, previous CE and combined carotid artery disease and CAD (8,12,14). Despite the fact that 25% of the patients in our study were >80 years, none had a procedural MI or major CVA, and there was no difference among the <70-year-old, 70- to 80-year-old and >80-year-old age groups with respect to major or minor CVA (Table 4). In all reported series, minor CVA was the most common complication. In NASCET, for a stroke to be “minor,” functional recovery needed to occur within 90 days, whereas in our study and others (17,20,21), functional recovery had to occur within seven days for category 1 minor CVA or within 30 days for category 2. These events would not have been recorded as strokes in NASCET (2), where a detailed neurologic examination was delayed for 30 days.

Interestingly, two patients had a lower 24-h stroke scale after the procedure as compared with baseline. This finding is similar that of Yadav et al. (20) and supports the notion of a “hibernating” state of the brain, analogous to hibernating myocardium (22).

Procedural considerations and late outcome. The importance of pretreatment with aspirin and ticlopidine, as well as its duration, in preventing complications is not clear, and a randomized trial is needed to rigorously examine this issue. However, given the demonstrated importance of these agents in coronary stenting, such a trial seems unlikely to be undertaken. In cases where there was a suggestion of thrombus, patients were also treated with warfarin for three to four weeks before CAS. Although this seems reasonable from first principles, the importance of such treatment in this setting has not been rigorously demonstrated. A temporary pacemaker was placed in all patients in this study, although it was rarely needed, and we no longer routinely place a temporary pacemaker.

Overlapping stents (i.e., covering the body of the lesion)

Table 4. Adverse Events by Age Group

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>n</th>
<th>Major CVA</th>
<th>Minor CVA*</th>
<th>All Events†</th>
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<td>42</td>
<td>0</td>
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*There were two category 2 minor strokes as well as two category 1 minor strokes.
†This includes all minor strokes (category 1 or 2) and major strokes combined (p = 0.77).
CVA = cerebrovascular accident.
were used to increase the radial strength and metallic coverage of the Palmaz stents. Although we had only one case of stent deformation, Mathur et al. (23) have reported a 15% stent deformation rate. Current self-expanding stents, which we now use exclusively, have sufficient radial strength to make overlapping stents unnecessary. In fact, deformation is virtually absent with self-expanding stents.

There were no late major CVAs or neurologic deaths after hospital discharge. At a mean follow-up 19 ± 11 months, there were only three patients (2%) with restenosis, all of whom were successfully redilated. These results are comparable to those reported by other investigators (17–20).

**Clinical implications and future studies.** In the low-risk patients randomized into NASCET and ACAS, relief of obstruction has been shown to lower the risk of CVA. Whether relief of the obstruction in other patient groups with different baseline characteristics would have the same treatment advantage is not known with certainty, nor is the relative effectiveness of CAS and CE in preventing CVAs and death in these high-risk patients. During the 19-month follow-up of patients in this study, there were very few neurologic events, suggesting that the effectiveness of obstruction relief may well be reflected in long-term clinical benefit. For this reason, randomized, controlled trials of CE versus CAS are now the next step in evaluating CAS. Until randomized trials are available, caution should be exercised in discarding CE in patient groups in which it has been proven effective. One randomized trial—the Carotid And Vertebral Artery Transluminal Angioplasty Study (CAVATAS), which examined the role of angioplasty versus CE—has been completed (24). This trial, although underpowered, suggested that balloon angioplasty without routine stenting has a similar safety profile to elective CE. These data suggest that routine stent implantation will further improve the percutaneous management of carotid artery disease. A second trial that compares CE and CAS—the Carotid Revascularization Endarterectomy versus Stent Trial (CREST), sponsored by the NIH—is planned (25).

The final results of CREST will not be available for at least five to six years. In the interim, there are sufficient published reports to support the use of CAS by experienced operators in patients known to be at high risk for CE (16–21). Such procedures require an experienced team of neurologists and interventionalists. Patients at high risk for CE include patients with carotid artery lesions above the C2 or C3 cervical vertebrae or at the ostium of the common carotid artery and patients with cervical spine disease or fixation, previous radical neck dissection, fibromuscular dysplasia, previous cervical radiation, previous CE and the presence of important comorbid conditions, including unstable angina, recent MI and severe congestive heart failure.

Whether the safety of CAS can be improved by the use of glycoprotein IIb/IIIa inhibitors or distal neuroprotection devices should be studied. In addition, there will be a continuing evolution of new stents and postdilation strategies that will require evaluation.

**Study limitations.** The primary limitation of this study is that it is not a randomized trial. Also, CAS was performed by one highly experienced operator in a single center. Whether similar results will be obtained by less experienced operators is not known. This study represents early clinical experience with equipment designed for coronary and peripheral vascular interventions. Devices designed specifically for carotid artery intervention may improve outcome.

**Conclusions.** This study demonstrates that CAS is feasible and safe, even in patients who would have been excluded from the NASCET and ACAS trials. Furthermore, patients known to be at high risk for CE (i.e., those with contralateral carotid artery occlusion, previous CE, previous radiation angitis and those undergoing a combined or staged coronary intervention with CAS) had a complication rate comparable to that of patients in the ACAS and NASCET trials. Multicenter, randomized trials are under way and will define the ultimate role of CAS.

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