Immediate and Late Clinical Outcomes of Carotid Artery Stenting in Patients With Symptomatic and Asymptomatic Carotid Artery Stenosis

A 5-Year Prospective Analysis

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Background—Carotid stenting is a less invasive percutaneous procedure than carotid endarterectomy for the treatment of carotid stenosis. Reports suggest that it can be performed with periprocedural complication rates similar to those of carotid endarterectomy. The purpose of this study was to determine short- and long-term outcomes in the largest prospective cohort of carotid stenting patients.

Methods and Results—This study followed 528 consecutive patients (604 hemispheres/arteries) undergoing carotid stenting. There was a 0.6% (n = 3) fatal stroke rate and 1% (n = 5) nonstroke death rate at 30 days. The major stroke rate was 1% (n = 6), and the minor stroke rate was 4.8% (n = 29). The overall 30-day stroke and death rate was 7.4% (n = 43). Over the 5-year study period, the 30-day minor stroke rate improved from 7.1% (n = 7) for the first year to 3.1% (n = 5) for the fifth year (P < 0.05 for trend). The best predictor of 30-day stroke and death was age ≥80 years. After the 30-day period, the incidence of fatal and nonfatal stroke was 3.2% (n = 31). On Kaplan-Meier analysis, the 3-year freedom from ipsilateral or fatal stroke was 92 ± 1%.

Conclusions—Experience from a single group of operators demonstrates that carotid stenting can be performed with an acceptable 30-day complication rate. Late follow-up also demonstrates a low rate of fatal and nonfatal stroke. These results suggest that carotid stenting may be comparable to carotid endarterectomy, and it underscores the clinical equipoise and premise for the National Institute of Health-supported, randomized Carotid Revascularization Endarterectomy Versus Stent Trial comparing carotid stenting with carotid endarterectomy. (Circulation. 2001;103:532-537.)

Key Words: stents ■ stenosis ■ stroke

Approximately 600,000 people suffer a stroke each year in the United States. This leads to nearly 160,000 deaths and leaves many more people with major disability.1 The advantage of carotid endarterectomy (CEA) over medical therapy in patients with significant carotid stenoses has been established in recent randomized studies.2–4 Carotid stenting (CS) is a less invasive percutaneous procedure that has been under investigation in the United States since 1994.5 CS may allow avoidance of some of the perioperative complications of CEA. The National Institute of Health/National Institute of Neurological Disorders and Stroke recently approved funding for the Carotid Revascularization Endarterectomy Versus Stent Trial (CREST), a multicenter, randomized trial, to compare these 2 techniques.6 The success of recruitment in this trial will depend on evidence for “clinical equipoise—genuine uncertainty within the expert medical community about the preferred treatment.”7 Preliminary reports suggest that CS can be performed with an acceptable 30-day complication rate.8–16 Whether CS is a reasonable alternative to CEA and thus should be compared directly depends on more definitive evidence. This prospective study on outcomes after CS was undertaken to better define the incidence of immediate and late stroke in a large series of patients.
Immediate and Late Outcomes From Carotid Stenting

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Methods

Patient Population
From September 8, 1994, through September 8, 1999, 528 consecutive patients (604 hemispheres/arteries) underwent CS at the University of Alabama at Birmingham Hospital and subsequently at Lenox Hill Hospital (performed by G.S.R., S.S.I., and J.J.V.). The outcomes in the first 107 patients in this report have been published previously. Small analyses in various subgroups have also been reported. Carotid stenosis was located at the extracranial internal carotid artery (ICA) at the bifurcation (n=565), proximal common carotid artery (CCA; n=34), separate stenoses of the ICA (at the bifurcation) and proximal CCA artery (n=3), or a functional external carotid artery (Fx-ECA; ie, occluded ICA and patent ECA that supplies ipsilateral middle cerebral artery via ophthalmic collaterals; n=2). Although not strictly bifurcational disease and not commonly treated by CEA, CCA and Fx-ECA lesions were included because the procedure may have a similar clinical sequel.

Patients were required to have either symptomatic (≥50% diameter) or asymptomatic (≥60% diameter) stenosis of the carotid artery. “NASCET ineligible” patients were defined as those symptomatic patients who were ineligible for enrollment according to the exclusion criteria of the North American Symptomatic Carotid Endarterectomy Trial (NASCET; >79 years of age, prior CEA, atrial fibrillation, etc.). Patients were excluded if they had a major neurological deficit or any other illness impeding informed consent, severe renal insufficiency (serum creatinine >3.0 mg/dL), or peripheral vascular disease precluding femoral artery access. Over the study period, selection criteria and techniques were modified as immediate outcomes were analyzed. Patients with severe diffuse atherosclerosis of the CCA, chronic total occlusions, and long preocclusive lesions (“string sign” lesions) were excluded. All patients were studied under Institutional Review Board–approved protocols at the above institutions, and all patients gave written informed consent to participate. The risks and benefits of CS were explained. The operator informed patients that they were undergoing an investigational procedure, told them about the proven efficacy of CEA in randomized trials, and offered them this treatment as an alternative.

CS Technique

Preprocedural Protocol
Patients were referred to our institutions after a carotid stenosis was suspected on screening. A CT scan or MRI of the brain was performed according to standard techniques. Intracranial views determined the patency of the circle of Willis. This allowed us to anticipate those patients who had a contralateral occlusion and/or an “isolated hemispheric blood supply” and therefore may not tolerate carotid artery occlusion. The principles of CS have been described. Patients were usually discharged the next day after examination by a neurologist and were prescribed ticlopidine or clopidogrel and aspirin 325 mg BID for 4 weeks and aspirin thereafter for the rest of their lives.

Angiography and CS Technique

No sedation was given before or throughout the procedure. Neurological assessment was performed at predetermined intervals throughout the procedure. Hemodynamics and oxygen saturation were continuously monitored. Nitroglycerin, atropine, metaraminol, and dopamine were administered as required to manage hypertension, bradycardia, and hypotension.

Cervical-cerebral angiography was performed according to standard techniques. Intracranial views determined the patency of the circle of Willis. This allowed us to anticipate those patients who had a contralateral occlusion and/or an “isolated hemispheric blood supply” and therefore may not tolerate carotid artery occlusion. The principles of CS have been described. Patients were usually discharged the next day after examination by a neurologist and were prescribed ticlopidine or clopidogrel and aspirin 325 mg BID for 4 weeks and aspirin thereafter for the rest of their lives.

Data Collection and Patient Follow-Up
Quantitative carotid angiography was performed on all arteries before and after stenting. Diameter stenosis was determined according to NASCET criteria. Clinical follow-up (mean±SD, 17±12 months) was available on 518 (99.6%) of the 520 patients who survived the periprocedural period. Follow-up phone interviews were conducted at 1 month and at 6-month intervals thereafter by a dedicated research coordinator. Patients were instructed to notify the coordinator if symptoms suggestive of a neurological event occurred. When a neurological event occurred, CT of the head was performed, and the physician was contacted to accurately document the episode. Hospital discharge diagnoses were also reviewed to adjudicate events. When a death occurred, the cause of death was obtained from the death certificate or postmortem.

A board-certified neurologist performed an NIH Stroke Scale ≥24 hours after the procedure. A transient ischemic attack was defined as a focal retinal or hemispheric event from which the patient made complete recovery within 24 hours. A minor nonfatal stroke was defined as a new neurological deficit that either resolved completely within 30 days or increased the NIH Stroke Scale by ≥3. A major nonfatal stroke was defined as a new neurological deficit that persisted >30 days and increased the NIH Stroke Scale by ≥4. Long-term outcomes are reported as neurological events and deaths. A fatal stroke was defined as death attributed to an ischemic stroke or intracerebral hemorrhagic stroke and did not include brain tumors or death resulting from head trauma.

Statistical Analysis
Data are expressed as mean±SD. All probability values were 2 tailed, and values of P<0.05 were considered statistically significant. Comparisons of 30-day outcomes included men versus women, <80 versus ≥80 years of age, and symptomatic versus asymptomatic patients (χ² analysis). Logistic regression analysis was performed to determine predictors of 30-day stroke and death. A χ² test of trend was performed on the 30-day death and stroke rates by calendar year to evaluate differences in outcomes over the study period. Time to treatment failure was analyzed by Kaplan-Meier methods and a log-rank statistic for symptomatic versus asymptomatic patients, patients ≥80 versus patients <80 years of age, and male versus female patients.

Results

Patient Characteristics
The clinical characteristics of all the patients are shown in Table 1.
Angiographic and Stenting Results
Two hundred seventy patients had bilateral carotid artery disease (≥50% stenosis), with 61 arteries (10%) having an occlusion of the contralateral ICA. Seventy-six patient (15%) had bilateral carotid artery stenting, with 30 being performed in the same procedure.

The mean stenosis before stenting was 74±14%. Seven arteries were total occlusions. The mean stenosis after stenting was 5±9%. On average, 1.2±0.6 stents were used per vessel, with 424 (70%) being self-expanding and the remainder being balloon-expandable stents. There was significant compromise of the origin of the ECA in 11 arteries that required treatment with angioplasty in the same procedure (not considered separate arteries). There were 12 technically unsuccessful procedures (2%) in which a carotid stent was unable to be delivered: 9 resulting from inadequate guiding sheath placement, 2 from air embolism, and 1 from inability to cross the lesion with a wire. One patient (0.2%) had a minor stroke after an air embolism. One patient (0.2%) had a major ipsilateral nonfatal stroke after a failed attempt to deliver a stent.

Thirty-Day Outcomes
Thirty-day stroke and death rates are listed in Table 2. There was 1 periprocedural acute non–Q-wave myocardial infarction. Symptomatic and asymptomatic patients had similar 30-day complication rates (8.0% versus 5.9%, respectively; P=0.47). Male and female patients also had similar periprocedural complication rates (8.0% versus 5.9%, respectively; P=0.4).

However, patients ≥80 years of age had higher rates of major nonfatal stroke compared with those <80 years old (see Table 3).

Table 4 shows the reduction in periprocedural events over the 5 years of this study. There was a decreasing trend in the major nonfatal stroke rate from the first through the fifth year of the study (P<0.05 for trend). On logistic regression analysis, age ≥80 years (OR, 3.64; 95% CI, 1.7 to 7.69) and a history of hypertension (OR, 3.45; 95% CI, 1.17 to 10.10) were the only predictors of 30-day events.

Late Follow-Up
After the 30-day periprocedural period, the incidence of late fatal and nonfatal stroke was 3.2% (see Table 5). In this series, 16 patients (3%) required repeated angioplasty for restenosis. Two patients (0.3%) required CEA, 1 for a failed attempt at CS and 1 for restenosis. There were 75 late nonneurological deaths (mainly attributed to cardiac disease and cancer), and 2 deaths of indeterminate cause.

The 3-year freedom from all fatal and nonfatal strokes was 88±2% (mean±SE; Figure 1A). Among those who survived the 30-day periprocedural period, the 3-year freedom from all fatal and nonfatal strokes was 95±2%; Figure 1B). Similarily, the 3-year freedom from all fatal and ipsilateral nonfatal strokes with and without the inclusion of 30-day periprocedural period was 92±1% and 99±1%, respectively (Figure 2). The 3-year freedom from all fatal and nonfatal strokes including and excluding 30-day periprocedural period for <80 versus ≥80 years of age was 90±2% versus 73±4% (P<0.0001) and 95±2% versus 91±1% (P<0.01), respectively (Figure 3). There were no differences in freedom from
stroke between men and women and symptomatic and asymptomatic patients.

**Discussion**

CS may provide an alternative to CEA, especially in those patients deemed to be at higher risk for endarterectomy. The short-term results derived from the largest series reported to date confirm other reports that suggest that the procedure can be performed with an acceptable complication rate.\(^8\)\(^\text{-}^{11}\),\(^12\)\(^\text{-}^{22}\) The long-term durability of CS, however, has not been previously examined. In this large series by a single group of operators, the high freedom from ipsilateral stroke at 3 years suggests that CS is durable and efficacious.

CS is now being performed in many centers around the world with low complication rates.\(^9\)\(^\text{-}^{11}\) Data from a worldwide registry reported a technical success rate of 98.4\%, an overall minor stroke rate of 2.72\%, a major stroke rate of 1.49\%, and a mortality rate of 0.86\%.\(^32\) Although techniques vary slightly between operators and centers, these results are concordant with the findings of this study, which suggest that CS can be carried out with acceptable procedural outcomes.

The only randomized study to date, the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS), comparing carotid angioplasty (with bailout stenting in 26\%) and CEA, demonstrated similar periprocedural stroke rates for the 2 groups (10\% and 9.9\%, respectively).\(^23\) Meaningful comparison of the results of this present study with complication rates from published CEA studies is limited by differences in case mix, completeness of neurological evaluation, and nonstandardized end points. In particular, a large proportion of symptomatic patients in this study were NASCET ineligible.\(^20\) Nonetheless, stroke rates after CS appear to be in a range similar to those observed in randomized trials of CEA for symptomatic patients. In NASCET, the 30-day minor stroke rate was 4.0\%, major stroke rate was 1.6\%, mortality rate was 1.2\%, and overall stroke and death rate was 6.7\% in patients with symptomatic carotid stenosis (≥50\% diameter stenosis) randomized to the CEA arm.\(^4\) The Veterans Affairs Cooperative Study (VACS) also reported a 6.5\% 30-day stroke and death rate.\(^24\) and the European Carotid Stent Trial (ECST) reported an overall 7.0\% major stroke and death rate in patients with symptomatic carotid stenosis.\(^2\) For asymptomatic patients, comparison is particularly difficult. The Asymptomatic Carotid Atherosclerosis Study (ACAS) reported a periprocedural stroke and death rate of 2.3\% in a lower-risk subset,\(^3\) and the asymptomatic surgical group in VACS suffered a 4.7\% permanent stroke and death rate.\(^25\)

This study demonstrated that symptomatic patients and asymptomatic patients had similar periprocedural complication rates after CS. The results in asymptomatic patients appear to be higher than that reported in ACAS. However, although criteria for symptom status are the same, differences may exist in other criteria, such as patient age and comorbidity, between the asymptomatic patients in this series and the patients in the CEA trials.\(^3\),\(^25\),\(^26\) In the latter part of the present study, complication rates for symptomatic patients fell within American Heart Association/Society of Vascular Surgery guidelines,\(^27\) whereas procedural outcomes for asymptomatic patients exceeded the recommended 3\% upper limit based on ACAS results.\(^26\) During the last 2 years of the study, asymptomatic patients <80 years of age had a periprocedural complication rate of 3.5\%. Again, these results cannot be directly compared with results of CEA. Whether future technical improvements, such as the use of distal-protection devices\(^10\) during stenting, will improve periprocedural outcomes for both asymptomatic and symptomatic patients remains to be determined. The potential advantages of CS over CEA include avoidance of neck wound complications and cranial nerve palsies and a reduction in periprocedural myocardial infarction. In the present study, 1 patient (0.2\%) experienced a myocardial infarction. In contrast, the NASCET study reported a 3.9\% myocardial infarction rate, an 8.9\% wound complication rate, and a 7.6\% cranial nerve palsy rate.\(^20\)

Long-term survival curves in the symptomatic patients in this present series demonstrate an 11\% fatal and nonfatal stroke rate estimated at 3 years. In CAVATAS, in which 96\% of patients were symptomatic, the 3-year freedom from ipsilateral stroke and death was similar between the angioplasty and CEA groups.\(^23\) NASCET, on the other hand, reported a 15.8\% 2-year any stroke or death rate and an 8.0\% major stroke or death rate.

Long-term survival curves in the asymptomatic group in this study demonstrated a 14\% fatal and nonfatal stroke rate at 3 years. In asymptomatic patients, ACAS reported a 5-year stroke or death rate of 20.7\%. Moreover, in this study, symptom status was not a predictor of periprocedural or late neurological events. Of importance, the need for repeated intervention was low in this cohort. This is consistent with the low angiographic restenosis rates reported by our group and that of others.\(^8\),\(^10\),\(^11\)

Similar periprocedural and late outcomes were observed for men and women in this study. This is in contrast to randomized and observational reports of CEA, which have consistently demonstrated poorer outcomes for women.\(^2\)\(^\text{-}^{4\text{-}28}\) Much of the sex difference can be attributed to the higher periprocedural complication rate rendering the long-term risk benefit ratio not in favor of surgical treatment for females. Perhaps CS may eliminate this sex dimorphism commonly observed in cardiovascular disease.

This study included patients who were ≥80 years of age. Age ≥80 years was a predictor of periprocedural events and late stroke. No comparison from randomized CEA trials can be made because age ≥80 years was one of the exclusion

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<td>Event</td>
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Stroke (n)=number of strokes/number of hemispheres. Death (n)=number of deaths/number of patients.

*Includes 1 stroke of unknown hemisphere and severity.
criteria. Observational data reported for CEA, however, concur with our results and demonstrate an increased risk of stroke for patients 75 years of age. The use of distal protection devices may improve periprocedural outcomes in this high-risk group. Since this analysis was completed, we have performed CS in patients $\geq 80$ years of age only with the aid of distal neuroprotection devices.

**Study Limitations**

This prospective study cannot be comparable to reported trials and series of CEA because of confounding factors that may make patients at higher or lower risk. This will ultimately be tested in randomized trials. In this study, stroke rate was calculated using the number of hemispheres/arteries treated, rather than the number of patients, as the denominator. Although this is a departure from the conventional method of reporting strokes in trials of CEA, it may be a more accurate reflection of outcomes from this procedure. Seventy-six patients had bilateral stenting, with the potential for bilateral neurological complications to occur. This is in contrast to CEA trials in which patients were usually excluded if a bilateral procedure was required, thereby reducing the possibility of bilateral neurological events. We have, however, shown both methods for calculating periprocedural events in Table 2. Similarly, Kaplan-Meier survival curves were analyzed in terms of fatal and nonfatal strokes rather than strokes and all-cause deaths as reported in trials of CEA. Selection criteria in these trials typically precluded patients with any serious illness deemed to be life limiting. The present study did not exclude patients with other life-threatening diseases, such as cancer, lung disease, and coronary ischemia. Therefore, long-term survival analyses in terms of all-cause deaths may reflect the level of comorbidity of the study population more than efficacy of this technique.

**Conclusions**

This large cohort of patients undergoing CS demonstrates acceptable 30-day periprocedural complications and a low incidence of late stroke. These results underscore the need to validate this less invasive procedure against CEA, the current

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**Figure 1.** A, Kaplan-Meier cumulative event rates for all fatal and nonfatal strokes. B, Kaplan-Meier cumulative event rates for all fatal and nonfatal strokes after 30 days. n indicates number at risk.

**Figure 2.** A, Kaplan-Meier cumulative event rates for all fatal and ipsilateral nonfatal strokes. B, Kaplan-Meier cumulative event rates for all fatal and ipsilateral nonfatal strokes after 30 days. n indicates number at risk.

**Figure 3.** A, Kaplan-Meier cumulative event rates for all fatal and nonfatal strokes. B, Kaplan-Meier cumulative event rates for all fatal and nonfatal strokes after 30 days. Solid line indicates $\geq 80$ years of age; dashed line, $<80$ years of age; and n, number at risk.
“gold standard,” surgically proven treatment for carotid artery disease. The National Institute of Neurological Disorders and Stroke–sponsored, multicenter, randomized CREST study will begin recruitment of patients at the end of 2000. The immediate and late results from the present study support the “clinical equipoise” necessary to begin randomization.

Acknowledgments

We would like to thank Thomas Brott, MD, for his critique of the manuscript and acknowledge Virginia Yates, Diana Alred, Kimberly Kretzer, and Emily Lawrence for their assistance.

References

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_Circulation_. 2001;103:532-537
doi: 10.1161/01.CIR.103.4.532
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/103/4/532

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