Stent Angioplasty for Cervical Carotid Artery Stenosis in High-Risk Symptomatic NASCET-Ineligible Patients

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Background and Purpose—Although the North American Symptomatic Carotid Endarterectomy Trial (NASCET) has shown carotid endarterectomy (CEA) to be protective compared with medical therapy alone, its stringent eligibility criteria excluded patients with severe medical, angiographic, and neurological risk factors. We sought to determine the safety and efficacy of stent angioplasty in this high-risk subset for whom the perioperative morbidity and mortality of surgery are elevated.

Methods—Twenty-eight consecutive symptomatic NASCET-ineligible patients (10 female; median age, 72.2 years) underwent microcatheter-based carotid stent angioplasty. Half of the patients had sustained a previous stroke. Classification of surgical risk by Sundt criteria yielded no patients in grade 1, 3 patients in grade 2 (10.7%), 8 in grade 3 (28.6%), and 17 (60.7%) in grade 4. Stratification of stroke risk for medical therapy according to the European Carotid Surgery Trial (ECST) 5-point score showed 8 patients with a score of 3 (28.6%), 12 with 4 (42.8%), and 8 with 5 (28.6%). Follow-up was obtained in all patients at a median of 14 months.

Results—The procedure was technically successful in all cases (100%), with immediate stenosis reduction from a mean of 80.3% to 2.7%. There were no periprocedural deaths, 1 major stroke (3.6%), no minor strokes, and 3 transient ischemic attacks (10.7%). In-hospital complications included 2 nonfatal myocardial infarctions, 1 case of acute renal failure, and 1 groin hematoma requiring transfusion. There were 5 deaths during the follow-up period, all beyond 30 days after the procedure: 3 from cardiac causes, 1 from lung cancer, and 1 following unrelated surgery. The patient with major stroke died at 7.8 months during rehabilitation. No surviving patients had further strokes, and all except 1 (95.5%) remained asymptomatic. Anatomic follow-up in 20 patients showed occlusion in 2 (10%) (1 symptomatic, 1 asymptomatic) and intimal hyperplasia in 3 asymptomatic patients (15%).

Conclusions—The clinical results and sustained freedom from symptoms and stroke during the short available follow-up period suggest that stent angioplasty may be useful in the treatment of symptomatic cervical carotid stenosis in high-risk patients despite a notable incidence of restenosis. (Stroke. 2000;31:3029-3033.)

Key Words: angioplasty ▪ carotid endarterectomy ▪ carotid stenosis ▪ endovascular therapy ▪ stents

The North American Symptomatic Carotid Endarterectomy Trial (NASCET)1 and the European Carotid Surgery trial (ECST)2 have demonstrated that surgical carotid endarterectomy (CEA) offers durable protection relative to medical therapy in patients with symptomatic cervical stenosis >70% provided that the combined morbidity and mortality is kept below 6%.3 The need to maximize the sensitivity and specificity of the comparison with medical treatment and to minimize confounding factors dictated a set of stringent restrictions for eligibility in NASCET that excluded patients with severe clinical risk factors.1 Currently no prospective randomized data exist to help guide optimal therapy of symptomatic high-risk patients who fail eligibility criteria set forth in the major trials.1,2 It has been postulated that the potential additional morbidity incurred in the treatment of high-risk patients may invalidate the documented benefit of carotid revascularization.4 The analysis of Sundt et al5,6 resulted in the formulation of a predictive instrument for estimating the risk of procedural morbidity of CEA. Medical risk factors increased the periprocedural risk of stroke and death from CEA from 0.9% (Sundt grade 1) to 1.7% (grade 2), while angiographic risk factors increased the rate to 3.7% (grade 3), and neurological instability further increased the rate to 8.1% (grade 4). Patients with multiple comorbid conditions may be denied surgical revascularization because of elevated periprocedural risk in favor of medical therapy, which may carry a higher cumulative risk of stroke.5-7 Recently, stent angioplasty has been proposed as an endovas-
cular technique for carotid revascularization that may be beneficial in certain patient subsets. To clarify the possible contribution of endovascular intervention to the treatment of carotid atherosclerosis, we present in this retrospective study the results and clinical outcome obtained in symptomatic NASCET-ineligible high-risk patients who were referred for stent angioplasty after consideration for surgical endarterectomy.

Subjects and Methods

Patient Selection
Twenty-eight patients with symptomatic carotid atherosclerotic stenosis who were ineligible by NASCET criteria were referred by a neurologist or vascular surgeon after evaluation for CEA and were treated consecutively between July 1996 and June 1999. Detailed informed consent was obtained from the patient or the patient’s legal guardian after disclosure of the procedural status in accordance with institutional guidelines. Patients who underwent stent angioplasty primarily for treatment of carotid dissection, pseudoaneurysm, intracranial or intrathoracic atherosclerosis, or thrombolytic therapy for recanalization of acute carotid occlusion were excluded from the present analysis.

Procedure
Twenty-four patients (86%) underwent light intravenous neuroleptic sedation, and the remainder had general endotracheal anesthesia (n=4, 14%) because of poor ability to cooperate (n=2) or because of the need for intracranial navigation (n=2). All patients were monitored by placement of transthoracic electrodes (Zoll Medical) in case of bradycardia or asystole during angioplasty. Patients were administered intravenous heparin (bolus of 70 U/kg) followed by either an hourly dose (bolus of 35 U/kg) or continuous infusion (15 U/kg per hour) to ensure an activated clotting time greater than twice baseline. After a complete diagnostic angiographic study, the stenotic lesion was treated with an angioplasty balloon catheter (predilatation) to enable subsequent passage of a balloon-mounted (Palmaz, Johnson & Johnson; GFX, AVE/Medtronic) or self-expanding stent (Wallstent, Schneider; S.M.A.R.T. stent, Cordis). In 7 cases (25%), primary stenting was performed without resorting to predilatation. Postdeployment high-pressure balloon angioplasty (12 to 21 atm) was then performed to achieve apposition of the stent interstices to the luminal surface of the artery. The patient was maintained on heparin for 12 hours and placed on an oral regimen of ticlopidine (75 mg PO QD) for 6 weeks and on daily aspirin (325 mg PO QD) indefinitely.

Risk Stratification
Patients were classified according to the Sundt grading system on the basis of angiographic, medical, and neurological risk factors and grouped according to risk of stroke with medical treatment as validated in the ECST on the basis of cerebral versus ocular symptoms, plaque surface irregularity, neurological event in past 2 months, and percentage of stenosis.

Clinical Outcome Measures
Members of the neurology department performed initial inpatient neurological examinations and clinical management, with initial postprocedural care in a neurological intensive care setting. Follow-up neurological examinations and ultrasonography were performed by the neurology team or at the patient’s referring institution and were supplemented by telephone interviews with a clinical nurse.

Quantitative Analysis and Statistics
Severity of stenosis was computed by the NASCET method with interconversion to ECST values as previously described. Statistical analysis was performed with software from SAS Institute. ANOVA was used to compare outcome scores versus presentation and treatment characteristics, and a Pearson’s χ² test was used to determine marginal homogeneity among nominal variables. A P value of 0.05 was considered statistically significant.

Results

Patient Demographics and Clinical Presentation
The demographic characteristics and comorbid medical conditions of the patient population are described in Table 1. The criteria for exclusion from NASCET eligibility appear in Table 2; some patients satisfied ≥1 criterion for exclusion, but a single disqualifying condition is shown. Half of the patients (14/28 patients, 50%) had suffered a previous clinically significant stroke in the territory of the treated vessel. Five patients (5/28 patients, 17.9%) had recurrent stenosis after CEA, and 4 patients (4/28, 14.3%) had radiation therapy–induced stenosis. The majority of patients fulfilled the criteria for medical (23/28 patients, 82.1%), radiographic (23/28, 82.1%), and neurological risk (17/28 patients, 60.7%)
Lesion Characteristics and Technique
Half of the lesions were left sided (14/28 patients, 50%). The mean pretreatment stenosis of 80.3±2.8% was immediately reduced to 2.7±1.2% by the procedure (P<0.001). The morphological characteristics of the plaque included presence of an ulcerated or irregular plaque in 15 patients (15/28 patients, 53.6%), tandem lesions in 9 patients (9/28 patients, 32.1%), and evidence of a string sign in 6 patients (6/28 patients, 21.4%). Fifteen patients (15/28 patients, 53.6%) had >50% stenosis in the contralateral internal carotid artery, and among these 9 (9/28 patients, 32.1%) had complete occlusion. Mean stenosis in the contralateral cervical internal carotid artery was 50.5±7.6%. Ten patients (10/28 patients, 35.7%) demonstrated extracranial posterior circulation atherosclerotic disease of >60%, and 9 (9/28 patients, 32.1%) had moderate to severe intracranial atherosclerotic disease as defined by Kappelle et al.14

To achieve an adequately smooth hemodynamic result, tandem stents were placed in 7 patients (7/28 patients, 25%) with overlap of 2 or 3 stents in 4 patients (4/28 patients, 14.3%). A total of 34 stents were used, including self-expanding Wallstent (n=24) and S.M.A.R.T. (n=2) stents and balloon-mounted Palmaz (n=6) and GFX (n=2) stents. Eight patients (8/28 patients, 28.6%) underwent combined simultaneous endovascular procedures either at the time of stent angioplasty or during the same hospital admission. These complex procedures included unsupported and stent-supported angioplasty of the intracranial portion of the internal carotid artery (n=4), of the vertebral artery (n=2), of the left proximal common carotid artery (n=1), and of the contralateral cervical internal carotid artery (n=1).

Complications
There were no perioperative deaths in this series. There was 1 major stroke event (1/28 patients, 3.6%) in a 78-year-old man (Sundt grade 4/ECST score 3) with previous stroke and progressively worsening neurological condition. The patient had poor angiographic hemodynamic reserve with an ulcerated left internal carotid artery lesion of 75% stenosis, contralateral carotid and right vertebral artery occlusion, and significant stenosis of the left vertebral artery. The procedure, performed under general endotracheal anesthesia because of poor cooperation, was characterized by a period of prolonged uncontrolled hypotension before endovascular intervention. The patient awoke with left-sided hemiparesis, and postprocedural imaging revealed infarction in the regions of the right basal ganglia and corona radiata, consistent with a hypoperfusion insult. There were no instances of minor stroke (0%) and 3 transient ischemic attack (TIA) episodes (3/28, 10.7%).

The TIA were encountered in patients belonging to each of Sundt grades 2, 3, and 4 and to each of the ECST score 3, 4, and 5 subgroups. No significant relationship between stroke/TIA event rate and Sundt grade or ECST score was found. Complex procedures (8/28 patients, 28.6%) were not associated with a higher risk of stroke (0 stroke) or TIA (1 TIA) compared with noncomplex procedures (20/28 patients, 71.4%). Primary stenting (7/28 patients, 25%) was associated with 1 TIA and 1 major stroke, while secondary stenting (after primary balloon angioplasty) (21/28 patients, 75%) was associated with 2 TIs and no stroke.

The immediate postoperative hospital course was complicated by a groin hematoma in 1 patient (1/28 patients, 3.6%) that required blood transfusion and ultrasound-guided external compression. Two patients had postprocedural non-Q-wave myocardial infarctions (2/28 patients, 7.1%), from which they recovered before discharge, and 1 patient suffered from acute renal failure (1/28, patients, 3.6%) with only partial recovery.

<table>
<thead>
<tr>
<th>TABLE 2. Conditions Leading to Exclusion of Patients From NASCET Eligibility*</th>
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<tr>
<td>NASCET Ineligibility Criteria</td>
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<tr>
<td>Age &gt;80 y</td>
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<tr>
<td>Intracranial atherosclerosis worse than cervical lesion</td>
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<tr>
<td>Unstable neurological examination</td>
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<tr>
<td>Surgically inaccessible cervical lesion</td>
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<tr>
<td>Previous CEA</td>
</tr>
<tr>
<td>Cancer with life expectancy &lt;5 y</td>
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<tr>
<td>Unstable congestive heart failure</td>
</tr>
<tr>
<td>Unstable angina</td>
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<tr>
<td>Failure to visualize both intracranial carotid arteries</td>
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<tr>
<td>Other intracranial vascular pathology</td>
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<tr>
<td>Values are number of patients (percentage).</td>
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</tbody>
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| *The age exclusion criterion applies to the first part of NASCET (before 1991) and was eliminated after the report of the initial results† to reflect the practice in North America.

as defined by Sundt et al.5 The stratification by surgical risk according to Sundt grade and by medical risk according to the ECST7 score is presented in Table 3.

<table>
<thead>
<tr>
<th>TABLE 3. Stratification of Patient Population With Respect to Surgical Risk of CEA According to Surgical Risk Classification of Sundt6 and With Respect to 5-Year Risk of Stroke Based on Medical Risk Score Defined by Rothwell in the ECST7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sundt Risk Grade</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>I</td>
</tr>
<tr>
<td>II</td>
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<tr>
<td>III</td>
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<tr>
<td>IV</td>
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</tbody>
</table>

Patient Stratification by Risk of Medical Treatment

<table>
<thead>
<tr>
<th>Rothwell/ECST Score</th>
<th>Count</th>
<th>Percent Total</th>
<th>Published 5-y Actuarial Risk of Stroke7</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>0%</td>
<td>6.0%</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>0%</td>
<td>13.1%</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>28.6%</td>
<td>20.0%</td>
</tr>
<tr>
<td>4</td>
<td>12</td>
<td>42.8%</td>
<td>45.2%</td>
</tr>
<tr>
<td>5</td>
<td>8</td>
<td>28.6%</td>
<td>38.1%</td>
</tr>
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</table>
Clinical Follow-Up
Clinical follow-up was obtained in all patients, with a median duration of 14 months (range, 0.8 to 26.7 months). During the follow-up period, there was 1 death in the patient who had the perioperative major stroke from complications related to his long-term rehabilitation at 7.8 months and 5 deaths that were unrelated to the treatment. The latter included 3 cardiac deaths (1 from fatal myocardial infarction at 4.4 months, 1 from cardiac arrest at 4.6 months, and 1 from intractable congestive heart failure at 13.3 months); 1 death from small-cell lung cancer (0.8 months); and 1 postoperative death after hip surgery (14 months). The patient who had cardiac arrest at 4.6 months was 1 of the 2 patients who had sustained a postprocedural myocardial infarction. Overall, 24 patients (85.7%) had clinical follow-up of duration >6 months; of the 4 who did not, 3 were the result of death as described above. Seventeen patients had clinical follow-up at >1 year.

Of the surviving 22 patients, 21 (21/22 patients, 95.5%) remained free of new symptoms or new strokes, while 1 patient (1/22 patients, 4.5%) who underwent simultaneous treatment of an intracranial internal carotid artery stenosis and a cervical carotid lesion developed delayed central retinal artery occlusion and ipsilateral ocular blindness at 2 months. Subsequent angiography revealed occlusion of the carotid artery at the siphon with proximal cervical carotid flow stasis at the level of the stented segment.

Anatomic follow-up was available at >6 months after the procedure and consisted of either ultrasonography or conventional angiography in 20 of the 28 patients (20/28 patients, 71%). Three asymptomatic patients (Sundt grade 3/ECST score 4 in 2; Sundt grade 4/ECST score 5 in 1) developed >60% intimal hyperplasia, 2 of which (65% and 80% restenosis) were treated successfully with further angioplasty and reconstitution of patency. Two patients, one symptomatic from occlusion of the ipsilateral central retinal artery (Sundt grade 4/ECST score 5) and another asymptomatic (Sundt grade 3 in 2; Sundt grade 4/ECST score 5 in 1) developed complete occlusion at follow-up. Neither underwent recanalization attempts because of the irreversible deficit in the first and the absence of related symptoms in the other. Pretreatment stenosis in the patients who subsequently had restenosis or occlusion (87.8%, n = 5) was not significantly different from those who did not (79.5%, n = 15) (P < 0.23).

Discussion
In the past 4 years there have been increased reports of stent angioplasty for carotid stenosis performed in patients with different risk profiles.8–12 These studies are difficult to compare with each other because they were performed in heterogeneous patient populations, they involved lesions with variable characteristics, different endovascular techniques were used, and outcome measures were dissimilar. Although the patient population in the study of Yadav et al19 represented a high proportion of patients with high-risk features, it also included a significant proportion (41%) of asymptomatic patients. In the series of Henry et al14 and Diethrich et al,15 the majority of the treated population (65% and 72%, respectively) was asymptomatic. Recent analysis of carotid stent angioplasty by Mathur et al16 has identified a higher risk in patients with advanced age, long or multiple stenoses, and severe lesions, but long-term clinical follow-up remains significantly shorter than that available for surgical endarterectomy.

The decision to treat carotid stenosis relies on a cost-benefit analysis that takes into account the cumulative risk of stroke in a patient undergoing medical treatment and the procedure-related risks of stroke and death from surgical or endovascular revascularization. Analysis of multiple published endarterectomy studies by Rothwell et al17 has identified a significantly higher combined risk of stroke and death in symptomatic (5.18%) than in asymptomatic (3.35%) patients, a finding confirmed by McCrory et al18 (9.5% in symptomatic versus 2.7% in asymptomatic patients). This difference may be the result of a higher rate of embolic events, as suggested by the greater frequency of high-intensity transient signals seen in symptomatic patients.19 Recent analysis of the NASCET surgical results has identified a greater perioperative risk in patients with hemispheric versus retinal symptoms (2.3-fold), contralateral carotid occlusion (2.2-fold), a left-sided procedure (2.3-fold), or an irregular/ulcerated lesion (1.5-fold).3 A similar effect of hemispheric symptoms and plaque ulceration has also been reported in ECST.7 In addition, available data to guide treatment in high-risk patients who fail to qualify by NASCET criteria are scarce. The predictive value of Sundt’s grading system, initially based on retrospective analysis at a single center,20 has been independently validated both retrospectively18,20 and prospectively in a study from the Academic Medical Center Consortium.18 Sieber et al20 found that total morbidity and mortality from CEA increased from 2% for Sundt grade 1 to 10% for grade 2, 11% for grade 3, and 18% for grade 4. McCrory et al18 reported total stroke or death rates of 2.5% for grade 1, 3.1% for grade 2, 5.1% for grade 3, and 7.9% for grade 4. Although it is impossible to predict the risk of surgical therapy for the patients in the present study, its computation based on the Sundt instrument yields a rate of procedure-related death and stroke rate ranging from 7.4% to 15.1%,20 which is higher than observed in this report (3.6%). Applying the ECST medical risk score and associated actuarial stroke rate (Table 3) to the patient population in the present study yields a predicted 5-year risk of ipsilateral stroke of 36.3%; however, direct comparison will not be possible until longer follow-up is available.

Even though the present series consists exclusively of symptomatic NASCET-ineligible patients with a high proportion of Sundt grade 3 and 4, the 30-day periprocedural combined risk of stroke and death (3.6%) is comparable to the surgical results of NASCET3 and other series.5–20 The risk of all in-hospital medical complications (including TIA) in this series was 25% (7/28 patients; 2 nonfatal myocardial infarction, 1 acute renal failure, 1 groin hematoma, 3 TIAs), which is higher than that encountered in NASCET (1% for myocardial infarction, 8.1% total medical complications excluding TIAs).21 The rate of wound-related complications (1 groin hematoma, 2.6%) is lower than in NASCET (9.3%), and no instances of perioperative cranial nerve injury were encoun-
tered (8.9% in NASCET).\(^3\) Although the majority (95.4%) of patients remained asymptomatic in the follow-up period, the risk of >60% restenosis or occlusion in the present study (5/20 patients, 25%) is higher than reported for the 3 to 18 months of follow-up of the 645 patients in the surgical arm of the Asymptomatic Carotid Atherosclerosis Study (ACAS) (7.6% to 11.4%)\(^2\) and greater than the 6- to 12-month rate reported in other series (8%).\(^2\) \(^3\) Since the original goal of the procedure was stroke prevention, the current management was effective in 4 of the 5 patients with >60% restenosis or occlusion for the limited length of follow-up. However, even if one were to consider only restenosis of >80% as clinically warranting retreatment, the rate in the present study remains significant at 15% (3/20 patients).

In conclusion, carotid stent angioplasty can be performed in NASCET-ineligible high-risk symptomatic patients with a periprocedural risk of stroke and death that is comparable to those of NASCET and other published endarterectomy series. A significant relief from neurological symptoms and stroke was encountered during the intermediate follow-up period along with significant restenosis in this cohort of patients with advanced medical and surgical risk factors.

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References


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