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The North American Symptomatic Carotid Endarterectomy Trial Surgical Results in 1415 Patients

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Background and Purpose—This study reports the surgical results in those patients who underwent carotid endarterectomy in the North American Symptomatic Carotid Endarterectomy Trial (NASCET).

Methods—The rates of perioperative stroke and death at 30 days and the final assessment of stroke severity at 90 days were calculated. Regression modeling was used to identify variables that increased or decreased perioperative risk. Nonoutcome surgical complications were summarized. The durability of carotid endarterectomy was examined.

Results—In 1415 patients there were 92 perioperative outcome events, for an overall rate of 6.5%. At 30 days the results were as follows: death, 1.1%; disabling stroke, 1.8%; and nondisabling stroke, 3.7%. At 90 days, because of improvement in the neurological status of patients judged to have been disabled at 30 days, the results were as follows: death, 1.1%; disabling stroke, 0.9%; and nondisabling stroke, 4.5%. Thirty events occurred intraoperatively; 62 were delayed. Most strokes resulted from thromboembolism. Five baseline variables were predictive of increased surgical risk: hemispheric versus retinal transient ischemic attack as the qualifying event, left-sided procedure, contralateral carotid occlusion, ipsilateral ischemic lesion on CT scan, and irregular or ulcerated ipsilateral plaque. History of coronary artery disease with prior cardiac procedure was associated with reduced risk. The risk of perioperative wound complications was 9.3%, and that of cranial nerve injuries was 8.6%; most were of mild severity. At 8 years, the risk of disabling ipsilateral stroke was 5.7%, and that of any ipsilateral stroke was 17.1%.

Conclusions—The overall rate of perioperative stroke and death was 6.5%, but the rate of permanently disabling stroke and death was only 2.0%. Other surgical complications were rarely clinically important. Carotid endarterectomy is a durable procedure. (*Stroke*. 1999;30:1751-1758.)

Key Words: carotid endarterectomy ■ complications ■ risk factors

The initial results from the North American Symptomatic Carotid Endarterectomy Trial (NASCET) reported in August 1991 demonstrated a highly beneficial effect of carotid endarterectomy (CE) in patients with angiographically confirmed high-grade carotid stenosis (70% to 99%).¹ The final results for patients with stenosis <70% revealed modest benefit from CE in selected patients with high-moderate degrees of stenosis (50% to 69%).²

This is a report of the surgical results in the 1415 patients who underwent CE in the surgical arm of NASCET. The rates

of perioperative stroke and death in the severe (70% to 99%) and moderate (<70%) stenosis groups, and for the study overall, are compared with the results achieved in the other large randomized trial of CE in symptomatic patients.³⁻⁵ A summary of the causes of the perioperative outcome events is presented. Included in this report is an evaluation of the risk factors for perioperative stroke and death and a summary of the nonoutcome perioperative surgical complications. The durability of CE is examined over the 10-year period of the study.

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Subjects and Methods

A complete description of the methods of the study has been published.^{2,6} To be eligible, patients were required to have had a hemispheric transient ischemic attack (TIA), transient monocular blindness, or a nondisabling stroke associated with a stenosis of 30% to 99% in the ipsilateral carotid artery based on linear diameter reduction.⁷ Patients were excluded if they were unable or unwilling to give informed consent, had no angiographic studies, had an intracranial lesion that was more significant than the proximal carotid lesion, were unlikely to survive 5 years because of intercurrent disease, had disabling stroke (Modified Rankin score ≥ 3), or had symptoms likely attributable to other disease or a prior ipsilateral CE. Eligible patients were randomized to either the medical or surgical arm from a computer-generated algorithm. During follow-up, all patients received best medical care. The only difference between the medical and surgical arms was that patients in the surgical arm underwent CE.

To participate in NASCET, centers were required to demonstrate that their participating surgeons had a perioperative rate of stroke and death of $<6\%$ in a minimum of 50 consecutive cases accumulated over 2 years. In centers with >1 surgeon, the number of patients could represent the aggregate experience of participating surgeons in the center, with a minimum of 30 personal cases for any single surgeon.

Accredited NASCET surgeons were not constrained to follow any standardized surgical technique, other than their normal practice. The details of anesthetic techniques, the use of intraoperative monitoring, intraoperative shunts, heparin, heparin reversal, patch grafts, occlusion times, suture techniques, and gross appearance of the plaques were reported in the Surgical Report Forms completed at 30 days after surgery or at discharge, whichever occurred first. The Surgical Report Form was reviewed in every case by the Surgical Co-Principal Investigator, as well as by the Medical Data Management Staff, for completeness and accuracy.

The clinical details of all perioperative outcome events (stroke or death) were carefully scrutinized. This information was then correlated with the results of perioperative CT scanning, ultrasonography, and angiography, when available. The cause of every perioperative event was sought. All perioperative strokes and deaths were also adjudicated in a blinded fashion. External adjudication was conducted by a panel of neurologists and surgeons not otherwise involved in the trial.

Strokes, as outcome events, were classified as disabling or nondisabling at 30 days postoperatively (perioperative stroke rate) and at 3 months, the time of the final assessment of stroke severity in each case,^{1,2} with the use of Modified Rankin disability scores.⁸ Disabling stroke was defined as a new and persisting neurological deficit of functional significance (Modified Rankin score ≥ 3). Nondisabling stroke was defined as any neurological symptom or sign lasting >24 hours but producing no disability of functional significance (Modified Rankin score <3).

Cox proportional hazards regression modeling was used to identify baseline, intraoperative, and postoperative risk factors that increased (or decreased) the 30-day perioperative risk of stroke and death. Adjusted hazard ratios (interpreted as relative risks) with corresponding 95% CIs were used to summarize the results. Adjusted hazard rates (ie, risks) were computed from the regression model by using the mean value for a factor being adjusted.⁹ Missing covariate data were replaced with mode values for categorical variables and median values for continuous variables. A risk factor was considered statistically significant if the 95% CI did not encompass the value 1.

All perioperative surgical and medical complications other than stroke and death were recorded in the 1415 patients undergoing CE in the surgical arm of NASCET. Mild complications were defined as those with no delay in discharge, no return to the operating room, or documented recovery of any cranial nerve dysfunction; moderate complications were defined as those associated with a delay in discharge, a return to the operating room or readmission, or documentation that cranial nerve dysfunction did not recover; and severe

complications were associated with permanent functional disability, including death.

Results

Altogether, 1453 patients were randomized to the surgical arm of the study. Seventeen patients were excluded: 9 patients randomized after February 21, 1991, had severe stenosis on central review, 5 patients did not have the disease under study, 2 patients failed to give informed consent, and 1 patient did not have angiography. Twenty-one patients were crossed over from the surgical arm to the medical arm after randomization: 11 patients refused to proceed with CE, 7 patients developed medical problems precluding CE, and in 3 instances the surgeon was unwilling to proceed with CE. Thus, 1415 patients proceeded to the operating room (moderate stenosis in 1087 and severe stenosis in 328). These numbers are the denominators for calculating the rates of outcome and nonoutcome complications. In 4 of the 1415 patients the procedure was not completed: in 2 patients the surgeon was unable to obtain adequate exposure of the plaque, and in 2 patients severe hypotension occurred during anesthetic induction and the procedure was abandoned. The mean age of the 1415 patients was 65.4 years. There were 997 men (70.5%) and 418 women (29.5%).

Study Surgeons

A total of 278 surgeons operated on the 1415 patients undergoing CE in the study (107 neurosurgeons, 165 vascular surgeons, and 6 nonparticipating surgeons). Neurosurgeons operated on 732 patients (51.7%), vascular surgeons on 677 patients (47.9%), and nonparticipating surgeons on 6 patients (0.4%). Canadian surgeons operated on 46%, American surgeons on 43%, and European and Australian surgeons on 11% of the patients in the trial.

Surgical Techniques

A summary of the surgical techniques used in the 1415 patients undergoing CE is presented in Table 1. Most procedures (93%) were performed with general anesthetic techniques, although a few surgeons routinely used local anesthesia. The median anesthetic time was 3 hours, implying a median surgical time of 2 to 2.5 hours. One or more techniques for intraoperative monitoring were used in 51% of the patients. Electroencephalographic monitoring was most commonly employed, although measurements of carotid stump pressure, evoked potential monitoring, and transcranial Doppler techniques were used by some surgeons. Cerebral blood flow monitoring was not used.

A change of unspecified severity was noted with carotid clamping in 89 of 438 patients (20%) monitored with electroencephalography, 35 of whom were shunted. A change was noted in 14 of 99 (14%) patients monitored with evoked potentials, 3 of whom were shunted. Eleven of 204 patients in whom carotid stump pressure was measured were shunted, and 8 of 41 patients with transcranial Doppler monitoring were shunted. The decision to use an intraluminal shunt often appeared to be unrelated to the results of monitoring.

Intraluminal shunts were used in 41% of cases, overall. In those patients in whom a shunt was not used, the median

TABLE 1. Summary of Surgical Techniques

Characteristics	Moderate Stenosis (n=1087)	Severe Stenosis (n=328)	All Patients (n=1415)
Anesthetic technique			
General	92%	96%	93%
Local	8%	4%	7%
Median anesthetic times, h	2.9	3.0	3.0
Intraoperative monitoring			
Electroencephalography	29%	39%	31%
Carotid stump pressure	16%	9%	14%
Evoked potentials	8%	5%	7%
Transcranial Doppler	3%	2%	3%
Intraluminal shunting	43%	34%	41%
Clamp time in unshunted patients, min			
Lowest	6	9	6
Median	31	31	31
Highest	95	83	95
Heparin/protamine use			
Median heparin dose, U	5000	5000	5000
Reversal	41%	44%	41%
Median protamine dose, mg	40	40	40
Arteriotomy closure			
Simple	79%	83%	79%
Fabric patch	10%	9%	10%
Vein patch	10%	7%	10%
Other	1%	1%	1%

unshunted clamp time was 31 minutes (range, 6 to 95 minutes). Heparinization was used during clamping in 98% of patients and was reversed with protamine in 41%. Simple arteriotomy closure was used in 79% of the patients. Mono-filament suture was used almost exclusively (most commonly, 6-0 [69%] or 5-0 [25%]). The reported gross appearance of the plaques was virtually identical for moderate and severe degrees of stenosis.

Perioperative Outcomes: Stroke and Death

The rates of perioperative stroke and death at 30 days and the final assessment of stroke severity at 90 days are given in Table 2. In total, there were 92 perioperative outcome events, for an overall rate of 6.5%. At 30 days, 15 patients had died (1.1%), equally divided between nonstroke deaths and stroke deaths, and 25 patients had suffered a disabling stroke (1.8%), giving a perioperative rate of disabling stroke and death of 2.9%. There was no statistically significant difference in the rate of disabling stroke and death at 30 days between the moderate stenosis (2.8%) and severe stenosis (3.0%) groups. Between 30 and 90 days, 1 patient with a disabling stroke died, while 8 patients with moderate stenosis and 3 patients with severe stenosis had an improvement in stroke severity from disabling to nondisabling. Thus, at 90 days, 1.1% of the surgical patients with a perioperative outcome had died, while 0.9% had a persisting, disabling stroke, giving an overall rate of persisting, disabling stroke and death in the surgical group of 2.0%. The rate of nondisabling stroke at 90 days was 4.5%.

There were 7 nonstroke deaths (0.5%) in the surgical group at 90 days. Two patients died of myocardial infarction, both within 24 hours of surgery, 2 patients died suddenly on days 3 and 6 postoperatively, presumably of cardiac cause, 2 patients died 12 and 16 hours postoperatively of airway obstruction secondary to wound hematomas, and 1 patient died as a consequence of blood loss due to dehiscence of the arteriotomy on day 3 postoperatively.

There were 9 stroke-related deaths (0.6%) in the surgical group at 90 days. Eight of these 9 patients died of massive ipsilateral cerebral infarction. Three awoke with severe neurological deficit in the territory of the CE, 2 of whom had occlusion at the endarterectomy site, while the other had CT scan evidence of multiple areas of ipsilateral hemispheric infarction. In 5 patients, the fatal stroke was delayed in onset (1, 2, and 15 hours and 3 days in 2 cases). All of these strokes were the result of proven occlusion, presumably delayed in onset, of the endarterectomy site. Four of these 5 patients returned to the operating room for reopening of the endarterectomy site, without benefit. The other patient died of a

TABLE 2. Incidence of Perioperative Outcome Events at 30 Days and Assessment of Stroke Severity at 90 Days

Perioperative Event	30 Days			90 Days		
	Moderate Stenosis (n=1087)	Severe Stenosis (n=328)	All Patients (n=1415)	Moderate Stenosis (n=1087)	Severe Stenosis (n=328)	All Patients (n=1415)
Nonstroke death	6 (0.6%)	1 (0.3%)	7 (0.5%)	6 (0.6%)	1 (0.3%)	7 (0.5%)
Stroke death	7 (0.6%)	1 (0.3%)	8 (0.6%)	8 (0.7%)*	1 (0.3%)	9 (0.6%)
All death	13 (1.2%)	2 (0.6%)	15 (1.1%)	14 (1.3%)	2 (0.6%)	16 (1.1%)
Disabling stroke	17 (1.6%)	8 (2.4%)	25 (1.8%)	8 (0.7%)†	5 (1.5%)†	13 (0.9%)
Disabling stroke and death	30 (2.8%)	10 (3.0%)	40 (2.9%)	22 (2.0%)	7 (2.1%)	29 (2.0%)
Nondisabling stroke	43 (4.0%)	9 (2.7%)	52 (3.7%)	51 (4.7%)†	12 (3.7%)†	63 (4.5%)
All stroke and death	73 (6.7%)	19 (5.8%)	92 (6.5%)	73 (6.7%)	19 (5.8%)	92 (6.5%)

*One patient with a disabling stroke died 33 days postoperatively.

†Between 30 and 90 days, 8 patients with moderate stenosis and 3 patients with severe stenosis had an improvement in stroke severity from "disabling" to "nondisabling."

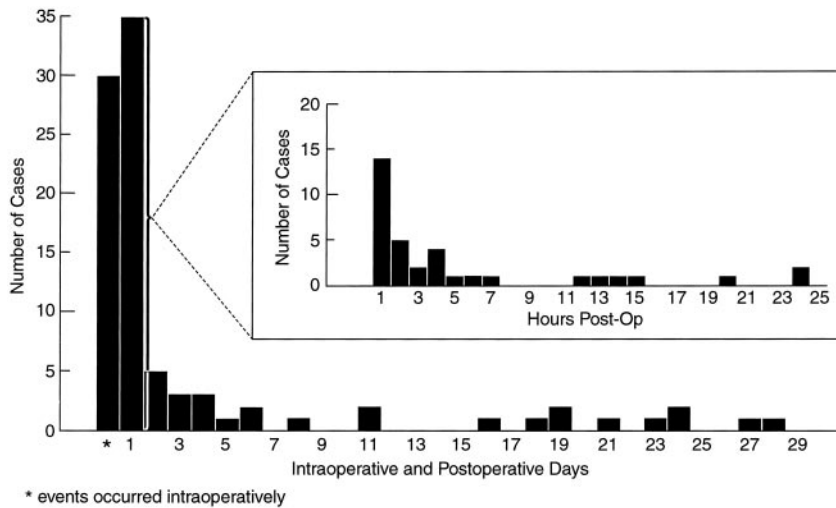


Figure 1. Time of onset of 92 perioperative outcome events.

subarachnoid hemorrhage on the sixth postoperative day. Autopsy failed to reveal the cause.

Thirteen patients (0.9%) suffered a persisting, disabling stroke at 90 days. Seven of the patients awoke with a major deficit in the territory of the CE. Two of these patients were returned to the operating room, and in neither of them was an abnormality found at the endarterectomy site. In 4 patients, a

disabling stroke in the territory of the CE was delayed in onset (2, 3, 4, and 6 hours). All 4 patients returned to the operating room, where acute occlusion was found and removed without clinical benefit. One patient, with a 70% stenosis, had an ipsilateral intracerebral hemorrhage on the sixth postoperative day, while 1 patient experienced a vertebrobasilar stroke 24 days postoperatively.

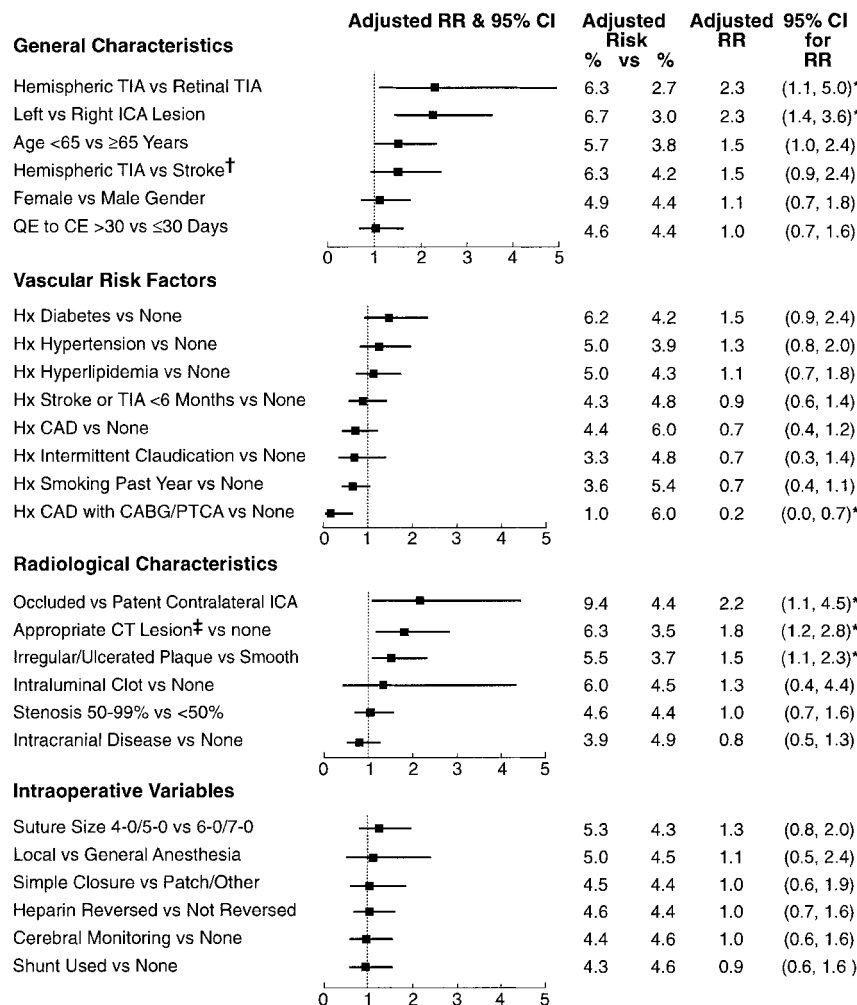


Figure 2. Multivariate analysis of 26 baseline and intraoperative variables for the 30-day perioperative risk of stroke and death. Within each category, the results have been ordered by decreasing adjusted relative risks (RR). *Statistically significant at $P < 0.05$. †Hemispheric TIA vs hemispheric stroke as the qualifying event (QE). ‡Ipsilateral ischemic lesion on entry CT scan. ICA indicates internal carotid artery; Hx, history; and PTCA, percutaneous transluminal coronary angioplasty.

TABLE 3. Summary of Perioperative Wound Complications

Complication	Severity			Total
	Mild	Moderate	Severe	
Wound hematoma	55 (3.9%)	42 (3.0%)	4 (0.3%)	101 (7.1%)
Wound infection	19 (1.3%)	10 (0.7%)	...	29 (2.0%)
Other wound complications*	2 (0.1%)	2 (0.1%)
Total	76	52	4	132
Risk (n=1415)	5.4%	3.7%	0.3%	9.3%

Severity was categorized as follows: mild complication, no delay in discharge, no return to operating room; moderate complication, delay in discharge, return to the operating room, or readmission; severe complication, permanent functional disability, including death.

*One superficial wound dehiscence, 1 parotid fistula that resolved spontaneously.

As judged at 90 days, 63 (4.5%) of the surgical patients experienced a nondisabling perioperative stroke. Nine (0.6%) of the patients with nondisabling stroke had symptoms or signs that lasted <7 days. Among the 63 patients, 20 awoke with a new deficit (19 ipsilateral and 1 contralateral to the territory of the CE). One patient returned to the operating room, and no abnormality was found. Forty-three patients had a delayed onset of nondisabling stroke. Thirty-five of these patients had an ipsilateral ischemic event (30 hemispheric, 5 retinal). The time of onset varied from 10 minutes to 28 days postoperatively. Five of the 35 patients returned to the operating room. Acute occlusion was found in 2 patients and nonoccluding thrombus in 3 patients. Subsequent patency was confirmed by carotid ultrasound in 4 of the 5 patients. Two patients with severe stenosis (85%, 95%) had an ipsilateral intracerebral hemorrhage (24 hours, 8 days). Four patients had contralateral strokes (1 and 24 hours, 4 and 8 days), and 2 patients had vertebrobasilar strokes (5, 23 days).

Of the 85 perioperative strokes and stroke-related deaths, 76 (89%) occurred in the territory of the CE, 5 (6%) were in the contralateral carotid territory, 3 (4%) were in the vertebrobasilar territory, and 1 (1%) was the result of subarachnoid hemorrhage. Altogether, 35% (30/85) of the perioperative strokes occurred intraoperatively, while 65% (55/85) occurred after the patient left the operating room (delayed events). Figure 1 illustrates the time of onset of the 92 surgical outcome events. Of the 62 delayed events, 35 (56%) occurred within the first 24 hours after surgery; the majority occurred within the first 6 hours.

Risk Factors for Perioperative Stroke and Death

Twenty-six potential baseline and intraoperative variables for the 30-day perioperative risk of stroke and death were analyzed (Figure 2). Six of these related to general baseline characteristics, 8 related to a history of cerebrovascular risk factors, and 6 related to radiological baseline characteristics. Six intraoperative variables were analyzed. The results for the multivariate analysis of these 26 variables have been ordered by decreasing adjusted relative risks within each category.

Five baseline variables were associated with a statistically significant increased risk of perioperative stroke and death: a hemispheric TIA compared with a retinal TIA as the qualifying event ($\times 2.3$), a left-sided procedure ($\times 2.3$), the pres-

TABLE 4. Summary of Perioperative Cranial Nerve Injuries

Injury	Severity			Total
	Mild	Moderate	Severe	
Facial nerve	28 (2.0%)	3 (0.2%)	...	31 (2.2%)
Vagus nerve	31 (2.2%)	5 (0.4%)	...	36 (2.5%)
Spinal accessory nerve	3 (0.2%)	3 (0.2%)
Hypoglossal nerve	50 (3.5%)	2 (0.2%)	...	52 (3.7%)
Total	112	10	...	122
Risk (n=1415)	7.9%	0.7%	...	8.6%

Severity was categorized as follows: mild complication, no delay in discharge, recovery documented in follow-up; moderate complication, delay in discharge, readmission, or documented that deficit never recovered; severe complication, permanent functional disability, including death.

ence of contralateral carotid occlusion ($\times 2.2$), an ipsilateral ischemic lesion on the entry CT scan ($\times 1.8$), and irregular or ulcerated plaque detected by angiography on the side of surgery ($\times 1.5$). Other baseline variables were associated with an increased risk of perioperative stroke and death, but they failed to reach statistical significance. These included patients aged <65 years compared with those aged ≥ 65 years of age, a hemispheric TIA compared with a hemispheric stroke as the qualifying event, a history of diabetes mellitus or hypertension, and the presence of an intraluminal clot in the ipsilateral carotid artery on the preoperative angiogram.

For a number of baseline variables, there was no association with either increased or decreased perioperative risk. These included the sex of the patient, a history of hyperlipidemia, whether or not the surgery was within 30 days of the qualifying event, whether or not a stroke or TIA other than the qualifying event had occurred within the 6 months before the CE, or whether the stenosis was $>50\%$.

One baseline variable was associated unexpectedly with a statistically significant reduced risk of perioperative stroke and death: patients with a history of coronary artery disease (CAD) who had a prior cardiac procedure ($\times 0.2$). Other baseline variables were associated with a decreased risk of perioperative stroke and death that failed to reach statistical significance. These included a history of CAD, intermittent claudication, or smoking within the past year or the presence of intracranial atherosclerosis on the preoperative angiogram.

None of the intraoperative variables examined were associated with a statistically significant increase or decrease in perioperative risk. In 269 cases, neither monitoring nor an intraluminal shunt was used during the procedure. There was no difference in the risk of perioperative stroke and death in these patients (6.7%) compared with those in whom monitoring, a shunt, or both were used (6.5%). An analysis of the 30-day perioperative risk of all stroke and death by the geographic location of the operating surgeon or by the type of surgeon (neurosurgeon versus vascular surgeon) revealed no statistically significant differences. There was no evidence of clustering of outcome events either by center or by surgeon.

Other Perioperative Surgical Complications

A total of 440 other perioperative medical and surgical complications occurred in 328 patients (1 complication in 245

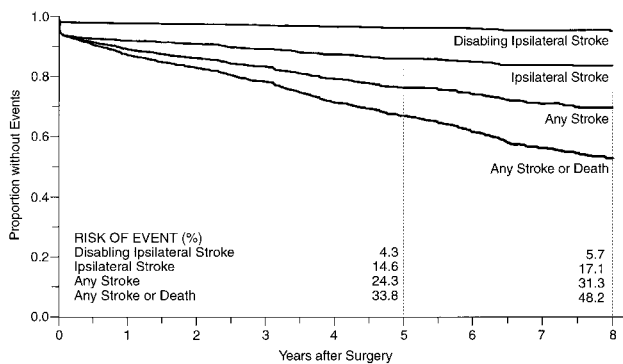


Figure 3. Kaplan-Meier curves for event-free survival after CE in 1409 patients with severe and moderate stenosis. The curves show the probability of avoiding an event, according to 4 different definitions of outcome. Point estimates are shown for the risk of each event at 5 and 8 years after the surgery and include all perioperative outcome events. The number of patients at risk at 5 years for the 4 definitions of outcome (disabling ipsilateral stroke, ipsilateral stroke, any stroke, any stroke or death) is 723, 653, 587, and 587 and for 8 years is 251, 226, 193, and 193, respectively.

patients, 2 complications in 63 patients, and ≥ 3 complications in 20 patients). Of these, 319 of 440 (72%) were noted as mild, 117 of 440 (27%) as moderate, and 4 of 440 (1%) as severe. The perioperative medical complications are detailed in a separate publication.¹⁰

As noted in Table 3, 132 wound complications occurred in 128 patients: wound hematomas (101 patients [7.1%]); wound infections (29 patients [2.0%]); and other wound complications (2 patients [0.1%]). The overall risk of wound complications in the 1415 patients was 9.3%, of which 58% were mild in severity, 39% moderate, and 3% severe. The occurrence of a postoperative wound hematoma is a statistically significant risk factor for perioperative stroke and death on the basis of a univariate analysis of the NASCET results (14.9% perioperative rate of stroke and death with wound hematoma versus 5.9% without a wound hematoma; relative risk=2.5; $P<0.001$).

As noted in Table 4, 122 cranial nerve injuries occurred in 102 patients: facial (31 patients [2.2%]); vagus (36 patients [2.5%]); spinal accessory (3 patients [0.2%]); and hypoglossal (52 patients [3.7%]). The overall risk of cranial nerve injury in the 1415 patients was 8.6%, of which 92% were mild in severity, 8% moderate, and none severe.

Anesthetic procedures resulted in 13 complications in 11 patients (edema requiring reintubation in 6; pneumothorax in 2; brachial plexus injury in 2; upper limb ischemia in 1; corneal abrasion in 1; and persistent vomiting in 1). Five of these 13 complications were mild in severity, 8 moderate, and none severe.

Long-Term Results of CE

The long-term results of CE in NASCET in patients with $\geq 70\%$ stenosis have been reported.² Those patients in whom the CE was completed ($n=326$) had a risk of disabling ipsilateral stroke, any ipsilateral stroke, any stroke, or all stroke and death at 8 years of 6.7%, 15.2%, 29.4%, and 46.6%, respectively. The corresponding 8-year risks for patients with $<70\%$ stenosis ($n=1083$) were 5.1%, 17.9%,

31.8%, and 48.7%. Figure 3 demonstrates the long-term results of CE for 1409 surgical patients in NASCET. Six of the 1415 surgical patients have been removed from this analysis (4 in whom CE was not completed, 1 who had a stroke before surgery, and 1 in whom surgery was >1 year after randomization).

With respect to sex, there was no difference in the long-term durability of CE. In men, the risk of disabling, ipsilateral stroke or any ipsilateral stroke at 8 years was 5.9% and 16.7%, respectively, while in women the corresponding risks were 5.2% and 18.1%.

Discussion

NASCET has reaffirmed that a multicenter trial of a surgical procedure can be conducted successfully despite the involvement of a large number of surgeons in institutions on 5 continents and extending over an 11-year period. No surgeon was accepted into this study whose experience disclosed a perioperative complication rate of stroke and death $>6\%$. At the conclusion of NASCET, the overall rate of perioperative stroke and death was 6.5%. The 30-day rate of disabling stroke and death was 2.9%. By 90 days of follow-up, this rate was only 2.0% (1.1% death; 0.9% disabling stroke). The European Carotid Surgery Trial (ECST), similar in size to NASCET, has reported results with comparable rates of perioperative rates of stroke and death.⁵ In 1745 patients, the death rate at 30 days was 1.0%, the disabling stroke rate 2.5%, and the nondisabling stroke rate 3.5%, for an overall rate of 7.0%. Comparison of the surgical results from these trials to large case series and community surveys is inappropriate, since such reports include nonrandomized patient selection and lack independent verification and evaluation of perioperative outcome events.¹¹ In severe, symptomatic carotid stenosis ($\geq 70\%$), the benefit from CE is very significant and increases dramatically as the stenosis increases up to 95%.^{2,3,12} In patients with high-moderate stenosis (50% to 69%), the benefit from CE is modest.^{2,4} Benefit will only be achieved in the latter group if there is a maximum disabling stroke and death rate of 2% coupled with selection of patients at highest risk.

The majority of perioperative strokes observed in NASCET were ipsilateral to the procedure, and two thirds occurred after the completion of the CE, most within the first 24 hours and particularly within 6 hours (Figure 1). Ipsilateral intracerebral hemorrhage, presumably related to hyperperfusion, was infrequent in NASCET (0.2%), and none were fatal. All occurred in patients with severely stenotic lesions. Intracerebral hemorrhage occurred in 0.6% in an earlier report of 2362 consecutive CEs.¹³ A recent retrospective study of 1471 patients, 82% of whom were hypertensive, attributed 35% of postoperative neurological events to intracerebral hemorrhage.¹⁴ Patients with uncontrolled hypertension were excluded from NASCET. There were 9 perioperative outcome events in NASCET that were unrelated to the CE site: 5 contralateral carotid ischemic events, 3 vertebrobasilar territory events, and 1 subarachnoid hemorrhage.

Perioperative deaths were nearly evenly divided between stroke-related and nonstroke deaths. Nonstroke deaths were

caused either by cardiac causes or hemorrhagic wound complications.

Most perioperative strokes seen in NASCET were attributable to events at the CE site that led to thrombus formation on the area of the denuded artery, resulting in acute occlusion or distal embolization. The majority of these events occurred after the procedure. Recognition of the importance of thromboembolic events in causing stroke in CE has implications regarding the use of intraoperative monitoring and shunts, importance of attention to the technical details of the conduct of the surgery, and management of perioperative stroke. To better understand the etiology and prevention of perioperative stroke in CE, it will be important in future surgical reports to note carefully the timing of events (intraoperative versus postoperative) and the subsequent investigations, treatments, and outcomes.

The concept that certain medical and angiographic characteristics are of potential importance in determining the perioperative risks in CE has long been recognized.¹⁵ Of 26 baseline and intraoperative variables for perioperative stroke and death examined in NASCET with the use of regression modeling, only 5 were found to be associated with a statistically significant increased risk (a hemispheric versus a retinal TIA as the qualifying event, a left-sided procedure, the presence of a contralateral carotid occlusion, an ipsilateral ischemic lesion on CT scan, and an irregular or ulcerated plaque seen on the angiogram). One baseline risk factor was associated with a statistically reduced risk (a history of CAD with a prior cardiac procedure).

In NASCET, the perioperative risk of stroke and death was not influenced in a statistically significant fashion by the age or sex of the patient, by whether or not a hemispheric qualifying event was a TIA or a minor stroke, or by the timing of the surgery relative to the time of the qualifying event. The widely recognized cerebrovascular risk factors of diabetes mellitus, hypertension, hyperlipidemia, CAD, intermittent claudication, and a recent history of smoking did not significantly affect perioperative risk. A history of recurrent cerebral ischemic events within 6 months of the qualifying event, the degree of carotid stenosis, and the presence of intracranial atherosclerosis did not influence perioperative risk. Although the presence of an intraluminal clot on the preoperative angiogram has been associated with increased perioperative risk in the literature,¹⁶ the relative risk of 1.3 (95% CI, 0.4 to 4.4) observed in the NASCET surgical group did not reach statistical significance since the number of patients with intraluminal clot was small ($n=25$).

NASCET was not designed to answer questions regarding the usefulness of intraoperative monitoring or intraoperative shunting in reducing the risk of intraoperative ischemia. Neither, used at the discretion of the surgeon, had an apparent influence on perioperative risk. Similarly, the choice of suture size, the form of anesthesia, the nature of the closure of the arteriotomy, and whether or not intraoperative heparin was reversed had no impact on the perioperative results.

Only 1 risk profile evaluation comparable to that presented here has been done. A multivariate analysis of risk factors for perioperative stroke and death has been reported from the ECST database.¹⁷ Four statistically significant risk factors

were found (ocular versus cerebral presenting symptoms, $\times 0.46$; female sex, $\times 1.41$; systolic hypertension ≥ 180 mm Hg, $\times 1.93$; peripheral vascular disease, $\times 1.44$). It would appear certain that patients presenting with ocular ischemic symptoms have a reduced risk of adverse perioperative events since this was observed in a statistically significant fashion in both NASCET and ECST.

Variations in the risk factor profiles generated from the databases of NASCET and ECST will be resolved only when the data from these trials, plus data from several large community observational studies, are combined. It is hoped that conflicting reports^{18,19} regarding the importance of age, sex, cerebrovascular risk factors, and contralateral carotid occlusion will be clarified by this pooling of data.

The increased risk carried by a left-sided procedure was unexpected. Most surgeons are right handed, and a left-sided CE appears to present unrecognized difficulties for right-handed surgeons. In a retrospective review and multivariate analysis of the determinants of outcome of 1280 CEs performed over a 3-year period,¹⁹ a left-sided procedure carried an increased risk for perioperative stroke and death (odds ratio, 1.72; 95% CI, 1.07 to 2.76). In the recently completed multicenter Aspirin and Carotid Endarterectomy (ACE) trial, the perioperative stroke and death rate among 2804 CEs for left-sided lesions was 6.6% versus 4.2% for right-sided lesions ($P=0.005$).²⁰

The explanation for the protective effect of a prior cardiac procedure is speculative. Such patients are known to have improved cardiac function, and this may reduce their vulnerability to perioperative myocardial infarction. Post-coronary artery bypass graft (CABG) patients have demonstrated an ability to survive a major surgical procedure, usually receive vigilant medical surveillance, and have often made significant changes to their lifestyle and risk profiles. In the ACE trial, patients with a history of CAD, but who had not had a CABG, had a perioperative risk of stroke and death of 5.9% compared with 3.4% for patients with a history of CAD with prior CABG ($P=0.16$) (ACE unpublished data, courtesy of W. Taylor, MA, 1999).

The incidence of nonoutcome surgical complications was documented prospectively and with particular care in NASCET. Consistent with earlier reports, the vast majority of patients with cranial nerve injuries recovered completely.²¹ The majority of wound complications were minor, but 3.3% of patients required reexploration for a postoperative wound hematoma. Four patients with wound hematomas died as a direct consequence. Such deaths should be avoidable. There is a need for extreme vigilance and early evacuation of the hematoma before overt signs of airway obstruction occur and before reintubation becomes difficult, if not impossible.

In conclusion, the results from NASCET demonstrate that in experienced surgical hands CE is safe and effective in the near term and remarkably effective in the longer term in preventing recurrence of ipsilateral carotid ischemia and, in particular, in preventing disabling ipsilateral stroke. The challenge for those investigating the usefulness of carotid angioplasty and stenting as an alternative to CE will be to demonstrate that not only is it as safe and effective as CE in

the near term but that it is as effective in preventing disabling stroke in the long term.

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