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# BENEFICIAL EFFECT OF CAROTID ENDARTERECTOMY IN SYMPTOMATIC PATIENTS WITH HIGH-GRADE CAROTID STENOSIS

NORTH AMERICAN SYMPTOMATIC CAROTID ENDARTERECTOMY TRIAL COLLABORATORS*

**Abstract** *Background.* Without strong evidence of benefit, the use of carotid endarterectomy for prophylaxis against stroke rose dramatically until the mid-1980s, then declined. Our investigation sought to determine whether carotid endarterectomy reduces the risk of stroke among patients with a recent adverse cerebrovascular event and ipsilateral carotid stenosis.

*Methods.* We conducted a randomized trial at 50 clinical centers throughout the United States and Canada, in patients in two predetermined strata based on the severity of carotid stenosis — 30 to 69 percent and 70 to 99 percent. We report here the results in the 659 patients in the latter stratum, who had had a hemispheric or retinal transient ischemic attack or a nondisabling stroke within the 120 days before entry and had stenosis of 70 to 99 percent in the symptomatic carotid artery. All patients received optimal medical care, including antiplatelet therapy. Those assigned to surgical treatment underwent carotid endarterectomy performed by neurosurgeons or vascular surgeons. All patients were examined by neurologists 1, 3, 6, 9, and 12 months after entry and then every 4 months. End points were assessed by blinded, independent case review. No patient was lost to follow-up.

*Results.* Life-table estimates of the cumulative risk of any ipsilateral stroke at two years were 26 percent in the 331 medical patients and 9 percent in the 328 surgical patients — an absolute risk reduction (±SE) of 17±3.5 percent ($P<0.001$). For a major or fatal ipsilateral stroke, the corresponding estimates were 13.1 percent and 2.5 percent — an absolute risk reduction of 10.6±2.6 percent ($P<0.001$). Carotid endarterectomy was still found to be beneficial when all strokes and deaths were included in the analysis ($P<0.001$).

*Conclusions.* Carotid endarterectomy is highly beneficial to patients with recent hemispheric and retinal transient ischemic attacks or nondisabling strokes and ipsilateral high-grade stenosis (70 to 99 percent) of the internal carotid artery. (N Engl J Med 1991; 325:445-53.)

CAROTID endarterectomy was introduced in 1954 as a logical procedure for the prevention of ischemic stroke distal to carotid-artery stenosis.[1] Although the first randomized trials of its effectiveness had negative results,[2-4] surgeons continued to perform carotid endarterectomy and began to report lower rates of perioperative complications.[5,6]

The number of patients undergoing endarterectomy in hospitals in the United States (other than Veterans Affairs hospitals) rose from 15,000 in 1971 to 107,000 in 1985.[7] However, continuing uncertainty about the efficacy of the operation was reflected in marked geographic variation in the rates of endarterectomy.[8] Adding to this uncertainty was the decline in the number of first and fatal strokes,[9-11] the influence of risk-factor management in reducing strokes,[12-14] and emerging recognition of the efficacy of antiplatelet drugs in preventing stroke.[15] When a randomized trial demonstrated that extracranial–intracranial bypass was ineffective in preventing stroke,[16] this presented an opportunity to reexamine the current efficacy of carotid endarterectomy as performed in North America, and several randomized trials were begun in both symptomatic and asymptomatic patients,[17] complementing the European Carotid Surgery Trial already under way.[18] This report describes the first definitive results of this new round of trials of carotid endarterectomy.

## METHODS

A full description of the methods of the study has been published elsewhere.[19] The key features of the conduct of the trial were as follows.

### Center Eligibility

The study was conducted at 50 centers in the United States and Canada. Each center had a rate of less than 6 percent for stroke and death occurring within 30 days of operation for at least 50 consecutive carotid endarterectomies performed within the previous 24 months, and each had obtained approval of the research protocol from its local institutional review board.

### Patient Eligibility

To be eligible for the trial, patients had to give informed consent, be less than 80 years old, and have had a hemispheric transient ischemic attack (distinct focal neurologic dysfunction) or monocular

*The collaborators in this trial are listed in the Appendix.

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blindness persisting less than 24 hours or a nondisabling stroke with persistence of symptoms or signs for more than 24 hours within the previous 120 days, in association with stenosis of 30 to 99 percent in the ipsilateral internal carotid artery; the artery had to be technically suitable for endarterectomy, as assessed by selective carotid angiography.

Using a jeweler's eyepiece marked in tenths of a millimeter, the principal neuroradiologist measured on the angiograms of each patient the luminal diameter (on two views) at the point of greatest stenosis and at the normal part of the artery beyond the carotid bulb. The percent stenosis was determined by calculating the ratio of these two measurements, with use of the view showing the greatest degree of narrowing. If review by the Data Management Center (Robarts Institute) found the stenosis to be less than 30 percent, the angiograms were submitted for independent external adjudication. Patients were categorized at entry as being in one of two predetermined strata: those with 30 to 69 percent stenosis and those with 70 to 99 percent stenosis. The reliability of this assignment was checked in a blinded fashion by the principal neuroradiologist in 127 randomly selected patients; this check revealed a high degree of consistency (kappa = 0.89).

Patients were excluded from the study if they (1) were mentally incompetent or unwilling to give informed consent; (2) had no angiographic visualization of both carotid arteries and their intracranial branches; (3) had an intracranial lesion that was more severe than the surgically accessible lesion; (4) had organ failure of the kidney, liver, or lung, or had cancer judged likely to cause death within five years; (5) had a cerebral infarction on either side that deprived the patient of all useful function in the affected territory; (6) had symptoms that could be attributed to nonatherosclerotic disease (e.g., fibromuscular dysplasia, aneurysm, or tumor); (7) had a cardiac valvular or rhythm disorder likely to be associated with cardioembolic symptoms; or (8) had previously undergone an ipsilateral carotid endarterectomy.

Patients were temporarily ineligible if they had uncontrolled hypertension, diabetes mellitus, or unstable angina pectoris; myocardial infarction within the previous 6 months; signs of progressive neurologic dysfunction; contralateral carotid endarterectomy within the previous 4 months; or a major surgical procedure within the previous 30 days. Such patients could become eligible if the disorder causing their temporary ineligibility resolved within 120 days after their qualifying cerebrovascular event. The data on all ineligible patients and all who were eligible but did not undergo randomization, including all patients undergoing carotid endarterectomy outside the trial, were reported to the Nonrandomized Data Center at the Mayo Clinic.[19]

### Base-Line Investigations

Patients underwent standardized history taking, physical and neurologic examinations, a 12-point assessment of functional status, laboratory tests, 12-lead electrocardiography, computerized tomography of the head, angiography and duplex ultrasonography of the carotid arteries, and chest roentgenography.

### Randomization

On transmission of base-line data to the Data Management Center, patients were randomly assigned to receive either medical care alone or medical care plus surgery, according to a computer-generated randomization schedule.

### Treatment

Antiplatelet treatment (usually 1300 mg of aspirin per day or a lower dose if necessitated by side effects) and, as indicated, antihypertensive, antilipid, and antidiabetic therapy was prescribed for all patients. Those assigned to surgery also underwent carotid endarterectomy. The surgical technique was left to the discretion of the surgeon, and the procedures have been described elsewhere.[19] Simultaneous coronary-artery bypass grafting and simultaneous bilateral carotid endarterectomy were proscribed. Patients with bilateral stenosis who were assigned to surgery could undergo bilateral endarterectomy if the symptomatic side of the carotid was operated on first.

### Follow-up

Study surgeons completed postoperative assessments 30 days after surgery or at the time of hospital discharge, whichever occurred first. Study neurologists performed medical, neurologic, and functional-status assessments of all patients one month after entry, then every three months for the first year, and every four months thereafter. The management of cardiovascular risk factors was monitored centrally, and reminders were sent to neurologists if necessary. Computed tomography of the head was performed if cerebrovascular events were suspected. Duplex ultrasonography was repeated one month after entry and after any cerebrovascular event in the carotid distribution. Carotid angiography was repeated after any cerebrovascular event when considered clinically appropriate.

### Events

All deaths were assessed for their immediate, underlying, and contributing causes. Strokes were assessed for location, type, laterality, severity, and duration, according to the definitions published by the Committee on Classification of Cerebrovascular Disease of the National Institute of Neurological Disorders and Stroke.[20] New lesions identified on computed tomography were not considered strokes unless appropriate signs or symptoms persisted beyond 24 hours.

Patient eligibility and events were assessed at three levels: by the participating neurologist and surgeon at each center, by the steering committee at the Data Management Center (where a staff neurologist tracked down missing or additional data as needed and then presented each case without revealing treatment assignment), and by a team of blinded external adjudicators who were not otherwise involved in the trial.

### Statistical Analysis

The original calculations of sample size allowed for independent analyses in each of four angiographic subgroups defined by the degree of stenosis and angiographic evidence of ulceration. However, the comparison of base-line angiograms and surgical specimens confirmed the insensitivity of angiography in detecting ulceration.[21] Accordingly, this stratification was removed from the primary analyses, leaving just the two strata of high-grade (severe) stenosis (70 to 99 percent) and medium-grade (moderate) stenosis (30 to 69 percent).

All analyses compared medical and surgical patients with respect to the length of time before treatment failure by means of the Mantel–Haenszel chi-square test and Kaplan–Meier survival curves. All reported P values are two-tailed. The primary analysis defined treatment failure as any fatal or nonfatal stroke ipsilateral to the carotid lesion. Other definitions included all strokes and all deaths as well as consideration of the severity of stroke. Strokes producing functional deficits persisting beyond 90 days were considered major. Each of these analyses included all strokes (regardless of location) and all deaths (regardless of cause) that occurred among surgical patients during the 30-day postoperative period and among medical patients during a comparable period after randomization.

Patients found to be ineligible because they did not have either an appropriate carotid lesion or corresponding symptoms were excluded from the primary analysis. Patients who were crossed over to the other treatment group were included in the primary analysis up to the date of crossover, but not after that date.

As dictated in the protocol, monthly interim analyses were initiated in January 1990 (two years after the randomization of the first patient). If the results of any of these monthly analyses, known only to the principal biostatistical investigator and a clinical epidemiologist, showed a difference between the medical and surgical groups that had reached a level of statistical significance of 0.1 percent ($P<0.001$), the chairman of the National Institutes of Health monitoring committee was to be notified. If this difference remained at

the 0.1 percent level over a six-month period, and if the supporting analyses indicated that the interpretation of these results was unambiguous and clinically important, the full monitoring committee was to be convened. The committee was also to be convened if it became possible to rule out, with a high level of confidence, a 10 percent reduction in relative risk as a result of carotid endarterectomy.

Analyses were conducted to ascertain the importance of risk factors by dividing patients into three risk groups of approximately equal size according to a simple count of the commonly recognized risk factors with the use of arbitrary cutoff points: age (>70 years), sex (male), systolic blood pressure (>160 mm Hg), diastolic blood pressure (>90 mm Hg), recency (<31 days) and type of prior cerebrovascular events (stroke, not transient ischemic attack), degree of stenosis (>80 percent), presence of ulceration on the angiogram, and a history of smoking, hypertension, myocardial infarction, congestive heart failure, diabetes, intermittent claudication, or high blood lipid levels. These risk factors and cutoff points were chosen in advance and were not derived through analysis of the data.

## Results

### Early Termination of the Study in Patients with High-Grade Stenosis

On February 1, 1991, the trial's preplanned rule for stopping randomization was invoked because of evidence of treatment efficacy among patients with high-grade stenosis (70 to 99 percent) who underwent carotid endarterectomy. On February 21, the monitoring and executive committees agreed that (1) randomization of patients with high-grade stenosis should be stopped, (2) a summary of the results in the patients with high-grade stenosis should be communicated immediately to the participating clinicians, along with a list of all patients given medical treatment alone to whom the results might apply, (3) reports of all strokes and deaths and all patient assessments occurring before February 21 should be collected as quickly as possible for inclusion in this report, and (4) the parallel study dealing with symptomatic patients with medium-grade stenosis (30 to 69 percent) should be continued. The sponsoring agency, the National Institute of Neurological Disorders and Stroke, independently issued a peer-reviewed Clinical Alert to convey immediately a summary of these interim results to physicians across North America.

### Patient Entry

Six hundred sixty-two patients with high-grade carotid stenosis (determined by central radiologic review) were enrolled between January 1, 1988, and February 21, 1991. Of these, three patients (0.5 percent) were subsequently excluded from the primary analysis by a blinded review panel because they did not meet entry criteria: one (assigned to surgical treatment) had symptoms due solely to glaucoma, one (assigned to medical therapy) had symptoms of a vertebrobasilar transient ischemic attack only, and one (assigned to surgical treatment) had occlusion of the internal carotid artery. Randomization created balanced treatment groups with respect to the qualifying cerebrovascular events, underlying vascular lesions, and important prognostic characteristics (Table 1).

Table 1. Base-Line Characteristics of the Treatment Groups.

| Characteristic | Medical (N = 331) | Surgical (N = 328) |
|---|---|---|
| Median age (yr) | 66 | 65 |
| | *% of group* | |
| Sex | | |
| Male | 69 | 68 |
| Female | 31 | 32 |
| Transient ischemic attack at entry | 69 | 67 |
| Stroke at entry | 31 | 33 |
| Ipsilateral stenosis | | |
| 70–79% | 43 | 40 |
| 80–89% | 33 | 38 |
| 90–99% | 24 | 22 |
| Contralateral stenosis, 70–99% | 9 | 8 |
| Race | | |
| White | 89 | 93 |
| Black | 4 | 2 |
| Other | 7 | 5 |
| Prior myocardial infarction | 18 | 18 |
| Stable angina pectoris | 25 | 22 |
| Hypertension | 61 | 60 |
| Diabetes | 21 | 17 |
| Hyperlipidemia | 25 | 21 |
| Intermittent claudication | 16 | 15 |
| Current cigarette smoking | 33 | 37 |
| Antithrombotic medications | 85 | 85 |

The similarity between the patients included and those excluded, reported elsewhere,[19] confirmed that no subgroup of eligible patients was systematically excluded from the trial.

### Patient Follow-up

No patient was lost to follow-up and none withdrew; 98 percent of the surviving patients had their last follow-up examination within 4 months of the February 21 closing date, and the average duration of follow-up was 18 months. Twenty-one medical patients (6.3 percent) were crossed over and underwent carotid endarterectomy on the same side as the lesion for which they were randomized (10 after transient ischemic attacks, 6 after a stroke, 2 as a prelude to other required surgery, 2 after refusing the random assignment, and 1 on the advice of a nonparticipating physician). Of the 328 patients assigned to surgery, only 1 refused the operation and received medical treatment alone. All the others underwent carotid endarterectomy, performed an average of two days after randomization. Medical regimens to reduce the risk of stroke were applied equally in both treatment groups. At the last reported follow-up examination, antihypertensive therapy was being given to 187 medical patients (57 percent) and 178 surgical patients (54 percent); elevation of the diastolic blood pressure (>95 mm Hg) was significantly more prevalent among the surgical patients than the medical patients (13 percent vs. 8 percent, $P<0.05$). Over 99 percent of both medical and surgical patients were taking anti-

thrombotic drugs at the last follow-up visit, most commonly aspirin, which was being used by 94 percent of the medical patients and 98 percent of the surgical patients.

### Perioperative Morbidity and Mortality

The perioperative period was considered the time from randomization to 30 days after surgery (which was performed a median of 2 days after randomization). None of the 328 surgical patients had a stroke or died between randomization and surgery. In the perioperative period, 18 surgical patients (5.5 percent) had cerebrovascular events; 12 events were minor, 5 were major (i.e., causing a functional deficit persisting ≥90 days), and 1 was fatal. In addition, one patient died suddenly after surgery, for a rate of 5.8 percent for all perioperative stroke and death. Restricting the analysis to the most serious events resulted in a rate of 2.1 percent for major stroke and death and a fatality rate of 0.6 percent.

In the comparable 32-day period after randomization among the 331 medical patients, 11 (3.3 percent) had cerebrovascular events; 8 events were minor, 2 were major, and 1 was fatal. This resulted in a rate of 3.3 percent for all stroke and death within 32 days of randomization, which included a rate of 0.9 percent for major stroke and death and a fatality rate of 0.3 percent.

Other surgical complications included cranial-nerve injury (7.6 percent), wound hematoma (5.5 percent), wound infection (3.4 percent), myocardial infarction (0.9 percent), congestive heart failure (0.6 percent), arrhythmia (1.2 percent), and other cardiovascular problems (1.2 percent). Of these complications, 81 percent were considered mild (of no lasting consequence and not prolonging hospitalization) and the rest were considered moderate (of no lasting consequence but prolonging the hospital stay).

### Events

As shown in the first row of Table 2, the life-table estimate of the risk of any fatal or nonfatal ipsilateral stroke by 24 months after randomization was 26 percent for the medical patients and only 9 percent for the surgical patients (including any stroke or death occurring postoperatively or within 32 days of randomization), resulting in an absolute risk reduction of 17 percent. Thus, for every 100 patients treated surgically, 17 were spared an ipsilateral stroke over the next two years. This represents a relative-risk reduction of 65 percent and shows that six such patients are the "number needed to be treated"[22] in order to prevent one adverse event by 24 months. The second through sixth rows of Table 2 show that carotid endarterectomy remained beneficial with respect to each of the five other definitions of outcome events.

The vast majority of first events were ipsilateral strokes (61 in medical patients vs. 26 in surgical patients), and although the overall difference between the treatment groups remained significant when other events were included, carotid endarterectomy proved beneficial in that it reduced ipsilateral strokes. The inclusion of stroke in the distribution of the contralateral carotid and vertebral basilar arteries added only three events to those in the medical group and eight to those in the surgical group, and the further addition of death from any cause added another nine and seven events, respectively. The treatment groups did not differ significantly in total mortality (Table 3).

Survival curves for the values reflected in each of the rows in Table 2 are shown in Figure 1. They reveal two additional points of interest. First, the early disadvantage to the surgical patients (who faced a risk of perioperative stroke and death) was rapidly overcome, with the curves for the medical and the surgical patients crossing about three months after randomization. Second, there was no evidence of convergence of the two curves for as long as 30 months, indicating that the beneficial effects of surgery persisted at least this long.

Among the patients who did not die or have a major stroke during the first month after randomization, the

**Table 2. First Adverse Events and Actuarial Failure Rates at Two Years of Follow-up, According to the Event Defining Treatment Failure.**

| Event Defining Failure* | Medical Patients (N = 331) | Surgical Patients (N = 328) | Absolute Difference ±SE | Relative-Risk Reduction |
|---|---|---|---|---|
| | *events (event rate, %†)* | | % | % |
| Any ipsilateral stroke | 61 (26.0) | 26 (9.0) | 17.0±3.5‡ | 65 |
| Any stroke | 64 (27.6) | 34 (12.6) | 15.0±3.8‡ | 54 |
| Any stroke or death | 73 (32.3) | 41 (15.8) | 16.5±4.2‡ | 51 |
| Major or fatal ipsilateral stroke | 29 (13.1) | 8 (2.5) | 10.6±2.6‡ | 81 |
| Any major or fatal stroke | 29 (13.1) | 10 (3.7) | 9.4±2.7‡ | 72 |
| Any major stroke or death | 38 (18.1) | 19 (8.0) | 10.1±3.5§ | 56 |

*"Death" refers to mortality from all causes. In addition to the events defining treatment failure, each value includes all strokes (any severity and any site) and deaths from any cause: in the surgical patients, between randomization and the 30th day after surgery, and in the medical patients, during the comparable 32-day period beginning with randomization.

†Failure rates were derived from Kaplan–Meier estimates of survival.

‡$P<0.001$ for the comparison of the treatment groups.

§$P<0.01$ for the comparison of the treatment groups.

**Table 3. Total Mortality According to Treatment Group.**

| Cause of Death | Medical (N = 331) | Surgical (N = 328) |
|---|---|---|
| | *no. of patients* | |
| Stroke | 5 | 2 |
| Myocardial infarction | 4 | 4 |
| Other ischemic heart disease | 3 | 1 |
| Sudden death | 1 | 3 |
| Other cardiovascular disease | 1 | 0 |
| Cancer | 2 | 2 |
| Respiratory disease | 1 | 1 |
| Other cause | 4 | 2 |
| Total — no. (%) | 21 (6.3) | 15 (4.6) |

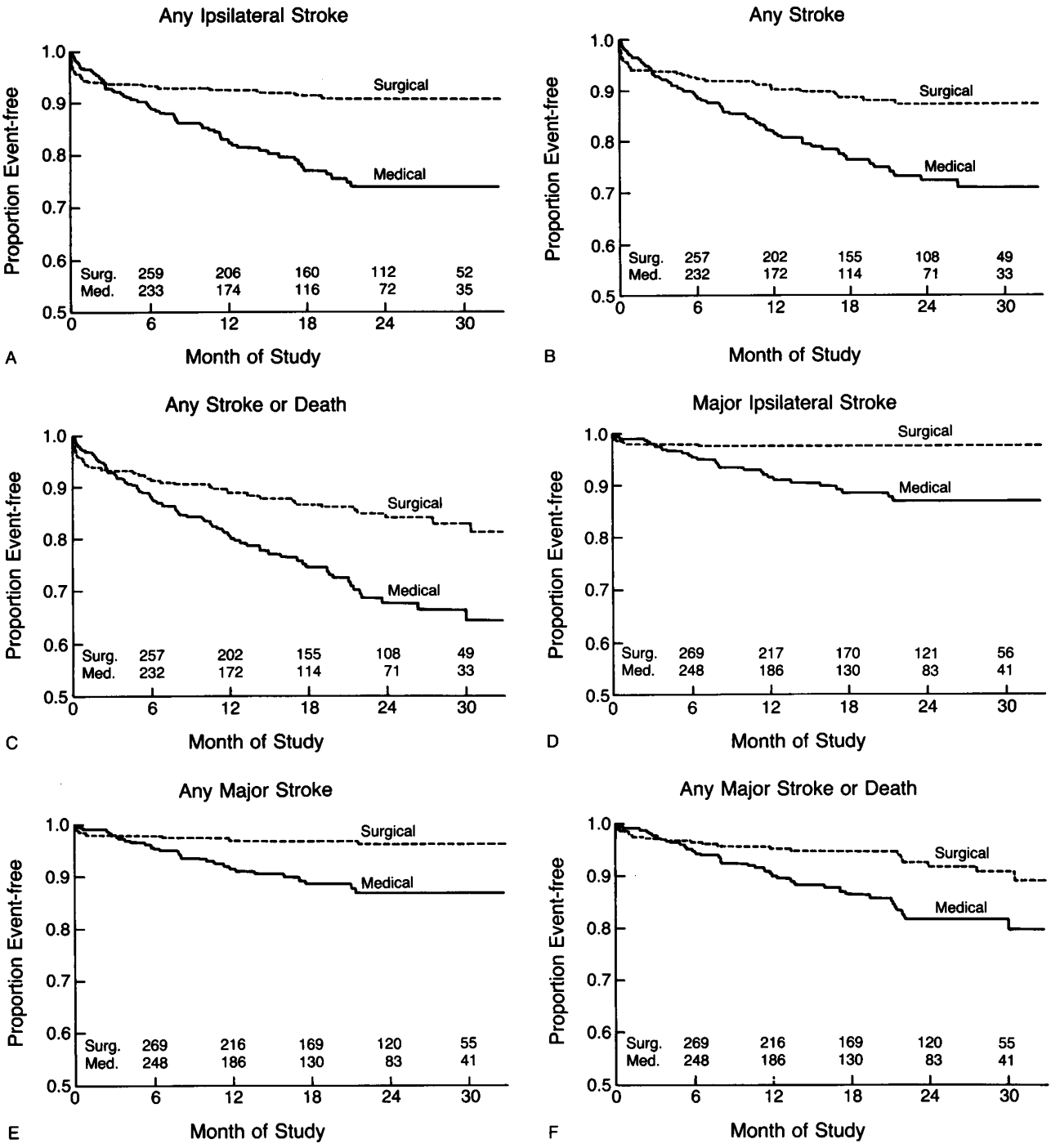


Figure 1. Survival Curves for the Treatment Groups.

These Kaplan–Meier survival curves show the probability of surviving six events indicating treatment failure after randomization. The number of patients who remained event-free in each treatment group is shown at six-month intervals at the bottom of each graph; the numbers at time zero are 328 in the surgical group and 331 in the medical group. The curves of the groups differed significantly (by Mantel–Haenszel chi-square test, $P<0.001$ for all events except "any major stroke or death," for which $P<0.01$).

risk of any major or fatal stroke within two years was 12.2 percent in the medical group and 1.6 percent in the surgical group ($P<0.00001$). Thus, the immediate postoperative increase in the risk of major stroke or death among the surgical patients, 1.2 percent (2.1 percent − 0.9 percent), was offset by an absolute risk reduction of 10.6 percent for major or fatal stroke during the subsequent two years.

Analyzing our results according to the intention-to-treat principle produced essentially the same levels of significance and standard errors for between-group differences. This analysis, which included the three

incorrectly randomized ineligible patients and counted events occurring in a patient after crossover according to the group to which the patient had originally been assigned, added just one event to those in the medical group and two events to those in the surgical group. The analyses reported in this paper include 30 patients found to be technically ineligible because of inadequate angiography (17 patients), severe intracranial stenosis (4), cerebral aneurysms (3), cardiac disorders (3), and other medical problems (3). Excluding these patients from the analysis reduced by five the events in the medical group and by three the events in the surgical group and did not alter the interpretation of the results. An analysis comparing results at large centers with those at small centers, and results at U.S. centers with those at Canadian centers, revealed no significant differences in the benefit of surgery according to the size or country of a study center.

The proportion of medical patients who had an ipsilateral stroke within two years was 17 percent in the low-risk group (0 to 5 risk factors), 23 percent in the moderate-risk group (6 risk factors), and 39 percent in the high-risk group ($\geq$7 risk factors) ($P<0.001$). The prognosis of the surgical patients did not vary significantly among risk groups and averaged 9 percent at two years.

A secondary analysis showed that finer divisions of the degree of high-grade carotid stenosis (i.e., 70 to 79, 80 to 89, and 90 to 99 percent) correlated with the degrees of risk reduction after surgery. The absolute risk reduction ($\pm$SE) for all ipsilateral stroke at two years was 26$\pm$8.1 percent among patients with stenosis of 90 to 99 percent at entry, 18$\pm$6.2 percent among those with stenosis of 80 to 89 percent, and 12$\pm$4.8 percent among those with stenosis of 70 to 79 percent.

## Discussion

Among symptomatic patients with high-grade stenosis (70 to 99 percent), those who underwent carotid endarterectomy had an absolute reduction of 17 percent in the risk of ipsilateral stroke at two years ($P<0.001$). This benefit was not diminished when strokes in other carotid and vertebral basilar territories and deaths from all causes were included in the analysis. Furthermore, clinically important and statistically significant beneficial effects persisted when the analyses excluded minor and nondisabling strokes and when they included patients with protocol violations.

Similar results have recently been reported from the European Carotid Surgery Trial.[18] Among 778 symptomatic patients with severe stenosis (70 to 99 percent) who were randomly assigned to treatment with carotid endarterectomy or medical care alone, 7.5 percent of the surgical patients had an ipsilateral stroke or died within 30 days of surgery. Life-table estimates of the risk of ipsilateral stroke during the next three years yielded an additional risk of 2.8 percent for surgical patients, as compared with 16.8 percent for medical patients ($P<0.0001$). The European study also concluded that the immediate risks of surgery outweighed any potential long-term benefit in the 374 symptomatic patients with mild stenosis (0 to 29 percent). Because definitive conclusions are not yet possible, both the European and North American trials are being continued in patients with moderate stenosis (30 to 69 percent).

After surgery, we observed no significant difference in event rates among patients with different numbers of base-line risk factors. Thus, the degree of benefit that individual patients received from carotid endarterectomy was directly proportional to the risk they faced without surgery, and those with the highest risk at entry gained the most. Our original estimates of the risk of stroke (4 to 7 percent per year), based on results in placebo groups in trials of antithrombotic drugs, substantially underestimated the risk of stroke among symptomatic patients with high-grade stenosis. The life-table estimates of the risk of stroke at two years among our medical patients were 26 percent for ipsilateral stroke, 28 percent for stroke in any territory, and 32 percent for any stroke or death.

We caution readers not to apply our conclusions too broadly. First, the study surgeons were selected only after audits of their endarterectomy results by our surgical committee confirmed a high level of expertise. If comparable expertise and quality control are not achieved in the widespread implementation of these results and the perioperative risk of major stroke and death exceeds the 2.1 percent reported here, the benefit of endarterectomy will diminish. If the rate of major complications approaches 10 percent, the benefit will vanish entirely. Second, our method of measuring stenosis was strict. The results reported here relate only to patients in whom the ratio of the narrowest diameter of the diseased artery (the numerator) to the diameter of the artery beyond the bulb and beyond recognizable disease involvement (the denominator) indicated stenosis of 70 to 99 percent. Our results do not apply if the diameter of the carotid bulb or a segment with poststenotic dilatation is used as the denominator of this ratio in the measurement of stenosis (the severity of stenosis would be overestimated). Third, we have no information about the efficacy of endarterectomy in patients whose ischemic events occur more than 120 days before surgery or who either have already had a devastating stroke or are in the throes of a progressing stroke. Nor did our study include patients who had failure of other major organs or heart disorders that might produce emboli. Also, as indicated by the preponderance of ipsilateral stroke, the patients included in this study did not have widespread cerebrovascular disease.

Patients in both treatment groups underwent cervical and intracranial carotid arteriography before randomization in order to rule out the presence of distal disease more severe than that in the surgically accessi-

ble cervical carotid artery. Because a major stroke complicating arteriography would preclude admission to the trial, the benefits reported here should be adjusted downward to include the risk of arteriography. The risk of major stroke or death due to angiography should be no more than 1 percent in patients studied because of arteriosclerotic disease of the cerebral arteries.[23-25] If the decision to perform angiography were based on the results of noninvasive ultrasound examination, patients with lesser degrees of stenosis could be spared the risks of angiography. A rigorous comparison of ultrasound with angiography in symptomatic patients would be required to give a precise estimate of the effect of this diagnostic strategy.

In our group of patients with high-grade stenosis, those with less severe stenosis had a lower risk of stroke, and their gains from surgery were smaller than those of patients with more severe stenosis. This observation reinforces a continuing uncertainty about the efficacy of carotid endarterectomy for stenosis in the range of 30 to 69 percent. The investigators in both the North American and the European trials are continuing to study symptomatic patients with moderate stenosis (30 to 69 percent). Together these trials will determine whether patients with this degree of stenosis will benefit from endarterectomy, and if so, will identify the point at which the risks of surgery outweigh its benefits.

The effects of publishing the results of both trials on the future frequency of carotid endarterectomy will be followed with considerable interest. Over the past few years, many referring physicians have shown a declining interest in carotid endarterectomy and have acted as if the absence of proof were the proof of absence. In 1985, 107,000 carotid endarterectomies were performed in hospitals (excluding Veterans Affairs hospitals) in the United States. By 1989, the number had diminished to 70,000 (Dyken ML, Pokras R: personal communication). In the light of the results reported here, this reduction in the number of carotid endarterectomies may have deprived some patients with high-grade stenosis of what is now confirmed to be a beneficial operation.

On the basis of these results and those of the European trial, patients with transient ischemic attacks or recent minor strokes without an obvious cardiac cause, who are otherwise fit for surgery, should be screened with noninvasive ultrasonographic techniques. Those with minimal narrowing or none should be treated with what is currently the best medical care. Those with moderate or severe narrowing should be seriously considered for arteriography. If those shown by arteriography to have moderate stenosis (30 to 69 percent) are referred to one of the study centers of the North American trial, the part of the trial focusing on moderate stenosis will be concluded sooner. Patients with high-grade stenosis (70 to 99 percent) should be considered for referral to institutions and surgeons who practice vigorous quality control and have the low rates of perioperative morbidity and mortality that have characterized the centers and physicians in this trial.

These positive findings among symptomatic patients with high-grade stenosis provide no answers to the question of the optimal treatment of patients with asymptomatic carotid stenosis. It is essential that the trials under way to study such patients be continued.

## Appendix

The following persons and institutions participated in the North American Symptomatic Carotid Endarterectomy Trial:

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