# Endarterectomy for Asymptomatic Carotid Artery Stenosis

Executive Committee for the Asymptomatic Carotid Atherosclerosis Study

**Objective.**—To determine whether the addition of carotid endarterectomy to aggressive medical management can reduce the incidence of cerebral infarction in patients with asymptomatic carotid artery stenosis.

**Design.**—Prospective, randomized, multicenter trial.

**Setting.**—Thirty-nine clinical sites across the United States and Canada.

**Patients.**—Between December 1987 and December 1993, a total of 1662 patients with asymptomatic carotid artery stenosis of 60% or greater reduction in diameter were randomized; follow-up data are available on 1659. At baseline, recognized risk factors for stroke were similar between the two treatment groups.

**Intervention.**—Daily aspirin administration and medical risk factor management for all patients; carotid endarterectomy for patients randomized to receive surgery.

**Main Outcome Measures.**—Initially, transient ischemic attack or cerebral infarction occurring in the distribution of the study artery and any transient ischemic attack, stroke, or death occurring in the perioperative period. In March 1993, the primary outcome measures were changed to cerebral infarction occurring in the distribution of the study artery or any stroke or death occurring in the perioperative period.

**Results.**—After a median follow-up of 2.7 years, with 4657 patient-years of observation, the aggregate risk over 5 years for ipsilateral stroke and any perioperative stroke or death was estimated to be 5.1% for surgical patients and 11.0% for patients treated medically (aggregate risk reduction of 53% [95% confidence interval, 22% to 72%]).

**Conclusion.**—Patients with asymptomatic carotid artery stenosis of 60% or greater reduction in diameter and whose general health makes them good candidates for elective surgery will have a reduced 5-year risk of ipsilateral stroke if carotid endarterectomy performed with less than 3% perioperative morbidity and mortality is added to aggressive management of modifiable risk factors.

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MORE THAN 500 000 new strokes occur annually in the United States, and it has been estimated that carotid artery disease may be responsible for 20% to 30% of them.[1] The annual stroke event rate for asymptomatic patients with hemodynamically significant carotid artery stenosis ranges from 2% to 5%.[2-5] Carotid artery stenosis usually is identified after transient ischemic attack (TIA), but for many patients, cerebral infarction caused by artery-to-artery embolism or carotid occlusion is the initial event. Progression of asymptomatic carotid artery stenosis to occlusion is unpredictable and can be disastrous; at the time of occlusion, disabling stroke may occur in 20% of patients, and thereafter in 1.5% to 5% annually.[6-8] On the other hand, the 30-day major morbidity and mortality for patients who undergo surgery for asymptomatic stenosis ranges from 0.0% to 3.8%, and that for patients with symptomatic stenosis may be 6%.[9] Because the role of carotid endarterectomy (CEA) for asymptomatic carotid artery stenosis had not been proved,[10-12] the Asymptomatic Carotid Atherosclerosis Study (ACAS) was initiated in 1987.[13] The ACAS is an investigator-initiated randomized trial designed to test whether CEA should be a component of management for selected patients with asymptomatic stenosis of the common carotid bulb, the internal carotid sinus, or both. The question addressed was: Will CEA added to aggressive reduction of modifiable risk factors and administration of aspirin reduce the 5-year risk of ipsilateral cerebral infarction in individuals with asymptomatic hemodynamically significant carotid artery stenosis?

**For editorial comment see p 1459.**

Secondary objectives were to determine the surgical success in lesion removal and the incidence of recurrent carotid stenosis, the rate of progression or regression of carotid atherosclerosis in the medically treated comparison group, and the incidence of all other vascular events, such as TIA, myocardial infarction, and death related to vascular disease during follow-up.

## METHODS

The design and organization of the ACAS are detailed elsewhere.[13] Thirty-nine clinical centers were chosen from an applicant pool of 55. All obtained institutional review board approval of the study protocol.

### Recruitment

Study participants were recruited from ultrasound vascular laboratories, practitioners who auscultated carotid bruits, and physicians who found carotid stenosis during evaluation for peripheral vascular surgery or contralateral CEA.

Inclusion criteria were age between 40 and 79 years; compatible history and findings on physical and neurological examinations; performance of required laboratory and electrocardiographic examinations no earlier than 3 months before randomization; patient accessibility and willingness to be followed for 5 years; and valid informed consent.

Exclusion criteria were cerebrovascular events in the distribution of the study carotid artery or in that of the vertebrobasilar arterial system; symptoms referable to the contralateral cerebral hemisphere within the previous 45 days; contraindication to aspirin therapy; a disorder that could seriously complicate surgery; or a condition that could prevent continuing participation or was likely to produce disability or death within 5 years. (Detailed information regarding eligibil-

A complete list of the collaborators in the Asymptomatic Carotid Atherosclerosis Study appears at the end of this article.

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ity and exclusion is available on request from the corresponding author.)

The ACAS definition of hemodynamically significant carotid stenosis required that at least one of three criteria was met: arteriography within the previous 60 days indicating stenosis of at least 60% reduction in diameter (if the arteriogram was performed 61 to 364 days before randomization, Doppler ultrasonography was required to verify that the artery had not occluded); Doppler examination within the preceding 60 days showing a frequency or velocity greater than the instrument-specific cut point with 95% positive predictive value (PPV); or Doppler examination showing a frequency or velocity greater than the instrument-specific 90% PPV cut point confirmed by ocular pneumoplethysmographic (OPG-Gee) examination performed within the previous 60 days.

A patient could enter the study with unilaterally or bilaterally asymptomatic, hemodynamically significant stenosis, but only one artery was the study artery. If two arteries were eligible, the one with the greater stenosis was selected. If the stenoses were identical, the left carotid artery was chosen. Patients randomized to surgery on the basis of Doppler or Doppler with OPG-Gee were required to have an arteriogram prior to CEA. If a postrandomization arteriogram revealed the contralateral artery to have the greater stenosis, it then became the study artery. The nonstudy artery was managed medically unless a cerebrovascular event occurred, at which time CEA could be considered.

### Arteriographic Measurements

The minimal residual lumen (MRL) and the distal lumen (DL) were measured on the same radiograph. The MRL was the smallest lumen diameter at the site of the stenotic lesion. The DL was the diameter at the first point distal to the MRL at which the arterial walls became parallel. Percentage of stenosis was calculated as $100 \times (1-[MRL/DL])$.

### Ultrasound Measurements

Because of the heterogeneity among ultrasound devices and techniques, we established a cut point for each by comparing Doppler ultrasonography with arteriograms performed within 42 days of each other. Doppler cut points were computed for peak systolic frequency or, if indeterminant, end diastolic frequency, based on data from 50 consecutive patients.[14]

### Randomization

An ACAS neurologist and an ACAS surgeon gave joint approval for entering patients. Once the eligibility criteria had been confirmed and after informed consent was obtained, the patient was randomized using the permuted block method with at least three different block sizes determined randomly, stratified by center, gender, number of eligible arteries, and previous contralateral CEA. The assignment category was communicated to each clinical center by the statistical coordinating center through an individualized computer program arranged so that the clinical center could neither predict nor reject an assignment.

### Medical Treatment

All patients received 325 mg of regular or enteric-coated aspirin daily (provided by Sterling Health USA, New York, NY). Stroke risk factors and their modification were reviewed with all patients at the time of randomization and again during subsequent interviews and telephone follow-up. This included discussion of diastolic and systolic hypertension, diabetes mellitus, abnormal lipid levels, excessive consumption of ethanol, and tobacco use. Whenever possible, the recommendations of the ACAS Risk Factor Reduction Committee were followed (available on request from the corresponding author).

### Surgical Treatment

In addition to 325 mg of aspirin daily and risk factor modification counseling, patients randomized to the surgical arm received the normal evaluation and care of a surgical patient. They were scheduled to undergo CEA within 2 weeks of randomization. If an arteriogram or cranial computed tomogram (CCT) had not been performed, the patient underwent the procedure(s) before CEA. The arteriogram must have demonstrated a stenosis of 60% or greater. Patients with a postrandomization, presurgery arteriogram demonstrating less than 60% stenosis or a distal abnormality such as aneurysm, arteriovenous malformation, or siphon stenosis exceeding the proximal stenosis did not undergo surgery but were retained in the surgical arm for comparison analyses. Asymptomatic cerebral infarction demonstrated by CCT was not an exclusion for surgery.[15] No attempt was made to standardize or control anesthesia or surgical techniques used by the 117 ACAS-credentialed surgeons.[16]

The surgeon, the ACAS neurologist, and the ACAS patient coordinator examined each patient 24 hours after CEA. All deficits occurring through the 30-day perioperative period required the administration of the end point review process (described below).

### Follow-up

Follow-up evaluations were conducted at 1 month and thereafter every 3 months, alternating between clinic visits and telephone contacts. During the clinic visit, patients completed a medical history questionnaire and TIA/stroke questionnaire and underwent physical and neurological examinations and a Mini-Mental State Examination.[17] Risk reduction management was reviewed and aspirin adherence was determined by pill count.

Doppler ultrasound studies were repeated at the 3-month follow-up, every 6 months thereafter during the first 24 months, then yearly, and at potential or verified end point or at exit from the study after 5 years; CCT was repeated at potential end point or exit. Electrocardiogram was repeated when clinically indicated and at exit.

Patients were instructed to notify the coordinator if symptoms suggesting possible TIA or stroke occurred. The coordinator scheduled urgent evaluations by the ACAS neurologist and surgeon, and activated the end point verification system.

In addition to identification of events from clinic visits and telephone contacts, hospital discharge diagnoses and death certificates were reviewed for coronary events and strokes.

### End Point Definition and Verification

A TIA was defined as a focal ischemic neurological deficit of abrupt onset lasting at least 30 seconds and resolving completely within 24 hours. Deficits persisting longer than 24 hours were classified as stroke.[18] All strokes or deaths occurring within 30 days after randomization in the surgical and 42 days in the medical groups were included as end points to reflect operative morbidity and mortality. The difference in times reflected an average 12-day interval between randomization and surgery.

Initial review was conducted under a stringent timetable involving one external expert masked for local diagnosis, treatment assignment, clinical center, and temporal relationship to surgery (if done). In addition, every potential event was abstracted, masked, and reviewed together by all six experts on the End Point Review Committee. Our analyses are based on their diagnoses.

Secondary analyses considered any stroke and perioperative death; any stroke and any death; and any ipsilateral TIA and stroke and any perioperative TIA, stroke, or death. The ACAS used categories 2 through 5 of the Glasgow scale to determine a major stroke, defined as a stroke resulting in moderate or severe disability, persistent vegetative state, or death.[19]

### Statistical Analyses

Initially, the primary end points for evaluation of the two treatments were

Table 1.—Baseline
Patients by Treatm

| Baseline Charact |
|---|
| Age, y |
| 40-49 |
| 50-59 |
| 60-69 |
| 70-79 |
| Race |
| White |
| Black |
| Other |
| Sex |
| M |
| F |
| History |
| Coronary artery d |
| Hypertension‡ |
| Cancer |
| Diabetes mellitus |
| Lung disease at ent |
| Current cigarette sm |
| Bilaterally eligible ar |
| Previous contralater |
| Endarterectomy |
| TIA or stroke§ |
| EC-IC bypass |
| Subclavian bypas |
| Bruits in neck‖ |
| Ipsilateral |
| Contralateral |
| Infarct on CT scan¶ |
| Any location |
| Ipsilateral silent |
| Contralateral occlus |
| by Doppler |

*TIA indicates tran
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‡Positive respons
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Table 1.—Baseline Characteristics of Randomized Patients by Treatment Assignment, in Percentages*

| Baseline Characteristic | Treatment Assignment: Surgical (n=825) | Treatment Assignment: Medical (n=834) |
|---|---|---|
| Age, y | | |
| 40-49 | 2 | 2 |
| 50-59 | 13 | 15 |
| 60-69 | 50 | 46 |
| 70-79 | 36 | 38 |
| Race | | |
| White | 94 | 95 |
| Black | 3 | 3 |
| Other | 3 | 2 |
| Sex | | |
| M | 66 | 66 |
| F | 34 | 34 |
| History | | |
| Coronary artery disease† | 69 | 69 |
| Hypertension‡ | 64 | 64 |
| Cancer | 12 | 10 |
| Diabetes mellitus | 25 | 21 |
| Lung disease at entry | 6 | 5 |
| Current cigarette smoker | 28 | 24 |
| Bilaterally eligible arteries | 10 | 9 |
| Previous contralateral | | |
| Endarterectomy | 20 | 19 |
| TIA or stroke§ | 22 | 27 |
| EC-IC bypass | <1 | 0 |
| Subclavian bypass | <1 | <1 |
| Bruits in neck‖ | | |
| Ipsilateral | 76 | 74 |
| Contralateral | 44 | 42 |
| Infarct on CT scan¶ | | |
| Any location | 22 | 24 |
| Ipsilateral silent | 8 | 9 |
| Contralateral occlusion by Doppler | 10 | 9 |

*TIA indicates transient ischemic attack; EC-IC, external carotid–internal carotid; and CT, computed tomographic.
†Defined as positive history of angina, coronary artery bypass, previous myocardial infarction, or abnormal electrocardiogram.
‡Positive response to "Has your doctor ever told you that you had high blood pressure or were hypertensive?"
§Significant difference between groups at .05 level (unadjusted for multiple comparisons).
‖Bruit question not evaluated for 51 surgical and 52 medical patients. Ipsilateral/contralateral refers to randomized artery.
¶CT scan was not available on 71 surgical and 60 medical patients.

Table 2.—Arteriographic Stenosis of the Ipsilateral Carotid Artery

| % Stenosis | Prerandomization Arteriogram: Medical | Prerandomization Arteriogram: Surgical | Prerandomization Arteriogram: Total (%) | Postrandomization Presurgery Arteriogram |
|---|---|---|---|---|
| 0-59 | Not applicable | NA | NA | 32 (8) |
| 60-69 | 131 | 137 | 268 (42) | 139 (34) |
| 70-79 | 94 | 93 | 187 (29) | 110 (26) |
| 80-89 | 75 | 79 | 154 (24) | 107 (26) |
| 90-99 | 13 | 20 | 33 (5) | 24 (6) |
| **Total** | **313** | **329** | **642*** | **412†** |

*Two patients were missing, one in each group.
†Two patients were missing.

ipsilateral TIA, stroke, or any perioperative TIA, stroke, or death. The primary analysis is the comparison of the 5-year risk of cerebrovascular events in the two groups. Because both treatments were in wide use, a two-sided test of the null hypothesis ($\alpha$=.05) was chosen. Power calculations included all randomized patients according to original treatment assignments (intention-to-treat analysis). Assuming an annual event rate in the worse-outcome group of 3% for TIA and 1% for cerebral infarction, these calculations indicated that 750 patients were needed in each treatment arm for 90% power to detect a 35% difference in 5-year event rates, allowing for as much as 20% loss to follow-up.

The results of the Veterans Affairs trial[20] demonstrated that CEA is preferable to medical management for preventing TIA in asymptomatic carotid stenosis, and the North American Symptomatic Carotid Endarterectomy Trial[21] demonstrated that infarction following TIA is better managed surgically. Neither resolved the issue of whether CEA prevents unheralded cerebral infarction. Therefore, in March 1993, the ACAS Executive Committee and the Data and Safety Monitoring Committee voted to restrict the primary end point to stroke and perioperative complications or death.

For baseline comparisons, we used two-tailed $t$ tests for comparing the means of continuous variables and $\chi^2$ for comparing distributions of categorical variables, with no adjustment for multiple comparisons. Kaplan-Meier estimates of 5-year aggregate risk were compared between treatment groups using either Greenwood's formula for variances, for a large-sample test ignoring randomization stratification,[22] or randomization tests, respecting randomization strata.[23] In the initial years of treatment comparison, 1991 through 1993, the tests were for 2-, 3-, or 4-year aggregate risk. The randomization test was the primary method for interim treatment comparisons (see below). By the time of study closure $P$ values from the two methods agreed within .002, so that all test results and confidence intervals (CIs) reported are based on large-sample tests unless otherwise noted.

Semiannual treatment comparison analyses were used to advise the Data Safety and Monitoring Committee whether a significance boundary had been crossed. The stopping rule was a modified O'Brien-Fleming[24] rule for maintaining the desired overall significance level despite repeated testing. The modification was for testing at selected intervals rather than predetermined numbers of events. The five analyses originally planned were changed to 10, because recruitment lagged and TIA was deleted as a primary end point. The critical value for the test statistic was 6.00 at the first test and 2.07 for the 10th, as compared with 1.96 for a single test at the significance level .05. The study was stopped after the eighth test, when the critical value was 2.38, corresponding to a nominal significance level of .017.

Treatment comparisons are reported herein in terms of relative risk reduction, the 5-year risk reduction due to surgery as a proportion of risk in the medical group.[25] Absolute treatment group–specific risk levels are also provided for calculation of absolute risk reduction. For the primary event the number of patients treated to prevent one event over 5 years was calculated as the inverse of the absolute risk reduction.[25]

Intention-to-treat analyses were used for all comparisons unless otherwise indicated, regardless of postrandomization ineligibility or crossover. End points for medical patients who received CEA after verified ipsilateral end point were categorized as perioperative if they occurred within 30 days of CEA. All tests were two tailed.

## COHORT CHARACTERISTICS

During the 6 years of the study, more than 42 000 patients were screened and 1662 patients were randomized. Twenty-four centers contributed more than 30 patients each, and 13 contributed more than 50 patients. The average number of patients recruited per center was 43.

From March 1988 through October 1993, 12 080 CEAs were performed at the sites. Six percent (683) were performed on "likely eligible nonrandomized" patients of ACAS physicians, 6% (758) were performed on already randomized ACAS patients, and the rest were performed on symptomatic patients, ineligible patients, or patients of surgeons not collaborating in the ACAS.

Patient characteristics are presented in Table 1. Of the 1662 randomized patients, three in the surgery group were lost to follow-up after randomization and are excluded from analysis, leaving 1659. The 825 surgical and 834 medical patients were compared for 189 baseline characteristics, with only six tests yielding nominal statistically significant differences at the .05 level. Two thirds of the patients were men, 95% were white, and 48% were aged 60 through 69 years. Mean age was 67 years; mean weight, 81 kg for men and 67 kg for women; mean systolic blood pressure, 146 mm Hg; mean diastolic blood pressure, 78 mm Hg; and mean total cholesterol concentration, 5.90 mmol/L (228 mg/dL). Approximately 75% of patients had a bruit associated with the study artery, and in 43%, a contralateral carotid bruit was heard; 21% had a previous myo-

Table 3.—Number of Observed Events in Median 2.7-Year Follow-up, Estimated Number and Percentage of Events in 5 Years, Reduction Due to Surgery in 5-Year Risk as a Proportion of Risk in the Medical Group (95% CI), and Large-Sample *P* Value for Treatment Group Difference, by Event Type*

| Event Type | Medical (n=834) | | Surgical (n=825) | | Reduction Due to Surgery in 5-y Risk as a Proportion of Risk in Medical Group (95% CI) | *P* |
|---|---|---|---|---|---|---|
| | Observed No. of Events in Median 2.7-y Follow-up | Kaplan-Meier Estimate of 5-y Event Risk, No. (%) | Observed No. of Events in Median 2.7-y Follow-up | Kaplan-Meier Estimate of 5-y Event Risk, No. (%) | | |
| Ipsilateral stroke or any perioperative stroke or death | 52 | 92 (11.0) | 33 | 42 (5.1) | 0.53 (0.22 to 0.72) | .004 |
| Major ipsilateral stroke or any perioperative major stroke or death | 24 | 50 (6.0) | 21 | 28 (3.4) | 0.43 (−0.17 to 0.72) | .12 |
| Ipsilateral TIA or stroke or any perioperative TIA or stroke or death | 102 | 160 (19.2) | 55 | 67 (8.2) | 0.57 (0.39 to 0.70) | <.001 |
| Any stroke or any perioperative death | 86 | 146 (17.5) | 60 | 102 (12.4) | 0.29 (−0.05 to 0.52) | .09 |
| Any major stroke or perioperative death | 40 | 76 (9.1) | 28 | 53 (6.4) | 0.30 (−0.30 to 0.62) | .26 |
| Any stroke or death | 155 | 266 (31.9) | 127 | 211 (25.6) | 0.20 (−0.02 to 0.37) | .08 |
| Any major stroke or death | 116 | 213 (25.5) | 100 | 171 (20.7) | 0.19 (−0.08 to 0.39) | .16 |

*CI indicates confidence interval; and TIA, transient ischemic attack.

cardial infarction, and 21% a previous coronary artery bypass. Sixty-four percent had hypertension, 26% were cigarette smokers, and 23% had diabetes mellitus.

Four hundred seven patients (25%) had had a previous hemispheric event contralateral to the study artery, and 1155 (70%) were asymptomatic in the distribution of both arteries.

Thirty-nine percent of patients were randomized on the basis of an arteriogram showing at least 60% stenosis of the carotid artery. Fifty-five percent were randomized with a Doppler PPV cut point of at least 95%, and 6% with a Doppler cut point of at least 90% confirmed by OPG-Gee. The positive predictive value of Doppler, estimated from the postrandomization presurgery angiogram, was 93%.

Table 2 shows the distribution of percentage of stenosis for prerandomization and postrandomization arteriograms before CEA. Because the health status of patients who received prerandomization arteriograms may differ from that of those who did not, a weighted estimate based on both categories is included. Five percent of patients had stenosis of the randomized artery less than 60%; 39%, 60% to 69% stenosis; 28%, 70% to 79% stenosis; 25%, 80% to 89% stenosis; and 5%, 90% to 99% stenosis, for a mean percentage of stenosis of 73%.

The Central Reading Center classified 536 baseline CCTs[15] as showing cerebral infarction. If an infarct was present, it was further classified by age, size, distribution, and volume. Local and central readers agreed on 89% of the cases. Using the Central Reading Center as the standard, the sensitivity of local reading was 71% and the specificity was 94%.

## RESULTS

Of the 825 surgical patients, 101 did not have ipsilateral arteriography or CEA, 45 because of patient refusal despite prior agreement to accept either treatment. Twelve patients were rejected for surgery because of severe cardiac disease. Three had a stroke or died before arteriography or surgery was performed. Arteriograms found 33 patients to be ineligible, six because of intracranial abnormalities and 27 because of less than 60% carotid artery stenosis. Eight patients did not have surgery for various other reasons. Of the 834 patients randomized to medical treatment, 45 received CEA without a verified ipsilateral TIA or stroke. Thus, 146 (9%) patients did not receive the assigned treatment. Eleven patients dropped out from follow-up in the medical and nine in the surgical group.

During the perioperative period, 19 surgical patients (2.3%) had a stroke or died. Two patients had a stroke, one died prior to hospitalization, and five had a cerebral infarction as a direct result of arteriography, one of whom died. There were 10 nonfatal strokes and one fatal myocardial infarction during the 30-day postsurgery period. In the comparable perioperative period for the medical group, three patients (0.4%) had a cerebral infarction (two patients) or died (one patient). For the surgical group, the risk in the perioperative period was 2.3% (95% CI, 1.28% to 3.32%), whereas for the medical group it was 0.4% (95% CI, 0.0% to 0.8%).

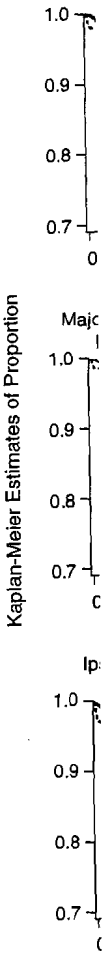
All patients randomized to the surgical group were required to have arteriography. Of the 414 patients who underwent arteriography prior to CEA, five experienced a cerebral infarction, for an arteriographic complication rate of 1.2%. It is estimated that if all 724 patients receiving CEA had undergone arteriography as a part of the ACAS, 8.7 arteriographic cerebral infarctions would have occurred in addition to the 11 primary events in the 30 days following surgery, for an overall rate of 2.7% for cerebral infarction or death from the procedure.

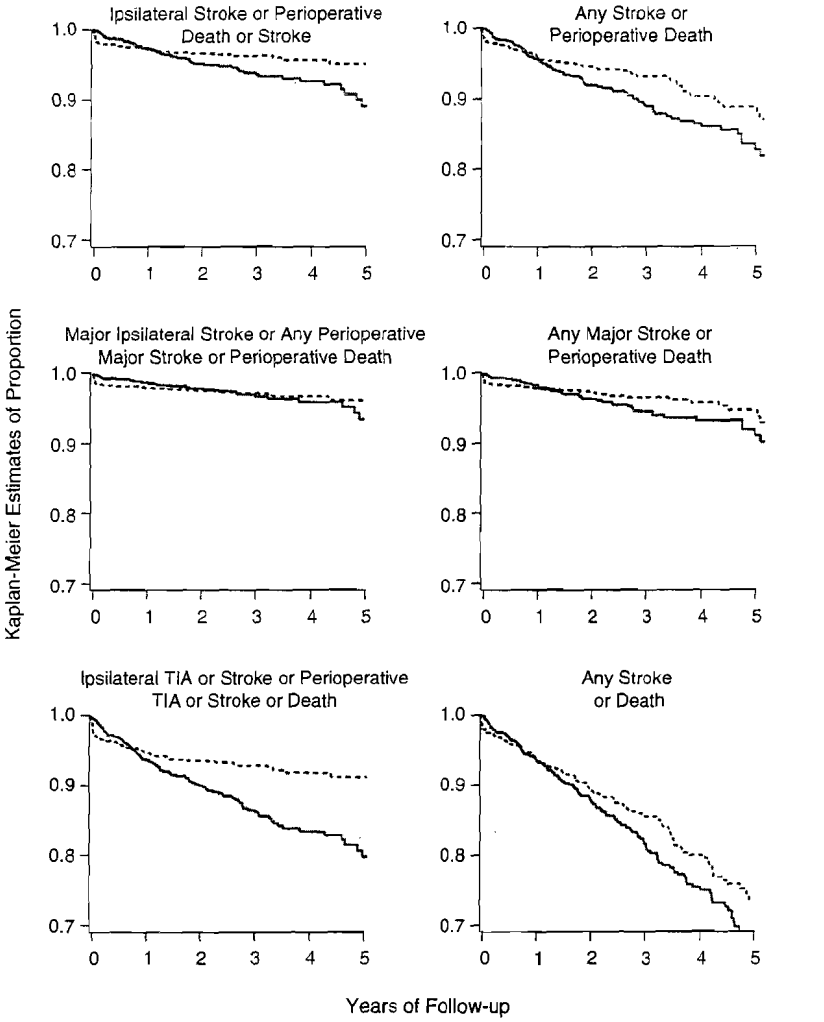
Sixteen fatalities, potentially due to strokes, were reviewed by the Cerebrovascular End Point Review Committee. In no case was there a difference between the End Point Review Committee diagnosis and the local physician diagnosis. These events included six hemorrhagic strokes, two cerebral infarctions in the distribution of the randomized artery, three cerebral infarctions in the nonrandomized distribution, and five deaths not due to stroke.

### Treatment Comparisons

The study achieved its significance boundary after a median of 2.7 years of follow-up, with 9% of patients having completed 5 years; 26%, 4; 44%, 3; 68%, 2; and 87%, 1 year of follow-up. Because surgical patients were at greatest risk during the first month after endarterectomy, whereas the risk for medical patients was distributed throughout 5 years, comparisons near term greatly understated the differences expected after 5 years. Table 3 presents the observed number of events and also the Kaplan-Meier estimates predicted if all patients had been followed for 5 years. The estimated 5-year risk of ipsilateral stroke and any perioperative stroke or death was 11.0% for the medical group and 5.1% for the surgical group. The reduction in 5-year ipsilateral stroke risk in the surgical group was 53% of the estimated 5-year risk in the medical group (95% CI, 22% to 72%). The *P* value for the test of the difference between the treatment groups in 5-year risk of primary event was .004 by the large-sample test and the randomization test. For the primary end point of ipsilateral stroke and any perioperative stroke or death, the survival curves in the Figure cross near 10 months and become significantly reduced in the surgical group by 3 years ($P<.05$).

The results for secondary end points are in the same direction although not always statistically significant (Table 3 and Figure). Ipsilateral TIA or stroke or any perioperative TIA, stroke, or death—the original primary end point for the ACAS—showed a 57% reduction in 5-year risk for the surgery group (95% CI, 39% to 70%). In terms of any stroke or death,






Proportion of patients without end point at a given time during follow-up, by treatment group, using Kaplan-Meier estimation method. Solid line indicates medical patients; broken line, surgical patients; and TIA, transient ischemic attack.

Table 4.—Number of Deaths, Overall and by Treatment Group, in the ACAS, December 1987 Through December 31, 1994*

| Cause of Death | Treatment Group | |
|---|---|---|
| | Surgical | Medical |
| Perioperative only | 3 | 1 |
| Ipsilateral stroke | 2 | 3 |
| Stroke on contralateral side or posterior circulation | 1 | 2 |
| Cerebral hemorrhage | 3 | 4 |
| Acute myocardial infarction | 21 | 24 |
| Other cardiac disease | 15 | 24 |
| Other vascular disorder | 1 | 2 |
| Respiratory failure | 10 | 9 |
| Cancer | 15 | 13 |
| Tuberculosis | 1 | 0 |
| Renal failure | 4 | 2 |
| Gastrointestinal system disease | 4 | 3 |
| Nervous system disease | 1 | 0 |
| Trauma | 2 | 0 |
| Unknown | 0 | 2† |
| **Total Deaths** | **83** | **89** |
| Deaths per 100 person-years of follow-up | 3.5 | 3.8 |

*ACAS indicates Asymptomatic Carotid Atherosclerosis Study.

†One patient died at home, the other at a non-ACAS facility. The patient coordinators were unable to obtain information as to the causes of deaths.

the surgery group had a 20% reduction in events (95% CI, –2% to 37%). The reduction due to CEA in major ipsilateral stroke or perioperative death was 43% (95% CI, –17% to 72%). Table 4 shows the causes of death were similar for the two groups, except for death not proved to result from myocardial infarction.

Table 5 summarizes results for ipsilateral stroke or any perioperative stroke or death by patient subgroups. In men, CEA reduced the 5-year event rate by 66% (95% CI, 36% to 82%); in women, the event rate was reduced by 17% (95% CI, –96% to 65%). However, the difference between genders was not statistically significant ($P$=.10). The proportion of women with perioperative complications was 3.6%, compared with 1.7% for men ($P$=.12). However, among patients who had no perioperative event, 5-year risk was reduced by 56% for women (95% CI, –50% to 87%), compared with a reduction of 79% for men (95% CI, 52% to 91%) (data not shown). Table 5 shows a larger risk reduction due to CEA for younger patients, but the difference is not statistically significant ($P$=.50).

Reanalysis excluding the 146 crossovers, ie, restricted to those patients who received the assigned treatment, shows that surgery reduced 5-year stroke risk by 55% (95% CI, 23% to 74%). Alternatively, for the 1155 patients who had no contralateral TIA, stroke, or endarterectomy prior to randomization, surgery reduced the 5-year stroke risk by 46% (95% CI, 0% to 71%) (Table 5).

The percentage of stenosis for the 642 patients who received an arteriogram within 6 months preceding randomization is shown in Table 5. Throughout the three groups, ie, for patients with 60% to 69%, 70% to 79%, and 80% to 99% stenosis, there was no statistically significant gradation in reduction of 5-year risk of primary event, but sample sizes were small. The patients for this comparison all had an arteriogram performed before randomization, so the risk of stroke from undergoing an arteriogram was not included in the calculations. If a 1.2% arteriogram risk were added to the surgery groups at the three stenosis levels, the risk reductions become 0.35, 0.49, and 0.13, respectively, which are consistent with the overall results of the ACAS.

## COMMENT

The ACAS was designed to test the efficacy of CEA for preventing ipsilateral stroke during a 5-year period. Even though this report includes patients followed up for a median of only 2.7 years, with 9% having completed 5 years of follow-up, the data demonstrate a statistically significant ($P$=.004) difference between the estimated 5-year ipsilateral stroke rates of 11.0% for the medical and 5.1% for the surgical group. Moreover, the results are in the same direction for all subgroups considered, including deciles of stenosis (although not statistically significant because of small sample size), and for various secondary cerebrovascular end points. Furthermore, the results are virtually the same when restricted to all patients receiving the assigned treatment, and are almost identical for patients without previous contralateral symptoms or endarterectomy.

Approximately 70% of our medical and surgical patients had arteriographic stenoses less than 80%. Even so, the estimated 5-year ipsilateral stroke rate in the ACAS medical group was 11.0% (about 2.3% annually). The stroke rate in the medically managed group decreased to the lower end of the previously reported range, perhaps as a re-

Table 5.—Number and Percentage of Perioperative Strokes or Deaths, Number of Observed Events in Median 2.7-Year Follow-up, Estimated Number and Percentage of 5-Year Ipsilateral Strokes or Perioperative Strokes or Deaths, and Reduction Due to Surgery in 5-Year Risk as a Proportion of Risk in the Medical Group, With 95% CI, by Subgroup*

| Patient Group | Treatment Group | No. at Risk | Total Events | | | Reduction Due to Surgery in 5-y Risk as Proportion of Risk in the Medical Group | |
|---|---|---|---|---|---|---|---|
| | | | Perioperative Events, No. (%) | No. of Events Observed in Median 2.7-y Follow-up | Estimated Events† for 5-y Follow-up, No. (%) | Estimate | 95% CI |
| All | Surgical | 825 | 19 (2.3) | 33 | 42 (5.1) | 0.53 | 0.22 to 0.72 |
| | Medical | 834 | 3 (0.4) | 52 | 92 (11.0) | ... | ... |
| Men | Surgical | 544 | 9 (1.7) | 18 | 22 (4.1) | 0.66 | 0.36 to 0.82 |
| | Medical | 547 | 3 (0.5) | 38 | 66 (12.1) | ... | ... |
| Women | Surgical | 281 | 10 (3.6) | 15 | 20 (7.3) | 0.17 | −0.96 to 0.65 |
| | Medical | 287 | 0 (0.0) | 14 | 25 (8.7) | ... | ... |
| Age <68 y | Surgical | 408 | 6 (1.5) | 13 | 19 (4.7) | 0.60 | 0.11 to 0.82 |
| | Medical | 394 | 2 (0.5) | 23 | 47 (11.8) | ... | ... |
| Age ≥68 y | Surgical | 417 | 13 (3.1) | 20 | 23 (5.5) | 0.43 | −0.07 to 0.70 |
| | Medical | 440 | 1 (0.2) | 29 | 43 (9.7) | ... | ... |
| Bilaterally asymptomatic | Surgical | 585 | 12 (2.1) | 24 | 32 (5.5) | 0.46 | 0.00 to 0.71 |
| | Medical | 570 | 3 (0.5) | 34 | 58 (10.2) | ... | ... |
| Previous contralateral endarterectomy or previous TIA or stroke | Surgical | 240 | 7 (2.9) | 9 | 11 (4.5) | 0.65 | 0.13 to 0.86 |
| | Medical | 264 | 0 (0.0) | 18 | 33 (12.6) | ... | ... |
| Patients receiving assigned treatment | Surgical | 724 | 16 (2.2) | 28 | 37 (5.1) | 0.55 | 0.23 to 0.74 |
| | Medical | 789 | 3 (0.4) | 50 | 91 (11.5) | ... | ... |
| % Stenosis‡ 60.0-69.9 | Surgical | 137 | 4 (2.9) | 7 | 9 (6.3) | 0.45 | −0.70 to 0.82 |
| | Medical | 131 | 0 (0.0) | 8 | 15 (11.4) | ... | ... |
| % Stenosis‡ 70.0-79.9 | Surgical | 93 | 1 (1.1) | 2 | 2 (2.2) | 0.67 | −0.65 to 0.94 |
| | Medical | 94 | 0 (0.0) | 5 | 6 (6.7) | ... | ... |
| % Stenosis‡ 80.0-99.9 | Surgical | 99 | 1 (1.0) | 2 | 2 (2.0) | 0.45 | −2.19 to 0.91 |
| | Medical | 88 | 0 (0.0) | 3 | 3 (3.7) | ... | ... |

*CI indicates confidence interval; and TIA, transient ischemic attack.
†Using Kaplan-Meier estimation.
‡Percentage of stenosis of randomized artery at baseline, for patients with prerandomization angiogram within 6 months of randomization.

sult of vigorous risk factor management and exclusion of high-risk patients.

There were no significant differences in primary event rates between patient groups with and without symptoms or previous CEA of the contralateral carotid artery. With an annual mortality rate of 3.7%, approximately 89% of patients survived long enough to benefit from the protective effect of the operation, because the crossover in favor of surgery occurred within the first year.

Four other randomized prospective studies of CEA for asymptomatic carotid artery stenosis have been reported. One did not include stenosis exceeding 90%,[26] another was terminated early because of excess cardiac events,[27] and a third, the European Asymptomatic Carotid Surgery Trial, is ongoing.[28]

The fourth, the Veterans Affairs Cooperative Trial, randomized 444 patients and published results based on a mean follow-up of 47.9 months. The Veterans Affairs study differed from the ACAS in that only men were studied and all patients had an arteriogram.[20]

Like the Veterans Affairs trial, the ACAS showed an advantage for CEA in preventing TIAs, cerebral infarctions, and death in men. In addition, the ACAS showed an advantage in reducing the risk of ipsilateral stroke alone. Our results are consistent with others that established that symptomatic patients with carotid stenosis greater than 70% were best treated by CEA.[21,29]

Because a 10% difference in lumen diameter on arteriogram is approximately 0.5 mm, and the lumen area stenosis difference is only 6%, this cannot be measured accurately, and when miniaturized images are used, these differences cannot be discerned. Therefore, we believe that stenoses with 60% and 70% reductions in diameter are both hemodynamically significant, and that putative difference by decile is within the range of observer variability.[30-32]

It has been suggested that arteriography should have been required for all ACAS patients to ensure that only those with greater than 60% stenosis were entered. However, it was the judgment of the ACAS group that the hazards and costs of arteriography were not warranted for patients in our medical group. This was borne out by the 1.2% stroke rate from arteriography. Our Doppler criteria were established to maintain a PPV of 95%.[14] Retrospective analysis of all postrandomization, presurgery arteriograms demonstrated that our actual PPV was 93%. This indicates that our medical patients did indeed have significant carotid artery stenosis, with fewer than 5% having less than the required 60%.

If all patients who underwent surgery had received arteriography as part of the surgical treatment, the absolute risk reduction would have been from 11.0% to 5.6%. Using ACAS eligibility requirements, 19 CEAs would be necessary to prevent one stroke over 5 years.[25] This ratio would be less if patient subsets at higher risk for stroke could be identified.

A CEA can be performed with a low complication rate even in elderly patients. In selected instances, some ACAS surgeons now operate without arteriography on the basis of noninvasive studies[33,34] and sometimes discharge patients 24 hours following surgery.[35] These and other measures may reduce costs if proved generally feasible.

## CONCLUSIONS

The ACAS has demonstrated that the incidence of cerebral infarction can be reduced by CEA and that stringent quality control measures can reduce surgical morbidity and mortality. A major reason was the 30-day morbidity and mortality of ACAS patients, estimated to have been 2.7% if all surgery patients had undergone arteriography as part of the study. This includes arteriographic complications of 1.2%. These results may be improved further by reducing risk associated with

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| | 0.36 to 0.82 |
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| | 0.11 to 0.82 |
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| | −0.07 to 0.70 |
| | ... |
| | 0.00 to 0.71 |
| | ... |
| | 0.13 to 0.86 |
| | ... |
| | 0.23 to 0.74 |
| | ... |
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| | −0.65 to 0.94 |
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contrast arteriography. The ACAS has established that men with a good life expectancy who have asymptomatic carotid artery stenosis with at least 60% reduction in diameter are protected from stroke by CEA, whereas the results for women are less certain. Following CEA, the relative stroke risk reduction for men and women combined is 53%, with an absolute 5-year risk reduction from 11.0% to 5.1%. The 5-year reduction in stroke risk among men was 66% and among women 17%, perhaps because of the higher perioperative complication rate in women. Excluding arteriographic and perioperative complications, the risk reduction was 79% for men and 56% for women.

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