# THE CAUSES AND RISK OF STROKE IN PATIENTS WITH ASYMPTOMATIC INTERNAL-CAROTID-ARTERY STENOSIS

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## ABSTRACT

***Background*** The causes of stroke in patients with asymptomatic carotid-artery stenosis have not been carefully studied. Information about causes might influence decisions about the use of carotid endarterectomy in such patients.

***Methods*** We studied patients with unilateral symptomatic carotid-artery stenosis and asymptomatic contralateral stenosis from 1988 to 1997. The causes, severity, risk, and predictors of stroke in the territory of the asymptomatic artery were examined and quantified.

***Results*** The risk of stroke at five years after study entry in a total of 1820 patients increased with the severity of stenosis. Among 1604 patients with stenosis of less than 60 percent of the luminal diameter, the risk of a first stroke was 8.0 percent (1.6 percent annually), as compared with 16.2 percent (3.2 percent annually) among 216 patients with 60 to 99 percent stenosis. In the group with 60 to 99 percent stenosis, the five-year risk of stroke in the territory of a large artery was 9.9 percent, that of lacunar stroke was 6.0 percent, and that of cardioembolic stroke 2.1 percent. Some patients had more than one stroke of more than one cause. In the territory of an asymptomatic occluded artery (as was identified in 86 patients), the annualized risk of stroke was 1.9 percent. Strokes with different causes had different risk factors. The risk factors for large-artery stroke were silent brain infarction, a history of diabetes, and a higher degree of stenosis; for cardioembolic stroke, a history of myocardial infarction or angina and hypertension; and for lacunar stroke, age of 75 years or older, hypertension, diabetes, and a higher degree of stenosis.

***Conclusions*** The risk of stroke among patients with asymptomatic carotid-artery stenosis is relatively low. Forty-five percent of strokes in patients with asymptomatic stenosis of 60 to 99 percent are attributable to lacunes or cardioembolism. These observations have implications for the use of endarterectomy in asymptomatic patients. Without analysis of the risk of stroke according to cause, the absolute benefit associated with endarterectomy may be overestimated. (N Engl J Med 2000;342:1693-700.)



WHETHER to perform carotid endarterectomy in asymptomatic patients is an important public health issue. On the basis of Medicare records, the number of carotid endarterectomies in the United States rose from 46,571 in 1989 to 108,275 in 1996.[1] The National Hospital Discharge Survey estimated that 144,000 endarterectomy procedures were performed in 1997 (Pokras R: personal communication). Half of the procedures are performed in asymptomatic patients.[2] Two million people in the United States who are over the age of 50 years are estimated to have asymptomatic carotid-artery stenosis of at least 50 percent of the luminal diameter.[3] Uncertainty about the ideal treatment for these patients makes it necessary for us to learn as much as possible about the causes and risk of stroke.

Atherosclerosis of the internal carotid artery is an important cause of stroke. Large multicenter trials have demonstrated that the risk of stroke is reduced by endarterectomy.[4-7] The three major factors that determine the magnitude of benefit derived from endarterectomy are the presence or absence of symptoms, the degree of carotid-artery stenosis, and the rate of perioperative stroke or death. Provided the perioperative rate is approximately 6 percent, patients with severe symptomatic carotid stenosis (70 to 99 percent) can expect an absolute reduction of 13.3 to 15.6 percent in the risk of stroke within five years.[4,6] In contrast, endarterectomy is only marginally effective for patients without symptoms. The largest trial of patients with asymptomatic carotid stenosis of 60 to 99 percent found less than half of this absolute reduction (5.9 percent) in the risk of stroke at five years.[8]

Decisions about whether to recommend endarterectomy for asymptomatic patients must take into account that not all future strokes will originate from the stenosed internal carotid artery. In patients with severe symptomatic stenosis, approximately 20 percent of subsequent ipsilateral strokes have a cardiac

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or lacunar cause.[9,10] If this percentage is similar or higher in asymptomatic patients, the reported absolute benefit of endarterectomy in the trials of endarterectomy for asymptomatic carotid-artery stenosis may be diminished by the occurrence of cardioembolic and lacunar strokes. Given this finding, the absolute reduction in risk attributable to endarterectomy should be calculated with large-artery stroke as the outcome. We examined the causes and risk of stroke in the territory of a carotid artery with asymptomatic stenosis. Data are from the North American Symptomatic Carotid Endarterectomy Trial (NASCET).

## METHODS

The NASCET was designed to determine the efficacy of endarterectomy for patients with symptomatic carotid stenosis. A total of 2885 patients were enrolled who had had a transient ischemic attack or nondisabling ischemic stroke within 180 days before randomization to medical care alone or medical care with endarterectomy. Patients were not eligible if they had a probable cardiac source of embolism or a serious disease likely to cause death within five years. All patients underwent a detailed history taking and physical examination at base line that included routine blood tests, electrocardiography, chest radiography, carotid angiography, and computed tomography (CT) or magnetic resonance imaging, or both, of the brain. All angiograms and brain scans were reviewed centrally. The degree of internal-carotid-artery stenosis was measured according to strict criteria.[11] Near-occlusions, which were identified on angiography as very severe stenosis proximal to a narrowed distal segment, were assigned to the category of 95 to 99 percent stenosis. Brain scans were evaluated to detect any brain infarctions and to rule out other disorders that could account for the symptoms. Details of the study methods have been published previously.[4,12]

Follow-up consisted of clinical examinations every four months during the trial. The mean follow-up was five years. Data on all strokes were centrally reviewed, and ischemic strokes were assigned by the NASCET outcomes committee to categories according to their underlying cause (large-artery, lacunar, or cardioembolic) and the level of disability they produced. Strokes that were not clearly lacunar or cardioembolic in origin were categorized as large-artery strokes. Lacunar strokes were defined by a combination of symptoms or signs and radiologic criteria: presentation with primary motor, primary sensory, or sensory–motor symptoms, the dysarthria–clumsy hand syndrome or the ataxia–hemiparesis syndrome, with deep white-matter lesions or basal-ganglia lesions 1 cm or less in diameter detected radiologically.[9] The NASCET definition of cardioembolic strokes, published elsewhere,[10] included strokes in patients who, after study entry, had cardiac disorders known to be associated with a substantial risk of cerebral embolism, particularly atrial fibrillation accompanied by two or more recognized cardiovascular risk factors, recent myocardial infarction and its thrombotic or cardiac-wall sequelae, symptomatic valvular lesions identified on echocardiography, and the need for cardiac interventional procedures. All suspected cardioembolic strokes were reviewed by a cardiologist, whose assessment was validated independently by a second cardiologist. When there were two possible causes for a stroke, a single cause was assigned by the outcomes committee in conjunction with the consulting cardiologist. Strokes were considered disabling if patients had a modified Rankin score of 3 or more (on a scale on which 0 indicates normal and independent functioning and 6 indicates death[13]) at 90 days after the onset of symptoms. All deaths were reviewed and assigned an underlying cause.

Of the 2885 patients enrolled in the NASCET, we excluded 375 patients who had a history of bilateral carotid-artery symptoms, an additional 52 who had previously undergone endarterectomy of the asymptomatic artery, and 81 for whom no angiogram showing the asymptomatic artery was available for central review. The remaining 2377 patients had a carotid artery that was asymptomatic up to the time of randomization and that was contralateral to the randomized symptomatic artery. An artery was defined as asymptomatic if there were no ipsilateral symptoms or signs of cerebral or retinal ischemia. Even if there was a silent lesion on the CT scan, the artery was regarded as asymptomatic. Among the 2377 patients, 471 had no visible internal-carotid-artery disease and 86 had an occlusion, leaving 1820 with a patent asymptomatic artery with angiographically visible stenosis.

The risk of any stroke at five years that was ipsilateral to the asymptomatic artery and the risk of such a stroke according to cause were derived from Kaplan–Meier curves for event-free survival. In the analyses of risk, only the first stroke with a particular cause was counted, and data were censored at the time of endarterectomy on the asymptomatic artery. The significance of differences in risk was ascertained with the use of the log-rank test. To permit comparisons with the Asymptomatic Carotid Atherosclerosis Study,[8] which used 60 percent stenosis as the cutoff, patients were divided into two categories according to the degree of angiographically visible asymptomatic stenosis: <60 percent or 60 to 99 percent. A secondary analysis, with use of Cox proportional-hazards regression modeling, was undertaken to determine whether different risk factors were associated with the three causes of stroke. The most common risk factors for stroke were examined. Adjusted hazard ratios, which served as measures of association, were used to report the results. All continuous variables were dichotomized.

## RESULTS

The risk of a first stroke at five years was 4.6 percent for patients with no visible disease in the asymptomatic artery, ranged up to 18.5 percent for those with 75 to 94 percent stenosis, and decreased thereafter as the degree of stenosis approached occlusion ($P<0.001$ for the overall comparison among the categories of stenosis). As Figure 1 shows, the magnitude of these risks was notably less than the risk of stroke in the territory of an artery with symptomatic stenosis.

Of the 1820 patients with asymptomatic stenosis, 1604 had less than 60 percent stenosis and 216 had 60 to 99 percent stenosis. Base-line characteristics of the entire group of 1820 patients are reported, since no appreciable differences were observed between the two subgroups. The mean age was 66 years (14 percent were 75 years old or older), and 68 percent were men. There was a recorded history of hypertension in 60 percent of the patients and of diabetes mellitus in 22 percent, and 36 percent had a history of myocardial infarction or angina. Twenty-four percent of the patients had a silent brain infarction in the territory of the asymptomatic carotid artery. During the 10-year duration of the trial, a total of 195 strokes (191 ischemic strokes and 4 strokes due to primary intracerebral hemorrhage) occurred in the territory of the previously asymptomatic artery in 165 of the 1820 patients.

The risk analysis involved 122 strokes. Data were censored at the time of endarterectomy in 102 patients (5.6 percent). Only the first occurrence of ipsilateral stroke within a five-year period was counted. The risk of ipsilateral stroke, due to any cause and of

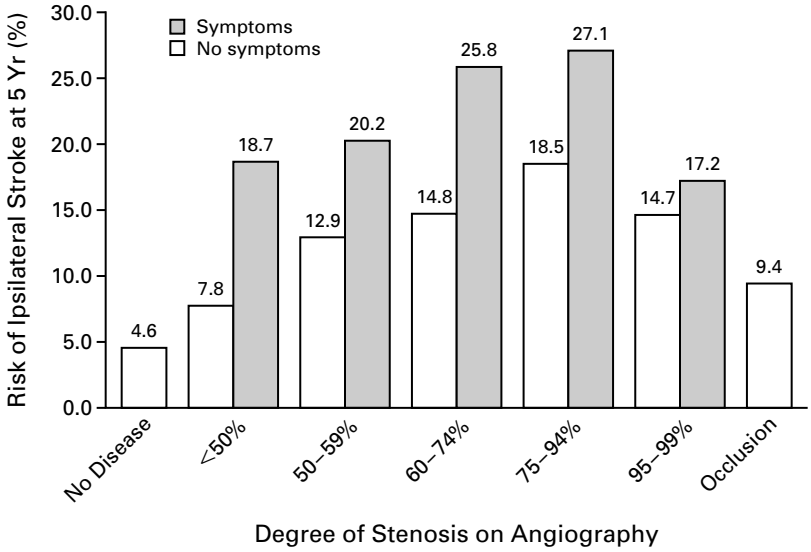


**Figure 1.** The Risk of a First Ipsilateral Stroke at Five Years after Study Entry in the Territories of Carotid Arteries with and without Symptoms, According to the Degree of Stenosis.

Stenosis of 95 to 99 percent represents near-occlusion. The numbers of patients with symptomatic carotid-artery stenosis were as follows: <50 percent stenosis, 690; 50 to 59 percent stenosis, 238; 60 to 74 percent stenosis, 267; 75 to 94 percent stenosis, 196; and 95 to 99 percent stenosis, 58. For asymptomatic carotid-artery stenosis, the numbers of patients were as follows: no disease, 471; <50 percent stenosis, 1496; 50 to 59 percent stenosis, 108; 60 to 74 percent stenosis, 113; 75 to 94 percent stenosis, 74; 95 to 99 percent stenosis, 29; and occlusion, 86.

any degree of severity, at five years among patients with less than 60 percent carotid-artery stenosis was 8.0 percent, as compared with 16.2 percent for those with 60 to 99 percent stenosis (absolute difference in risk, 8.2 percent; 95 percent confidence interval, 2.1 to 14.3 percent). The risk of disabling stroke (defined by a Rankin score of 3 or more) was higher among the patients with more severe stenosis but still less than half the risk of any stroke, regardless of severity. Approximately 80 percent of first strokes were not heralded by transient ischemia.

A substantial number of strokes in the territory of the asymptomatic carotid artery had causes other than large-artery disease (Fig. 2, top). The risk of lacunar stroke at five years was approximately one third the risk of large-artery stroke for patients with less than 60 percent stenosis and increased to approximately two thirds the risk of large-artery stroke among the patients with 60 to 99 percent stenosis. The risk of cardioembolic stroke was less than one quarter the risk of large-artery stroke in each of the corresponding stenosis categories. The combined risk of stroke with a lacunar or cardioembolic cause approached the risk of a large-artery stroke among the patients who had 60 to 99 percent stenosis (8.1 percent vs. 9.9 percent).

Of the 40 strokes that occurred in the group with 60 to 99 percent stenosis, 42.5 percent (27.5 percent plus 5.0 percent plus 10.0 percent) were disabling (Fig. 2, bottom). The odds of having a disabling stroke as compared with a nondisabling stroke in the group with 60 to 99 percent stenosis was calculated from the percentages in Figure 2. The odds were highest for cardioembolic stroke (2:1). For large-artery stroke the odds were 1:1. The odds that a lacunar stroke would be disabling were low (1:5).

The overall risk of death from any cause at five years was 17.5 percent for patients with asymptomatic stenosis of less than 60 percent and 21.0 percent for those with 60 to 99 percent stenosis. The risk of death not due to stroke at five years without the prior occurrence of a stroke was 15.3 percent among patients with less than 60 percent stenosis and 17.2 percent among those with 60 to 99 percent stenosis. In these two degree-of-stenosis categories the risk of death due to stroke (1.9 percent and 1.0 percent, respectively) or death due to myocardial infarction (3.4 percent and 2.0 percent) was low in comparison to the risk of death due to other vascular causes (6.2 percent and 10.7 percent) and death due to nonvascular causes (7.1 percent and 8.8 percent).

Results from the Cox proportional-hazards regression models indicated that the three causes of stroke were associated with different base-line risk-factor profiles (Fig. 3). Higher degrees of carotid-artery stenosis were predictive of large-artery and lacunar stroke, but not of cardioembolic stroke.

The asymptomatic artery was occluded in 86 pa-

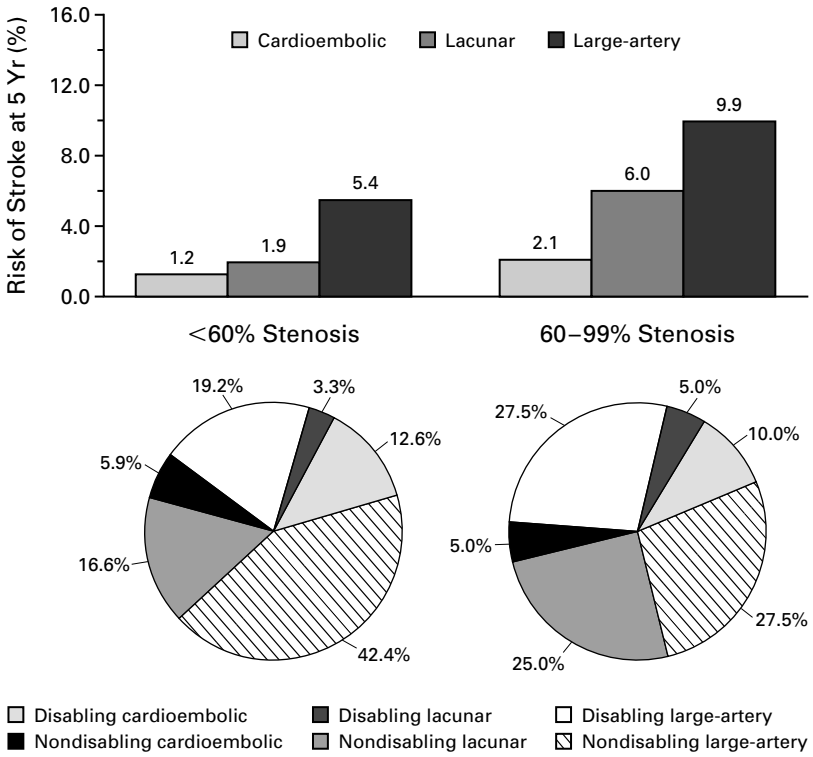


**Figure 2.** Risk and Severity of Stroke According to Cause.

The top panel illustrates the risk of a first ipsilateral stroke of cardioembolic, lacunar, or large-artery origin at five years after study entry, according to the degree of asymptomatic carotid-artery stenosis. The cause-specific risks are not additive; some patients had more than one stroke of more than one cause. The bottom panel shows the proportions of disabling and nondisabling ipsilateral strokes for each cause, within the categories of <60 percent stenosis and 60 to 99 percent stenosis.

tients. The five-year risk of stroke ipsilateral to the occlusion in these subjects was 9.4 percent (1.9 percent annually). Of the six strokes that occurred in this group, five were of large-artery origin, one was lacunar, and none were cardioembolic.

Table 1 shows the actual risk of ipsilateral stroke from any cause and the calculated risk of ipsilateral large-artery stroke on the basis of the Asymptomatic Carotid Atherosclerosis Study data. To prevent one stroke from any cause at two years, 67 patients would have to undergo carotid endarterectomy. To prevent one large-artery stroke at two years, 111 patients would have to undergo carotid endarterectomy.

## DISCUSSION

Recently, physicians have recognized that in clinical studies of stroke, the causes of stroke should be identified.[14,15] The causes of stroke have not been carefully reported in patients with asymptomatic carotid stenosis. In the present study, we observed that almost half the strokes in the territory of an asymptomatic carotid artery in patients with 60 to 99 percent stenosis were attributable to lacunar and cardioembolic disease. Our study excluded patients with cardiac diseases, which can cause emboli. Consequently, the number of cardioembolic strokes among patients with asymptomatic carotid stenosis was probably underestimated.

Considering that strokes with different causes may respond differently to a particular treatment and that the risk of large-artery stroke is low, our data suggest that endarterectomy may not be justified for most patients with asymptomatic carotid-artery stenosis. This is the case because counting only large-artery strokes as the outcome of interest, rather than strokes from any cause, cuts the absolute reduction in the risk of stroke from 5.9 percent to 3.5 percent and nearly doubles the number needed to treat (Table 1). The expected small absolute reduction (0.9 percent) in risk at two years translates to a large number of patients who would need to be treated to prevent a single large-artery stroke within two years (111 patients), even when the rate of perioperative stroke and death associated with endarterectomy is assumed to be the 2.3 percent reported by the Asymptomatic Carotid Atherosclerosis Study.[8] If, instead of 2.3 per-

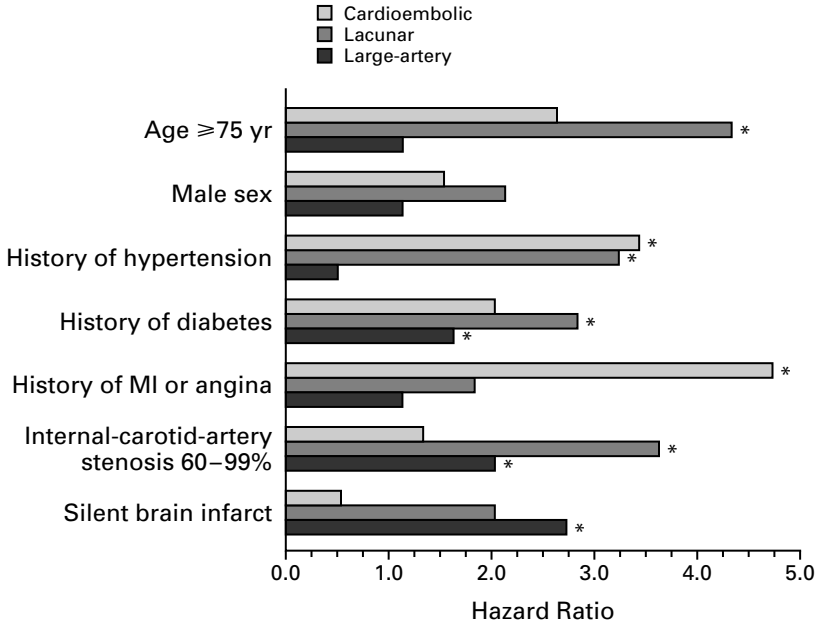


**Figure 3.** Base-Line Characteristics Associated with the Subsequent Risk of Stroke According to Cause (Cardioembolic, Lacunar, or Large-Artery).

The hazard ratios were derived from a Cox proportional-hazards regression model. MI denotes myocardial infarction. The three causes of stroke were associated with different risk factors: for large-artery strokes, silent brain infarction, a history of diabetes, and higher degrees of stenosis; for cardioembolic stroke, a history of myocardial infarction or angina and a history of hypertension; and for lacunar stroke, age ⩾75 years, hypertension, diabetes, and higher degrees of stenosis. An asterisk indicates a significant hazard ratio ($P<0.05$).

**TABLE 1.** RISK OF IPSILATERAL STROKE AT FIVE YEARS AND NUMBER NEEDED TO TREAT AT FIVE AND TWO YEARS.

| CAUSE | MEDICALLY TREATED GROUP | SURGICALLY TREATED GROUP | REDUCTION IN RISK | ABSOLUTE DIFFERENCE IN RISK | NO. NEEDED TO TREAT* | |
|---|---|---|---|---|---|---|
| | | | | | AT 5 YR | AT 2 YR |
| | percent | | | | | |
| Any stroke† | 11.0 | 5.1 | 54 | 5.9 | 17 | 67 |
| Large-artery stroke‡ | 6.6 | 3.1 | 54 | 3.5 | 29 | 111 |

*The number needed to treat is calculated as the reciprocal of the difference in risk. At two years, the number needed to treat is based on estimated differences in risk of 1.5 percent for stroke of any cause and 0.9 percent for large-artery stroke.

†The risk of stroke from any cause in the medical and surgical groups in the Asymptomatic Carotid Atherosclerosis Study is shown.[8]

‡The estimates of the risk of large-artery stroke were based on the observations that for subjects in the NASCET with 60 to 99 percent stenosis, the ratio of the risk of large-artery stroke to the risk of stroke from any cause in the territory of a symptomatic artery was similar in the medically and surgically treated subjects, and the risk of large-artery stroke was approximately 60 percent of the risk of stroke from any cause in the territory of an asymptomatic artery (i.e., 6.6 percent = 60 percent of 11.0 percent, and 3.1 percent = 60 percent of 5.1 percent).

cent, the rate of perioperative stroke and death were to reach 4 or 5 percent, endarterectomy would cause more strokes than it would prevent.

Although some centers report low rates of operative complications in asymptomatic patients, recent large multicenter studies report higher rates of perioperative stroke and death.[16-19] For example, among the 1512 patients who underwent endarterectomy for asymptomatic carotid stenosis in the Acetylsalicylic Acid and Carotid Endarterectomy (ACE) Trial, the 30-day rate of perioperative stroke and death was 4.6 percent.[18] The rate was 4.0 percent among the 350 asymptomatic patients in the prospective Toronto registry.[19]

The current perioperative mortality rate based on data from large programs, such as Medicare, ranges from 1.7 to 2.5 percent.[20] Morbidity due to stroke, which is not included in routine Medicare reports, is at least twice as high as the perioperative mortality rate. When stroke and death, the two most serious complications of endarterectomy, are combined, the perioperative risk can easily reach an unacceptable 5 percent or higher.

The marginal benefit expected from endarterectomy in the prevention of large-artery stroke is incongruent with the recommendation of the expert panel of the American Heart Association. This panel's guidelines include a "Grade A recommendation" of the use of endarterectomy in asymptomatic patients with 60 to 99 percent stenosis, provided the rate of perioperative stroke and death is less than 3 percent and life expectancy is at least five years.[21] A consensus panel of the National Stroke Association stated that endarterectomy cannot be recommended without assurance that the local risk associated with surgery is less than 3 percent.[22] At the time these recommendations were issued, neither consensus panel had information about stroke due to specific causes in asymptomatic patients.

The benefit of endarterectomy in symptomatic patients is less impressive when stenosis is less severe. A moderate benefit of surgery (an absolute difference in risk of 7 percent at five years) was found among patients in the NASCET who had symptomatic stenosis of 60 to 69 percent. By comparison, in the Asymptomatic Carotid Atherosclerosis Study, the absolute difference in risk at five years for patients with 60 to 69 percent stenosis was only 5.1 percent.[8] It seems paradoxical to recommend endarterectomy for asymptomatic patients with 60 to 69 percent stenosis on the basis of a projected clinically important benefit, when for symptomatic patients with the same degree of stenosis, as well as a much greater risk of subsequent stroke, the benefit was small.

In the medical literature, endarterectomy has been recommended for use only in carefully selected circumstances.[3,23-27] Some surgeons have modified the recommendations for asymptomatic patients and operate only when the stenosis is 80 percent or more but will consider endarterectomy for patients with lesser degrees of stenosis when the contralateral carotid artery is occluded.[16] The latter practice may not be advisable, since an increased risk of perioperative stroke and death (12.3 percent) was observed among asymptomatic patients in the ACE Trial when the contralateral artery was occluded (Fig. 4). An increased perioperative risk was also observed in patients with symptomatic stenosis and a contralateral occlusion. However, for patients with symptoms, despite the increased risk in the perioperative period, endarterectomy is beneficial in the long term.[28] For asymptomatic patients, the long-term benefit is unknown.

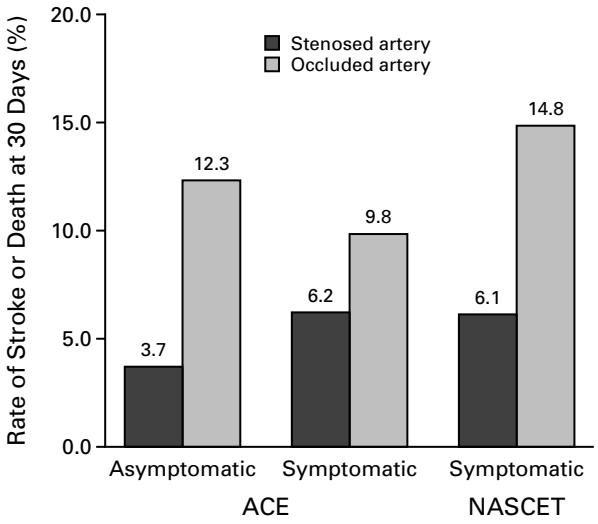


**Figure 4.** Rate of Perioperative Stroke and Death at 30 Days in Patients with Contralateral Occlusion as Compared with the Rate in Patients with Contralateral Stenosis.

Data are from surgically treated patients with either asymptomatic or symptomatic stenosis in the Acetylsalicylic Acid and Carotid Endarterectomy (ACE) Trial[18] and surgically treated symptomatic patients in the NASCET.[4] The numbers of patients represented in the bars are, from left to right, 1358, 154, 1210, 82, 1354, and 61. Three of 18 strokes in asymptomatic patients in the ACE Trial, 0 of 6 strokes in symptomatic patients in the ACE Trial, and 3 of 9 strokes in surgically treated symptomatic patients in NASCET occurred in the territory of the occluded artery.

The patients with asymptomatic arteries whom we followed in the present study were patients with a history of contralateral symptoms and were not simply persons from the community discovered by chance to have asymptomatic carotid stenosis. We recognized the possibility that the results might not be regarded as generalizable to other groups because of the particular sample of patients under study; we therefore compared our findings in these patients with available, detailed results from prospective studies of patients with asymptomatic arteries.[8,29-31] A striking sim-

ilarity was observed between the patients in our study and those in other studies in terms of risk factors, annual mortality rates (which ranged from 3.4 percent to 4.9 percent), and annual rates of stroke (from 2.2 percent to 3.2 percent). The observed homogeneity in results between our study and the other reported studies suggests that our observations are generally applicable to persons living in the community.

Our findings confirm previous reports that the risk of stroke rises with increasing degrees of asymptomatic carotid stenosis but remains much lower than in patients with symptomatic arteries.[29,32-36] In addition, we found, using angiography, that the risk of stroke in the territory of an asymptomatic artery peaks at very high degrees of stenosis and then decreases with near-occlusion. This phenomenon has previously been demonstrated in symptomatic patients.[37,38]

The conclusions of this study may be summarized as follows. The benefit attributable to endarterectomy should be calculated on the basis of the prevention of large-artery strokes. Approximately half the strokes that occur in the territory of an asymptomatic internal carotid artery are not of large-artery origin. Endarterectomy cannot prevent stroke of cardioembolic origin, and lacunar strokes are uncommonly of large-artery origin. The risk of stroke in the territory of an asymptomatic carotid artery is substantially less than the risk of stroke in the territory of a symptomatic artery with a similar degree of stenosis. The risk of stroke declines with near-occlusion (95 to 99 percent stenosis) of the carotid artery. Only 20 percent of patients were warned of impending stroke by a transient ischemic attack. The greatest risk of large-artery stroke appears to be among patients with the highest degrees of stenosis, a history of diabetes, the presence of a silent brain infarction beyond the asymptomatic lesion, or a combination of these factors. Physicians should closely monitor patients with asymptomatic carotid-artery lesions in order to supervise risk-factor management, detect and treat cardiac disorders, and identify early symptoms of cerebral ischemia.

Data from the present study do not rule out the possibility that there may be a subgroup of asymptomatic patients who will derive a clinically meaningful benefit from endarterectomy. Two major studies are under way that will add to our knowledge about the medical and surgical prevention of stroke in patients with asymptomatic carotid-artery disease.[39,40] Ideally, the cause of each stroke that occurs in these studies should be determined. When asymptomatic patients at the highest risk for large-artery stroke have been identified, a trial should be conducted to determine the efficacy of endarterectomy in this group. Meanwhile, the scales are tipped against the routine use of endarterectomy in patients who have no symptoms.

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