Causes and Severity of Ischemic Stroke in Patients With Internal Carotid Artery Stenosis

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OBSERVATIONAL STUDIES AND clinical trials generally have made little attempt to distinguish between stroke outcomes according to cause,[1,2] but this pattern is changing.[3-5] From the source documents of the North American Symptomatic Carotid Endarterectomy Trial (NASCET), all ischemic stroke outcomes were identified by cause (large artery, lacunar, and cardioembolic). The working hypothesis was that a stenosing arterial lesion should not be assumed to be the cause of all subsequent strokes originating from this site. In the age group at risk of arteriosclerotic stenosis, concomitant disease develops in other sites, including the heart and intracranial small arteries.

Identifying the causes of stroke among patients with carotid stenosis is certain to assist physicians and patients making decisions about the acceptability of a treatment program. Accordingly, the aims of this study were to determine (1) the risk and the proportion of large-artery, lacunar, and cardioembolic stroke in the territories of symptomatic and asymptomatic arteries; (2) the occurrence of the different causes of stroke in patients with varying degrees of carotid stenosis; (3) the influence of endarterectomy on the occurrence of dif-

For editorial comment see p 1479.

Context Therapeutic trials generally have not distinguished outcomes of stroke according to cause.

Objective To determine whether stroke and subsequent disability was of large-artery, lacunar, or cardioembolic origin in patients with different degrees of symptomatic and asymptomatic carotid stenosis.

Design Observational study of prospective data collected from the North American Symptomatic Carotid Endarterectomy Trial between 1987 and 1997.

Setting and Patients A total of 2885 patients from 106 sites in the United States and abroad (median age, 67 years; 70% male) who had symptomatic internal carotid artery stenosis.

Main Outcome Measure Risk of stroke from each of the 3 causes at 5 years by territory and degree of stenosis.

Results During an average follow-up of 5 years, 749 patients had 1039 strokes, including 112 of cardioembolic, 211 of lacunar, 698 of large-artery, 17 of primary intracerebral hemorrhage, and 1 of subarachnoid hemorrhage origin. The 5-year risk of first stroke after entry into the trial in any territory was 2.6% of cardioembolic cause, 6.9% of lacunar cause, and 19.7% of large-artery cause. The proportion of cardioembolic strokes in the territory of the symptomatic artery was 12.0% and 6.9% in 60% to 69% and 70% to 99% arterial stenosis, respectively; large-artery strokes predominated (78.4%) at 70% to 99% arterial stenosis. With 70% to 99% arterial stenosis, the proportion of strokes of cardioembolic and lacunar origin was 43.5% and 21.6% in asymptomatic and symptomatic arteries, respectively. A total of 67.6% of cardioembolic, 16.7% of lacunar, and 33.0% of large-artery strokes in the territory of the asymptomatic artery were disabling or fatal.

Conclusions Our data suggest that approximately 20% and 45% of strokes in the territory of symptomatic and asymptomatic carotid arteries with 70% to 99% stenosis, respectively, are unrelated to carotid stenosis. The cause of subsequent strokes in similar types of patients should be considered when making treatment decisions involving carotid endarterectomy for patients with asymptomatic carotid stenosis, since lacunar and cardioembolic strokes cannot be prevented by endarterectomy.

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ferent causes of stroke; and (4) the level of disability of stroke related to cause.

The present study reports data gathered from the long-term follow-up of 2885 patients with symptomatic carotid artery stenosis, half of whom received carotid endarterectomy and half of whom received medical care alone.

METHODS

NASCET confirmed the efficacy of carotid endarterectomy in reducing the risk of stroke and death in patients who experienced a transient ischemic event

or nondisabling stroke and who had 70% to 99% stenosis of the ipsilateral carotid artery.[6] The benefit was re-

duced for those with 50% to 69% stenosis.[7] Patients with less than 50% stenosis did not benefit. Patients in NASCET differed from other patients with stroke in several large registries[4,8-12] and reviews.[13,14] Individuals with cardiac conditions likely to produce cardioembolism, including atrial fibrillation (AF), recent myocardial infarction (MI), unstable angina, dilated cardiomyopathy, recent congestive heart failure, and valvular disease prone to the production of emboli, were excluded from the trial.

In total, 2885 patients with symptomatic internal carotid artery stenosis were randomly assigned from December 1987 to December 1996 to undergo endarterectomy or receive medical management alone. The average follow-up was 5 years. In patients with hypertension, diabetes mellitus, and hyperlipidemia, best contemporary treatment was administered and centrally monitored. Cigarette smoking was discouraged. Enteric-coated aspirin was recommended for all medical and surgical patients throughout the trial. In the event of recurrent ischemic events despite aspirin use, other platelet inhibitors or anticoagulants were permitted at the discretion of the treating physician.

Initial assessment included standardized history taking, history taking and examination for cardiovascular symptoms or disorders, neurological examination, laboratory tests, 12-lead electrocardiogram, chest radiograph, cross-sectional imaging of the brain (usually computed tomography), angiography, and duplex ultrasonography of the carotid arteries. Study neurologists in the participating centers performed medical, neurological, and functional status assessments on all patients at entry; at 1, 3, 6, 9, and 12 months; every 4 months thereafter; and at the time of any stroke. Cardiology consultations were requested by treating physicians when a cardioembolic origin of stroke was suspected.

All strokes and deaths were assessed at 4 levels: by the participating neurologist and surgeon at each center, by staff neurologists at the data center, by the outcomes committee (consisting of an internist, neurologists, surgeons, and methodologists), and by external adjudicators. Among all strokes, a distinction in territory was made among those on the same side as the recently symptomatic randomized artery (ipsilateral), those on the opposite side (contralateral), and those in the vertebrobasilar circulation. The severity (using a modified Rankin scale at 90 days to determine stroke disability) and type of stroke (hemorrhagic or ischemic) were assigned. A stroke was considered to be disabling if the Rankin score was 3 or greater.

Table. NASCET Classification of 112 Cardioembolic Strokes by Clinical and Transthoracic Echocardiographic Risk Factors*

	No. of Strokes
Classified as possibly due to	
Nonvalvular atrial fibrillation with 2 of the following risk factors[16-20]:	17
History of hypertension[21] (blood pressure ≥160/90 mm Hg)	10
Recent congestive heart failure†	2
Regional/global left ventricular dysfunction	0
Left ventricular hypertrophy (by TTE)	4
Left atrial enlargement (>4 cm by TTE)	1
Age, y	
65-75	8
≥75	9
Regional/global left ventricular dysfunction[10,12,17,22-25]	37
Acute myocardial infarction (within 3 months but excluding acute anterior myocardial infarction <3 weeks)[22]	5
Left ventricular thrombus[22,23,26-28]	0
Left ventricular aneurysm[29]	0
Other (patent foramen ovale [2], anticardiolipin antibody and history of myocardial infarction [1])	3
Subtotal	**62**
Classified as probably due to	
Nonvalvular atrial fibrillation with ≥3 of the following risk factors:	21
History of hypertension (blood pressure ≥160/90 mm Hg)	19
Recent congestive heart failure†	11
Regional/global left ventricular dysfunction	12
Left ventricular hypertrophy (by TTE)	5
Left atrial enlargement (>4 cm by TTE)	11
Age, y	
65-75	11
≥75	9
Nonvalvular atrial fibrillation with left atrial thrombus	1
Mitral stenosis plus atrial fibrillation	0
Deteriorated bioprosthetic mitral valve plus atrial fibrillation	0
Mechanical mitral valve	1
Bacterial endocarditis with vegetations	0
Verrucose endocarditis with terminal cancer	1
Acute anterior myocardial infarction (within 3 weeks)[13,22]	6
Myocardial infarction with echocardiographic evidence of thrombus[13,22]	0
Left ventricular aneurysm with echocardiographic evidence of thrombus	2
Cardiac surgery (occurrence during or shortly after the procedure)	11
Cardiac catheterization or PTCA (occurrence during or shortly after the procedure)	6
Left atrial thrombus	0
Temporally proximate systemic embolism	1
Subtotal	**50**

*NASCET indicates North American Symptomatic Carotid Endarterectomy Trial; TTE, transthoracic echocardiogram; and PTCA, percutaneous transluminal coronary angioplasty.
†Identified by dyspnea or peripheral edema with radiographic evidence of cardiac enlargement and pulmonary edema.

All ischemic strokes, including those within 30 days of endarterectomy, were designated as to cause: large artery, lacunar, or cardioembolic. Outcomes were evaluated for other potential uncommon stroke causes. Each stroke was categorized as having 1 etiology only. Strokes not clearly lacunar or cardioembolic in origin were categorized as large-artery strokes. Because all patients entered the trial with symptoms or signs associated with a putative ischemic event of large-artery origin, no strokes were expected to be assigned to an "unknown" cause, and none were.

Lacunar strokes were defined by a combination of clinical and radiological criteria: patients presenting with primary motor, primary sensory, or sensory-motor symptoms; the dysarthria–clumsy hand syndrome or the ataxia-hemiparesis syndrome; and with and without radiologically deep white matter lesions or basal ganglia lesions no more than 1 cm in diameter.[15]

Cardioembolic strokes were identified by a combination of clinical and echocardiographic features. Single or combined cardiac risk factors considered to be indicative of a cardiac source for an embolic event were tabulated (**TABLE**). The guidelines for this classification were consistent with several reports.[13,16-20,22-24,30,31] Each cardioembolic stroke was designated as possible or probable. Criteria influencing these 2 assignments were the number of associated risk factors (in AF), the time relationship (in MI and invasive cardiac procedures), the location of the cardiac abnormality (in MI and intracavitary thrombus), and the characteristics of the associated clinical condition (in cardiac valvular abnormality).
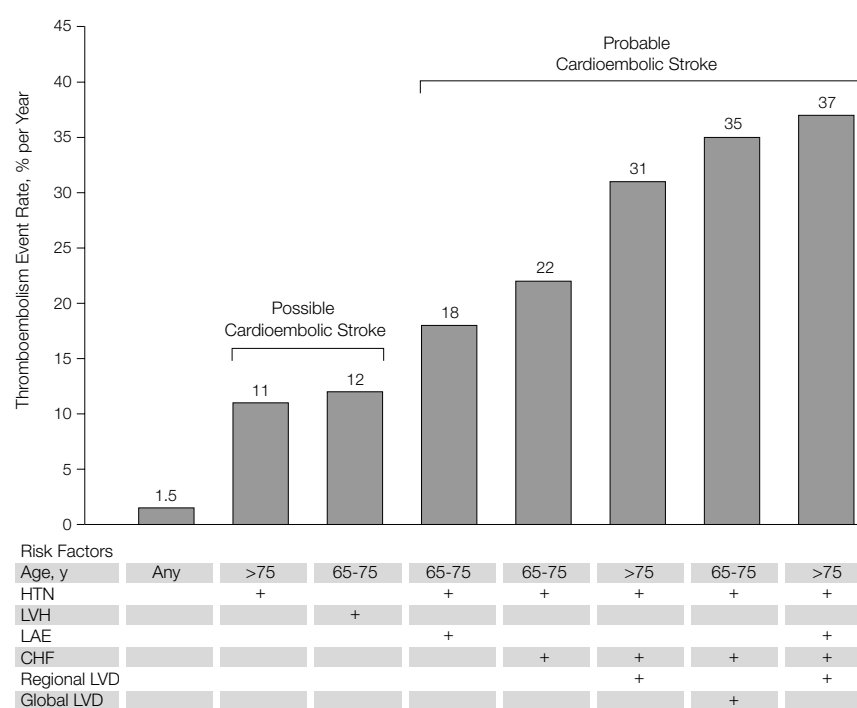
In nonvalvular AF (NVAF), the event rates for thromboembolism, derived from multiple clinical and echocardiographic risk factors, provided the basis for postulating a possible or probable cardiac source (**FIGURE 1**).[16-18] Strokes in patients with NVAF who had 2 cardiac risk factors were designated as possible cardioembolic. These patients are predicted to have an annual cerebral thromboembolism event rate of 11% to 12%, based on the sum of event rates for 2 risk

factors.[16-18] This is approximately 8 times higher than for NVAF patients without cardiac risk factors (1.5% rate).[18] When 3 or more cardiac risk factors were identified, the stroke was designated as probable cardioembolic. Nonvalvular AF in the presence of 3 or more risk factors carries a considerably greater risk of thromboembolism (18%-37%) based on the sum of event rates for 3 or more risk factors.[16-18] This is compared with the 4% annual rate for large-artery stroke observed in symptomatic NASCET patients and the 2% annual rate observed in Asymptomatic Carotid Atherosclerosis Study patients.[32] Because of such a marked discrepancy in the risk of thromboembolism between high-risk NVAF and large-artery lesions, it was appropriate to select AF as the cause of the stroke. No distinction was made between paroxysmal and established AF.[18]

Patients with lone AF were not classified as having a cardioembolic stroke.

When a cardioembolic cause appeared likely and required further clarification, transthoracic echocardiograms (TTEs) were requested by the outcomes committee if these studies had not already been obtained by the attending neurologist or the consultant cardiologist. Transthoracic echocardiograms were not always requested when AF developed or an acute Q-wave electrocardiogram was present in the setting of clinical findings and enzyme changes consistent with MI. Transesophageal echocardiography, refined in the closing years of the study, was available for only a few patients. Left ventricular dysfunction was described qualitatively as regional/local akinesia or dyskinesia or global dysfunction. Left ventricular function was

Figure 1. Predicted Annual Thromboembolic Event Rates Based on SPAF Publications[16,17] for Selected Combinations and Number of Cardiac Risk Factors of NASCET Patients With Nonvalvular Atrial Fibrillation

Risk Factors							
Age, y	Any	>75	65-75	65-75	65-75	>75	65-75	>75
HTN		+		+	+	+	+	+
LVH			+					
LAE				+				+
CHF					+	+	+	+
Regional LVD						+		+
Global LVD							+	

SPAF indicates Stroke Prevention in Atrial Fibrillation trial; NASCET, North American Symptomatic Carotid Endarterectomy Trial; plus sign, risk factor present; HTN, history of hypertension; LVH, left ventricular hypertrophy; LAE, left atrial enlargement; CHF, congestive heart failure; and LVD, left ventricular dysfunction. Data are displayed using the method illustrated by Rosenthal and Halperin.[45] Twenty-five of 39 cardioembolic strokes caused by nonvalvular atrial fibrillation were associated with the risk factor combinations listed along the horizontal axis.

assessed by TTE at participating centers by echocardiographers who reported on left ventricular segment wall motion abnormalities, global left ventricular dysfunction, and ejection fraction measurements. Left ventricular hypertrophy was based on the echocardiographic diagnosis.

Potential cardioembolic strokes identified by the outcomes committee were separately adjudicated by the study cardiologist (R.W.G.), blinded to patient treatment category and severity of carotid disease, using the template in the Table. Six months later, the same cardiologist, again blinded, reviewed a random sample of 45 strokes, deliberately including some already designated as noncardiac in origin. His intraobserver κ was 0.96. A second cardiologist, also blinded, reviewed these outcome events and the interobserver κ was 0.72.

The risk of each cause of stroke at 5 years in the medically treated and surgically treated groups by territory (ipsilateral, contralateral, or vertebrobasilar) and by degrees of carotid artery stenosis were estimated from Kaplan-Meier event-free survival curves. For the purpose of correctly ascribing strokes to medical or surgical therapy, the risk analyses censored patients at the time of crossover to the alternate therapy from their assigned treatment group at baseline. The risk analyses counted only the first stroke of each cause in each territory.

The risk of each cause of stroke in the territory of an asymptomatic carotid artery was also estimated in the subgroup of 1820 patients who had an asymptomatic stenosed carotid artery on the contralateral side. The artery was regarded as asymptomatic if there was no recent or remote history of symptoms or physical signs in the territory of that artery. Presence of a lesion on a computed tomography scan in the absence of symptoms or signs was considered to be asymptomatic. The risk analyses censored data at the time of carotid endarterectomy for individuals who subsequently had surgery on the side of the asymptomatic artery.

In a further analysis, the risks of disabling and nondisabling stroke of each cause, ipsilateral to the symptomatic and asymptomatic carotid territories, were estimated from Kaplan-Meier event-free survival curves.

RESULTS

Baseline characteristics of patients in NASCET were previously reported.[6,7] In brief, the median age was 67 years and 70% were men. There was a recorded history of hypertension (61%), diabetes mellitus (22%), hyperlipidemia (34%), smoking within the past year (42%), and prior MI or angina (36%). Spanning the duration of the trial, a total of 1039 strokes (1021 ischemic, 17 primary intracerebral hemorrhage, and 1 subarachnoid hemorrhage) involving any territory occurred in 749 of 2885 patients in the NASCET. Recurrent strokes in the same patient did not always originate from the same cause. Cardioembolic origin accounted for 112 (10.8%) of the strokes occurring in 95 patients, lacunar strokes were identified 211 times (20.3%) in 184 patients, and large-artery disease strokes occurred 698 times (67.2%) in 542 patients.

Causes of Cardioembolic Strokes

Among the 95 patients who had cardioembolic strokes, 80 had 1 stroke, 13 had 2 strokes, and 2 had 3 strokes. Sixty-two cardioembolic strokes were designated possible and 50 probable. Echocardiograms were performed in 64 events (57.1%).

The most frequent cause was NVAF, identified in 39 of the 112 cardioembolic strokes (34.8%) (Table). Twenty-two strokes were assigned to the probable category and 17 to the possible category. Of the 39 strokes occurring in 34 patients who developed AF, 5 patients were taking anticoagulants prior to the event and 12 others began taking long-term anticoagulants after the event. During follow-up, another 195 patients developed NVAF without experiencing a stroke, 56 of whom were given anticoagulants.

Regional/global left ventricular dysfunction based on TTE findings at the time of the outcome event was deemed to be due to ischemia and classified as a possible cause in 37 (33%) of 112 strokes. Excluding left bundle-branch block in 4 patients, 23 of the 33 remaining strokes were associated with significant electrocardiographic Q waves recorded at the time of or prior to the outcome event, strongly suggesting transmural MI. Three strokes involved patients with previous coronary artery bypass graft; 20 (54%) had a remote history of MI.

Acute MI was associated with 11 cardioembolic strokes. In 6 patients with acute anterior MI, a probable cause was assigned. The strokes occurred within 3 weeks of the infarction. A possible cause was assigned in 5 other patients when the stroke occurred within 3 months of the infarction.

Invasive cardiac procedures were identified as the probable cause of 17 strokes occurring within 24 hours of the procedure. Eleven followed cardiac surgical procedures, coronary artery bypass graft, or aortic valve replacement, and 6 followed catheterization procedures, coronary angiography, and/or percutaneous transluminal angioplasty.

Other cardiac risk factors for probable and possible strokes of cardioembolic origin are listed in the Table.

Analysis of Stroke Risk

Of the 1021 ischemic strokes, 727 remained in the risk analyses after accounting for crossovers, first occurrence, and the 5-year period. The 5-year risk of a cardioembolic stroke in any territory was 2.6% (95% confidence interval [CI], 2.0%-3.4%), approximately one third the risk of lacunar stroke (6.9%) and one seventh the risk of large-artery stroke (19.7%) (**FIGURE 2**, top). Cardioembolic strokes in any territory occurred equally in medically and surgically treated patients (2.6%). Patients were at reduced risk of all causes of stroke in the contralateral and vertebrobasilar territories.

The proportion of each cause of stroke was calculated using data from all 1021 ischemic strokes. Thirty percent of all strokes were not of large-artery origin, irrespective of treatment group and territory (Figure 2, bottom).

Cardioembolic strokes occurring on the side of the randomized artery (ipsilateral to symptoms) accounted for 8.5% and 9.9% of all strokes in the medical and surgical groups, respectively.

In medically treated symptomatic patients, the risk of an ipsilateral large-artery stroke increased as expected with severity of stenosis (**FIGURE 3**, top). The risk of lacunar and cardioembolic strokes did not rise with increasing stenosis. In the territory of an asymptomatic artery, there was a lower risk of all causes of stroke (Figure 3, top). The risk of large-artery stroke increased with the degree of stenosis, but even in the 70% to 99% stenosis category, it only reached about one third of that in the symptomatic artery. Cardioembolic strokes did not increase in the presence of increasing stenosis in the asymptomatic artery. The risk of lacunar strokes increased moderately.

For symptomatic arteries with severe (70%-99%) stenosis, the highest proportion of strokes were of large-artery origin (78.4%) (Figure 3, bottom). Of all strokes in the territory of a symptomatic 70%- to 99%-stenosed artery, 21.6% were cardioembolic or lacunar in origin (6.9% + 14.7%, respectively). At lesser degrees of stenosis, although large-artery strokes still predominated, the proportion of lacunar and cardioembolic strokes was higher than in the territory of a 70% to 99% stenosis.

For asymptomatic arteries, the proportion of strokes of combined lacunar and cardioembolic origin accounted for one third to nearly half of strokes (Figure 3, bottom). The proportion of lacunar and cardioembolic strokes in the territory of the asymptomatic artery was somewhat higher in subjects with greater degrees of stenosis. Of all strokes on the asymptomatic 70%- to 99%-stenosed side, 43.5% (8.7% + 34.8%, respectively) were of cardioembolic or lacunar origin.

The 5-year risks of disabling and nondisabling strokes in the territory of a symptomatic carotid artery for medically treated and surgically treated patients are shown in **FIGURE 4**, top. The risk of stroke of any degree of disability was highest in medically treated pa-

tients whose strokes were attributed to large-artery disease (11.0% nondisabling and 5.6% disabling). The risks of disabling stroke due to lacunar and cardioembolic causes were only 0.2% and 1.2%, respectively. The 5-year risk of stroke by cause in the territory of asymptomatic arteries is shown in Figure 4, top. The reduced risk of large-artery stroke compared with the territory of a symptomatic artery is shown, as are the equal risks of cardioembolic and lacunar strokes.

The proportion of ipsilateral stroke by cause and disability was calculated (Figure 4, bottom). About 51% (25.8% + 25.8%) of the cardioembolic strokes in the territory of a symptomatic ar-

Figure 2. Kaplan-Meier Risks at 5 Years and Proportions of Each Cause of Stroke by Territory and Assigned Treatment Group
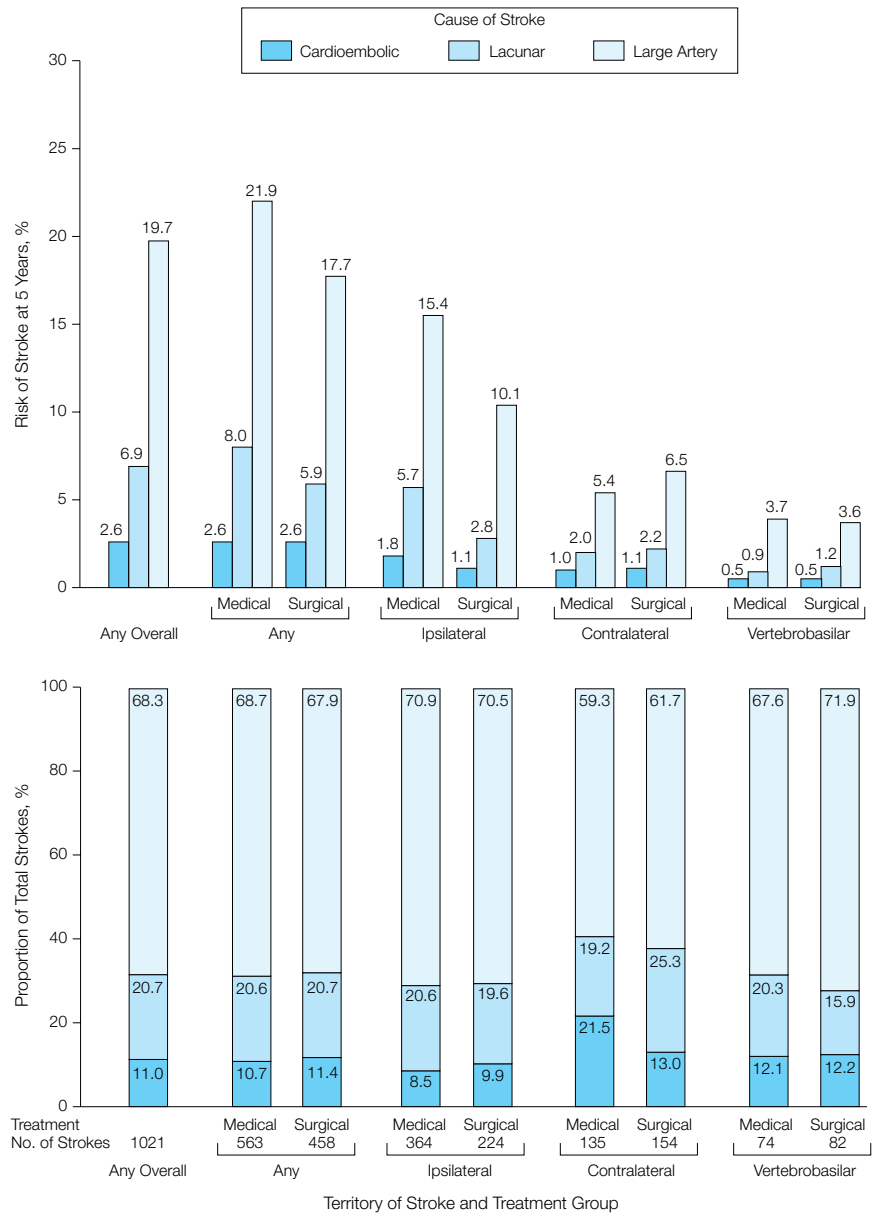
The overall number of patients analyzed was 2885 (medically treated patients, 1449 and surgically treated patients, 1436).

tery in medically treated patients were disabling. The proportion of disabling strokes of lacunar cause was substantially lower (4%). None were in the most severe or fatal categories. The proportion of disabling or fatal large-artery strokes was 33.7% (19.8%+ 13.9%, respectively).

Similarly, in the territory of an asymptomatic artery, strokes that were disabling or fatal were more common with cardioembolic cause (67.6%) than disabling strokes of lacunar (16.7%) or large-artery (33.0%) cause (Figure 4, bottom). In the territory of an asymptomatic artery, more lacunar strokes

had no disability (Rankin score of 0) at 90 days than was observed in strokes of cardiac or large-artery origin.
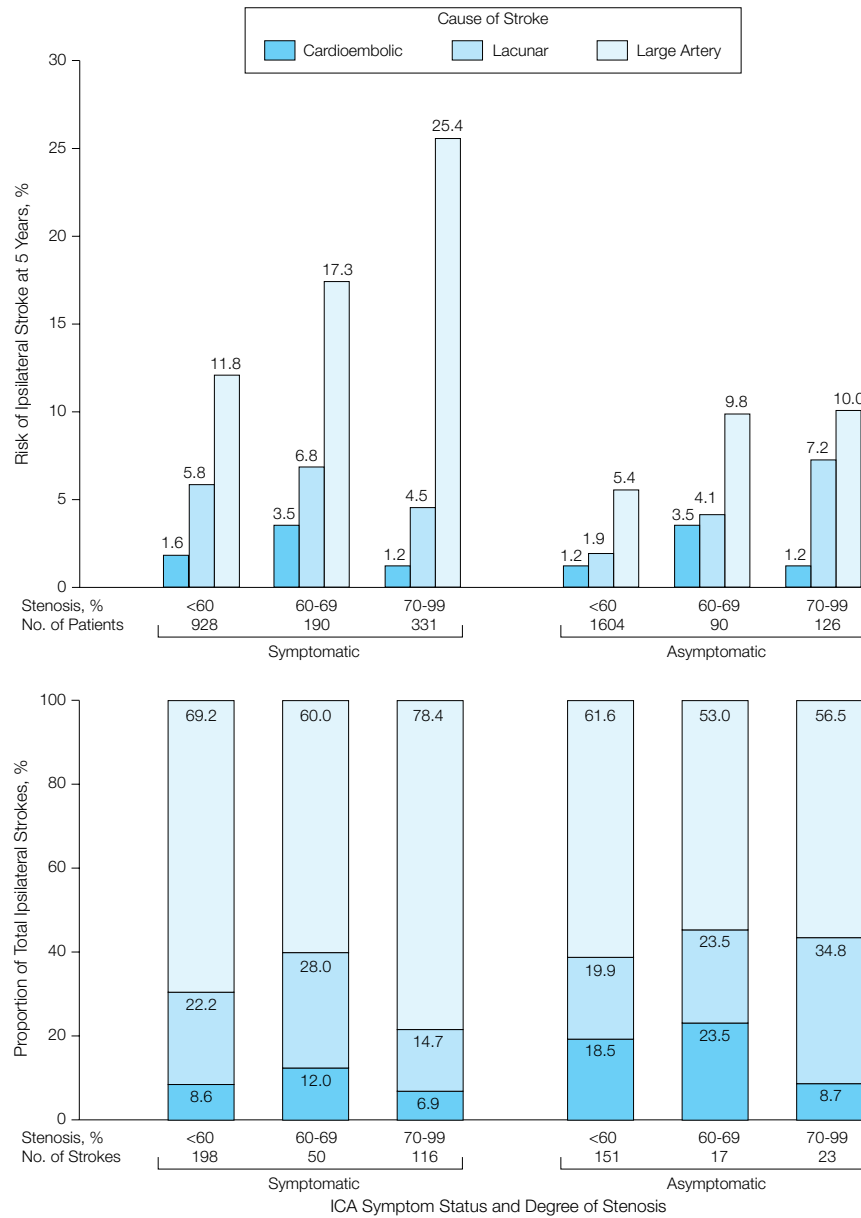
COMMENT

The results of this study demonstrate that even in the presence of large-artery lesions, strokes arise from a variety of causes. To our knowledge, no previous large trials or case-series of carotid endarterectomy have attempted to assign the proportion of subsequent strokes by cause. This omission may be of critical consequence, considering that subsequent strokes arising from cardiac or aortic sources and the penetrating arteries of the brain (producing lacunes) are not likely to be prevented by an operative procedure (endarterectomy) that is not expected to eradicate these potential causes.

Although previous data bank and case-series studies have examined the relative disability of strokes by cause,[34-39] the disability imposed by the various causes of stroke had not been addressed in patients with proven carotid artery disease. The present study shows that strokes of cardioembolic origin account for the highest proportion of disabling strokes. Strokes of lacunar origin are least disabling, and those attributable to large arteries have a disability between strokes of cardioembolic origin and lacunar origin, whether the subsequent strokes were in the territory of the symptomatic artery or the asymptomatic artery.

Cardiogenic stroke was diagnosed less often in this trial than in large case-series and data banks. Stroke data banks have identified cardiac causes in 15% to 20% of strokes,[9-11,40-42] whereas in NASCET, the proportion was lower at 10.8%. This finding is attributable to exclusion from entry in NASCET of patients with cardiac diseases known to be a source of embolism. These patient-selection criteria imply that the observations from the present study cannot be generalized to all patient populations with carotid stenosis but are applicable to patients being considered for carotid endarterectomy in whom serious cardiac conditions were judged to be a barrier to the procedure. The proportion of cardioembolic events in this study may only be half that occurring in patients

Figure 3. Kaplan-Meier Risks at 5 Years and Proportions of Each Cause of Stroke for Medically Treated Patients by Symptom Status of the ICA and Degree of Stenosis

ICA indicates internal carotid artery. Cut points at 60% and 70% stenosis correspond to the current American Heart Association guidelines for recommending carotid endarterectomy to asymptomatic and symptomatic patients, respectively.[33]

commonly undergoing endarterectomy in community practice.

Not surprisingly for this population of patients with a median age of 67 years, NVAF developing after randomization headed the list of probable causes of cardioembolic stroke. Atrial fibrillation becomes more common with increasing age, affects 2 million people in the United States in any given year, causes 36% of strokes among patients older than 80 years, and increases stroke risk 6-fold.[43,44] Two large stroke registries have identified AF as the most common risk factor for cardioembolic stroke.[10,12] Anticoagulant therapy (for which benefit has been proven since NASCET began) was administered to only about one quarter of these patients, but should be recommended more frequently in the future.

The second most common risk factor identified was regional/global left ventricular dysfunction. Both left atrial thrombi and left ventricular thrombi as cerebral embolic sources have been associated with left ventricular wall motion abnormalities[23] and left ventricular dysfunction,[24,25] with and without AF.[21,23-29,45]

In addition to NVAF, cardiac sequelae of atherosclerosis developed in NASCET subjects, including symptomatic coronary heart disease, MI, and congestive heart failure, in some cases requiring invasive therapeutic interventions. All these factors are known to have potential for the formation or dislodgement of aortic, atrial, and ventricular thrombi or atheromatous fragments causing embolic stroke.

Among ipsilateral strokes in symptomatic patients with 70% to 99% stenosis, a small proportion (6.9%) were of cardioembolic origin. By contrast, patients with moderate (60%-69%) symptomatic stenosis had 12.0% of their strokes from cardiac sources. The proportion of lacunar and cardioembolic strokes (approximately 35%) in symptomatic patients with less than 70% stenosis was approximately twice that observed in patients with 70% to 99% stenosis. This proportion of strokes not caused by large-artery lesions must be weighed in any decisions about endarterectomy for patients with only moderate stenosis.

Of strokes occurring in the territory of the asymptomatic artery, the proportion of large-artery origin was less than in the territory of the symptomatic artery, particularly in the presence of severe stenosis. For patients with asymptomatic arteries with 60% to 99% stenosis (the range of stenosis believed to benefit from endarterectomy), nearly half of strokes were from the small vessels or the heart.

CONCLUSIONS

Disorders of the heart and small penetrating arteries are important causes of stroke, even in the presence of stenosing arteriosclerotic extracranial carotid lesions. Non-

Figure 4. Kaplan-Meier Risks at 5 Years and Proportions of Disabling and Nondisabling Stroke by Assigned Treatment Group and Cause in the Territory of a Symptomatic and Asymptomatic Carotid Artery
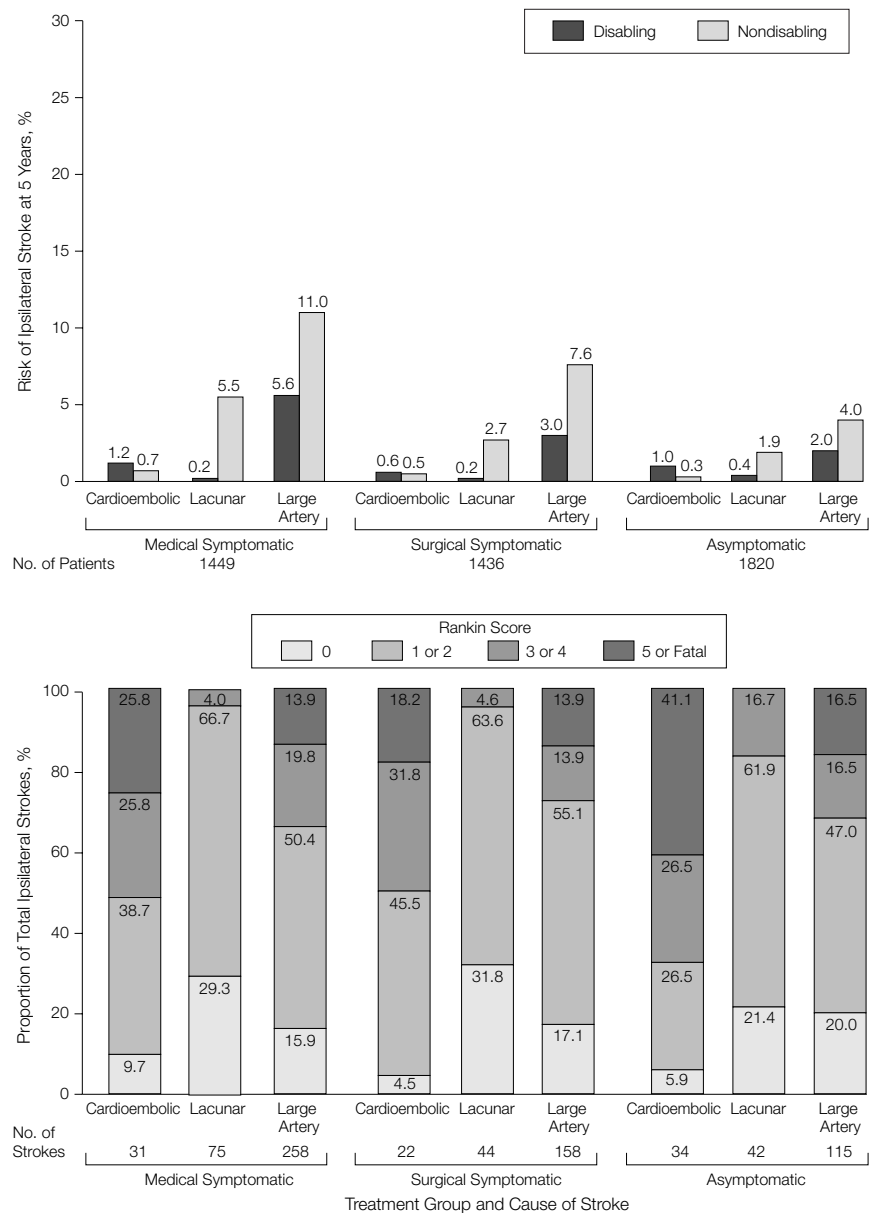
A Rankin score of 3 or more is considered a disabling stroke; a Rankin score of less than 3 is considered a nondisabling stroke.

valvular AF and the consequences of myocardial ischemia account for most of the strokes of cardiac origin. The risk and proportion of cardioembolic stroke outcome events in this group of patients with symptomatic carotid artery disease was similar in the medically and surgically treated patients. Surgical treatment of the diseased artery would not be expected to reduce the later occurrence of cardioembolic stroke and did not. Strokes of cardioembolic origin were more commonly disabling or fatal compared with those that arose from the large or small arteries.

Approximately 35% of strokes occurring subsequently in symptomatic patients with moderate carotid disease (<70% stenosis) were due to causes other than the large-artery lesion. Approximately 50% of strokes occurring in the territory of the asymptomatic artery with 60% to 99% stenosis were not of large-artery origin.

Expectations of benefit from endarterectomy in symptomatic patients with moderate disease or in asymptomatic subjects must consider the evidence that a large number of future strokes will not be related to the carotid artery lesion. The risk of stroke expected from the large-artery lesion is only part of the story. In patients with carotid stenosis suspected of causing ischemic events, risk factors must be modified. Before deciding on the final treatment strategy, consideration should be given to investigations to identify other potential causes (eg, cardiac, aortic, lacunar, prothrombotic hematological conditions) of stroke.

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