Long-Term Clinical and Angiographic Outcomes in Symptomatic Patients With 70% to 99% Carotid Artery Stenosis

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Background and Purpose—In 1991, the North American Symptomatic Carotid Endarterectomy Trial (NASCET) reported the benefit of carotid endarterectomy for 659 patients with 70% to 99% stenosis. Follow-up continued until 1997.

Methods—The present study examined the risks and causes of ipsilateral stroke in the randomized groups and in those who had delayed endarterectomy or continued on medical therapy and also examined the evolution of carotid disease on follow-up imaging.

Results—By on-treatment (efficacy) analysis, the risk of any ipsilateral stroke at 3 years was 28.3% for medically randomized and 8.9% for surgically randomized patients (19.4% absolute risk reduction, \( P < 0.001 \)). For combined disabling or fatal ipsilateral stroke, the risks were 14.0% and 3.4%, respectively (10.6% absolute risk reduction). In medical patients, >80% of the first strokes at 3 years were of large-artery origin. After February 1991, 116 suitable medical patients underwent endarterectomy within 6 months, and 115 continued on medical therapy. The 3-year risk of any ipsilateral stroke in the groups of 116 and 115 patients was 7.9% and 15.0%, respectively (7.1% absolute risk reduction). During follow-up, 81 patients had angiograms comparable to the baseline images. Progression by \( \geq 10\% \) occurred in 7 patients; regression, in 8; no change, in 39; and occlusion, in 27. By use of both angiography and ultrasound, 63 (25.5%) of the 247 medically treated patients progressed to occlusion, of whom 31.7% had an ipsilateral stroke before or on the day of occlusion.

Conclusions—Endarterectomy for patients with 70% to 99% stenosis and recent symptoms was efficacious in the long term. Compared with patients who continued on medical therapy, medical patients with delayed endarterectomy experienced a moderate benefit. Medically treated patients experienced a high risk of occlusion. (Stroke. 2000;31:2037-2042.)

Key Words: carotid stenosis ■ cerebral ischemia ■ endarterectomy ■ occlusion

On February 21, 1991, the North American Symptomatic Carotid Endarterectomy Trial (NASCET) reported in a clinical alert that endarterectomy was highly beneficial for symptomatic patients with severe (70% to 99%) internal carotid artery (ICA) stenosis, and randomization for these patients was stopped.¹ By intention-to-treat analysis, the risk of any ipsilateral stroke at 2 years was 26% for the 331 patients who received medical care alone compared with 9% for the 328 patients who received medical care plus endarterectomy.² The absolute risk reduction in stroke risk in favor of endarterectomy was 17%, with a relative risk reduction of 65%. Immediately after the clinical alert, endarterectomy was recommended for the patients randomized to the medical arm, provided that they were still suitable candidates for the procedure. All patients continued to be followed for an additional 7 years, and the present study examined the outcome events and evolution of stenosis in these patients.

Subjects and Methods
The severe stenosis phase of NASCET was conducted at 50 medical centers across North America. Randomization began in December 1987, and follow-up ended in December 1997. Patients with severe stenosis at the carotid bifurcation and ipsilateral transient ischemic attack or nondisabling stroke were recruited if their focal symptoms had occurred within 120 days before entry. No cardiac source of potential embolism was identified. Other exclusion criteria included age >80 years, angiographic evidence of an intracranial lesion that was more severe than the extracranial lesion, and life-threatening or other disabling conditions. NASCET

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required multplanar, anteroposterior, lateral, and oblique selective angiography of the randomized ICA at entry. Hard copies of all angiograms were sent to the central office and were reviewed by the principal neuroradiologist, who used previously described methods.3 Full details of the study protocol have been published elsewhere.4 Before February 1991, follow-up for severe stenosis patients consisted of clinic visits every 4 months. After February 1991, patients were followed up with annual clinic visits and telephone assessments twice a year, and an annual carotid ultrasound study was required. When a stroke occurred, a clinic visit was required. All patients were supplied with enteric-coated aspirin, and when indicated, antihypertensive, antilipidemic, and antidiabetic therapies were prescribed.

The primary outcome event for the trial was any fatal or nonfatal stroke ipsilateral to the randomized carotid artery. Secondary outcomes included strokes in any territory and any death. All strokes and deaths were centrally reviewed by the blinded NASCET Outcomes Committee and then by a group of independent blinded external adjudicators. Ischemic strokes were assigned to a single underlying cause (large artery, lacunar, or cardioembolic) and to level of disability. Lacunar strokes were defined by a combination of symptoms or signs and radiological criteria.5 The criteria for cardioembolic strokes have been reported elsewhere.6 Strokes not clearly lacunar or cardioembolic in origin were categorized as large-artery strokes. Disabling strokes were defined as having a Rankin score of ≥3 at 90 days after the onset of symptoms. The results of the present study are presented in 3 parts.

Part 1 reports an on-treatment (efficacy) analysis for the risk of ipsilateral stroke at 6 months and at 1, 2, and 3 years after randomization in both the medical and surgical groups as well as at 8 years for the surgical group. To achieve an on-treatment analysis, data were censored in the medical arm at the time the patient had endarterectomy on the randomized ICA during follow-up. Risk estimates were derived from Kaplan-Meier event-free survival curves and were compared for statistical significance by using a log-rank test. The Kaplan-Meier analyses also counted all deaths and any strokes (regardless of location) that occurred during the 30-day perioperative period for patients who had carotid endarterectomy and a comparable 32-day period after randomization for the patients treated medically. Comparison between treatment groups was restricted to a 3-year time period, because approximately one half of the medically assigned patients underwent surgery after February 1991, leaving a smaller number of patients in the medical arm for long-term follow-up. Unlike the previous analysis of patients with severe symptomatic stenosis,2 the present study also examined the cause and severity of first stroke after randomization in relation to 2 categories of severe stenosis: 70% to 84% and 85% to 99% stenosis. In addition, the risk and cause of ipsilateral stroke after carotid artery occlusion were examined.

Part 2 reports on the risks and benefits of endarterectomy for the medically treated patients in whom the procedure was delayed until the benefit for severe stenosis was reported by the clinical alert in February 1991. Vascular risk factors were reexamined in patients who underwent endarterectomy within 6 months of the clinical alert (delayed endarterectomy group) and were compared with those who were, at the time, eligible for surgery but opted to remain under best medical care (continuing medical group). Estimates of ipsilateral stroke risk at 3 years were derived in a manner identical to that in part 1, except that time zero for patients who underwent endarterectomy was the day of surgery, whereas the date of the clinical alert was used for those who continued on medical treatment.

Part 3 reports the evolution of carotid artery disease on follow-up imaging. Baseline and follow-up angiograms were reviewed to assess changes in the baseline degree of stenosis when patients were randomized to best medical care. Only follow-up angiograms with views and angles comparable to the baseline examination were considered, except in the case of occlusion. Angiograms after endarterectomy were not included in this study. Change in stenosis was classified into 4 categories: progression of ≥10%, <10% change, and regression to occlusion. An important change between a baseline and follow-up angiogram was defined as an occlusion, or an increase or decrease of 10% in the degree of stenosis. This level of change was chosen because it is outside the range of measurement error7 and because meaningful increments in stroke risk occur between decile levels.8

In the evaluation of the ICA progression to occlusion, additional data were also obtained from ultrasound follow-up examinations for patients who did not have a comparable follow-up angiogram. The vast majority of the ultrasound transducers used were in the 5-MHz range, and almost all the recordings were made at a reasonably standard angle of 60°. Occlusion was defined as an absence of flow in the ICA at the level of bifurcation.

Results

Clinical follow-up to the end of December 1997 was available for 99% of the 659 patients. Four patients were lost to follow-up after an average follow-up of 4 years. The baseline patient characteristics between the randomized surgical and medical groups were similar and are shown as a single column in the Table. The mean follow-up time was 3.6 years for the medical group (censored at the time of ipsilateral carotid endarterectomy) and 7.0 years for the surgical group.

### Part 1: On-Treatment Analysis for Risk of Ipsilateral Stroke

For part 1, the risk of any ipsilateral stroke and of combined disabling or fatal ipsilateral stroke at different time periods during follow-up is shown in Figure 1A. Benefit from surgery was attained shortly after the operation. A 38% relative reduction in ipsilateral stroke risk was observed at 6 months. Over the next 3 years, there was a marked increase in the cumulative risk of stroke for medically treated patients, but only a marginal increase for those treated surgically. The absolute risk reduction at 3 years was 19.4% (69% relative), indicating a need for only 5 patients to undergo endarterectomy (number needed to treat [NNT]) to prevent one ipsilateral stroke during this time period. A similar pattern was observed for combined disabling or fatal ipsilateral strokes. The absolute risk reduction at 3 years was 10.6% (76% relative), corresponding to an NNT of 9.

The incremental increase in cumulative stroke risk for medically treated patients was not constant over time. The risk of stroke facing patients in the first year, after recent ischemic events, was 16.9%. Patients who remained stroke
free during the first year had an 8.2% risk of stroke in the second year. Those who continued to remain stroke free had a stroke risk of only 3.2% in the third year. By comparison, the average annual risk of stroke for surgically treated patients, over the first 3-year period, was 3.0%.

Over 80% of the first ipsilateral strokes at 3 years in medically treated patients were of large-artery origin (Figure 2). Patients with lower degrees of stenosis were more likely to have lacunar strokes than those with higher degrees of stenosis (17% versus 9%). A cardioembolic origin accounted for only a small percentage of the strokes. Although approximately the same proportion of strokes were of large-artery origin in the 2 stenosis groups, 65% of the strokes were disabling or fatal in the 85% to 99% stenosis group compared with only 30% in the 70% to 84% stenosis group.

Part 2: Delayed Endarterectomy and Continuing Medical Groups

Of the 331 patients randomized to the medical arm, 100 were no longer available or suitable for endarterectomy at the time of the clinical alert and are excluded from part 2. Of these 100 patients, 21 had died, 20 had already undergone endarterectomy, 38 had angiographic and/or ultrasound evidence of ICA occlusion before or in the 6-month period after the clinical alert, 11 were not fit for endarterectomy because of a disabling stroke, and 10 others were medically unfit for endarterectomy.

Of the 231 patients remaining eligible for endarterectomy, 116 had endarterectomy within 6 months of the clinical alert (delayed endarterectomy group). The remaining 115 patients constituted the continuing medical group. Of this medical group, 80 remained on medical therapy for the duration of the trial, and 35 had endarterectomy at some time after the clinical alert and were censored at the time of endarterectomy. The risk factors were similar between the delayed endarterectomy and continuing medical groups at the time of the clinical alert and are reported as a single column in the Table. By the time of the clinical alert, several differences had developed from the risk factors at baseline. The patients remaining eligible for endarterectomy were, on average, 2 years older and were more likely to have developed a history of myocardial infarction or angina, and fewer smoked. Of the 115 patients continuing on medical therapy, only 15% had ischemic symptoms in the year before the clinical alert, whereas 40% of the patients in the delayed endarterectomy group had symptoms in the year before the date of their endarterectomy.

The risk of ipsilateral stroke at 3 years for the delayed endarterectomy group was 7.9% (which included a 30-day perioperative risk of any stroke or death of 2.6%) compared with 15.0% for the continuing medical group (Figure 1B, \( P = 0.11 \)). Despite the delay to operate on these patients and the lower risk that faced the medically treated patients after the clinical alert, a 7.1% absolute risk reduction in stroke risk was achieved (47% relative risk reduction). The NNT was 14 patients. Only a small difference in stroke risk was observed in the delayed endarterectomy group between patients who had and did not have ischemic symptoms in the year before endarterectomy (8.9% versus 7.2%). In contrast, continuing medical patients had almost twice the risk of ipsilateral stroke of the clinical alert and are excluded from part 2. Of these 100 patients, 21 had died, 20 had already undergone endarterectomy, 38 had angiographic and/or ultrasound evidence of ICA occlusion before or in the 6-month period after the clinical alert, 11 were not fit for endarterectomy because of a disabling stroke, and 10 others were medically unfit for endarterectomy.

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at 3 years if they had symptoms in the past year compared with those who were symptom free (21.9% versus 14.0%).

Part 3: Carotid Artery Disease on Follow-Up Imaging
In part 3, of the 331 patients assigned to medical therapy, 91 patients had follow-up angiography. Ten studies were excluded because the follow-up angiogram did not have views and/or angles comparable to those provided by the baseline angiogram. For the 81 comparable pairs, the mean time period between the baseline and follow-up angiograms was 1.9 years (range 86 days to 7 years). One third (n = 27) of the arteries progressed to occlusion, 7 lesions progressed ≥10% (mean change 17%, range 11% to 23%), 8 lesions regressed (mean change 20%, range 10% to 34%), and 39 lesions showed <10% change (Figure 3). In total, 42% progressed (34 [7/27] of 81), and 58% remained the same or regressed.

Of the 250 patients without adequate follow-up angiograms, 84 patients did not have adequate ultrasound data. In the remaining 166 patients with ultrasound studies, 36 lesions progressed to occlusion. In total, 63 (27/36) of 247 (81+166) patients had an artery that progressed to occlusion. Occlusions occurred more frequently with higher degrees of baseline stenosis: 21.2% in the 70% to 84% group compared with 32.3% in the 85% to 99% group (P = 0.05). Of the 63 patients who progressed to occlusion over a mean follow-up of 2.0 years, 20 (31.7%) had an ipsilateral stroke before or at the time of occlusion. Of the 184 patients who remained with a patent ICA over a mean follow-up of 5.5 years, 49 (26.6%) had an ipsilateral stroke. After accounting for the different numbers of patients and lengths of follow-up, patients whose ICA progressed to occlusion had ~3 times as many strokes per mean follow-up year as those whose ICA remained patent. After occlusion, 3 of 63 patients had a stroke in the territory of their occluded ICA. The overall ipsilateral stroke risk at 3 years was 5.1%. All strokes were of large-artery origin.

Discussion
NASCET randomized patients into a group given best-known medical care and an equal number of patients into a group given best-known medical care plus endarterectomy. Two years and 2 months after the first patients were randomized, a clinical alert advised that there was benefit from endarterectomy provided the focal symptoms were related to a carotid stenosis of 70% to 99%. The trial was over for this category of patients. A unique opportunity presented itself to continue following these patients and to compare the benefit of endarterectomy when it was performed soon after the onset of their latest symptoms and after a delay of ≥2 years from entry into the trial.

Endarterectomy proved durable in the long term and reduced the risk of stroke sufficiently so that only 5 patients need to be treated to prevent one stroke in 3 years. Fourteen patients were required if the procedure was delayed. For the delayed endarterectomy group, the absolute risk reduction at 3 years was 7.1% compared with 19.4% if the procedure was performed shortly after the occurrence of ischemic symptoms.

Although the risk of ipsilateral stroke in medically treated patients continued to accumulate, the longer the patient remained stroke free, the lower was their subsequent risk. If circumstances prevent patients who have known severe stenosis and a history of symptoms dating back 2 to 3 years from coming to surgical attention, benefit from endarterectomy will still occur, but it will be less. The prerequisites for performing delayed endarterectomy are as follows: the imaging that verifies continuing patency should be recent, the condition of the patient’s heart and other vital organs should not preclude an operative procedure, and the surgeon should have proven expertise.

Perioperative events occurred in only 3 (2.6%) of the 116 patients who had delayed endarterectomy, whereas 19 (5.8%) of the 328 patients randomized to immediate surgical treatment had perioperative events. The difference between 2.6% and 5.8% may be by chance alone. The surgeons for both groups were the same. However, the explanation could be that 60% of the patients who had delayed endarterectomy had been without symptoms in the previous year and were becoming comparable to the asymptomatic patients who have been found to have a perioperative rate lower than that of symptomatic patients.9

NASCET10 and the European Carotid Surgery Trial11 both have reported the risk of stroke in medically treated patients who remained without symptoms decreased over time. The time of greatest risk of stroke after the development of symptoms was in the first 6 months, and the incremental risk decreased out to 2 years. Thereafter, the future risk of stroke was much decreased, and the outlook for previously symptomatic patients was similar to that for patients who had undergone endarterectomy or who had always been asymptomatic. The longer the patients were free of symptoms, the less likely they were to have a stroke and the less likely they were to benefit from endarterectomy. Beyond 2 years of being symptom free, endarterectomy may be unnecessary in most patients because between years 2 and 3, the additional risk added was only 3.2%. Of the 115 patients who continued with medical therapy, 85% had been asymptomatic for at least 1 year. It appears that these patients may constitute a lower risk group, which may partially account for their lower risk of future stroke and lesser benefit from endarterectomy in the later years.
It is unclear why these medically treated patients have a lower risk at the end of 3 years. In part, it is reasonable to suggest that by this time there had been a “harvesting” effect causing the most vulnerable medically treated patients to die, suffer a major stroke, or develop other serious disease. Consequently, the remaining patients could be considered a healthier cohort. Looking at the vascular risk factors was not helpful in distinguishing patients who would develop stroke from the patients who became asymptomatic. Subtle differences might have been present, so that the overall burden of cardiac, carotid, and small-vessel diseases was less severe. This remains speculative, as is the other possibility that the rate of arterial progression in these patients was intrinsically slower.

The rate of progression of carotid lesions in symptomatic and asymptomatic patients is an important clinical issue. Progression and regression of internal carotid artery stenosis have been demonstrated in asymptomatic populations. This information is needed to decide how often images should be repeated in patients known to have such lesions. On follow-up angiograms, 10% of this unique group of patients showed regression of ≳20%. The stenosis in one patient regressed by 34%. Improvement in angiographic appearance may be due to several factors: the method of angiographic measurement has a margin of error of slightly <10%, 14 and regression of atherosclerosis by risk factor management may occur,15–17 as may resolution of an intraplaque hemorrhage. The latter was the probable explanation for the patients with marked regression. It came as a surprise that the majority of patients showed no progression and, conversely, that such a small number had any progression short of occlusion.

Total ICA occlusion is a serious condition facing medically treated patients with severe symptomatic carotid stenosis. In NASCET, occlusion was identified in 63 (25.5%) of 247 patients. Twenty (31.7%) had an ipsilateral stroke before or on the day of carotid artery occlusion, although it was difficult to determine the precise date of occlusion. Previous studies in asymptomatic patients have shown that progression to occlusion was accompanied by stroke in numbers covering a wide range.18–20

It was erroneously speculated at one time that carotid occlusion would be followed by a cessation of any new symptoms. However, strokes do occur in the territory of the occluded artery at a rate of 5% per year. Cote et al21 found that 32% had strokes after documented occlusion in a mean time of 34 months. In the NASCET, 3 of 63 patients had strokes after documented occlusion. Thromboembolism is the likely explanation for the cerebral ischemia in the majority of these patients: from the tail of thrombus in the internal carotid distal to the occlusion, from the external carotid artery, from the stump of the ICA,22 and from the heart and aorta.23 Hemodynamic mechanisms presumably play a role for some patients, particularly if the collateral blood supply is poor.

Conclusions were as follows: (1) Endarterectomy had a long-lasting benefit of reducing the risk of ipsilateral stroke. (2) Large-artery stroke, the most common cause of stroke, increased in frequency with the degree of stenosis. (3) Disabling large-artery stroke was more common in patients with the most severe stenosis. (4) Patients with and without recent ischemic symptoms who underwent delayed endarterectomy showed a moderate benefit compared with patients who continued on medical therapy. An NNT of 14 still makes endarterectomy worthy of consideration for these patients. (5) A surprising number of patients in the present study had no meaningful progression of the carotid lesion. The number of patients whose lesions progressed short of occlusion was similar to the number of patients whose lesions regressed. (6) These data do not support the need to perform frequent follow-up imaging studies on every patient with known severe stenosis whose symptoms have ceased. (7) Nearly one quarter of the medically treated patients progressed to carotid artery occlusion, and one third of the occlusions were associated with ipsilateral stroke.

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