Carotid Endarterectomy

A Neurotherapeutic Advance

Henry J. M. Barnett, MD; Heather E. Meldrum

Egaz Moniz,¹ the pioneer of angiography, in the 1920s identified carotid artery lesions in patients who had experienced a stroke. In the early 1940s, Hultquist² published early pathological observations. It remained for C. Miller Fisher’s³ meticulous observations in the 1950s to focus attention on the importance of the extracranial portion of the carotid arteries as a prominent cause of ischemic stroke. Quickly the concept evolved of transient ischemic attacks as forerunners of ischemic infarction. Because surgeons had learned to repair arteries in the battlefields of World War II, it was predictable that pioneers would attempt to remove offending carotid arterial lesions. First to publish was the English team of Eastcott et al.⁴ An Argentinean and Americans missed the accolades of primacy by delaying publication.⁵,⁶

Fields and colleagues⁷ had the vision in the early days of randomized trials to assign patients with cerebral ischemic events to either undergo carotid endarterectomy or receive medical care. Small numbers (n = 316), crossovers, loss to follow-up, mixed enrollment criteria including 42% of the total number of patients with only vertebral-basilar symptoms, and an unacceptably high postoperative complication rate of stroke and death (11%) doomed this seminal trial to a negative result.

Enthusiasm persisted for the use of the procedure; more surgeons developed the necessary skills, technical expertise was sharpened, and practicing physicians learned to recognize the potential candidates. All this resulted in ever-increasing numbers of patients with symptoms and individuals without symptoms undergoing endarterectomy. The number on record in the nonveteran hospitals in the United States rose from 15 000 in 1971 to 107 000 in 1985. By this time, 1 million patients worldwide had undergone the operation. Questions were raised about the evidence justifying these numbers.⁸,⁹

Disturbing surveys from several communities identified unacceptably high complication rates. The answer to the enigma posed for appropriateness of endarterectomy in those with symptoms and those without was sought in new randomized clinical trials, 3 performed on symptomatic patients and 4 on asymptomatic subjects.

THE EVIDENCE FROM THE TRIALS ON SYMPTOMATIC PATIENTS

The North American Symptomatic Carotid Endarterectomy Trial (NASCET)¹⁰ and the European Carotid Surgery Trial (ECST)¹¹ between them randomized close to 6000 patients, of whom two thirds were men and one third were women. A Veterans Affairs trial randomized 189 male patients.¹² All patients were studied by conventional angiography and received the best medical care. Half of those in the NASCET and in the Veterans Affairs study were randomly assigned to the additional therapy of endarterectomy; 2 of 3 patients in the ECST were randomized to endarterectomy. This report relates particularly to the evidence amassed from the 2 large trials, with special emphasis on the NASCET data.

A different formula was used in each of the 2 trials to calculate the percentage of stenosis. When the stenosis for each patient was compared by careful remeasurement, using the NASCET formula, the dif-

From The John P. Robarts Research Institute, London, Ontario.
ferences in measurement were rationalized. A simple conversion formula has been calculated. When the degrees of stenosis measured by the NASCET are 50% and 70%, the degrees from the ECST are 75% and 85%, respectively. When the enrollment and outcome data were assembled using the NASCET measurement as the baseline for both studies, the conclusions of the 2 trials were similar.

An arbitrary division at the onset of the NASCET and the ECST divided patients by degree of stenosis into a “severe” group (≥70%) and a “moderate” group (<70%). In the severe group of the NASCET, the benefit from endarterectomy was highly significant (P < .001) when compared with best medical care alone. In the 659 patients with severe stenosis, of whom 328 underwent endarterectomy and 331 received medical care only, the benefit favored surgical therapy with a relative risk reduction of 65% and an absolute reduction of 17%. The number needed to treat (NNT) by endarterectomy to prevent 1 additional stroke in 2 years requires that only 6 patients undergo the procedure (Table 1). The NNT for the patients in the ECST with severe stenosis was 8 (Table 1).

The evidence favoring endarterectomy for patients with moderate stenosis (50%-69%) was muted. The relative risk reduction was 36%, the absolute reduction was 5.3%, and the NNT was 19. Patients with symptoms associated with less than 50% stenosis were not benefited (P = .20). In the NASCET and ECST, there was a slight increase in perioperative complications encountered in the patients with the lower rather than the higher degrees of stenosis.

Secondary analyses allowed preliminary observations regarding the most ideal candidates for endarterectomy. In the patients with severe stenosis, there was only 1 subgroup who did not benefit: patients in whom an intraluminal thrombus was visualized on the angiogram at enrollment. Subgroups in which patients received a more favorable benefit in the moderate range included men but not women, those with hemispheric but not retinal events, those with an infarction at enrollment rather than a transient ischemic attack as the qualifying event, and, unexpectedly, those with evidence of concomitant intracranial carotid artery stenosis rather than normal intracranial arteries. The hypothesis had been that patients with intracranial disease would benefit less from carotid endarterectomy. The converse was observed.

The results of the trials were predicated on visualization of the arterial lesions by angiography and the insinence that surgical skill be such that the perioperative complication rate demonstrated by the participating surgeons was 6% or less. The surgical results in the total NASCET group, as well as a breakdown into patients with moderate and severe stenosis, are illustrated in Table 2. Patients with moderate stenosis were less likely to have a disabling postoperative stroke than were patients with severe stenosis. However, the combination of disabling stroke and death at 30 days was similar in the 2 groups. At 90 days, the occurrence of nondisabling stroke and death was 2.0% and 2.1% for patients in the moderate and severe groups, respectively, averaging 2.0% for all patients with 50% to 99% stenosis.

Perioperative complications were increased in the presence of certain risk factors, an occlusion of the nonoperated-on (contralateral) carotid artery, a thrombus visible on the angiogram of the symptomatic lesion, the presence of a computed tomographic image showing a lesion compatible with ischemia in the area of the brain supplied by the diseased artery, a history of diabetes, a diastolic blood pressure higher than 90 mm Hg, an irregular or ulcerated plaque visible on the angiogram, and, surprisingly, a lesion on the left side rather than the right side. This unexpected phenomenon would have been dismissed were it not for the fact that it has been observed in 2 other contemporary carotid endarterectomy databases. In the NASCET, a survey was made of the handedness of the surgeons. The left-handed surgeons did not experience the doubling of complications when operating on the left side that was observed for the surgeons who were right handed. When performing endarterectomy on the right side, the left-handed surgeons had a complication rate similar to that of right-handed surgeons (NASCET, unpublished data, 1998). These risk factors lead to a doubling or slightly greater immediate operative risk. All factors that individually increased the perioperative risk, except for the presence of an intraluminal thrombus, were

### Table 1. Number Needed to Treat (NNT) by Endarterectomy for Symptomatic Patients*

<table>
<thead>
<tr>
<th>Stenosis, %</th>
<th>No. of Patients</th>
<th>Risk at 2 y, %</th>
<th>Relative Risk Reduction, %</th>
<th>NNT</th>
<th>Perioperative Stroke and Death Rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>70-99</td>
<td>NASCET</td>
<td>659</td>
<td>24.5</td>
<td>5.9</td>
<td>6.1</td>
</tr>
<tr>
<td></td>
<td>ECST†‡</td>
<td>501</td>
<td>19.9</td>
<td>12.9</td>
<td>8.6</td>
</tr>
<tr>
<td>50-69</td>
<td>NASCET</td>
<td>858</td>
<td>14.6</td>
<td>5.3</td>
<td>36.0</td>
</tr>
<tr>
<td></td>
<td>ECST†‡</td>
<td>684</td>
<td>9.7</td>
<td>−1.4</td>
<td>−14.0</td>
</tr>
<tr>
<td>&lt;50</td>
<td>NASCET</td>
<td>1368</td>
<td>11.7</td>
<td>1.5</td>
<td>13.0</td>
</tr>
<tr>
<td></td>
<td>ECST†‡</td>
<td>1822</td>
<td>4.3</td>
<td>−5.2</td>
<td>−109.0</td>
</tr>
</tbody>
</table>

* Reprinted with permission from Barnett et al. NNT indicates the number of patients needed to treat by endarterectomy to prevent 1 additional ipsilateral stroke in 2 years after the procedure compared with medical therapy alone; NASCET, North American Symptomatic Carotid Endarterectomy Trial; ECST, European Carotid Surgery Trial; and ellipses, data not applicable.

† Additional data supplied by P. Rothwell, MD, PhD.
‡ Obtained by NASCET measurement.
followed by ultimate benefit as evidenced by improved stroke-free survival at 5 years compared with patients treated only with the best medical care.

The protocol of the NASCET allowed patients with stroke symptoms to be randomized despite clinical-radiological evidence of lacunar disease. Outcome events were separately analyzed and compared with those of patients who enrolled into the NASCET with hemispheric strokes judged not to be lacunar. At 3 years, the patients who received the best medical care and who had 50% to 99% stenosis and a nonlacunar stroke at enrollment had a 21.8% risk of ipsilateral stroke compared with a 10.5% risk in the surgical patients (P = .003). Benefit from endarterectomy was absent in those enrolling with a probable lacunar stroke. The 3-year rate of ipsilateral stroke was 23.4% for the patients with lacunar stroke treated medically and 24.0% for the patients in the surgical group (P = .90) (NASCET, unpublished data, 1999).

THE EVIDENCE FROM THE TRIALS ON ASYMP TOMATIC INDIVIDUALS

Individuals without symptoms but known to have varying degrees of stenosis are more common than patients who experience symptoms presumed to be related to carotid atherosclerotic lesions. There are probably 2 million subjects with this identifiable lesion in the United States at any time. It is not accurate to describe them as patients. They have no symptoms and many, if not most of them, require nothing more than monitoring and attention to manageable risk factors. Particular attention should be given to maintaining a normal blood pressure, a normal cholesterol level, and a normal blood sugar level, and to the cessation of cigarette smoking.

Observational series involving people with asymptomatic carotid lesions have been described. The clinical outcomes have been recorded, and the lesions have been studied by serial ultrasonography. The annual risk of stroke related to these lesions has proved to be too low to justify any consideration of the potential for surgical intervention until the lesion has reached at least a level of 75% stenosis. The annual risk of death from myocardial infarction was greater in these observational studies than was the stroke risk.

Four randomized trials have been published. Two were methodologically flawed. The details of the others, the Veterans Affairs Cooperative Study and the Asymptomatic Carotid Atherosclerosis Study (ACAS), are summarized in Table 3. The Veterans Affairs Cooperative Study, based on angiographic evaluation of the degrees of stenosis, was beset by a high perioperative complication rate. Despite a 7.7% rate of stroke and death at 2 years, the stroke-free survival was not improved by endarterectomy. A total of 48 persons need to be treated by end-

<table>
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<th>Table 2. Incidence of Perioperative Outcome Events at 30 Days and Assessment of Stroke Severity at 90 Days*</th>
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<tbody>
<tr>
<td><strong>Perioperative Event</strong></td>
</tr>
<tr>
<td>----------------------</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>All stroke and death</td>
</tr>
<tr>
<td>Nondisabling stroke</td>
</tr>
<tr>
<td>Disabling stroke</td>
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<tr>
<td>Disabling stroke and death</td>
</tr>
<tr>
<td>Stroke death</td>
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<tr>
<td>Nonstroke death</td>
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<tr>
<td>All death</td>
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* Data are given as number (percentage) of patients. Modified with permission from Ferguson et al.†
† Between 30 and 90 days, 8 patients with moderate stenosis and 3 patients with severe stenosis had an improvement in stroke severity from “disabling” to “nondisabling.”
‡ One patient with a disabling stroke died 33 days after surgery.

<table>
<thead>
<tr>
<th>Table 3. Number Needed to Treat (NNT) by Endarterectomy for Asymptomatic Individuals*</th>
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<tbody>
<tr>
<td><strong>Study</strong></td>
</tr>
<tr>
<td>---------</td>
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<tr>
<td>VA (men only, ≥50% stenosis)</td>
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<tr>
<td>ACAS (≥60% stenosis)</td>
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<tr>
<td>ACE (stenosis present)</td>
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</table>

* Reprinted with permission from Barnett et al.® NNT indicates the number of subjects needed to treat by endarterectomy to prevent 1 ipsilateral stroke in 2 years after the procedure compared with medical therapy alone. VA, Veterans Affairs Cooperative Study; ACAS, Asymptomatic Carotid Atherosclerosis Study; ACE, Aspirin and Carotid Endarterectomy; and ellipses, data not applicable.
† Extrapolated from the results. The perioperative risk is calculated for the 203 subjects who actually underwent surgery.
‡ Assigning a perioperative risk of 2.6% based on 724 of 825 subjects who actually underwent endarterectomy in the surgical arm of the ACAS, and using a 0.6% risk of stroke in each of the 2 years after endarterectomy. The same 1.2% risk is assumed for the patients in the ACE trial and the VA.
§ No medical arm; value assumed from ACAS data.
national Stroke Association was more cautious. 25 Experts

cations is underscored by several observations. The

est degree of stenosis operated on by surgeons with

firm the suspicion held by many that men with the high-

low risk is difficult to overcome other than by an excep-

tive low perioperative complication rate. The periop-

ation of surgical morbidity and mortality using only

complication rate and calculation of the NNT were based

Even this low rate results in an NNT of 67 at 2 years. This

erative rate reported in the ACAS indeed was low at 2.3%.

low risk of operative compli-

the 724 patients who actually underwent the procedure

Arterial 5-year Kaplan-Meier curves of freedom

omitted stroke and perioperative stroke and death indicate a 5.9%
difference favoring endarterectomy at 5 years in the Asymptomatic Carotid
Atherosclerosis Study (ACAS). A marginal significance by the Greenwood
formula (P = .004) exists for this difference at 5 years, with 149 patients
available for analysis. Superimposed is the projected outcome of 1521
asymptomatic individuals undergoing carotid endarterectomy in the Aspirin
and Carotid Endarterectomy (ACE) trial, based on a 4.6% stroke and death
rate at 30 days, extrapolating the outcomes to 5 years. Using the projected
7.4% rate, the difference between treatment groups is 3.6% (11.0% – 7.4%),
only 0.7% benefit per year (P = .10). Adapted from the ACAS.21

THE IMPACT OF AN OCCLUDED ARTERY
IN ASYMPTOMATIC PERSONS
Some have recommended that subjects with occlusion on one side, and who have an asymptomatic lesion on the other side, might be advised to undergo endarterectomy on the patent asymptomatic lesion. Data from the NASCET have shown that this combination of arterial lesions in symptomatic patients confers a higher risk than in those without occlusion.26 Nevertheless, a long-term benefit of endarterectomy was shown for these patients. In the Aspirin and Carotid Endarterectomy trial, of the 151 asymptomatic persons who had contralateral occlusion, the perioperative complication rate after endarterectomy on the patent artery was a forbidding 12.6% (unpublished data, 1999). The trial was designed only for a follow-up of 90 days. Nevertheless, a long-term follow-up would not be anticipated to achieve other than negative benefit because of the high complication rate in the 30 days after the procedure. This observation will be validated in other databases wherein the required information has been recorded.

THE IMPACT OF STROKE CAUSE ON RECOMMENDATIONS FOR CAROTID
ENDARTERECTOMY
The impact of stroke cause on the outcome events (stroke and death) in the NASCET was studied. The extensive case report forms submitted for each patient in the trial required sufficient detail of the symptoms, signs, computed tomographic lesions, cardiac status, and angiographic appearances to allow distinctions between subacute strokes thought to be of large artery, cardioembolic, or lacunar origin. Stroke outcome events were all scrutinized and assigned as to cause. When the lesions on the “other,” asymptomatic side of patients in the NASCET were followed up for 5 years, 40% of the strokes in the territory of this asymptomatic artery were of cardioembolic or lacunar origin (Figure 2). Clearly any attempt to improve, by surgical therapy, the risk of stroke for a person with an asymptomatic artery must assume that a maximum of 60% of the subsequent strokes will be of large artery origin. This 60% figure in routine practice may
be higher. The occurrence of cardioembolic strokes was lower than in many nonrandomized case series and stroke databanks. The NASCET excluded patients with recent myocardial infarction, atrial fibrillation, recent congestive heart failure, unstable angina, and notable valvular lesions. Articles describing the details of the cardioembolic and lacunar strokes in the NASCET are being separately published.

**UNSETTLED PROBLEMS REGARDING CAROTID ENDARTERECTOMY**

The clinical trials have made it clear that the gap is narrow between the benefit for patients with moderate stenosis who undergo carotid endarterectomy and those who receive medical care alone. Even a 2% increase in perioperative stroke morbidity and mortality will close this gap, and the benefit favoring endarterectomy will diminish. A perioperative complication rate of 10% for any stroke and death will eliminate benefit even in patients with severe stenosis. Such unacceptable figures are being reported. In asymptomatic subjects, the gap in benefit between medical and surgical treatment is narrow. Only with an exceptionally low perioperative risk of stroke and death can the procedure be contemplated. The 2.3% perioperative risk reported in the ACAS included a high 1.2% angiographic risk. Thus, the upper limit of an acceptable operative complication rate for the surgeon has been set at a formidable 1.1%. This is in sharp contrast to the 4.6% in the 1521 asymptomatic subjects in the Aspirin and Carotid Endarterectomy trial and a 5.6% single institution rate recently published. How widespread this unacceptable rate is is a matter of conjecture.

Three recommendations emerge from these unsettling data. First, surgical departments in the institutions where this procedure is carried out are obliged to monitor the complication rates. They need to regulate the performance of the procedure so that benefit can be anticipated in all patients about to undergo carotid endarterectomy. Second, the public should have ready access to the results of this ongoing monitoring.

Finally, the degree of stenosis in symptomatic patients has been shown to be the most compelling prognostic feature. Patients should not be denied surgery because the degree of stenosis is erroneously reported to be low. This still happens in some instances of near occlusion of the artery, even with color Doppler ultrasonography. The artery is declared falsely to be occluded. Conversely, overreading falsely declares eligibility in too many instances. With the exception of patients with the most obvious and severely narrowed lesions, endarterectomy should not be recommended based on ultrasonography alone. Reliance on ultrasonography with or without magnetic resonance imaging is not rendered valid simply by the declared policy of some institutions to accept images made by these methods as the sole imaging before endarterectomy. The authority of experience is not sufficiently convincing to establish noninvasive methods as the standard of preoperative investigation. The minimal risk of 2% disabling stroke and death facing most symptomatic candidates for endarterectomy requires a compelling accuracy of diagnosis. Angiography, safely performed, should be the gold standard until it has been replaced by advances in noninvasive technology. Angiography carries a risk of stroke. In NASCET centers, it was 0.6% for nondisabling stroke and estimated at 0.1% for disabling stroke. The latter figure is one twentieth of the risk facing the candidate for endarterectomy in centers of excellence. If angiography is being performed at too high a rate, the skill of the angiographer should be scrutinized.

In summary, ultrasonography is an excellent screening tool and occasional patients with severe stenosis may be spared angiography. Where conversions from ultrasonography are made at levels below 80% to 85%, an angiographic image is a desirable protection against unnecessary endarterectomy. Imaging techniques need ongoing development and improvement.

Data have been discussed herein in which particular subgroups with moderate stenosis showed most benefit. These are data-generated observations and require validation from other available large databases to be more convincing. This is in progress. Until validation has been completed, decisions about the importance of these subgroups as individual and collective prognostic variables should be regarded as tentative.

For asymptomatic disease, there remains a large void in knowledge to help decide which subjects, if any, should undergo endarterectomy for asymptomatic disease. It is probable that in North America the procedure is done as often for these individuals as for patients with symptoms. The evidence is sparse and the possibility strong that many of those who undergo endarterectomy for asymptomatic disease would fare as well or better with medical care.

**SUMMARY OF RECOMMENDATIONS REGARDING CAROTID ENDARTERECTOMY**

Patients with symptoms related to severe stenosis of the carotid artery must be considered for endarterectomy. Only patients who probably will not survive the anesthetic or already have serious organ failure, life-threatening heart

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**Figure 2.** The outcome events of large artery, lacunar, and cardioembolic strokes in the North American Symptomatic Carotid Endarterectomy Trial were evaluated as they occurred during the 8 years of follow-up. For patients whose “other side” was totally asymptomatic and the degree of stenosis measured by angiography was 60% to 99%, only 53.6% of the outcomes of stroke were of large artery origin. This figure was 64.7% for the patients with less than 60% stenosis.
and pulmonary disease, or a progressive cancer should be denied the operation.

Expertness in surgical technique, anesthesia, and postoperative care is mandatory. A record of postoperative complications of stroke and death for symptomatic patients with severe stenosis must not exceed 7%.

Symptomatic patients with 50% to 69% stenosis should be considered for endarterectomy. Women, those presenting with retinal but not hemispheric events, and those presenting with a transient ischemic attack rather than a stroke and without intracranial disease, for the most part, are best treated with medical care alone.

A low operative complication rate is a particular obligation when the symptomatic disease is still in the moderate range.

The observations regarding the impact of risk factors made from subgroup analyses require further validation by comparison with other carotid artery databases.

Before performing endarterectomy for symptomatic disease, most lesions suspected of being within the potential range of benefit (50%-99% stenosis) should be confirmed by conventional angiography.

Patients with symptoms and less than 50% stenosis do not benefit from endarterectomy.

Asymptomatic individuals will only benefit from endarterectomy if the perioperative complication rate is 2% or less. Most should receive only the best medical care.

Further studies are required to determine if there is a high-risk group of asymptomatic individuals who can be shown clearly to benefit from endarterectomy.

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Reprints: Henry J. M. Barnett, MD, The John P. Robarts Research Institute, 100 Perth Dr, PO Box 5015, London, Ontario, Canada N6A 5K8 (e-mail: Barnett@rri.on.ca).

REFERENCES