Carotid Endarterectomy for the Prevention of Strokes in Patients with Symptomatic Carotid Stenosis

Claudio S. Cinà, MSc, FRCSC, Associate Clinical Professor, Department of Surgery, Division of Vascular Surgery, McMaster University, Hamilton, ON.

Catherine M. Clase, MSc, FRCPC, Associate Professor, Department of Medicine, Division of Nephrology, McMaster University, Hamilton, ON.

Carotid endarterectomy is effective in preventing strokes in patients with symptomatic carotid stenosis greater than 50%. The magnitude of the benefit is greater with increasing degree of stenosis, male sex, greater number of risk factors for strokes, strokes or hemispheric transient ischemic attacks rather than amaurosis fugax, recurrent events, plaque ulceration, contralateral carotid occlusion and tandem (intracranial and extracranial) stenosis. The effectiveness of carotid endarterectomy, however, is very sensitive to the rate of perioperative events, and centres providing care for these patients need to prospectively monitor their complication rates.

Key words: carotid stenosis, carotid endarterectomy, stroke, transient ischemic attacks.

Introduction
Stroke is the most important cause of long-term disability,¹ and second only to ischemic heart disease as a cause of death.² Carotid endarterectomy (CE) was introduced in the 1950s for the prophylaxis of strokes. Since the early 1990s, a number of randomised trials have addressed the effectiveness of this intervention. The indications and benefit of this intervention depend on a number of factors, including the presence or absence of symptoms, type of symptoms, degree of stenosis, anatomic features of the plaque, sex and coexistent risk factors.

Since there are substantial differences between the management of symptomatic and asymptomatic patients, we will discuss only the management of patients with symptomatic carotid disease.

Neurologic Symptoms
Traditionally, transient ischemic attacks (TIAs) are defined as brief episodes of focal loss of brain function lasting less than 24 hours.³ Symptoms may include hemiparesis, dysarthria, dysphasia, diplopia and monocular blindness (amaurosis fugax). A new definition for TIAs has recently been proposed based on the presence or absence of associated brain infarct as diagnosed by computerised tomography or magnetic resonance imaging.⁴ A similar episode of focal neurological dysfunction, without evidence of trauma or hemorrhage, is designated an ischemic stroke if it lasts more than 24 hours or causes death.⁵ If the patient has a history of any symptoms in the ipsilateral eye or brain, the carotid stenosis would be regarded neurologically symptomatic, and the relevant question is whether the patient may be a candidate for CE.

The Trials
The effectiveness of CE for symptomatic patients with greater than 50% ipsilateral symptomatic carotid artery stenosis has been demonstrated in two randomised controlled trials: the North American Symptomatic Carotid Endarterectomy Trial (NASCET),⁵-¹⁶ and the European Carotid Surgery Trial (ECST).¹⁷-²⁰ Overall, 6,078 patients have been randomised (3,777 to surgery, 2,301 to medical treatment). Angiography was used to assess the severity of carotid stenosis in all patients, but the method of calculation of percentage of stenosis differed between studies (Figure), and must be taken into consideration when assessing the results (Table 1). In this article, all references to degrees of stenosis are according to the formula used in NASCET.

Although there are caveats in the application of the results of subgroup analysis to clinical practice, the ECST and NASCET trials provided analyses which suggest factors other than degree of stenosis that can be taken into account when considering indications for CE. Consistency of clinically and statistically significant results across studies, presence of a gradient effect and biologic plausibility suggest which observations may be applied to clinical practice.

<table>
<thead>
<tr>
<th>Severity of Disease</th>
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<td>Minimal</td>
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<tr>
<td>ECST</td>
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<td>NASCET</td>
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Conversion from ECST to NASCET was done using the formula: ECST % stenosis = 0.6(NASCET % stenosis) + 40°
Main Results and Degree of Stenosis
Surgery is harmful in patients with stenosis < 50%, while the benefits are most evident in those with high-grade stenosis. A meta-analysis of the results of the ECST and NASCET trials showed that in patients with a 70–99% carotid stenosis, CE is associated with a 48% relative risk reduction (RRR) in the number of disabling or fatal strokes or death, and a 6.7% absolute risk reduction (ARR), corresponding to a number needed to treat (NNT) of 15 (i.e., 15 surgeries need to be done to prevent one fatal stroke or death over the subsequent three-year period). Surgery is beneficial in patients with 50–69% stenosis, but the RRR was 27% and the ARR was 4.7% with a corresponding NNT of 21 (Table 2). Increasing degrees of stenosis (70–79%, 80–89%, 90–99%) are associated with increasing benefit from surgery (Table 3). A similar gradient effect was observed in ECST, which also showed that surgery for patients with carotid stenosis less than 50% was harmful.

In conclusion, symptomatic patients with > 50% carotid stenosis benefit from CE and this benefit increases with the severity of disease, from an NNT of 21 in patients with 50–69% stenosis to an NNT of four in those with 90–99% stenosis.

Other Outcomes

Perioperative Complications
Serious complications during CE other than strokes are rare: 1–2% myocardial infarction, 3% postoperative wound infections, 5% hematoma, and reversible nerve injury in 5–7%. In the NASCET trial, the incidence of stroke or death was 6.7%, and that of nonfatal disabling stroke was 1.6%. The presence of a contralateral carotid occlusion, surgery for the left carotid, female sex, diabetes mellitus, hemispheric infarct on CT or MRI and diastolic blood pressure > 90 mmHg each are associated with an increase in the risk of perioperative events.

Functional Status Outcomes
NASCET provided an analysis of the functional status in patients undergoing CE with 70–99% stenosis compared with medical treatment. A functional status score capturing the domains of vision, language comprehension, speech fluency, swallowing, upper and lower limb function and the integrated functions of ability to go shopping and to make visits outside one’s home, was used to evaluate patients at baseline and over time. The mean scores diverged over time, with a statistically significant difference in favour of the surgical group. The NNT to prevent one previously non-disabled person from suffering major disability at three years was 11 patients.

In conclusion, in patients with high-grade stenosis, CE not only reduces the number of strokes compared with medical treatment but also results in improved functional outcome over time.

Age and Sex
Older age and male sex are associated with greater benefit of surgery. Surgery appears to provide the largest benefit in surgically-fit patients older than 75 years: the ARR is 29% (NNT 6) for stenosis > 70%, and 17% (NNT 6) for stenosis of 50–69%.

Women have a lower risk of stroke compared with men for any degree of stenosis. Accordingly, the benefit of surgery is less evident: in patients with a moderate degree of stenosis (50–60%), the NNT to prevent one disabling stroke is 16 for men and 125 for women.

Surgically-fit elderly patients therefore benefit greatly from CE. Surgery should be considered for symptomatic men and women with > 70% stenosis, may be indicated in symptomatic men with 50–70% stenosis, but is generally not indicated for women with stenosis in this range.

Medical Risk Factors
Data from the NASCET study show that for symptomatic patients with > 70% carotid stenosis, a greater number of identifiable clinical risk factors (Table 4) was associated with a higher annual risk of stroke (0 to three risk factors, 7%; four to five, 9%; six or more, 16%), and with an increased benefit from CE as demonstrated by increased ARR and reduced NNT (Table 5). However, patients in NASCET and ECST were excluded if they had coexisting medical disease likely to produce significant mortality and morbidity (e.g., cardiac valvular or
rhythm disorders, uncontrolled hypertension or diabetes, unstable angina pectoris or myocardial infarction in the previous four months). Results of these trials, therefore, are not generalizable to patients who have these conditions. Further evidence for the impact of operative risk on outcomes is provided by a retrospective review of 562 patients undergoing CE for symptomatic and asymptomatic disease in a large community hospital. In patients rated as Goldmann class I and II, overall incidence of mortality and non-fatal myocardial infarction was 2%, while 21% of patients in class III and IV experienced one of these complications.

When considering patients’ preoperative vascular risk profiles, a balance must therefore be maintained between exclusion of those whose surgical risks are most profound, but inclusion of those whose concomitant vascular risk factors increase their ability to benefit from the intervention.

### Outcomes by Neurologic Symptom

Retinal transient ischemic attacks have a better prognosis compared with hemispheric TIAs: the risk of stroke at three years for > 50% stenosis is 10% and 20%, respectively. Surgery is, accordingly, less beneficial in patients with amaurosis fugax: for example, the NNT to prevent one stroke at three years is 77 when the most recent neurologic event is amaurosis fugax, and 11 when it is a hemispheric TIA. Similarly, the benefit of CE is greater in patients who have had a hemispheric stroke compared to those with TIAs: for example, in patients with 50–69% stenosis, the NNT to prevent one disabling stroke is 13 for patients with a recent stroke compared to 59 in patients with TIA.

Among patients whose most recent neurologic event is amaurosis fugax, a number of risk factors have been identified that increase the risk of stroke and the benefit of surgery. These include age greater than 75 years, male sex, previous history of hemispheric TIA or stroke, history of intermittent claudication, high grade stenosis (80–99%) and the absence of cerebrovascular collateral circulation assessed by angiography. The risk of stroke at three years is 2% in those with one or fewer risk factors, 12% in those with two, and 24% in patients with three or more risk factors.

In conclusion, patients with amaurosis fugax have a better prognosis than those with hemispheric TIAs. Patients at low risk for stroke (one or no risk factors) are better treated medically (NNH 45; i.e., 45 CEs need to be done to harm one patient). Patients with two or more risk factors benefit from CE (NNT 20 and NNT 7, respectively).

### Recurrent Events

In NASCET and ECST, an inclusion criterion was a recent neurologic event, called the qualifying event. In patients with no events prior to their qualifying event or whose neurologic events all occurred in the six months immediately preceding the qualifying event, CE is associated with an ARR for stroke of 11% (NNT 9), while in patients with longstanding recurrent events over a period of 12 months prior to the qualifying event the ARR is 30% (NNT 3).

Thus, patients with longer histories of recurrent ischemic events appear to have greater ability to benefit from surgery than those whose ischemic events are more recent in onset.

### Lacunar Strokes

Pathologic studies have suggested that the underlying process in lacunar strokes may not be artery-to-artery embolism. If this was the case, patients with a lacunar event might be expected to benefit less from CE than others, perhaps having a response more in keeping with asymptomatic carotid stenosis. A subgroup analysis from NASCET in patients with 50–99% stenosis showed that patients with non-lacunar and lacunar strokes benefit from CE, but the benefit is, as anticipated, greater in those with non-lacunar strokes (NNT=7 and NNT=11, respectively). Delay to Surgery in Patients with Stroke

One of the clinical questions in patients with a recent stroke and ipsilateral carotid stenosis is the timing of CE. The concern is that operating immediately might carry a risk of hemorrhagic transformation of the ischemic stroke, while delay exposes the patient to a further period at risk of recurrent artery-to-artery embolism and stroke. A subgroup analy-
sis from NASCET found no difference between patients who suffered a stroke and underwent CE within or after 30 days from the event. Similar results were obtained when the 14- or 21-day intervals were analysed.

These data offer no support for either those who advocate urgent surgery for patients with stroke and carotid stenosis or those who have cautioned that complications of CE are higher with early surgery. The only conclusion that can be drawn is that early surgery after hemispheric stroke is not associated with very high risk in carefully selected cases.

Plaque Ulceration
In symptomatic patients with 70–99% stenosis, patients with angiographic evidence of plaque ulceration experience a higher risk of stroke compared to those without ulceration, and greater benefit from surgery (Table 6). However, sensitivity and specificity for detecting ulcerated plaques by angiogram was 46% and 74%, respectively, with a positive predictive value of 72%. Plaque ulceration likely increases the benefit of surgery and may be helpful in making the final decision of whether to offer CE.

Near Occlusion of the Carotid Artery
It has been hypothesized that patients with near occlusion of the symptomatic carotid artery (i.e., very severe stenosis, delayed flow of angiographic material and reduced distal arterial calibre) have a different prognosis and greater risk from surgery than patients with lesser degrees of stenosis. A subgroup analysis from NASCET found no statistically significant differences across categories for either perioperative events or one-year risk of ipsilateral stroke.

Within the limitation of this subgroup analysis, with its small number of patients and events, patients with near occlusion of the carotid artery can be considered similar in risk to other patients with high-grade stenosis.

Contralateral Carotid Disease
The risk of perioperative complications (stroke or death) in patients with contralateral occlusion is higher (15%) than in those whose contralateral artery is stenosed but patent (6%). In spite of this increased risk, however, the benefit of surgery in terms of the outcome “any stroke or death” at two years is greater in the group with contralateral occlusion than the group with contralateral high-grade stenosis (ARR 20%, NNT 5). Interestingly, the group with an occluded contralateral carotid had a higher incidence (52%) of ipsilateral plaque ulceration than the group with contralateral high-grade stenosis and the group without contralateral stenosis (34% and 35%, respectively). If these effects of plaque ulceration on the ability to benefit from CE were real, then plaque ulceration might be an important confounder in this analysis of the effect of contralateral carotid occlusion.

In conclusion, a contralateral carotid occlusion does not represent a contraindication for surgery, but patients should be warned of a higher perioperative risk.

Tandem Extracranial and Intracranial Carotid Stenosis
The presence of intracranial carotid (ICC) stenosis detected by contrast or magnetic resonance angiography is an independent risk factor for stroke, and ICC stenosis of some degree is found in 20–50% of patients who have internal carotid artery (ICA) stenosis.

### Table 4
<table>
<thead>
<tr>
<th>Demographic factors</th>
<th>Stroke risk factors</th>
<th>Vascular morbidity</th>
<th>Anatomic factors</th>
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</thead>
<tbody>
<tr>
<td>Age &gt; 70</td>
<td>Smoking</td>
<td>Prior stroke</td>
<td>Stenosis &gt; 80%</td>
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<tr>
<td>Male sex</td>
<td>Diabetes</td>
<td>Cardiovascular accident within 31 days</td>
<td>Plaque ulceration</td>
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<td></td>
<td>Hyperlipidemia</td>
<td>Myocardial infarction</td>
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<tr>
<td></td>
<td>Hypertension</td>
<td>Congestive heart failure</td>
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<tr>
<td></td>
<td>SBP &gt; 160mmHg</td>
<td>Intermittent claudication</td>
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<td>DBP &gt; 90mmHg</td>
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### Table 5
| Number of Medical Risk Factors and Two-Year Risk for Ipsilateral Stroke |
|--------------------------|--------------------------|
| No. of risk factors | ARR (%) | NNT |
| 0–5 | 8 | 13 |
| 6 | 14 | 7 |
| ≥ 7 | 30 | 3 |

ARR, absolute risk reduction; NNT, number needed to treat.

### Table 6
| Effects of Plaque Ulceration and Ipsilateral Stenosis on Benefits of Surgery, Expressed as ARR and NNT for the Outcome any Stroke or Death, at Two Years |
|--------------------------|--------------------------|--------------------------|--------------------------|
| % Stenosis | Nonulcerated (n=429) | Ulcerated (n=230) |
| ARR | NNT | ARR | NNT |
| 75 (n=270) | 12 | 9 | 24 | 4 |
| 85 (n=237) | 11 | 9 | 37 | 3 |
| 95 (n=152) | 10 | 10 | 56 | 2 |

ARR, absolute risk reduction; NNT, number needed to treat.
A subgroup analysis from NASCET showed that symptomatic patients with concomitant ICA and ICC disease have a higher risk of subsequent stroke than patients with isolated ICA stenosis, but CE is not associated with a higher perioperative complication rate or long-term risk of stroke.33 This means that CE is more effective in these patients because the higher baseline risk of stroke translates into more favourable NNTs: for patients with > 70% ICA stenosis, the NNT at three years is 4 for patients with, and 7 for those without, ICC disease; and for patients with 50–69% stenosis, the NNTs are 12 and 26, respectively.

The presence of tandem intracranial and extracranial carotid disease thus increases the benefit of surgery, and this may be particularly important for decision making in patients whose angiogram shows 50–69% ICA stenosis.

Conclusions

Carotid endarterectomy reduces the risk of death or disabling stroke in surgically fit symptomatic patients with greater than 50% ipsilateral carotid stenosis. Consideration of the degree of stenosis, age, sex, other medical risk factors, stroke (rather than TIA), hemispheric (rather than retinal) events, plaque ulceration and the concomitant existence of ipsilateral intracranial carotid disease may be used to modify the decision as to whether to recommend carotid endarterectomy in addition to continued medical management and risk factor modification.

A final caveat is the low rate of perioperative stroke and death observed in these studies; the overall results are very sensitive to an increase in early postoperative events. It is therefore important that centres providing care for these patients prospectively monitor their complication rates.

References


No competing financial interests declared.