

Clinical Practice

This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.

EXTRACRANIAL CAROTID STENOSIS

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A 64-year-old man with a history of smoking and hypercholesterolemia has a sudden, transient loss of vision in his left eye. He reports a prior episode during which he had difficulty speaking and mild weakness of the right hand. The results of an examination are normal except for a bruit in the left side of the neck. He is found to have stenosis of the left carotid artery of 60 to 79 percent on high-resolution carotid ultrasonography, confirmed by magnetic resonance angiography. How should he be treated?

THE CLINICAL PROBLEM

Carotid stenosis is an important cause of transient ischemic attacks and stroke. With the introduction of cerebral angiography in the 1920s, carotid-artery disease was found among persons with stroke. Beginning in the 1950s, C.M. Fisher called attention to atherosclerosis involving the bifurcation of the extracranial carotid artery as an important cause of stroke and suggested surgery as a possible therapy.¹ The cause of carotid stenosis is most often atherosclerosis; endothelial injury, inflammation, lipid deposition, plaque formation, fibrin, platelets, and thrombin all contribute to the pathogenesis of the lesion. Carotid atherosclerosis accounts for 10 to 20 percent of cases of brain infarction, depending on the population studied.²

In a patient with sudden, transient loss of vision in one eye — known as transient monocular blindness, or amaurosis fugax — who has a history of diabetes, hypercholesterolemia, or cigarette smoking, carotid stenosis should rank first on the differential-diagnosis list. In patients with clonic, limb-shaking transient ischemic attacks that resemble focal seizures, a fractional hemiparesis in which the hand is weaker than the

shoulder, or a mild sensorimotor syndrome in the absence of localizing cortical signs such as aphasia or neglect, the diagnosis may be more difficult.³ Methods of diagnostic evaluation include high-resolution Doppler ultrasonography, magnetic resonance angiography, and spiral computed tomography, all of which have reasonable sensitivity and specificity for the diagnosis of carotid stenosis. These noninvasive techniques have reduced the need for conventional cerebral angiography.⁴ Other imaging techniques — such as positron-emission tomography, xenon computed tomography, single-photon-emission computed tomography, and transcranial Doppler ultrasonography with evaluation of vasoreactivity and detection of embolism — have been developed to identify patients who have hemodynamic insufficiency due to carotid disease and are thus at increased risk for stroke.⁵

STRATEGIES AND EVIDENCE

There are two main strategies for the treatment of carotid stenosis. The first approach is to stabilize or halt the progression of the carotid plaque through risk-factor modification and medication (Table 1). Hypertension, diabetes, smoking, obesity, and high cholesterol levels are closely associated with carotid stenosis and stroke; control of these factors may decrease the risk of plaque formation and progression. A small study of obese patients demonstrated that weight loss over a period of four years may reduce the progression of carotid plaques.⁶ Studies of statin therapy among high-risk patients with signs of subclinical carotid atherosclerosis have shown that plaque regression can be achieved, although it may be restricted to patients with nonstenosing carotid plaque.^{7,8} Treatment with angiotensin-converting-enzyme inhibitors has also reduced the intima-media thickness of the carotid artery and decreased the risk of stroke in high-risk patients.^{9,10} Finally, antithrombotic therapies have been proved to reduce the risk of stroke among those with a history of transient ischemic attacks or stroke, whereas a benefit of oral anticoagulants has not been shown.^{11,12}

The second approach is to eliminate or reduce carotid stenosis through carotid endarterectomy or carotid angioplasty and stenting. Carotid endarterectomy is the mainstay of therapy and is discussed later. Extracranial-intracranial bypass surgery was not found to provide a significant benefit in patients with carotid-artery occlusion or narrowing of the carotid artery distal to the carotid bifurcation.¹³ The use of more sensitive imaging techniques to refine the selection criteria in randomized clinical trials of extracranial-intracranial bypass surgery will be necessary if this procedure is to be reconsidered.¹⁴

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TABLE 1. MANAGEMENT OF RISK FACTORS FOR STROKE IN PATIENTS WITH ATHEROSCLEROTIC CAROTID STENOSIS.

RISK FACTOR	TARGET	COMMENT
Hypertension	Systolic blood pressure of less than 140 mm Hg and diastolic blood pressure of less than 90 mm Hg (for patients with diabetes, systolic blood pressure of less than 130 mm Hg and diastolic blood pressure of less than 85 mm Hg)	Use of angiotensin-converting-enzyme inhibitors should be encouraged.
Diabetes	Fasting blood glucose levels of less than 126 mg/dl (7 mmol/liter)	Diet and oral hypoglycemic agents or insulin should be prescribed as needed.
Elevated lipid levels	Low-density lipoprotein of less than 100 mg/dl (2.6 μ mol/liter)	The American Heart Association Step II diet (no more than 30 percent fat, less than 7 percent saturated fat, and less than 200 mg of cholesterol per day) is recommended. If lipid levels remain elevated, statin therapy is recommended.
Cigarette smoking	Stop smoking	Counseling, nicotine-replacement therapies, bupropion therapy, and formal smoking-cessation programs may all be helpful.
Alcohol use	Eliminate excessive use	Mild-to-moderate use (1 to 2 drinks per day) has been associated with a reduction in the risk of stroke.
Physical activity	30 to 60 minutes of exercise at least 3 times per week	

Angioplasty and stenting of the carotid artery have only recently become available, and therefore, there is no evidence that this approach is more effective than conventional carotid endarterectomy. Thus far, early trials and case series have shown that the outcomes of stenting are worse than or no different from those of carotid endarterectomy.¹⁵⁻¹⁷ Most of these studies were small, involved highly selected patients (many of whom would not have met the criteria for surgery), and were limited by the inexperience of the physicians with this new procedure. The recently initiated Carotid Revascularization with Endarterectomy or Stent Trial should provide more definitive evidence. As physicians performing carotid angioplasty and stenting become more skilled, the risks and benefits may approach those of carotid endarterectomy. More evidence is needed before we can advocate the widespread use of angioplasty plus stenting as routine care for patients with extracranial carotid stenosis.

Carotid Endarterectomy for Symptomatic Carotid Stenosis

For patients with symptomatic carotid stenosis of more than 70 percent, the value of carotid endarterectomy has been firmly established on the basis of the results of three major randomized trials, the North American Symptomatic Carotid Endarterectomy Trial (NASCET), the European Carotid Surgery Trial (ECST), and the trial by the Veterans Affairs Cooperative Studies Program.¹⁸⁻²⁰ Among patients with high-grade, symptomatic carotid stenosis, each trial showed

impressive relative and absolute reductions in risk for those randomly assigned to surgery.²¹ In NASCET, the two-year rate of ipsilateral stroke was 26 percent in the medical group and 9 percent in the surgical group, providing a relative reduction in risk of 65 percent and an absolute reduction in risk of 17 percent.¹⁸ Both NASCET and ECST showed that only seven or eight patients would need to undergo endarterectomy to prevent one stroke in a five-year period. A consensus was reached that carotid endarterectomy was the best option for the prevention of a recurrent event in the case of patients with symptomatic, ipsilateral carotid stenosis of more than 70 percent.

For patients with symptomatic carotid stenosis of less than 50 percent, these trials showed that there was no significant benefit of surgery. In ECST, no benefit of surgery was demonstrated among those with ipsilateral carotid stenosis of less than 30 percent.¹⁹ Among patients with stenosis of less than 50 percent in NASCET, there was no significant difference in the risk of ipsilateral stroke between those who were treated with endarterectomy and those who were treated medically.²²

The benefits of endarterectomy in patients with moderate symptomatic carotid stenosis (i.e., of 50 to 69 percent) in NASCET and ECST were clearly less than those seen in patients with more severe stenosis.^{22,23} In ECST, there was no significant benefit of surgery for those with moderate stenosis. In NASCET, the five-year risk of fatal or nonfatal ipsilateral stroke among patients with stenosis of 50 to 69 percent was

22.2 percent in the medical group and 15.7 percent in the surgical group ($P=0.045$).²² The absolute reduction in risk was 6.5 percent — in other words, for every 15 patients treated one stroke was prevented within five years after surgery.

The benefits of carotid endarterectomy for moderate carotid stenosis were greatest in those with more severe stenosis, those 75 years of age and older, men, patients with a recent (within three months) history of stroke (rather than transient ischemic attacks) as the qualifying event, and patients with hemispheric transient ischemic attacks rather than transient monocular blindness.^{22,24} Patients with transient monocular blindness have a better prognosis than those with hemispheric transient ischemic attack; however, when other risk factors are present, the benefits of endarterectomy are more apparent.²⁵ Radiographic factors that predicted more favorable outcomes after carotid endarterectomy included the presence of intracranial stenosis, the absence of microvascular ischemia (i.e., leukoariosis, or periventricular white-matter lucencies seen on computed tomography of the head), and the presence of collateral vessels.^{26,27} Sex, age, the presence or absence of coexisting conditions, and the experience of the surgeon must be considered during evaluation of treatment options for patients with stenosis of 50 to 69 percent, because the absolute benefit of surgery is less than that for patients with severe stenosis.

Carotid Endarterectomy for Asymptomatic Carotid Stenosis

Asymptomatic carotid stenosis is a clear risk factor for stroke; however, the risk is lower than that associated with symptomatic disease. In observational studies, the rate of ipsilateral stroke was 1 to 3 percent per year among patients with asymptomatic stenosis of greater than 50 percent,^{28,29} and the risk in NASCET was 3.2 percent per year for asymptomatic stenosis of 60 to 99 percent.³⁰ The risk of stroke increased only slightly with increasing stenosis. The occurrence of symptoms may depend on the severity and progression of the stenosis, the adequacy of collateral vessels, the character of the atherosclerotic plaque, and the presence or absence of other risk factors for stroke.

The surgical treatment of asymptomatic carotid stenosis is a source of continuing debate. Four randomized, controlled trials have addressed this question.³¹⁻³⁴ Some have been impaired by small sample sizes, a lack of uniform treatment of the medical and surgical groups with aspirin, high perioperative mortality rates, or the exclusion of certain high-risk groups.^{31,32} The Veterans Affairs Cooperative Study of carotid endarterectomy randomly assigned 444 men with asymptomatic carotid stenosis of at least 50 percent (determined by cerebral angiography) to undergo carotid endarterectomy or receive 650 mg of aspirin twice daily.³³ The incidence of fatal or nonfatal stroke after angiography and surgery was 4.7 percent. The inci-

dence of the primary outcome of ipsilateral transient ischemic attacks, transient monocular blindness, or stroke within two years of follow-up was significantly lower in the surgical group (8.0 percent vs. 20.6 percent; relative risk reduction, 61 percent; $P<0.001$). The incidence of fatal or nonfatal ipsilateral stroke was not significantly lower in the surgical group (4.7 percent vs. 9.4 percent, $P=0.08$), but a much larger sample would have been needed to detect a difference in the risk of stroke alone.

The largest randomized trial to evaluate the efficacy of endarterectomy for patients with asymptomatic disease was the Asymptomatic Carotid Atherosclerosis Study (ACAS).³⁴ Patients were younger than 80 years and had asymptomatic carotid stenosis of 60 percent or more, as determined by Doppler ultrasonography, and stable cardiac disease. Complications of angiography occurred in 1.2 percent, and the perioperative risk of stroke was 2.3 percent. After a median follow-up of 2.7 years, the study was stopped early because a significant benefit from surgery was found. The risk of ipsilateral stroke or any perioperative stroke or death was 5 percent during five years of follow-up in surgically treated patients and 11 percent in medically treated patients. The absolute annual rates of adverse events — 1 percent in the surgically treated group and 2 percent in the medically treated group — were consistent with the results of the Veterans Affairs Cooperative Studies. As compared with the trials in patients with symptomatic disease, ACAS found smaller absolute reductions in risk (approximately 6 percent at five years), indicating that 17 patients would need to undergo surgery to prevent one event within five years.

In ACAS, the benefit of surgery was greater for men than women (reduction in risk, 66 percent vs. 17 percent), and the rate of perioperative complications was higher among women than men (3.6 percent vs. 1.7 percent). The benefit of surgery was not related to the degree of carotid-artery stenosis. On the basis of the absolute risks of stroke, it was clear that a rate of perioperative complications (stroke or death) of more than 3 percent would eliminate the potential benefit of the operation. Such low complication rates are unusual in community-hospital settings.³⁵ There are numerous risks associated with the surgical procedure that need to be considered.³⁶ At present, any decision regarding the use of endarterectomy depends on minimizing the complication rates by having an experienced surgeon (one whose patients have a complication rate of less than 3 percent) perform the surgery.³⁷

AREAS OF UNCERTAINTY

Effective strategies are needed to identify which patients with asymptomatic carotid stenosis or symptomatic moderate stenosis are likely to benefit from surgery. Two ongoing trials may provide more information to direct the care of patients with asymptomatic disease.^{38,39} More data on the role of hemodynamic

testing, schemes for risk stratification, and preoperative cardiac testing are needed to help select the best candidates for surgery. The optimal time to perform carotid surgery in a patient with symptomatic disease remains uncertain, as does the optimal short-term therapy for patients awaiting endarterectomy. More data are needed to clarify the role of carotid angioplasty with stenting; this is currently being studied. Finally, it is not known whether patients with carotid stenosis should be routinely treated with statins and angiotensin-converting-enzyme inhibitors.

GUIDELINES

The American Heart Association and the National Stroke Association have published the most comprehensive guidelines for the prevention of stroke among persons with carotid stenosis^{28,40-43} (Tables 1 and 2). Management algorithms are dependent on whether the patient has symptomatic or asymptomatic disease, the degree of carotid stenosis, and the underlying risk of stroke on the basis of coexisting conditions. The American Heart Association guidelines for the care of patients with transient ischemic attacks and minor stroke due to carotid stenosis include recommendations regarding risk factors, the use of antithrombotic medications, and the use of angioplasty and endarterectomy.⁴² The guidelines for asymptomatic carotid stenosis have not been accepted as widely as those for symptomatic carotid stenosis (Table 2).

CONCLUSIONS AND RECOMMENDATIONS

Among patients with severe symptomatic carotid stenosis, the evidence in favor of endarterectomy is

clear (Fig. 1). Unless there is a major contraindication, I discuss the benefits of surgery with my patients and their families, and most undergo carotid endarterectomy. This would be my approach for the patient described in the case vignette. For those for whom surgery carries a particularly high risk (e.g., those with coexisting conditions, atherosclerotic disease beyond the bifurcation, or recurrent carotid stenosis), I would consider referral for angioplasty and stenting, especially if medical therapies are failing. Surgery is not indicated for patients with mild symptomatic carotid stenosis (of less than 50 percent). Some patients with symptomatic stenosis of 50 to 69 percent will benefit from surgery, but the decision should be individualized on the basis of several factors, including the presence or absence of risk factors for stroke and local surgical expertise (Fig. 1).

For patients with asymptomatic carotid stenosis of 60 percent or more, the decisions are difficult. From a public health perspective, it is clear that carotid endarterectomy would not be cost effective for all patients with asymptomatic disease.⁴⁴ Clinicians should consider surgery for patients without apparent contraindications at a center where they know the surgeons can perform the operation at a rate of perioperative stroke or death of less than 3 percent. Preoperative cardiac or hemodynamic evaluation may help in risk stratification. After the risks and benefits are explained to the patient, the ultimate decision depends on whether the patient is willing to accept the early risk and nuisance of the surgery in the hope of long-term benefit.

In all cases, risk-factor control should be emphasized. I more frequently recommend angiotensin-con-

TABLE 2. GUIDELINES FOR THE CARE OF PATIENTS WITH CAROTID DISEASE.*

THERAPY	RECOMMENDATIONS
Symptomatic carotid stenosis	
Antithrombotic medications	All patients should receive an antiplatelet agent. Aspirin, clopidogrel, and the combination of aspirin and dipyridole are all acceptable options for initial therapy. Anticoagulant therapy is not routinely recommended.
Endovascular therapy	This approach is not routinely recommended.
Carotid endarterectomy	This approach is indicated for patients with stenosis of 70 to 99 percent and for those who are good candidates for surgery and have had symptoms within the previous two years. It should be considered for patients with stenosis of 50 to 69 percent, on the basis of the clinical features that influence the risk of stroke and surgical morbidity. It is not indicated for patients with stenosis of less than 50 percent.
Asymptomatic carotid stenosis	
Carotid endarterectomy	This approach should be considered in patients under the age of 80 with stenosis of more than 60 percent if an experienced surgeon is available. Factors such as the presence or absence of coexisting conditions, life expectancy, and the preference of the patient should be considered.

*Data are from the American Heart Association^{28,42} and the National Stroke Association.⁴³

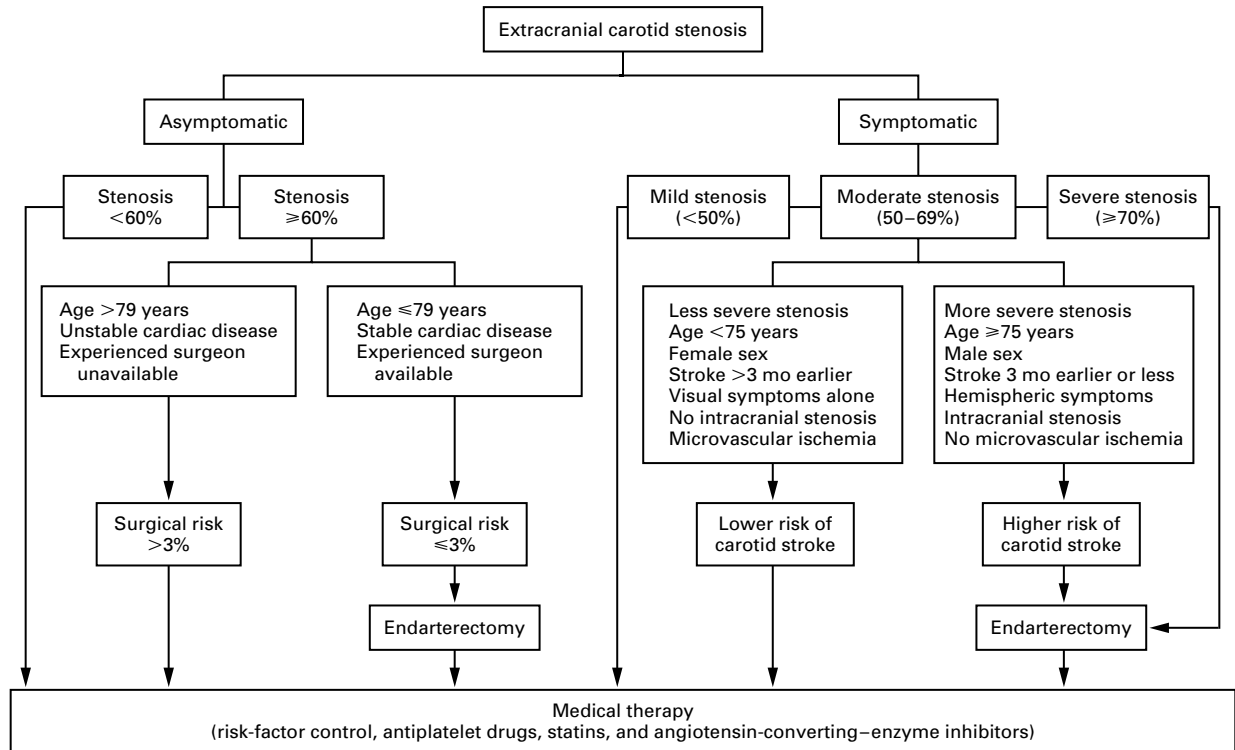


Figure 1. Algorithm for the Management of Extracranial Carotid Stenosis.

The algorithm is partially based on the Guidelines of the American Heart Association and the National Stroke Association.^{28,41-43} Other factors not included in the figure may also be relevant in risk stratification (e.g., the results of cardiac evaluation or hemodynamic testing).

verting-enzyme inhibitors to patients with hypertension and prescribe statins even for patients with normal-to-borderline cholesterol levels. Antiplatelet therapy is appropriate for all patients who do not have a contraindication, and changes in lifestyle (smoking cessation, weight control, exercise, and avoidance of excessive alcohol consumption) should be routinely encouraged.

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