

CLINICAL DECISIONS

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Management of Carotid Stenosis

This interactive feature addresses the diagnosis or management of a clinical case. A case vignette is followed by specific clinical options, none of which can be considered either correct or incorrect. In short essays, experts in the field then argue for each of the options. In the online version of this feature, available at www.nejm.org, readers can participate in forming community opinion by choosing one of the options and, if they like, providing their reasons.

CASE VIGNETTE

A 67-year-old man with a history of hypertension and hyperlipidemia is seen for a routine examination. His medications include hydrochlorothiazide (25 mg daily), simvastatin (20 mg daily), and aspirin (81 mg daily). He drinks alcohol rarely and does not smoke.

His body-mass index (the weight in kilograms divided by the square of the height in meters) is 27, consistent with overweight. His blood pressure is 140/85 mm Hg, and his heart rate is 72 beats per minute and regular. His cardiac examination is normal. Auscultation of the neck shows normal carotid upstrokes but reveals a middle-pitched bruit only in systole at the angle of the right jaw. A detailed neurologic examination is normal.

On questioning, the patient does not report any history of transient neurologic deficits — specifically, no unilateral weakness or sensory symptoms, visual disturbances, or speech or language difficulty.

Noninvasive testing of the carotid arteries reveals a stenosis of 70 to 80% of the proximal right

carotid artery with an irregular plaque and peak velocity of 339 cm per second. There is 20% stenosis in the left proximal carotid artery.

Which one of the following initial treatment options, any of which could be considered correct, would you find most appropriate for this patient? Base your choice on the published literature, your past experience, recent guidelines, and other sources of information, as appropriate.

1. Medical management.
2. Carotid stenting.
3. Carotid endarterectomy.

To aid in your decision making, each of these approaches to treatment is defended by an expert in the management of carotid stenosis in the following short essays. Given your knowledge of the condition and the points made by the experts, which treatment approach would you choose? Make your choice on our Web site (www.nejm.org).

TREATMENT OPTION 1

Medical Management

Cathy A. Sila, M.D.

Recommendations for the treatment of a patient with asymptomatic carotid stenosis of 70 to 80%, such as the patient in the case vignette, should be based on an understanding of the adverse events that are most likely to occur and the benefits and risks of the treatment over time.

The best outcome-based data for patients with asymptomatic carotid stenosis come from the Asymptomatic Carotid Atherosclerosis Study (ACAS) and the Asymptomatic Carotid Surgery

Trial (ACST; Current Controlled Trials number, ISRCTN26156392).^{1,2} Although stroke may be the most feared consequence of carotid disease, the most common adverse event in these studies was death from myocardial infarction or other (non-stroke) cardiovascular causes. Nonfatal myocardial infarctions were not reported separately, but the rate of fatal events alone is consistent with a high risk of coronary heart disease according to the Framingham model (>20% over a 10-year period). Fatal or nonfatal strokes were the next-most-common adverse events, but only one third to one half of these strokes were ischemic and ipsilateral and could be attributed to the carotid stenosis.

Aggressive medical management of vascular risk factors can reduce both coronary and cerebrovascular events in patients with carotid disease, although the definition and execution of medical therapy vary from trial to trial. In five randomized clinical trials (including ACAS and ACST) of medical therapy alone for asymptomatic carotid stenosis as compared with endarterectomy plus medical therapy, the medical therapy consisted of an antiplatelet regimen and counseling about risk factors, but the subsequent care of patients was delegated to the primary physician. Although the degree of compliance with antiplatelet therapy was reported, the degree of success with control of risk factors was not. In the ACST, the definition of best medical therapy evolved during the study, with patients in the final cohort receiving antiplatelet therapy (given to 90% of patients), antihypertensive therapy (81%), and lipid-lowering therapy (70%). Three of the five trials, including a total of 925 patients with asymptomatic carotid stenosis of more than 50%, showed no significant reduction in the risk of stroke or death with endarterectomy as compared with medical therapy alone. In the two larger trials, including a total of 4782 patients with asymptomatic carotid stenosis of 60 to 99% or 70 to 99%, adding endarterectomy to medical therapy did reduce the combined rate of ipsilateral stroke at 5 years and perioperative stroke and death (11.0 to 11.8% reduced to 5.1 to 6.4%), with low procedural risk (2.3 to 3.1%). However, the goal of preventing a disabling or fatal stroke with the use of surgery was achieved only in ACST, and that reduction of 0.5% per year means that 40 patients would need to be treated to prevent one major stroke over a 5-year period.

Medical therapy alone should be recommended if procedural risks (of surgery as well as angiography) are expected to exceed 3.0%. Unfortunately, in contrast to rates in the trials discussed above, rates as high as 4.7 to 6.7% have been reported with endarterectomy in other clinical trials and in the Medicare population.³ Published postapproval carotid-stenting registries have also reported procedural risks exceeding the safety threshold set by the American Heart Association and the American Academy of Neurology. Currently, carotid stenting for asymptomatic stenosis in low-risk patients is reimbursed by the Centers for Medicare and

Medicaid Services only in the context of a clinical trial approved by the Food and Drug Administration (FDA). Such patients should be referred to ongoing randomized trials — the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST; ClinicalTrials.gov number, NCT00004732) or the Carotid Stenting vs. Surgery of Severe Carotid Artery Disease and Stroke Prevention in Asymptomatic Patients (ACT I) trial (ClinicalTrials.gov number, NCT00106938). Also, since the risks of revascularization are immediate, whereas the benefit to an asymptomatic patient is accrued only over time, high-risk asymptomatic patients with poor 5-year survival (e.g., those with previous vascular surgery, claudication, cardiac disease, an abnormal electrocardiogram, diabetes mellitus, or older age) should also be treated medically.⁴

Available data from the clinical trials probably underestimate the benefit that could be derived from medical intervention. For the patient in the case vignette, I would encourage lifestyle modifications including weight and girth loss, dietary counseling, and lipid-lowering therapy to achieve a low-density lipoprotein level of less than 100 mg per deciliter (2.6 mmol per liter) (with consideration of a target of <70 mg per deciliter [1.8 mmol per liter]), a triglyceride level of less than 150 mg per deciliter (1.7 mmol per liter), and a high-density lipoprotein level of more than 40 mg per deciliter (1.0 mmol per liter). For patients who smoke, I also recommend smoking cessation. Antihypertensive therapy should be adjusted to maintain blood pressure below 140/90 mm Hg or, if there is evidence of diabetes or kidney disease, below 130/80 mm Hg. Diabetes screening should be performed and hyperglycemia treated, with a target glycated hemoglobin level of less than 7%. Given the high risk of concomitant coronary heart disease, provocative testing should be performed before initiation of a moderate-intensity aerobic physical exercise program (≥ 30 minutes most days of the week).⁵ Patients and their families should be educated about the symptoms of transient ischemic attack and stroke, which require urgent reevaluation and treatment.

No potential conflict of interest relevant to this article was reported.

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TREATMENT OPTION 2

Carotid Stenting

Randall T. Higashida, M.D.

Carotid atherosclerotic disease is responsible for a significant proportion of major disabling strokes and death. Effective prevention by means of revascularization is the best course of treatment, if performed at a center with an acceptably low procedural complication rate.

The ACAS, published in 1995, involved 1662 patients with asymptomatic carotid stenosis of more than 60%.¹ Patients were prospectively, randomly assigned to undergo either surgical revascularization or aggressive medical management. The primary outcome was any major stroke or death; the median follow-up was 2.7 years. The aggregate risk of any stroke or perioperative death over a 5-year period favored revascularization (5.1%, vs. 11.0% for medical therapy; 95% confidence interval [CI], 0.9 to 9.1; relative risk reduction, 53.6%). The authors concluded that elective surgical revascularization will reduce the 5-year risk of ipsilateral stroke if performed at a center associated with a perioperative morbidity rate of less than 3%. In 2004, the results of the ACST, a confirmatory randomized trial of 3120 patients with asymptomatic stenosis of more than 60%, were published.² An absolute reduction of 5.3% (95% CI, 3.0 to 7.8) in the rate of the primary end point — any stroke or perioperative death at 5 years — with early treatment translated into a significant relative risk reduction of 54.0% ($P < 0.001$).

Over the past decade, numerous clinical trials have compared surgery with an alternative, less invasive treatment: carotid-artery stenting with the use of distal-protection devices. The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) involved the random assignment of 504 patients to undergo either angioplasty, with or without stenting, or surgery. The 30-day rates of stroke and death were similar in the two groups. In the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial, 334 patients who had symptomatic stenosis of more than 50% or asymptomatic stenosis of more than 80% and who were high-risk surgical candidates were randomly assigned to undergo either stenting or surgery.⁶ The primary

end point of stroke, death, or myocardial infarction within 30 days after the procedure, or ipsilateral stroke between 31 days and 1 year after, strongly favored stenting over surgery (12.2% of patients vs. 20.1%; absolute difference, 7.9%; 95% CI, -16.4 to 0.7; $P = 0.004$ for noninferiority and $P = 0.053$ for superiority).

A Cochrane analysis in 2005 evaluated data from five randomized trials, involving 1269 patients, comparing the safety and efficacy of endovascular stenting with that of surgery.⁷ The 30-day and 1-year safety data showed no significant difference between the two groups in the odds of having a treatment-related stroke or the odds of any stroke, death, or both. In addition, the rates of cranial nerve injury and minor complications were significantly lower with stenting than with surgery.

On the basis of these studies, the FDA granted approval in 2005 for carotid stenting for both symptomatic and asymptomatic patients who are high-risk surgical candidates and are enrolled in postapproval studies, and the Centers for Medicare and Medicaid Services approved payment for these procedures.⁸ The ongoing National Institutes of Health–sponsored CREST, a prospective, multicenter, randomized study of 2500 patients, is nearing completion. This trial may provide clinically directive information about the relative safety and efficacy of surgery, as compared with carotid stenting, for both symptomatic and asymptomatic patients.

The advantages of carotid stenting are numerous. Stenting is performed under local anesthesia, permitting continuous neurologic monitoring, and is considered minimally invasive, involving only a small opening (<3 mm in diameter) in the femoral artery, as compared with the much larger, open incision across the neck required for endarterectomy. Direct surgical exposure of the neck vessels increases the risks of wound infection, cranial nerve deficits, vocal cord paralysis, hoarseness, and dysphagia; 8 to 10% of surgical patients experience one or more of these complications. Scarring and other major surgical complications are significantly less common with stenting. Complete recovery time is much shorter with stenting, averaging 2 to 4 days, as compared with 2 to 4 weeks with surgery. As the design of both stents and distal-protection devices improves, so do the outcomes. Large database registries indicate that the

real-world experience of stenting in both symptomatic and asymptomatic patients makes it acceptable for routine clinical use.

The patient in the case vignette should be counseled that with the best medical therapy, his risk of a major stroke or death over a 5-year period is 11 to 12% and that by undergoing a revascularization procedure he can reduce his risk to approximately 5 to 6%. There are now two viable revascularization options: open surgery, requiring a large incision across the neck, and the much less invasive stenting procedure, which is performed under local anesthesia. Although this patient is not considered to be at high surgical risk, private insurance companies and Medicare will consider, on a case-by-case basis, payment for carotid-artery stenting performed in qualified centers or as part of a clinical trial. Both procedures, when performed in centers with capable and experienced physicians, have a periprocedural rate of major complications of less than 3%. I would strongly advise the patient to undergo carotid-artery stenting as definitive therapy to improve his longevity and quality of life.

Dr. Higashida reports being the National Co-Principal Investigator of the Medtronic Self-Expanding Carotid Stent System with Distal Protection in the Treatment of Carotid Stenosis (MAVERIC) trials I, II, and III and participating in the Abbott Carotid Artery Stent Trial and Guidant's Capture 2 Post Market Carotid Artery Stenting Registry. No other potential conflict of interest relevant to this article was reported.

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TREATMENT OPTION 3

Carotid Endarterectomy

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The patient in the case vignette is an ideal candidate for carotid endarterectomy to prevent stroke because of the favorable benefit-to-risk ratio. Two large-scale, rigorous trials evaluating the use of carotid endarterectomy in asymptomatic patients with advanced stenoses (>60%) reached similar conclusions despite being carried out on different continents a decade apart.^{1,2} In both, as compared with the best medical therapy, the use of carotid endarterectomy resulted in a significantly reduced rate of stroke and death at 5 years (absolute risk

reduction, 5.4 to 5.9%; relative risk reduction, 46.0 to 53.0%; $P < 0.001$).

Because the patient has a low operative risk, there is no reason that he should not realize the benefit of carotid endarterectomy. He is also unlikely to be harmed by the procedure. In the U.S. trial,¹ the 30-day rate of perioperative stroke or death was 1.1%, after exclusion of the 1.2% rate of stroke from arteriography, a procedure that is rarely performed today in patients with carotid occlusive disease. It has been argued that these results, showing exceptionally low morbidity and mortality, are unlikely to be replicated in routine clinical practice because of the rigorous selection and vetting of surgeons participating in clinical trials. However, recent, large-scale database analyses from the United States⁹ and Canada¹⁰ document overall rates of stroke and death in patients undergoing carotid endarterectomy to be well within the range of those found in clinical trials, with stroke rates as low as 0.5%.

The absolute reduction in the risk of stroke or death of 5 to 6% with carotid endarterectomy in asymptomatic patients, although significant, is relatively modest and suggests that approximately 17 patients would need to undergo surgery to prevent one stroke or death. This has led to unsuccessful attempts to define more precisely the patients with asymptomatic carotid stenosis who would most likely benefit from the operation. The converse — identifying patients who may be less likely to benefit and more likely to suffer complications from surgery — has been more feasible. Symptomatic disease, age older than 75 years, female sex, contralateral occlusion, left-sided procedure, severe systolic hypertension, and previous angina or congestive heart failure have all been associated with an increased risk of perioperative stroke or death.¹¹ Our hypothetical patient has none of these risk factors for adverse outcomes.

Other strategies to treat this patient are possible, but none have been shown to be as effective as carotid endarterectomy. The most compelling alternative is intensive medical therapy with aggressive suppression of platelet function, targeted blood-pressure control (possibly with the addition of beta-blockade and an angiotensin-converting-enzyme inhibitor), and statin therapy. The argument has been made that the “best medical therapy” received by patients in past clinical trials did not include widespread use of these current thera-

pies that have been shown to reduce the risk of stroke. Would intensive medical therapy erase the benefit of carotid endarterectomy in asymptomatic patients and therefore make it unnecessary? This important question can be answered only by a proper clinical trial comparing the two treatments. Until this is accomplished, any claim regarding a benefit of intensive medical therapy as compared with carotid endarterectomy remains conjectural.

The other therapy that might be considered is carotid angioplasty and stenting. Although this intervention has a role in patients considered for carotid endarterectomy who are deemed to be at high surgical risk, the role of angioplasty and stenting in low-risk, asymptomatic patients is unknown.

Ultimately, the patient will decide whether he wants to undergo carotid endarterectomy, after a thorough, unbiased presentation of the risks and potential benefits of the procedure. If he elects not to have the operation, intensive medical therapy, counseling of the patient and his family about the warning symptoms of transient ischemic attacks, and careful follow-up are indicated. Before surgery is scheduled, it may be important to confirm the results of duplex ultrasonography by performing magnetic resonance or computed tomographic arteriography, although this is unnecessary if the duplex images came from an appropriately accredited and reliable vascular laboratory. Finally, the surgeon's level of experience is extremely important in realizing a beneficial outcome from carotid endarterectomy.⁹ The chosen surgeon should be well trained and have documentation of good outcomes (overall rate of stroke or death, <3%).

No potential conflict of interest relevant to this article was reported.

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