CLINICAL PRACTICE

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Carotid Stenosis

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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.*

A 53-year-old woman who smoked and had hypertension had brief numbness of the right side of her body. Six months later, aphasia and right hemiparesis suddenly developed, and they resolved after 48 hours. Computed tomographic angiography (CTA) showed left internal-carotid-artery stenosis of 70% just distal to the bifurcation. Magnetic resonance imaging (MRI) confirmed a left frontotemporal infarct without hemorrhagic transformation or cerebral edema. Cardiac evaluation was normal. What is the appropriate management of this patient's carotid stenosis?

THE CLINICAL PROBLEM

Carotid artery disease causes approximately 10 to 20% of strokes, and appropriate intervention is important for secondary and possibly primary stroke prevention. The degree of carotid stenosis is the strongest determinant of stroke risk.

ATHEROSCLEROSIS

Atherosclerosis, the most common disease affecting the carotid artery, occurs most frequently at its bifurcation (Fig. 1A and 1B). Atherosclerotic plaques cause symptoms most often through distal embolism to branches of the retinal or cerebral arteries; hemodynamically significant luminal stenosis may also result in critical reduction of perfusion.

Most emboli result from activation of platelets on the plaque surface; less frequently, they result from cholesterol particles. An "unstable plaque" with rupture of the cap may cause emboli.[1] Emboli in retinal arterioles lead to transient monocular blindness (amaurosis fugax).[2] Emboli in the cerebral circulation most often lodge in the middle cerebral-artery branches, but they can also end up in anterior or posterior cerebral-artery branches, depending on the anatomy of the circle of Willis. If patients who have had a stroke attributed to carotid disease are questioned closely, at least 50% report symptoms preceding the stroke that are consistent with a transient ischemic attack (TIA).[3] Stroke syndromes related to carotid disease involve some combination of motor or sensory symptoms (involving the contralateral face, arm, or leg) or speech, language, or visual symptoms.

Reduction of flow due to high-grade stenosis causes symptoms referable to brain regions at the border zones between the anterior, middle, and posterior cerebral arteries, where perfusion pressure is the lowest and most vulnerable to further reduction by proximal stenosis.[4] Such lesions often cause repetitive TIAs that are brief (<1 minute), sometimes with limb shaking, as compared with embolic TIAs, which tend to be longer (5 to 30 minutes).[5] Border-zone ("watershed") infarcts can be distinguished from embolic infarcts on brain imaging (see Fig. S1a and S1b in the Supplementary Appendix, available with the full text of this article at NEJM.org).

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KEY CLINICAL POINTS

CAROTID STENOSIS

- Carotid artery disease is a common cause of stroke and should be assessed by means of one of several readily available noninvasive tests in all patients who have had a transient ischemic attack (TIA) or stroke in the carotid-artery distribution.
- Control of smoking, hypertension, and hyperlipidemia and the use of an antiplatelet agent are indicated to reduce the risk of stroke among persons with carotid artery disease.
- In patients with an ischemic stroke or a TIA in the carotid-artery distribution, carotid endarterectomy should be considered within 2 weeks if there is stenosis of more than 70% of the diameter of the ipsilateral carotid artery (measured according to the method used in the North American Symptomatic Carotid Endarterectomy Trial) due to atherosclerosis. There is less benefit in patients with stenosis of 50 to 69% and in asymptomatic patients, and there is no benefit in patients with stenosis of less than 50%.
- Carotid stenting is an alternative to carotid endarterectomy, particularly in patients at high surgical risk and in younger patients (<70 years of age).

The prognosis for patients with carotid disease is most closely linked to the degree of stenosis, with a 2-mm residual luminal diameter or a 60 to 70% reduction in diameter associated with a marked increase in the risk of stroke.[6] Plaque ulcerations are common, but they do not strongly correlate with subsequent ipsilateral ischemic stroke.[7]

Whereas total occlusion of the carotid in some patients results in a devastating stroke, it can be asymptomatic in patients with adequate collateral flow to the intracranial arteries.[8] The contralateral carotid provides collateral flow through the anterior communicating artery (Fig. S2 in the Supplementary Appendix). Consequently, contralateral carotid stenosis or occlusion is an important determinant of risk that should be considered in planning treatment. Carotid siphon atherosclerosis can also cause TIAs and strokes.[9]

DISSECTION AND FIBROMUSCULAR DYSPLASIA

Dissection of the carotid artery is a common cause of stroke in patients younger than 45 years of age, and it is frequently detected by means of noninvasive vascular imaging.[10,11] Carotid dissection usually occurs about 2 cm distal to the bifurcation (Fig. S3a in the Supplementary Appendix), and it may be related to trauma to the artery by the transverse processes of the C2 and C3 vertebrae or the styloid process. Dissection, which can occur spontaneously, is due to a hematoma in the tunica media that ruptures through the intima and compromises the arterial lumen. If the dissection extends toward the adventitia, a dissecting aneurysm (often erroneously called a pseudoaneurysm) can develop, but these aneurysms rarely bleed unless the dissection extends intracranially. Considerable ipsilateral neck, facial, or head pain occurs in more than 60% of dissections, and if such pain is present after trauma or in association with a TIA or stroke, dissection should be suspected. Horner's syndrome may also be present as a result of injured sympathetic nerves in the arterial wall, and lower cranial nerves may be compressed. Genetic collagen abnormalities such as the Ehlers–Danlos syndrome (type IV) should be considered in patients with spontaneous dissection.

Fibromuscular dysplasia is twice as common in women as in men,[11] and it is marked by fibrotic thickening of the arterial wall, most often the media (Fig. S3b in the Supplementary Appendix). Fibromuscular dysplasia is associated with intracranial aneurysms and carotid dissection. Both dissection and fibromuscular dysplasia can cause strokes due to embolization or hemodynamically significant narrowing of the luminal diameter.

Other, less common arterial diseases are beyond the scope of this review. Coiling, looping, and kinking of the extracranial carotids are common but rarely of pathologic significance.[12]

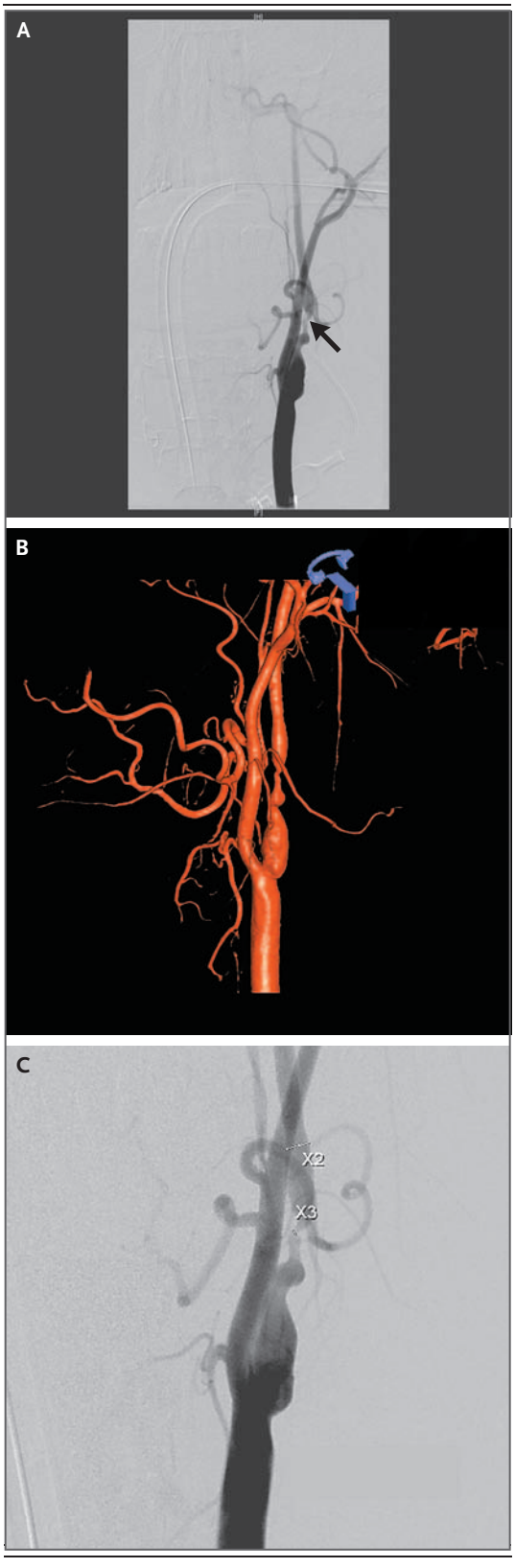
STRATEGIES AND EVIDENCE

DIAGNOSIS

A carotid bruit may signal the presence of clinically significant internal carotid artery disease; this finding is present in 70 to 89% of patients with a

Figure 1. Atherosclerosis at the Bifurcation of the Carotid Artery in the Patient in the Case Vignette.

Panel A shows a cerebral arteriogram indicating stenotic plaque (arrow) before stenting. Panel B shows a three-dimensional reconstruction of the angiogram. Panel C shows calculation of the percentage of stenosis with the use of the North American Symptomatic Carotid Endarterectomy Trial criteria. The minimal diameter (X3) is 0.89 mm, and the distal diameter (X2) is 3.30 mm. The percentage of stenosis is calculated as [1 – (X3 ÷ X2)] × 100, which in this case is 73%. Images courtesy of Peng Chen, M.D.



2-mm luminal narrowing. However, a bruit is a nonspecific finding, since it is heard in 5% of patients who are 45 to 80 years of age in the absence of clinically significant internal carotid disease.[13]

The various tests for evaluating carotid disease are listed in Table 1. The most common screening test is duplex Doppler ultrasonography (Fig. 2). Ultrasonography is highly accurate in identifying calcification of carotid-artery plaque and intraplaque hemorrhage and measuring the degree of stenosis,[14] and it is indicated in patients who have had ischemic symptoms in the carotid-artery distribution or who have a carotid bruit and would be candidates for intervention. A peak systolic velocity in excess of 200 cm per second usually indicates stenosis of 50% or more.[15]

CTA (Fig. 3) and magnetic resonance angiography (MRA) are widely used to evaluate the carotid artery.[16,17] Carotid Doppler ultrasonography with either CTA or MRA may be sufficient for making clinical decisions about the management of carotid disease. However, in some cases, cerebral angiography may be necessary to provide additional anatomical detail[18] (Fig. 1A and 1B).

The most important information gained from each of these tests is the percentage of stenosis. The measurement method used in the North American Symptomatic Carotid Endarterectomy Trial (NASCET)[19] is used most widely (Fig. 1C). The diameter of the smallest residual lumen is compared with the diameter of the normal artery distal to the carotid bifurcation, according to the following formula: the percentage of stenosis = [1 – (minimal diameter ÷ distal diameter)] × 100. Imaging also identifies the location of the bifurcation in relation to the angle of the jaw, the extent of plaque, distal arterial tortuosity or stenosis, and the status of contralateral carotid and

Table 1. Tests to Detect Carotid Stenosis.

Test	Feasibility	Accuracy	Risks
Ultrasonography	Widely available, rapidly performed	Detects bifurcation only	None
Magnetic resonance angiography	Requires patient to be immobile for duration of test; not feasible in patients with metallic implants or in severely obese patients	Cannot discriminate subtotal from total occlusion	Gadolinium usually not needed; when used, it carries risk of nephrogenic systemic fibrosis; gadolinium contraindicated in patients with renal insufficiency
Computed tomographic angiography	Widely available, rapidly performed	Provides good resolution of entire vascular tree	Iodinated contrast material carries risk of nephrotoxic effects; computed tomographic angiography should be avoided in patients with renal insufficiency
Catheter angiography	Requires angiography team	Excellent	0.5–1.0% Risk of stroke, myocardial infarction, arterial injury, retroperitoneal bleeding

collateral flow, and it can usually be used to distinguish atherosclerosis from other conditions (Fig. S3a and S3b in the Supplementary Appendix).

Other techniques to assess carotid atherosclerosis have been described; these include high-resolution MRI of the arterial wall to examine the morphologic characteristics of the plaque,[1] ultrasonographic assessment of the carotid intima–media thickness,[20] detection of microemboli by means of ultrasonography,[21] and imaging of adhesion molecules on the surface of the plaque or inflamed area.[22] However, data are lacking to determine the role of these techniques, if any, in clinical practice.

MEDICAL MANAGEMENT

Aggressive treatment of modifiable risk factors for carotid atherosclerosis — especially hypertension and hyperlipidemia — and cessation of smoking are central to stroke prevention. Measures to reduce stroke risk have been reviewed in a previous Clinical Practice article[23] and in guidelines for primary and secondary stroke prevention.[24,25]

Some aspects of risk-factor management particular to patients with severe carotid-artery stenosis warrant mention. In patients with hypertension, treatment goals must take into account the risk of reduced cerebral perfusion with overly aggressive treatment, pending correction of stenosis. Treated patients should be followed carefully for clinical deterioration, and relative hypotension should be immediately corrected. Furthermore, special attention to blood-pressure control is required to avoid hypoperfusion during carotid endarterectomy or stenting and the hyperperfusion syndrome immediately afterward.[26]

Statin drugs are effective for both primary and secondary stroke prevention, and they may lead to stabilization and even regression of intima–media thickness of the carotid-artery wall.[27]

Antiplatelet drugs logically would be of particular benefit in patients with carotid plaques that cause platelet activation. Patients undergoing carotid endarterectomy have a reduced risk of perioperative stroke if they receive aspirin preoperatively.[28] For long-term secondary prevention of stroke, current guidelines recommend aspirin, clopidogrel, or the combination of aspirin and dipyridamole.[24] The combination of aspirin and clopidogrel is not recommended because of an increased risk of bleeding, but data from studies of coronary stenting suggest that this combination should be routinely used for a short period (e.g., 1 to 3 months) after carotid-artery stenting.[29]

Current guidelines suggest that anticoagulation therapy with heparin followed by warfarin can be used for 3 to 6 months in patients with acute extracranial dissection.[24] Newer oral anticoagulants have not been studied in these patients. Patients with extensive trauma, intracranial dissection, or dissection that is discovered weeks after it occurred probably should not receive anticoagulation therapy. Treatment with antiplatelet agents is a reasonable alternative; a study comparing warfarin with aspirin in patients with a carotid dissection is ongoing.[30] Patients with fibromus-

cular dysplasia usually receive aspirin for stroke prevention.

CAROTID ENDARTERECTOMY

Symptomatic Carotid Stenosis

In several randomized trials involving patients who had a TIA or stroke associated with ipsilateral carotid stenosis (symptomatic stenosis), carotid endarterectomy reduced the subsequent risk of stroke.[31-34] In the NASCET,[31,32] among patients with stenosis of 70% or more, the 2-year risk of ipsilateral stroke was 9% in the group of patients randomly assigned to carotid endarterectomy (plus medical therapy) versus 26% in the group assigned to medical therapy alone (P<0.001). The 5-year risks were 15.7% in the endarterectomy group versus 22.2% in the medical-therapy group (P=0.04) among patients with stenosis of 50 to 69%. There was no benefit of carotid endarterectomy in patients with stenosis of less than 50%. Among all patients who were randomly assigned to carotid endarterectomy, perioperative strokes occurred in 5.5% (nondisabling in 3.7% and disabling in 1.8%), death in 1.1%, and wound hematoma in 5.5%. The European Carotid Surgery Trial,[33] another randomized trial comparing carotid endarterectomy plus medical management with medical management alone, yielded similar results, with a significant benefit of surgery in patients with stenosis of at least 70%.

A meta-analysis of the major trials of carotid endarterectomy showed that the benefit from this procedure was greatest when it was performed within 2 weeks after a TIA or stroke, rather than later.[35]

Asymptomatic Carotid Stenosis

Carotid stenosis that is not associated with ipsilateral symptoms (asymptomatic stenosis) is typically detected on screening ultrasonographic examination or as part of the investigation of a symptomatic contralateral artery. The most appropriate management of asymptomatic stenosis is less clear than that for symptomatic disease, despite several randomized trials addressing this question.[36-41] The Asymptomatic Carotid Atherosclerosis Surgery study,[39] which involved patients with stenosis of more than 60% who were randomly assigned to carotid endarterectomy with medical management or medical management alone, was discontinued after a mean follow-up of 2.7 years. The combined risk of perioperative stroke or death was 1.5%. The risk of ipsilateral stroke projected over 5 years was 5.1% with carotid endarterectomy versus 11.0% without carotid endarterectomy (P=0.004). A similar study in Europe, the Asymptomatic Carotid Surgery Trial,[40] showed a similar projected reduction in the risk of stroke with carotid endarterectomy but a higher rate of perioperative stroke or death (3.1%). In both studies, the absolute risk reduction for stroke associated with carotid endarterectomy was only 1 percentage point per year; this finding indicates that a substantial benefit is likely only in patients with a prolonged life expectancy. The absolute risk reduction was 11.0 percentage points among men but only 2.8 percentage points among women. In post hoc analyses, besides female sex, factors associated with increased surgical risk included a long plaque dimension and contralateral carotid stenosis or occlusion.[41] Surgical expertise and surgical technique are critically important for minimizing the risk of perioperative complications and realizing the small benefit of carotid endarterectomy. Since these trials were carried out more than two decades ago, before the use of statins and other aggressive approaches to the management of risk factors, it is possible that a benefit of carotid endarterectomy in asymptomatic patients would no longer be observed if both groups received current medical treatment.

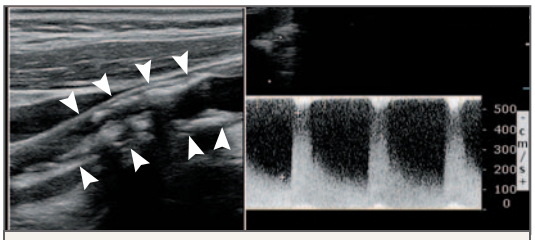


Figure 2. Duplex Ultrasonography of the Carotid Artery Showing Severe Carotid Stenosis.

On the left, the arrowheads outline the internal carotid artery. The plaque is visible in the lumen. On the right, the spectral Doppler waveform shows elevated peak systolic and end diastolic velocities (486 and 164 cm per second, respectively) that are consistent with stenosis of more than 70%. The ultrasonographic device (CX50, Philips Healthcare) had a linear 3-to-12-MHz transducer. Images courtesy of Andrew Barreto, M.D.

CAROTID STENTING

Carotid-artery angioplasty with stenting has emerged as an alternative to carotid endarterectomy in patients at high risk for complications

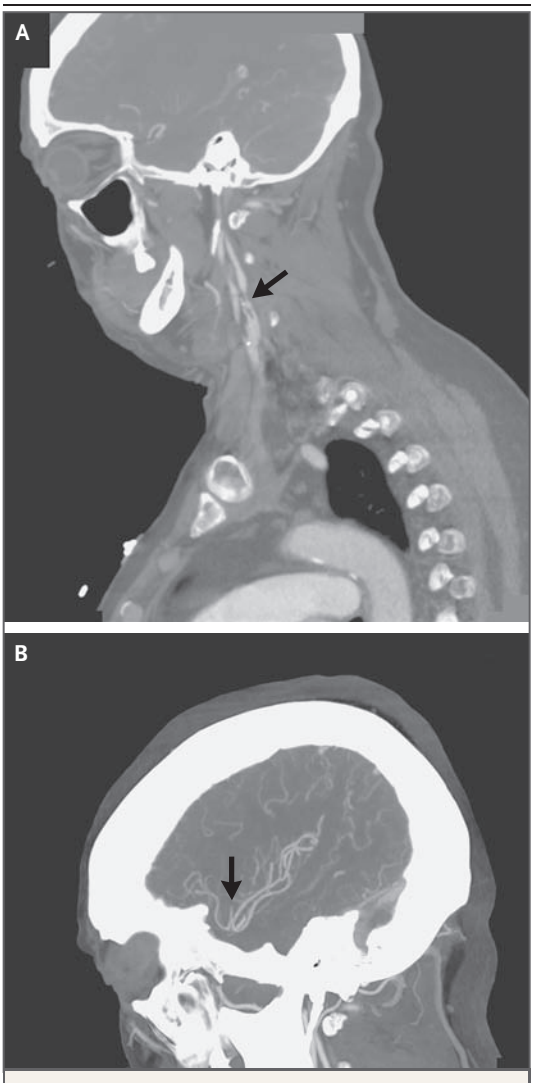


Figure 3. Computed Tomographic (CT) Arteriography in the Patient in the Case Vignette.

In Panel A, a CT arteriogram shows left carotid-artery stenosis (arrow). In Panel B, embolic occlusion (arrow) of the left middle cerebral-artery branch is shown.

from endarterectomy such as contralateral occlusion or severe coronary artery disease. The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy study[42] showed that stenting (with an emboli-protection device) was not inferior to endarterectomy with respect to the rate of a composite outcome of stroke, myocardial infarction, or death at 30 days (4.8% vs. 9.8%) and the rate of ipsilateral stroke or death between 31 days and 1 year. Other trials, however, were discontinued because of high rates of periprocedural neurologic events with carotid stenting.[43-46] More recently, the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST)[47] and the International Carotid Stenting Study (ICSS)[48] have provided additional informative results. In CREST, symptomatic and asymptomatic patients with stenosis of 50% on angiography or 70% or more on ultrasonography or CTA were randomly assigned to the study treatments; this study required training of interventionists and used distal protection devices. CREST showed no significant difference between the stenting and endarterectomy groups overall in the rates of a composite outcome that included major periprocedural complications (stroke, myocardial infarction, or death) and ipsilateral stroke over a 4-year follow-up period (7.2% vs. 6.8%). Whereas the presence or absence of symptoms did not significantly affect the findings, there was a significant interaction of treatment with age: patients younger than 70 years of age had a slightly better outcome after carotid stenting, whereas older patients benefited more from carotid endarterectomy. The endarterectomy group, as compared with the stenting group, had a higher frequency of periprocedural myocardial infarction (2.3% vs. 1.1%) but a lower frequency of periprocedural stroke (2.3% vs. 4.1%). At 2 years of follow-up, the rate of carotid restenosis (a predictor of subsequent stroke) was relatively low (approximately 6%) in both groups.[49] Among patients in the ICSS, only short-term follow-up has been reported, but for those randomly assigned to carotid stenting there was a significantly increased risk of stroke, death, or myocardial infarction at 120 days. In both studies, medical management was at the discretion of the treating physician.

In aggregate, the available data provide support for carotid endarterectomy or carotid stenting in most patients with symptomatic stenosis of more than 70% (number needed to treat to prevent one stroke at 24 months, 6),[31] in selected patients with symptomatic stenosis of 50 to 69% (number needed to treat to prevent one stroke at 5 years, 15),[32] and in a selected subgroup of asymptomatic patients with a low risk of periprocedural complications (e.g., no clinically significant cardiopulmonary or other coexisting conditions and an age younger than 70 years) (number needed to treat to prevent one stroke at 5 years, 17).[39] Carotid endarterectomy is currently considered the preferable intervention in most patients, although selected patients (e.g., those

younger than 70 years of age with favorable anatomical features or symptomatic patients with severe stenosis who have coexisting conditions conferring a high surgical risk) may benefit more from carotid stenting.

AREAS OF UNCERTAINTY

The benefits of carotid endarterectomy or carotid stenting in addition to current medical therapy, as compared with current medical therapy alone, are uncertain in patients with asymptomatic carotid stenosis, especially women. The most appropriate timing and choice of carotid intervention after stroke also remain uncertain, as do the timing and choice of procedure in patients with carotid stenosis who require other major surgery, especially coronary-artery bypass grafting. It is not known whether improvements in techniques of carotid stenting will result in reduced rates of complications. Data are lacking on the benefits and risks of carotid stenting in patients with dissection or fibromuscular dysplasia; these patients are at high risk for complications from intervention, and dissections often heal with medical management.[11] The most appropriate duration of dual antiplatelet therapy after carotid stenting is also uncertain.

GUIDELINES

Guidelines for the treatment of patients with carotid stenosis have been published previously.[24,25,29,50] The recommendations in this article are generally consistent with these guidelines.

CONCLUSIONS AND RECOMMENDATIONS

The patient described in the vignette had a TIA, and 6 months later she had a stroke due to embolization from a stenotic atherosclerotic plaque in the left internal carotid artery. She is at high risk for subsequent stroke, and the carotid stenosis should be treated. On the basis of a meta-analysis of randomized trials and current guidelines, I would recommend treatment within 2 weeks after her stroke.[29,35,50] Either carotid endarterectomy or stenting is an option for management. Whereas carotid endarterectomy is preferred in many cases, given this patient's relatively young age as well as her recent stroke, which increases the risks associated with surgery and general anesthesia, I would consider her to be a good candidate for carotid stenting as long as the lesion could be treated with this approach. Advice and treatment are needed to help her quit smoking. Her hypertension should be well controlled; she should receive statin therapy. Although the most appropriate duration of combined therapy with aspirin and clopidogrel after stent placement remains unclear, I would provide treatment with aspirin and clopidogrel for 1 month and then aspirin indefinitely.

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Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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