

## CLINICAL PRACTICE

## Secondary Prevention after Ischemic Stroke or Transient Ischemic Attack

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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 authors' clinical recommendations.*

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**A 62-year-old woman is seen 1 week after an ischemic stroke. She had presented to another hospital with dysphasia and right-sided weakness; magnetic resonance imaging (MRI) showed a recent infarction in the left parietal cortex, and computed tomographic angiography (CTA) showed a high-grade stenosis in the left proximal internal carotid artery with normal intracranial vessels (Fig. 1). She was treated with intravenous recombinant tissue plasminogen activator and discharged home, taking aspirin and a statin. She stopped smoking 12 years ago. On examination, the blood pressure is 145/90 mm Hg. She reports some mild residual clumsiness of her right hand. What would you advise to reduce the risk of stroke recurrence?**

### THE CLINICAL PROBLEM

Worldwide, stroke is the second most common cause of death after myocardial infarction and is a leading cause of acquired disability. In some regions, the combined incidence of stroke and transient ischemic attacks (TIAs) exceeds the incidence of coronary vascular events.<sup>1</sup> More than 85% of fatal strokes occur in low- and middle-income countries.<sup>2,3</sup>

Patients with stroke are at high risk for subsequent vascular events, including recurrent stroke (highest risk), myocardial infarction, and death from vascular causes. Because the risk of stroke is highest in the early period after the acute event, prompt initiation of tailored prevention strategies is essential.<sup>4</sup> A meta-analysis showed that the risk of stroke was as high as 12.8% during the first week after a TIA, but the risk was lowest when emergency treatment had been given by specialized stroke services.<sup>4</sup> It is estimated that at least 80% of recurrent events might be prevented with the use of a comprehensive approach that includes dietary modification, exercise, blood-pressure lowering, antiplatelet therapy, and statin therapy.<sup>4,5</sup>

### STRATEGIES AND EVIDENCE

#### EVALUATION

Stroke is categorized as ischemic stroke (80% of cases), intracerebral hemorrhage (15%), or subarachnoid hemorrhage (5%).<sup>3</sup> TIAs were traditionally defined as brief neurologic episodes of vascular origin lasting less than 24 hours. More recently, TIAs have been classified as transient neurologic events without signs of acute infarction on imaging.<sup>6</sup> This updated definition is based on the evidence that many strokes detected on imaging, particularly MRI, last less than 24 hours or are clinically silent. This review focuses on secondary prevention after a TIA or ischemic stroke.

  
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In planning secondary prevention, it is important to attempt to identify the pathogenesis of the TIA or ischemic stroke, particularly to detect clinically significant cardiac or large-artery causes that warrant the use of strategies tailored to the individual patient. In clinical practice, the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification for ischemic stroke is useful in delineating major pathogeneses on the basis of clinical findings and investigations.<sup>7</sup> These include cardioembolism (most commonly from atrial fibrillation), large-artery disease, small-vessel occlusion (lacunar stroke), stroke of other determined cause (e.g., arterial dissection, drug-related stroke, or a hypercoagulable disorder), and stroke of undetermined cause (two or more identified causes or negative or incomplete evaluation). Even when fully investigated, up to 30% of cases of cerebral ischemia remain unexplained (“cryptogenic stroke”).

Urgent evaluation is warranted after a stroke or TIA, because many recurrent events occur early. Brain imaging is mandatory for diagnosis, classification, and management. MRI is much more sensitive than computed tomography (CT) in the diagnosis of acute ischemia, although CT is more widely available. Arterial imaging with the use of carotid Doppler ultrasonography, CTA, or magnetic resonance angiography (MRA) is usually necessary. In many centers, CT is now combined with CTA. Electrocardiography is routinely performed. To detect paroxysmal atrial fibrillation, ambulatory monitoring is useful. Transthoracic or transesophageal echocardiography is often used to detect cardiac sources of embolism other than

atrial fibrillation. Routine blood tests may reveal predisposing causes, such as polycythemia, renal impairment, electrolyte disturbances, and hyperglycemia.

#### MANAGEMENT

Aggressive risk-factor management and lifestyle advice are essential for all patients. Observational studies of patients with a history of stroke indicate that healthy lifestyle behaviors, including regular exercise and abstinence from smoking, are associated with reduced mortality.<sup>8,9</sup> In the INTERSTROKE case-control study involving first acute strokes,<sup>10</sup> 10 risk factors accounted for 90% of stroke risk: hypertension, current smoking, a high waist-to-hip ratio, a high dietary risk score, lack of regular physical activity, diabetes mellitus, excess alcohol consumption, psychosocial stress or depression, cardiac causes (e.g., previous myocardial infarction or atrial fibrillation), and a high ratio of apolipoprotein B to apolipoprotein A1.<sup>10</sup> Diabetes and the metabolic syndrome are common in patients with stroke or TIA and may not have been previously recognized.

In secondary prevention, three principal strategies are appropriate for nearly all patients: blood-pressure lowering, cholesterol lowering with statins, and antiplatelet therapy (except in patients in whom anticoagulant therapy is indicated). Other strategies are specific to the cause of stroke (Table 1).

#### BLOOD-PRESSURE LOWERING

Blood pressure is the most important modifiable risk factor in both primary and secondary preven-

#### KEY CLINICAL POINTS

##### SECONDARY PREVENTION AFTER ISCHEMIC STROKE OR TRANSIENT ISCHEMIC ATTACK

- Patients who have had an ischemic stroke or TIA are at high risk for recurrent stroke, myocardial infarction, and death from vascular causes.
- Investigations (including brain imaging and arterial and cardiac assessment) are warranted promptly after a TIA or stroke to determine the cause and guide interventions to reduce subsequent risk.
- Attention to lifestyle factors (including smoking cessation, regular exercise, and weight control) is routinely warranted.
- Blood-pressure lowering, cholesterol lowering with statins, and antiplatelet drugs have been shown to reduce the risk of recurrent stroke and other vascular events.
- Effective secondary-prevention strategies for selected patients include carotid revascularization for high-grade carotid stenosis and anticoagulation therapy for atrial fibrillation.



tion of stroke. Observational studies and clinical trials support blood-pressure reduction for secondary prevention in most patients, regardless of the initial blood-pressure level. Data are lacking to determine the most effective blood-pressure target and extent of lowering, and guidelines recommend that treatment be individualized, but benefits have been linked to absolute blood-pressure reductions of approximately 10/5 mm Hg.<sup>8</sup> Given data suggesting the risks of immediate blood-pressure lowering after stroke, caution is warranted in the acute care setting.<sup>8,22</sup>

A systematic review of trials of secondary prevention after stroke with the use of agents in various classes of antihypertensive drugs showed reductions in all strokes, nonfatal strokes, myocardial infarction, and all vascular events; the magnitude of the reduction in stroke risk was directly related to the degree of systolic-blood-pressure lowering.<sup>23</sup> In the Perindopril Protection against Recurrent Stroke Study (PROGRESS),<sup>11</sup> patients with a prior stroke or TIA were randomly assigned to treatment with an angiotensin-converting-enzyme (ACE) inhibitor (plus the diuretic indapamide, at the discretion of the physician) or placebo. There was a 28% lower risk of stroke over a period of 4 years in the ACE-inhibitor group, with an average blood-pressure reduction of 9/4 mm Hg. Data from another large trial involving high-risk patients, including those with a prior stroke, also support blood-pressure lowering with an ACE inhibitor.<sup>24</sup>

Whether the benefits of blood-pressure lowering depend on the particular class of antihypertensive drugs or simply on the antihypertensive effect of all such drugs remains controversial, although most of the evidence appears to support the latter.<sup>25</sup> The PROGRESS trial showed a greater reduction in the risk of stroke and other vascular outcomes among patients treated with a combination of an ACE inhibitor and a diuretic than among those treated with an ACE inhibitor alone, but blood-pressure reduction was greater with combination therapy.<sup>11</sup> One secondary-prevention trial showed a reduction in the combined incidence of stroke and TIA with an angiotensin-receptor blocker (ARB) as compared with a calcium antagonist, despite similar effects on blood pressure.<sup>26</sup> Yet a much larger trial, the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) study, failed to show a significant benefit of an ARB over placebo in reducing the risk of recurrent stroke<sup>27</sup>; however, the negative results may

**Table 1. Strategies of Proven Benefit for Secondary Prevention of Stroke.\***

Indication and Strategy	Study	Key Trial or Meta-Analysis	Results†
Routine‡			
Blood-pressure lowering		PROGRESS <sup>11</sup> : ACE inhibitor plus diuretic vs. placebo; primary end point: total strokes	RRR, 28.0%; ARR, 4.00 percentage points; NNT, 97
Cholesterol lowering (statin)		SPARCL <sup>12</sup> : statin vs. placebo; primary end point: first stroke	RRR, 16.0%; ARR, 2.20 percentage points; NNT, 220
Antiplatelet therapy (unless anticoagulation indicated)			
Aspirin (first-line therapy)		ATTC <sup>1,3,14</sup> : aspirin vs. placebo; primary end points: nonfatal stroke, nonfatal MI, and death from vascular causes	RRR, 13.0%; ARR, 1.00 percentage points; NNT, 100§
Clopidogrel		CAPRIE <sup>15</sup> : clopidogrel vs. aspirin; primary end points: ischemic stroke, MI, and death from vascular causes	RRR, 8.7%; ARR, 0.51 percentage points; NNT, 196
Aspirin plus dipyridamole		ESPS2 <sup>16</sup> : aspirin plus dipyridamole vs. aspirin; primary end point: stroke	RRR, 23.8%; ARR, 2.97 percentage points; NNT, 74
Symptomatic high-grade stenosis: carotid endarterectomy		NASCET <sup>17</sup> : carotid endarterectomy plus medical treatment vs. medical treatment alone; primary end point: any ipsilateral ischemic stroke	RRR, 65.0%; ARR, 17 percentage points; NNT, 9
Atrial fibrillation			
Warfarin		EAF <sup>18</sup> : warfarin vs. placebo; primary end point: all strokes	RRR, 66.0%; ARR, 8.0 percentage points; NNT, 12
Dabigatran		RE-LY <sup>19</sup> : dabigatran vs. warfarin; primary end points: stroke and systemic embolism	RRR, 34.0%; ARR, 0.58 percentage points; NNT, 172¶
Rivaroxaban		ROCKET AF <sup>20</sup> : rivaroxaban vs. warfarin; primary end points: stroke and systemic embolism	RRR, 13.0%; ARR, 0.30 percentage points; NNT, 333
Apixaban		ARISTOTLE <sup>21</sup> : apixaban vs. warfarin; primary end points: stroke and systemic embolism	RRR, 21.0%; ARR, 0.33 percentage points; NNT, 303

\* All trials are based on level 1 evidence. The list of trials is not comprehensive; instead, a definitive trial or meta-analysis is cited for each intervention. The number needed to treat (NNT) to prevent one primary-outcome event (secondary prevention) per year was calculated with the use of data on absolute risk reduction (ARR) during the mean or median trial follow-up period. All values are approximate and derived from previous analyses, Cochrane database reviews, or individual trials if these are the only data available. ACE denotes angiotensin-converting enzyme, ARISTOTLE Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation, ATTC Antithrombotic Trialists' Collaboration, CAPRIE Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events, EAF European Atrial Fibrillation Trial, ESPS2 European Stroke Prevention Study 2, MI myocardial infarction, NASCET North American Symptomatic Carotid Endarterectomy Trial, PROGRESS Perindopril Protection against Recurrent Stroke Study, RE-LY Randomized Evaluation of Long-Term Anticoagulation Therapy, ROCKET AF Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation, RRR relative risk reduction, and SPARCL Stroke Prevention by Aggressive Reduction in Cholesterol Levels.

† The RRR and ARR are annualized for all the studies except PROGRESS, SPARCL, ESPS2, and NASCET, for which the RRR and ARR are for the duration of the trial.

‡ The indication is routine in the absence of clinical contraindications.

§ The results are based on a meta-analysis of trials comparing aspirin with placebo in patients with a previous stroke or transient ischemic attack (TIA).

¶ The results are for dabigatran at a dose of 150 mg twice per day.

have been explained by the small reduction in blood pressure with active treatment.<sup>27</sup>

#### CHOLESTEROL LOWERING WITH STATINS

Cholesterol lowering with statin drugs, which is effective in primary stroke prevention, has also proved effective in secondary prevention after stroke or TIA. A subgroup analysis involving patients with a history of cerebrovascular disease in the Heart Protection Study with an initial total cholesterol level of at least 135 mg per deciliter (3.5 mmol per liter) showed that simvastatin (at a dose of 40 mg per day), as compared with placebo, resulted in a 20% reduction in the risk of all vascular end points and a 25% reduction in the risk of stroke.<sup>28</sup> In the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study,<sup>12</sup> a placebo-controlled trial involving patients with a recent TIA or stroke and baseline low-density lipoprotein (LDL) cholesterol levels of 100 to 190 mg per deciliter (2.6 to 4.9 mmol per liter), those randomly assigned to atorvastatin (at a dose of 80 mg per day) had significant reductions in the risks of stroke and all cardiovascular events (absolute risk reductions, 2.2 percentage points and 3.5 percentage points, respectively, over a period of 5 years). The benefits appear to be greatest in patients with the greatest reductions in LDL levels (50% or more).<sup>29</sup> Secondary-prevention guidelines recommend treatment for patients with an LDL cholesterol level of 100 mg per deciliter (2.6 mmol per liter) or higher, with the aim of reducing the level by at least 50% or achieving a target level of less than 70 mg per deciliter (1.8 mmol per liter).<sup>8</sup> Despite the overall benefit, statins have been associated with a slightly increased risk of intracerebral hemorrhage, and their use may be contraindicated in patients with the disorder.<sup>12,30</sup>

#### ANTIPLATELET THERAPY

Unless anticoagulation is indicated, patients should receive antiplatelet therapy for secondary stroke prevention. In trials involving high-risk patients, including those with a history of stroke, aspirin reduced the risk of subsequent vascular events overall by about a quarter.<sup>13</sup> However, a meta-analysis of trials specifically of aspirin (vs. placebo), limited to patients with a prior stroke or TIA, suggested that aspirin reduced the risk of subsequent vascular events by only 13%.<sup>14</sup> Low doses of aspirin (ranging from 75 to 325 mg per

day) appear to be as effective as higher doses in reducing the risk of stroke, with a lower risk of gastrointestinal toxic effects.

Secondary-prevention trials have also shown benefits of other antiplatelet strategies. Both clopidogrel (an adenosine diphosphate–receptor inhibitor)<sup>15</sup> and the combination of aspirin plus dipyridamole (a phosphodiesterase inhibitor)<sup>16,31</sup> were shown in randomized trials to be superior to aspirin, but the absolute benefits were very small. In a trial comparing the combination of aspirin plus dipyridamole with clopidogrel for the prevention of recurrent stroke, outcomes were similar in the two treatment groups.<sup>32</sup> Current guidelines indicate that aspirin alone, clopidogrel, and aspirin plus dipyridamole are all acceptable first-line options in secondary stroke prevention.<sup>8</sup> Randomized trials have shown no benefit, and increased hemorrhagic risks, with the combined use of clopidogrel and aspirin as compared with clopidogrel alone<sup>33</sup> or aspirin alone<sup>34</sup> for long-term secondary prevention after stroke. In the Secondary Prevention of Small Subcortical Strokes (SPS3; ClinicalTrials.gov number, NCT00059306) trial, which is evaluating antiplatelet therapy with aspirin plus clopidogrel versus aspirin alone, as well as two approaches to blood-pressure lowering, the combination antiplatelet therapy was recently terminated prematurely owing to excess hemorrhages and deaths.

Short-term use of the combination of aspirin and clopidogrel has been proposed early after stroke or TIA, when the risk of recurrent stroke is highest (Table 2). A brief duration of exposure would be expected to reduce the risks associated with combination therapy. In a randomized, controlled pilot trial, the rate of stroke recurrence at 90 days was 10.8% among patients randomly assigned to aspirin within 24 hours versus 7.1% among those randomly assigned to combined aspirin and clopidogrel; this difference was not significant, but the trial was underpowered.<sup>35</sup> A larger trial comparing these regimens is under way (NCT00991029).

#### CAROTID ENDARTERECTOMY AND CAROTID-ARTERY STENTING

Carotid endarterectomy is indicated for the treatment of patients with a history of TIA or nondisabling ischemic stroke who have high-grade (70 to 99%) carotid stenosis or, in selected cases, moderate (50 to 69%) stenosis.<sup>17,44-46</sup> In the North

**Table 2. Controversial or Investigational Secondary-Prevention Strategies.\***

Target	Possible Strategy	Comments
Early recurrent stroke	Combined aspirin and clopidogrel for 90 days from stroke onset	Increased risk with combination therapy vs. aspirin or clopidogrel alone, but meta-analysis suggests possible benefit of combination therapy after a TIA or minor stroke <sup>35</sup> ; POINT (NCT00991029): combination therapy vs. aspirin, ongoing
Carotid stenosis	Carotid-artery stenting	Higher risks of periprocedural stroke and death with stenting than with endarterectomy, <sup>36-39</sup> although risks similar with the two treatments among patients 70 years of age or younger <sup>40</sup>
Aortic-arch atheroma	Antiplatelet therapy vs. anticoagulation	Common cause of stroke; most effective treatment unknown; ARCH (NCT00235248) <sup>41</sup> : aspirin plus clopidogrel vs. warfarin, ongoing
Intracranial arterial stenosis	Intracranial stenting	Higher rates of stroke and death with intracranial stenting than with aggressive medical therapy in one trial (SAMMPRIS), <sup>42</sup> but other trials ongoing
Carotid dissection	Antiplatelet therapy vs. anticoagulation	Optimal treatment unclear; CADISS (NCT00238667): aspirin vs. warfarin, ongoing
Patent foramen ovale	Percutaneous closure device vs. medical therapy	No benefit observed with percutaneous closure in CLOSURE I <sup>43</sup> ; other trials ongoing

\* ARCH denotes Aortic Arch Related Cerebral Hazard, CADISS Cervical Artery Dissection in Stroke Study, CLOSURE I Evaluation of the STARFlex Septal Closure System in Patients with a Stroke and/or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a Patent Foramen Ovale, POINT Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke, and SAMMPRIS Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis.

American Symptomatic Carotid Endarterectomy Trial (NASCET), participants with high-grade carotid stenosis who were randomly assigned to endarterectomy had an absolute reduction of 17 percentage points in the risk of stroke over a period of 18 months.<sup>46</sup> Surgery resulted in a more modest benefit (absolute risk reduction of 6.5 percentage points over a period of 5 years) in patients with moderate stenosis and no benefit in those with mild (<50%) stenosis.<sup>44,45</sup> Careful attention to the results of carotid endarterectomy in any given center is essential to ensure that the surgical risks do not exceed those in the clinical trials.<sup>8</sup>

The timing of carotid endarterectomy after a TIA or ischemic stroke involves balancing the risk of early recurrent events with the risk of reperfusion injury and hemorrhagic transformation. Early intervention, within 2 weeks after the onset of symptoms, is now recommended, given evidence that the benefits of surgery rapidly diminish with increasing time since the ischemic event.<sup>47</sup>

The use of carotid-artery stenting as an alternative to carotid endarterectomy is more controversial. Carotid-artery stenting is less invasive than endarterectomy and is associated with a more

rapid recovery and a much lower risk of cranial-nerve palsies. However, studies have shown that the periprocedural risks (chiefly death and recurrent stroke within 30 days) are significantly higher with carotid-artery stenting than with carotid endarterectomy.<sup>36-39</sup> In the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST), these risks were offset by a reduced rate of myocardial infarction in the stenting group, such that overall outcomes (stroke, myocardial infarction, and death) were similar with the two procedures at 30 days and at 4 years.<sup>39</sup> However, the purported equivalence of these procedures has been questioned, given that the longer-term health effects of stroke outweigh those of myocardial infarction. Data from CREST and European stenting trials indicate that the relative benefits and risks of the procedures vary according to age. In patients older than 70 years of age, carotid endarterectomy appears to be superior to carotid-artery stenting, whereas in patients 70 years of age or younger, the periprocedural risks of stroke and death are similar with the two procedures,<sup>39,40</sup> and carotid-artery stenting (performed by interventionists with acceptable complication rates) is a reasonable alternative to car-

rotid endarterectomy. However, there are limited long-term data regarding the outcomes of carotid-artery stenting to guide decision making.<sup>8</sup>

#### ATRIAL FIBRILLATION AND ANTICOAGULATION

Atrial fibrillation causes at least 15% of cases of ischemic stroke. Dose-adjusted warfarin has been the mainstay of therapy. A meta-analysis of trials comparing warfarin with placebo or aspirin showed reductions in the risk of stroke of 60% and 40%, respectively, although these were chiefly primary-prevention trials.<sup>48</sup> Warfarin has also been shown to be more effective than aspirin<sup>18</sup> or the combination of aspirin plus clopidogrel<sup>49</sup> for secondary prevention of stroke in patients with atrial fibrillation.

Newer oral anticoagulant strategies, which do not require monitoring, are now available and are likely to replace warfarin in many cases, although they are more costly. In a randomized trial of patients with atrial fibrillation (20% of whom had a prior stroke or TIA), dabigatran (a direct thrombin inhibitor), at a dose of 150 mg twice per day, was superior to warfarin in the prevention of stroke or systemic embolism, with a similar risk of overall major bleeding but a significantly lower risk of intracranial hemorrhage.<sup>19</sup> At a lower dose (110 mg twice per day), dabigatran was noninferior to warfarin, with a lower risk of overall major bleeding. Randomized trials have also shown the efficacy of factor Xa inhibitors in reducing stroke risk among patients with atrial fibrillation. Like dabigatran, rivaroxaban was noninferior to warfarin, with a lower risk of bleeding.<sup>20</sup> Apixaban has been shown to be superior to warfarin, with reductions in the risk of bleeding and mortality,<sup>21</sup> and for persons in whom warfarin has unacceptable adverse effects, apixaban has been shown to be superior to aspirin.<sup>50</sup>

#### AREAS OF UNCERTAINTY

Patent foramen ovale is more common in patients with cryptogenic stroke than in the general population, and patients with both patent foramen ovale and atrial septal aneurysm appear to be at increased risk for stroke.<sup>51</sup> Antiplatelet therapy is generally recommended for patients with patent foramen ovale after a stroke or TIA. The efficacy and safety of endovascular closure for the prevention of recurrent stroke in such patients remains questionable; one recent trial showed no benefit of endovascular closure.<sup>43</sup>

Studies of secondary-prevention strategies for other conditions associated with an increased risk of stroke, including aortic-arch atheroma<sup>41</sup> and intracranial atherosclerosis, are needed; intracranial atherosclerosis accounts for up to 50% of ischemic strokes in Asian populations.<sup>52</sup> Antiplatelet therapy and intensive risk-factor management are recommended for such patients. A randomized trial comparing warfarin with aspirin in patients with stroke or TIA caused by intracranial stenosis was terminated early owing to higher risks of adverse outcomes with warfarin,<sup>53</sup> and a trial comparing angioplasty and stenting with aggressive medical management in such patients was halted because of increased hazards with stenting.<sup>42</sup>

Arterial dissection is one of the most common causes of stroke in young adults; the most effective therapy after a dissection remains unclear.<sup>54</sup> A large trial comparing aspirin and warfarin in such patients is under way (NCT00238667).

#### GUIDELINES

The American Stroke Association and European Stroke Organization have published guidelines for the prevention of stroke in patients with an initial stroke or TIA.<sup>8,55</sup> Our recommendations are largely consistent with these guidelines.

#### CONCLUSIONS AND RECOMMENDATIONS

The patient described in the vignette had an ischemic stroke and has a high-grade carotid stenosis. We would refer this patient for prompt carotid endarterectomy, although carotid stenting would also be reasonable, given her age. We would recommend continuing her statin therapy, providing low-dose aspirin (e.g., 81 mg daily), and lowering her blood pressure. We would favor treatment with an ACE inhibitor and a diuretic, given their efficacy in a randomized secondary-prevention trial,<sup>13</sup> while recognizing that there is uncertainty about which strategy is most effective. The patient should be informed about lifestyle factors and the importance of avoiding smoking and obesity and exercising regularly.

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

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