

## 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.*

## TRANSIENT ISCHEMIC ATTACK

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A 72-year-old woman telephones her physician immediately after recovering from a 30-minute episode of difficulty speaking and weakness of the right side of the face and right arm. Her medical history is unremarkable. How should she be treated?

### THE CLINICAL PROBLEM

In the United States, estimates of the annual incidence of transient ischemic attacks that come to medical attention vary from 200,000 to 500,000. The true incidence may be much higher, because many apparent episodes never come to medical attention.<sup>1-3</sup> On the basis of the results of a large nationwide survey, more than 5 million Americans have been given a diagnosis of a transient ischemic attack.<sup>4</sup>

Transient ischemic attack is defined as a neurologic deficit lasting less than 24 hours that is attributed to focal cerebral or retinal ischemia. The initial aim of the requirement that resolution must occur within 24 hours was to exclude patients with infarction. However, infarctions can occur in those without neurologic deficits, and evidence of acute infarction is identified by magnetic resonance imaging (MRI) in up to 50 percent of patients who meet the criteria for a transient ischemic attack.<sup>5</sup> Some have suggested specifying that symptoms resolve within one hour.<sup>6,7</sup> Although this criterion reduces the likelihood that infarction is present, infarction may not develop even if symptoms last longer. Others have proposed subclassifying transient ischemic attack according to the presence or absence of infarction.<sup>8</sup> A rapid recovery may be the most important characteristic in defining a distinct clinical entity, regardless of the presence of some mild residual deficit or infarct; paradoxically, rapid recovery may

indicate a more unstable pathophysiology and a less favorable natural history because the ischemic tissue that has recovered remains at risk.<sup>9</sup> If an unstable atherosclerotic plaque is responsible for the symptoms, it could still produce new or recurrent symptoms after a transient ischemic attack but is less likely to do so when the territory involved is already infarcted.

The diagnosis of transient ischemic attack remains problematic even if the standard definition is accepted. The diagnosis is generally based on clinical history alone and specifically on the recollections of the patient, who was neurologically impaired during the event. Nonischemic causes of the symptoms, such as seizure, migraine, and anxiety, or global cerebral ischemia from hypotension may be impossible to distinguish from focal cerebral ischemia. Given these difficulties in diagnosis, it is not surprising that practitioners frequently disagree on whether a transient ischemic attack has occurred.<sup>10,11</sup> Episodes misdiagnosed as transient ischemic attacks are heterogeneous and include those due to migraine, seizure, vasovagal syncope, arrhythmia, compressive neuropathy, anxiety, and conversion disorder.

The causes of true transient ischemic attacks — such as atrial fibrillation, carotid-artery disease, and large- and small-artery disease in the brain — are identical to those of stroke, so strategies to prevent further attacks are similar to those for stroke. However, by definition, once the episode subsides, patients with a transient ischemic attack no longer have a new neurologic deficit; therefore, the appropriate timing of evaluation and treatment for such patients is unclear. Patients with stroke generally require urgent attention, even if thrombolysis is not an option, to manage complications of the neurologic impairment, such as the inability to swallow or walk. Whether emergency evaluation and hospitalization are required for patients with a transient ischemic attack is not clear<sup>12</sup>; some neurologists hospitalize most patients with a transient ischemic attack, whereas others recommend nonurgent outpatient evaluations.

Many prior trials of stroke prevention have either excluded patients with transient ischemic attacks or combined them with patients who have had a stroke. Thus, most of the data on management are not specifically devoted to transient ischemic attack.

### STRATEGIES AND EVIDENCE

#### Risk of Stroke after Transient Ischemic Attack

Urgent evaluation and treatment after a transient ischemic attack are necessary only if the short-term risk

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of stroke and other adverse events is great. Most studies of the outcome after a transient ischemic attack have excluded the first few days after the event, since it is difficult to enroll patients during this period. Only a few studies have followed patients from the time the diagnosis was made.

The largest study of the short-term prognosis of transient ischemic attack was conducted in northern California and included all 1707 patients given this diagnosis by the treating physician.<sup>13</sup> During a 90-day period after the event, about one in nine patients had a stroke; half of all strokes occurred in the first 2 days. Another 2.6 percent of patients were hospitalized with a cardiac event, and 2.6 percent died. Several risk factors for stroke were identified (e.g., age, diabetes, duration of symptoms for more than 10 minutes, and weakness or speech impairment with the episode). The 90-day risk of stroke among patients with atrial fibrillation was 11 percent, although many of these patients were treated with anticoagulation.

Two smaller population-based studies found similar rates of stroke after transient ischemic attack. In a study of 198 patients, the 90-day risk of stroke was 10 percent.<sup>14</sup> Another population-based study reported a 4 percent risk of stroke in the first month among 184 patients enrolled a median of three days after the index transient ischemic attack,<sup>15</sup> which was similar to the risk expected during this period in the larger study in California. The risk of stroke after transient ischemic attack was also high in the North American Symptomatic Carotid Endarterectomy Trial.<sup>16</sup> For those with a nonretinal transient ischemic attack attributable to a 70 to 99 percent stenosis of the internal carotid artery, the 90-day risk of stroke exceeded 25 percent. A recent extension of this analysis, which included patients with any degree of stenosis, found a 90-day risk of stroke of 20 percent among those with nonretinal transient ischemic attacks, a risk that is about eight times as great as the risk after a completed stroke.<sup>17</sup> The risk of stroke after retinal transient ischemic attack was about half the risk after nonretinal events.<sup>16,18</sup>

#### Evaluation

A detailed history is most helpful in determining potential causes of an episode of neurologic impairment that appears consistent with a transient ischemic attack. A patient's history may also be useful in identifying the distribution and cause of focal cerebral ischemia, but the reliability of history alone is limited.<sup>19</sup> A neurologic examination may identify persistent deficits that clarify the cause.

Laboratory testing is helpful in ruling out metabolic and hematologic causes of neurologic symptoms, such as hypoglycemia, hyponatremia, and thrombocytosis, and often includes measurement of sodium and glucose levels, hematocrit, white-cell count, and

platelet count, with other tests conducted on the basis of clinical history. An elevated erythrocyte sedimentation rate may suggest bacterial endocarditis or temporal arteritis. An electrocardiogram may reveal unsuspected atrial fibrillation or a recent myocardial infarction.

Cranial imaging by computed tomography (CT) or MRI may reveal an unsuspected cause of a transient ischemic attack, such as a brain tumor or a subdural hematoma. There may also be evidence of acute infarction, even if a patient has no signs or symptoms of stroke. Infarction is more likely to be revealed by MRI than CT<sup>5,19</sup>; its presence confirms that the episode was due to focal cerebral ischemia.

Imaging of the carotid arteries is important for ruling out internal-carotid-artery stenosis as a cause of a transient ischemic attack. Such imaging can be performed safely with Doppler ultrasonography or magnetic resonance angiography, each of which has a sensitivity of 83 to 86 percent for a stenosis of 70 percent or greater.<sup>19</sup> Angiography with catheterization is generally reserved for the confirmation of noninvasive findings. CT angiography may also be an option, but the technique is not widely available and requires further validation. Magnetic resonance angiography or CT angiography of the intracranial arteries and the vertebral arteries in the neck may reveal a stenosis or dissection.

#### Treatment

##### *Aspirin and Other Antiplatelet Agents*

No trial has evaluated the effect of aspirin when it is initiated immediately after a transient ischemic attack. However, aspirin reduces the long-term risk of stroke and cardiovascular events after stroke or a transient ischemic attack, with an overall relative reduction in risk of 22 percent.<sup>20</sup> Furthermore, in patients with acute stroke, aspirin reduces the risk of recurrent stroke and improves functional outcomes.<sup>20,21</sup> The benefit of aspirin in patients with acute stroke is small (relative reduction in the risk of death or recurrent stroke in the hospital, 10 percent), in part because it elevates the risk of brain hemorrhage.<sup>21</sup> The risk of brain hemorrhage is probably less after a transient ischemic attack, so the net benefit is likely to be greater in this setting.

The optimal dose of aspirin is not known. Reductions in the rates of vascular events are similar with doses of aspirin ranging from 75 mg to 1300 mg.<sup>20</sup> In two trials comparing high doses and low doses after stroke or a transient ischemic attack, the risk of stroke and other vascular events was similar, but gastrointestinal symptoms and bleeding were less frequent with the lower doses.<sup>22,23</sup>

Other antiplatelet agents have not been tested spe-

cifically after transient ischemic attack or as treatments given immediately after ischemic stroke. In secondary-prevention studies in patients with stroke, the thienopyridines clopidogrel and ticlopidine were slightly more effective than aspirin (relative reduction in the risk of serious vascular events, 8 to 9 percent).<sup>24,25</sup> Neutropenia, rash, diarrhea, and thrombotic thrombocytopenic purpura are more frequent with ticlopidine than with clopidogrel, so its use has declined. In a single trial, the combination of extended-release dipyridamole and aspirin was superior to aspirin alone in reducing the risk of stroke among patients who had previously had a stroke or transient ischemic attack, but the difference was not significant for the combined outcome of stroke and death.<sup>26</sup>

#### **Anticoagulant Therapy**

Anticoagulation has not been evaluated specifically in patients with transient ischemic attacks but has been extensively tested after ischemic stroke. In patients with atrial fibrillation, long-term oral anticoagulation reduces the risk of recurrent stroke.<sup>27</sup> In patients who had had a stroke but not atrial fibrillation, oral anticoagulation with warfarin was no better than aspirin in reducing the risk of death and recurrent ischemic stroke.<sup>28</sup> In 21 placebo-controlled trials of several anticoagulant agents in patients with acute ischemic stroke, there was no overall benefit of anticoagulants, since the reduction in the risk of recurrent stroke was offset by the increased risk of brain hemorrhage.<sup>29</sup>

#### **Carotid Endarterectomy**

Carotid endarterectomy is beneficial in patients with internal-carotid-artery stenosis of 70 to 99 percent who have had a stroke or a transient ischemic attack attributable to the stenosis.<sup>30,31</sup> Endarterectomy is marginally beneficial in selected patients with stenosis of 50 to 69 percent,<sup>32</sup> but, as reviewed in a recent Clinical Practice article, the benefits are less pronounced and are highly dependent on the surgical experience of the treatment center.<sup>33</sup>

#### **Treatment of Risk Factors for Cardiovascular Disease**

Other medical interventions that reduce the risk of stroke among patients with a history of coronary artery disease or stroke are also likely to reduce the risk of stroke after a transient ischemic attack. Lipid-lowering agents, particularly hydroxymethylglutaryl coenzyme A reductase inhibitors (statins), appear to reduce the risk of stroke and cardiovascular events in patients with coronary artery disease (relative reduction in risk, 29 percent),<sup>34</sup> even when dyslipidemia is absent,<sup>35</sup> and gemfibrozil appears effective in patients with low levels of both high-density and low-density cholesterol.<sup>36</sup>

Antihypertensive medications also reduce the long-

term risk of stroke after transient ischemic attack or stroke,<sup>37</sup> even among patients without hypertension (relative reduction in risk, 25 to 30 percent).<sup>38,39</sup> Reductions in blood pressure have been proposed to explain most of the protective effects of antihypertensive agents; however, in one trial in which similar blood-pressure reductions were obtained in treated groups of patients with hypertension, the angiotensin-receptor blocker losartan reduced the risk of stroke more than did atenolol (relative reduction in risk, 25 percent) and reduced the risk of the combined outcome of death, myocardial infarction, and stroke (relative reduction in risk, 13 percent).<sup>40</sup> Antihypertensive agents and lipid-lowering agents have not been specifically tested in patients after a transient ischemic attack. Although no trials have explicitly evaluated the benefit of lifestyle changes after a transient ischemic attack, observational studies suggest that smoking cessation, exercise, moderate alcohol consumption, and weight control may reduce the risk of stroke.<sup>41</sup>

#### **AREAS OF UNCERTAINTY**

Whether heparin should be started immediately after a transient ischemic attack in patients with atrial fibrillation is unknown. In one small trial involving 449 patients, a low-molecular-weight heparin did not reduce the risk of recurrent stroke during the first 14 days after a stroke that was attributed to atrial fibrillation.<sup>42</sup> However, in a large subgroup (3169 patients) of similar patients in a trial of subcutaneous unfractionated heparin, heparin reduced the 14-day risk of ischemic stroke by more than 50 percent, but an increase in brain hemorrhage eliminated this benefit.<sup>43</sup> Given the lower risk of hemorrhage with smaller infarcts,<sup>44</sup> the risk of brain hemorrhage is probably greater after a stroke than after a transient ischemic attack, so the net benefit of such therapy after a transient ischemic attack may be greater.

Endarterectomy is generally indicated for patients with a transient ischemic attack that is attributable to severe internal-carotid-artery stenosis,<sup>30,32</sup> but the optimal timing of surgery is unknown. After stroke, endarterectomy is often delayed more than six weeks to reduce the risk of brain hemorrhage into the infarct, although there is little evidence to support this strategy.<sup>45,46</sup> After a transient ischemic attack, the risk of brain hemorrhage with endarterectomy appears to be lower than after a stroke, but unstable plaque or acute thrombus could increase the risk of urgent endarterectomy. No large-scale trial has studied the optimal timing of endarterectomy, so it is unknown whether a reduction in the high short-term risk of stroke justifies the potential risks entailed by surgery.

The benefit of hospitalization for transient ischemic attacks is unknown. Hospitalization may hasten evaluation and initiation of therapy. Observation units

within the emergency department or specialized stroke clinics may provide a more cost-effective option. The benefit of consultation with a neurologist or stroke specialist, who may assist in directing the evaluation and treatment, is also unknown.

### GUIDELINES

Consensus guidelines on the management of transient ischemic attack have been promulgated by the American Heart Association<sup>41,47-49</sup> and the National Stroke Association<sup>50</sup> (Table 1). The guidelines from these groups are similar, with an emphasis on prompt

evaluation and directed therapy based on the suspected cause of the transient ischemic attack. Additional testing, such as echocardiography or laboratory tests for hypercoagulability, is recommended if diagnostic uncertainty persists.<sup>41</sup>

### CONCLUSIONS AND RECOMMENDATIONS

The high short-term risk of stroke after a transient ischemic attack supports an approach involving rapid evaluation and initiation of treatment in patients such as the one described in the clinical vignette. Many

**TABLE 1. CONSENSUS GUIDELINES FOR THE CARE OF PATIENTS WITH A TRANSIENT ISCHEMIC ATTACK.\***

INTERVENTION	AMERICAN HEART ASSOCIATION GUIDELINES	NATIONAL STROKE ASSOCIATION GUIDELINES
<b>Evaluation</b>		
Timing	Prompt evaluation	Evaluation within hours after onset of symptoms
Hospitalization	No recommendation	Recommended if appropriate imaging studies are not immediately available
Laboratory testing	Determined on the basis of history; used to identify causes of transient ischemic attack that would require specific therapy, to assess modifiable risk factors, and to determine prognosis	No specific recommendation
Electrocardiography	Recommended	Recommended
Imaging of the head	CT in all patients; routine use of MRI not recommended owing to higher cost and lower tolerability	No specific recommendation
Imaging of carotid arteries	Prompt ultrasonography, magnetic resonance angiography, or CT angiography	Urgent evaluation; not further specified
<b>Antithrombotic medications</b>		
Cardioembolic cause	No specific recommendation on short-term use of heparin; long-term oral anticoagulation for patients with atrial fibrillation	Acute anticoagulation can be considered (limited evidence in support of this approach)
Noncardioembolic cause	Antiplatelet therapy with aspirin (50–325 mg/day), clopidogrel, ticlopidine, or aspirin plus dipyridamole; anticoagulation not generally recommended	Antiplatelet therapy with aspirin (50–325 mg/day); consider clopidogrel, ticlopidine, or aspirin plus dipyridamole in patients who are intolerant of aspirin or who had the transient ischemic attack while taking aspirin; anticoagulation not generally recommended
<b>Carotid endarterectomy</b>	Recommended for good surgical candidates with 70–99 percent stenosis and transient ischemic attack during previous two years; consider for patients with 50–69 percent stenosis on the basis of clinical features that influence the risk of stroke and surgical complications; timing not discussed	Recommended without delay for those with symptomatic stenosis of 50–99 percent
<b>Risk-factor management†</b>		
Hypertension	Maintain systolic blood pressure below 140 mm Hg and diastolic blood pressure below 90 mm Hg; for patients with diabetes, maintain systolic blood pressure below 130 mm Hg and diastolic blood pressure below 85 mm Hg	
Diabetes	Maintain fasting blood glucose levels below 126 mg/dl (7.0 mmol/dl)	
Hyperlipidemia	Diet modification, lipid-lowering agent, or both with goal of maintaining low-density lipoprotein cholesterol level below 100 mg/dl (2.59 mmol/liter)	
Cigarette smoking	Counseling, nicotine-replacement therapy, and bupropion to support cessation efforts	
Inadequate physical activity	Exercise 30–60 min three or more times per week	
Excessive alcohol consumption	Formal alcohol-cessation programs to eliminate excessive use‡	
Obesity	Diet and exercise to reduce weight to less than 120 percent of ideal weight for height	

\*Data are from the American Heart Association<sup>41,47-49</sup> and National Stroke Association.<sup>50</sup> CT denotes computed tomography, and MRI magnetic resonance imaging.

†The guidelines of the National Stroke Association are limited to short-term management.

‡Mild-to-moderate use of alcohol (1 to 2 drinks/day) may be beneficial.

strokes occur in the first few days after a transient ischemic attack, so even a short delay in treatment could have important consequences. Most patients should be sent to the emergency department immediately after reporting symptoms suggestive of a transient ischemic attack. Hospitalization is indicated only if the evaluation cannot be completed within 24 hours.

The initial evaluation of a patient in whom a transient ischemic attack is suspected should include laboratory tests, electrocardiography, and imaging studies. Since imaging of the head may reveal a nonischemic cause, such as a tumor or subdural hematoma, and may provide information about the cause of ischemia, I recommend that CT or MRI of the head be part of the evaluation of all patients. Doppler ultrasonography or another noninvasive method of imaging the carotid arteries should be performed rapidly, ideally within 24 hours.

Treatment to prevent a subsequent stroke should be initiated as soon as possible. For most patients, aspirin at a dose of 50 to 325 mg per day will be the treatment of choice. Clopidogrel and aspirin plus dipyridamole are alternatives in patients who cannot tolerate aspirin or who were taking aspirin at the time of the event. For patients with atrial fibrillation, anticoagulation with warfarin should be initiated. Given the high short-term risk of stroke after a transient ischemic attack in patients with atrial fibrillation and the relatively low risk of brain hemorrhage, treatment with unfractionated or low-molecular-weight heparin is probably justified until warfarin has produced effective anticoagulation.

The short-term risk of stroke after a transient ischemic attack is also high among patients with severe stenosis of the internal carotid artery. Although data are lacking on the optimal timing of endarterectomy, when infarction is absent or limited urgent endarterectomy is probably indicated for patients with internal-carotid-artery stenosis of 70 to 99 percent and in selected patients with stenosis of 50 to 69 percent who can be treated surgically with a low risk of complications.

Stroke is a devastating event that many patients consider worse than death.<sup>51</sup> The occurrence of a transient ischemic attack provides an opportunity to prevent stroke in a group at very high risk. However, interventions will need to be rapid to be effective, and the efficacy of several treatments that are useful after stroke is unproved after a transient ischemic attack. Trials have established the efficacy of several interventions in patients with acute coronary syndromes, but no trial has studied the efficacy of an intervention initiated immediately after a transient ischemic attack. In the longer term, the treatment of cardiovascular risk factors and lifestyle modification (including diet and exercise), although not studied explicitly after a transient ische-

mic attack, are also likely to help prevent stroke in these patients.

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