

# AHA Medical/Scientific Statement

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## Special Report

### Guidelines for the Management of Transient Ischemic Attacks

#### From the Ad Hoc Committee on Guidelines for the Management of Transient Ischemic Attacks of the Stroke Council of the American Heart Association

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**I**schemic stroke is among the leading causes of death and disability in the United States and many other industrialized nations. Approximately 500 000 people in the United States have a new or recurrent stroke each year, and approximately 150 000 will die as a result.<sup>1</sup> There are more than 3 000 000 survivors of stroke in the United States.<sup>1</sup> The annual economic costs of stroke in the United States due to health care expenses and lost productivity are estimated to be more than \$18 billion.<sup>1</sup> Every year 50 000 Americans suffer transient ischemic attacks (TIAs), and about one third of these people will develop a stroke. A TIA identifies a patient at substantial risk of stroke, providing a warning that allows the physician to intervene before stroke occurs.

A large body of evidence is now available on the evaluation and management of patients with cerebrovascular disease. From this evidence the Stroke Council of the American Heart Association has formulated these guidelines. Guidelines have also been developed for the management of acute ischemic stroke<sup>2</sup> and subarachnoid hemorrhage.<sup>3</sup> In the preparation of these guidelines, members of the committee applied rules of levels of evidence for specific treatments developed by other, similar panels<sup>4</sup> (Table 1). Recommendations have been graded based on the strength of the evidence. These rules have not been applied to the recommendations for diagnostic procedures because these procedures have rarely been evaluated in randomized trials.

TIAs are temporary focal brain or retinal deficits caused by vascular disease that clear completely in less than 24 hours. (The 24-hour limit is arbitrary, selected in prospective surveys in the early 1970s.<sup>5</sup>) Most TIAs are much shorter, the majority clearing within 1 hour.<sup>6-8</sup>

In the Cooperative Study of Transient Ischemic Attacks the median duration of carotid distribution TIAs was 14 minutes and that of vertebrobasilar TIAs was 8 minutes.<sup>6</sup> If a symptom is present for more than 1 hour, only 14% of TIAs will resolve within 24 hours.<sup>7</sup> Treatment of a patient with a deficit that persists more than 24 hours is described in "Guidelines for the Management of Acute Ischemic Stroke."<sup>2</sup>

TIAs are a syndrome of diverse causes. Proper diagnosis is crucial in choosing the appropriate therapy to minimize stroke. Occasionally, a transient neurological deficit from a nonvascular cause may mimic a TIA (e.g., focal seizure, complicated migraine, tumor, and subdural hematoma). Metabolic abnormalities, particularly hypoglycemia and hyperglycemia, may occasionally cause focal neurological deficits. Transient neurological episodes may occasionally be seen in patients with brain hemorrhage.<sup>9-11</sup> In patients who later have aneurysmal subarachnoid hemorrhage, these premonitory spells may be due to small, so-called "sentinel" warning leaks, expansion of the aneurysm with pressure on adjacent nerves and brain, or intra-arterial embolism of thrombus within the aneurysm.<sup>12,13</sup> In patients with intracerebral hemorrhage, transient spells may be due to small hematomas or coexistent occlusive small or large artery disease.

In older patients and those with cerebrovascular risk factors, atherosclerosis of the arteries supplying the brain is the most frequent cause of TIA (Fig). TIAs may herald strokes of all types, but their frequency varies, depending on their etiology<sup>9-11,14,15</sup> (Table 2). TIAs are most common in patients with large-artery atherothrombotic disease. In recent stroke series, TIAs occurred before 25% to 50% of atherothrombotic infarcts but only 11% to 30% of cardioembolic strokes and 11% to 14% of lacunar infarcts.<sup>9-11,14,15</sup> Less common causes of TIA include hypercoagulable states, arterial dissection, arteritis, and drug use. There is controversy about whether the duration of a TIA is diagnostically significant. The results of several studies indicate that longer

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**TABLE 1. Levels of Evidence Used in Assessing Clinical Studies and Grading of Recommendations**

Levels of Evidence	
Level I:	Data from randomized trials with low false-positive (alpha) and low false-negative (beta) errors
Level II:	Data from randomized trials with high false-positive (alpha) and high false-negative (beta) errors
Level III:	Data from nonrandomized concurrent cohort studies
Level IV:	Data from nonrandomized cohort studies using historical controls
Level V:	Data from anecdotal case series

Recommendations	
Grade A:	Supported by level I evidence
Grade B:	Supported by level II evidence
Grade C:	Supported by level III, IV, or V evidence

TIAs occurred in patients with nonstenotic carotid arteries, suggesting that these TIAs were embolic in origin.<sup>16,17</sup> However, this finding is not supported by the results of other series.<sup>18</sup> Thus, although the occurrence of a TIA may suggest certain stroke etiologies, a TIA is not diagnostic for any specific stroke type. Careful and prompt evaluation is necessary to determine the cause of TIAs.

### Symptoms of Transient Ischemic Attacks

A careful medical history is crucial to the proper management of TIAs, because the patient often seems normal by the time he or she is seen by the physician. Even when a careful history is taken, recognition of TIAs is sometimes difficult, and experienced observers do not always agree.<sup>19,20</sup> The symptoms of TIAs are protean and depend on the vascular territory involved.<sup>5,19,21,22</sup>

When the carotid artery territory is involved, the symptoms reflect ischemia to the ipsilateral eye or brain. The visual disturbance is a transient graying, fogging, or blurring of vision, sometimes with a “shade” seeming to descend over the line of sight. Hemispherical ischemia usually causes weakness or numbness of the contralateral face or limbs. Language difficulties and cognitive and behavioral changes may also occur.

Vertebrobasilar TIAs often include vestibulocerebellar symptoms (ataxia, dizziness, vertigo, dysarthria), abnormalities of eye movements (diplopia), and unilat-

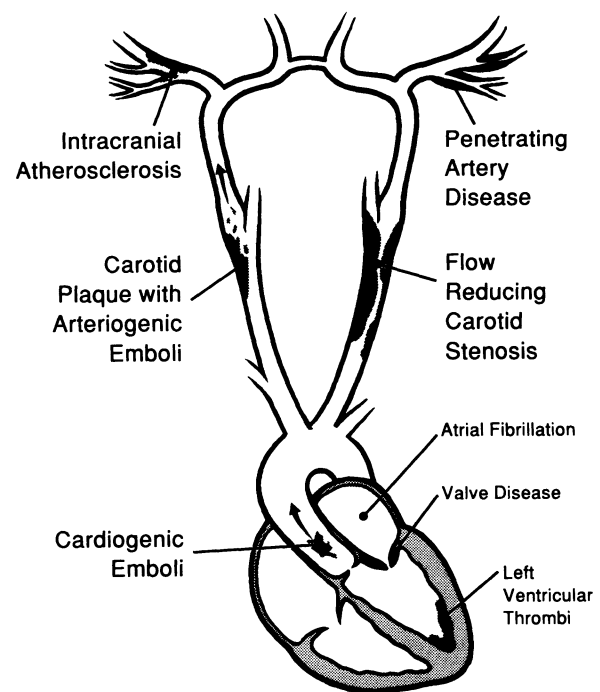


Diagram of common causes of transient ischemic attack in patients over age 50 (see text for details).

eral or bilateral motor and sensory symptoms. Hemianopia and bilateral loss of vision also occur. *Isolated* vertigo, dizziness, or nausea are seldom caused by TIAs. Patients with vertebrobasilar ischemia may have episodes of transient vertigo, but they will usually have other symptoms at other times. Other isolated symptoms that are very unlikely to be due to TIAs are syncope, light-headedness, incontinence, confusion, amnesia, or seizures.

The time course of the episodes is also important. Transient ischemic attacks generally last less than 1 hour. The onset is usually sudden. A “march” of symptoms (different parts of the body affected in succession) suggests another etiology such as migraine or seizure.

### Prognosis

People who have had TIAs have a much higher risk of stroke than does the general population. Overall, the risk of stroke after a TIA is 24% to 29% during the next 5 years.<sup>23-25</sup> The risk is 4% to 8% in the first month<sup>23-25</sup> and 12% to 13% during the first year.<sup>24,25</sup> The stroke risk of patients with TIAs is increased 13- to 16-fold

**TABLE 2. Transient Ischemic Attacks in Various Cerebrovascular Syndromes in Recent Series**

Series	Atherothrombosis (%)	Embolism (%)	Lacune (%)	Hematoma (%)	SAH
Harvard Stroke Registry (1978)	50	23	11	8	7
Michael Reese Stroke Registry (1983)	41.5	11	...	...	...
Stroke Data Bank (1988)	20	13	13	3	1
Lausanne Stroke Registry (1988)	29	30	14	6	...
University of California, San Diego, Stroke Registry (1993)	23	12	12	...	...

Numbers represent percentage of each stroke type preceded by transient ischemic attack. SAH indicates subarachnoid hemorrhage.

**TABLE 3. Stepwise Diagnostic Evaluation for Patients With Transient Ischemic Attack\****Initial evaluation*

1. Complete blood count with platelet count
2. Chemistry profile (including fasting cholesterol level and glucose tolerance)
3. Prothrombin time, activated partial thromboplastin time
4. Erythrocyte sedimentation rate, syphilis serology
5. Electrocardiogram
6. Cranial computed tomography (particularly in hemispheric transient ischemic attacks)
7. Noninvasive arterial imaging (ultrasound, magnetic resonance angiography)

*Second step (to resolve persistent diagnostic uncertainty)*

1. Transthoracic echocardiography
2. Transesophageal echocardiography
3. Transcranial Doppler ultrasound
4. Magnetic resonance angiography
5. Cerebral arteriography
6. Antiphospholipid antibodies

*Other options*

1. Ambulatory electrocardiographic monitoring
2. Further screening for prothrombotic states (eg, protein C, protein S, antithrombin III, thrombin time, hemoglobin electrophoresis, serum protein electrophoresis)
3. Cerebrospinal fluid examination
4. Testing for silent myocardial ischemia (exercise electrocardiogram and/or thallium perfusion)

\*Guidelines only for TIA patients more than 50 years old without obvious diagnosis on initial examination; evaluation must be individualized to specific patient (see text for details).

during the first year and approximately sevenfold during the subsequent 5 years. These general numbers, however, conceal important differences in prognosis between subgroups.<sup>24,26,27</sup> Patients with hemispheric TIA and carotid stenosis of more than 70% have a particularly ominous prognosis, with a stroke rate of more than 40% in 2 years.<sup>28</sup> In contrast, isolated monocular visual symptoms have a better prognosis,<sup>24,26</sup> and younger patients with TIA have a generally lower stroke risk.<sup>29</sup> The evaluation of patients with TIA should attempt to define the cause to determine prognosis and treatment.

### Evaluation of Patients with TIA

There is no routine, standard evaluation of patients with TIA because the individual medical history and specific characteristics of the TIA influence the optimal sequence and extent of diagnostic testing. For example, evaluation of an elderly hypertensive man who has multiple episodes of unilateral amaurosis fugax should focus immediately on the ipsilateral carotid artery. In contrast, a young woman with a history of spontaneous abortions, venous thrombosis, and multifocal TIAs should be assessed initially for antiphospholipid antibodies. A stepwise approach tailored to specific symptoms and associated illnesses is recommended (Table 3). The goals of diagnostic testing are to identify or

exclude etiologies of TIA requiring specific therapy, to assess modifiable risk factors, and to determine prognosis. The indication for a specific diagnostic test is a complex equation that includes the yield of the test (its likelihood of being positive), the management implications of a positive (or negative) result, its cost, and risk to the patient. A minimum evaluation is usually necessary to exclude diagnoses that would significantly alter management, but this too depends on the individual patient.

When considering optimal evaluation of patients with TIAs, the cost of diagnostic testing raises controversial questions. For example, about one in 800 patients with cerebral ischemia harbors a left atrial myxoma that can be reliably detected by precordial echocardiography, a safe, painless, but expensive test.<sup>30</sup> In this test justified for this purpose for all TIA patients? Should it be performed in a 65-year-old man with severe carotid stenosis to exclude concomitant myxoma? The yield of diagnostic testing depends on patient selection.<sup>31,32</sup> There is some lower limit to the yield, even with safe diagnostic tests that potentially influence management, that precludes the necessity of testing. Cost is an important factor in this equation. If the result of a diagnostic test that would significantly influence management is estimated at less than 1% for a given patient, it may not be warranted. However, as diagnostic evaluation proceeds, a revised estimate of the yield is frequently required if the initial studies are negative, and the indication for a diagnostic test must then be reassessed. This is the key to the stepwise approach recommended (Table 3).

A TIA should be promptly evaluated, because delaying diagnosis risks preventable stroke. The risk of stroke is highest soon after the TIA and is approximately 5% in the first month.<sup>23-25</sup> The early risk is probably greater in certain subgroups of patients, including those with multiple frequent and recent ("crescendo") TIAs and those with ventricular thrombi.

Is hospitalization justified to expedite diagnostic evaluation and treatment of TIA? There are no prospective data on this question. The specific type and pattern of the TIA, the efficiency with which a patient can be evaluated, and the patient's ability to return quickly if further symptoms occur are all factors in this decision. The diagnostic evaluation of patients seen within 1 week of a TIA should be completed within 1 week or less. Hospitalization is often justified to expedite evaluation and lessen the possibility of stroke. Some patients may be at increased risk of stroke and warrant closer observation, while the physician may elect to treat others with intravenous medication. The decision whether to hospitalize a patient depends on that patient's individual circumstances.

### Computed Tomographic and Magnetic Resonance Imaging

Computed tomography (CT) is useful in patients with transient neurological symptoms to rule out lesions that may mimic a TIA. CT shows a nonvascular lesion accounting for neurological symptoms (tumors, subdural hematoma) in about 1% of patients with TIA.<sup>31,33,34</sup> The yield for relevant nonvascular lesions is very low in patients with brainstem or ocular TIAs.<sup>31</sup> CT may also identify vascular lesions such as aneurysms or arterio-



venous malformations that can be present in patients with TIAs. CT after a hemispheric TIA shows hypodensities suggestive of brain infarction in about 20% of patients (and in even more when magnetic resonance [MR] imaging is used).<sup>31,33,34</sup> The implications for management of patients with these “silent” strokes are still unclear; occult brain infarction identified by CT in TIA patients may predict prognosis,<sup>33-35</sup> and the number, location, and vascular distribution of the lesions may provide additional information about the source of the TIA. At present, there is no indication for routine MR imaging of patients with TIA.

### Cerebrovascular Arterial Imaging

Noninvasive ultrasound evaluation may provide crucial information in patients with TIA. Ultrasound allows noninvasive evaluation of the extracranial carotid and vertebral arteries.<sup>36</sup> In patients with carotid territory symptoms, cervical carotid artery imaging is often required to exclude high-grade stenosis because endarterectomy is optimal therapy for most TIA patients with such lesions. Carotid ultrasonography is widely used for this purpose; its accuracy depends on the specific techniques and equipment used, laboratory quality control, and patient anatomy.<sup>37</sup> Carotid duplex ultrasonography is reported to have an accuracy of 90% to 95%<sup>36</sup> but has some limitations. The accuracy of ultrasonography in assessing mild-to-moderate stenosis is poor,<sup>38</sup> and total occlusion cannot always be distinguished from very high-grade stenosis by this technique. Nevertheless, ultrasonography should be an initial diagnostic test in most patients with TIA.

Cerebral arteriography by means of selective arterial catheterization is usually required before surgery to precisely define the degree and extent of carotid atherosclerosis in patients with TIA. Arteriography is also necessary to evaluate the vertebral and basilar arteries and to define intracranial stenosis or occlusion, although newer imaging techniques (see below) may allow noninvasive assessment of these vessels. Cerebral arteriography is relatively expensive and uncomfortable. Complications are generally minor and transient, but even in skilled hands serious complications (mostly stroke) may occur in 0.5% to 1.0% of patients with cerebrovascular disease.<sup>38-40</sup> Cerebral arteriography is required when diagnoses of vasculitis, dissections, and emboli are suspected but remain in doubt. Precise diagnosis of intracranial atherosclerosis (particularly common in Asians and African-Americans) requires selective intra-arterial cerebral arteriography, but because this diagnosis does not affect some physicians' initial antithrombotic management, it is often not pursued.

Rapid advances in technology are improving our ability to assess the intracranial circulation and may affect the diagnostic workup for a TIA. Transcranial Doppler ultrasound can be used to detect severe intracranial stenosis, evaluate the vertebrobasilar vessels, and assess patterns and extent of collateral circulation in patients with known arterial stenosis or occlusion.<sup>41</sup> It may also be able to detect emboli passing through the cerebral vessels and may provide noninvasive evaluation of the cerebral circulation prior to angiography. Its role in evaluating the patient with TIA is currently being studied.

**TABLE 4. Common Risk Factors for Cardiogenic Embolism**

Major risk factors*
Atrial fibrillation
Mitral stenosis
Prosthetic cardiac valves
Recent myocardial infarct
Left ventricular thrombus (especially if mobile or protruding)
Atrial myxoma
Infective endocarditis
Dilated cardiomyopathies—ischemic and nonischemic
Marantic endocarditis
Minor risk factors†
Mitral valve prolapse, especially in the presence of myxomatous changes
Severe mitral annular calcification
Patent foramen ovale
Atrial septal aneurysm
Calcific aortic stenosis
Left ventricular regional wall motion abnormalities
Aortic arch atheromatous plaques
Spontaneous echocardiographic contrast

\*These are associated with a substantial absolute risk of stroke, firmly linked to an embolic mechanism.

†These are associated with a low absolute risk of initial or recurrent stroke or are incompletely established, based on current knowledge, as a direct embolic source.

Adapted from Reference 46.

MR angiography is a relatively new technology, less widely available at present than ultrasonography or intra-arterial catheter arteriography. MR angiography provides noninvasive imaging of the carotid, vertebral, basilar, and major intracranial and extracranial arteries but with less detail than selective catheter arteriography.<sup>42</sup> Use of MR angiography frequently leads to overestimation of the degree of arterial stenosis. When MR angiography and ultrasound are concordant, there is a very good correlation with conventional angiography.<sup>43,44</sup> In most centers MR angiography is more costly than cerebrovascular ultrasound. Improvements in MR angiography and wider availability may increase its role in routine evaluation of patients with TIA.<sup>45</sup>

### Cardiac Imaging

Advances in cardiac imaging techniques, particularly ultrasonography, have resulted in more reliable identification of potential cardioembolic sources (Table 4).<sup>46,47</sup> With transesophageal echocardiography (TEE), the ultrasound transducer is placed in the esophagus adjacent to the left atrium, affording improved visualization of the atrium, its appendage, the interatrial septum, and the ascending aorta. Compared with conventional transthoracic echocardiography, TEE more sensitively detects abnormalities of the interatrial septum (atrial septal aneurysms, patent foramen ovale, atrial septal defects), atrial appendage thrombi associated with atrial fibrillation, the mitral valvular vegeta-

tions of infective endocarditis, and atherosclerotic disease of the aortic arch.<sup>48,49</sup> Contrast echocardiography (with either transthoracic echocardiography or TEE) greatly increases the identification of patent foramen ovale.

In patients without clinical evidence of heart disease, the yield of transthoracic echocardiography is low (<3%) for detection of major embolic sources (Table 4) that would clearly alter management.<sup>30</sup> In such patients, transthoracic echocardiography should be reserved for young subgroups in whom there is no obvious cause of TIA or subgroups who are without major risk factors for primary cerebrovascular disease, and possibly for those in whom no source of TIA has been identified after other tests are completed. If management would be altered by the identification of minor embolic sources (Table 4) or by the detection of left atrial thrombus associated with atrial fibrillation, TEE should be considered. At present, the management implications of abnormalities commonly detected by TEE are unclear and do not justify use of the procedure in unselected patients with TIA.

The yield of ambulatory ECG monitoring in unselected patients with TIA is low.<sup>30</sup> This test should probably be reserved for patients with suspicious palpitations close in time to TIAs who have suggestive ECGs and enlarged left atria, and possibly those patients in whom no other cause of TIA has been determined.<sup>30,31</sup>

About 25% of TIA patients with cerebrovascular atherosclerosis also have symptomatic coronary artery disease (prior myocardial infarct or angina), and perhaps an additional 20% have asymptomatic coronary artery disease.<sup>50-53</sup> Ischemic heart disease is the most frequent cause of death in elderly patients with TIA; hence its optimal management is an important part of care. Although asymptomatic coronary artery disease may identify patients with TIA who are at risk for cardiac death,<sup>50</sup> it is unclear whether diagnostic investigation to detect silent myocardial ischemia in patients with TIA who do not have symptoms or electrocardiographic evidence of coronary artery disease will lead to improved outcome.<sup>31,53</sup>

### Other Testing

Special testing for prothrombotic states causing or contributing to TIA should be reserved for selected patients (particularly those less than 50 years old) or those for whom no other explanation for the TIA can be found after initial diagnostic evaluation.<sup>54</sup> Testing is indicated in young patients (less than 50 years old) without obvious cause for stroke and in patients with prior venous thrombosis (especially in unusual locations), those with a family history of thrombosis, and possibly those for whom no other explanation of the TIA can be found after initial evaluation (especially when there have been multiple strokes). Abnormalities on routine screening laboratory tests (hemoglobin, hematocrit, platelet count, and prothrombin time or partial thromboplastin time) should also prompt consideration of further coagulation testing. Lumbar puncture is not routinely indicated in patients with TIAs but should be considered in patients with signs or symptoms suggesting central nervous system infection.

Evaluation of young patients with TIA who do not have risk factors for atherosclerosis is a particular

challenge, because the differential diagnosis includes many uncommon diseases.<sup>55-57</sup> Clues from the history and examination are critical to the initial evaluation.<sup>58</sup> The cause is not determined in up to one third of young patients,<sup>56</sup> and the extent of evaluation required is controversial. In a young patient a single episode of minor TIA-like symptoms (sensory or visual spells, minor weakness of one extremity) without apparent cause after thorough history and examination may not require extensive diagnostic testing (eg, intra-arterial cerebral arteriography, TEE).<sup>59</sup> Recurrent episodes or major TIA symptoms (ie, profound hemiparesis or symptoms that last >1 hour) should prompt thorough evaluation for uncommon etiologies. MR imaging may be indicated in selected young patients with symptoms of TIA to exclude demyelinating disease and identify occult stroke, which would prompt a more extensive evaluation.

### Recommendations

Patients with TIAs should be evaluated promptly. The evaluation should follow a stepwise approach as outlined in Table 3. The evaluation should be guided by a careful history and physical exam, and thus varies from patient to patient.

### Risk Reduction

#### Hypertension

Hypertension is the most powerful, prevalent, and treatable risk factor for stroke.<sup>60-62</sup> Both systolic and diastolic blood pressure are independently related to stroke incidence. In the Framingham Study the age-adjusted relative risk of stroke in hypertensive subjects was 3.1 for men and 2.9 for women.<sup>60</sup> Even borderline hypertension increases stroke risk by approximately 50%.<sup>60</sup> Isolated systolic hypertension, which is common in the elderly, also considerably increases risk of stroke.<sup>63</sup>

Fortunately, people with hypertension can substantially reduce their risk of stroke by controlling their blood pressure. A large number of prospective, randomized hypertension treatment trials have documented substantial reductions in stroke risk with control of hypertension. An analysis of 14 treatment trials with a total of more than 37 000 hypertensive patients indicated that an average diastolic blood pressure reduction of 6 mm Hg produced a 42% reduction in stroke risk.<sup>64</sup> In the Systolic Hypertension in the Elderly Program (SHEP) trial, subjects over the age of 60 with isolated systolic hypertension (>160 mm Hg) who were randomly assigned to receive antihypertensive medication had a 36% reduction in stroke compared with those in the placebo group.<sup>65</sup>

In patients with acute stroke, aggressive treatment of hypertension is not recommended,<sup>2,66</sup> and a small proportion of patients with TIA will actually have had a small stroke. Further, occasionally patients with a high-grade arterial stenosis have a hemodynamic basis for the TIA, and blood pressure lowering could theoretically precipitate symptoms. Thus, although aggressive treatment of hypertension is important to the follow-up care of these patients, it might be advisable to delay it until after definitive evaluation and treatment of the TIA.

## Cigarette Smoking

Several large studies have clearly indicated that cigarette smoking substantially increases the risk of stroke.<sup>60,67-69</sup> In general, most studies have documented relative risk values of 1.5 to 2. Heavy smokers have even higher relative risks. It is also clear that smoking cessation dramatically reduces stroke risk. Data from the Framingham Study,<sup>70</sup> the Nurses Health Study,<sup>68</sup> and the Honolulu Heart Program<sup>67</sup> have shown that smoking cessation can promptly reduce stroke risk. In the Framingham Study the risk of stroke in former cigarette smokers was no different, after only 5 years of not smoking, from that of people who had never smoked.<sup>70</sup>

## Heart Disease

A variety of cardiac abnormalities increase stroke risk. These include coronary artery disease, congestive heart failure, atrial fibrillation, and a variety of valvular disorders. Appropriate treatment for these cardiac conditions decreases the risk of stroke.

## Oral Contraceptive Use

Several studies have indicated an approximately five-fold increased risk of stroke in women who take oral contraceptives.<sup>71-74</sup> The increased risk occurs primarily in women over the age of 35, particularly those who smoke or have other cardiovascular risk factors. The risk of stroke is highest with high-estrogen oral contraceptives. Although no prospective randomized trials have been done, it is likely that discontinuation of oral contraceptives will diminish stroke risk. One large study has shown that subjects who discontinued oral contraceptives had no higher risk of stroke than those who had never used them.<sup>75</sup>

## Postmenopausal Estrogen Use

The cardiovascular risk associated with postmenopausal estrogen replacement has been controversial. In the Framingham Study, women reporting postmenopausal estrogen use had a more than twofold increased risk for cerebrovascular disease.<sup>76</sup> However, in the 10-year follow-up of 50 000 women in the Nurses Health Study, current postmenopausal estrogen use was associated with a reduction in the incidence of coronary heart disease and cardiovascular mortality and was not associated with any change in the risk of stroke.<sup>77</sup> Recently an analysis of follow-up data from the National Health and Nutrition Examination Survey (NHANES I) cohort revealed that postmenopausal hormone use by white women was associated with a 31% decrease in stroke incidence and a 63% reduction in stroke mortality.<sup>78</sup> The weight of evidence suggests that postmenopausal estrogen use does not increase stroke risk and may lower the risk, and there is no need to discontinue postmenopausal hormone therapy in patients with TIA.

## Alcohol Consumption

Heavy alcohol use, either daily or in binges, is related to excess stroke risk.<sup>79,80</sup> In contrast, light or moderate alcohol consumption appears to raise the high-density lipoprotein cholesterol level and lower the risk of coronary artery disease<sup>80,81</sup> and has no effect or a mild protective effect against the risk of stroke.<sup>82,83</sup> The

mechanisms by which heavy alcohol use increases stroke risk are not known for certain. Proposed explanations include increased hematocrit and blood viscosity, rebound thrombocytosis during abstinence, and cardiac rhythm disturbances such as "holiday heart syndrome."<sup>84</sup> Although prospective trials have not been conducted, it appears likely that the risk of stroke associated with heavy alcohol consumption can be reduced by decreasing alcohol intake.

## Blood Lipids

Increased levels of serum cholesterol and triglycerides are independently related to the development of coronary artery disease,<sup>85</sup> but their relation to stroke is less clear. High stroke rates have been noted in families with hyperlipidemias. In addition, serum lipid levels have been related to carotid artery atherosclerosis in a variety of ultrasonographic and angiographic studies.<sup>86</sup> However, no prospective trials have indicated that medical therapy to reduce excessive blood lipid levels can reduce the risk of stroke. A recent meta-analysis of randomized, controlled trials found that cholesterol lowering was not associated with a significant reduction in stroke mortality or morbidity in middle-aged men.<sup>87</sup> Medications for hyperlipidemia reduce the risk of coronary artery disease; therefore, cholesterol lowering may be recommended for these patients for reasons other than stroke reduction.<sup>88</sup> Whether cholesterol lowering has a beneficial effect on cerebrovascular disease in patients with familial hyperlipidemias is unknown.

## Diabetes

Several trials have indicated that diabetes is an independent risk factor for ischemic stroke.<sup>89,90</sup> Whether strict control of blood glucose in diabetic patients will ameliorate their risk of stroke is unknown.

## Physical Activity

Exercise may exert a beneficial effect on risk factors for atherosclerotic disease by reducing blood pressure, increasing high-density lipoprotein cholesterol levels, lowering low-density lipoprotein cholesterol levels, and improving glucose tolerance. No prospective trials have addressed the relation between physical activity and stroke risk. However, because of the benefits mentioned above, it is possible that increased physical activity by sedentary people will reduce stroke risk.

## Recommendations

The following recommendations are appropriate to help reduce the risk of stroke for people who have had a TIA.

1. After definitive evaluation and treatment of the TIA, hypertension should be treated aggressively to maintain systolic blood pressure below 140 mm Hg (<160 mm Hg for patients more than 60 years old) and diastolic blood pressure below 90 mm Hg.
2. Cigarette smoking should be discontinued.
3. Coronary artery disease, cardiac arrhythmias, congestive heart failure, and valvular heart disease should be treated appropriately.
4. Excessive alcohol use should be eliminated.
5. Use of oral contraceptives should be discontinued, or as a minimum a low-estrogen agent should be used.



6. Hyperlipidemia should be treated as recommended for reduction of coronary artery disease.<sup>91</sup>

7. Physical activity should be recommended as tolerated.

8. Discontinuation of postmenopausal estrogen is *not* recommended.

## Medical Therapy of TIAs

### Antiplatelet Agents

Over the past decades evidence has accumulated from rigorous clinical trials that antiplatelet agents are effective in the prevention of stroke in patients at high risk. Numerous randomized, double-blind, placebo-controlled trials have evaluated the use of various antiplatelet agents for the secondary prevention of brain infarction after TIA or minor stroke. Different outcome measures were used in different trials to assess the success of therapy. Some trials have a single outcome measure such as nonfatal stroke, nonfatal myocardial infarction, or vascular death. In other trials a composite outcome was used, such as the outcome cluster of TIA, stroke, and death. Overall, there is strong support for the use of antiplatelet agents to prevent stroke.

### Aspirin

Aspirin (acetylsalicylic acid) is the standard medical therapy used for prevention in patients at risk of stroke. Aspirin inhibits platelet function, probably by blocking cyclooxygenase. Aspirin was approved by the US Federal Drug Administration for management of cerebrovascular disease on the basis of two seminal studies, the Canadian Cooperative Study Group<sup>92</sup> and Fields and collaborators.<sup>93</sup>

The Canadian Cooperative Study Group evaluated 585 patients (69% of whom were men) with TIA or minor stroke.<sup>92</sup> Patients were randomly assigned to receive either 1300 mg of aspirin per day, or 800 mg of sulfinpyrazone per day, a combination of both, or placebo. Aspirin reduced the risk of stroke or death by 31%. There was a significant (48%) reduction of risk of stroke or death in men but no significant reduction in women. The gender difference in response to aspirin was probably due to the small number of women studied and the lesser risk of stroke for women who have had a TIA compared with men.<sup>94</sup> No beneficial effect was noted with sulfinpyrazone alone, and sulfinpyrazone provided no additional benefit in combination with aspirin.

Fields et al<sup>93</sup> enrolled 178 patients (66% of whom were men) with carotid distribution TIAs in a double-blind, placebo-controlled trial of aspirin for stroke prevention. Patients were randomly assigned to receive either 1300 mg of aspirin daily or placebo. There was no statistically significant difference between aspirin and placebo in the absolute end points of mortality or cerebral and retinal infarction. In the aspirin-treated group, 11 of 88 (13%) patients had a stroke compared with 14 of 90 (16%) in the placebo group. In post hoc analysis, aspirin was superior to placebo in reducing the risk of mortality, cerebral infarction, and retinal infarction in patients with multiple TIAs and in those with carotid artery stenosis greater than 50% or ulceration in the artery appropriate to symptoms.

Subsequently, a number of studies reported results that in most instances were consistent with a beneficial effect of aspirin.<sup>95-98</sup> Some negative studies were probably too small to show a benefit of aspirin.<sup>94</sup> Although in most of these studies there was a trend toward reduced stroke risk in patients treated with antiplatelet agents, in some studies it was only with the combination of end points including TIA, stroke, myocardial infarction, and death that a statistically significant benefit for aspirin was demonstrated.

**Dosage of Aspirin.** Since 1987 three large trials have confirmed the benefit of different aspirin dosages in preventing vascular ischemic events in patients who have had a TIA or minor stroke. The UK-TIA aspirin trial was the first placebo-controlled multicenter trial to compare two doses of aspirin, 1200 mg/d and 300 mg/d. The 2435 patients (73% of whom were men) enrolled in the study were observed for a mean of 4 years.<sup>99</sup> Aspirin (both doses combined) decreased by 15% the risk of the combined end points of myocardial infarction, major stroke, and death compared with placebo. There was a 7% (nonsignificant) reduction in the risk of disabling stroke or vascular death. There was no significant outcome difference between the two doses, but the event rate was low and this could have been a type II (beta) statistical error. Upper gastrointestinal symptoms were more common with the higher dose of aspirin than with the lower dose. The incidence of gastrointestinal bleeding was 3% for 300 mg aspirin and 5% for 1200 mg aspirin, but this difference was not statistically significant.

In the Dutch TIA trial 3131 patients with TIA (one third) or minor stroke were enrolled and a carbaspirin calcium dose of 30 mg/d was compared with one of 283 mg/d. There was no placebo group. There was no difference between the two aspirin doses in the end point events of TIA or stroke. The 30-mg dose of carbaspirin calcium was less gastrotoxic.<sup>100</sup> In the Swedish Aspirin Low-dose Trial (SALT) 1360 patients with TIA or minor stroke received either 75 mg aspirin per day or placebo; there was an 18% reduction in stroke or death in the low-dose aspirin group compared with the placebo group.<sup>101</sup> Neither the Dutch TIA trial nor the SALT trial compared low-dose aspirin with larger doses of aspirin used in earlier TIA trials.

Although controversy remains about the optimal dose of aspirin to prevent stroke,<sup>102</sup> at present there is no compelling evidence that either a high or a low dose is more efficacious than the other. In view of the slightly lower incidence of side effects with lower doses, and the possibility of increased compliance, many authors recommend 325 mg/d as an initial dose.

### Dipyridamole and Other Antiplatelet Agents

The combination of aspirin, a cyclooxygenase inhibitor, and dipyridamole, a cyclic nucleotide phosphodiesterase inhibitor, theoretically offers a pharmacologic advantage. This combination was evaluated in four trials involving patients with cerebral ischemia, and three of these trials included a comparison with aspirin alone. The French Toulouse Study involved 440 patients (85% of whom were men) with TIAs. There was no statistically significant difference in outcome measures among groups receiving 900 mg/d aspirin, aspirin plus dihydroergotamine, aspirin plus dipyridamole and dihydroergotamine, or dihydroergotamine alone.<sup>103</sup> A study by

Bousser and collaborators<sup>104</sup> included 604 patients (67% of whom were men) with TIAs (16%) or small strokes (84%). Patients were randomly assigned to receive 1000 mg/d aspirin, aspirin combined with 225 mg/d dipyridamole, or placebo. There was a 42% reduction in the risk of stroke with aspirin compared with placebo. The effect of aspirin was similar in men and women. No added benefit was noted with dipyridamole. In the American-Canadian Cooperative Study 890 patients (67% of whom were men) with carotid distribution TIAs were evaluated.<sup>105</sup> Brain or retinal infarction occurred in 60 of 442 patients (14%) on aspirin and in 53 of 448 (12%) of patients on aspirin plus dipyridamole (no significant difference). There was no difference in the incidence of fatal or nonfatal myocardial infarctions between the two groups. Thus, none of these studies showed any additional benefit from adding dipyridamole to aspirin.

The European Stroke Prevention Study (ESPS) compared placebo with 975 mg/d aspirin plus 225 mg/d dipyridamole in 2500 patients with TIAs (33%), reversible ischemic neurological deficits (7%), or stroke (60%). There was an overall reduction of 33% in the risk of stroke and death, and a reduction of 38% in the risk of stroke only, for those assigned to active treatment.<sup>106</sup> Because no patients were given aspirin only, this study does not permit comparison of the combination to aspirin alone.

In the only trial comparing placebo and dipyridamole (400-800 mg/d) alone, there was no evidence the latter had any benefit.<sup>107</sup> A Canadian study evaluated the effectiveness of suloctidil in patients with recent thromboembolic stroke. The results were negative, and the study was interrupted because of suloctidil's hepatotoxicity.<sup>108</sup>

### **Ticlopidine**

Ticlopidine hydrochloride is a new antiplatelet agent recently approved in the United States for prevention of stroke in patients with TIA or minor stroke. Its antiplatelet action is distinct from that of aspirin or dipyridamole, and it does not affect cyclooxygenase. Two large, multicenter, randomized trials have evaluated the efficacy of ticlopidine in patients with cerebrovascular disease.

The Canadian American Ticlopidine Study (CATS) evaluated the efficacy of ticlopidine in patients who had had a recent moderate to severe atherothrombotic (74%) or lacunar (26%) stroke (no TIAs were included) for reducing the incidence of important vascular events (recurrent nonfatal stroke, nonfatal myocardial infarction, and vascular mortality).<sup>109</sup> In 25 centers in Canada and the United States 1053 patients were admitted to the study between 1 week and 4 months of the qualifying stroke. Patients were randomly assigned to receive 250 mg ticlopidine twice a day or placebo. According to an intention-to-treat analysis, the relative risk reduction for the cluster of important vascular events was 23.3%. Benefits were observed in both men and women.

The Ticlopidine-Aspirin Stroke Study (TASS) compared the efficacy of ticlopidine and of aspirin in reducing the incidence of stroke and death of all causes in patients with a recent TIA or minor stroke.<sup>110</sup> At 56 centers in the United States and Canada 3069 patients were randomly assigned to receive either 250 mg ticlopidine twice a day or 650 mg aspirin twice a day.

According to an intention-to-treat analysis, the overall risk reduction by ticlopidine at 3 years for fatal and nonfatal stroke was 21%; ticlopidine also reduced the risk of stroke and all causes of death by 12% (compared with aspirin). A post-hoc intention-to-treat analysis found that the relative risk reduction was greatest in the first year after entry into the study.

Diarrhea was the most frequent side effect of ticlopidine, occurring in 12.5% of patients. Neutropenia was more common in the ticlopidine groups of the TASS and CATS studies than in the comparison groups and occurred in 2.4% of all patients. The neutropenia was severe in 0.8% of patients but was reversible in all. The severe neutropenia occurred within 90 days of starting therapy, which led to the recommendation to screen for this potential side effect by obtaining a complete blood count with differential every 2 weeks in the first 3 months of therapy. Considering the slight benefit of ticlopidine compared with its increased cost, the incidence of side effects, and the need for hematologic monitoring, the committee considered aspirin appropriate initial antiplatelet therapy in most cases. Ticlopidine is a useful alternative, particularly in patients who cannot take aspirin or who have continued symptoms despite aspirin therapy.

### **Antiplatelet Trialists' Collaboration**

The Antiplatelet Trialists' Collaboration initially compiled results of 25 completed randomized trials involving 29 000 patients with TIA, stroke, unstable angina, or myocardial infarction who took primarily aspirin, sulfapyrazone, dipyridamole, or various combinations of these agents.<sup>111</sup> A 15% reduction of vascular mortality and a 30% reduction of nonfatal cardiovascular events were reported in patients taking antiplatelet medication.

This group of investigators has now compiled results of 145 completed, randomized trials involving almost 100 000 patients with coronary, cerebral, or peripheral vascular atherosclerotic disease or other high-risk vascular conditions.<sup>112</sup> Seven antiplatelet drug regimens were studied, including aspirin, ticlopidine, dipyridamole, sulfapyrazone, suloctidil, and the combinations of aspirin plus dipyridamole and aspirin plus sulfapyrazone. All patients received antiplatelet therapy for at least 1 month. The most widely used antiplatelet agent was aspirin at dosages of 160 to 325 mg/d.

Comparing antiplatelet therapy with control, the Antiplatelet Trialists' overview analysis revealed a 23% risk reduction for the cluster of nonfatal stroke, nonfatal myocardial infarction, and vascular death in patients who had a history of TIA or stroke. The overview analysis also found significant risk reductions for death from any cause, nonfatal stroke, nonfatal myocardial infarction, and the outcome cluster of "vascular death or death from unknown cause"<sup>112</sup> (Table 5).

The relative benefit of antiplatelet therapy was remarkably constant irrespective of age and gender. Antiplatelet agents reduced the risk of important vascular events both in patients younger than 65 and in those older than 65 and in men and women alike. The relative benefit of antiplatelet therapy was also remarkably constant irrespective of blood pressure or the presence or absence of diabetes mellitus.<sup>112</sup>



**TABLE 5. Risk Reduction by Antiplatelet Therapy in Patients With Previous Transient Ischemic Attack or Stroke\***

Event	Odds reduction (%) ( $\pm$ SD)
Nonfatal stroke, nonfatal myocardial infarction, or vascular death	22 (4)
Vascular death or death from unknown cause	14 (7)
Death from any cause	16 (6)
Nonfatal stroke	23 (6)
Nonfatal myocardial infarction	36 (11)

\*Data from the Antiplatelet Trialists' Collaboration. Adapted from Reference 112.

### Anticoagulants

Oral anticoagulants have been used for decades to prevent stroke in patients with TIAs, but there is no conclusive data supporting their use. The number of patients included in clinical trials of anticoagulants after TIA is only a fraction of the number studied in trials of antiplatelet agents. Oral anticoagulant therapy for TIAs has been evaluated in four randomized<sup>113-116</sup> and six nonrandomized studies.<sup>117-122</sup> The randomized trials were performed almost 30 years ago and in aggregate included only 178 patients.<sup>113-116</sup> There was no significant benefit of warfarin compared with placebo. Three later studies compared warfarin with aspirin alone or in combination with dipyridamole. Aggregate data in 501 patients who had TIAs showed no significant difference in the rate of cerebral infarction or death between the patient groups.<sup>123-125</sup> Eriksson<sup>126</sup> also randomly assigned 188 patients with TIA to a combination of aspirin and dipyridamole or heparin followed by warfarin. He found no significant difference between the two groups in stroke or in stroke or death. Recurrent TIAs or amaurosis fugax were more frequent in the antiplatelet agent-treated group, particularly in the first 2 months after onset of TIAs.

In summary, there is no evidence to recommend the routine administration of anticoagulants to patients with TIAs.

### TIA Subtypes

None of the prospective randomized trials of antiplatelet agents have been designed to evaluate the agents' effectiveness in patients with specific TIA subtypes or TIAs due to specific etiologies. Post hoc subgroup analyses have found that antiplatelet agents are effective in vertebrobasilar TIAs as well as TIAs in the carotid circulation.<sup>127-129</sup> Although no prospective randomized trials have been performed, on the basis of level IV and V evidence some authorities advocate the use of anticoagulants in patients with TIAs who have significant occlusive disease of the vertebrobasilar vessels.<sup>130-132</sup> Anticoagulants have also been recommended by some authors for stenotic disease of the intracranial vessels, but again there is only level IV and V evidence for this recommendation. No prospective trials have been done on antithrombotic therapy in small vessel occlusive (lacunar) disease. A subgroup analysis in the French AICLA trial suggested a benefit of aspirin in these patients.<sup>104</sup>

There is general agreement that most patients with stroke due to cardiac embolism should be given anticoagulation therapy. This practice is based on extrapolation from level I evidence from primary prevention studies in atrial fibrillation<sup>133,134</sup> and coronary artery disease,<sup>135</sup> as well as level III and IV evidence from a number of studies of secondary prevention. Until recently no prospective trial had specifically examined cardioembolic TIAs. The recent European Atrial Fibrillation Trial compared warfarin (INR [International Normalized Ratio] 2.5 to 4.0), aspirin (300 mg/d), or placebo in 1007 patients with nonrheumatic atrial fibrillation and a TIA or small stroke.<sup>136</sup> Twenty-three percent of the patients had a TIA and 77% had a minor ischemic stroke. The study demonstrated a 66% reduction in subsequent stroke with anticoagulation therapy compared with placebo. Aspirin was less effective than warfarin, with a 14% reduction in stroke compared with placebo. Because atrial fibrillation accounts for about half of cardiac emboli,<sup>30</sup> this study provides further support for anticoagulation therapy in patients with cardioembolic TIAs.

### Management of Recent TIAs

Considerable controversy remains about the proper management of patients with recent TIAs. Some authors advocate immediate intravenous administration of heparin for high-risk patients with recent TIAs, for patients with TIAs of increasing severity, frequency, or duration, and as an interim medical measure while patients are evaluated before surgery or being given maintenance medical therapy.<sup>137,138</sup> However, no randomized trial of adequate size has evaluated use of heparin in any of these clinical situations. In a small prospective study 55 patients were enrolled within 1 week of a carotid or vertebrobasilar TIA. Patients received either 1300 mg/d aspirin or intravenous heparin. Recurrent TIAs occurred in 30% of 27 patients assigned to heparin and in 25% of 28 patients given aspirin for a mean of 6 days. One patient (4%) in the heparin group had a stroke, compared with four (14%) patients treated with aspirin.<sup>139</sup> The small number of patients studied precludes any definitive recommendations regarding intravenous use of heparin in patients with recent TIAs.

### Recommendations

The antiplatelet agents aspirin and ticlopidine are both beneficial in the prevention of stroke following a TIA (Grade A recommendation). The modest beneficial effects of antiplatelet agents are similar in men and women, diabetic and nondiabetic persons, normotensive and hypertensive persons, and both the old and the young. Considering the relative benefits, side effects, and cost of ticlopidine and aspirin, the committee considered aspirin appropriate initial therapy for most patients. The optimal dose of aspirin is controversial; a dose of 325 mg/d promotes compliance and may minimize gastrointestinal side effects. The range of acceptable doses is 30 to 1300 mg/d (Table 6) (Grade B recommendation). The recommended dose of ticlopidine is 250 mg twice a day. The combination of aspirin and dipyridamole for stroke prevention in patients with TIA is not recommended (Grade A recommendation).

TABLE 6. Use of Antithrombotic Agents in Patients With TIAs

Event	Recommended therapy	Therapeutic options
TIA*†	Aspirin 325 to 1300 mg/d‡§	Aspirin 30 to 1300 mg/d‡   or ticlopidine 250 mg twice a day§
TIA*† if patient is aspirin intolerant or if TIA occurs while patient is on aspirin therapy	Ticlopidine 250 mg twice a day§	Warfarin (INR 2 to 3)¶
Crescendo TIAs*†		Intravenous heparin (aPTT 1.5 to 2.0), or aspirin 325 to 1300 mg/d, or ticlopidine 250 mg twice a day after aspirin loading (325 mg)¶

\*Carotid endarterectomy is indicated for angiographically documented symptomatic ipsilateral carotid stenosis of 70% or more, unless surgery is contraindicated.

†Anticoagulation is indicated if a definite cardiac source of embolism is identified.

‡Experts disagree about whether an aspirin dosage of 325 mg/day offers as much benefit as higher dosages.

§Grade A recommendation (see Table 1).

||Grade B recommendation (see Table 1).

¶Grade C recommendation (see Table 1).

TIA indicates transient ischemic attack; INR, International Normalized Ratio; aPTT, activated partial thromboplastin time.

There is no persuasive evidence of benefit from dipyridamole, sulfinpyrazone, or suloctidil.

Anticoagulation therapy is not routinely recommended for patients with TIAs, either acutely or as long-term therapy (Grade B recommendation). Anticoagulation therapy is an option in patients with TIA who continue to have symptoms despite antiplatelet therapy (Grade C recommendation). Anticoagulation therapy is recommended for patients with TIA who have a major cardiac source of embolism (Table 4), except for those with infective endocarditis (Grade A recommendation).

### Surgical Therapy

#### Carotid Endarterectomy for Extracranial Carotid Disease

Carotid endarterectomy was first performed in 1954 and its use as a strategy for stroke prevention grew rapidly. The annual number of operations in the United States rose from about 17 000 in 1971 to 104 000 in 1984.<sup>140</sup> In 1984 several articles appeared questioning the efficacy and appropriate use of carotid endarterectomy<sup>140-144</sup> and the number of procedures dropped significantly.<sup>145</sup> As a result of this controversy several large prospective randomized trials were initiated.

Until recently only two randomized trials examined carotid endarterectomy.<sup>146,147</sup> These studies failed to show its efficacy but were limited by an unacceptably high surgical morbidity rate. In the Joint Study of Extracranial Arterial Occlusion there were design flaws such as the inclusion of patients with noncarotid territory symptoms, patients with only mild stenosis, and an unacceptably high loss to follow-up.<sup>146</sup> The small study by Shaw et al<sup>147</sup> was terminated early (after only 41 patients were entered) because of a very high surgical mortality and morbidity rate. Although there is level III and IV evidence that after a successful carotid endarterectomy in patients with a TIA the stroke rate is 1% to 2% per year,<sup>148-152</sup> the support for carotid endarterectomy has rested on nonrandomized comparisons with the "natural history" of TIAs.<sup>153,154</sup>

Two large prospective randomized trials, one in North America and one in Europe, have begun to

provide definitive data on which to base decisions about endarterectomy. Results from both trials for patients with high-grade carotid stenosis (70% to 99%) were announced in the same week in February 1991.

The North American Symptomatic Carotid Endarterectomy Trial (NASCET) included 659 patients with 70% to 99% stenosis and TIA or minor stroke within 120 days. Patients were randomly allocated to receive endarterectomy plus best medical care, including antiplatelet therapy (328 patients), or best medical therapy alone (331 patients). After 2 years ipsilateral stroke had occurred in 26% of the medical group and 9% of the surgical group. There was a 27.6% incidence of fatal or nonfatal stroke in any location in the medical group compared with a 12% incidence in the surgical therapy group ( $P < .001$ ).<sup>27</sup> The trial was stopped early for those with high-grade stenosis because of these dramatic results, and the National Institutes of Health issued a clinical alert. The investigators found a graded benefit, with the greatest benefit for those with the highest degrees of stenosis.<sup>27</sup> Benefit was also greater for those with hemispheric TIAs than for those with transient visual disturbance<sup>28</sup> and for those with ulceration on angiogram than for those without an ulcer.<sup>155</sup> The results were dependent on a strict method of measuring the degree of stenosis from arteriograms, comparing the linear diameter of the narrowest segment of the diseased portion to the diameter of the artery beyond the bulb and beyond the disease.

The beneficial results of surgery were found with a 30-day perioperative complication rate of 5.8% for stroke or death and a 2.1% complication rate for persistent disabling stroke or death. Perioperative stroke rates at or above 10% for any stroke or death would preclude the possibility of benefit even for patients with very severe disease. The NASCET study is continuing for patients with 30% to 69% carotid artery stenosis.

The European Carotid Surgery Trial (ECST) randomly allocated 2518 patients over a 10-year period. Again, patients were stratified based on the degree of stenosis: mild (0% to 29%), moderate (30% to 69%), or severe (70% to 99%). As in the NASCET trial, there

was a significant benefit in the surgically treated patients with severe stenosis, and the investigators stopped this portion of the study. For the 778 patients with severe stenosis, during the mean follow-up period of 3 years the risk of disabling or fatal stroke or surgical death was 11.0% in the medically treated patients and 6.0% in the surgical group ( $P < .05$ ). The 30-day rate of any stroke or death in the surgical group was 7.5%. The ECST investigators also reported that the surgically treated patients with mild (0% to 29%) stenosis fared worse than those treated with medical therapy alone, and they also stopped this portion of the trial.<sup>156</sup> The method of measurement included more patients with moderate disease than were in NASCET and may have reduced the benefit observed. The ECST continues to enter patients with 30% to 69% stenosis.

The Veterans Affairs Cooperative Studies Program 309 was also a randomized trial comparing endarterectomy with medical therapy for patients with TIA, transient monocular blindness, or recent small stroke.<sup>38</sup> Patients with more than 50% carotid stenosis were eligible for inclusion. The trial was stopped when the NASCET and ECST results were reported because it was thought to be unethical to continue to randomize these patients. Only 189 patients had been entered into the trial with a mean follow-up of 11.9 months, but a significant reduction in the combined end points of stroke or crescendo TIA had already been noted in the surgical therapy group. The benefit was much greater in those with more than 70% stenosis.

An important variable in considering the efficacy of carotid endarterectomy is the associated complication rate. Although many centers have achieved combined mortality and morbidity rates of less than 5%, reported complication rates for patients with TIA have ranged from 3% to 18%.<sup>148,157-164</sup> The AHA Stroke Council has previously recommended that endarterectomy in patients with TIA should carry no more than a 5% 30-day mortality or stroke morbidity.<sup>165</sup> To ensure a low surgical complication rate, those who perform the operation should have acceptable mortality and morbidity rates as documented by individual audit.<sup>165-167</sup>

The indications for carotid endarterectomy in a patient with a TIA are complex and dependent on multiple factors, including the percentage compromise of the internal carotid artery lumen and the risk of surgery as performed by an individual surgeon in a specific hospital. Other factors that may be important include the frequency and severity of the transient ischemic symptoms, plaque composition including ulceration as documented by B-mode ultrasound or angiography, and the responsiveness of the individual patient to antiplatelet drugs. The benefit for patients with carotid stenosis of more than 70% has now been demonstrated by randomized trials, but the role of endarterectomy for patients with lesser degrees of stenosis or those with nonstenotic ulcerative disease is still under study in randomized trials.

### Extracranial/Intracranial Bypass

An international multicenter randomized trial of extracranial/intracranial bypass for the treatment of TIAs and mild completed strokes was funded by the National Institutes of Health and conducted in 71 North American, European, and Asian centers.<sup>168</sup> Follow-up of the

714 patients randomly assigned to medical therapy and the 663 randomly assigned to surgery was for an average of 55 months. The groups were comparable in symptoms, age, and associated conditions. No patients were lost to follow-up. Although a high patency rate of the bypass was demonstrated, the conclusion was that extracranial/intracranial bypass had no advantage over medical therapy for patients with TIAs in the anterior circulation due to arteriosclerotic disease.

Some authors have suggested that if only patients with hemodynamic TIAs had been included there would have been a greater chance of demonstrating a benefit. Newer imaging techniques such as positron emission tomography, single photon emission computed tomography, or xenon CT have been used to identify patients with inadequate hemodynamic reserve who might respond to extracranial/intracranial bypass.<sup>169,170</sup> However, a recent clinical series in which positron emission tomography was used failed to identify such a group.<sup>171</sup> Studies have provided level IV and V evidence for a possible use for bypass procedures for patients with moyamoya disease<sup>172,173</sup> and retinal ischemia.<sup>174-176</sup> More randomized clinical trials are needed before bypass surgery can be recommended for these patients.

### Surgery for Vertebrobasilar Disease

No randomized clinical trials of the surgical treatment of vertebrobasilar disease have been done. There is level IV and V evidence from surgical series for the feasibility of surgery on the extracranial vertebral artery<sup>177-179</sup> as well as for intracranial vertebrobasilar disease.<sup>180-182</sup> Surgical treatment of posterior circulation disease has been reserved for patients who are refractory to maximal medical therapy and are good candidates for surgery. Surgery has been performed primarily on symptomatic patients with hemodynamically significant lesions, but vertebral artery disease may also cause symptoms by embolic mechanisms, for which some authors have suggested surgical therapy.<sup>183,184</sup>

### Recommendations

#### Extracranial Carotid Artery Disease

**Stenosis of 70% or greater.** Single or multiple transient ischemic attacks, irrespective of response to antiplatelet drugs, in the presence of high-grade ipsilateral stenosis and in a good candidate for surgery, are indications for carotid endarterectomy (Grade A recommendation).

**Stenosis of less than 70%.** Patients with 30% to 69% stenosis are currently included in the NASCET and ECST studies. A patient with a single TIA should be treated with antiplatelet medication (see "Medical Therapy"). If a patient has repeated TIAs despite maximal medical therapy, carotid endarterectomy may be appropriate (Grade C recommendation).

Based on level III and IV evidence, patients with 50% to 69% stenosis may be at increased risk for stroke (compared with those with less than 50% stenosis), but definitive recommendations for this group await the results of ongoing randomized trials. If a patient has had crescendo TIAs and no other source can be identified, based on level III and IV evidence carotid endarterectomy may be appropriate (Grade C recommendation). If a patient has an ulcer on angiography and no other



source for TIAs is identified, carotid endarterectomy may be appropriate (Grade C recommendation).

### **Vertebrobasilar and Intracranial Disease**

Extracranial/intracranial bypass is not recommended for patients with anterior circulation TIAs due to carotid occlusion or intracranial stenosis or occlusion (Grade A recommendation). Further study is necessary to determine whether a subgroup of patients with anterior circulation ischemia unresponsive to medical therapy would benefit from bypass surgery. Surgical therapy may occasionally be appropriate for patients with vertebrobasilar disease who have continued symptoms despite maximal medical therapy (Grade C recommendation).

### **Summary**

A person who has had a TIA is at high risk for stroke. Although areas of controversy remain, a great deal of information is available to guide the management of these patients. The goals of diagnostic testing are to identify or exclude etiologies of TIA requiring specific therapy, to assess modifiable risk factors, and to determine prognosis. Treatment should be based, if possible, on the specific cause of the TIA as well as individual patient factors and should include reduction of general stroke risk factors as well as specific medical or surgical therapy.

### **Recommendations**

#### **Evaluation of a TIA**

Patients with TIAs should be evaluated promptly. The evaluation of the patient with TIA should follow a stepwise approach as outlined in Table 3. The evaluation should be guided by a careful history and physical exam, and thus varies from patient to patient.

#### **Risk Factor Management**

1. After definitive evaluation and treatment of the TIA, hypertension should be treated aggressively to maintain systolic blood pressure below 140 mm Hg (<160 mm Hg for individuals more than 60 years old) and diastolic blood pressure below 90 mm Hg.
2. Cigarette smoking should be discontinued.
3. Coronary artery disease, cardiac arrhythmias, congestive heart failure, and valvular heart disease should be treated appropriately.
4. Excessive use of alcohol should be eliminated.
5. Oral contraceptives should be discontinued, or as a minimum a low-estrogen agent should be used.
6. Hyperlipidemia should be treated as recommended for reduction of coronary artery disease.<sup>91</sup>
7. Physical activity should be recommended as tolerated.
8. Discontinuation of postmenopausal estrogen is *not* recommended.

#### **Medical Therapy (Table 6)**

The antiplatelet agents aspirin and ticlopidine are both beneficial in the prevention of stroke after a TIA (Grade A recommendation). The modest beneficial effects of antiplatelet agents are similar in men and women, diabetic and nondiabetic persons, normotensive and hypertensive persons, and both the old and the

young. Considering the relative benefits, side effects, and cost of ticlopidine and aspirin, the committee believes that aspirin is an appropriate initial therapy for most patients. The optimal dose of aspirin is controversial; a dose of 325 mg/d helps with compliance and may minimize gastrointestinal side effects. The acceptable range includes daily doses between 30 and 1300 mg (Grade B recommendation). The recommended dose of ticlopidine is 250 mg twice a day. The combination of aspirin and dipyridamole for stroke prevention in patients with TIA is not recommended (Grade A recommendation). There is no persuasive evidence of benefit from dipyridamole, sulfinpyrazone, or suloctidil.

Anticoagulant therapy is not routinely recommended for patients with TIAs, either acutely or as long-term therapy (Grade B recommendation). Anticoagulant therapy is an option in patients with TIA who continue to have symptoms despite antiplatelet therapy (Grade C recommendation). Anticoagulant therapy is recommended for patients with TIA who have a major cardiac source of embolism (Table 4), except for those with infective endocarditis (Grade A recommendation).

### **Surgical Management**

#### **Extracranial Carotid Artery Disease**

*Stenosis of 70% or greater.* Single or multiple transient ischemic attacks, irrespective of response to antiplatelet drugs, in the presence of high-grade ipsilateral stenosis and in a good candidate for surgery, are indications for carotid endarterectomy (Grade A recommendation).

*Stenosis of less than 70%.* Patients with 30% to 69% stenosis are currently included in the NASCET and ECST studies. A patient with a single TIA should be treated with antiplatelet medication (see "Medical Therapy"). In a patient who has had repeated TIAs despite maximal medical therapy, carotid endarterectomy may be appropriate (Grade C recommendation).

Based on level III and IV evidence, patients with 50% to 69% stenosis may be at increased risk for stroke (compared with those with less than 50% stenosis), but definitive recommendations for this group await the results of ongoing randomized trials. In a patient with crescendo TIAs and in whom no other source can be identified, based on level III and IV evidence carotid endarterectomy may be appropriate (Grade C recommendation). If a patient has an ulcer on angiography and no other source for TIAs is identified, carotid endarterectomy may be appropriate (Grade C recommendation).

**Vertebrobasilar and Intracranial Disease.** Extracranial/intracranial bypass is not recommended for patients with anterior circulation TIAs due to carotid occlusion or intracranial stenosis or occlusion (Grade A recommendation). Further study is necessary to determine whether a subgroup of patients with anterior circulation ischemia unresponsive to medical therapy would benefit from bypass surgery. Surgical therapy may occasionally be appropriate for patients with vertebrobasilar disease who have continued symptoms despite maximal medical therapy (Grade C recommendation).

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