

Transient Ischemic Attacks: Part II. Treatment

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Risk factors for stroke should be evaluated in patients who have had a transient ischemic attack. Blood pressure, lipid levels, and diabetes mellitus should be controlled. When applicable, smoking cessation and weight loss also are important. Angiotensin-converting enzyme inhibitor therapy may help prevent stroke. Aspirin is the treatment of choice for stroke prevention in patients who do not require anticoagulation. Clopidogrel is an alternative therapy in patients who do not tolerate aspirin. Atrial fibrillation, a known cardioembolic source (confirmed thrombus), or a highly suspected cardioembolic source (e.g., recent large myocardial infarction, dilated cardiomyopathy, mechanical valve, rheumatic mitral valve stenosis) are indications for anticoagulation. (Am Fam Physician 2004;69:1681-8. Copyright© 2004 American Academy of Family Physicians.)

This is part II of a two-part article on transient ischemic attacks. Part I, "Diagnosis and Evaluation," appears in this issue on page 1665.

New data suggest that long-term management of stroke risk factors after a transient ischemic attack (TIA) generally is inadequate.¹ Part II of this two-part article reviews recent information on the management of the more important risk factors for stroke, the use of antiplatelet therapy, and special management issues in patients with TIAs.

Risk Factor Management

BLOOD PRESSURE

Elevated blood pressure (above 140/90 mm Hg) is the most important treatable risk factor for TIA and stroke. Antihypertensive drugs reduce the risk of strokes, regardless of whether patients have hypertension.² Currently, however, the American Heart Association (AHA) does not have any recommendations for antihypertensive drug therapy in "nonhypertensive" patients after a TIA or stroke.³

Hypertension occurs more frequently and more severely in blacks; therefore, this patient group merits special attention. Patients with diabetes mellitus or chronic renal disease also are at increased risk for hypertension and, thus, TIA or stroke. In patients with diabetes mellitus or chronic renal disease, the treatment goal is to keep blood pressure below 130/80 mm Hg.

Important new guidelines from the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) require lifestyle modi-

fications (weight reduction, sodium restriction, regular aerobic activity, limited alcohol intake) to prevent cardiovascular disease in prehypertensive patients with a systolic blood pressure of 120 to 139 mm Hg or a diastolic blood pressure of 80 to 89 mm Hg.⁴ [SOR C, consensus opinion]

Starting Antihypertensive Drug Therapy After a TIA or Stroke. Typically, blood pressure lowers without treatment in the first two weeks after a stroke. Therefore, it is rational to wait two weeks before continuing or beginning antihypertensive drug therapy.

In the patient found to have high blood pressure after a stroke or TIA, evidence of end-organ damage should be sought, because such damage suggests a chronic disorder rather than an acute condition. In some patients with chronically elevated blood pressure, the brain may depend on abnormally higher perfusion pressures because of derangement of the normal cerebral autoregulation of intracranial blood vessels. In this setting, abrupt lowering of blood pressure could promote cerebral ischemia or even extend an evolving infarction. Rarely, TIA is a manifestation of hemodynamically significant critical stenosis of an extracranial or intracranial vessel. In this condition, the brain requires increased cerebral perfusion pressure, and overtreatment of blood pressure may promote cerebral ischemia. The physician may note that TIAs occur when the patient's blood pressure drops or when the patient stands up or sits up.

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See page 1591 for definitions of strength-of-recommendation labels.

Patients with diabetes mellitus or chronic renal disease should maintain a blood pressure lower than 130/80 mm Hg.

In most patients, blood pressure should not be treated aggressively immediately (i.e., within the first 24 hours) after a stroke or TIA unless the systolic blood pressure is higher than 220 mm Hg or the diastolic blood pressure is above 120 mm Hg.⁵ Important exceptions include patients with acute myocardial infarction (especially with left ventricular failure), hypertensive crisis or hypertensive encephalopathy, renal failure, aortic dissection, or retinal hemorrhages.

If, in the absence of the previously mentioned conditions, treatment is necessary, blood pressure should be reduced slowly over days to prevent worsening ischemia.

Angiotensin-Converting Enzyme (ACE) Inhibitors. Increased attention is being directed at ACE inhibitors because of the results of the recent Heart Outcomes Prevention Evaluation (HOPE) study.⁶ In this large, randomized trial, inpatients considered to be at “high cardiovascular risk” were treated with ramipril or placebo. Over four years, the relative reduction in the risk of stroke was 32 percent (within a composite outcome) in the patients who received ramipril. Debate currently centers on whether the HOPE study findings were unique to ACE inhibitors as a class or occurred because of a more general blood pressure-lowering effect that also could be obtained with other antihypertensive drug classes.

In the Perindopril Protection Against Recurrent Stroke Study (PROGRESS),⁷ patients with stroke or TIA within the previous five years were given placebo or combination therapy consisting of perindopril (an ACE inhibitor) and indapamide (a diuretic). In both hypertensive and “non-hypertensive” patients, the drug combination resulted in a 43 percent reduction in the relative risk of recurrent stroke (four-year follow-up). In PROGRESS, hypertension was defined as a systolic blood pressure of 160 mm Hg or higher or a diastolic blood pressure of 90 mm Hg or higher.

To date, however, no consensus statements indicate a preference for one antihypertensive drug or drug class over another for use in secondary (or primary) stroke prevention.^{2,8,9} In particular, the use of ACE inhibitors after acute stroke remains controversial.² [Reference 2: SOR B, unknown effectiveness]

SMOKING

A meta-analysis¹⁰ of 32 studies found that the risk of stroke in persons of either sex and all ages was 50 percent higher in smokers than in nonsmokers. Therefore, the family physician should make a vigorous attempt, at every clinic visit, to implement a smoking cessation plan, particularly in the patient who has had a TIA. Smoking cessation may be more likely to be successful if the physician encourages all family members to quit smoking simultaneously.

HEART DISEASE

Cardiac disease (i.e., rheumatic heart disease, mitral valve stenosis, atrial fibrillation with or without valvular disease) is a predisposing factor for TIA and stroke. In addition, the electrocardiographic finding of left ventricular hypertrophy resulting from prolonged hypertension is associated with a fourfold increased risk of stroke.

Patients with atrial fibrillation who also have other risk factors are at particularly high risk for TIA or stroke. These additional risk factors include a history of hypertension, poor left ventricular function, rheumatic mitral valve disease, prosthetic heart valves, previous stroke, systemic embolism, and age greater than 75 years. Patients with atrial fibrillation who have already had a TIA are considered to be at high risk for stroke. The results of one study¹¹ of patients with atrial fibrillation and TIA or minor stroke indicate that anticoagulant therapy is significantly more effective than aspirin in preventing recurrent stroke.

In addition, short-term cardiac morbidity is substantial after a TIA. One recent study¹² suggested that among patients who have a TIA, the 90-day risk for a cardiac event is higher in those who have any abnormal finding on an electrocardiogram (ECG). In this study, the ECG findings of left ventricular hypertrophy, atrial fibrillation, and atrioventricular conduction abnormalities in patients with TIA were independently associated with more than a doubling of the risk of a cardiac event.

BLOOD LIPID LEVELS

Convincing evidence from observational studies shows that elevated blood lipid levels are a risk factor for ischemic stroke.¹³ High cholesterol levels are a risk factor for coronary heart disease (CHD) and, thus, a substantial secondary risk factor for stroke.

Recent data indicate that in patients with CHD, treatment with statins (3-hydroxy-3-methylglutaryl coenzyme

TABLE 1

Summary of Antiplatelet Therapy After TIA

In most patients, aspirin in a dosage of 50 to 325 mg per day is the recommended initial agent for antiplatelet therapy.^{3,30}

In patients who cannot tolerate aspirin, clopidogrel (Plavix) may be a good second choice; this agent currently is considered to be safer than ticlopidine (Ticlid).³

Rarely, thrombotic thrombocytopenic purpura has been reported with the use of ticlopidine and clopidogrel.²⁷

Extended-release dipyridamole may potentiate the effect of very-low-dose aspirin therapy.²⁹

Whether combined aspirin-dipyridamole (Aggrenox) provides equal or better stroke prevention than 325 mg per day of aspirin alone is not known.³¹

TIA = transient ischemic attack.

Information from references 3, 27, and 29 through 31.

A reductase inhibitors) results in a 30 to 32 percent reduction of the stroke risk.^{2,14,15} [Reference 2: SOR A, beneficial] Because statins have multiple vascular effects, as well as cholesterol-lowering properties, the exact mechanism of stroke prophylaxis is unknown.

Current guidelines^{16,17} recommend consideration of statin therapy in patients with known CHD, many of whom could present with TIA or stroke. According to a recent Cochrane review,¹⁸ it is not clear whether statin therapy is as effective in the prevention of recurrent stroke or TIA as it is in the primary prevention of stroke in patients with CHD.

DIABETES MELLITUS

Diabetes mellitus, independent of its association with hypertension, increases the overall risk of stroke by approximately 25 to 50 percent.¹⁹ There is no conclusive evidence that "tight" glucose control results in a reduction of ischemic stroke or other macrovascular events.^{20,21}

Recent data from the Microalbuminuria, Cardiovascular, and Renal Outcomes in HOPE (MICRO-HOPE) sub-study^{22,23} indicate that ramipril therapy reduces cardiovascular and cerebrovascular events in patients with diabetes mellitus and one cardiac risk factor. In MICRO-HOPE, stroke events were reduced by 33 percent, and stroke-related deaths were reduced by 37 percent.

Antiplatelet Therapy

Currently available antiplatelet agents for stroke prophylaxis include aspirin, clopidogrel (Plavix), ticlopidine (Ticlid), and aspirin-dipyridamole (Aggrenox). Except in patients with special conditions such as atrial fibrillation, anticoagulation has no advantages over antiplatelet therapy and is associated with an increased risk of bleeding.^{2,24,25} [Reference 2: SOR A, likely to be harmful or ineffective]

ASPIRIN

Aspirin is the most widely used and most economical antiplatelet agent. Aspirin therapy after a stroke or TIA reduces the long-term relative risk of stroke and increases the chance of a full recovery.²⁶ The optimal aspirin dosage for use in the prevention of stroke or TIA remains controversial, but a range of 50 to 325 mg per day has been recommended.³

OTHER ANTIPLATELET AGENTS

Because of safety and tolerance issues associated with ticlopidine, clopidogrel is the more widely used second-line antiplatelet agent. Neutropenia, rash, diarrhea, and thrombotic thrombocytopenic purpura (TTP) occur less frequently with clopidogrel than with ticlopidine. The incidence of ticlopidine-related TTP is estimated to be one case per 1,600 to 5,000 patients treated.³ Although clopidogrel and aspirin have similar safety profiles, there have been rare reports of clopidogrel-related TTP, with the majority of cases occurring within two weeks of initiation of the drug.²⁷

One large, randomized, double-blind clinical trial²⁸ compared clopidogrel (75 mg per day) and aspirin (325 mg per day), with the composite outcome being the primary end points of stroke, myocardial infarction, and vascular death. There was a slight trend for clopidogrel to reduce annual outcome events compared with aspirin (5.3 percent versus 5.8 percent; $P = .043$). Based on this marginal difference and the fact that clopidogrel currently is more expensive than aspirin, many physicians favor the use of aspirin in a standard dosage (325 mg per day) for antiplatelet therapy but choose clopidogrel when patients cannot tolerate aspirin.

The U.S. Food and Drug Administration recently approved the use of combination aspirin-dipyridamole (Aggrenox) for stroke prevention. The combination drug contains 50 mg of aspirin (low dose) and 400 mg of extended-release dipyridamole. A single large, randomized study²⁹ found that this specific aspirin-dipyridamole combination reduced stroke by 22 percent compared with low-dose aspirin therapy alone. However, the expected similar benefits for reducing myocardial infarction and vascular death were not observed with aspirin, dipyridamole, or combination therapy.

Debate continues about the value of combination therapy and the interpretation of study data. *Table 1*^{3,27,29-31} summarizes key points about antiplatelet therapy in

patients who have had a TIA.

Special Management Issues

TIA OR STROKE RECURRENCE DURING ANTIPLATELET THERAPY

Although well-established evidence supports the role of antiplatelet therapy in the prevention of recurrent stroke, fewer data are available to guide therapeutic decisions in patients who are receiving antiplatelet therapy but have another TIA or stroke. In patients who are taking an antiplatelet agent (most often, aspirin), the annual rate of recurrent stroke is estimated to be about 8 percent (range: 4 to 14 percent).^{30,32}

Patient compliance with antiplatelet therapy should be determined. When possible, the cause of the TIA or stroke should be identified. If there is evidence of new-onset atrial fibrillation or a cardioembolic source, anticoagulation (rather than antiplatelet therapy) may be required, depending on the patient's age and other risk factors. All stroke risk factors should be immediately reevaluated and aggressively treated.

Many physicians question the therapeutic value of increasing the dosage of an antiplatelet agent, switching to a new agent, adding a second antiplatelet agent, or adding a low-dose anticoagulant drug.³

SYMPTOMATIC CAROTID DISEASE

Carotid Endarterectomy. There is little controversy surrounding the use of carotid endarterectomy for secondary prevention of stroke in patients with symptomatic severe carotid stenosis, defined as 70 to 99 percent vessel occlusion, based on the results of the North American Symptomatic Endarterectomy Trial (NASCET).³³ In the initial trial analysis (two-year follow-up), carotid endarterectomy reduced the relative risk of stroke by 65 percent compared with medical management.

The NASCET collaborators³⁴ recently reported that carotid endarterectomy may result in only a modest reduction of the stroke rate in patients with symptomatic moderate stenosis, defined as 50 to 69 percent vessel occlusion. The incidence of ipsilateral stroke was 16 percent in surgically treated patients and 22 percent in medically managed patients ($P = .045$). Based on their results, the authors recommended restraint rather than promotion of carotid endarterectomy.

A substudy analysis of patients from NASCET³⁵ who presented with bilateral carotid stenosis—one side that

was symptomatic (noncardioembolic TIA or stroke) and the other side that was asymptomatic—revealed that the overall risk of stroke at five years was relatively low. Patients with 60 to 99 percent stenosis in the asymptomatic carotid artery had an overall 10 percent risk of a first stroke in the territory of the asymptomatic carotid, and a total 16 percent risk of stroke when lacunar and cardioembolic strokes were included (3.2 percent annual risk of stroke). High-risk patients included those with diabetes mellitus, silent brain infarction, or higher degree of stenosis. AHA guidelines for carotid endarterectomy recommend the use of aspirin (unless contraindicated) before surgery.³⁶

Vascular Angioplasty and Stenting. The roles of vascular angioplasty and stenting procedures in stroke prevention remain controversial. The controversy has been fueled by the rapid development of new technologies and techniques, including distal cerebral protection devices.³⁷ It has been argued that patients with symptomatic high-grade carotid stenosis (70 percent vessel stenosis or higher) who are not candidates for routine carotid endarterectomy may represent a small subpopulation of patients who can benefit from extracranial carotid stenting or angioplasty; to date, however, this view has not been supported by published data from any large clinical trial.

ANTICOAGULATION

Unless contraindicated, anticoagulation therapy is appropriate in patients with high-risk cardioembolic conditions.³ These conditions include atrial fibrillation, a known cardioembolic source (confirmed thrombus), or a suspected cardioembolic source (recent large myocardial infarction, mechanical valve, dilated cardiomyopathy, rheumatic mitral valve stenosis).

Anticoagulation has a well-established role in the primary prevention of stroke in patients with atrial fibrillation, especially high-risk patients with hypertension, poor left ventricular function, rheumatic mitral valve disease, prosthetic heart valves, a previous stroke, a TIA, systemic embolism, or age greater than 75 years. There is also evidence that warfarin (Coumadin) is useful for secondary prevention of stroke, as well as primary prevention.³⁸ It is unclear whether heparin should be started immediately after a TIA in patients with atrial fibrillation.

The rate of stroke recurrence after acute stroke in patients with atrial fibrillation currently is under debate. Reported recurrence rates for the initial weeks vary widely

(2.5 to 20 percent).³⁹ The Cerebral Embolism Task Force⁴⁰ concluded that the risk of recurrent stroke was low during the first two weeks after a stroke in patients with nonvalvular atrial fibrillation. Whether the risk of recurrent TIA or the risk of stroke also is low in the patient with atrial fibrillation and TIA alone is unknown.

Patients who have atrial fibrillation also have noncardioembolic strokes. Therefore, even in the patient with atrial fibrillation, an evaluation for noncardioembolic risk factors should be performed. In the patient who previously has been diagnosed with TIA or stroke and is adequately anticoagulated, a second TIA or stroke could represent a noncardioembolic source.⁴¹

In patients with cardiogenic emboli, consensus is lacking on whether to start intravenous heparin therapy before chronic oral anticoagulation is initiated.^{37,42,43}

HORMONE THERAPY IN WOMEN AFTER A TIA

The Women's Estrogen for Stroke Trial^{44,45} was a randomized, blinded, placebo-controlled study that evaluated the effects of estrogen alone in a large cohort of postmenopausal women who had had a stroke or TIA. In this trial, estrogen therapy did not affect the incidence of nonfatal

Unless contraindicated, anticoagulation is appropriate for use in patients with atrial fibrillation or a known or suspected cardioembolic source.

stroke during a mean follow-up period of 2.8 years.

New data indicate that certain menopausal hormone therapies increase the risk of CHD and ischemic stroke.^{45,46} Therefore, the benefits and risks of hormone therapy should be weighed carefully in women who have had a TIA.

A recent meta-analysis⁴⁷ found an increased risk of stroke in women who use oral contraceptive pills (OCPs), including those who use low-dose OCPs. However, because of the low incidence of stroke in this young population, the overall benefit of OCPs may outweigh the risk. In women with previous stroke or TIA, it may be prudent to withhold OCPs or hormone therapy.

VERTEBROBASILAR ISCHEMIA

Anticoagulation commonly is used in patients who have had a vertebrobasilar stroke. However, a joint committee

TABLE 2

Summary of Guidelines for the Management of Stroke Risk Factors After TIA

<i>Stroke risk factor</i>	<i>Management goal</i>	<i>Treatments</i>
Hypertension	Systolic blood pressure <140 mm Hg and diastolic blood pressure <90 mm Hg or Systolic blood pressure <130 mm Hg and diastolic blood pressure <80 mm Hg if the patient has end-organ damage, diabetes mellitus, or chronic renal disease	Consult JNC 7 recommendations, ⁴ including new data on "prehypertension" (systolic blood pressure of 120 to 139 mm Hg and diastolic blood pressure of 80 to 89 mm Hg), which requires aggressive lifestyle modifications.
Smoking	Smoking cessation	Smoking cessation program, including nicotine replacement, drug therapy, and counseling as indicated Consult national guideline for specific treatment. ⁵⁰
Diabetes mellitus	Blood glucose level <126 mg per dL (7.0 mmol per L)	Consult AAFP and ADA evidence-based policy statement. ⁵¹
Lipid levels	Low-density lipoprotein cholesterol level <100 mg per dL (2.60 mmol per L)	Dietary control, lipid-lowering agent (e.g., statin) ^{16,17,52}

TIA = transient ischemic attack; JNC 7 = the seventh report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure; AAFP = American Academy of Family Physicians; ADA = American Diabetes Association.

Information from references 4, 16, 17, 21, and 50 through 53.

TABLE 3

Summary of Guidelines for the Management of Specific Conditions After TIA

<i>Condition</i>	<i>Treatment</i>	<i>Comments</i>
Noncardioembolic source	Aspirin in a dosage of 50 to 325 mg per day ^{3,30,49} or Clopidogrel (Plavix), ticlopidine (Ticlid), or aspirin-dipyridamole (Aggrenox) ⁴⁹	If aspirin therapy is not tolerated or is contraindicated, consider alternative antiplatelet agent. With ticlopidine therapy, monitor blood cell count; consider the same monitoring during initial treatment with clopidogrel. Clopidogrel has not been tested for TIA prophylaxis only.
Cardioembolic source		
Known thrombus	Oral anticoagulation, unless contraindicated ^{3,40}	AHA: recommended for high-risk patients who have had a TIA NSA: consider IV heparin therapy.
Mechanical valve	Warfarin (Coumadin); INR of 3.0 to 4.0 (long term) ^{30,54,55}	Consult AHA and EUSI recommendations. ^{30,55}
Nonvalvular atrial fibrillation	Warfarin: INR of 2.0 to 3.0 (long term) ^{3,21,43,54,55}	Consult AHA, ACC, and EAC combined recommendations for timing of treatment and role of cardioversion. ^{30,54,55} Monitor the INR frequently, particularly when there is coadministration of protein-bound medications, during major illness, or when there is a major change in diet.
Recent myocardial infarction or left ventricular thrombus	Warfarin; INR of 2.0 to 3.0 (6 months) ^{3,21,30,43,54,55}	Monitor the INR frequently, particularly when there is coadministration of protein-bound medications or during major illness.
Possible cardioembolic source	Antiplatelet agents ³⁰	In most patients, aspirin in a dosage of 50 to 325 mg per day (unless contraindicated)
Carotid artery stenosis (atherosclerosis)	Symptomatic (ipsilateral), severe (70% to 99% occlusion) carotid endarterectomy if patient is good surgical candidate ^{3,21,33,36} Symptomatic (ipsilateral), moderate (50% to 69% occlusion) carotid endarterectomy in selected patients ^{3,21,34,56}	Beneficial if surgical complication rate of less than 3%; life expectancy of 5 years or greater; continue to maximize treatment of other risk factors. Antiplatelet therapy is recommended before and after surgery. Consider the patient's sex, comorbid conditions, and life expectancy in the decision-making process; continue to maximize treatment of other risk factors. Antiplatelet therapy is recommended before and after surgery.

TIA = transient ischemic attack; AHA = American Heart Association; NSA = National Stroke Association; IV = intravenous; INR = International Normalized Ratio; EUSI = European Stroke Initiative; ACC = American College of Cardiology; EAC = European Society of Cardiology.

Information from references 3, 21, 30, 33, 34, 36, 43, 49, and 54 through 56.

from the American Academy of Neurology and the American Stroke Association⁴⁸ found no clear evidence addressing this specific clinical situation and therefore provided no specific recommendations for the use of anticoagulation in these patients during acute cerebral ischemia. There is no mention of the use of anticoagulation in patients who have had a TIA, or of the use of surgical or endovascular treatments in patients with significant vertebrobasilar stenosis.

In patients with recurrent vertebrobasilar symptoms, interventions such as angioplasty, stenting, surgical reconstruction, and decompression have unproven efficacy.

In an acute life-threatening situation such as midbasilar thrombotic occlusion (a condition associated with high morbidity and mortality rates), intra-arterial thrombolysis (if available) is an extreme option. Patients with refractory vertebrobasilar TIA should be evaluated by a neurologist before invasive procedures are performed, because these procedures can be associated with significant morbidity and mortality.^{21,49}

Guidelines for the management of patients with TIAs are summarized in *Tables 2*^{4,16,17,21,50-53} and *3*,^{3,21,30,33,34,36,43,49,54-56}

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