Stroke: Strategies for Primary Prevention

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Stroke is a leading cause of morbidity and mortality in North America. Primary prevention of stroke includes lifestyle modifications and measures to control blood pressure, cholesterol levels, diabetes mellitus, and atrial fibrillation. Lowering blood pressure in patients with hypertension prevents both hemorrhagic and ischemic stroke (relative risk reduction, 35 to 45 percent). Observational studies suggest that higher cholesterol levels are associated with an increased risk of ischemic stroke, and treatment with statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) may reduce the risk of fatal and nonfatal stroke by 25 percent. Although high-quality evidence linking tighter glucose control with stroke reduction is lacking, good glucose control and aggressive treatment of hypertension and hyperlipidemia in patients with diabetes mellitus are recommended. The risk of stroke in patients with atrial fibrillation and the role of anticoagulation depend on factors such as age and the presence of comorbid conditions. Controversy exists about the roles of angiotensin-converting enzyme inhibitors and aspirin in the primary prevention of stroke. (Am Fam Physician 2003; 68:2379-86,2389-90. Copyright© 2003 American Academy of Family Physicians.)

A patient information handout on stroke prevention, written by the authors of this article, is provided on page 2389.

See page 2306 for definitions of strength-of-evidence levels.

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Stroke is a leading cause of morbidity and mortality. Every year, approximately 500,000 Americans have a first stroke, and approximately 20 percent die within 30 days.[1,2] This article summarizes strategies that have been shown to be effective in stroke prevention (including blood pressure control, treatment of hyperlipidemia, lifestyle modifications such as smoking cessation and, in patients with atrial fibrillation, use of anticoagulation or antithrombotic therapy), and is derived from our earlier systematic review of the evidence in this field.[3]

Risk Factors for Stroke

Most risk factors for stroke are associated with atherosclerosis.[4-8] Nonmodifiable risk factors include older age, male sex, nonwhite race, presence of congestive heart failure or coronary heart disease, and family history of myocardial infarction or stroke. The most common modifiable risk factors for ischemic stroke are listed in *Table 1*.[3-8] Until the results of definitive studies are available, the roles of other potential risk factors (e.g., homocysteine) remain controversial.

See editorial on page 2335.

Strategies for Primary Prevention

Various stroke prevention strategies, including primary and secondary measures, are summarized in *Table 2*.[3]

OPTIMIZATION OF LIFESTYLE

While obesity, lack of regular aerobic exercise, excessive alcohol intake, and smoking all increase the risk of stroke, no high-quality randomized trials have evaluated the effects that modifications of these factors have on stroke risk. However, given the strength of observational data and the overall health benefits of weight loss, alcohol restriction, regular aerobic physical activity, and smoking cessation, these lifestyle modifications should be discussed and encouraged.

Systematic reviews have shown that one-time advice from health care workers during routine interactions can have an

TABLE 1
Modifiable Risk Factors for Ischemic Stroke

Risk factor	*Prevalence (%)*	*Relative risk*
Hypertension	25 to 40	3 to 5
Elevated total cholesterol level	6 to 40	1.8 to 2.6
Smoking	25	1.5
Physical inactivity	25	2.7
Obesity	18	1.8 to 2.4
Diabetes	4 to 8	1.8 to 3
Alcohol consumption (more than five drinks per day)	2 to 5	1.6
Atrial fibrillation	1	5 (nonvalvular); 17 (valvular)

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TABLE 2
Effectiveness of Stroke Prevention Strategies

Strategy	*RR reduction, % (95% CI)*
Primary prevention	
Antihypertensive drug therapy if blood pressure is elevated	42 (33 to 50)
Statin therapy if cholesterol level is elevated	25 (14 to 35)
Antiplatelet therapy	
Aspirin	RR increase, 7 (RR reduction of 5 to RR increase of 22)
Aspirin after myocardial infarction	36 (15 to 51)
Angiotensin-converting enzyme inhibitor therapy	30 (15 to 43)
Carotid endarterectomy for asymptomatic stenosis	RR increase, 423 (127 to 1,107)
Secondary prevention	
Antihypertensive drug therapy if blood pressure is elevated	28 (15 to 39)
Statin therapy if cholesterol level is elevated	25 (14 to 35)
Warfarin (Coumadin) therapy for nonrheumatic atrial fibrillation	62 (48 to 72)
Smoking cessation	33 (29 to 38)
Antiplatelet drug therapy	
Aspirin	28 (19 to 36)
Thienopyridines (versus aspirin)	13 (3 to 22)
Carotid endarterectomy for symptomatic moderate or severe tenosis	44 (21 to 60)

RR = relative risk; CI = confidence interval.

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appreciable impact.[9-12] For example, 2 percent of smokers stopped smoking for at least one year after a single recommendation from their physician.[11] Because the excess stroke risk disappears within five years of smoking cessation, it is important to emphasize that it is never too late to quit smoking.[13]

TREATMENT OF HYPERTENSION

Numerous randomized placebo-controlled trials have demonstrated that lowering blood pressure in patients with hypertension prevents both hemorrhagic and ischemic strokes (relative risk [RR] reduction, 35 to 45 percent).[14-18] [Reference 16—Evidence level A, meta-analysis of randomized controlled trials (RCTs)] This benefit has been shown even in patients older than 80 years (RR reduction, 34 percent; 95 percent confidence interval [CI], 18 to 41 percent),[19] as well as in elderly patients with isolated systolic hypertension (odds reduction, 30 percent; 95 percent CI, 18 to 41 percent).[20] Indeed, systolic blood pressure is a stronger risk factor for stroke than is diastolic pressure.[21] Many patients who are receiving drug therapy for hypertension are not taking dosages high enough to control systolic blood pressure.[22]

The stroke prevention benefits of antihypertensive drug therapy are continuous across the usual range of blood pressures, and the relative benefits for each mm Hg reduction in blood pressure are similar regardless of the baseline systolic pressure (i.e., whether the systolic pressure is 170 mm Hg or 150 mm Hg). Thus, there does not appear to be a J curve in antihypertensive drug efficacy.[23]

The benefits of antihypertensive drug therapy for stroke prevention are achieved rapidly (within three years of starting therapy).[24] Furthermore, a recent systematic review of antihypertensive drug trials confirmed that more aggressive blood pressure reduction results in greater stroke prevention (RR reduction, 20 percent; 95 percent CI, 2 to 35 percent), for an extra reduction of 3 mm Hg in both diastolic and systolic blood pressure with more

intensive treatment.[24] [Evidence level A, meta-analysis]

Although debate continues about relative efficacies, trials have shown that thiazide diuretics, beta-adrenergic antagonists, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers, and long-acting dihydropyridine calcium channel blockers all reduce the incidence of stroke.[25] However, given the results of the recently published Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial and the relative costs of the various drugs, thiazide diuretics remain the agents of first choice for the primary prevention of cardiovascular and cerebrovascular disease in most patients with hypertension.[26] [Evidence level A, RCT] Regardless of the selected drug, treatment to achieve the target blood pressure (diastolic pressure below 90 mm Hg and systolic pressure below 140 mm Hg) is fundamental to stroke prevention.

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TREATMENT OF HYPERLIPIDEMIA

Information from observational studies suggests that higher total and low-density lipoprotein (LDL) cholesterol levels are associated with an increased risk of ischemic stroke.[27-31] Although no randomized trials have evaluated lipid-lowering therapy for the prevention of stroke as a primary outcome, information can be extrapolated from randomized trials[32,33] of lipid-lowering therapy for the primary and secondary prevention of coronary disease (because most patients enrolled in the studies had not had a stroke or transient ischemic attack). While most individual trials of lipid-lowering therapies (e.g., resins, fibrates, dietary measures) have not shown a decreased risk of stroke,[32] a meta-analysis[3] of 11 trials found that treatment with statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) is associated with a 25 percent reduction (95 percent CI, 14 to 35 percent) in the risk of fatal and nonfatal stroke.

Statin therapy is safe and appears to be associated with a significant reduction in stroke risk. However, evidence-based guidelines developed by the National Cholesterol Education Program[34] suggest that the decision to initiate lipid-lowering therapy should be based on the presence of cardiovascular risk factors, as well as the actual lipid levels. In the absence of clinical manifestations of atherosclerosis or diabetes, and with no or only one cardiovascular risk factor, the recommended LDL cholesterol target level is 160 mg per dL (4.15 mmol per L). In patients with overt atherosclerosis (including asymptomatic carotid stenosis) or diabetes mellitus, the recommended target LDL cholesterol level is less than 100 mg per dL (2.60 mmol per L).

REDUCTION OF OTHER RISK FACTORS

Diabetes Mellitus. Patients with diabetes are at increased risk for all forms of ischemic stroke and also are more likely to have hypertension and hyperlipidemia.[4,7,8] However, no high-quality evidence supports reduction of stroke risk through improved glucose control. The three major randomized trials[35-37] that have tested the glucose-control hypothesis demonstrated no significant reductions in the risk of ischemic stroke or any other macrovascular outcome. Nonetheless, several guidelines[38,39] recommend tight glucose control to reduce the development or progression of microvascular complications in patients with type 1 or type 2 diabetes.

Because hypertension, hyperlipidemia, and type 2 diabetes (or at least glucose intolerance) frequently coexist, it is important to screen patients with any one of these risk factors for the other factors and to institute aggressive risk-factor modification for all three conditions to prevent a wide variety of atherosclerotic events. In particular, aggressive blood

A systematic review demonstrated that when added to standard therapy (including other antihypertensive drugs) in patients with established coronary disease, angiotensin-converting enzyme inhibitors were associated with a 30 percent reduction in the risk of stroke.

pressure reduction (to a target of less than 130/80 mm Hg) is important in patients with diabetes.[23]

Atrial Fibrillation. The mortality rate in patients with atrial fibrillation has been shown to be double that for age- and sex-matched control subjects without atrial fibrillation, mainly because of the increased risk of stroke.[40] In average patients with nonrheumatic atrial fibrillation, the risk of stroke is approximately 5 percent per year.[41] Patients with valvular atrial fibrillation have an even greater risk (17-fold increase over that in age- and sex-matched control subjects).[41]

The stroke risk in patients with atrial fibrillation varies widely, depending on the presence of risk factors associated with underlying atrial fibrillation. Treatment recommendations from the American College of Chest Physicians consider the baseline risk of stroke in patients with nonrheumatic atrial fibrillation *(Table 3)*.[3,42]

Controversies in Primary Prevention of Stroke

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

In patients with hypertension, ACE inhibitors are unlikely to confer more protection against stroke than agents from other antihypertensive drug classes. In fact, data suggest a possible trend in the other direction, particu-

TABLE 3
Risk Stratification of Patients with Nonvalvular Atrial Fibrillation

Annual stroke risk (%)	*Patient features*	*2001 ACCP recommendations**
Low (~1)	Age <65 years with no major risk factors†	Aspirin
Low moderate (~1.5)	Age 65 to 75 years with no major risk factors	Aspirin or warfarin (Coumadin): target INR of 2.0 to 3.0
High moderate (~2.5)	Age 65 to 75 years with no major risk factors, but with diabetes mellitus or coronary artery disease	Warfarin: target INR of 2.0 to 3.0
High (~6)	Age <75 years with hypertension or left ventricular dysfunction; or age >75 years without other risk factors	Warfarin: target INR of 2.0 to 3.0
Very high (~10)	Age >75 years with hypertension or left ventricular dysfunction; or any age with previous stroke, transient ischemic attack, or systemic embolism	Warfarin: target INR of 2.0 to 3.0

ACCP = American College of Chest Physicians; INR = International Normalized Ratio.

**—These recommendations apply only to patients without contraindications to the suggested therapies.*
†—Major risk factors for stroke are as follows: previous stroke, systemic embolism, or transient ischemic attack; hypertension; and poor left ventricular function (clinical history of heart failure or a left ventricular ejection fraction below 50% on an echocardiogram).

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larly in nonwhite patients.[24,26] Nevertheless, a systematic review of four RCTs demonstrated that when added to standard therapy (including other antihypertensive drugs) in patients with established coronary disease, ACE inhibitors were associated with a 30 percent reduction in the risk of stroke (95 percent CI, 15 to 43 percent).[24] In this meta-analysis, 94 percent of the stroke outcomes were contributed by one trial, the Heart Outcomes Prevention Evaluation (HOPE) study.[43,44]

The HOPE study was an RCT that compared ramipril therapy with placebo in 9,297 normotensive patients (mean blood pressure, 139/79 mm Hg) who were determined to be at high risk for cardiovascular events. Although this trial has been widely cited as a study of primary prevention, 88 percent of the study subjects had established cardiovascular disease at study entry. Over four years, the risk of stroke declined by 32 percent (95 percent CI, 16 to 44 percent).[44] The extent to which this benefit was related to blood pressure lowering rather than to a ramipril-specific effect on atherogenesis is unclear and awaits clarification from the ongoing Prevention of Events with Angiotensin Converting Enzyme inhibition trial.

While thiazide diuretics should be used as first-line antihypertensive drug therapy, the addition of an ACE inhibitor such as ramipril should be considered in patients whose blood pressure is not well controlled or who have adequate control but remain at high risk for an event.

ANTIPLATELET THERAPY

Aspirin and other antiplatelet agents are highly efficacious for secondary prevention after a stroke or transient ischemic attack,[45] but their effectiveness for primary prevention of stroke is controversial. Four large observational studies demonstrated a consistent association between regular use of aspirin and an increased risk of stroke.[46] A meta-analysis[3] of eight randomized trials (59,977 patients) comparing aspirin with placebo for the primary prevention of stroke found that aspirin reduced the frequency of all cardiovascular events (RR reduction, 11 percent; 95 percent CI, 4 to 18 percent), largely because of substantial reductions in coronary events but not ischemic stroke.[3] [Evidence level A, meta-analysis] Furthermore, the use of aspirin increased the risk of major bleeding (RR increase, 53 percent; 95 percent CI, 15 to 104 percent). Thus, aspirin and other antiplatelet agents cannot be recommended for prevention of a first stroke, except in young patients with atrial fibrillation and no other risk factors for stroke.

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CAROTID ENDARTERECTOMY FOR ASYMPTOMATIC CAROTID STENOSIS

The optimal management of patients with high-grade asymptomatic carotid stenosis (more than 50 percent occlusion) remains unclear. A systematic review[26] of five randomized trials comparing carotid endarterectomy and medical therapy in more than 2,400 such patients found that the risk of stroke or death was increased in the immediate perioperative period (RR increase, 423 percent; 95 percent CI, 127 to 1,107 percent). However, the risk of the combined end point of stroke or death was reduced over the subsequent three years (RR reduction, 30 percent; 95 percent CI, 9 to 45 percent). The authors of this article believe that more evidence is necessary to identify subgroups of patients at lower risk for surgical complications who may benefit from surgery.

Primary Stroke Prevention in Clinical Practice

ILLUSTRATIVE CASE

A 64-year-old man presented to a primary care clinic for the first time after a recent move

to the area. He had a longstanding history of hypertension, which was being treated with hydrochlorothiazide in a dosage of 25 mg per day. He was a smoker with a 30-pack-year history. The patient was an avid fisherman, but had no other regular physical activity. The review of systems was negative.

The physical examination revealed an overweight man with a blood pressure of 164/96 mm Hg, a regular pulse at 72 beats per minute, and a right carotid bruit. An electrocardiogram revealed sinus rhythm and left ventricular hypertrophy. Renal function tests (including urinalysis), electrolyte levels, and a fasting blood glucose level were normal; however, the fasting lipid profile showed an LDL cholesterol level of 158 mg per dL (4.10 mmol per L) and a high-density lipoprotein cholesterol level of 45 mg per dL (1.15 mmol per L).

This patient had several risk factors for cerebrovascular and cardiovascular disease, including hypertension, hyperlipidemia, left ventricular hypertrophy, and potential carotid artery disease. Consequently, his 10-year risk for myocardial infarction, stroke, or cardiovascular mortality was determined to be between 15 and 20 percent.[47]

Efforts were made to optimize the patient's antihypertensive drug regimen by adding ramipril, in a dosage of 2.5 mg per day, to the hydrochlorothiazide he already was taking. His creatinine and electrolyte levels were checked within 14 days after ramipril was added.

A regular exercise plan was suggested (based on guidelines from the American Heart Association[48]), and the patient also was referred to a dietitian for three months of dietary counseling. Plans were made to recheck the patient's fasting lipid levels and to institute statin therapy if his LDL cholesterol level was not less than 130 mg per dL (3.50 mmol per L) after lifestyle modifications.

The patient underwent carotid Doppler ultrasound examination, which revealed 40 percent smooth internal carotid stenosis on the right side. The patient was not referred for a surgical opinion.

The need for tobacco cessation was reinforced; counseling and a nicotine substitute were instituted. The decision was to see the patient monthly until his blood pressure was clearly under control and to reinforce his lifestyle changes.

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