

AHA/ASA Guidelines on Prevention of Recurrent Stroke

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Persons who survive a stroke or transient ischemic attack (TIA) are at increased risk of experiencing another stroke. In the United States, about one-fourth of the nearly 800,000 strokes that occur each year are recurrent events. The risk of stroke within 90 days of a TIA may be as high as 17 percent, with the greatest risk during the first week.

The American Heart Association (AHA) and the American Stroke Association (ASA) have released updated guidelines on preventing recurrent stroke in patients who have had a previous stroke or TIA. The guidelines address risk factors for stroke, including treatable vascular risk factors (*Table 1*) and modifiable behavioral risk factors (*Table 2*); interventional approaches for patients with large-artery atherosclerosis; medical treatments for patients with cardiogenic embolism; and antithrombotic therapy for noncardioembolic stroke or TIA. This summary focuses on risk factors and antithrombotic therapy.

Treatable Vascular Risk Factors

HYPERTENSION

Meta-analyses of randomized controlled trials have shown that lowering blood pressure can reduce the risk of stroke by 30 to 40 percent. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommends lifestyle modifications to

manage hypertension. Lifestyle changes associated with a reduction in blood pressure include losing weight; restricting salt intake; consuming a diet high in fruits, vegetables, and low-fat dairy products; participating in regular aerobic exercise; and limiting alcohol intake. Although there is a lack of definitive data addressing the management of hypertension immediately following a stroke, a meta-analysis of randomized trials found that treatment with antihypertensive medications significantly reduces the risk of recurrent stroke. The reduction in risk was seen in patients taking diuretics alone and in combination with angiotensin-converting enzyme inhibitors, but not in patients taking beta blockers or angiotensin-converting enzyme inhibitors alone.

DIABETES

The prevalence of diabetes mellitus in patients with ischemic stroke is 15 to 33 percent. Although diabetes is a risk factor for first stroke, there are limited data showing that diabetes is a risk factor for recurrent stroke. It is estimated that diabetes causes approximately 9 percent of recurrent strokes. Diet, exercise, oral hypoglycemic drugs, and insulin are recommended in patients with diabetes to control glycemic levels. Existing guidelines recommend glycemic control and blood pressure management in patients with diabetes who have had a stroke or TIA. Intensive glucose management has not been shown to reduce rates of cardiovascular events or death in persons with a history of cardiovascular disease, stroke, or additional vascular risk factors.

LIPIDS

Large epidemiologic studies have demonstrated a modest association between elevated total cholesterol or low-density lipoprotein levels and an increased risk of ischemic stroke.

Table 1. Recommendations for Treatable Vascular Risk Factors to Prevent Recurrent Stroke

<i>Risk Factor</i>	<i>Recommendations</i>	<i>Class/level of evidence*</i>
Hypertension	Blood pressure reduction is recommended for prevention of recurrent stroke and prevention of other vascular events in persons who have had an ischemic stroke or TIA and are beyond the first 24 hours.	Class I; level A
	Because this benefit extends to persons with and without a documented history of hypertension, this recommendation is reasonable for all patients with ischemic stroke or TIA who are considered appropriate for blood pressure reduction.	Class IIa; level B
	An absolute target blood pressure level and reduction are uncertain and should be individualized, but benefit has been associated with an average reduction of approximately 10/5 mm Hg, and normal blood pressure levels have been defined as < 120/80 mm Hg by JNC7.	Class IIa; level B
	Several lifestyle modifications have been associated with blood pressure reduction and are a reasonable part of a comprehensive antihypertensive therapy. Modifications include salt restriction; weight loss; consumption of a diet rich in fruits, vegetables, and low-fat dairy products; regular aerobic physical activity; and limited alcohol consumption.	Class IIa; level C
	The optimal drug regimen to achieve the recommended level of reduction is uncertain because direct comparisons between regimens are limited. The available data indicate that diuretics or the combination of diuretics and an angiotensin-converting enzyme inhibitor are useful.	Class I; level A
	The choice of specific drugs and targets should be individualized on the basis of pharmacologic properties, mechanism of action, and consideration of specific patient characteristics for which specific agents are probably indicated (e.g., extracranial cerebrovascular occlusive disease, renal impairment, cardiac disease, and diabetes). (<i>New recommendation</i>)	Class IIa; level B
Diabetes mellitus	Use of existing guidelines for glycemic control and blood pressure targets in patients with diabetes is recommended for patients who have had a stroke or TIA. (<i>New recommendation</i>)	Class I; level B
Lipids	Statin therapy with intensive lipid-lowering effects is recommended to reduce the risk of stroke and cardiovascular events in patients with ischemic stroke or TIA who have evidence of atherosclerosis, an LDL cholesterol level \geq 100 mg per dL (2.59 mmol per L), and who are without known CHD.	Class I; level B
	For patients with atherosclerotic ischemic stroke or TIA and without known CHD, it is reasonable to target a reduction of at least 50 percent in LDL cholesterol levels or a target level of < 70 mg per dL (1.81 mmol per L) to obtain maximal benefit. (<i>New recommendation</i>)	Class IIa; level B
	Patients with ischemic stroke or TIA with elevated cholesterol or comorbid coronary artery disease should be otherwise managed according to NCEP-ATP III guidelines, which include lifestyle modification, dietary guidelines, and medication recommendations.	Class I; level A
	Patients with ischemic stroke or TIA with low HDL cholesterol levels may be considered for treatment with niacin or gemfibrozil (Lopid).	Class IIb; level B

CHD = coronary heart disease; HDL = high-density lipoprotein; JNC7 = Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; LDL = low-density lipoprotein; NCEP-ATP III = National Cholesterol Education Program, Adult Treatment Panel III; TIA = transient ischemic attack.

*—See the full guidelines at <http://stroke.ahajournals.org/cgi/content/full/42/1/227> for explanations of classes and levels of evidence.

Adapted from Furie KL, Kasner SE, Adams RJ, et al.; American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Clinical Cardiology, and Interdisciplinary Council on Quality of Care and Outcomes Research. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2011;42(1):231.

Other studies have found a link between high serum triglyceride levels and ischemic stroke and large-artery atherosclerotic stroke. Low levels of high-density lipoproteins have also been linked to ischemic stroke. Statin therapy is recommended in patients with ischemic stroke or TIA,

even without known coronary heart disease, to reduce the risk of stroke and cardiovascular events. The National Cholesterol Education Program, Adult Treatment Panel III recommends reducing low-density lipoprotein levels as the primary target in managing dyslipidemia. Lifestyle ►

Table 2. Recommendations for Modifiable Behavioral Risk Factors to Prevent Recurrent Stroke

<i>Risk factor</i>	<i>Recommendations</i>	<i>Class/level of evidence*</i>
Cigarette smoking	Health care professionals should strongly advise every patient with stroke or TIA who has smoked in the past year to quit.	Class I; level C
	It is reasonable to avoid environmental (passive) tobacco smoke.	Class IIa; level C
	Counseling, nicotine products, and oral smoking cessation medications are effective for helping smokers to quit.	Class I; level A
Alcohol consumption	Patients with ischemic stroke or TIA who are heavy drinkers should eliminate or reduce their consumption of alcohol.	Class I; level C
	Light to moderate levels of alcohol consumption (no more than two drinks per day for men and one drink per day for nonpregnant women) may be reasonable; nondrinkers should not be counseled to start drinking.	Class IIb; level B
Physical activity	For patients with ischemic stroke or TIA who are capable of engaging in physical activity, at least 30 minutes of moderate-intensity physical exercise, typically defined as vigorous activity sufficient to break a sweat or noticeably raise heart rate, one to three times a week (e.g., walking briskly, using an exercise bicycle) may be considered to reduce risk factors and comorbid conditions that increase the likelihood of recurrent stroke.	Class IIb; level C
	For persons with a disability following ischemic stroke, supervision by a health care professional, such as a physical therapist or cardiac rehabilitation professional, at least on initiation of an exercise regimen, may be considered.	Class IIb; level C
Metabolic syndrome	At this time, the effectiveness of screening patients for metabolic syndrome after stroke has not been established. (<i>New recommendation</i>)	Class IIb; level C
	For patients who are screened and classified as having metabolic syndrome, management should include counseling for lifestyle modification (diet, exercise, and weight loss) for vascular risk reduction. (<i>New recommendation</i>)	Class I; level C
	Preventive care for patients with metabolic syndrome should include appropriate treatment for individual components of the syndrome that are also risk factors for stroke, particularly dyslipidemia and hypertension. (<i>New recommendation</i>)	Class I; level A

TIA = transient ischemic attack.

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modifications that include decreasing saturated fat and cholesterol intake, achieving ideal body weight, and increasing physical activity are also recommended.

Modifiable Behavioral Risk Factors

CIGARETTE SMOKING

Cigarette smoking is an independent risk factor for ischemic stroke, and growing evidence has shown that exposure to environmental smoke increases the risk of cardiovascular disease, including stroke. Smoking cessation is recommended in persons who have experienced a stroke or TIA.

ALCOHOL CONSUMPTION

Chronic alcoholism and heavy drinking are risk factors for stroke. One cohort study found a significant increase

in stroke recurrence in patients with previous heavy alcohol use who had experienced ischemic stroke. Although light or moderate drinking may provide a protective effect against ischemic stroke by increasing high-density lipoprotein levels, heavy drinking can cause hypertension, hypercoagulable state, reduced cerebral blood flow, and atrial fibrillation or cardioembolism from cardiomyopathy. Alcoholism has also been linked to insulin resistance and metabolic syndrome.

OBESITY

Although obesity (defined as a body mass index greater than 30 kg per m²) is an independent risk factor for coronary heart disease and premature mortality, no studies have demonstrated that weight loss reduces the risk of recurrent stroke. ►

Practice Guidelines

PHYSICAL ACTIVITY

Physical activity has a beneficial effect on several stroke risk factors. However, persons who have had a stroke may experience substantial disability that can make exercising difficult. Studies have shown that aerobic exercise and strength training improve cardiovascular fitness, mobility, balance, and endurance after a stroke, but it has not been determined that therapeutic exercise reduces the risk of recurrent stroke. Results from one survey found that patients who received advice on physical activity after a stroke were more likely to exercise than those who did not receive advice. Also, those who exercised after surviving a stroke were less likely to have days with limited activity or poor physical health than those who did not exercise.

METABOLIC SYNDROME

Metabolic syndrome is used to describe the convergence of several abnormalities that increase the risk of vascular disease, including hypertriglyceridemia, low high-density lipoprotein cholesterol levels, high blood pressure, and hyperglycemia. Patients with metabolic syndrome have an increased risk of diabetes, cardiovascular disease, and all-cause mortality. The prevalence of metabolic disease in patients with ischemic stroke is 40 to 50 percent. Studies have confirmed an association between metabolic syndrome and first ischemic stroke, but only one study has examined

the association with recurrent stroke. Results found that participants with metabolic syndrome were more likely to have a stroke, myocardial infarction (MI), or vascular death within 1.8 years of follow-up than those without metabolic syndrome. Diet, exercise, and use of medications that enhance insulin sensitivity have been shown to benefit persons with metabolic syndrome.

Antithrombotic Therapy

ANTIPLATELET AGENTS

Four antiplatelet medications have been approved by the U.S. Food and Drug Administration for preventing vascular events in patients with a stroke or TIA: aspirin, ticlopidine, clopidogrel (Plavix), and combination aspirin/dipyridamole (Aggrenox). On average, these agents have been shown to reduce the relative risk of stroke, MI, or death by more than 20 percent. *Table 3* lists recommendations for antithrombotic therapy for noncardioembolic stroke or TIA.

Aspirin. Aspirin therapy prevents stroke in patients who have had a recent stroke or TIA. Although the level of benefit is comparable for dosages between 50 and 1,500 mg per day, higher dosages are associated with an increased risk of gastrointestinal hemorrhage. The increased risk of hemorrhagic stroke in patients taking aspirin is smaller than the risk of ischemic stroke, which results in a net benefit of aspirin therapy.

Table 3. Recommendations for Antithrombotic Therapy for Noncardioembolic Stroke or TIA

<i>Recommendations</i>	<i>Class/level of evidence*</i>
For patients with noncardioembolic ischemic stroke or TIA, the use of antiplatelet agents rather than oral anticoagulation is recommended to reduce the risk of recurrent stroke and other cardiovascular events.	Class I; level A
Acceptable options for initial therapy include aspirin monotherapy at a dosage of 50 mg to 325 mg per day (<i>class I; level A</i>); the combination of aspirin and extended-release dipyridamole (Aggrenox) at a dosage of 25/200 mg twice per day (<i>class I; level B</i>); and clopidogrel (Plavix) monotherapy at a dosage of 75 mg per day (<i>class IIa; level B</i>).	Class I; level A Class I; level B Class IIa; level B
Selection of an antiplatelet agent should be individualized on the basis of patient risk factor profiles, cost, tolerance, and other clinical characteristics.	
The addition of aspirin to clopidogrel increases the risk of hemorrhage and is not recommended for routine secondary prevention after ischemic stroke or TIA.	Class III; level A
For patients allergic to aspirin, clopidogrel is a reasonable alternative.	Class IIa; level C
For patients who have an ischemic stroke while taking aspirin, there is no evidence that increasing the dose of aspirin provides additional benefit. Although alternative antiplatelet agents are often considered, no single agent or combination has been studied in patients who have had an event while receiving aspirin.	Class IIb; level C

TIA = transient ischemic attack.

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Ticlopidine. Three randomized trials have investigated the use of ticlopidine in patients with cerebrovascular disease with mixed results. One trial evaluated ticlopidine therapy and placebo for prevention of stroke, MI, or vascular death in patients with ischemic stroke. Persons assigned to ticlopidine therapy had fewer outcomes per year after a mean follow-up of two years. A second trial compared ticlopidine with aspirin use in patients with recent minor stroke or TIA, and found that those taking ticlopidine had a lower rate of stroke or death. A third trial assigned black patients with recent noncardioembolic ischemic stroke to receive aspirin or ticlopidine. No difference was found between the groups in the risk of the combination of stroke, MI, or vascular death at two years.

Adverse effects associated with ticlopidine use include diarrhea and rash. Ticlopidine is also associated with thrombotic thrombocytopenic purpura. Rates of gastrointestinal bleeding are similar or lower in patients taking ticlopidine than in patients taking aspirin.

Clopidogrel. Two trials have evaluated the use of clopidogrel for secondary stroke prevention. One trial compared clopidogrel with aspirin alone, and the other with combination aspirin/dipyridamole. Results from both trials found that rates of primary outcomes were similar between treatment groups. Adverse effects of clopidogrel include diarrhea and rash, although gastrointestinal symptoms and hemorrhage are less common than in persons taking aspirin. Proton pump inhibitors have been shown to reduce the effectiveness of clopidogrel, and may also increase the risk of major cardiovascular events when taken with clopidogrel.

Aspirin/dipyridamole. Four large randomized trials have examined the effects of combination aspirin/dipyridamole in patients with TIA or stroke. Results showed that combination therapy is at least as effective as aspirin alone for prevention of stroke; however, it is not tolerated as well by patients.

Clopidogrel and aspirin. Compared with clopidogrel alone, the combination of clopidogrel and aspirin for prevention of vascular effects in persons with a recent TIA or ischemic stroke was not found to have a significant benefit. There was a significantly increased risk

of major hemorrhage in persons taking combination therapy compared with those taking clopidogrel alone. When compared with aspirin alone, combination clopidogrel and aspirin did not have a statistically significant benefit but did increase the risk of bleeding in patients who had previously had a stroke.

Selecting oral antiplatelet therapy. Selecting between aspirin, ticlopidine, clopidogrel, and combination aspirin/dipyridamole should be based on relative effectiveness, safety, cost, patient characteristics, and patient preference. Evidence shows that each therapy is effective for the prevention of secondary stroke. In persons who experience a stroke while on antiplatelet therapy, no studies have shown that switching to a different antiplatelet agent reduces the risk of a subsequent event.

Three additional antiplatelet agents are being investigated for effectiveness in secondary stroke prevention: triflusal, cilostazol (Pletal), and sarpogrelate. At this time, none has been approved by the U.S. Food and Drug Administration for prevention of recurrent stroke.

ORAL ANTICOAGULANTS

Oral anticoagulants have been evaluated for the prevention of recurrent stroke in patients with noncardioembolic stroke. One trial was stopped and reformatted because of increased bleeding in patients taking high-intensity oral anticoagulants. After reformulating the study to compare warfarin (Coumadin) with aspirin alone or with aspirin plus extended-release dipyridamole, the trial was halted again because of the superiority in patients taking combination aspirin/dipyridamole. Compared with patients taking aspirin alone, patients taking warfarin experienced a significantly higher rate of major bleeding, but a nonstatistically significant decrease in the rate ischemic events. ■

Answers to This Issue's CME Quiz

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| Q1. A | Q5. A, B, C, D | Q9. E |
| Q2. C | Q6. C | Q10. A, B |
| Q3. D | Q7. A, B, C, D | Q11. A, C |
| Q4. C | Q8. A, B, C, D | Q12. C |