

Prevention of Secondary Stroke/Transient Ischemic Attack

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Learning Objectives

After reading this *CME Bulletin*, you should be able to:

- Identify the risk factors for transient ischemic attack and stroke, including the risk factors for secondary stroke.
- Describe the appropriate use of primary and secondary preventive measures (including lifestyle modifications and medications) for transient ischemic attack and stroke.
- Prescribe appropriate antiplatelet and antithrombotic medication when indicated for the management of thrombus and emboli.

Introduction

Stroke is the third leading cause of death and the leading cause of disability in the United States. Current research indicates that there are more than 4.4 million American stroke survivors. Approximately 780,000 individuals experience a stroke each year; 180,000 of these are recurrent strokes.¹

Strokes can be categorized as ischemic or hemorrhagic. Ischemic strokes, caused by lack of blood flow due to arterial obstruction, account for 87% of all strokes. Hemorrhagic strokes, caused by arterial rupture, account for 13% of strokes. A discussion of hemorrhagic stroke is beyond the scope of this *Bulletin*; the focus will be on the prevention of ischemic stroke.

A transient ischemic attack (TIA), defined as a focal neurological deficit lasting <24 hours, is a stroke warning that is critical to recognize. Following a TIA, the 90-day stroke risk is between 3 and 17.3%, with the greatest risk occurring within the first 30 days.¹ Because of their frequent contact with patients, family physicians, physician assistants, and nurse practitioners in the primary care setting are ideally positioned to educate patients about risk factors and to manage long-term treatment plans for preventing secondary strokes. This *Bulletin* will review the risk factors for ischemic stroke or TIA and strategies for the secondary prevention of ischemic stroke.

Risk Factors for Ischemic Stroke

Several factors increase a patient's risk of secondary stroke. While some risk factors cannot be changed, many others are modifiable. Risk factors that cannot be modified include age older than 55 years; male gender; black race; family history of diabetes or previous stroke; and prior stroke or TIA.

Secondary Prevention Through Management of Modifiable Risk Factors

Managing modifiable risk factors via lifestyle interventions and/or medications will improve a patient's overall quality of life and reduce

the chance of future stroke. Numerous studies have shown that smoking cessation, limited alcohol consumption, and aggressive management of atrial fibrillation, diabetes, dyslipidemia, hypertension, and other modifiable risk factors can significantly reduce the incidence of secondary stroke.² *Table 1* summarizes the modifiable risk factors for stroke and recommendations for stroke risk reduction.

Atrial Fibrillation

Atrial fibrillation (AF) is an independent risk factor for primary and secondary stroke and is associated with a five-fold increase in stroke risk. The risk of AF-related stroke increases with age over 65 years. Fifteen to 20% of all strokes are attributed to AF.³ Patients with AF tend to have more severe strokes, longer hospital stays, and greater levels of disability and dependency. AF-associated ischemic stroke is more likely to result in mortality in the short-term (within one month of the event) and in the long-term (within one year).

Anticoagulant therapy with the coumarin anticoagulant warfarin has been extensively studied and is recommended for primary stroke prevention in patients with valvular AF or nonvalvular AF at intermediate to high stroke risk, based on their CHADS₂ score.^{2,4} Warfarin anticoagulation is also recommended for secondary stroke prevention in the absence of contraindications for its use.⁵ Antiplatelet agents such as aspirin or clopidogrel are used to prevent cardioembolic events in patients with AF when warfarin is contraindicated (this is an off-label use of clopidogrel).

Guidelines based on the work of Sacco, et al., recommend the use of long-term oral anticoagulation to prevent cardioembolic cerebral ischemic events in patients with AF who have recently had a non-hemorrhagic stroke.⁴ Because hemorrhagic risks are associated with anticoagulant therapy, careful monitoring of the International Normalized Ratio (INR) is recommended during use of warfarin. Long-term warfarin anticoagulation is recommended in all patients with AF associated with valvular heart disease, or with a CHADS₂ score of 2 or more. Warfarin anticoagulation should also be considered for cardioembolic strokes associated with rheumatic mitral valve disease, dilated cardiomyopathy, prosthetic heart valves, and after an acute myocardial infarction (MI) complicated by a left ventricular mural thrombus.⁴

Diabetes

Diabetes increases the risk of stroke between 1.8- and 6-fold.⁶ The 2006 American Heart Association (AHA) guidelines for secondary stroke prevention recommend that patients with diabetes should maintain "rigorous control" of hypertension, dyslipidemia, and glucose levels in order to reduce the risk of stroke as well as microvascular and possibly macrovascular complications. Angiotensin-converting



Prevention of Secondary Stroke/Transient Ischemic Attack (Continued from front page)

enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are first-line antihypertensives prescribed to achieve a target blood pressure level of 130/80 mm Hg. Furthermore, glucose control aiming for a hemoglobin A1c of <7% is also recommended.⁴

Table 1. Modifiable Risk Factors and Recommendations

Risk Factor	Recommendation
Alcohol	<ul style="list-style-type: none"> Eliminate or reduce consumption: no more than 2 drinks/day for men; no more than 1 drink/day for non-pregnant women
Atrial fibrillation	<ul style="list-style-type: none"> Warfarin for patients at high risk of stroke (target INR 2.5, range 2.0-3.0) (those with valvular heart disease or CHADS₂ score ≥ 2) Aspirin 81-325 mg/day for patients at low-risk (CHADS₂ score ≤ 1 or those unable to take oral anticoagulants)
Body mass index, obesity, exercise	<ul style="list-style-type: none"> Weight loss with goal waist circumference of <88 cm (<35 in) for women, <102 cm (<40 in) for men BMI of 18.5-24.9 kg/m² 30-60 min/day of continuous or accumulated exercise, most days of the week
Diabetes	<ul style="list-style-type: none"> Glucose to near-normoglycemic levels Hemoglobin A1c goal <7% Target blood pressure: <130/80 mm Hg ACEIs and ARBs are first-choice medications
Dyslipidemia	<ul style="list-style-type: none"> On the basis of the SPARCL trial, administration of a statin agent recommended for patients with prior ischemic stroke or TIA and without known CHD to reduce risk of future stroke or cardiovascular event Target for those with CHD or symptomatic atherosclerotic disease is LDL-C level of <100mg/dL. An LDL-C <70 mg/dL is recommended for individuals at very high risk with multiple risk factors
Hypertension	<ul style="list-style-type: none"> JNC-recommended level: 140/80 mm Hg or <130/80 mm Hg for patients with diabetes or chronic kidney disease Aspirin not recommended for patients with uncontrolled hypertension
Smoking	<ul style="list-style-type: none"> Smoking doubles ischemic stroke risk Encourage patients to quit immediately Help set quit date; plan and offer pharmacologic smoking deterrent

ACEIs=angiotensin-converting enzyme inhibitors; ARBs=angiotensin receptor blockers; BMI=body mass index; CHADS₂=congestive heart failure, hypertension, age 75 years or older, diabetes, previous stroke or transient ischemic attack; CHD=coronary heart disease; INR=International Normalized Ratio; JNC=Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; LDL-C=low-density lipoprotein cholesterol; SPARCL=Stroke Prevention by Aggressive Reduction in Cholesterol Levels; TIA=transient ischemic attack.

Information from Duncan PW, Zorowitz R, Bates B, et al. Management of Adult Stroke Rehabilitation Care: A clinical practice guideline. *Stroke*. 2005;36(9):e100-43; and Thom T, Haase N, Rosamond W, et al. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*. 2006;113(6):e85-151. Erratum in: *Circulation*. 2006;113(14):e696. *Circulation*. 2006;114(23):e630.

Dyslipidemia

The relationship between stroke and hyperlipidemia is unclear, but the target low-density lipoprotein cholesterol (LDL-C) level for individuals with coronary heart disease (CHD) or symptomatic atherosclerotic disease is <100 mg/dL. The National Cholesterol Education Program (NCEP III) Expert Panel on Detection, Evaluation, and Treatment of High Cholesterol in Adults (Adult Treatment Panel III) suggests lifestyle modifications and use of medication if indicated to lower LDL-C levels. Low high-density lipoprotein cholesterol (HDL-C) levels are also a known risk factor for carotid artery disease and stroke. An LDL-C <70 mg/dL is recommended for individuals at very high risk with multiple risk factors.^{2,4} Lifestyle modifications include reducing weight, reducing intake of dietary fat and cholesterol, and increasing physical activity. In conjunction with lifestyle modifications, statin agents are recommended as the primary cholesterol medication to achieve appropriate LDL-C levels to prevent stroke.⁴ The SPARCL trial, which evaluated the effects of statin therapy in patients who had previously experienced a stroke or TIA and who had no cardiovascular disease, also demonstrated that aggressive statin therapy was associated with a significant reduction in recurrent stroke/TIA in patients with normal lipid levels and no coronary heart disease who have had a prior ischemic stroke or TIA.⁷

Hypertension

The relationship between ischemic stroke risk and hypertension is well established.⁴ Approximately 50% of all strokes can be attributed to hypertension.⁸ The report by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) states that the risk of cardiovascular disease increases when the blood pressure exceeds a systolic blood pressure level of 115 mm Hg and a diastolic blood pressure level of 75 mm Hg. JNC7 encourages lifestyle modifications for the management of hypertension as a first step. Suggested modifications include weight loss; a low-fat diet rich in fruits and vegetables; regular aerobic exercise; smoking cessation; and limited consumption of alcohol and sodium. The use of antihypertensive drugs has been shown to reduce the risk of recurrent stroke, but there is no definitive evidence that supports any particular class of antihypertensive drug. The JNC7 report indicates that recurrent stroke rates can be lowered with a combination of an ACEI and thiazide-type diuretic.⁴ Beta blockers, ARBs, and/or calcium channel blockers also may be considered. Aspirin should be used cautiously in patients with uncontrolled hypertension, which is defined as a systolic blood pressure level of 160 mm Hg and a diastolic blood pressure level of 95 mm Hg.⁹

Antiplatelet Therapy for Secondary Prevention of Ischemic Stroke

Aspirin is the most widely used antiplatelet agent for secondary prevention of stroke. For patients without contraindications such as aspirin allergy or gastrointestinal bleeding, aspirin (50-325 mg/d) is an acceptable choice for long-term therapy. Aspirin use following an ischemic stroke or TIA decreases the incidence of cardiovascular events (combined endpoint of stroke, TIA, MI, or vascular death) by 10% to 20%.¹⁰ The risk of hemorrhagic stroke increases with aspirin use, but the benefits of aspirin for prevention of ischemic stroke outweigh the increased risk of hemorrhagic stroke.⁸ For patients who experience a TIA while taking aspirin, there is no evidence to suggest that increasing the aspirin dose will provide additional protection against future events.⁴

The Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial compared the use of clopidogrel (75 mg once daily) with that of aspirin (325 mg once daily) in reducing the risk of

ischemic stroke, MI, or vascular death in more than 19,000 patients who had experienced recent ischemic stroke, MI, or symptomatic peripheral vascular disease. The use of clopidogrel resulted in a 5.32% annual risk in the combined outcome of ischemic stroke, MI, or vascular death, compared with a 5.83% risk with aspirin use; however, no significant reduction in stroke risk alone was found: absolute risk reduction was 0.1% per year.⁸ The safety of aspirin and clopidogrel are comparable, and for patients who cannot tolerate aspirin, clopidogrel is an appropriate substitute. Combining clopidogrel and aspirin, however, increases the risk of bleeding events and is not recommended.^{2,4}

Another antiplatelet option is the combination of aspirin and extended-release dipyridamole. The second European Stroke Prevention Study (ESPS-2) evaluated a population at high risk of stroke and found the greatest risk reduction—approximately double that of either aspirin or extended-release dipyridamole alone—could be achieved by using the combination agent. Compared with aspirin alone, the combination of aspirin 25 mg and extended-release dipyridamole 200 mg twice daily resulted in an absolute stroke risk reduction of 3%.⁹ The European/Australasian Stroke Prevention in Reversible Ischemia Trial (ESPRIT) showed that compared with aspirin alone, aspirin plus extended-release dipyridamole provided an absolute risk reduction of 1% per year in the combined endpoint of vascular death, stroke, and MI.¹¹ While aspirin alone or clopidogrel alone are acceptable options, a combination of aspirin plus extended-release dipyridamole is currently the recommended choice for antiplatelet therapy if cost is not a factor. *Table 2* lists recommendations for antiplatelet therapy.¹²

Table 2. Recommendations for Antiplatelet Therapy

Class I:

For patients with noncardioembolic stroke or TIA, antiplatelet agents rather than oral anticoagulation are recommended to reduce the risk of recurrent stroke and other cardiovascular events.

Aspirin (50-325 mg/d) monotherapy, the combination of aspirin and extended-release dipyridamole, and clopidogrel monotherapy are all acceptable options for initial therapy.

The combination of aspirin and extended-release dipyridamole (25/200 mg bid) is recommended over aspirin alone.

Class II:

Clopidogrel may be considered over aspirin alone on the basis of direct-comparison trials.

For patients with aspirin allergy, clopidogrel is reasonable.

Class III:

The addition of aspirin to clopidogrel increases the hemorrhage risk.

Combination therapy of aspirin and clopidogrel is not routinely recommended for ischemic stroke or TIA unless a specific indication exists for this therapy (ie, coronary stent or acute coronary syndrome).

bid=twice a day; TIA=transient ischemic attack.

Adapted from Adams RJ, Albers G, Alberts MJ, et al. American Heart Association, American Stroke Association. Update to the AHA/ASA recommendations for the prevention of stroke in patients with stroke and transient ischemic attack. *Stroke*. 2008;39(5):1647-52. Epub 2008.

The Prevention Regimen for Effectively Avoiding Second Strokes (ProFESS), the largest secondary stroke prevention trial ever conducted, is currently underway. ProFESS is comparing the safety and efficacy of aspirin plus extended-release dipyridamole versus clopidogrel and the ARB telmisartan versus placebo in 20,333 patients from 720 sites in 35 countries; results are expected to be released later in 2008.¹³

Tools for Predicting Secondary Stroke Risk

Three tools that can help healthcare professionals predict the risk of secondary stroke are the ABCD² score, the CHADS₂ score, and an equation developed from the Framingham Heart Study data.^{2,14}

The ABCD² score (*Table 3*) predicts the two-day stroke risk after a TIA event by assigning points for the presence of five factors (age, blood pressure level, clinical features, duration of episode, and diabetes).¹¹ A low ABCD² score of 0 to 3 represents a two-day stroke risk of 1%; a moderate score of 4 to 5 indicates a two-day risk of 4.1%; and a high score of 6 to 7 represents a two-day risk of 8.1% and warrants hospitalization and an expeditious workup and management plan.

Table 3. ABCD² Scoring System for Predicting 2-Day Stroke Risk Following TIA

ABCD²

A = Age, B = Blood pressure, C = Clinical features, D² = Duration of symptoms + Diabetes

Age

1 point for age 60 years or older

Blood pressure

1 point for systolic blood pressure level at or above 140 mm Hg

1 point for diastolic blood pressure level at or above 90 mm Hg

Clinical features

2 points for unilateral weakness

1 point for speech impairment without weakness

Duration

2 points for TIA duration of 60 minutes or more

1 point for TIA duration of 10 to 59 minutes

Diabetes

1 point for diabetes

TIA=transient ischemic attack

Adapted with permission from Johnson SC, Rothwell PM, Nguyen-Huynh MN, et al.

Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. *Lancet*. 2007. 369:283-292.

CHADS₂—congestive heart failure, hypertension, age 75 years or older, diabetes, and previous stroke or transient ischemic attack—is a stroke risk stratification method used to determine appropriate antiembolic therapy (*see Table 4*).¹¹ Points are assigned in the following manner: 1 point each for age older than 75 years, diabetes, heart failure exacerbation in the past 100 days, hypertension, and 2 points for a history of stroke or transient ischemic attack. Patients at low risk of cardioembolic events may be treated with aspirin 81-325 mg/day.¹⁵ Unless contraindicated, patients who are at moderate to high risk or who are unable to tolerate aspirin should be treated with warfarin titrated to a goal INR of 2 to 3. Warfarin is not routinely indicated after stroke.¹¹

Using data from the Framingham Heart Study, scores have been derived to predict 5-year risk of stroke or death following a first occurrence of AF.¹⁴ The Framingham scores are determined by adding data to an equation that looks at eight factors: age, systolic blood pressure level, diabetes, cigarette smoking, prior cardiovascular disease, atrial fibrillation, left ventricular hypertrophy, and use of hypertensive medication. An interactive risk score calculator is available at <http://www.nhlbi.nih.gov/about/framingham/stroke.htm>.

Table 4. CHADS₂ Risk Score for Predicting Stroke

Score	Adjusted Stroke Rate	Stroke Risk Level
0	1.9	Low
1	2.8	Low
2	4.0	Moderate
3	5.9	Moderate
4	8.5	High
5	12.5	High
6	18.2	High

CHADS₂=congestive heart failure, hypertension, age 75 years or older, diabetes, previous stroke or transient ischemic attack.

Adapted with permission from Snow V, Weiss KB, LeFevre M, et al. Management of newly detected atrial fibrillation: a clinical practice guideline from the American Academy of Family Physicians and the American College of Physicians. *Ann Intern Med.* 2003;139:1012.

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Self-Assessment Quiz

- Following a transient ischemic attack, the 90-day stroke risk is between 3 and 17.3%, with the greatest risk occurring within the first 30 days.
 - True
 - False
- The report by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) states that the risk of cardiovascular disease increases when the blood pressure level exceeds which of the following?
 - A systolic blood pressure level of 115 mm Hg and a diastolic blood pressure level of 75 mm Hg.
 - A systolic blood pressure level of 125 mm Hg and a diastolic blood pressure level of 75 mm Hg.
 - A systolic blood pressure level of 130 mm Hg and a diastolic blood pressure level of 80 mm Hg.
 - A systolic blood pressure level of 140 mm Hg and a diastolic blood pressure level of 80 mm Hg.
- During an office visit, a 65-year-old diabetic patient experiences a transient ischemic attack that lasts for 33 minutes. The patient's blood pressure level, strength examination results and speech are all normal. According to the ABCD² scoring method for predicting stroke risk, the patient's two-day stroke risk is:
 - 1 %.
 - 4.1 %.
 - 5.9 %.
 - 8.1 %.
- Which of the following is not associated with atrial fibrillation?
 - Longer hospital stays.
 - Less severe strokes.
 - A five-fold increase in stroke risk.
 - Greater levels of disability.
- Which of the following factors is not addressed by the CHADS₂ scoring method?
 - Congestive heart failure.
 - Hypertension.
 - Age 75 years or older.
 - Duration of transient ischemic attack.

Answers: 1.A; 2.A; 3.A; 4.B; 5.D

CME Bulletin Self-Assessment Quiz Answer Sheet

Answers (Please circle one):

- A B
- A B C D
- A B C D
- A B C D
- A B C D

Note: On this scale, 5 is the highest rating, 1 is the lowest.

Relevance of topic to my practice	5	4	3	2	1
Currency of clinical information	5	4	3	2	1
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