Prevention of Recurrent Ischemic Stroke

LORI M. DICKERSON, PharmD, PETER J. CAREK, MD, MS, and ROBERT GLEN QUATTLEBAUM, MD, MPH
Trident Medical Center/Medical University of South Carolina Family Medicine Residency Program, Charleston, South Carolina

Recurrent ischemic stroke and transient ischemic attack are common problems in primary care, with stroke survivors averaging 10 outpatient visits per year. Risk factors such as hypertension, diabetes, and hypercholesterolemia should be evaluated during each office visit. Attention should be given to lifestyle modification including management of obesity, smoking cessation, reduction in alcohol consumption, and promotion of physical activity. The choice of an antiplatelet agent (e.g., aspirin, ticlopidine, clopidogrel, dipyridamole) or the anticoagulant warfarin is based on the safety, tolerability, effectiveness, and price of each agent. Aspirin is a common first choice for prevention of recurrent stroke, but the combination of dipyridamole and aspirin should be considered for many patients because of its superior effectiveness in two clinical trials. Clopidogrel is recommended for patients with aspirin intolerance or allergy, or for those who cannot tolerate dipyridamole. Warfarin and the combination of aspirin and clopidogrel should not be used in the prevention of ischemic stroke. Carotid endarterectomy is appropriate for select patients; carotid stenting was recently shown to be less effective and less safe than endarterectomy. (Am Fam Physician 2007;76:382-8, 389. Copyright © 2007 American Academy of Family Physicians.)

ILLUSTRATION BY ROBERT MARGULIES

▶ **Patient information:** A handout on stroke prevention, written by the authors of this article, is provided on page 389.

AGF This article exemplifies the AAFP 2007 Annual Clinical Focus on the management of chronic illness.

Every year in the United States, 700,000 persons have a stroke; in 200,000 of these patients, the strokes are recurrent.[1] Of the 500,000 patients with a new stroke, 14 percent will have a another stroke within one year. Approximately 270,000 persons die each year because of stroke, ranking it third in mortality behind heart disease and cancer. Stroke leads to more long-term disability than any other disease process, and it directly and indirectly costs the United States $57.9 billion a year.

Most strokes (88 percent) are ischemic. The rates of intracerebral hemorrhage and subarachnoid hemorrhage are much lower (9 and 3 percent, respectively).[1] Recent trials use a mixture of clinical and radiographic evidence to define ischemic stroke versus transient ischemic attack (TIA). An ischemic stroke is defined as acute onset of neurologic symptoms lasting longer than 24 hours or radiographic evidence of an ischemic event in patients with loss of symptoms within 24 hours.[2] A TIA is an event that lasts less than 24 hours and that is without evidence of pathology on radiographic studies.[2] Although these terms are strict, the pathology and clinical significance overlap.

Because most clinical trials include patients with ischemic stroke and TIA, and because it is probably just as important to prevent a recurrent TIA, this article will use the term "ischemic stroke" to indicate both. In addition, this article will only discuss the management of noncardioembolic stroke and not atrial fibrillation or embolic stroke.

Stroke survivors account for a significant proportion of family practice office visits, with one study finding that a stroke survivor has an average of 10 outpatient visits a year.[3] Appropriate, cost-effective, office-based care of these patients is critical to minimize future disability and to reduce the risk of death from recurrent stroke.

This article reviews the most current information on the prevention of recurrent ischemic stroke based on recent guidelines from the American Heart Association, the American Stroke Association Council on Stroke, and the American College of Chest Physicians.[4,5] These organizations provide recommendations on controlling

Downloaded from the American Family Physician Web site at www.aafp.org/afp. Copyright © 2007 American Academy of Family Physicians. For the private, noncommercial use of one individual user of the Web site. All other rights reserved. Contact copyrights@aafp.org for copyright questions and/or permission requests.

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*
For patients with a history of stroke, hypertension treatment is recommended; optimal antihypertensive agents include diuretics and diuretics plus angiotensin-converting enzyme inhibitors.	A	4, 6, 9
Patients with cerebrovascular disease should have a blood pressure goal of less than 140/90 mm Hg; patients who also have diabetes should have a blood pressure goal of less than 130/80 mm Hg.	A	4, 6, 9
Other target organ damage (e.g., renal impairment, diabetes) should be considered when choosing antihypertensive therapy.	A	4, 6, 9
Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are first-line antihypertensive agents for patients with diabetes. Thiazide diuretics, beta blockers, and calcium channel blockers also may be considered.	A	4, 6, 12
Statins are recommended to achieve a target low-density lipoprotein cholesterol level of less than 100 mg per dL (2.60 mmol per L); patients with multiple risk factors should have a target value of less than 70 mg per dL (1.80 mmol per L).	A	4, 13-15
Patients should be strongly encouraged not to smoke and to avoid environmental tobacco smoke.	C	4
Heavy drinkers (more than five drinks per day) should eliminate or reduce their consumption of alcohol.	A	4
Light to moderate drinking (less than two drinks per day for men and one drink per day for nonpregnant women) may be considered.	C	4
Patients should be strongly encouraged to engage in moderate-intensity exercise for at least 30 minutes on most days of the week.	C	4
Weight reduction should be considered to maintain a goal body mass index of 18.5 to 24.9 kg per m^2 and a waist circumference of less than 35 inches for women and less than 40 inches for men.	C	4

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see page 323 or http://www.aafp.org/afpsort.xml.

risk factors, interventions for improving atherosclerotic disease, and the use of antithrombotic therapy for the prevention of recurrent ischemic stroke.

Risk Factors for Recurrent Stroke

Stroke prevalence varies by sex and race, with the highest rates found in black men *(Table 1)*.[1] Observational studies have documented relationships between initial stroke, vascular risk factors (e.g., hypertension, diabetes, hyperlipidemia), and lifestyle risk factors (e.g., smoking, alcohol use, obesity, lack of physical activity).[4,6] Factors associated with recurrent stroke include diabetes mellitus, previous multiple strokes, disability after initial stroke, and large artery atherosclerosis.[7,8]

Management of Risk Factors

Extensive evidence supports the treatment of hypertension for the prevention of recurrent ischemic stroke.[4,6,9] In a systematic review

Table 1. Stroke Prevalence and Annual Incidence by Race and Sex in the United States

Population	*Prevalence (%)*	*Incidence**
Total	2.6	700,000
Total men	2.5	327,000
Total women	2.6	373,000
White men	2.3	277,000
White women	2.6	312,000
Black men	4.0	50,000
Black women	3.9	61,000
Mexican-American men	2.6	—
Mexican-American women	1.8	—
Hispanic or Latino	2.2	—
Asian	1.8	—
American Indian/Alaska Native	3.1	—

**—Includes new and recurrent strokes.*

Adapted with permission from Thom T, Haase N, Rosamond W, Howard VJ, Rumsfeld J, Manolio T, et al. Heart disease and stroke statistics—2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2006;113:e103.

of seven trials with more than 15,000 patients who had a history of ischemic stroke, treatment with antihypertensive agents reduced the risk of stroke, nonfatal stroke, myocardial infarction (MI), and total vascular events but not vascular or all-cause mortality.[9] Antihypertensive therapy, preferably diuretics or diuretics plus angiotensin-converting enzyme (ACE) inhibitors, should be initiated after the hyperacute period.[4,6,9] There is no consensus on the definition of the hyperacute period or how to treat patients within this time frame. However, some authors recommend a waiting period of 24 to 48 hours during which blood pressure is only treated if it exceeds 220/120 mm Hg.[10]

In patients with a history of stroke, statins should be used to achieve a low-density lipoprotein cholesterol level of less than 100 mg per dL, or 70 mg per dL for patients with multiple risk factors.

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7) recommends a blood pressure goal of less than 140/90 mm Hg for patients with cerebrovascular disease.[6] However, the American Heart Association/American Stroke Association guidelines recommend considering treatment in patients with or without hypertension. They also recommend an average blood pressure reduction of 10/5 mm Hg.[4]

The PROGRESS trial studied 6,105 patients with or without hypertension after ischemic stroke in an effort to determine the safety and effectiveness of blood pressure lowering in this population. Specifically, they evaluated the effects of an ACE inhibitor (perindopril [Aceon]) compared with an ACE inhibitor plus a diuretic (indapamide [Lozol; brand not available in the United States]).[11] Over four years, combination therapy significantly reduced the risk of stroke (number needed to treat [NNT] = 25) in both patient populations.[11] Perindopril alone did not reduce the risk of stroke, but this may be because of a lesser reduction in blood pressure than that observed with combination therapy.[11]

In patients with diabetes, most of the data on stroke prevention is in the primary rather than secondary prevention population. Hypertension is the most important risk factor; it should be managed aggressively in diabetes. Tight blood pressure control with beta blockers and ACE inhibitors has been shown to reduce the risk of stroke (NNT = 26 for eight years).[4,12] Glycemic control has been shown to reduce the risk of microvascular complications but not the risk of stroke.[12] The JNC 7 guidelines recommend a goal blood pressure of less than 130/80 mm Hg in patients with diabetes.[6] Treatment regimens should include ACE inhibitors or angiotensin receptor blockers because they also slow the progression of renal disease in this population.[4] However, JNC 7 also recommends thiazide diuretics, beta blockers, and calcium channel blockers for treating hypertension in patients with diabetes.[6]

Hypercholesterolemia in patients with a history of ischemic stroke should be managed according to the National Cholesterol Education Panel guidelines.[4,13] Patients should be instructed on lifestyle modification and dietary restrictions. Statins should be used to achieve a low-density lipoprotein (LDL) cholesterol level of less than 100 mg per dL (2.60 mmol per L) or less than 70 mg per dL (1.80 mmol per L) for patients with multiple risk factors.

In the Heart Protection Study, more than 20,000 patients with a history of diabetes, cerebrovascular disease, or other occlusive arterial diseases were treated with simvastatin (Zocor) for five years. Simvastatin reduced the risk of recurrent stroke (NNT = 71) and mean LDL level from 131 mg per dL (3.40 mmol per L) to 92 mg per dL (2.40 mmol per L).[14] In a recent placebo-controlled trial, 4,731 patients with a history of stroke treated with 80 mg atorvastatin (Lipitor) over five years reduced their risk of fatal or nonfatal stroke (NNT = 52) and major cardiovascular events (NNT = 29) but not overall mortality. Mean LDL level at baseline was 133 mg per dL (3.45 mmol per L), which decreased to 73 mg per dL (1.90 mmol per L) in the atorvastatin group.[15]

The most important lifestyle recommendation for patients with a history of ischemic stroke is to stop smoking.[4] Also, patients who are heavy drinkers (more than five drinks per day) should eliminate or reduce their alcohol consumption; light to moderate consumption (less than two drinks per day for men and one drink per day for nonpregnant women) may be considered.[4] For weight reduction to a goal body mass index of less than 25 kg per m^2 and a waist circumference less than 35 inches for women and less than 40 inches for men, patients should be encouraged to engage in physical activity for at least 30 minutes on most days of the week.[4]

Antithrombotic Therapy

In addition to risk-factor modification, antithrombotic agents are recommended for prevention of recurrent stroke. Antithrombotic agents include antiplatelet agents (aspirin, ticlopidine [Ticlid], clopidogrel [Plavix], and dipyridamole [Persantine]) and the anticoagulant warfarin (Coumadin). In a large meta-analysis of antiplatelet

agents for prevention of recurrent stroke, the NNT was 28 for 2.5 years to prevent one stroke.[16]

ASPIRIN

A wide range of aspirin dosages (30 to 1,300 mg per day) have been studied in the prevention of ischemic stroke.[4,5] When compared with placebo, patients with a history of ischemic stroke treated with aspirin had a lower risk of stroke and death (NNT = 22 for three years).[17] High-dosage (325 mg per day) and low-dosage (50 to 166 mg per day) aspirin regimens have similar effectiveness in preventing vascular events, but higher dosages are associated with more gastrointestinal side effects and bleeding episodes.[16,18,19] Specifically, patients receiving more than 200 mg of aspirin per day for at least one month have more gastrointestinal bleeding (number needed to harm [NNH] = 58), fatal or life-threatening bleeding (NNH = 76), and total bleeding episodes (NNH = 16) compared with those receiving less than 100 mg per day.[18] However, the overall risk of major bleeding associated with aspirin use (75 to 500 mg per day) is small (NNH = 344) compared with placebo.[19]

Aspirin is not recommended for patients with uncontrolled hypertension. The U.S. Preventive Services Task Force (USPSTF) concluded that uncontrolled hypertension attenuates the effectiveness of aspirin and increases the risk of bleeding in the primary prevention population.[20] The USPSTF does not make specific recommendations about aspirin use in the secondary prevention population. In the trials for prevention of recurrent stroke, many patients had the diagnosis of hypertension, but studies often excluded patients with uncontrolled hypertension.[21]

CLOPIDOGREL

Clopidogrel is approved by the U.S. Food and Drug Administration for the prevention of recurrent vascular events (e.g., MI, stroke, vascular death).[22] In a randomized controlled trial (RCT), patients with recent ischemic stroke, MI, or symptomatic peripheral arterial disease received clopidogrel (75 mg) or aspirin (325 mg) daily for two years.[21] There was a statistically significant difference in effectiveness with clopidogrel compared with aspirin (5.32 versus 5.83 percent risk of ischemic event; NNT = 196 for two years), but this was of borderline clinical significance. In the subgroup of patients with previous stroke, clopidogrel offered no benefit over aspirin for prevention of recurrent events. Clopidogrel was associated with more reports of rash (NNH = 71) and diarrhea (NNH = 91) than aspirin, but patients taking aspirin experienced more gastrointestinal upset (NNH = 39) and bleeding (NNH = 149).[21]

CLOPIDOGREL AND ASPIRIN

Clopidogrel has also been studied in combination with aspirin for the prevention of recurrent stroke. Although short-term (six to nine months) combination therapy has been shown to be effective in patients with coronary stents and acute coronary syndrome, combination therapy is not recommended in patients with a history of stroke.[23,24] In a recent trial, more than 7,000 patients with a previous stroke received clopidogrel (75 mg) and aspirin (325 mg) or clopidogrel alone for 18 months.[25] Combination therapy was not more effective than clopidogrel alone in preventing ischemic stroke, MI, vascular death, or rehospitalization for ischemic events. However, the combination regimen increased the risk of life-threatening bleeding (NNH = 50) and major bleeding (NNH = 100). In patients with a history of cardiovascular disease and multiple risk factors, combination therapy also increased the risk of severe bleeding (NNH = 250 over two years) but did not reduce the risk of ischemic stroke.[26]

The combination of clopidogrel and aspirin is no more effective than clopidogrel alone for preventing ischemic stroke, but it increases the risk of bleeding.

DIPYRIDAMOLE AND ASPIRIN

Extended-release dipyridamole and aspirin are available as a combination product (Aggrenox) approved for the prevention of recurrent stroke.[27] Two RCTs have demonstrated the benefit of combination therapy versus aspirin alone. In the first trial, 6,602 patients receiving dipyridamole (200 mg twice per day) and aspirin (25 mg twice per day) had a lower risk of ischemic stroke (NNT = 33) and TIA (NNT = 47) during the two-year study compared with aspirin alone.[28]

In the second trial, 2,739 patients were randomized to aspirin (30 to 325 mg per day, mean dose of 75 mg) or combination therapy with aspirin (30 to 325 mg day, mean dose of 75 mg) and dipyridamole (200 mg twice per day; 83 percent of patients received the extended-release formulation) for an average of 3.5 years.[29] The dipyridamole and aspirin combination significantly reduced the risk of death from all vascular causes and nonfatal stroke, MI, and major bleeding complications (NNT = 33). This number was confirmed when the investigators combined data from both combination therapy trials.[29]

In addition, combination therapy did not increase the risk of major or minor bleeding. One fourth of patients who discontinued therapy with dipyridamole reported

headache as at least one of the reasons. Only 13 percent of patients stopped aspirin therapy, mainly for medical reasons (e.g., need for anticoagulant therapy).[29] An ongoing trial is comparing clopidogrel with aspirin and dipyridamole for the prevention of recurrent stroke.[30]

There have been concerns about using immediate-release dipyridamole in patients with stable angina because its vasodilatory effects have the potential to cause chest pain. However, one trial evaluated this risk and found no excess of adverse cardiac events in patients receiving extended-release dipyridamole compared with aspirin.[31]

WARFARIN

Warfarin is commonly recommended for the prevention of recurrent stroke in patients with atrial fibrillation, but it has a lesser role in the prevention of noncardioembolic ischemic stroke. In a comparative trial of 2,206 patients with a history of ischemic stroke, investigators found no difference in effectiveness between warfarin (International Normalized Ratio [INR] of 1.4 to 2.8) and aspirin (325 mg) for the prevention of recurrent ischemic stroke or death over two years.[32] Patients receiving warfarin, however, had a significant increase in risk of minor bleeding (NNH = 13). In 569 patients with ischemic stroke caused by intracranial arterial stenosis, warfarin (mean INR of 2.5) also increased the risk of bleeding (NNH = 20 over two years) and total mortality (NNH = 19) compared with aspirin 1,300 mg per day.[33] Given the risk/benefit ratio, cost of monitoring therapy, and difficulty in maintaining a therapeutic INR in a community setting, antiplatelet agents are preferred over warfarin for prevention of recurrent ischemic stroke.

CHOICE OF ANTITHROMBOTIC THERAPY

The choice of antithrombotic therapy for the prevention of recurrent ischemic stroke should be made based on the safety, tolerability, effectiveness, and price of each agent *(Table 2*[16-19,21,22,25,27-29,32]*)*.[4,5] Because of its minimal cost, aspirin in a dosage of 50 to 325 mg per day remains a good choice for the prevention of recurrent ischemic stroke.[4] However, considering the significant increase in effectiveness with a combination of dipyridamole and aspirin versus aspirin alone, this regimen should be strongly considered for many patients.[4,5] For patients intolerant of aspirin (e.g., those with gastrointestinal distress or bleeding), with an aspirin allergy (e.g., those with nasal polyps, rhinorrhea, bronchospasm), or who experience headaches with dipyridamole, clopidogrel is an appropriate alternative.[4,5] Combination therapy with

Table 2. Comparison of Antithrombotic Agents for Prevention of Recurrent Ischemic Stroke

Antithrombotic agent	*Safety*	*Tolerability*	*Effectiveness*	*Average monthly cost**
Aspirin	Intracranial hemorrhage: 0.49%[21]; major bleeding: 0.8%[19]; GI bleeding: 3.0%[18]; possibility of aspirin allergy[22]	GI upset: 17.6%[21]	Stroke or death: NNT = 22 (versus placebo)[17] Stroke, MI, or vascular death: NNT = 28 (versus placebo)[16]	$1 to 2
Aspirin and clopidogrel (Plavix)	Major bleeding: 2%[25]; life-threatening bleeding: 3%[25]; possibility of aspirin allergy[22]	GI upset, diarrhea, rash	No difference in effectiveness (versus aspirin)[25]	$141 to 142
Aspirin and dipyridamole (Aggrenox)	Intracranial hemorrhage: 0.8%[29]; extracranial hemorrhage: 1.7%[29]; possibility of aspirin allergy[22,27]	Headache: 26%; GI upset[28,29]	Death from all vascular causes, nonfatal stroke: NNT = 33 (versus aspirin)[29]	$142
Clopidogrel	Intracranial hemorrhage: 0.35%[21]; life-threatening bleeding: 1.0%[25]; GI bleeding: 2.0%[21]	GI upset: 15%; diarrhea: 4.5%; rash: 6.0%[21]	Stroke, MI, vascular death: NNT = 196[21]	$140
Warfarin (Coumadin)	Major bleeding: 2.2%; minor bleeding: 20.8%[32]	—	No difference in effectiveness (versus aspirin)[32]	$19 to 20 (generic) $28 (brand)

GI = gastrointestinal; NNT = number needed to treat; MI = myocardial infarction.

**—Estimated cost to the pharmacist based on average wholesale prices (rounded to the nearest dollar) in Red Book. Montvale, N.J.: Medical Economics Data, 2006. Cost to the patient will be higher, depending on prescription filling fee.*

Information from references 16 through 19, 21, 22, 25, 27 through 29, and 32.

Table 3. Indications for Carotid Artery Endarterectomy

Degree of stenosis (%)	*Patient factors**	*Eligibility for surgery†*
> 75	Stable patient; symptomatic disease	Surgery clearly indicated
50 to 75	Younger than 75 years; hemispheric symptoms rather than transient monocular blindness; intracranial stenosis; male; presence of collaterals; recent stroke (within two weeks); symptomatic disease	Surgery based on risk/benefit ratio
< 50	—	Surgery clearly not indicated

**—Patient factors listed make the patient a better candidate for carotid artery endarterectomy. These factors are not absolutely necessary for the performance of the procedure.*

†—Recommend using a surgeon with perioperative morbidity and mortality of less than 6 and 3 percent, respectively.

Information from references 4 and 34.

clopidogrel and aspirin should only be used in patients with recent acute coronary syndromes or after coronary stenting because this regimen increases the risk of bleeding in patients with ischemic stroke.[4] Warfarin should be reserved for patients who cannot tolerate antiplatelet agents.[4,5] There is no evidence to guide the treatment decision for patients who experience an ischemic stroke while taking aspirin. Expert opinion recommends switching to dipyridamole and aspirin or clopidogrel in this situation.[4]

Surgical Treatment for Patients with Atherosclerosis

Three types of surgical interventions are available for treatment of patients with ischemic stroke and carotid atherosclerosis documented by radiologic techniques. They are carotid endarterectomy, extracranial/intracranial bypass, and carotid artery balloon angioplasty and stenting.[4,34] Carotid endarterectomy is the best-studied surgical intervention. It has been shown to prevent stroke compared with medical management in carefully selected patients. Only certain patients will benefit from surgery, based on degree of stenosis and other risk factors *(Table 3)*.[4,34]

A recent RCT showed that patients with carotid artery balloon angioplasty and stenting had higher rates of death and recurrent stroke than patients with carotid endarterectomy.[35] Because of this increased risk, carotid artery balloon angioplasty and stenting may only benefit patients with severe stenosis (more than 75 percent) who have a history of trauma or surgeries to the neck that make them difficult to access with carotid endarterectomy or re-stenosis after carotid endarterectomy.[35] Carotid artery balloon angioplasty and stenting should only be used in centers with experience with the surgery. Extracranial/intracranial bypass is not routinely recommended.

The Authors

LORI M. DICKERSON, PharmD, is a professor in the Trident Medical Center/Medical University of South Carolina Family Medicine Residency Program in Charleston. She received a doctorate of pharmacy from and completed a clinical pharmacy residency in family medicine at the Medical University of South Carolina. Dr. Dickerson also is a fellow of the American College of Clinical Pharmacists, and is a board-certified pharmacotherapy specialist.

PETER J. CAREK, MD, MS, is a professor in and director of the Trident Medical Center/Medical University of South Carolina Family Medicine Residency Program. He received his medical degree from and completed a family medicine residency at the Medical University of South Carolina. Dr. Carek completed a sports medicine fellowship at the Ohio Physical Therapy and Sports Medicine Clinic in Beachwood and earned a master's degree from the University of Tennessee in Knoxville.

ROBERT GLEN QUATTLEBAUM, MD, MPH, is a third-year resident in the Trident Medical Center/Medical University of South Carolina Family Medicine Residency Program. He received his medical degree and a master of public health degree from the University of North Carolina at Chapel Hill.

Address correspondence to Lori M. Dickerson, PharmD, Trident/MUSC Family Medicine Residency Program, 9298 Medical Plaza Dr., Charleston, SC 29406 (e-mail: macfarll@musc.edu). Reprints are not available from the authors.

Author disclosure: Nothing to disclose.

REFERENCES

1. Thom T, Haase N, Rosamond W, Howard VJ, Rumsfeld J, Manolio T, et al. Heart disease and stroke statistics—2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee [Published corrections appear in Circulation 2006;113:e696 and Circulation 2006;114:e630]. Circulation 2006;113:e85-e151.
2. Albers GW, Caplan LR, Easton JD, Fayad PB, Mohr JP, Saver JL, et al., for the TIA Working Group. Transient ischemic attack—proposal for a new definition. N Engl J Med 2002;347:1713-6.
3. Iwashyna TJ, Zhang JX, Christakis NA. Disease-specific patterns of hospice and related healthcare use in an incidence cohort of seriously ill elderly patients. J Palliat Med 2002;5:531-8.
4. Sacco RL, Adams R, Albers G, Alberts MJ, Benavente O, Furie K, et al. Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke: co-sponsored by the Council on Cardiovascular Radiology and Intervention: the American Academy of Neurology affirms the value of this guideline. Stroke 2006;37:577-617.

5. Albers GW, Amarenco P, Easton JD, Sacco RL, Teal P. Antithrombotic and thrombolytic therapy for ischemic stroke: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126(3 suppl):483S-512S.
6. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al., for the National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, and the National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report [Published correction appears in JAMA 2003;290:197]. JAMA 2003;289:2560-72.
7. Ruland S, Richardson D, Hung E, Brorson JR, Cruz-Flores S, Felton WL 3rd, et al., for the AAASPS Investigators. Predictors of recurrent stroke in African Americans. Neurology 2006;67:567-71.
8. Lovett JK, Coull AJ, Rothwell PM. Early risk of recurrence by subtype of ischemic stroke in population-based incidence studies. Neurology 2004;62:569-73.
9. Rashid P, Leonardi-Bee J, Bath P. Blood pressure reduction and secondary prevention of stroke and other vascular events: a systematic review. Stroke 2003;34:2741-8.
10. Adams HP Jr, Adams RJ, Brott T, del Zoppo GJ, Fulan A, Goldstein LB, et al. Guidelines for the early management of patients with ischemic stroke: a scientific statement from the Stroke Council of the American Stroke Association. Stroke 2003;34:1056-83.
11. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack [Published corrections appear in Lancet 2001;358:1556 and Lancet 2002;359:2120]. Lancet 2001;358:1033-41.
12. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38 [Published correction appears in BMJ 1999;318:29]. BMJ 1998;317:703-13.
13. Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, et al., for the National Heart, Lung, and Blood Institute, American College of Cardiology Foundation, American Heart Association. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines [Published correction appears in Circulation 2004;110:763]. Circulation 2004;110:227-39.
14. Collins R, Armitage J, Parish S, Sleight P, Peto R, for the Heart Protection Study Collaborative Group. Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20,536 people with cerebrovascular disease or other high-risk conditions. Lancet 2004;363:757-67.
15. Amarenco P, Bogousslavsky J, Callahan A III, Goldstein LB, Hennerici M, Rudolph AE, et al., for the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators. High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med 2006;355:549-59.
16. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients [Published correction appears in BMJ 2002;324:141]. BMJ 2002;324:71-86.
17. The SALT Collaborative Group. Swedish Aspirin Low-Dose Trial (SALT) of 75 mg aspirin as secondary prophylaxis after cerebrovascular ischaemic events. Lancet 1991;338:1345-9.
18. Serebruany VL, Steinhubl SR, Berger PB, Malinin AI, Baggish JS, Bhatt DL, et al. Analysis of risk of bleeding complications after different doses of aspirin in 192,036 patients enrolled in 31 randomized controlled trials. Am J Cardiol 2005;95:1218-22.
19. Berger JS, Roncaglioni MC, Avanzini F, Pangrazzi I, Tognoni G, Brown DL. Aspirin for the primary prevention of cardiovascular events in women and men: a sex-specific meta-analysis of randomized controlled trials [Published correction appears in JAMA 2006;295:2002]. JAMA 2006;295:306-13.
20. U.S. Preventive Services Task Force. Aspirin for the primary prevention of cardiovascular events: recommendations and rationale. Accessed March 9, 2007, at: http://www.ahrq.gov/clinic/3rduspstf/aspirin/asprr.htm.
21. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet 1996;348:1329-39.
22. Plavix—clopidogrel bisulfate tablets [Prescribing information]. New York, N.Y.: Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership, 2006. Accessed March 9, 2007, at: http://products.sanofi-aventis.us/plavix/plavix.html.
23. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK, for the Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation [Published corrections appear in N Engl J Med 2001;345:1716 and N Engl J Med 2001;345:1506]. N Engl J Med 2001;345:494-502.
24. Steinhubl SR, Berger PB, Mann JT 3rd, Fry ET, DeLago A, Wilmer C, et al., for the CREDO Investigators. Clopidogrel for the reduction of events during observation. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial [Published correction appears in JAMA 2003;289:987]. JAMA 2002;288:2411-20.
25. Diener HC, Bogousslavsky J, Brass LM, Cimminiello C, Csiba L, Kaste M, et al., for the MATCH Investigators. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. Lancet 2004;364:331-7.
26. Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE, et al., for the CHARISMA Investigators. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. N Engl J Med 2006;354:1706-17.
27. Aggrenox (aspirin/extended-release dipyridamole) [Prescribing information]. Ridgefield, Conn.: Boehringer Ingelheim Pharmaceuticals, Inc., 2006. Accessed March 9, 2007, at: http://bidocs.com/renetnt:/Prescribing+Information/PIs/Aggrenox+Caps/Aggrenox.pdf.
28. Diener HC, Cunha L, Forbes C, Sivenius J, Smets P, Lowenthal A. European Stroke Prevention Study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. J Neuro Sci 1996;143:1-13.
29. Halkes PH, van Gijn J, Kappelle LJ, Koudstaal PJ, Algra A, for the ESPRIT Study Group. Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial [Published correction appears in Lancet 2007;369:274]. Lancet 2006;367:1665-73.
30. Diener HC. Prevention regimen for effectively avoiding second strokes. Accessed March 9, 2007, at: http://www.strokecenter.org/trials/TrialDetail.aspx?tid=495.
31. Diener HC, Darius H, Bertrand-Hardy JM, Humphreys M. Cardiac safety in the European Stroke Prevention Study 2 (ESPS2). Int J Clin Pract 2001;55:162-3.
32. Mohr JP, Thompson JL, Lazar RM, Levin B, Sacco RL, Furie KL, et al., for the Warfarin-Aspirin Recurrent Stroke Study Group. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. N Engl J Med 2001;345:1444-51.
33. Chimowitz MI, Lynn MJ, Howlett-Smith H, Stern BJ, Hertzberg VS, Frankel MR, et al., for the Warfarin-Aspirin Symptomatic Intracranial Disease Trial Investigators. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. N Engl J Med 2005;352:1305-16.
34. Chaturvedi S, Bruno A, Feasby T, Holloway R, Benavente O, Cohen SN, et al. Carotid endarterectomy—an evidence-based review: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2005;65:794-801.
35. Mas JL, Chatellier G, Beyssen B, Branchereau A, Moulin T, Becquemin JP, et al., for the EVA-3S Investigators. Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis. N Engl J Med 2006;355:1660-71.