Update on Pharmacologic Therapy for Secondary Stroke Prevention with a Focus on Antiplatelet Strategies

Kiwon Lee, MD
Carissa Pineda, MD
David G. Brock, MD
Rodney Bell, MD

In the United States, a stroke occurs every 45 seconds, and a fatal stroke occurs every 3 minutes. Stroke is the third leading cause of death and the leading cause of long-term disability in the United States. It accounted for $57.8 billion in direct and indirect health care costs in 2005, and a similar estimate was reported for 2006.[1] Ischemia is the most common etiology of stroke, accounting for 88% of cases, with hemorrhage accounting for the remaining 12%.[1]

Of the 700,000 strokes that occur yearly in the United States, 200,000 are recurrent events.[1] The risk of recurrent stroke has been reported as 11.5% at 7 days, 6% to 15% at 30 days, and 18.5% at 3 months.[2,3] Following a transient ischemic attack (TIA), the estimated risk of recurrent stroke was 8% at 7 days, 11.5% at 1 month, and 17.3% at 3 months.[3] Given this increased risk, secondary stroke prevention is crucial. Preventive measures instituted at the time of hospital discharge may have the greatest impact on stroke prevention because patients appear to be at highest risk for recurrent stroke during the first 3 months after the initial event[1,3] and because instituting medications in the hospital after a serious event has been shown to optimize patient adherence to therapy.[4] Therefore, the physician treating an inpatient for acute stroke may be best positioned to initiate critical pharmacologic agents to prevent recurrence.

It has been shown that only 11.3% of stroke patients are managed solely by a neurologist.[5] Hospitalists frequently provide most, if not all, of the care for a stroke patient and are likely to care for the majority of acute stroke patients in the United States, with or without assistance from a neurologist.[6] Therefore, the hospitalist will likely be responsible for instituting critical secondary stroke prevention measures at the time of a patient's hospital discharge. Practicing hospitalists should stay abreast of evidence for secondary stroke prevention measures as the growing number of stroke

TAKE HOME POINTS

- Following a first transient ischemic attack (TIA) or stroke, aspirin, clopidogrel, and aspirin plus extended-release dipyridamole (ER-DP) are acceptable initial therapy for secondary stroke prevention.
- Evidence suggests that clopidogrel and aspirin plus ER-DP have increased efficacy and similar safety in secondary stroke prevention compared with aspirin monotherapy.
- There is no added benefit of aspirin plus clopidogrel for secondary stroke prevention. Routine use of such therapy is not recommended due to an increased risk of symptomatic hemorrhage.
- Antihypertensive therapy for secondary stroke prevention leads to a relative risk reduction of 30% to 40%.
- Patients with ischemic stroke or TIA should be treated with a statin to a low-density lipoprotein level below 100 mg/dL, and below 70 mg/dL for patients with multiple risk factors.
- Warfarin should be prescribed in patients with clear evidence of cardiogenic thrombus and cardioembolic stroke and in those with paroxysmal or chronic atrial fibrillation in the absence of contraindications.

At the time this article was written, Dr. Lee was an assistant professor in neurology and neurosurgery and director of the neuro-intensive care unit, Jefferson Medical College, Philadelphia, PA; he is currently an assistant professor of neurology and neurosurgery, Division of Stroke and Critical Care, Columbia University College of Physicians and Surgeons, New York, NY. Dr. Pineda is an assistant professor of neurology; Dr. Brock is an assistant professor of neurology; and Dr. Bell is a professor of neurology and chief, Division of Cerebrovascular Disease and Neurocritical Care; all are at Jefferson Medical College.

survivors in the United States[1] will likely fall under their care.

OVERVIEW OF SECONDARY STROKE PREVENTION

Secondary stroke prevention is focused on the treatment of modifiable independent risk factors for stroke.[1,7] Lifestyle modifications should be encouraged in all patients in addition to initiating pharmacologic therapy. Smoking, excessive consumption of alcoholic beverages, obesity (particularly central obesity), and physical inactivity are associated with stroke risk. Smoking cessation should be stressed in patients who have smoked in the past year, and smoking cessation aids should be made available to these patients. Patients also should be advised to limit alcohol intake to 2 drinks per day for men and 1 drink per day for nonpregnant women. Clinicians should recommend that patients exercise—ideally, 30 minutes of moderate intensity exercise most days of the week or supervised exercise for those with disabilities—and balance caloric intake to lose weight or maintain a body mass index of 18.5 to 24.9 kg/m^2 and a waist circumference of less than 35 in for women and less than 40 in for men.[1,7]

Emerging risk factors, such as exogenous estrogen therapy, have been correlated with increased stroke risk and should be discontinued in patients who have had a stroke or TIA.[7] Elevated homocysteine levels also have been associated with increased risk of cardiovascular disease and stroke. However, lowering homocysteine levels with folic acid therapy, with or without vitamins B_6 and B_{12}, has not been shown to decrease cardiovascular or stroke risk in published trials.[7–9]

For patients with symptomatic carotid artery stenosis, revascularization by surgical intervention may be indicated to decrease the risk of recurrent stroke.[10] The conventional method, carotid endarterectomy, has been the mainstay of surgical intervention. Recently, however, less invasive surgical treatment using an endovascular technique with balloon angioplasty and stenting has become an option.[11]

Tight control of serum glucose to near normal levels in patients with diabetes will decrease risk of microvascular complications and may reduce macrovascular complications. Patients with diabetes should maintain a hemoglobin A_{1C} of 7% or less.

Core pharmacologic therapy for secondary stroke prevention comprises antithrombotic therapy with either antiplatelet or anticoagulant agents as indicated and tight control of blood pressure and lipid levels.[7] The following sections will review the key evidence for each component of pharmacologic therapy for stroke prevention and summarize recommendations from current guidelines regarding their use in patients who have experienced a stroke.

ANTIPLATELET THERAPY

Because disruption of atherosclerotic plaque and subsequent thrombosis is the main pathophysiology of stroke, antithrombotic therapy is a cornerstone of therapy for treatment and secondary prevention. All patients with noncardioembolic stroke or TIA should receive treatment with an antiplatelet agent for secondary prevention.[7,12] A meta-analysis of 21 trials comparing 18,270 patients receiving antiplatelet agents with patients receiving placebo for secondary prevention showed a 28% relative odds reduction in nonfatal strokes and a 16% reduction in fatal strokes.[13] There are currently 4 antiplatelet agents that have shown efficacy and are approved by the US Food and Drug Administration (FDA) for secondary stroke prevention: aspirin, ticlopidine, clopidogrel, and the combination of aspirin and extended-release dipyridamole (ER-DP). These agents decrease platelet aggregation through varying mechanisms of action. Aspirin acts by irreversibly inhibiting the cyclooxygenase enzyme, blocking the prostaglandin-mediated pathway of platelet activation. Ticlopidine and clopidogrel are structurally related thienopyridines that selectively inhibit adenosine diphosphate–induced platelet aggregation.[14] Clopidogrel has essentially replaced ticlopidine in clinical practice because of its similar efficacy and superior hematologic safety profile. Dipyridamole is a potent vasodilator and antiplatelet agent that may exhibit antiplatelet effects by inhibiting phosphodiesterases or blocking uptake of adenosine.[14] ER-DP is approved for secondary stroke prevention combined with aspirin therapy. The decision to choose an agent or a combination of agents should be the result of careful clinical judgment based on knowledge of currently available clinical evidence, patient-specific factors, and cost.

Aspirin

A meta-analysis of 11 randomized, placebo-controlled studies showed that aspirin monotherapy appears to reduce the incidence of stroke recurrence by 15% (relative risk [RR], 0.85; 95% confidence interval [CI], 0.77–0.94) and that efficacy seems consistent across doses from 50 to 1500 mg/day.[13,15] Aspirin doses of less than 75 mg/day have been suggested to be more desirable because they "spare" prostacyclin (a platelet antiaggregant and potent vasodilator) and are associated with less gastrotoxicity.[13] The incidence of total bleeding, especially gastrointestinal bleeding, has been correlated to dose in a large meta-analysis in which the incidence of bleeding was

Table 1. Grading System for Evidence

American College of Chest Physicians Guidelines (2004)[12]		American Heart Association/American Stroke Association Guidelines (2006)[7]	
1A	Clear benefit shown in RCTs	I	Evidence or agreement there is benefit
1C+	No RCTs, but strong results are extrapolated or observational studies show clear overwhelming benefit	II	Conflicting evidence/divergence of opinion on benefit
		IIA	Weight of evidence or opinion in favor of procedure/treatment
1B	Clear benefit from RCTs with inconsistent results or methodological flaws	IIB	Usefulness less well established by evidence or opinion
1C	Clear benefit from observational studies	III	General agreement or evidence that treatment is not beneficial and/or may be harmful
2A	Unclear benefit in RCTs		
2C+	Unclear benefit extrapolated or from observational studies	Level A	Data from multiple RCTs
2B	Unclear benefit from RCTs with inconsistent results or methodological flaws	Level B	Data from a single randomized study or nonrandomized studies
2C	Unclear benefit from observational studies	Level C	Expert opinion or case studies

RCTs = randomized, controlled trials.

3.6% when the dose was less than 100 mg/day and 9.1% when the dose was 100 to 325 mg/day.[16] Major bleeding incidence has not been well correlated to aspirin dose; however, these studies may have been underpowered to detect this difference.[13,15,16]

Recurrent thrombotic episodes occur while patients are on aspirin at a rate of 2% to 6% per year.[17] Aspirin resistance is a poorly understood concept, but it has been considered to mean any of the following: (1) failure to obtain the expected aspirin-induced abnormalities by classic platelet aggregation studies; (2) failure to prolong closure time with the Platelet Function Analyzer; and (3) failure to decrease thromboxane B_2 levels.[18] The prevalence of aspirin resistance appears to be approximately 15%.[19] The explanation for aspirin resistance is unclear, although several potential mechanisms have been postulated. These include mutations in cyclooxygenase-1, increased available thromboxane A_2, and drug interference with nonsteroidal anti-inflammatory drugs.[18] The ultimate clinical significance of aspirin resistance is unclear, but it may have increasing therapeutic implications because aspirin is likely to be taken over a long length of time.

Current guidelines from the American College of Chest Physicians (ACCP)[12] as well as from the American Heart Association/American Stroke Association (AHA/ASA)[7] recommend aspirin 50 to 325 mg/day for noncardioembolic ischemic stroke prevention (Grade 1A [ACCP] and Class IIA, Level of Evidence A [AHA/ASA]; *see* **Table 1** for an explanation of grading of evidence from the guidelines). The ACCP guidelines also state it may be prudent to use doses at the lower end of this range (ie, 50–100 mg/day), especially in patients at moderate to high risk for bleeding,[12] because there appears to be similar efficacy for secondary prevention of stroke and a lower risk of gastrotoxicity and bleeding.

Finally, timing of initiation of aspirin therapy is important. Two large randomized, placebo-controlled efficacy trials demonstrated that aspirin therapy should be initiated as soon as possible, ideally within the first 24 hours after acute stroke onset, and continued over the long term to prevent stroke recurrence or death.[20,21]

Clopidogrel

The Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial compared aspirin 325 mg/day with clopidogrel 75 mg/day in 19,185 patients with atherosclerotic vascular disease. The results showed a significant RR reduction of 8.7% with clopidogrel in the composite endpoint of ischemic stroke, myocardial infarction (MI), or vascular death.[22] However, these results were primarily driven by the results of the peripheral vascular disease cohort, whereas in the ischemic stroke cohort there was only a nonsignificant trend toward benefit with clopidogrel. The safety of clopidogrel appeared to be similar to that of aspirin therapy.[22] A post hoc analysis of CAPRIE evaluating clopidogrel versus aspirin in patients with a history of cerebrovascular accident or MI showed a significant absolute risk reduction of ischemic stroke, MI, or vascular death of 3.4% with clopidogrel.[23] The authors concluded that clopidogrel has a more pronounced benefit over aspirin in this high-risk group. Current ACCP guidelines and AHA/ASA guidelines indicate that clopidogrel should be used in patients with hypersensitivity to aspirin (Grade 1C+ [ACCP] and Class IIa, Level of Evidence B [AHA/ASA]) and should be considered

instead of aspirin therapy (Grade 2B [ACCP] and Class IIb, Level of Evidence B [AHA/ASA].[7,12]

Two recent trials were designed to evaluate whether dual antiplatelet therapy with aspirin and clopidogrel was superior to monotherapy with either drug. The Management of Atherothrombosis with Clopidogrel in High-Risk Patients (MATCH)[24] study evaluated 7599 high-risk patients specifically for secondary stroke prevention. Patients received the combination of aspirin 75 mg/day plus clopidogrel 75 mg/day or clopidogrel monotherapy. Results showed a trend toward benefit in the dual antiplatelet therapy group for the primary composite cardiovascular endpoint (RR reduction, 6.4%; 95% CI, –4.6–16.3; $P = 0.244$) and reduction in ischemic stroke (RR reduction, 7.1%; 95% CI, –8.5–20.4; $P = 0.353$), but these results were not significant. There was a significant increase in the occurrence of life-threatening bleeding with combination therapy (RR, 1.26; 95% CI, 0.64–1.88; $P < 0.0001$).[24]

The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA)[25] trial examined 15,603 patients with clinically evident cardiovascular disease or multiple risk factors who were receiving the combination of aspirin (75–162 mg/day) and clopidogrel or aspirin monotherapy. These results echoed those of the MATCH trial. There was no significant difference between groups in the primary endpoint, which was a composite of MI, stroke, or cardiovascular death. There was a suggestion of benefit for dual antiplatelet therapy in patients with evidence of cardiovascular disease, although the results were only marginally significant (RR, 0.88; 95% CI, 0.77–0.998; $P = 0.046$). There was a trend toward a greater incidence of major bleeding (RR, 1.25; 95% CI, 0.97–1.61; $P = 0.09$) and a statistically significant increase in moderate bleeding in the combination group (RR, 1.62; 95% CI, 1.27–2.08; $P < 0.001$). Moderate bleeding was clinically significant bleeding that required transfusion.[25]

Taken together, the results of MATCH and CHARISMA indicate that clinicians should exercise great caution when considering the use of the combination of aspirin and clopidogrel therapy for secondary stroke prevention because of the lack of demonstrated superior efficacy, the increased risk of serious bleeding complications, and the increased cost compared with low-dose monotherapy with either agent. The AHA/ASA guidelines state that the addition of aspirin to clopidogrel increases the risk of hemorrhage and is not routinely recommended for patients with ischemic stroke or TIA (Class III, Level of Evidence A).[7]

It should be noted that there are several exceptions which may compel clinicians to institute dual aspirin/clopidogrel therapy for secondary stroke prevention. The landmark Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial demonstrated that the addition of clopidogrel to aspirin in patients with a recent non–ST elevation MI significantly decreased the risk of a composite of cardiovascular death, MI, or stroke, with a small increase in risk of major bleeding.[26] This combination may be appropriate for cerebrovascular patients who have a history of recent cardiac ischemia and appear to be at low risk for hemorrhagic complications, especially if they have suffered a recurrent stroke while on another antiplatelet therapy. Patients with symptomatic intracranial stenosis are usually treated with an antiplatelet agent initially, followed by oral anticoagulation if the initial antiplatelet therapy fails. If the oral anticoagulation therapy fails, they may be offered an endovascular treatment with balloon angioplasty and stenting. The FDA has recently granted humanitarian device exemption approval for a self-expanding stent (Wingspan Stent System, Boston Scientific) for use in patients who are at high risk of recurrent strokes with known intracranial stenosis. It is our experience that the use of combination antiplatelet therapy is appropriate for patients who have received intracranial stenting in order to prevent thrombotic events.

The concept of clopidogrel resistance exists and was formulated because of reports of rethrombosis after stenting. Lack of the inhibition of the adenosine phosphate response has been documented in some patients.[18] The reason for this lack of response is unclear, although several mechanisms have been postulated: lack of good measurement guidelines, interaction with aspirin, receptor polymorphisms, differences in metabolism, and drug interactions.[18]

Aspirin Plus Extended-Release Dipyridamole

The first large trial evaluating the combination of aspirin and ER-DP, the European Stroke Prevention Study-2 (ESPS-2), evaluated aspirin plus ER-DP for secondary stroke prevention in 6602 patients with previous stroke or TIA.[27] Patients received either aspirin 25 mg twice daily, ER-DP 200 mg twice daily, the combination twice daily, or placebo, and patients were followed up for 2 years. Aspirin and ER-DP monotherapy reduced the risk of stroke by 18% and 16%, respectively, compared with placebo. Combination therapy with aspirin plus ER-DP reduced stroke risk by 37% compared with placebo. Thus, combination therapy was twice as effective as either agent alone in the secondary prevention of stroke after 2 years. The absolute risk reduction with the

combination of aspirin plus ER-DP in ESPS-2 was 3% after 2 years. A post hoc analysis by Sacco et al[28] stratified efficacy data by risk subgroup and found that patients at highest risk (eg, those with hypertension; those with prior stroke, TIA, or cardiovascular disease; current smokers) accrued the greatest benefit from the combination of aspirin and ER-DP therapy.

The most common adverse event experienced in patients receiving dipyridamole was headache.[27] This headache is upsetting to patients and may result in early discontinuation of an effective treatment strategy. The headache appears to be due to cerebral vascular dilatation[29] and is similar to that experienced by patients taking nitrates. It is characterized as bilateral, frontotemporal throbbing, is particularly evident during the first month of therapy, and usually resolves with chronic use.[30] One study demonstrated that initiating once daily aspirin/ER-DP at bedtime for the first 10 days of therapy, then titrating the dose to twice daily significantly decreased headaches and reduced patient discontinuation of therapy compared with initiating twice daily dosing.[30] Acetaminophen has been suggested as prophylaxis or treatment for dipyridamole-induced headaches. Lipton et al[31] showed that acetaminophen 1000 mg was no more effective than placebo for prevention or treatment, although the authors added that most headaches resolved in 2 hours without treatment, and thus there was a pronounced benefit with placebo.

Risk of bleeding was not increased with combination therapy compared with aspirin monotherapy in ESPS-2. Diener et al[32] performed a post hoc analysis of patients with coronary disease or history of MI at the time of enrollment in ESPS-2 to determine whether dipyridamole was associated with increased cardiac events in these patients. This analysis mitigated fears that dipyridamole may increase the number of cardiac events by causing cardiac "steal" and showed it was safe and beneficial in this population.

The European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT) included 2739 patients with history of stroke of arterial origin who received aspirin 30 to 325 mg/day (median, 75 mg/day) with or without dipyridamole 200 mg twice daily; ER-DP was used by 83% (n = 1131) of patients taking the combination regimen.[33] The primary composite cardiovascular endpoint occurred in 13% of patients taking combination therapy and 16% of patients taking aspirin monotherapy, demonstrating a benefit with the combination (hazard ratio, 0.80; 95% CI, 0.66–0.98). Addition of this data to the meta-analysis of previous trials resulted in an overall risk ratio of 0.82 for the composite of vascular-related death, stroke, or MI (95% CI, 0.74–0.91; **Figure**). There was no difference in bleeding between groups; however, more patients discontinued therapy in the combination group, mainly due to headache.[33]

The ESPS-2 and ESPRIT results are consistent and provide evidence that the combination of aspirin and ER-DP improves secondary stroke prevention and prevention of other vascular events following stroke or TIA compared with aspirin monotherapy, without increasing bleeding risk. Current guidelines recommend use of the combination of aspirin 25 mg and ER-DP 200 mg twice daily for initial therapy for patients with noncardioembolic stroke or TIA. They also suggest use of this combination over aspirin monotherapy (Grade 2A [ACCP] and Class IIa, Level of Evidence A [AHA/ASA]).[7,12]

Summary of Antiplatelet Data

The guidelines for antiplatelet therapy for secondary stroke prevention are summarized in **Table 2**.[7,12] Low-dose aspirin therapy remains acceptable due to its well-documented efficacy, low risk of serious adverse effects, and minimal cost. However, evidence suggests that clopidogrel and aspirin plus ER-DP have increased efficacy and similar safety in secondary stroke prevention compared with aspirin monotherapy. These therapies should be considered in all patients for secondary stroke prevention and given special consideration in high-risk patients[25] and in patients with a history of stroke or TIA while receiving aspirin therapy. Both regimens have demonstrated superior efficacy compared with aspirin monotherapy,[22,27,33] although no trials have specifically evaluated therapy for patients who have an event while taking aspirin therapy.

Aspirin plus ER-DP is currently recommended with a higher level of evidence than clopidogrel therapy[12] and is further supported by the recent ESPRIT results.[33] An indirect comparison of studies may demonstrate that the combination of aspirin and ER-DP is superior to clopidogrel therapy for secondary stroke prevention.[12] However, there are currently no head-to-head trials published evaluating clopidogrel versus aspirin plus ER-DP for secondary stroke prevention. The Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS; www.profess-study.com) trial, the largest secondary stroke prevention trial thus far, is comparing the efficacy and safety of aspirin plus ER-DP with clopidogrel, and the efficacy of telmisartan with placebo in secondary prevention of stroke.[34] PRoFESS represents the first head-to-head trial of alternative antiplatelet regimens to aspirin for secondary stroke prevention and aims to determine which (if any) is the superior regimen. More than 20,000 patients have

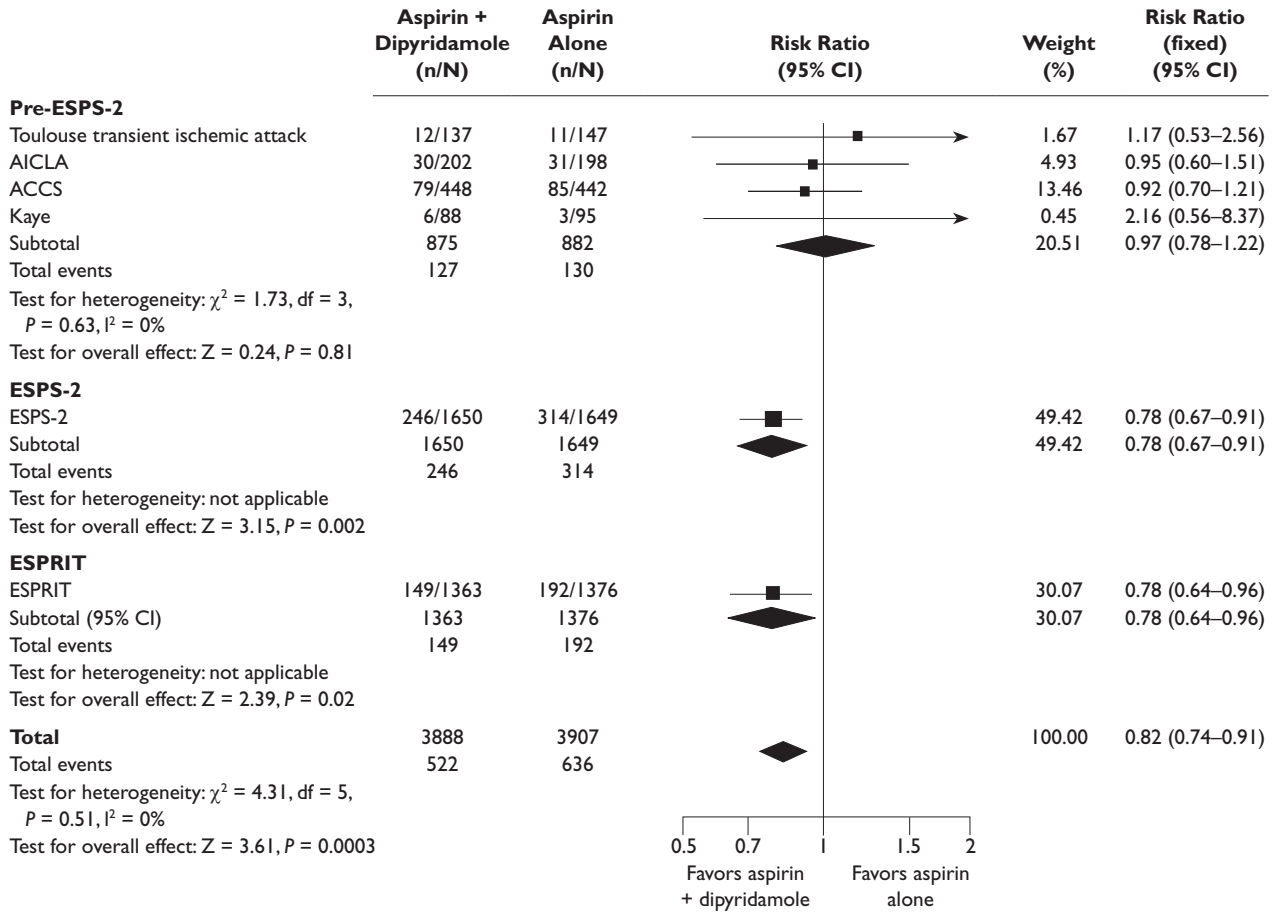

Figure. Meta-analysis for composite outcome of vascular death, nonfatal stroke, or nonfatal myocardial infarction in patients with cerebral ischemia. ACCS = American-Canadian Co-operative Study; AICLA = Accidents Ischémiques Cérébraux Liés à l'Athérosclérose; CI = confidence interval; ESPRIT = European/Australasian Stroke Prevention in Reversible Ischaemia Trial; ESPS-2 = European Stroke Prevention Study 2. (Reprinted from the ESPRIT Study Group. Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin [ESPRIT]: randomised controlled trial. Lancet 2006;367:1670. Copyright 2006, with permission from Elsevier.)

been recruited from 720 sites in 35 countries, and results are anticipated in 2008. Mean age of the patients is 66.3 years, 36% are women, 57.5% are white, and 32.5% are Asian. Patients in PRoFESS have a typical vascular risk profile: 73% with hypertension, 28% with diabetes, 47% with hyperlipidemia, and 17% with ischemic coronary artery disease; 21% are current smokers. According to the TOAST criteria, 28% had large vessel disease, 52% had small vessel disease, 2% had cardioembolism, 2% had other determined etiology, and 16% had stroke of undetermined etiology.

ANTICOAGULATION THERAPY

Warfarin therapy demonstrated similar efficacy to aspirin therapy for secondary stroke prevention in patients with noncardioembolic stroke or symptomatic intracranial stenosis in 2 recent trials.[35,36] However, treatment with warfarin was associated with a significantly higher risk of adverse bleeding events at an international normalized ratio goal of 2 to 3 and 3 to 4.5;[36,37] quality-of-life concerns are also associated with its use. In addition, the rates of death from vascular and nonvascular causes were higher in the warfarin group in 1 trial.[36] Therefore, current guidelines indicate that for most patients with noncardioembolic stroke or TIA, antiplatelet agents are recommended over oral anticoagulation (Grade 1A [ACCP] and Class I, Level of Evidence A [AHA/ASA]), unless the patient has concomitant prothrombotic conditions that require oral anticoagulation.[7,12]

Warfarin is recommended for secondary stroke prevention in patients with cardioembolic stroke or TIA,

Table 2. Summary of ACCP and AHA/ASA Guideline Recommendations for Antiplatelet Therapy for the Secondary Prevention of Noncardioembolic Stroke or Transient Ischemic Attack

	American College of Chest Physicians Guidelines (2004)	American Heart Association/American Stroke Association Guidelines (2006)
Antiplatelet agents	Recommended in all patients (Grade 1A)	Recommended rather than anticoagulants to reduce risk of recurrent stroke and cardiovascular events (Class I, Level of Evidence A) Insufficient data exist to make recommendations between agents other than aspirin
Aspirin	Recommended dose of 50–325 mg/day Recommended dose of 50–100 mg/day in patients with moderate to high risk of bleeding (Grade 1C+)	Recommended dose of 50–325 mg (Class IIa, Level of Evidence A) No evidence to support increasing the dose if patient has an event while on therapy or to change to a specific therapy No single agent or combination has been well studied in patients who have an event while receiving aspirin
Clopidogrel	Recommended over aspirin (Grade 2B) Recommended if patient has aspirin hypersensitivity (Grade 1C+)	Recommended over aspirin (Class IIb, Level of Evidence B) Reasonable if patient has aspirin hypersensitivity (Class IIa, Level of Evidence B) Monotherapy considered safe (Class IIa, Level of Evidence A) Addition to aspirin increases risk of hemorrhage and is not routinely recommended (Class III, Level of Evidence A)
Aspirin and extended-release dipyridamole	Recommended dose of 25/200 mg twice daily Recommended over aspirin (Grade 2A)	Considered safe and suggested over aspirin (Class IIa, Level of Evidence A)

most commonly secondary to atrial fibrillation (AF) (Grade 1A [ACCP] and Class I, Level of Evidence A [AHA/ASA]).[12] Warfarin has been shown to be superior to aspirin therapy for secondary stroke prevention in patients with nonrheumatic AF.[38] Although essentially a primary prevention study, a recent trial demonstrated superiority of warfarin over the combination of aspirin and clopidogrel therapy for stroke prevention in patients with AF.[39] Warfarin is indicated for secondary prevention of stroke or TIA in patients with other potential cardiogenic sources, such as mechanical prosthetic heart valves, and should be considered in patients with MI with left ventricular thrombus or dilated cardiomyopathy.[7]

Although warfarin is currently the most effective approved agent for prevention of stroke in patients with AF, its narrow therapeutic index, need for continuous laboratory monitoring, and extensive drug-drug and drug-diet interactions limit its usefulness. Therefore, the search continues for an equally efficacious agent that has a more predictable dose response and superior pharmacokinetic profile, thus requiring less aggressive monitoring. A potential future alternative to warfarin, with once or twice daily oral dosage and without need for adjustments, is the family of drugs known as direct thrombin inhibitors. Two studies, SPORTIF III and SPORTIF V (Stroke Prevention Using the Oral Direct Thrombin Inhibitor Ximelagatran in Patients with Atrial Fibrillation), compared ximelagatran with warfarin in patients with AF and showed noninferiority of ximelagatran in preventing stroke.[40,41] Ximelagatran patients had fewer hemorrhagic complications, and this drug has practical advantages of fixed dosing and no need for serologic monitoring. Unfortunately, 6% of patients receiving ximelagatran experienced an increase in liver enzymes greater than 3 times the upper limit of normal, and there were rare instances of liver failure. Because of this adverse effect, Exanta (melagatran/ximelagatran) was withdrawn from the market, and the manufacturers have terminated its development.

Current phase 3 trials are ongoing comparing warfarin therapy with a new oral direct thrombin inhibitor, dabigatran, in patients with AF and prior stroke or 1 additional risk factor. Dabigatran appears to have a predictable dose response, eliminating the need for regular laboratory monitoring and indicating minimal drug-drug and drug-diet interactions.

ANTIHYPERTENSIVE THERAPY

A meta-analysis of major randomized, controlled trials showed that antihypertensive therapy for secondary stroke prevention resulted in an approximately 30% to 40% reduction in the risk for stroke (Level of Evidence A).[42] However, the management of blood pressure during acute stroke is controversial. Blood pressure in the immediate post-stroke period is often elevated and is thought to be a compensatory mechanism to maximize cerebral perfusion. Therefore, it is standard practice to reduce or withhold antihypertensive therapy—except in extreme cases when systolic blood pressure is above 220 mm Hg or diastolic blood pressure is 120 to

140 mm Hg or when thrombolytics are warranted[7]—until the patient is stabilized.[43] Evidence defining the specific time period when it is safe to initiate chronic antihypertensive therapy after acute stroke is lacking, and clinical guidelines fail to comment on this dilemma. Clinically, we tend to initiate aggressive antihypertensive therapy after the hyperacute phase, approximately 72 hours following the initial stroke onset in most patients.

No specific antihypertensive agent has proved to be superior to all others for stroke protection.[43] Limited data exist specifically for antihypertensive therapies for secondary stroke prevention. The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) evaluated 6105 hypertensive and nonhypertensive patients with a history of stroke or TIA.[44] Patients received the angiotensin-converting enzyme (ACE) inhibitor perindopril with or without the diuretic indapamide (at the physician's discretion) or placebo. The combination of perindopril and indapamide reduced blood pressure by 12/5 mm Hg and stroke risk by 43% compared with placebo (95% CI, 30–54). Single-drug therapy decreased blood pressure by 5/3 mm Hg and produced no discernable reduction in stroke risk. Benefit was seen in patients who were hypertensive and nonhypertensive at study admission.

In a systematic review of 7 trials including 15,527 participants with stroke (ischemic or hemorrhagic) or TIA, antihypertensive medications were associated with reductions in all recurrent stroke, nonfatal recurrent stroke, MI, and all vascular events. These benefits were seen in hypertensive and nonhypertensive patients and were related to reductions in blood pressure.[45] The Evaluation of Acute Candesartan Cilexetil Therapy in Stroke Survivors (ACCESS) study, a small study not included in the systematic review, recruited 500 stroke patients requiring treatment of hypertension according to guidelines based on measurements taken within 36 hours after hospital admission. Cumulative 12-month mortality and number of vascular events differed significantly in favor of candesartan (odds ratio, 0.475; 95% CI, 0.252–0.895), leading investigators to stop the study after 342 patients had been randomized.[46]

Other studies have shown benefit for stroke prevention with ramipril,[47] losartan,[48] candesartan,[49] hydrochlorothiazide,[50] and amlodipine.[50] However, these studies were mainly primary prevention studies, as few subjects had a history of stroke or TIA, and occurrence of stroke was not the primary endpoint.

Current guidelines state that antihypertensive therapy is indicated for secondary stroke prevention and prevention of other vascular events in patients who are beyond the hyperacute period. Therapy should be considered in patients with and without hypertension. Benefit has been associated with a reduction of 10/5 mm Hg, and normal blood pressure has been defined as less than 120/80 mm Hg. The choice of drug should be patient specific; however, current data support the use of ACE inhibitors and diuretics.[7,43]

LIPID-LOWERING THERAPY

The Heart Protection Study Collaborative Group evaluated 20,536 patients with a history of coronary artery disease, diabetes, or other arterial occlusive disease receiving simvastatin 40 mg/day or placebo. In the subgroup enrolled with prior stroke or TIA and no other evidence of coronary artery disease, there was a 21% risk reduction in vascular events. This made the number needed to treat 102 per year to prevent 1 event. Benefit in this trial extended to patients with an initial low-density lipoprotein (LDL) cholesterol level below 116 mg/dL, in whom levels were lowered to below 77 mg/dL.[51,52] A meta-analysis of 38 randomized trials of lipid-lowering therapies for stroke prevention (83,161 patients; mean follow-up, 4.7 yr) demonstrated that statin drugs reduced rates of stroke and cardiovascular disease independent of cholesterol levels or individual statin drug.[53]

The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study was the first trial of statins for secondary stroke prevention in patients without other evidence of coronary artery disease. This trial evaluated 4732 patients with LDL cholesterol levels of 100 to 190 mg/dL who had stroke or TIA in the past 1 to 6 months and were receiving atorvastatin 80 mg/day or placebo. Atorvastatin was associated with a 16% risk reduction in the primary endpoint of time to occurrence of fatal or nonfatal stroke ($P = 0.03$); this risk reduction increased to 23% when TIAs were included in the endpoint ($P < 0.001$).[54]

These studies all lend support to the use of statin drugs for secondary stroke prevention. Current guidelines indicate that patients with ischemic stroke or TIA should be treated with a statin agent to an LDL level below 100 mg/dL[7,55] and below 70 mg/dL for very-high-risk patients with multiple risk factors (Class I, Level of Evidence A).[7,56] Patients with ischemic stroke and no indication for statin therapy (normal cholesterol levels, no history of coronary artery disease or atherosclerosis) are reasonable candidates for statin therapy (Class IIa, Level of Evidence B).[7] Given early benefits seen in trials, including patients with acute coronary syndromes, initiation of statins during hospitalization for first ischemic stroke of atherosclerotic origin is probably justified and may increase rates of long-term use.[52]

CONCLUSION

Stroke is a significant cause of morbidity and mortality that is best prevented by modification of patient risk factors. All patients who experience a noncardioembolic stroke or TIA should receive an antiplatelet agent unless there is a contraindication to therapy. Clopidogrel or the combination of aspirin plus ER-DP appear to be superior to aspirin monotherapy; however, head-to-head trials are necessary to identify the superior antiplatelet regimen. Results of the PRoFESS trial should provide more information regarding optimal antiplatelet therapy. Warfarin should be prescribed in patients with clear evidence of cardiogenic thrombus and cardioembolic stroke; those with either paroxysmal or chronic AF should be started on warfarin therapy in the absence of contraindications. Blood pressure–lowering therapy should be administered to all patients with stroke. ACE inhibitors and thiazide diuretics appear efficacious, but head-to-head trials are necessary to identify whether there is a superior antihypertensive agent. Finally, statin therapy should be administered to patients with ischemic stroke. Atorvastatin and simvastatin have demonstrated benefit, but data suggest that all statins may be beneficial. Hospitalists should expect to encounter more stroke patients because the number of available neurologists is limited and the number of stroke survivors is increasing. Hospitalists are best positioned to implement these critical, evidence-based secondary prevention measures at the time of patients' hospital discharge. **HP**

Test your knowledge and comprehension of this article with the *Clinical Review Quiz* on page 41.

Corresponding author: Kiwon Lee, MD, Stroke and Critical Care Division, Neurological Institute, Columbia University College of Physicians and Surgeons, 710 West 168th Street, Box 114, New York, NY 10032; KL2356@columbia.edu.

REFERENCES

1. 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 [published errata appear in Circulation 2006;113:e696 and 2006;114:e630]. Circulation 2006;113:e85–151.
2. Sacco RL, Shi T, Zamanillo MC, Kargman DE. Predictors of mortality and recurrence after hospitalized cerebral infarction in an urban community: the Northern Manhattan Stroke Study. Neurology 1994;44:626–34.
3. Coull AJ, Lovett JK, Rothwell PM; Oxford Vascular Study Investigators. Population based study of early risk of stroke after transient ischaemic attack or minor stroke: implications for public education and organisation of services. BMJ 2004;328:326.
4. Ovbiagele B, Saver JL, Fredieu A, et al. In-hospital initiation of secondary stroke prevention therapies yields high rates of adherence at follow-up. Stroke 2004;35:2879–83.
5. Ringal SP. The neurologist's role in stroke management [editorial]. Stroke 1996;27:1935–6.
6. Likosky DJ, Amin AN. Who will care for our hospitalized patients [letter]? Stroke 2005;36:1113–4.
7. Sacco RL, Adams R, Albers G, et al; American Heart Association; American Stroke Association Council on Stroke; Council on Cardiovascular Radiology and Intervention; American Academy of Neurology. Guidelines for the 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.
8. Bonaa KH, Njolstad I, Ueland PM, et al; NORVIT Trial Investigators. Homocysteine lowering and cardiovascular events after acute myocardial infarction. N Engl J Med 2006;354:1578–88.
9. Lonn E, Yusuf S, Arnold MJ, et al; Heart Outcomes Prevention Evaluation (HOPE) 2 Investigators. Homocysteine lowering with folic acid and B vitamins in vascular disease [published erratum appears in N Engl J Med 2006;355:746]. N Engl J Med 2006;354:1567–77.
10. Henderson RD, Eliasziw M, Fox AJ, et al. Angiographically defined collateral circulation and risk of stroke in patients with severe carotid artery stenosis. North American Symptomatic Carotid Endarterectomy Trial (NASCET) Group. Stroke 2000;31:128–32.
11. Yadav JS, Wholey MH, Kuntz RE, et al; Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy Investigators. Protected carotid-artery stenting versus endarterectomy in high-risk patients. N Engl J Med 2004;351:1493–501.
12. Albers GW, Amarenco P, Easton JD, et al. Antithrombotic and thrombolytic therapy for ischemic stroke: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126(3 Suppl):483S–512S.
13. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomized trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients [published erratum appears in BMJ 2002;324:141]. BMJ 2002;324:71–86.
14. Patrono C, Coller B, Fitzgerald GA, et al. Platelet-active drugs: the relationships among dose, effectiveness, and side effects: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126 (3 Suppl):234S–264S.
15. Johnson ES, Lanes SF, Wentworth CE 3rd, et al. A metaregression analysis of the dose-response effect of aspirin on stroke. Arch Intern Med 1999;159:1248–53.

16. Serebruany VL, Malinin AI, Eisert RM, Sane DC. Risk of bleeding complications with antiplatelet agents: meta-analysis of 338,191 patients enrolled in 50 randomized controlled trials. Am J Hematol 2004;75:40–7.
17. Sanderson S, Emery J, Baglin T, Kinmonth AL. Narrative review: aspirin resistance and its clinical implications. Ann Intern Med 2005;142:370–80.
18. Billett HH. Antiplatelet agents and arterial thrombosis. Clin Geriatr Med 2006;22:57–74, viii.
19. Bhatt DL. Aspirin resistance: more than just a laboratory curiosity [editorial]. J Am Coll Cardiol 2004;43:1127–9.
20. The International Stroke Trial (IST): a randomized trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischemic stroke. International Stroke Trial Collaborative Group. Lancet 1997;349: 1569–81.
21. CAST: randomised placebo-controlled trial of early aspirin use in 20,000 patients with acute ischemic stroke. CAST (Chinese Acute Stroke Trial) Collaborative Group. Lancet 1997;349:1641–9.
22. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. Lancet 1996;348:1329–39.
23. Ringleb PA, Bhatt DL, Hirsch AT, et al; Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events Investigators. Benefit of clopidogrel over aspirin is amplified in patients with a history of ischemic events. Stroke 2004;35:528–32.
24. Diener HC, Bogousslavsky J, Brass LM, et al; MATCH investigators. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischemic attack in high-risk patients (MATCH): randomized, double-blind, placebo-controlled trial. Lancet 2004;364:331–7.
25. Bhatt DL, Fox KAA, Hacke W, et al; CHARISMA Investigators. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. N Engl J Med 2006;354:1706–17.
26. Yusuf S, Zhao F, Mehta SR, et al; 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 errata appear in N Engl J Med 2001;345:1506 and 2001;345:1716]. N Engl J Med 2001;345:494–502.
27. Diener HC, Cunha L, Forbes C, et al. European Stroke Prevention Study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. J Neurol Sci 1996; 143:1–13.
28. Sacco RL, Sivenius J, Diener HC. Efficacy of aspirin plus extended-release dipyridamole in preventing recurrent stroke in high-risk populations. Arch Neurol 2005;62: 403–8.
29. Kruuse C, Jacobsen TB, Lassen LH, et al. Dipyridamole dilates large cerebral arteries concomitant to headache induction in healthy subjects. J Cereb Blood Flow Metab 2000;20:1372–9.
30. Chang YJ, Ryu SJ, Lee TH. Dose titration to reduce dipyridamole-related headache. Cerebrovasc Dis 2006;22: 258–62.
31. Lipton RB, Bigal ME, Kolodner KB, et al. Acetaminophen in the treatment of headaches associated with dipyridamole-aspirin combination. Neurology 2004;63:1099–101.
32. Diener HC, Darius H, Bertrand-Hardy JM, Humphreys M; European Stroke Prevention Study 2. Cardiac safety in the European Stroke Prevention Study 2 (ESPS2). Int J Clin Pract 2001;55:162–3.
33. Halkes PH, van Gijn J, Kappelle LJ, et al; ESPRIT Study Group. Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial [published erratum appears in Lancet 2007;369:274]. Lancet 2006;367:1665–73.
34. Diener HC. Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS) baseline results. Presented at the Joint World Congress on Stroke: International Stroke Society, Mediterranean Stroke Society and Southern African Stroke Foundation; 2006 Oct 26–29; Cape Town, South Africa. Available at http://www.kenes.com/stroke2006/2nd_Announcement.pdf. Accessed 30 May 2007.
35. Mohr JP, Thompson JL, Lazar RM, et al; 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.
36. Chimowitz MI, Lynn MJ, Howlett-Smith H, et al; 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.
37. A randomized trial of anticoagulants versus aspirin after cerebral ischemia of presumed arterial origin. The Stroke Prevention in Reversible Ischemia Trial (SPIRIT) Study Group. Ann Neurol 1997;42:857–65.
38. Secondary prevention in non-rheumatic atrial fibrillation after transient ischemic attack or minor stroke. EAFT (European Atrial Fibrillation Trial) Study Group. Lancet 1993; 342:1255–62.
39. Connolly S, Pogue J, Hart R, et al. ACTIVE Writing Group on behalf of the ACTIVE Investigators. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial Fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. Lancet 2006;367:1903–12.
40. Olsson SB; Executive Steering Committee on behalf of the SPORTIF III Investigators. Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in patients with non-valvular atrial fibrillation (SPORTIF III): randomised controlled trial. Lancet 2003;362:1691–8.
41. Albers GW, Diener HC, Frison L, et al; SPORTIF Executive Steering Committee for the SPORTIF V Investigators. Ximelagatran vs warfarin for stroke prevention in patients with nonvalvular atrial fibrillation: a randomized trial. JAMA 2005;293:690–8.
42. Psaty BM, Smith NL, Siscovick DS, et al. Health outcomes associated with antihypertensive therapies used as

first-line agents. A systematic review and meta-analysis. JAMA 1997;277:739–45.
43. Chobanian AV, Bakris GL, Black HR, et al; Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute. National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003;42:1206–52.
44. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischemic attack [published errata appear in Lancet 2001;358:1556 and 2002;359:2120]. Lancet 2001; 358:1033–41.
45. Rashid P, Leonardi-Bee J, Bath P. Blood pressure reduction and secondary prevention of stroke and other vascular events: a systematic review. Stroke 2003;34:2748–9.
46. Schrader J, Luders S, Kulschewski A, et al; Acute Candesartan Cilexetil Therapy in Stroke Survivors Study Group. The ACCESS Study: evaluation of Acute Candesartan Cilexetil Therapy in Stroke Survivors. Stroke 2003;34: 1699–703.
47. Yusuf S, Sleight P, Pogue J, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators [published errata appear in N Engl J Med 2000;342:748 and 2000;342:1376]. N Engl J Med 2000;342:145–53.
48. Kizer JR, Dahlof B, Kjeldsen SE, et al. Stroke reduction in hypertensive adults with cardiac hypertrophy randomized to losartan versus atenolol: the Losartan Intervention for endpoint reduction in hypertension study. Hypertension 2005;45:46–52.
49. Papademetriou V, Farsang C, Elmfeldt D, et al; Study on Cognitive and Prognosis in the Elderly study group. Stroke prevention with the angiotensin II type-1 receptor blocker candesartan in elderly patients with isolated systolic hypertension: the study on cognition and prognosis in the elderly (SCOPE). J Am Coll Cardiol 2004;44:1175–80.
50. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [published errata appear in JAMA 2003;289:178 and JAMA 2004;29:1296]. JAMA 2002; 288:2981–97.
51. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,356 high-risk individuals: a randomized placebo-controlled trial. Lancet 2002;360:7–22.
52. Stroke Council, American Heart Association; American Stroke Association. Statins after ischemic stroke and transient ischemic attack: an advisory statement from the Stroke Council, American Heart Association and American Stroke Association. Stroke 2004;35:1023.
53. Corvol JC, Bouzamondo A, Sirol M, et al. Differential effects of lipid-lowering therapies on stroke prevention: a meta-analysis of randomized trials. Arch Intern Med 2003; 163:669–76.
54. Amarenco P, Bogousslavsky J, Callahan A 3rd, et al; 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.
55. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2486–97.
56. Grundy SM, Cleeman JI, Merz NB, et al; National Heart, Lung, and Blood Institute; American College of Cardiology Foundation; American Heart Association. Implications of recent clinical trails for the National Cholesterol Education Program Adult Treatment Panel III guidelines [published erratum appears in Circulation 2004;110:763]. Circulation 2004;110:227–39.

Call for Submissions to *Image Clinic*

The editors of *Hospital Physician* are currently seeking submissions of original, high-quality images (photographs, photomicrographs, radiographs, scans, ECGs, etc) for the Image Clinic feature. Priority will be given to images that are both visually and clinically interesting, and images of common and uncommon conditions will be considered. A paragraph or two of text (≤ 300 words) should describe the clinical context in which the image was obtained as well as explain what the image illustrates and why it is important. Up to 5 references should be included. For images showing a patient, signed informed consent must be obtained from the patient and submitted with the manuscript.

Prior to submission, we ask that authors read the *Hospital Physician* Information for Authors (available at www.turner-white.com) on how to prepare and submit images and manuscripts to the journal. Please contact the Editor, Robert Litchkofski, with any comments, suggestions, or questions (rlitchkofski@turner-white.com).