Choices in Medical Management for Prevention of Acute Ischemic Stroke

James D. Fleck, MD, and José Biller, MD

Address
Department of Neurology, Indiana University School of Medicine, 541 Clinical Drive, CL 365, Indianapolis, IN 46202, USA.
E-mail: jdfleck@iupui.edu

Current Neurology and Neuroscience Reports 2001, **1:**33–38
Current Science Inc. ISSN 1528-4042

Stroke is a leading cause of death and disability. Although advances are being made in the treatment of acute ischemic stroke, its prevention is equally as important. Identification and management of risk factors are essential. Medical therapy is also helpful in the secondary prevention of ischemic stroke. There are currently four platelet-antiaggregating agents used to prevent ischemic stroke: aspirin, aspirin plus dipyridamole, clopidogrel, and ticlopidine. The relevant studies proving their efficacy are noted, as are some of their similarities and differences. The use of warfarin is also discussed.

Introduction

Stroke is a leading cause of death and disability. It is estimated that approximately 600,000 people suffer a new or recurrent stroke each year in the United States. Stroke killed an estimated 160,000 people in the United States in 1996 and ranks behind only heart disease and cancer as the leading cause of death [1]. Ischemic stroke accounts for approximately 80% to 85% of all strokes [2]. Significant advances have been made in the past few years regarding the acute treatment of ischemic stroke. Perhaps most notable is the use of intravenous tissue plasminogen activator (tPA), which was approved for the treatment of acute ischemic stroke by the United States Food and Drug Administration (FDA) in 1996. More recently, intra-arterial pro-urokinase and intravenous ancrod were shown to be effective in selected patients with ischemic stroke [3••,4••]. Although it appears our armamentarium to treat patients with acute ischemic stroke is growing, it is important to keep in mind that stroke prevention still plays a crucial role. We cannot forget the importance of risk factor management. Newer techniques such as cerebrovascular angioplasty and stenting may complement carotid endarterectomy in patients with significant cerebrovascular atherosclerotic disease. This article concentrates on the choices in medical management for preventing ischemic stroke, and focuses on secondary prevention. We discuss the platelet antiaggregating drugs, as they are the mainstays in the prevention of stroke in arterial atherothromboembolic disease. However, we also discuss other interventions, such as warfarin therapy, and some relatively new risk factor treatments.

Platelet Antiaggregants

Aspirin

Aspirin (ASA) works by irreversibly inhibiting platelet cyclooxygenase, which prevents the formation of thromboxane A2, a potent vasoconstrictor and inducer of platelet aggregation. In healthy individuals, a single aspirin tablet (325 mg) results in 98% inhibition of thromboxane A2 production within 1 hour of ingestion. Several large, randomized, controlled clinical trials have shown it to be beneficial in the secondary prevention of cardiovascular events and death [5]. An overview of randomized trials of platelet antiaggregant therapy in patients with a history of transient ischemic attack (TIA) or stroke showed a reduction in the risk of nonfatal stroke, nonfatal myocardial infarction (MI), and death from vascular causes of approximately 25% [6]. This risk reduction was independent of age, gender, and other risk factors. Another advantage of ASA is its effect on reducing cardiovascular mortality, which is helpful in patients with cerebrovascular disease, given their frequent combination of carotid and coronary atherosclerosis. Aspirin is also helpful in reducing mortality following carotid endarterectomy [7]. In a retrospective analysis of the medically treated patients of the VA Cooperative Study on Asymptomatic Stenosis [8], those patients not taking ASA had a higher incidence of stroke and death, providing indirect evidence that aspirin may be useful in asymptomatic patients with significant carotid stenosis. The appropriate dose of ASA in preventing stroke remains controversial. The studies proving its effectiveness in the secondary prevention of stroke used doses ranging from 30 to 1500 mg/d. Some authors have advocated higher doses of ASA, given that these doses may have useful effects unrelated to cyclooxygenase inhibition [9]. In the Aspirin in Carotid Endarterectomy Trial (ACE) [10], 2804 patients who had had a carotid endarterectomy were randomly assigned to compare the benefits of low-dose aspirin (81 to 325 mg/d) with high-dose aspirin (650 to 1300 mg/d). The primary endpoints in the ACE trial were stroke, MI, or death. At 3 months after surgery, the risk of stroke, MI, or

death was 6.2% in the low-dose aspirin group versus 8.4% in the high-dose aspirin group. The difference was less apparent when only stroke or death was evaluated as the endpoint. Recently, the FDA recommended a dose of 50 to 325 mg/d of aspirin for prevention of strokes [11].

Ticlopidine

Ticlopidine is a platelet antiaggregant agent that irreversibly interferes with platelet membrane function by inhibiting ADP-induced platelet-fibrinogen binding and subsequent platelet-platelet interactions. When compared with placebo, it has been proven to reduce the risk of stroke, MI, or vascular death in patients with recent noncardioembolic stroke [12]. Ticlopidine (500 mg/d) was compared with aspirin (1300 mg/d) in patients with TIAs and mild strokes. The 3-year rate for nonfatal stroke or death was lower in the ticlopidine group than in the aspirin group (17% vs 19%, respectively). Rates of fatal and nonfatal stroke were also lower in the ticlopidine group (10% vs 13%, respectively) [13]. The recommended dose of ticlopidine is 250 mg two times per day. Ticlopidine has more side effects than aspirin, including diarrhea, nausea, dyspepsia, and rash. However, its use has been limited by significant hematologic side effects including a reversible neutropenia/agranulocytosis, aplastic anemia, pancytopenia, and thrombocytopenia. Fatal cases of thrombotic thrombocytopenic purpura (TTP) have also occurred in patients taking ticlopidine [14]. The estimated incidence of ticlopidine-associated TTP is one per 1600 to 5000 patients treated [15••]. Complete blood counts with leukocyte differentials and platelet counts must be done every 2 weeks for the first 3 months of use. The drug must be discontinued if the neutrophil count falls below 1200/mm^3 or if thrombocytopenia is detected.

Clopidogrel

Clopidogrel is a thienopyridine derivative that selectively inhibits the binding of ADP to its platelet receptor and the subsequent ADP-mediated activation of the glycoprotein (GP) IIb/IIIa complex. In a study enrolling over 19,000 patients with atherosclerotic vascular disease manifested as either recent ischemic stroke, recent MI, or symptomatic peripheral arterial disease, 75 mg of clopidogrel was more effective than 325 mg of ASA in reducing the combined risk of ischemic stroke, MI, or vascular death [16]. After nearly 2 years of follow-up, the absolute risk reduction was modest (annual risk of endpoints in clopidogrel-treated patients was 5.32% vs 5.83% in ASA-treated patients), although it was statistically significant. In the group of over 6400 patients who entered the study with a stroke, there was a nonsignificant relative risk reduction of 7.3% in favor of clopidogrel and the majority of these patients developed a recurrent stroke as their first outcome measure. Its side effect profile was thought to be relatively benign, with no increased incidence of neutropenia, and a lower incidence of gastrointestinal hemorrhage and gastric or duodenal ulcers compared with aspirin. However, a very recent report associates clopidogrel with TTP in 11 patients [15••]. In the majority of patients, clopidogrel had been used for less than 14 days before the onset of TTP. Several patients were taking concomitant medications, including statins in five patients, atenolol in three patients, and cyclosporine in one patient. How this serious, potentially fatal, complication affects the clinical use of clopidogrel remains to be seen.

Dipyridamole and aspirin

Dipyridamole is a phosphodiesterase inhibitor that increases the levels of cyclic adenosine monophosphate (cAMP). Although previous studies could not demonstrate the benefit of adding dipyridamole to aspirin, a large, randomized, placebo-controlled, double-blind trial was published in 1996. This European Stroke Prevention Study (ESPS-2) [17] randomized 6602 patients with prior TIA or stroke to treatment with aspirin alone (25 mg twice per day), modified-release dipyridamole (200 mg twice per day), the two agents in combination, or placebo. The ESPS-2 investigators reported an additive effect of dipyridamole when coprescribed with aspirin, showing a decrease in stroke rate in the combined-treatment arm (37%) versus either agent alone (ASA 18%, dipyridamole 16%); both low-dose aspirin and high-dose dipyridamole in a modified release form alone were better than placebo. Among the 25% of patients who withdrew from the study, most were in the dipyridamole and the combination groups. The main side effects of dipyridamole are gastrointestinal distress and headaches. The combination of ASA and dipyridamole was effective in reducing nonfatal strokes, but had little effect on MI or fatal stroke.

Platelet glycoprotein IIb-IIIa receptor inhibitors

Platelet glycoprotein IIb-IIIa receptor inhibitors have been evaluated in cardiovascular disease but their benefit in ischemic stroke is unproven. Abciximab was evaluated for use in acute ischemic stroke in a pilot, placebo-controlled, randomized, dose-escalation trial [18]. There were no cases of symptomatic parenchymal hemorrhage, and there were trends of improved outcome in abciximab-treated patients. Further studies in acute ischemic stroke are planned. These medications have not been studied in the secondary prevention of ischemic stroke.

Warfarin

Warfarin has also been used in the prevention of ischemic stroke. It is well established that patients at high risk for embolism, such as those with valvular heart disease and atrial fibrillation or prosthetic mechanical heart valves, benefit from warfarin anticoagulation to prevent thromboembolism. In patients with nonrheumatic or nonvalvular atrial fibrillation (NVAF), several large, randomized, and controlled primary prevention trials and one

secondary prevention trial proved that warfarin was able to lower the risk of thromboembolic events without an excessive number of hemorrhagic complications [19–23]. Factors that increase the risk of thromboembolism in the setting of nonvalvular atrial fibrillation are recent congestive heart failure, hypertension, previous thromboembolism, diabetes, increasing age, previous MI, left ventricular dysfunction, and increased size of the left atrium [24,25]. When using warfarin to prevent ischemic stroke in patients with atrial fibrillation, the goal is an international normalized ratio (INR) of 2 to 3. A combination of fixed-dose, low-intensity warfarin (INR 1.2 to 1.5) and aspirin (325 mg) was found to be less effective in reducing ischemic stroke or systemic embolism in high-risk patients with atrial fibrillation [26]. Patients less than 65 years of age with atrial fibrillation and no other risk factors, known as "lone atrial fibrillation," have only a 1% annual stroke risk. In these patients, warfarin has more risk than benefit and antiplatelet therapy is preferred [25].

Although it is unequivocally effective in reducing stroke recurrence in patients with selective cardiac sources of emboli, especially NVAF, its relative efficacy compared with antiplatelet therapy in patients with atherothrombotic TIA or stroke has not been adequately studied. Certainly, many clinicians do use warfarin in patients with high-grade intracranial stenosis and severe internal carotid artery stenosis, but randomized, prospective, clinical data are not available to support its use. The Warfarin-Aspirin Symptomatic Intracranial Disease Study (WASID) [27] was a retrospective multicenter study that compared the efficacy of warfarin with aspirin for the prevention of major vascular events. A total of 151 patients with a symptomatic 50% to 99% stenosis of an intracranial artery (carotid; anterior, middle, or posterior cerebral; vertebral; basilar) were prescribed warfarin or aspirin according to local physician preference. The rates of major vascular events (ischemic stroke, MI, or sudden death) and stroke were lower in the warfarin-treated group, but major hemorrhagic complications were also slightly higher in the warfarin-treated group. Currently, a prospective, double-blind, multicenter WASID study is randomizing patients with a symptomatic stenosis of a major intracranial artery to warfarin (INR 2 to 3) or aspirin (1300 mg/d). The Warfarin-Aspirin Recurrent Stroke study (WARRS) is an ongoing study comparing warfarin (INR 1.4 to 2.8) versus aspirin (325 mg/d) for secondary prevention of noncardioembolic stroke. The results of these studies, including subgroup analysis, should give us much information on the efficacy and safety of warfarin in these clinical settings.

Risk Factors

Although there are modifiable risk factors for ischemic stroke, their current management is more adequately covered in a different section of these reports. However, a few are worth reiterating as potential new treatment strategies have developed in the past few years.

Hypertension

Hypertension is the most prevalent and modifiable risk factor for stroke [28]. Its treatment substantially reduces the risk of stroke. A review of several prospective, randomized, controlled trials indicates that a decrease in diastolic blood pressure of 5 to 6 mm Hg reduces the risk of stroke by 42% [29]. The treatment of isolated systolic hypertension in the elderly decreases the risk of stroke by 36% [30]. When choosing an antihypertensive agent, it is certainly worth discussing the use of angiotensin-converting enzyme (ACE) inhibitors. In the Heart Outcomes Prevention Evaluation Study [31••], 9297 high-risk patients with coronary artery disease (CAD), stroke, peripheral vascular disease, or diabetes plus at least one other cardiovascular risk factor were randomized to receive either ramipril, 10 mg/d or placebo. There was a significant risk reduction in the ramipril-treated group (14%) versus the placebo-treated group (17.8%) for the primary outcome of the composite of MI, stroke, or death from cardiovascular causes. The number of strokes occurring in the patients taking ramipril was also significantly reduced (3.4% vs 4.9%). Interestingly, the authors thought only a small part of the benefit could be attributed to a reduction in blood pressure, as the majority of patients did not have hypertension at baseline (or were already being treated for hypertension) and the mean reduction in blood pressure with treatment was extremely small (3 mm Hg systolic and 2 mm Hg diastolic). They thought it was likely that ACE-inhibitors likely exert additional beneficial effects, such as antagonizing the direct effects of angiotensin II on vasoconstriction, the proliferation of vascular smooth muscle cells, and rupture of plaques, as well as improving vascular endothelial function, reducing left ventricular hypertrophy, and enhancing fibrinolysis.

Hypercholesterolemia

The relationship between hypercholesterolemia and stroke remains controversial, mainly because lipid-lowering regimens in the past have shown inconsistent results in preventing strokes [32]. However, recent large-scale, randomized, double-blind, placebo-controlled trials have shown that the HMG-CoA reductase inhibitors (*ie*, statins) can lower MI rates and fatal coronary events in patients with a history of CAD and varying levels of total cholesterol and low-density lipoprotein (LDL) cholesterol [33–35]. A couple of these studies did specify stroke as a secondary endpoint, and it appears these medications lower the risk of stroke in these patients with CAD by 19% to 32% [35,36•]. Two meta-analyses of the data from reported clinical trials of the effectiveness of HMG-CoA reductase inhibitors in patients with CAD also showed a 27% to 32% reduction in stroke rate [37,38]. Statins may prevent atherothrombotic events because of

effects other than lowering total and LDL cholesterol levels. They may improve endothelial vasomotor function, increase endothelial cell fibrinolytic activity, block platelet activation, and stabilize the atherosclerotic plaque [39•,40]. We await the results of trials evaluating the effectiveness of these medications in lowering cholesterol and preventing strokes in patients with primary cerebrovascular disease. At this point, we recommend following the guidelines on the detection, evaluation,and treatment of high blood cholesterol published by the National Cholesterol Education Program [41].

Homocysteine and hyperhomocyst(e)inemia

Homocysteine, and specifically hyperhomocyst(e)inemia, is a risk factor for atherosclerosis and endothelial dysfunction; therefore, it is also a likely risk factor for stroke. Proposed mechanisms for its pro-atherogenic effects are endothelial cell injury, increased platelet aggregation, enhancement of a prothrombotic environment, and smooth muscle cell proliferation [42•,43]. A case-control study in a group of British men aged 40 to 59 years showed that hyperhomocyst(e)inemia was a strong risk factor for stroke even after adjustments were made for multiple other risk factors [44]. A graded increase in the number of strokes was noted as the homocysteine levels increased. Elderly patients with an elevated homocysteine level also appear to be at higher risk of cardiovascular disease, including strokes [45]. In a case-control study, there was a strong, graded association between increasing plasma homocysteine and first-ever ischemic stroke caused by large artery atherosclerosis and, to a much lesser extent, small artery disease [46]. It did not appear that elevated homocysteine levels were associated with cardioembolic or other etiologic subtypes of ischemic stroke. It may be important to recognize hyperhomocyst(e)inemia in patients with ischemic stroke, as we may be able treat it. Vitamins B_{12}, B_6, and folate are involved in the metabolism of homocysteine, and treatment with them may lower plasma homocysteine concentrations. However, their effectiveness in preventing ischemic stroke has not been determined. Current ongoing trials of vitamins in preventing noncardioembolic ischemic strokes are underway and should help answer that question.

Conclusions

In deciding on a proper secondary preventative therapy for acute ischemic stroke, it is important to focus on several key issues. The first step is attempting to determine the mechanism that caused the stroke or TIA. Obviously, if a severe proximal carotid stenosis is thought to be the cause of cerebral ischemia, then consideration of performing a carotid endarterectomy is warranted. Consideration of warfarin therapy is necessary in several clinical situations, most notably atrial fibrillation. Proper management of all vascular risk factors is also of utmost importance. If no surgical or endovascular intervention is planned and the patient is not a candidate for warfarin, then nearly all patients will be placed on a platelet-antiaggregating agent. As mentioned previously, there are four choices which have been proven to be effective in preventing ischemic stroke: aspirin, aspirin plus dipyridamole, clopidogrel, and ticlopidine. We consider aspirin to be the first choice of antiplatelet agents in the secondary prevention of ischemic stroke given its efficacy, tolerability, and low cost. The proper dose of aspirin remains controversial, but doses of 50 to 1500 mg/d are acceptable. The other three medications could certainly be used as first-line treatments, but are often used in aspirin-intolerant patients or in patients who failed aspirin treatment. The indirect comparison of the efficacy of these alternative antiplatelet agents has been attempted [47]. However, indirect comparisons are always fraught with error and incorrect assumptions, and the only scientific way to determine the relative efficacy and safety of these medications is with direct or head-to-head comparisons. Each medication has its pros and cons. As noted before, ticlopidine may be more effective than 1300 mg/d of aspirin in preventing ischemic stroke, but it is more expensive than aspirin. It also has been associated with some severe hematologic side effects. Clopidogrel largely replaced ticlopidine in clinical practice because of its side effect profile. It was proven to be slightly better than 325 mg/d of aspirin in preventing the combined endpoints of ischemic stroke, MI, or vascular death in patients with a variety of vascular diseases. However, its side effect profile may not be as benign as once thought, and it is relatively costly. Certainly, combinations of ASA plus ticlopidine and ASA plus clopidogrel are used in clinical practice, but no data exists to demonstrate their benefit over the single agents alone in preventing ischemic stroke or to demonstrate the safety of these combinations in stroke patients. The combination of ASA and dipyridamole appears to more effective than 50 mg/d of ASA alone at preventing nonfatal strokes. However, previous trials of this combination (with lower doses of dipyridamole and different doses of aspirin) were unable to show a benefit over aspirin alone. The combination also appeared to have little additional benefit in preventing MI or fatal stroke. Some patients may be intolerant of side effects, especially headaches. At this point, the only way to improve and refine our ability to prevent ischemic stroke is to continue to define (and hopefully better manage) risk factors and continue to carry out well-designed therapeutic trials to answer our questions.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. American Heart Association. Stroke facts. Available at: http://www.americanheart.org/Heart_and_Stroke_A_Z_Guide/strokes.html. Accessed June 1, 2000.
2. Mohr JP, Caplan LR, Melski JW, *et al.*: **The Harvard Cooperative Stroke Registry: a prospective registry.** *Neurology* 1978, **28:**754-762.
3. •• Furlan A, Higashida R, Wechsler L, *et al.*: **Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial.** *JAMA* 1999, **282:**2003-2011.

The first large, randomized, controlled trial to show the benefit of intra-arterial pro-urokinase in middle cerebral artery thrombosis.

4. •• Sherman DG, Atkinson RP, Chippendale T, *et al.*: **Intravenous ancrod for treatment of acute ischemic stroke. The STAT study: a randomized controlled trial.** *JAMA* 2000, **283:**2395-2403.

A large, randomized, double-blind, placebo-controlled trial showing that ancrod, a defibrinogenating agent, had a favorable benefit-risk profile for patients with acute ischemic stroke.

5. Fuster V, Dyken ML, Vokonas PS, *et al.*: **Aspirin as a therapeutic agent in cardiovascular disease. .**In *American Heart Association Scientific Statement* American Heart Association, Dallas 1993:659-675.
6. Antiplatelet Trialists' Collaboration: **Collaborative overview of randomised trials of antiplatelet therapy-I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients.** *BMJ* 1994, **308:**81-106.
7. Kretschmer G, Pratschner T, Prager M, *et al.*: **Antiplatelet treatment prolongs survival after carotid bifurcation endarterectomy. Analysis of the clinical series followed by a controlled trial.** *Ann Surg* 1990, **211:**317-322.
8. Hobson RW, Krupski WC, Weiss DG: **Influence of aspirin in the management of asymptomatic carotid artery stenosis. VA Cooperative Study Group on Asymptomatic Carotid Stenosis.** *J Vasc Surg* 1993, **17:**257-263.
9. Dyken ML, Barnett HJ, Easton JD, *et al.*: **Low-dose aspirin and stroke. "It ain't necessarily so".** *Stroke* 1992, **23:**1395-1399.
10. Taylor DW, Barnett HJ, Haynes RB, *et al.*: **Low-dose and high-dose acetylsalicylic acid for patients undergoing carotid endarterectomy: a randomised controlled trial. ASA and Carotid Endarterectomy (ACE) Trial Collaborators.** *Lancet* 1999, **353:**2179-2184.
11. *Federal Register* 1998, **63:**56802-56819.
12. Gent M, Blakely JA, Easton JD, *et al.*: **The Canadian American Ticlopidine Study (CATS) in thromboembolic stroke.** *Lancet* 1989, **1:**1215-1220.
13. Hass WK, Easton JD, Adams HP, Jr, *et al.*: **A randomized trial comparing ticlopidine hydrochloride with aspirin for the prevention of stroke in high-risk patients. Ticlopidine Aspirin Stroke Study Group.** *N Engl J Med* 1989, **321:**501-517.
14. Wysowksi DK, Bacsanyi J: **Blood dycrasias and hematologic reactions in ticlopidine users [letter].** *JAMA* 1996, **276:**952.
15. •• Bennett CL, Connors JM, Carwile JM, *et al.*: **Thrombotic thrombocytopenic purpura associated with clopidogrel.** *N Engl J Med* 2000, **342:**1773-1777.

An important reference reporting the association of clopidogrel with thrombotic thromocytopenic purpura. Clopidogrel had largely replaced ticlopidine in clinical practice because of its side effect profile. The clinical characteristics of the 11 patients are well documented.

16. CAPRIE Steering Committee: **A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE).** *Lancet* 1996, **348:**1329-1339.
17. 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.
18. Adams HP, Bogousslavsky J, Barnathan E, *et al.*: **Preliminary safety report of a randomized, double-blind, dose-escalation trial of abciximab in acute ischemic stroke [abstract].** *Cerebrovasc Dis* 1999, **9(suppl 1):**1-128.
19. The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. **The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation.** *N Engl J Med* 1990, **323:**1505-1511.
20. Connolly SJ, Laupacis A, Gent M, *et al.*: **Canadian Atrial Fibrillation Anticoagulation (CAFA) Study.** *J Am Coll Cardiol* 1991, **18:**349-355.
21. EAFT (European Atrial Fibrillation Trial) Study Group: **Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke.** *Lancet* 1993, **342:**1255-1262.
22. Ezekowitz MD, Bridgers SL, James KE, *et al.*: **Warfarin in the prevention of stroke associated with nonrheumatic atrial fibrillation. Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Investigators.** *N Engl J Med* 1992, **327:**1406-1412.
23. Stroke Prevention in Atrial Fibrillation Study. **Final results.** *Circulation* 1991, **84:**527-539.
24. The Stroke Prevention in Atrial Fibrillation Investigators: **Predictors of thromboembolism in atrial fibrillation: I. Clinical features of patients at risk.** *Ann Intern Med* 1992, **116:**1-5.
25. Atrial Fibrillation Investigators: **Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials.** *Arch Intern Med* 1994, **154:**1449-1457.
26. **Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation. Stroke Prevention in Atrial Fibrillation III randomised clinical trial.** *Lancet* 1996, **348:**633-638.
27. Chimowitz MI, Kokkinos J, Strong J, *et al.*: **The Warfarin-Aspirin Symptomatic Intracranial Disease Study.** *Neurology* 1995, **45:**1488-1493.
28. Gorelick PB, Sacco RL, Smith DB, *et al.*: **Prevention of a first stroke: a review of guidelines and a multidisciplinary consensus statement from the National Stroke Association.** *JAMA* 1999, **28:**1112-1120.
29. Collins R, Peto R, MacMahon S, *et al.*: **Blood pressure, stroke, and coronary heart disease. Part 2, Short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context.** *Lancet* 1990, **335:**827-838.
30. SHEP Cooperative Research Group: **Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP).** *JAMA* 1991, **265:**3255-3264.
31. •• 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.** *N Engl J Med* 2000, **342:**143-153.

The HOPE study showed that ramipril, an angiotensin-converting enzyme inhibitor, reduced the risk of myocardial infarction, stroke, or cardiovascular death over placebo in patients with known cardiovascular disease.

32. Atkins D, Psaty BM, Koepsell TD, *et al.*: **Cholesterol reduction and the risk for stroke in men. A meta-analysis of randomized, controlled trials.** *Ann Intern Med* 1993, **119:**136-145.
33. **Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S).** *Lancet* 1994, **344:**1383-1389.

34. Sacks FM, Pfeffer MA, Moye LA, *et al.*: **The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators.** *N Engl J Med* 1996, **335:**1001-1009.

35. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group: **Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels.** *N Engl J Med* 1998, **339:**1349-1357.

36.• Plehn JF, Davis BR, Sacks FM, *et al.*: **Reduction of stroke incidence after myocardial infarction with pravastatin: the Cholesterol and Recurrent Events (CARE) study. The Care Investigators.** *Circulation* 1999, **99:**216-223.

This large, randomized, placebo-controlled study showed that pravastatin significantly reduced stroke incidence after myocardial infarction in patients with average serum cholesterol levels and high concurrent use of antiplatelet therapy.

37. Blauw GJ, Lagaay AM, Smelt AH, *et al.*: **Stroke, statins, and cholesterol. A meta-analysis of randomized, placebo-controlled, double-blind trials with HMG-CoA reductase inhibitors.** *Stroke* 1997, **28:**946-950.

38. Crouse JR, Byington RP, Hoen HM, *et al.*: **Reductase inhibitor monotherapy and stroke prevention.** *Arch Intern Med* 1997, **157:**1305-1310.

39.• Hess DC, Demchuk AM, Brass LM, *et al.*: **HMG-CoA reductase inhibitors (statins): a promising approach to stroke prevention.** *Neurology* 2000, **54:**790-796.

A thorough review of the statins and their use in stroke prevention.

40. Delanty N, Vaughan CJ: **Vascular effects of statins in stroke.** *Stroke* 1997, **28:**2315-2320.

41. **Summary of the second report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II).** *JAMA* 1993, **269:**3015-3023.

42.• Welch GN, Loscalzo J: **Homocysteine and atherothrombosis.** *N Engl J Med* 1998, **338:**1042-1050.

A review of homocysteine including its metabolism and causes, pathophysiologic mechanisms, and treatment of hyperhomocyst(e)inemia.

43. Stein JH, McBride PE: **Hyperhomocysteinemia and atherosclerotic vascular disease: pathophysiology, screening, and treatment.** *Arch Intern Med* 1998, **158:**1301-1306.

44. Perry IJ, Refsum H, Morris RW, *et al.*: **Prospective study of serum total homocysteine concentration and risk of stroke in middle-aged British men.** *Lancet* 1995, **346:**1395-1398.

45. Bots ML, Launer LJ, Lindemans J, *et al.*: **Homocysteine and short-term risk of myocardial infarction and stroke in the elderly: the Rotterdam Study.** *Arch Intern Med* 1999, **159:**38-44.

46. Eikelboom JW, Hankey GJ, Anand SS, *et al.*: **Association between high homocyst(e)ine and ischemic stroke due to large- and small-artery disease but not other etiologic subtypes of ischemic stroke.** *Stroke* 2000, **31:**1069-1075.

47. Albers GW, Easton JD, Sacco RL, *et al.*: **Antithrombotic and thrombolytic therapy of ischemic stroke.** *Chest* 1998, **114(suppl):**683-698.