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Secondary Stroke Prevention: Review of Clinical Trials

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Summary: Patients who experience a stroke or transient ischemic attack (TIA) are at high risk for subsequent vascular events, most commonly stroke. This article focuses on clinical trials examining secondary prevention of stroke and reviews the various commonly used methods of stroke prevention: surgical approaches, antihypertensive treatment, lipid- and cholesterol-lowering medications, anticoagulant therapies, and antiplatelet therapies.

Key words: transient ischemic attack, stroke, stroke prevention, antiplatelet

Introduction

Epidemiological studies have established that patients experiencing a nonfatal stroke or transient ischemic attack (TIA) are at high risk for subsequent vascular events. After stroke, recurrence occurs in 3–8% of patients within the first 30 days.[1,2] Long-term stroke recurrence rates vary from 4 to14% annually, depending on the population studied and the type of stroke. In the Framingham Study, the 5-year cumulative recurrence rate for atherothrombotic brain infarction was higher for men than for women (42 and 24%, respectively).[1] The 5-year cumulative recurrence in Rochester, Minnesota, was 29%, with no difference between genders.[3] In northern Manhattan, stroke recurred in 12% of patients within 1 year, and in 25% within 5 years following ischemic stroke.[4]

Patients with TIA are similarly at very high risk of subsequent events. In one study among 1,707 patients belonging to Health Maintenance Organizations (HMO), who had been given a diagnosis of TIA by an emergency room physician and who were followed for 90 days, 25% experienced stroke, death, recurrent TIA, or other cardiovascular events. The risk of stroke was approximately 10% at 90 days, with half of these occurring within the first 2 days.[5] In fact, improved imaging technologies, especially diffusion-weighted magnetic resonance imaging (DW MRI), which is exquisitely sensitive to the earliest changes of ischemia, have made the distinction between stroke and TIA difficult. One-third of patients with symptoms lasting < 1 h, and up to 70% of those with symptoms < 24 h, will manifest DW MRI changes consistent with infarction.[6] Based on these data, in 2002 the TIA Working Group proposed a new definition for TIA: a brief episode of neurologic dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting < 1 h and without evidence of acute infarction. Any attack with persistent clinical signs or imaging abnormalities would then be classified as a stroke.[7]

From the neurologist's point of view, the classification of an event as stroke or TIA must be considered secondary to understanding its cause and to preventing future events that may be more serious or even fatal. Therefore, in this article no distinction is made regarding secondary prevention following stroke or TIA.

The focus of this article is the secondary prevention of stroke. However, brief reviews of primary prevention using various interventions are also included where appropriate, as they provide a context from which to review secondary prevention trials. In addition, although the scope of this article is limited to a review of clinical trials, it should be stressed that the core of both primary and secondary stroke prevention remains the reduction of risk from modifiable behaviors identified in epidemiological studies (including smoking cessation, weight loss, exercise, and avoidance of alcohol abuse), for which no clinical trials have been or likely will be undertaken.

Surgical Interventions

Primary Prevention Overview

The role of endarterectomy in the management of patients with asymptomatic carotid stenosis is somewhat controversial. Although four early trials failed to demonstrate definite benefit for surgery in the reduction of stroke or death,[8–11] all had methodological flaws, such as small sample size and inadequate follow-up.

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The Asymptomatic Carotid Atherosclerosis Study (ACAS) randomized 1,662 patients with carotid stenosis ≥ 60% to either carotid endarterectomy and best medical therapy (aspirin 325 mg daily plus risk factor modification) or best medical therapy alone. The ACAS demonstrated a significant reduction in relative risk (RR) of ipsilateral stroke and perioperative stroke or death in the surgical group after 5 years (5.1 vs. 11.0%; RR reduction, 53%; p = 0.004). There was no correlation between benefit and degree of stenosis, although the study was not empowered to detect such differences.[12] This study needs to be interpreted cautiously for several reasons, however. For example, the overall perioperative stroke or death risk was 2.3%, but in subgroup analyses it was greater among women (3.6%) than men (1.7%). These gender differences were not statistically significant, but they might provide a rationale for greater caution in recommending carotid endarterectomy to women with asymptomatic disease. Moreover, ACAS was designed to maintain a risk of perioperative morbidity and mortality of ≤ 3%, excluding patients over age 79 and those with symptomatic vertebrobasilar disease or with serious medical illnesses that could complicate surgery. For this reason, generalization of the ACAS results to patients not meeting these criteria remains speculative. Finally, since the time ACAS was conducted, improved medical therapy, such as the increased use of statins (discussed below), may have narrowed the gap between medical therapy and carotid endarterectomy. Nevertheless, based on these results, carotid endarterectomy may be considered for generally healthy persons up to 80 years of age with stenosis of ≥ 60% to reduce the risk of future stroke.

Secondary Prevention

With regard to symptomatic carotid stenosis, the clinical picture is somewhat clearer. The North American Symptomatic Carotid Endarterectomy Trial (NASCET) demonstrated that among patients with TIA or minor stroke and ipsilateral carotid stenosis of ≥ 70%, the 2-year risk of ipsilateral stroke was reduced from 26% in a medically treated group (aspirin 1,300 mg/day) to 9% in a surgical group (p < 0.001). When major or fatal ipsilateral stroke was used as the outcome measure, the risks were 13 and 2.5%, respectively (p < 0.001). Even when all strokes and deaths were included in the analysis, carotid endarterectomy was still associated with a significant (p < 0.001) reduction of risk. These benefits appeared to be largely independent of the degree of stenosis within the range of 70–99%.[13]

The European Carotid Surgery Trial (ECST) produced similar results in symptomatic patients with a stenosis ≥ 70%, demonstrating a decrease in 3-year risk for surgical stroke, surgical death, or any ischemic stroke (endarterectomy, 12.3%; medical-only treatment, 22%; p < 0.005). This was in contrast to results from patients with mild (< 30%) stenosis, in whom the small risk of subsequent stroke was outweighed by the risks of surgery.[14]

The Veterans Administration Cooperative Study, which compared endarterectomy to medical-only therapy among patients with a > 50% stenosis and a history of TIA or small completed strokes, demonstrated stroke risk of 19.4% in the medical-only group versus 7.7% in the surgical group (mean follow-up, 11.9 months; p = 0.011). In addition, the degree of benefit was greater (absolute risk reduction, 17.7%; p = 0.004) among patients with a stenosis > 70%.[15]

The NASCET results were recently extended to symptomatic patients with moderate stenosis (50–69%). Surgical treatment was associated with a 29% reduction in RR versus medical-only treatment for the primary outcome measure, 5-year incidence of ipsilateral stroke (surgical, 15.7%; medical only, 22.2%; p = 0.045; 95% confidence interval [CI] for RR reduction, 7–52%). The benefit was similar in magnitude when outcome measures included any disabling stroke or death from any cause (RR reduction, 27%; p = 0.032).[16]

Subgroup analyses of the NASCET data for moderate stenosis suggested that the benefit of surgery is greater for men than for women, probably because the underlying risk of stroke with medical therapy is lower in women than in men. The overall perioperative rate of disabling stroke or death was 2.0%. Certain characteristics doubled the risk of perioperative stroke or mortality: diabetes, diastolic blood pressure (BP) > 90 mmHg, contralateral carotid occlusion, left carotid artery disease, taking < 650 mg aspirin daily at study entry, absence of history of myocardial infarction (MI) or angina, and an imaged infarct. Symptomatic patients with < 50% stenosis showed no benefit with carotid endarterectomy.[16]

Future Directions in Surgical Approaches to Stroke Prevention

Carotid angioplasty and stenting are also being evaluated in clinical trials as an alternative to carotid surgery. In the CArotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS), 504 patients with carotid stenosis (97% symptomatic) were randomized to surgery or angioplasty with or without stenting. Patients were excluded if they were deemed at excessive risk from surgery. Stents were used in 26% of patients and angioplasty alone in 74%. The 30-day rate of major outcomes did not differ between the two groups, with a 10% death or any stroke rate within that time. Minor complications were lower in the group treated endovascularly than surgically (cranial nerve palsies 0 vs. 9%, p < 0.0001; groin or neck hematoma requiring surgery or extending hospital stay 1 vs. 7%, p < 0.0015). Persistent severe stenosis of the carotid artery at 1 year was present more commonly in the endovascular group (14 vs. 4%; p < 0.001). During 3 years there were no significant differences in ipsilateral stroke or in a combined outcome of death or disabling stroke.[17]

In the recently completed Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial, patients with carotid stenosis at increased risk for complications with surgery were randomly assigned to carotid endarterectomy or angioplasty and stenting. High-risk conditions included age > 80 years, congestive heart failure, recent MI or unstable angina, severe pulmonary disease, contralateral internal carotid artery occlusion, neck radiation,

and prior carotid endarterectomy. Patients could have either symptomatic stenosis ≥ 50% or asymptomatic stenosis ≥ 80%. A total of 307 patients were randomized. Technical success was achieved in 91% of stented patients. The 30-day stroke, MI, and death rate was significantly reduced in the group treated with stents (5.3 vs. 12.6%, respectively). The 30-day stroke rate did not differ significantly. Long-term follow-up is ongoing.[18]

These studies suggest that carotid angioplasty and stenting may have a role, particularly in reducing minor complications of carotid revascularization procedures and in patients at high risk of surgery, although there is no evidence that endovascular procedures are more effective for patients more generally. The ongoing Carotid Revascularization Endarterectomy versus Stent Trial (CREST) will compare the efficacy of carotid endarterectomy and angioplasty and stenting in symptomatic patients with stenosis of at least 50%.[19]

The observed difference in surgical benefits for symptomatic patients with severe stenosis, moreover, compared with those with mild to moderate stenosis, suggests that stratification of patients based on disease characteristics may be the most effective approach to maximizing the benefits of surgical intervention. A number of contemporary studies have provided evidence that measures of cerebral hemodynamics can provide important prognostic differentiation between patient groups.

Increased oxygen extraction fraction (OEF) is an indicator of reduced hemodynamic reserve that can be evaluated using positron emission tomography (PET); oxygen extraction is increased in areas of the brain in which blood flow is reduced relative to oxygen demand.

In a study of 81 patients with a history of TIA or stroke, hemodynamic failure defined using PET criteria (OEF outside the normal range based on studies in normal volunteers) distal to carotid artery occlusion was strongly predictive of stroke; among 39 patients with hemodynamic failure, 11 (28%) suffered ipsilateral strokes during follow-up, compared with 2 ipsilateral strokes among 42 patients (5%) without hemodynamic failure ($p = 0.004$; mean follow-up, 31.5 months).[20]

Another potential predictor of increased stroke risk is poor cerebrovascular reactivity, assessed using middle cerebral artery transcranial Doppler testing during induced hypercapnia, which can identify patients with both asymptomatic and symptomatic carotid occlusion.[21] Among 94 patients with asymptomatic carotid stenosis ≥ 70%, increased cerebrovascular reactivity was also highly predictive of a reduced risk of cerebrovascular ischemic events, even after adjusting for other potential risk factors (hazard ratio, 0.09; 95% CI 0.02–0.38).[22]

Clinical series have shown that superficial temporal artery to middle cerebral artery bypass surgery can restore normal cerebral perfusion pressure and other markers of hemodynamics, potentially reducing the risk of stroke in patients with hemodynamic impairment.[23] The Extracranial-Intracranial (EC-IC) Bypass Study, however, failed to demonstrate a benefit for bypass surgery in this setting. The trial randomized 1,377 patients with symptomatic carotid or middle cerebral artery disease (minor stroke or TIA) to undergo optimal medical care alone (n = 714) or combined with superficial temporal artery to middle cerebral artery anastomosis (n = 663). Despite excellent bypass patency (96%), after a mean follow-up of 55.8 months the prognosis was clearly worse among surgically treated patients, with 30-day combined surgical mortality and major stroke rates of 0.6 and 2.5% in the medically and surgically treated patients, respectively.[24] Because the EC-IC bypass study, however, did not account preoperatively for differences in hemodynamics among patients, it may have failed to distinguish those patients most likely to benefit from surgery. A new clinical trial, the Carotid Occlusion Surgery Study (COSS), will test the role of bypass surgery in patients with evidence of hemodynamic failure. Eligibility criteria include complete occlusion of a carotid artery due to atherosclerosis and hemispheric TIA or mild to moderate ischemic stroke in the territory of that carotid artery within 120 days of enrollment. Following PET measurement of OEF, patients with increased OEF will be eligible for randomization to bypass surgery or to continued medical therapy.

Medical Therapy

Antihypertensive Treatment in Secondary Prevention of Stroke

Several trials have demonstrated the benefits of blood pressure reduction in reducing the risk of a first stroke in hypertensive patients.[25–28] Until recently, however, very few clinical trial data were available to provide evidence that antihypertensive therapy could reduce the risk of a recurrent stroke among those with hypertension and a first cerebrovascular event. Theoretical concerns about reducing cerebral blood flow in those with cerebrovascular disease mandated caution in reducing BP in this group of patients. Recent meta-analyses of epidemiological data from several large-scale prospective cohort studies, however, have suggested that relative elevations in BP, even within the range traditionally considered normal, are also associated with an increased risk of stroke.[29] There appears to be no strict threshold below which further observed decrements in BP are not associated with additional decreases in stroke risk. The risk of stroke associated with BP is, in other words, continuous. Whether treatment to reduce BP in nonhypertensive patients who experience a stroke or TIA lowers the risk of future strokes has also remained a largely unexplored question. Recent results from the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) address the role of BP therapy in secondary stroke prevention.

The PROGRESS was an international randomized, double-blind, placebo-controlled trial of antihypertensive therapy among 6,105 patients with a history of stroke (hemorrhagic or ischemic) or TIA within the preceding 5 years.[30] Patients were enrolled independent of hypertension status, and 52% were considered nonhypertensive (i.e., systolic BP ≤ 160 and diastolic BP ≤ 90 mmHg). Mean BP among nonhypertensives was 136/79 at baseline. Active treatment utilized the ACE inhibitor perindopril 4 mg daily (or placebo) with or without the addition of diuretic therapy with indapamide 2.5 mg daily (or pla-

cebo) according to the preference of the treating physician. Patients were followed for 4 years for the occurrence of stroke and other major vascular events. Active therapy (i.e., either perindopril alone or the combination of both agents) led to a mean BP reduction of 9/4 mmHg, with a statistically significant 28% RR reduction in risk of recurrent stroke (absolute risk reduction from 14% in the placebo group to 10% in the active treatment group). Major vascular events were reduced 26%, from 5.5 to 4.1% annually in placebo and active groups, respectively, but total mortality was not significantly different. Treatment with perindopril alone achieved a 5/3 mmHg reduction in blood pressure, and no statistically significant decrease in stroke or other events compared with placebo, while treatment with the combination perindopril plus indapamide achieved a 12/5 mmHg reduction in BP and a 43% reduction in stroke risk. Perhaps of most interest, the benefit of combination therapy was of a similar magnitude among both hypertensive and nonhypertensive patients (44 and 42% stroke risk reduction, respectively). The trial therefore supports the contention that among patients who experience a first stroke or TIA, BP reduction with an ACE inhibitor and a diuretic, when tolerated, can reduce the risk of recurrence, independent of baseline BP.

Similar results were obtained in the Heart Outcomes Prevention Evaluation (HOPE) study, which evaluated the effect of the ACE inhibitor ramipril in patients at high risk of cardiovascular events.[31] The trial may be considered in part to be a secondary stroke prevention trial, as approximately 10% of the patients in the study had a history of cerebrovascular disease. The HOPE study demonstrated a 22% reduction in the risk of cardiovascular death and other vascular events in patients on ramipril, despite a modest decrease in BP compared with baseline (approximately a 3/2 mmHg systolic/diastolic reduction with ramipril compared with placebo). The results were similar among patients with or without a history of stroke, and with or without a history of hypertension. Ramipril use was also associated with a 32% RR reduction for stroke as an independent outcome (stroke incidence: ramipril, 3.4%; placebo, 4.9%; $p = 0.0002$). Because the reduction in blood pressure was modest in HOPE, it may be that the benefits of ramipril in stroke risk reduction are related to properties of the drug other than its BP effects. Because these other BP-independent benefits of ACE inhibition were not seen in the PROGRESS trial, the relative merits of BP reduction and ACE inhibition remain uncertain in the context of secondary stroke prevention.

Ongoing Trials

The Secondary Prevention of Small Subcortical Strokes (SPS3) trial is intended to compare "intensive" control of BP, to reach a target systolic BP of < 130 mmHg, with "usual" management (target systolic BP of 130–149 mmHg). The patient population will be limited to those with small-vessel, subcortical ("lacunar") infarcts. Outcome measures include recurrent stroke rate, cognitive decline, and rates of other major vascular events, as well as discontinuation and adverse event rates resulting from intensive BP control. The goal of SPS3 is to compare the effects of two levels of BP control, rather than compare the efficacy of specific antihypertensive agents. Management of hypertension in SPS3 to achieve the assigned targets will be based on "best practice" recommendations from national guidelines.

The hypothesis that drugs that affect the renin-angiotensin system may have benefits beyond their effects on BP reduction has led to the evaluation of angiotensin-II receptor blockers (ARBs). The ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) will compare monotherapy with the ARB telmisartan to ramipril monotherapy and to combination therapy with both agents in patients with a history of CAD, stroke, peripheral vascular disease, or diabetes with demonstrated end-organ damage. The Telmisartan Randomised AssessmeNt Study in ACE- iNtolerant subjects with cardiovascular Disease (TRANSCEND) trial will evaluate telmisartan monotherapy against placebo in a similar population that is intolerant of ACE inhibitor therapy. In the 2×2 factorial-design Prevention Regimen for Effectively Avoiding Second Strokes trial (PRoFESS), patients with a history of ischemic stroke within 90 days will be randomized to telmisartan or placebo, as well as to two different antiplatelet regimens (described below). The primary outcome will be recurrent ischemic stroke.[32]

Trials of Lipid- and Cholesterol-Lowering Medications

The benefits of the hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, or statins, in reducing vascular risk among patients with coronary artery disease (CAD) have been established for many years. However, trials of older cholesterol-lowering agents have produced inconsistent results with regard to reducing the risk of stroke, which may be due in part to the choice of the particular agent. Earlier primary and secondary prevention studies failed to show a reduction in stroke incidence in middle-aged men, despite showing reductions in the incidence of MI. In fact, studies of clofibrate, in a meta-analysis, demonstrated significantly increased treatment-associated risk of fatal stroke (pooled odds ratio, 2.64).[33]

More recent studies utilizing statins have demonstrated benefits in reducing stroke risk. Secondary analyses of the Scandinavian Simvastatin Survival Study (4S) and Cholesterol And Recurrent Events trial (CARE), involving treatment of patients with a history of MI using simvastatin and pravastatin, respectively, revealed treatment-associated reductions of approximately 30% in the RR of stroke versus placebo.[34, 35] The recent Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) study demonstrated a statistically significant 19% RR reduction for stroke among patients with a history of unstable angina or MI, as well as a reduction in overall mortality; total cholesterol levels in this patient population ranged from 155–271 mg/dl.[36]

Both the LIPID and CARE trials randomized patients without elevated baseline blood cholesterol levels, which suggests that all survivors of a first MI or those with unstable angina should be considered for treatment with statins for prevention of both stroke and ischemic heart disease. In a primary preven-

tion trial among those with elevated cholesterol, the risk of stroke was more modestly reduced by 11% among those treated with pravastatin.[37]

Until recently, the role of statins in secondary prevention of stroke in patients without CAD has remained uncertain, especially for stroke patients with normal or low cholesterol levels. The landmark Medical Research Council/British Heart Foundation (MRC/BHF) Heart Protection Study, however, suggests that statins should be considered for a much broader role in treating patients with a history of stroke.

The MRC/BHF study was a multicenter, randomized, placebo-controlled trial of simvastatin therapy for the secondary prevention of ischemic events in patients at high risk of vascular disease. A total of 20,536 patients aged 40–80 years, with total cholesterol ≥ 135 mg/dl and a history of CAD, diabetes mellitus, treated hypertension (among men > 65 years of age), or other occlusive arterial diseases including stroke or TIA, were randomized to placebo or 40 mg simvastatin daily. Of the total patient population, 3,280 had a history of cerebrovascular disease.[38]

After follow-up (mean = 5 years), the risk of a first major vascular event among patients receiving simvastatin was 19.8%, compared with 25.2% for placebo (absolute risk reduction, 5.4%; $p < 0.0001$). Mortality was also significantly reduced among patients receiving simvastatin versus placebo (12.9 vs. 14.7%; $p = 0.0003$), with the reduced mortality attributable primarily to a 17% risk reduction for vascular deaths. Simvastatin treatment was also associated with a statistically significant 25% RR reduction in occurrence of stroke (from 5.7 to 4.3%; $p < 0.0001$).[38]

An important finding of the MRC/BHF study was that these benefits were observed among patients with normal low-density lipoprotein (LDL) levels, even for those with LDL < 100 mg/dl. The benefits were similar in magnitude among patients with a history of cerebrovascular disease with or without a history of CAD. For patients without a history of CAD, the absolute risk reduction for a major vascular event was 4.9% (23.6 to 18.7%), yielding a number needed to treat of approximately 20. Simvastatin did not increase risk of cerebral hemorrhage, and therapy was very well tolerated.[38]

Among patients with a history of stroke or TIA, the MRC/BHF study provides the first definitive evidence for benefits of statin therapy in the reduction of risk for stroke, MI, vascular death, and overall mortality. It further provides evidence that these benefits can be realized independent of baseline lipid values. These results indicate that statin therapy should be strongly considered for all stroke patients, regardless of cholesterol level. They also suggest that there may be benefits to statin therapy beyond its ability to lower cholesterol.

An ongoing trial, the Stroke Prevention by Aggressive Reduction of Cholesterol Levels (SPARCL) study, should help clarify the results suggested by the MRC/BHF study. The SPARCL study has been designed to evaluate prospectively risk reduction resulting from aggressive lipid-lowering therapy for recurrent cerebrovascular events among patients with a history of stroke or TIA but no prior history of coronary artery disease.[39]

Trials of Anticoagulant Therapies

Trials of anticoagulant therapies in primary stroke prevention have generally evaluated efficacy in patients with atrial fibrillation (AF), a strong independent risk factor for stroke. Several randomized controlled trials have demonstrated the efficacy of warfarin in preventing a first stroke among patients with nonvalvular AF, with RR reductions ranging from 42 to 86%.[40–42]

The Stroke Prevention in Atrial Fibrillation study (SPAF I) demonstrated a benefit of aspirin (325 mg daily) versus placebo in reducing the risk of stroke associated with AF.[41] In contrast, other trials using 75 mg of aspirin—Atrial Fibrillation, Aspirin, AntiKoagulation (AFASAK),[42] 300 mg aspirin—European Atrial Fibrillation Trial (EAFT),[43] or 325 mg aspirin plus minidose warfarin (SPAF III)[44] failed to demonstrate significant benefit. For most patients in these trials, warfarin use in conjunction with AF was safe, with an annual rate of 1.3% for major bleeding, compared with 1% in patients on placebo or aspirin.

In extending the use of anticoagulants to secondary prevention of stroke, EAFT randomized 1,007 patients with recent minor stroke or TIA and established AF to open-label treatment with warfarin or double-blind treatment with aspirin or placebo. Warfarin treatment significantly reduced the risk of recurrent stroke in patients with a history of stroke to a degree consistent with that observed in studies of primary prevention (4% warfarin vs. 12% placebo; RR reduction, 66%; $p < 0.001$).[45] Warfarin treatment also significantly decreased the risk of the combined primary endpoint of vascular death, nonfatal stroke, MI, or nonfatal systemic embolism (8% warfarin vs. 17% placebo; RR reduction, 47%; $p = 0.001$).[45]

When compared with aspirin, warfarin significantly reduced the risk of recurrent stroke (RR reduction, 62%; $p < 0.001$), which was the main effect underlying significant reduction in risk of the combined primary endpoint (40% RR reduction; $p = 0.008$).[45] Although randomized trials have not been performed in persons with all other forms of cardioembolic stroke, a general consensus has developed that in those who have experienced stroke or TIA, the presence of a high-risk cardioembolic source (apart from infective endocarditis or atrial myxoma) is an indication for anticoagulation therapy.[47, 48] Potential cardioembolic sources, classified by risk level, are listed in Table I.

Based on the results of the Warfarin Aspirin Recurrent Stroke Study (WARSS), the role of warfarin in secondary stroke prevention among patients without definite cardioembolism has been revised in recent years. The WARSS study, designed to test the efficacy of warfarin (International Normalized Ratio 1.4–2.8) versus aspirin (325 mg) in preventing recurrent stroke, was a randomized, blinded trial in 2,206 patients (2,173 evaluable) who had experienced an ischemic stroke within 30 days of randomization in the absence of severe carotid stenosis or cardioembolic stroke.[49]

The WARSS trial demonstrated no significant difference between warfarin and aspirin in the combined primary endpoint of recurrent stroke or death among patients overall (warfarin, 17.8%; aspirin, 16.0%; $p = 0.25$) or among subgroups of

TABLE I Cardioembolic sources

High risk	Low or uncertain risk
Atrial fibrillation	Mitral valve prolapse
Mitral stenosis	Mitral annular calcification
Prosthetic mechanical valves	Patent foramen ovale
Recent myocardial infarction	Atrial septal aneurysm
Left ventricular thrombus	Calcific aortic stenosis
Dilated cardiomyopathies	Mitral valve strands [a]
Marantic endocarditis	
Atrial myxoma	
Infective endocarditis	

[a] Mitral valve strands are echocardiographically visible valvular excrescences that are believed to represent fibrinous threads, although they may have varying pathologies (also called Lambl's excrescences).
Adapted from Ref. No. 48 with permission.

patients defined by the etiologic subtype of the primary stroke. Of equal importance, however, was the fact that warfarin was nearly as safe as aspirin (annual risk for major hemorrhage: 2.2 per 100 patient-years on warfarin, 1.5 per 100 patient-years on aspirin; p = 0.10).[49]

Warfarin is still indicated for prevention of secondary stroke among patients with AF or other high-risk sources of cardiogenic embolism, such as valvular heart disease and left ventricular thrombus (Table I). Its utility in the majority of stroke patients, however, including those with patent foramen ovale, may be limited.[50]

Trials of Antiplatelet Therapies

Antiplatelet therapy is indicated for secondary prevention in patients with symptomatic ischemic cerebrovascular disease, with multiple studies consistently demonstrating significant benefit. The most recent meta-analysis performed by the Antithrombotic Trialists' Collaboration,[51] using pooled data from more than 18,000 randomized patients with cerebrovascular disease, demonstrated a statistically significant 22% odds reduction in the composite endpoint of MI, stroke, or vascular death. The absolute benefit was approximately 4%, with 17.8% of those on antiplatelet therapy and 21.4% of those not on antiplatelet therapy suffering a vascular event or death. (The Antithrombotic Trialists' Collaboration is a collaborative meta-analysis of randomized trials of antiplatelet therapy prevention of death, MI, and stroke in high-risk patients.)

Aspirin

Aspirin irreversibly acetylates an amino acid residue in platelet cyclooxygenase, thereby reducing production of thromboxane A_2 and decreasing platelet aggregability for the life of the platelet. The Canadian Cooperative Study showed that 1,300 mg of aspirin daily reduced the risk of stroke or death by 31% among those with TIA or minor stroke.[52] The placebo-controlled Swedish Aspirin Low-dose Trial (SALT) randomized 1,360 patients to treatment with either aspirin (75 mg/day) or placebo. The SALT demonstrated an 18% reduction in the primary endpoint, stroke or death, in patients treated with aspirin versus placebo (p = 0.02). The risk of the combined secondary outcome used in the trial, stroke or two or more TIAs within a week necessitating a change in therapy, was reduced 20% for aspirin versus placebo (p = 0.03). To facilitate comparison with meta-analyses such as those used by the Antiplatelet Trialists' Collaboration, the composite endpoint of stroke, MI, and vascular death was also computed, showing a reduction in risk with aspirin treatment of 17% versus placebo (p = 0.03).[53]

In one of its arms, the factorial-design European Stroke Prevention Study 2 (ESPS2) tested a low dose of aspirin, 25 mg twice daily, versus placebo in 6,602 patients with a history of ischemic stroke or TIA. Primary endpoints were stroke, death, and combined stroke or death. Aspirin reduced the risk of stroke by 18% (p = 0.013) compared with placebo, and the risk of stroke or death by 13% (p = 0.016).[54]

Two studies have compared different doses of aspirin in patients with stroke or TIA. The Dutch TIA trial compared aspirin 30 mg daily versus 273 mg daily in more than 3,000 patients who had experienced a TIA in the 3 months preceding randomization. The rates of vascular death, nonfatal stroke, or nonfatal MI were similar between patients receiving the two dosage regimens (14.7% for 30 mg, 15.2% for 273 mg).[55] The lower aspirin dose was associated with 23% fewer major bleeding complications and 42% fewer minor bleeding complications.[55]

The United Kingdom Transient Ischaemic Attack (UK-TIA) trial randomized 2,435 patients with TIA or minor ischemic stroke to 1,200 mg aspirin, 300 mg aspirin, or placebo, and showed no difference in efficacy between the two aspirin doses despite an increase in gastrotoxicity.[56] There is thus no evidence that higher doses of aspirin provide greater protection against recurrent stroke than lower doses, above a threshold of 30 mg daily.[48] Although the optimal dosage of aspirin for secondary prevention remains controversial, the American College of Chest Physicians' 5th Consensus Conference on Antithrombotic Therapy states, "There is no compelling evidence that any specific dose is more efficacious than another, and fewer side effects occur with lower doses," while recommending a starting dose of 50 to 325 mg per day.[48]

Other Antiplatelet Agents

Several alternative antiplatelet agents are available as well. Ticlopidine and clopidogrel are related thienopyridine-derivative compounds that inhibit adenosine diphosphate (ADP)-induced platelet aggregation. In the double-blind Canadian American Ticlopidine Study (CATS), 1,053 patients who experienced a recent atherothrombotic or lacunar stroke received either ticlopidine 250 mg twice daily or placebo. Treatment with ticlopidine was associated with a significant reduction in the risk of the combined endpoint of stroke, MI, or vascular death versus placebo (ticlopidine, 10.8%; placebo, 15.3%; RR reduction, 30.2%; p = 0.006).[57]

In the Ticlopidine Aspirin Stroke Study (TASS), ticlopidine 250 mg twice daily demonstrated significantly greater efficacy than aspirin 650 mg b.i.d. in reducing the 3-year risk of fatal and nonfatal stroke among 3,069 patients with a history of TIA or minor stroke (ticlopidine, 10%; aspirin, 13%; RR reduction, 21%; $p = 0.024$); however, the benefit of ticlopidine in reducing the composite endpoint of nonfatal stroke or death by any cause was less clear (ticlopidine, 17%; aspirin, 19%; RR reduction, 12%; $p = 0.048$).[58]

Similarly, in the recently completed African American Antiplatelet Stroke Prevention Study (AASPS), there was no evidence of a benefit for ticlopidine over aspirin among black men and women with a history of noncardioembolic stroke: 133 (14.7%) of 902 patients assigned to ticlopidine and 112 (12.3%) of 907 patients assigned to aspirin reached the primary outcome of recurrent stroke, MI, or vascular death (hazard ratio, 1.22; 95% CI 0.94–1.57).[59]

The benefits provided by ticlopidine, moreover, may be outweighed by its pronounced side-effect profile, which includes diarrhea, skin rash, thrombotic thrombocytopenic purpura, and severe but reversible neutropenia.[57, 58]

Clopidogrel, a related compound, was initially tested in the Clopidogrel versus Aspirin in Patients at Risk of Recurrent Ischemic Events (CAPRIE) trial. The CAPRIE investigators took the point of view that the significant overlap among patients with ischemic cerebrovascular disease, coronary artery disease, and peripheral arterial disease warranted inclusion of patients with any of these different manifestations in one trial. The study demonstrated a statistically significant benefit of clopidogrel over aspirin in reducing the rate of the composite outcome cluster of ischemic stroke, MI, or vascular death among 19,185 randomized patients with either recent ischemic stroke, recent MI, or symptomatic peripheral artery disease (annual outcome rates: clopidogrel, 5.32%; aspirin, 5.83%; absolute risk reduction, 0.51%; RR reduction, 8.7%; $p = 0.043$). However, the reduction in risk for the combined outcome cluster for the group of patients enrolled with stroke was not significant (RR reduction, 7.3%; $p = 0.26$). Clopidogrel was generally well tolerated, with a side-effect profile similar to that of aspirin.[60]

Recent reports of clopidogrel-associated thrombotic thrombocytopenic purpura (at an estimated rate between 1 in 1,600 to 1 in 5,000) have led to the suggestion that platelet levels should be routinely monitored after initiating therapy.[61] In addition, a recent report has suggested that atorvastatin, a commonly used HMG-CoA inhibitor, may reduce the inhibition of platelet aggregation by clopidogrel,[62] although this view has been challenged.[63]

An alternative approach to antiplatelet treatment involves combination therapy using two different agents with distinct modes of action. Dipyridamole is a well-known vasodilator that also inhibits platelet aggregation; both effects stem primarily from its inhibition of cellular adenosine uptake. Although it demonstrated little efficacy when used as an immediate-release drug, the availability of an extended-release formulation (with a plasma half-life of 13 h) has led to a reevaluation of its efficacy in secondary prevention. An in vitro study has demonstrated an additive effect from combining dipyridamole with aspirin in reducing shear-induced platelet aggregation, believed to be an important thrombotic mechanism.[64]

The ESPS2 tested the use of aspirin in addition to extended-release dipyridamole, as described above. In this factorial design study, an extended-release formulation of dipyridamole was evaluated as monotherapy (200 mg twice daily) and in combination with low-dose aspirin (200 mg dipyridamole + 25 mg aspirin twice daily) versus aspirin alone (25 mg twice daily) and placebo, in a total of 6,602 patients with a history of stroke or TIA. There was an additive benefit to the addition of extended-release dipyridamole to aspirin. The risk of stroke versus placebo was reduced 18% in the aspirin-only group, 16% in the extended-release dipyridamole-only group, and 37% in the combination group ($p = 0.013$, $p = 0.039$, and $p < 0.001$, respectively). Aspirin plus extended-release dipyridamole reduced the risk of fatal and nonfatal stroke by 23% versus aspirin alone. For the composite endpoint of stroke and death, RR reductions versus placebo were 13.2% in the aspirin-only group, 15.4% in the extended-release dipyridamole-only group, and 24.4% in the combination group ($p = 0.016$, $p = 0.015$, and $p < 0.001$, respectively). The number of stroke or death events prevented per 1,000 patients treated over 2 years, compared with placebo, was 30 for aspirin, 35 for extended-release dipyridamole, and 56 for aspirin and extended-release dipyridamole combined. Aspirin alone was associated with significantly higher risk for all-site and gastrointestinal bleeding versus either dipyridamole alone or placebo. The addition of extended-release dipyridamole to aspirin did not increase the risk of bleeding, nor was it associated with any increase in cardiac events.[54]

These data suggest that the efficacy of dipyridamole alone in reducing the risk of secondary stroke is comparable with aspirin, but more important, that the beneficial effects of aspirin and extended-release dipyridamole are additive. As a result, the combination of 25 mg aspirin and 200 mg extended-release dipyridamole has been approved by the U.S. Food and Drug Administration as an agent for stroke prevention in patients with a history of stroke or TIA.[65] The recommendations of the American College of Chest Physicians" 5th Consensus Conference on Antithrombotic Therapy state that "the combination of dipyridamole and aspirin bid may be more effective than clopidogrel and has a similarly favorable adverse event profile," while acknowledging that "expert opinions vary regarding the merits of individual agents."[48]

Table II summarizes selected trials of antiplatelet agents in the secondary prevention of stroke.

Future Approaches to Antiplatelet Therapy

A once-promising avenue for antiplatelet therapy involves the inhibition of the final common pathway in platelet aggregation using antagonists to the glycoprotein IIb/IIIa (GP IIb/IIIa) receptor. However, trials of several oral GP IIb/IIIa receptor agonists, including orbofiban, sibrafiban, and lotrafiban, for chronic oral prophylaxis in patients at risk of vascular events have been disappointing. In these trials, treatment using

TABLE II Selected trials of antiplatelet therapies in secondary stroke prevention

Study/Ref. No.	Population	Treatment(s)	Comparator(s)	Stroke results	Other results	Notes
Aspirin						
SALT (53)	Patients age 50–79 with TIA, mild stroke, TMB within 90 days N = 1,360	Aspirin 75 mg/day	Placebo	18% RRR for stroke (p = 0.02); 20% RRR for stroke or 2+ TIAs within a week (p = 0.03)	17% RRR in combined endpoint [a]	Bleeding episodes significantly more frequent in aspirin group
Dutch TIA (55)	Patients with TIA, mild stroke within 90 days N = 3,131	Aspirin 30 mg/day Aspirin 283 mg/day	None		Combined endpoint: 14.7% for 30 mg 15.2% for 283 mg	30 mg group: 23% fewer major bleeding episodes, 42% fewer minor bleeding episodes
UK-TIA (56)	Patients with TIA, mild stroke N = 2,435	Aspirin 300 mg/day Aspirin 600 mg 2×/day	Placebo		15% RRR for combined endpoint in pooled aspirin vs. placebo	No difference in efficacy between two doses, higher dose more gastrotoxic
ESPS 2 (56)	Patients with ischemic stroke or TIA N = 6,602	Aspirin 25 mg 2×/day	Placebo	18% RRR for stroke (p = 0.013)	13% RRR for stroke or death (p = 0.016)	
Ticlopidine						
CATS (57)	Patients with recent atherothrombotic or lacunar stroke N = 1,053	Ticlopidine 250 mg	Placebo	33.5% RRR for stroke or stroke death (p = 0.008)	30.2% RRR for combined endpoint (p = 0.006)	AEs: neutropenia, skin rash, diarrhea
TASS (58)	Patients with recent min or stroke, TIA, TMB N = 3,069	Ticlopidine 250 mg 2×/day	Aspirin 650 mg 2×/day	21% RRR for stroke or stroke death (p = 0.024)	12% RRR for combined endpoint (p = 0.048)	AEs for ticlopidine: neutropenia, skin rash, diarrhea
AASPS (59)	Black patients with recent noncardioembolic stroke N = 1,809	Ticlopidine 250 mg 2×/day	Aspirin 650 mg/day		Nonsignificant difference (favoring aspirin) for combined endpoint	Trial halted early
Clopidogrel						
CAPRIE (60)	Patients with symptomatic vascular disease N = 19,185	Clopidogrel 75 mg/day	Aspirin 325 mg/day		8.7% RRR for combined endpoint (all patients) (p = 0.043); 7.3% RRR for combined endpoint for stroke patients (p = 0.26)	
Dipyridamole + Aspirin						
ESPS 2 (54)	Patients with stroke or TIA N = 6,602	Dipyridamole 200 mg 2×/day; dipyridamole 200 mg 2×/day + aspirin 25 mg 2×/day; aspirin 25 mg 2×/day	Placebo	Stroke or stroke death vs. placebo: 16% RRR for dipyridamole alone (p = 0.039); 18% RRR for aspirin alone (p = 0.013); 37% RRR for dipyridamole + aspirin (p < 0.001)	Composite endpoint stroke or death: 15.4% RRR for dipyridamole alone (p = 0.015); 24.4% RRR for dipyridamole + aspirin (p < 0.001); 13.2% RRR for aspirin alone (p = 0.016)	2-year reduction in stroke or death/1,000 patients: 35 for dipyridamole alone; 30 for aspirin alone; 56 for dipyridamole + aspirin

[a] Combined endpoint = nonfatal stroke + nonfatal myocardial infarction + vascular death.

Abbreviations: TMB = transient monocular blindness, RRR = relative risk reduction, TIA = transient ischemic attack, AE = adverse events.

oral GP IIb/IIIa receptor agonists was associated with increased mortality, increased frequency of bleeding complications, and no improvement in the risk of recurrent events compared with placebo.[66]

The additive effects of aspirin and extended-release dipyridamole demonstrated in ESPS 2 suggest that combination antiplatelet therapies will play an important role in future prevention strategies; there are several current trials in which combination therapies are being evaluated. The ongoing Management of Atherothrombosis with Clopidogrel in High-Risk Patients (MATCH) study (7,600 patients) is evaluating the combination of clopidogrel and aspirin for secondary stroke prevention,[67] based on the efficacy of this combination in prevention of coronary events demonstrated in the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study.[68] Inclusion criteria for MATCH are not only recent stroke or TIA, but also additional cardiovascular risk factors such as diabetes or prior vascular events; therefore, this group may not be representative of the overall population of patients with stroke and TIA.

It may not be appropriate simply to extrapolate the CURE results to patients with stroke/TIA, however.[69] Despite the obvious similarities between patients with stroke and MI, clinical data suggest that there are also important differences. Patients who had a stroke tend to be older than those who had an MI, and they experience a higher rate of bleeding complications.[69, 70] Patients with stroke also tend to experience recurrent strokes more often than MIs. For example, in the CAPRIE trial, patients with stroke suffered seven times more strokes than MIs; in the CURE trial, which enrolled patients with unstable angina or suspected MI, MIs were five times more common than strokes.

The European Stroke and Australian Stroke Prevention in Reversible Ischemia Trial (ESPRIT), involving 4,500 patients, will compare the efficacy of dipyridamole plus aspirin with oral anticoagulants (warfarin, phenprocoumon, or acenocoumarol) and aspirin monotherapy, using a composite endpoint of first occurrence of death from all vascular causes, nonfatal stroke, nonfatal MI, and major bleeding complication.[71]

Finally, in the largest prospective stroke prevention study yet, PRoFESS (described briefly above in reference to telmisartan) will evaluate the efficacy of two dual antiplatelet regimens: aspirin plus extended-release dipyridamole versus aspirin plus clopidogrel.[63]

References

1. Sacco RL, Wolf PA, Kannel WB, McNamara PL: Survival and recurrence following stroke: The Framingham Study. *Stroke* 1982; 13:290–295
2. Sacco RL, Foulkes MA, Mohr JP, Wolf PA, Hier DB, Price TR: Determinants of early recurrence of cerebral infarction: Stroke Data Bank. *Stroke* 1989;20:983–989
3. Petty GW, Brown RD Jr, Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO: Survival and recurrence after first cerebral infarction: A population-based study in Rochester, Minnesota, 1975 through 1989. *Neurology* 1998;50:208–216
4. 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;44:626–634
5. Johnston SC, Gress DR, Browner WS, Sidney S: Short-term prognosis after emergency department treatment of TIA. *J Am Med Assoc* 2000;284:2901–2906
6. Kidwell CS, Alger JR, Di Salle F, Starkman S, Villablanca P, Bentson J, Saver JL: Diffusion MRI in patients with transient ischemic attacks. *Stroke* 1999;30:1174–1180
7. Albers GW, Caplan LR, Easton JD, Fayad PB, Mohr JP, Saver JL, Sherman DG: Transient ischemic attack—proposal for a new definition. *N Engl J Med* 2002;347:1713–1716
8. Clagett GP, Youkey JR, Brigham RA, Orecchia PM, Salander JM, Collins GJ Jr, Rich NM: Asymptomatic cervical bruit and abnormal ocular plethysmography: A prospective study comparing two approaches to management. *Surgery* 1984;96:823–830
9. The CASANOVA Study Group: Carotid surgery versus medical therapy in asymptomatic carotid stenosis. *Stroke* 1991;22:1229–1235
10. Mayo Asymptomatic Carotid Endarterectomy Study Group: Results of a randomized controlled trial for asymptomatic carotid stenosis. *Mayo Clin Proc* 1992;67:513–518
11. Hobson RW II, Weiss DG, Fields WS, Goldstone J, Moore WS, Towne JB, Wright CB: Efficacy of carotid endarterectomy for asymptomatic carotid stenosis. *N Engl J Med* 1993;328:221–227
12. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study: Endarterectomy for asymptomatic carotid artery stenosis. *J Am Med Assoc* 1995;273:1421–1428
13. North American Symptomatic Carotid Endarterectomy Trial Collaborators: Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade stenosis. *N Engl J Med* 1991;325: 445–453
14. European Carotid Surgery Trialists' Collaborative Group: MRC European Carotid Surgery Trial: Interim results for symptomatic patients with severe (70–99%) or with mild (0–29%) stenosis. *Lancet* 1991;337:1235–1243
15. Mayberg MR, Wilson SE, Yatsu F, Weiss DG, Messina L, Hershey LA, Colling C, Eskridge J, Deykin D, Winn HR, for the Veterans Affairs Cooperative Studies Program 309 Trialist Group: Carotid endarterectomy and prevention of cerebral ischemia in symptomatic carotid stenosis. *J Am Med Assoc* 1991;266:3289–3294
16. Barnett HJ, Taylor DW, Eliasziw M, Fox AJ, Ferguson GG, Haynes RB, Rankin RN, Clagett GP, Hachinski VC, Sackett DL, Thorpe KE, Meldrum HE, for the North American Symptomatic Carotid Endarterectomy Trial Collaborators: Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. *N Engl J Med* 1998;339:1415–1425
17. CAVATAS Investigators: Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): A randomized trial. *Lancet* 2001;357:1729–1737
18. Holmes DR Jr: Best of AHA Scientific Sessions 2002. *Rev Cardiovasc Med* 2003;4:25–46
19. Hobson RW II: Update on the Carotid Revascularization Endarterectomy Versus Stent Trial (CREST) Protocol. *J Am Coll Surg* 2002;194:S9–S14
20. Grubb RL, Derdeyn C, Fritsch SM, Carpenter DA, Yundt KD, Videen TO, Spitznagel EL, Powers WJ: Importance of hemodynamic factors in the prognosis of symptomatic carotid occlusion. *J Am Med Assoc* 1998;280:1055–1060
21. Markus H, Cullinane M: Severely impaired cerebrovascular reactivity predicts stroke and TIA risk in patients with carotid artery stenosis and occlusion. *Brain* 2001;124:457–467
22. Silvestrini M, Vernieri F, Pasqualetti P, Matteis M, Passarelli F, Troisi E, Caltagirone C: Impaired cerebral vasoreactivity and risk of stroke in patients with asymptomatic carotid artery stenosis. *J Am Med Assoc* 2000;283:2122–2127

23. Gibbs JM, Wise RJS, Thomas DJ, Mansfield AO, Ross Russell RW: Cerebral haemodynamic changes after extracranial-intracranial bypass surgery. *JNNP* 1987;50:140–150
24. EC/IC Bypass Study Group: Failure of extracranial-intracranial arterial bypass to reduce the risk of ischemic stroke. Results of an international randomized trial. *N Engl J Med* 1985;313:1191–1200
25. Hypertension Detection and Follow-up Program Cooperative Group: Five-year findings of the Hypertension Detection and Follow-up Program. III. Reduction in stroke incidence among persons with high blood pressure. *J Am Med Assoc* 1982;247:633–638
26. Medical Research Council Working Party: MRC trial of treatment of mild hypertension: Principal results. *Br Med J* 1985;291:97–104
27. SHEP Cooperative Research Group: Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. *J Am Med Assoc* 1991;265:3255–3264
28. Dahlöf B, Lindholm LH, Hansson L, Scherstén B, Ekbom T, Wester P-O: Morbidity and mortality in the Swedish Trial in Old patients with Hypertension (STOP-Hypertension). *Lancet* 1991; 338:1281–1285
29. MacMahon S, Peto R, Cutler J, Collins R, Sorlie P, Neaton J, Abbott R, Godwin J, Dyer A, Stamler J: Blood pressure, stroke, and coronary heart disease. Part 1: Prolonged differences in blood pressure: Prospective observational studies corrected for the regression dilution bias. *Lancet* 1990;335:765–774
30. PROGRESS Collaborative Group: Randomised trial of perindopril-based blood-pressure lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. *Lancet* 2001; 358:1033–1041
31. The Heart Outcomes Prevention Evaluation Study Investigators: Effects of an angiotensin–converting enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000;342: 145–153
32. ONTARGET/TRANSCEND Web site. Available at: www.ontarget-micardis.com/default.asp. Accessed: May 2003
33. Atkins D, Psaty BM, Koepsell TD, Longstreth WT Jr, Larson EB: Cholesterol reduction and the risk for stroke in men. A meta-analysis of randomized, controlled trials. *Ann Intern Med* 1993;119: 136–145
34. Scandinavian Simvastatin Survival Study Group: Randomized trial of cholesterol-lowering in 4,444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383–1389
35. Sacks FM, Pfeffer MA, Moyé LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JM, Wun CC, Davis BR, Braunwald E: 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
36. 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
37. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, McKillop JH, Packard CJ: Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 1995;333:1301–1307
38. Heart Protection Study Collaborative Group: MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high risk individuals: A randomised placebo-controlled trial. *Lancet* 2002;360:7–22
39. Callahan A: Cerebrovascular disease and statins: A potential addition to the therapeutic armamentarium for stroke prevention. *Am J Cardiol* 2001;88(7B):33J–37J
40. 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
41. Laupacis A, Albers G, Dalen JE, Dunn MI, Jacobson AK, Singer DE: Antithrombotic therapy in atrial fibrillation. *Chest* 1998;114: 579S–589S
42. Boston Area Anticoagulation Trial in 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
43. Stroke Prevention in Atrial Fibrillation (SPAF) Investigators: Stroke prevention in atrial fibrillation study, final results. *Circulation* 1991; 84:527–539
44. Petersen P, Boysen G, Gotfredsen J, Andersen ED, Andersen B: Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation: The Copenhagen AFASAK Study. *Lancet* 1989;1:175–179
45. EAFT (European Atrial Fibrillation Trial) Study Group: Secondary prevention in nonrheumatic atrial fibrillation after transient ischaemic attack or minor stroke. *Lancet* 1993;342:1255–1262
46. Stroke Prevention in Atrial Fibrillation Investigators: 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
47. Wolf PA, Clagett GP, Easton JD, Goldstein LB, Gorelick PB, Kelly-Hayes M, Sacco RL, Whisnant JP: Preventing ischemic stroke in patients with prior stroke and transient ischemic attack: A statement for healthcare professionals from the Stroke Council of the American Heart Association. *Stroke* 1999;30:1991–1994
48. Albers GW, Easton JD, Sacco RL, Teal P: Antithrombotic and thrombolytic therapy for ischemic stroke. *Chest* 1998;114: 683S–698S
49. Mohr JP, Thompson JLP, Lazar RM, Levin B, Sacco RL, Furie KL, Kistler JP, Albers GW, Pettigrew LC, Adams HP Jr, Jackson CM, Pullicino P, 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;345:1444–1451
50. Homma S, Sacco RL, Di Tullio MR, Sciacca RR, Mohr JP: Effect of medical treatment in stroke patients with patent foramen ovale: Patent Foramen Ovale in Cryptogenic Stroke Study. *Circulation* 2002;105:2625–2631
51. Bosch J, Yusuf S, Pogue J, Sleight P, Lonn E, Rangoonwala B, Davies R, Ostergren J, Probstfield J, and the HOPE Investigators: Heart outcomes prevention evaluation. Use of ramipril in preventing stroke: Double blind randomised trial. *Br Med J* 2002;324:699–702
52. The Canadian Cooperative Study Group: A randomized trial of aspirin and sulfinpyrazone in threatened stroke. *N Engl J Med* 1978; 299:53–59
53. The SALT Collaborative Group: Swedish Aspirin Low-dose Trial (SALT) of 75 mg aspirin as secondary prophylaxis after cerebrovascular ischemic events. *Lancet* 1991;338:1345–1349
54. 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 Neurol Sci* 1996; 143:1–13
55. The Dutch TIA Trial Study Group: A comparison of two doses of aspirin (30 mg vs. 283 mg a day) in patients after a transient ischemic attack or minor ischemic stroke. *N Engl J Med* 1991;325: 1261–1266
56. Farrell B, Godwin J, Richards S, Warlow C: The United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: Final results. *J Neurol Neurosurg Psychiat* 1991;54:1044–1054
57. Gent M, Blakely JA, Easton JD, Ellis DJ, Hachinski VC, Harbison JW, Panak E, Roberts RS, Sicurella J, Turpie AG: The Canadian American Ticlopidine Study (CATS) in thromboembolic stroke. *Lancet* 1989;1:1215–1220
58. Hass WK, Easton JD, Adams HP Jr, Pryse-Phillips W, Molony BA, Anderson S, Kamm B: A randomized trial comparing ticlopidine hydrochloride with aspirin for the prevention of stroke in high-risk patients. *N Engl J Med* 1989;321:501–507

59. Gorelick PB, Richardson D, Kelly M, Ruland S, Hung E, Harris Y, Kittner S, Leurgans S: African American Antiplatelet Stroke Prevention Study Investigators. Aspirin and ticlopidine for prevention of recurrent stroke in black patients: A randomized trial. *J Am Med Assoc* 2003;289:2947–2957
60. CAPRIE Steering Committee: A randomised, blinded trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996;348:1329–1339
61. Bennett CL, Connors JM, Carwile JM, Moake JL, Bell WR, Tarantolo SR, McCarthy LJ, Sarode R, Hatfield AJ, Feldman MD, Davidson CJ, Tsai H-M: Thrombotic thrombocytopenic purpura associated with clopidogrel. *N Engl J Med* 2000;342:1773–1777
62. Lau WC, Waskell LA, Watkins PB, Neer CJ, Horowitz K, Hopp AS, Tait AR, Carville DGM, Guyer KE, Bates ER: Atorvastatin reduced the ability of clopidogrel to inhibit platelet aggregation. A new drug-drug interaction. *Circulation* 2003;107:32–37
63. Serebruany VL, Steinhubl SR, Hennekens CH: Are antiplatelet effects of clopidogrel inhibited by atorvastatin? A research question formulated but not yet adequately tested. *Circulation* 2003;107: 1568–1569
64. Nakamura T, Uchiyama S, Yamazaki M, Iwata M: Effects of dipyridamole and aspirin on shear-induced platelet aggregation in whole blood and platelet-rich plasma. *Cerebrovasc Dis* 2002;14:234–238
65. Aggrenox® package insert. Ridgefield, Conn: Boehringer Ingelheim; March 2001
66. Chew DP, Bhatt DL, Sapp S, Topol EJ: Increased mortality with oral platelet glycoprotein IIb/IIIa antagonists: A meta-analysis of phase III multicenter randomized trials. *Circulation* 2001;103: 201–206
67. Nappi J, Talbert R: Dual antiplatelet therapy for prevention of recurrent ischemic events. *Am J Health Syst Pharm* 2002;59: 1723–1735
68. 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. *N Engl J Med* 2001;345:494–502
69. Albers GW, Amarenco P: Combination therapy with clopidogrel and aspirin: Can the CURE results be extrapolated to cerebrovascular patients? *Stroke* 2001;32:2948–2949
70. Antithrombotic Trialists' Collaboration: Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *Br Med J* 2002;324:71–86
71. De Schryver EL: Design of ESPRIT: An international randomized trial for secondary prevention after non-disabling cerebral ischaemia of arterial origin. *Cerebrovasc Dis* 2000;10:147–150