ORIGINAL RESEARCH

Evidence-Based Medicine: Review of Guidelines and Trials in the Prevention of Secondary Stroke

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Editorial assistance for the development of these manuscripts was provided by Vaibhav Katkade, Laurel Ranger, and Ann Sherwood, PhD, Boehringer Ingelheim Pharmaceuticals, Inc. This supplement was supported by Boehringer Ingelheim Pharmaceuticals, Inc.

Transient ischemic attack (TIA) carries a substantial short-term risk for stroke, which is a leading cause of disability and death in the United States. Despite the existing evidence-based guidelines for secondary prevention of stroke, variability in the assessment, diagnostic testing, and treatment of patients with TIA in actual clinical practice remains. Identification of stroke etiology via radiological examination is of paramount importance for the appropriate treatment of patients after TIA or stroke. Management of ischemic stroke or TIA includes lifestyle modifications, reduction of modifiable risk factors (eg, hypertension, diabetes, and elevated cholesterol), and appropriate therapeutic treatments. Antiplatelet therapy is the cornerstone of secondary prevention of stroke; guidelines for its use for noncardioembolic cases have been developed from a solid evidence base. Additional therapeutic approaches include HMG-CoA reductase inhibitors (statins), antihypertensives, and anticoagulants. The results of ongoing large trials will further clarify the role of specific antiplatelet agents for the secondary prevention of stroke in patients with noncardioembolic ischemic stroke or TIA. ***Journal of Hospital Medicine*** **2008;3(4 Suppl):S6–S19.** © *2008 Society of Hospital Medicine.*

KEYWORDS: guidelines, secondary prevention, stroke, antiplatelets.

Stroke is a leading cause of disability and the third leading cause of death in the United States.[1] Transient ischemic attack (TIA) carries a substantial short-term risk for stroke.[1] The risk of stroke following TIA ranges from 2% to 5% within 48 hours, is 10.5% within 90 days, and ranges from 24% to 29% within 5 years.[2–4] Among the 780,000 new or recurrent strokes that occur each year, 180,000 are recurrent attacks.[1,5] Several evidence-based guidelines for secondary prevention of stroke are available. To reduce variability in the assessment, diagnostic evaluation, and treatment of patients with TIA in actual clinical practice and to simplify the management of TIA or ischemic stroke, this article will review the available guidelines for secondary prevention of stroke and the data from clinical trials that support these guidelines.

PATHOPHYSIOLOGY AND SUBTYPES/CLASSIFICATION

Stroke is broadly classified as hemorrhagic or ischemic stroke. Hemorrhagic stroke, including intraparenchymal and subarachnoid hemorrhage, accounts for 13% of strokes and ischemic stroke for 87%.[1] Ischemic stroke is caused by inadequate cerebral blood flow as a result of either stenosis or occlusion of the

DOI 10.1002/jhm.337
Published online in Wiley InterScience (www.interscience.wiley.com).

vessels supplying the brain.[6] The average rate of cerebral blood flow is 50 mL/100 g a minute. Flow rates below 20–25 mL/100 g a minute are usually associated with cerebral impairment, and rates below 10 mL/100 g a minute are associated with irreversible brain damage.

Approximately 20% of ischemic strokes are of cardioembolic origin; 25% are a result of atherosclerotic cerebrovascular disease; 20% are a result of penetrating artery disease (lacunes); 5% are due to other causes, such as hypercoagulable states, including protein S and C deficiency, sickle cell disease, and various types of vasculitis; and 30% are cryptogenic.[7,8] Cardioembolic stroke can be a manifestation of atrial fibrillation, valvular disease, ventricular thrombi, and other cardiac conditions.[9] Large arteries, such as the carotid arteries and the proximal aorta, are a source of atherogenic emboli.[10] Atherosclerotic plaques in the arteries may narrow the lumen of the blood vessel or produce emboli, which results in occlusion of the distal arteries, causing a stroke.

RISK FACTORS

Several risk factors, both nonmodifiable and modifiable, predispose individuals to stroke. Nonmodifiable risk factors include age, sex, race, and family or personal history of stroke or myocardial infarction (MI).[1,5] After the age of 55, the stroke rate doubles for every 10-year increase in age.[1] African Americans have a 50% greater risk of death due to stroke than whites.[1] The appropriate management of modifiable risk factors can significantly reduce the risk of recurrent stroke and improve survival. The many modifiable factors include hypertension, heart disease, smoking, diabetes, atrial fibrillation, dyslipidemia, obesity, and alcohol abuse.[1,5] The mechanisms of how these factors increase the risk for stroke and management of these factors are discussed later in this article. It is important to educate individuals, particularly those who also have nonmodifiable risk factors, about modifiable risk factors in order to enable early and appropriate intervention.

DIAGNOSIS

Most patients with TIA are asymptomatic when they present to the emergency department (ED). The risk of stroke following an episode of TIA has been found to be 3.5% within 48 hours in a meta-analysis based on a random effects model;[11] therefore, it is critical to quickly identify patients with high short-term risk for recurrent stroke.[12] The $ABCD^2$ score was recently validated in TIA patients to estimate the near-term risk of completed stroke.[13] Patients with a score of 0–3 on the $ABCD^2$ are at low risk, those with a score of 4 or 5 are at moderate risk, and those with a score 6 or 7 are at severe risk for recurrent stroke (Table 1).[13] Risk scores, although highly predictive, should complement clinical judgment in the assessment of individual stroke risk.

TABLE 1
$ABCD^2$ Score[13]

Risk factors	Points
A—Age > 60 years	1
B—Blood pressure	
Systolic ≥ 140 mm Hg	1
Diastolic ≥ 90 mm Hg	1
C—Clinical features	
Unilateral weakness	2
Speech impairment without weakness	1
D—Duration of symptoms	
10–59 minutes	1
≥60 minutes	2
D—Diabetes	1

The $ABCD^2$ score provides a single tool to assess stroke risk 2, 7, and 90 days after transient ischemic attack. A score of 0–3 indicates low risk, a score of 4–5 indicates moderate risk, and a score of 6–7 indicates high risk.

Currently, there are no specific guidelines for the diagnostic evaluation of patients with suspected TIA. However, the following approach, including elements of acute evaluation for both stroke and TIA as well as risk factor identification that may aid in choosing specifics of secondary prevention, may be adopted in the management of patients with TIA (Table 2).[14,15]

A computed tomography (CT) scan of the head or magnetic resonance imaging (MRI) of the brain should be performed as soon as possible to distinguish between ischemic and hemorrhagic stroke, eliminate other pathologies that mimic TIA or stroke, and guide selection of the appropriate treatment approach. CT scanning is often the best initial imaging choice because it reliably excludes intracranial hemorrhage and is rapidly available in most settings. For those for whom the diagnosis is uncertain, diffusion-weighted MRI may be more helpful. Because of the time issues surrounding the use of tissue plasminogen activator, waiting for an MRI may not always be the best choice,

TABLE 2
Diagnostic Evaluation of Patients with Stroke or TIA*

Diagnostic test	Indication
Acute phase	
CT brain (noncontrast)	Rule out intracerebral or subarachnoid hemorrhage and may show early signs of stroke; if clinically suspected subarachnoid hemorrhage, lumbar puncture should be performed
CT angiogram with CT perfusion	Visualize occluded vessel and identify infarcted versus at-risk tissue
Chest radiograph	Potentially identify aortic aneurysm or lung masses prone to hemorrhage
Finger stick (glucometer testing)	Rule out hypoglycemia as etiology; follow-up glucose screening may identify diabetes as a risk factor
Basic metabolic panel	Rule out metabolic problems leading to symptomatology and renal disease, which may prevent contrast imaging
Coagulation profiles	Rule out preexisting coagulopathy that would make patient prone to hemorrhage or ineligible for some therapies, including tissue plasminogen activator
Stool guaiac	Rule out gastrointestinal bleed, which may make patient ineligible for some therapies
Electrocardiogram	Rule out concurrent myocardial infarction or cardiac arrhythmia
Post–acute phase	
MRI/MRA: diffusion and perfusion studies	Quantify region of infarcted tissue and affected artery—may be useful in acute phase if available on an expedited basis
Transthoracic/transesophageal echocardiogram	Rule out cardioembolic stroke etiology (ie, mural thrombus, patent foramen ovale, valvular disease)
Carotid duplex	Rule out carotid stenosis as stroke risk factor (secondary prevention)
Lipid profile	Rule out hyperlipidemia as stroke risk factor (secondary prevention)
Blood tests: antinuclear antibodies, rapid plasma reagin test, thyroid panel, antiphospholipid antibodies; other tests for hypercoagulability	Rule out other reasons for hypercoagulable state in the appropriate patient population

* Diagnostic evaluation should not include all of the above studies but should be tailored to the individual patient based on presenting age, medical history, and present illness. The goal of the diagnostic evaluation in the acute phase involves avoiding tissue plasminogen activator–related complications and in the post–acute phase is directed at identifying stroke etiology and providing intervention for secondary stroke prevention.

CT, computed tomography; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; TIA, transient ischemic attack.

although some institutions are now able to provide quick access to MRI imaging. Imaging can detect silent cerebral infarcts associated with an increased risk of stroke. In patients with previous TIA and/or stroke, MRI is more sensitive than CT in detecting small, old infarcts (although most are seen on CT) and in visualizing the posterior fossa (cerebellum and brain stem).[12]

Holter electrocardiography or inpatient telemetry monitoring can be performed to identify atrial fibrillation, a known risk factor for stroke or TIA.[16] Transesophageal echocardiography (TEE) has been reported to be more sensitive than transthoracic echocardiography (TTE) for detecting cardioembolic sources of TIA or ischemic stroke across multiple age groups.[17] TEE has several advantages over TTE, such as the creation of clearer images of the aorta, the pulmonary artery, valves of the heart, both atria, the atrial septum, and the left atrial appendage.

Cerebral angiography is indicated in several instances, including in children or young patients with ischemic stroke because vascular abnormalities and cerebral vasculitis are relatively more common causes in patients in these age groups.[18] Furthermore, in centers in which intra-arterial procedures are frequently performed, angiography is indicated to confirm the suspicion of posterior circulation vessel (ie, vertebral or basilar artery) occlusion prior to intervention. Angiography has the highest diagnostic validity compared with other noninvasive techniques and may be indicated if cerebral vasculitis or nonatherosclerotic disease of extracranial arteries (eg, dissections, vascular malformations) is suspected. Angiography of intracranial vessels is the gold standard for the study of cerebral aneurysms and is recommended in patients with subarachnoid hemorrhage, but there is evidence that magnetic resonance angiography (MRA) and digital subtraction angiography have better discriminatory ability in the 70%–99% range of stenosis compared with duplex ultrasonography (DUS) for determining candidacy for carotid endarterectomy (CEA) or stenting.[19,20]

The MRA and CT angiography (CTA) are generally used to visualize the intracranial and extracranial—both anterior and posterior—cerebral circulation. The use of MRA or CTA to image cerebral circulation has generally supplanted the use of carotid and transcranial ultrasonography and obviated the need for catheter angiography in investigating the etiology of most ischemic strokes

and TIAs. The degree of carotid stenosis should be primarily estimated using noninvasive techniques (DUS, MRA, CTA).[21] Duplex ultrasonography is recommended after CEA 6 months and every 1–2 years after the procedure in order to monitor recurrent stenosis.[22] Angiography should be performed when the results of noninvasive examinations are discordant; when significant atherosclerotic disease of intracranial arteries is suspected, especially in vertebrobasilar arteries; or when MRA or CT angiography provides technically poor images.[23]

Transcranial Doppler ultrasonography and color Doppler ultrasound (TCD) are used to evaluate the intracranial vessels and may provide additional information on patency of cerebral vessels, recanalization, and collateral pathways. Compared with the gold standard of conventional angiography, TCD has a positive predictive value of 36% and a negative predictive value of 86% for a diagnosis of intracranial stenosis.[24] This technique also can be used as a complementary examination in patients undergoing CEA in order to aid in preoperative evaluation and intraoperative monitoring of blood flow in the territory of the operated artery.[12]

TREATMENT

The management of ischemic stroke or TIA includes lifestyle modifications, reduction of modifiable risk factors, and appropriate surgical and medical intervention.[12]

Lifestyle Modifications

There is strong evidence for smoking as an independent risk factor for ischemic stroke, irrespective of age, sex, or ethnic background.[25] Among smokers, the risk for ischemic stroke is twice that of nonsmokers.[26] All patients with previous ischemic stroke or TIA are strongly encouraged not to smoke and to avoid smoke in their environments as much as possible. These patients are also recommended to obtain counseling and smoking cessation medications as needed; these interventions should be started at the time of hospital admission.

The relationship of alcohol consumption to cardiovascular risk is controversial because most studies suggest a J-shaped association between alcohol and ischemic stroke: a protective effect for those who consume light-to-moderate amounts of alcohol (<60 g ethanol/day)[27] and elevated stroke risk for heavy drinkers.[28] The protective effect of moderate drinking may be related to an increase in high-density lipoprotein cholesterol,[29,30] reduced platelet aggregation,[31] and lower plasma fibrinogen concentration.[32] In contrast, heavy drinking can lead to alcohol-induced hypertension,[33] a hypercoagulable state, reduced cerebral blood flow, and atrial fibrillation. Patients with prior ischemic stroke or TIA who are heavy drinkers are recommended to reduce or eliminate alcohol consumption.[34]

Obesity (body mass index [BMI] > 30 kg/m^2) is an independent risk factor for coronary heart disease and premature mortality.[1] Obesity is also associated with several other risk factors, such as hypertension, diabetes, dyslipidemia, and obstructive sleep apnea.[35] Indeed, obesity is often a symptom of metabolic syndrome, a combination of medical disorders that increases a person's risk for cardiovascular disease and diabetes (the International Diabetes Federation consensus worldwide definition of metabolic syndrome). All ischemic stroke or TIA patients who are overweight should maintain a goal BMI of 18.5–24.9 kg/m^2 and a waist circumference of less than 35 inches, if female, or less than 40 inches, if male, because abdominal obesity is more related to stroke risk.[36] Clinicians should recommend caloric restriction as the cornerstone of weight loss along with diets low in fat and cholesterol, increased physical activity, and behavioral counseling. A recent retrospective review suggests that moderately or highly active individuals have a lower risk of stroke or mortality than those whose physical activity is low.[37] Physical activity exerts its beneficial effects by lowering blood pressure and weight, enhancing vasodilation, improving glucose tolerance, and promoting cardiovascular health.

Management of Modifiable Risk Factors

Hypertension

An estimated 73 million Americans have hypertension.[1] Meta-analyses of randomized trials confirm that lowering blood pressure is associated with a 30%–40% reduction in stroke risk.[38,39] Because hypertension is a risk factor for many cardiovascular and cerebrovascular conditions, detailed evidence-based recommendations for blood pressure screening and treatment of individuals with hypertension are summarized in the American Heart Association (AHA)/American Stroke Association

(ASA) guidelines on the primary prevention of ischemic stroke.[40] More detailed information is available in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.[41] Antihypertensive treatment is recommended for the prevention of recurrent stroke and other vascular events in individuals with ischemic stroke who are beyond the period immediately after an ischemic stroke regardless of whether they have a history of hypertension. Average blood pressure reduction of 10/5 mm Hg or maintenance of normal blood pressure (<120/80 mm Hg) is associated with benefits via diet, exercise, or medication.[42] In a meta-analysis of 7 trials that included a total of 15,527 patients, treatment with antihypertensive agents was associated with a 24% reduction in total stroke ($P = .005$), a 21% reduction in nonfatal stroke ($P = .01$), and a nonsignificant 24% reduction in fatal stroke ($P = .08$).[42] The choice of specific drugs, discussed in the antihypertensive section of this article, and the target blood pressure should be individualized.

Diabetes

Diabetes affects 8% of the adult U.S. population, and several studies have reported that 15%–33% of patients with ischemic stroke have diabetes.[43–45] The prevalence of diagnosed diabetes is projected to rise to 29 million by 2050 from the current 11 million, an increase of 165%.[46] Diabetes is a critical independent risk factor for ischemic stroke. Rigorous control of blood pressure and lipid level is recommended in patients with diabetes, as well as in patients with hypertension and/or elevated cholesterol.[5] Several agents used to treat diabetes, such as metformin and pioglitazone, improve glucose and lipid metabolism and exert antiatherogenic effects, aiding in the prevention of atherosclerosis.[47] Glycemic control is recommended for patients with diabetes in order to prevent stroke and cardiovascular disease, but data are limited. Randomized trial data have shown that continual reduction of vascular events is correlated with control of glucose to normal levels.[48]

Elevated Cholesterol

The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) guidelines recommend that lifestyle modification, diet, and medications be used to manage ischemic stroke or TIA patients with elevated cholesterol, comorbid coronary artery disease, or evidence of atherosclerosis. The target goal for those with coronary heart disease or symptomatic atherosclerosis is low-density lipoprotein (LDL) cholesterol below 100 mg/dL.[49] The 2004 update to the NCEP guidelines proposed an LDL cholesterol target below 70 mg/dL in very high-risk patients or in those with established CHD plus multiple major risk factors (especially diabetes), severe and poorly controlled risk factors (especially continued cigarette smoking), multiple risk factors of the metabolic syndrome (especially high triglycerides [≥ 200 mg/dL] plus non–high-density lipoprotein [HDL] cholesterol ≥ 130 mg/dL with low HDL-C [<40 mg/dL]), or patients with acute coronary syndromes.[50]

Medical Treatment

Antiplatelet therapy is the cornerstone of secondary prevention of stroke.[51] Four antiplatelet drugs are available—aspirin, clopidogrel, dipyridamole, and ticlopidine—that are approved by the U.S. Food and Drug Administration for secondary prevention of stroke. The following sections review the evidence for the efficacy and safety of these drugs for the secondary prevention of stroke (Table 3).[52–68] The role of anticoagulation for secondary prevention of noncardioembolic stroke is also discussed (Table 4).[69–71]

Aspirin

The Antiplatelet Trialists' Collaboration (ATC) determined the effect of prolonged antiplatelet therapy on vascular events (nonfatal MI, nonfatal stroke, or vascular death) in various patient groups.[52] This retrospective analysis included about 70,000 high-risk patients and 30,000 low-risk patients from 145 randomized trials that compared prolonged antiplatelet therapy versus control and about 10,000 patients from 29 randomized trials that directly compared different antiplatelet regimens. Overall, the typical reduction in risk for these vascular events was 25% (SD 2%) with antiplatelet therapy compared with placebo ($P < .001$). The most commonly used antiplatelet regimen was medium-dose aspirin (75–325 mg/day). The number needed to treat (NNT) was 30 (absolute risk reduction [ARR], 3.3%) for 2.5 years for prevention of vascular events with aspirin.

TABLE 3
Antiplatelet Therapy Summary: Risk Reduction in Key Stroke Trials

Study	Population	Treatment	Duration	Risk reduction	Outcome
ATC[52]	70,000 High-risk patients	Antiplatelet (mostly aspirin 75–325 mg/day), placebo	>1 month	RRR, 25% vs. placebo; ARR, 3.3%	Vascular events (nonfatal MI, nonfatal stroke, vascular death)
IST[53]	19,435 Patients with acute ischemic stroke	Heparin 5000 or 12,500 U/day, aspirin 300 mg/day, heparin + aspirin, placebo	14 days	Risk of ischemic stroke, 2.8% with aspirin vs. 3.9% in nonaspirin groups	Nonfatal stroke
CAPRIE[56]	19,185 Patients with recent ischemic stroke, MI, or atherosclerotic PAD	Clopidogrel 75 mg/day, aspirin 325 mg/day	1–3 years (mean, 1.91 years)	RRR, 8.7% clopidogrel vs. aspirin; ARR, 0.5% with clopidogrel	MI, stroke, or vascular death
MATCH[58]	7599 Patients with recent ischemic stroke or TIA plus 1 additional vascular risk factor	Clopidogrel 75 mg/day, clopidogrel + aspirin 75 mg/day	1.5 years	RRR, 6.4% combination vs. aspirin (NS)	Ischemic stroke, MI, vascular death, hospitalization for ischemic event
CHARISMA[59]	15,603 Patients with established cardiovascular disease or multiple risk factors	Clopidogrel 75 mg/day + aspirin 75–162 mg/day, aspirin alone	2 years	RRR, 7% for combination vs. aspirin	MI, ischemic stroke, vascular death
ESPS-2[61]	6602 Patients with TIA or stroke in previous 3 months	Aspirin 50 mg/day, dipyridamole 200 mg twice daily, aspirin + dipyridamole, placebo	2 years	RRR, 37% combination vs. placebo; ARR, 3.4% combination vs. aspirin	Secondary stroke
ESPRIT[65]	2739 Patients with TIA or minor ischemic stroke	Aspirin (30–325 mg/day), aspirin + dipyridamole (200 mg twice daily), oral anticoagulants	5 years	RRR, 20% combination vs. aspirin; ARR, 1% per year combination vs. aspirin	Vascular death, nonfatal MI, nonfatal stroke

ARR, absolute risk reduction; ATC, Antiplatelet Trialists' Collaboration; CAPRIE, Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events; CHARISMA, Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance; ESPRIT, European/Australasian Stroke Prevention in Reversible Ischemia Trial; ESPS-2, Second European Stroke Prevention Study; IST, International Stroke Trial; MATCH, Management of Atherothrombosis with Clopidogrel in High-Risk Patients with TIA or Stroke; MI, myocardial infarction; NS, nonsignificant; PAD, peripheral arterial disease; RRR, relative risk reduction; TIA, transient ischemic attack.

The International Stroke Trial was a large, randomized, open-label trial of up to 14 days of antithrombotic therapy immediately following the onset of stroke.[53] In this trial, 19,435 patients were randomly assigned to receive unfractionated heparin (5000 or 12,500 IU twice daily) or aspirin (300 mg/day), alone or in combination, or placebo. The primary outcomes were death within 14 days and death or dependency at 6 months. Heparin treatment was not associated with a significant reduction in deaths within 14 days (876 [9.0%] vs. 905 [9.3%] with placebo) or rate of death or dependency at 6 months (62.9% in both groups). Heparin treatment was associated with an increase in the rate of hemorrhagic stroke and a significant excess of 9 (SD 1) transfused or fatal extracranial bleeds per 1000. Aspirin was not associated with a significant reduction in death within 14 days (872 [9.0%] vs. 909 [9.4%]; however, at 6 months, there was a nonsignificant trend toward a smaller proportion of deaths or dependency in those receiving aspirin (62.2% vs. 63.5%; $P = .07$), a difference of 13 (SD 7) deaths per 1000. Patients receiving aspirin had significantly fewer recurrent ischemic strokes within 14 days (2.8% vs. 3.9%; $P < .001$) with no significant increase in hemorrhagic strokes (0.9% vs. 0.8%), resulting in a significant reduction in the incidence of death or nonfatal recurrent stroke (11.3% vs. 12.4%, $P = .02$). Aspirin alone was associated with an excess of 2 (SD 1) transfused or fatal extracranial bleeds per 1000. These data suggest that aspirin should be started immediately after an ischemic stroke. The NNT for 14 days was 91 to prevent 1 nonfatal stroke.[53]

The efficacy of a lower dose of aspirin (30 mg/day) was compared with that of aspirin 238 mg/day by the Dutch TIA Trial Study Group. The results showed that the lower dose of aspirin was

TABLE 4
Summary of Results: Trials of Oral Anticoagulant Therapy Versus Antiplatelet Therapy

Study	Key efficacy results	Key safety results
WARSS[70]	No difference between warfarin and aspirin in prevention of recurrent ischemic stroke, death, or rate of major hemorrhage	Although safety profile of warfarin was similar to aspirin in this study, there is potential increased risk in a community setting
WASID[71]	Warfarin provided no additional benefit over high-dose aspirin (1300 mg/day) for prevention of recurrent stroke or death	Warfarin was associated with significantly higher rates of adverse events
ESPRIT[69]	Oral anticoagulants did not provide additional benefit over aspirin for prevention of TIA or minor stroke of arterial origin	Oral anticoagulants were associated with increased incidence of bleeding complications

ESPRIT, European/Australasian Stroke Prevention in Reversible Ischemia Trial; TIA, transient ischemic attack; WARSS, Warfarin Aspirin Recurrent Stroke Study; WASID, Warfarin-Aspirin Symptomatic Intracranial Disease.

as effective as the higher dose in the prevention of a recurrent vascular event, and patients taking the lower dose had fewer adverse events.[54]

However, aspirin resistance is an issue of ongoing research and debate. It is one of several explanations for the limited efficacy of aspirin in the stroke population. Results of one study showed that resistance to aspirin in platelet function was not uncommon, as measured by platelet aggregation 24 hours and 3, 6, and 12 months following initiation of aspirin therapy.[55]

Clopidogrel

The Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study was a randomized, blinded trial designed to assess the relative efficacy of clopidogrel (75 mg/day) and aspirin (325 mg/day) in reducing the risk of the composite outcome of ischemic stroke, MI, or vascular death.[56] In this study, 19,185 patients with atherosclerotic vascular disease (recent ischemic stroke, recent MI, or symptomatic peripheral arterial disease) were followed up for 1.91 years. Clopidogrel was associated with a 5.32% risk of the primary composite outcome compared with 5.83% with aspirin (relative risk reduction [RRR], 8.7%; 95% CI, 0.3%–16.5%; $P = .043$). The NNT was 196 (ARR, 0.51%; 95% CI, 102–4188; $P = .043$) for 1 year with clopidogrel instead of aspirin to prevent 1 patient from having a stroke, MI, or vascular death.[56] Both treatments were associated with a similar safety profile. In a prespecified subgroup analysis among patients with a previous stroke, the risk reduction with clopidogrel was nonsignificant. However, in a post hoc analysis of patients with diabetes enrolled in the CAPRIE trial (n = 3866), clopidogrel was associated with a greater benefit than aspirin (ARR, 2.1%; $P = .042$) compared with no benefit in nondiabetic patients.[57]

In the Management of Atherothrombosis with Clopidogrel in High-Risk Patients with TIA or Stroke (MATCH) trial, 7599 patients with a prior stroke or TIA plus additional risk factors received clopidogrel 75 mg/day or combination therapy of clopidogrel 75 mg/day plus aspirin 75 mg/day.[58] The primary outcome was the composite of ischemic stroke, MI, vascular death, or rehospitalization secondary to ischemic events. There was no significant benefit of combination therapy compared with clopidogrel alone in reducing the primary outcome (RRR, 6.4%; 95% CI, −4.6%–16.3%; ARR, 1%; 95% CI, −0.6%–2.7%) or any of the secondary outcomes. The risk of major hemorrhage was significantly increased in the combination group compared with clopidogrel alone, with a significant 1.3% absolute increase in life-threatening bleeding (95% CI, 0.6%–1.9%). Although clopidogrel plus aspirin is recommended over aspirin for acute coronary syndromes, with most guidelines advocating up to 12 months of treatment, the results of the MATCH trial do not suggest a similar risk reduction for stroke patients.[58]

The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial investigated the efficacy of dual antiplatelet therapy with clopidogrel (75 mg/day) plus low-dose aspirin (75–162 mg/day) versus low-dose aspirin alone in reducing subsequent stroke and MI and death from cardiovascular causes in 15,603 men and women with clinically evident cardiovascular disease or multiple cardiovascular risk factors.[59] At the end of follow-up, there was no significant difference between treatments in the primary efficacy outcome (6.6% with clopidogrel plus aspirin vs. 7.3%

with aspirin alone; relative risk [RR], 0.93; 95% CI, 0.83–1.05; $P = .22$). The combination was associated with a greater incidence of gastrointestinal bleeding (number needed to harm, 88; 95% CI, 59-170) over 28 months. There was a nonsignificant increase in the risk of severe bleeding with clopidogrel in combination with aspirin compared with aspirin alone (RR, 1.2; 95% CI, 0.91–1.59; $P = .20$). Among patients with multiple risk factors (but no clinically evident cardiovascular disease), cardiovascular mortality was significantly higher with clopidogrel plus aspirin (3.9%) versus aspirin alone (2.2%; $P = .01$).[59]

Recently, a post hoc analysis of data from CHARISMA was performed to assess the possible benefit of dual antiplatelet therapy in a subgroup of patients (n = 9478) with a documented history of MI, ischemic stroke, or symptomatic peripheral arterial disease.[60] In this subgroup, the rate of cardiovascular death, MI, or stroke was significantly lower in the clopidogrel-plus-aspirin group compared with aspirin alone (7.3% versus 8.8%; hazard ratio [HR], 0.83; 95% CI, 0.72–0.96; $P = .01$). There was no significant difference in severe bleeding between the clopidogrel-plus-aspirin and aspirin-alone groups in this subpopulation (1.7% vs. 1.5%; HR, 1.12; 95% CI, 0.81–1.53; $P = .50$). However, there was a significantly higher increase in moderate bleeding with clopidogrel plus aspirin compared with aspirin alone (2.0% versus 1.3%; HR, 1.60; 95% CI, 1.16–2.20; $P = .004$). These data from the post hoc subanalysis suggest that a large proportion of patients with documented prior MI, ischemic stroke, or symptomatic peripheral artery disease may derive significant benefit from dual antiplatelet therapy with clopidogrel plus aspirin.[60] These observations do not support the observations in the MATCH trial; therefore, additional studies are required to validate these findings.

Aspirin Plus Extended-Release Dipyridamole

In the Second European Stroke Prevention Study (ESPS-2), 6602 patients with prior stroke or TIA were assigned to low-dose aspirin (25 mg twice daily) plus extended-release dipyridamole (ER-DP; 200 mg twice daily), aspirin alone, ER-DP alone, or placebo.[61] The extended-release formulation of dipyridamole provided the benefits of continuous absorption and steady serum levels, resulting in a more consistent response in a narrow therapeutic index, especially in the elderly.[62] The relative risk of stroke was reduced by 37% with the combination treatment versus 18% with low-dose aspirin alone or 16% with dipyridamole alone. The combination treatment was also associated with a significant reduction (36%) in the risk of TIA compared with placebo ($P < .001$).[61] Thus, significantly greater protective effects were seen with the combination therapy. Gastrointestinal bleeding was more common in patients receiving aspirin than in those receiving placebo or ER-DP. No significant additional bleeding was observed with the aspirin-plus-ER-DP combination compared with aspirin alone. The 3.4% ARR with aspirin plus ER-DP compared with aspirin alone suggests an NNT of 34 for 2 years to prevent 1 recurrent stroke.[63] In addition, the ESPS-2 data meta-analysis combined with 14 smaller trials of aspirin and dipyridamole was found to reduce the odds of nonfatal stroke by 23% relative to aspirin monotherapy.[64]

The European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT) was designed to assess the efficacy and safety of aspirin plus dipyridamole versus aspirin alone for secondary prevention of cardiovascular events in patients with ischemic stroke of presumed arterial origin.[65] In this trial, 2739 patients were randomly assigned to aspirin (30–325 mg/day) with or without dipyridamole (200 mg twice daily) within 6 months of TIA or minor stroke of presumed arterial origin. The primary outcome was a composite of death from all vascular causes, nonfatal stroke, nonfatal MI, or major bleeding complication, whichever occurred first. Median aspirin dose was 75 mg/day in both treatment groups, and ER-DP was used by 83% of the patients in the combination group. The primary outcome occurred in 173 (13%) of patients receiving aspirin plus dipyridamole and in 216 (16%) of those receiving aspirin alone (HR, 0.8; 95% CI, 0.66–0.98; ARR, 1.0% per year, 95% CI, 0.1%–1.8%). The NNT was 33 over 3.5 years to prevent 1 primary outcome with aspirin plus dipyridamole.[65] These results, confirming those of ESPS-2, strongly suggest that use of combination aspirin plus ER-DP among patients with recent brain ischemia provides significant benefit compared with aspirin alone, without additional adverse effects.

Ticlopidine

Ticlopidine was found to be more effective than aspirin or placebo in risk reduction for recurrent stroke.[66] However, the results of several studies

showed that its use was associated with serious adverse effects, such as gastrointestinal events, neutropenia, skin rash, and thrombotic thrombocytopenic purpura.[66,67] The more recent African American Antiplatelet Stroke Prevention Study (AAASPS), which included more than 1800 stroke patients, showed that 250 mg of ticlopidine twice daily was no more effective than 325 mg of aspirin twice daily in an African American population.[68] Overall, ticlopidine use for prevention of recurrent stroke is not supported by trial data, especially considering the substantial risk of adverse effects.

Anticoagulation

In an additional arm of the ESPRIT trial, 1068 patients were randomly assigned either anticoagulants (target international normalized ratio [INR], 2.0–3.0) or aspirin (30–325 mg/day) within 6 months of a TIA or minor stroke of presumed arterial origin (Table 4).[69] In a post hoc analysis, anticoagulants were also compared with the combination of aspirin and dipyridamole (200 mg twice daily). The primary outcome was the composite of death from all vascular causes, nonfatal stroke, nonfatal MI, or major bleeding complication, whichever occurred first. The primary event was observed in 20% of patients (106 of 523) receiving anticoagulants compared with 16% of patients (82 of 509) receiving aspirin plus dipyridamole (HR, 1.31; 95% CI, 0.98–1.75). The risk for major bleeding was at least 60% lower in patients receiving aspirin plus dipyridamole compared with anticoagulants (2% versus 9%; HR, 4.37; 95% CI, 2.27–8.43).[69] These data confirm that the combination of aspirin plus dipyridamole is more effective than aspirin alone or warfarin for secondary prevention of stroke in patients with stroke of arterial origin.

The Warfarin Aspirin Recurrent Stroke Study (WARSS) compared warfarin (target INR, 1.4–2.8) versus aspirin (325 mg/day) for the prevention of recurrent ischemic stroke among 2206 patients with a noncardioembolic stroke (Table 4).[70] Results of this randomized, double-blind, multicenter trial showed no significant difference in the rates of recurrent stroke or death (warfarin, 17.8%; aspirin, 16.0%). Warfarin and aspirin were also associated with similar rates of major bleeding (2.2% and 1.5% per year, respectively). Although there were no differences between the 2 treatments, the potential increased risk of bleeding and cost of monitoring were considered in the recommendation of the AHA/ASA to choose antiplatelets over anticoagulants in the setting of noncardioembolic stroke.[5]

The Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial was designed to test the efficacy of warfarin (target INR, 2.0–3.0 [mean, 2.5]) versus aspirin among patients with >50% angiographically documented intracranial stenosis (Table 4).[71] WASID was stopped prematurely because of warfarin's association with significantly higher rates of adverse events and evidence of no benefit over high-dose aspirin (1300 mg/day). During a mean follow-up of 1.8 years, adverse events in the 2 groups were death (aspirin, 4.3%, vs. warfarin, 9.7%; HR, 0.46; 95% CI, 0.23–0.90; $P = .02$), major hemorrhage (aspirin, 3.2%, vs. warfarin, 8.3%; HR, 0.39; 95% CI, 0.18–0.84; $P = .01$), and MI or sudden death (aspirin, 2.9%, vs. warfarin, 7.3%; HR, 0.40; 95% CI, 0.18–0.91; $P = .02$). The primary end point (ischemic stroke, brain hemorrhage, and nonstroke vascular death) occurred in approximately 22% of patients in both treatment arms (HR, 1.04; 95% CI, 0.73–1.48; $P = .83$).

Statins

Statins reduce the risk of stroke among patients with vascular disease, primarily through LDL cholesterol reduction.[72] In the Heart Protection Study (N = 20,536), treatment with simvastatin 40 mg resulted in a 25% relative reduction in the first-event rate for stroke ($P < .0001$) and a 28% reduction in presumed ischemic strokes ($P < .0001$) in patients with cerebrovascular disease, other occlusive vascular disease, or diabetes. No apparent difference in strokes was attributed to hemorrhage (0.5% vs. 0.5%; $P = .8$). Among patients with preexisting cerebrovascular disease (n = 3280), simvastatin therapy resulted in a 20% reduction in the rate of any major vascular event ($P = .001$).[72]

The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial examined the effect of high-dose atorvastatin specifically on secondary prevention of stroke in patients who had a recent history of stroke or TIA and LDL cholesterol levels of 100–190 mg/dL (2.6–4.9 mmol/L) but no known coronary disease.[73] In this double-blind, randomized, placebo-controlled study, 4731 patients received 80 mg of atorvastatin or placebo. The primary end point was fatal or nonfatal stroke. The mean LDL cholesterol level was 73 mg/dL (1.9 mmol/L) in patients receiving atorvastatin and

129 mg/dL (3.3 mmol/L) in patients receiving placebo. During a median follow-up of 4.9 years, the incidence of recurrent stroke was lower among patients receiving atorvastatin, with 265 patients (11.2%) experiencing fatal or nonfatal stroke versus 311 (13.1%) of those receiving placebo (5-year absolute reduction in risk, 2.2%; adjusted HR, 0.84; 95% CI, 0.71–0.99; $P = .03$; unadjusted $P = .05$). Eighty-seven percent of patients in both treatment groups were receiving concomitant antiplatelet therapy, and 65% were receiving antihypertensives. Atorvastatin treatment resulted in a significant reduction in the risk of fatal stroke but not nonfatal stroke.

In SPARCL, the reduction in risk of fatal or nonfatal stroke, which included hemorrhagic stroke, was maintained despite increased incidence of hemorrhagic stroke with atorvastatin (55 of 273, 20%) versus placebo (33 of 307, 11%).[73] The primary end point (fatal and nonfatal strokes) was inclusive of hemorrhagic stroke. Therefore, these results indicate that the benefit seen with atorvastatin therapy was greater than the potential risk of hemorrhagic stroke. High-dose atorvastatin should be considered for routine secondary prevention on the basis of these findings.

Several studies have evaluated the efficacy of statin therapy in primary prevention of stroke; however, statins were not associated with a decrease in the risk of hemorrhagic stroke.[72,74,75] Therefore, the potential risk of recurrent hemorrhagic stroke should be considered prior to initiating statin therapy. There is some evidence to suggest that statins can reduce stroke incidence, even in those patients with normal lipid levels, presumably via lowering blood pressure.[76]

Antihypertensives

High blood pressure is a strong risk factor for initial and recurrent stroke. It is well established that lowering blood pressure reduces the risk of both fatal and nonfatal stroke in a variety of patient groups. The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) quantified the effects of treating hypertension on long-term disability and dependency among patients with cerebrovascular disease.[77] In this randomized, double-blind, placebo-controlled study, 6105 patients with a history of stroke or TIA were randomly assigned to receive perindopril 4 mg with or without a diuretic or to receive a placebo. Treatment with perindopril reduced the rate of disability, compared with placebo (19% vs. 22%; adjusted odds ratio, 0.76; 95% CI, 0.65–0.89; $P < .001$), primarily by reducing the incidence of recurrent stroke. The NNT for 4 years was 30 (95% CI, 19–79) to prevent 1 case of long-term disability. Interestingly, treatment reduced the risk of stroke in both hypertensive and nonhypertensive patients.[78]

SUMMARY OF GUIDELINES FOR SECONDARY PREVENTION OF STROKE

The AHA/ASA, American College of Chest Physicians (ACCP), and National Stroke Association (NSA) have developed and published practice guidelines for the management of TIA, with detailed information on secondary prevention of stroke.[5,79,80] The key recommendations from these 3 organizations are summarized in Table 5.[5,79,80] This section summarizes the current guidelines regarding the use of antiplatelets and anticoagulants for the secondary prevention of stroke.

Antiplatelets Versus Anticoagulants

The latest guidelines from the AHA/ASA and the ACCP recommend the use of anticoagulants (adjusted-dose warfarin) for the secondary prevention of stroke in patients with persistent or paroxysmal atrial fibrillation and in those with artificial heart valves.[5,80] Warfarin therapy (INR, 2.0–3.0) is also a reasonable option for secondary prevention of stroke in TIA patients with dilated cardiomyopathy. Although warfarin may be prescribed to reduce cardioembolic events in this population, it is controversial whether there is benefit to the use of warfarin in patients with cardiac failure or a reduced left ventricular ejection fraction.[81,82] The Warfarin and Antiplatelet Therapy in Chronic Heart Failure Trial (WATCH) was initiated to evaluate warfarin versus aspirin 162 mg/day or clopidogrel 75 mg/day in patients with symptomatic heart failure in sinus rhythm with an ejection fraction less than or equal to 35%, but was terminated for poor recruitment.[83] Results of observational studies have shown that treatment with warfarin may reduce the risk of recurrent embolism in those with rheumatic mitral valve disease.[5,84]

In contrast, for patients with noncardioembolic stroke or TIA, antiplatelet agents are recommended for the secondary prevention of stroke and prevention of other cardiovascular events.[5,79,80,85]

Currently, there are no data from prospective, randomized, controlled studies to support the use of intravenous heparin or warfarin in patients

TABLE 5
Summary of Guidelines for Secondary Prevention of Stroke

	AHA/ASA[5]	NSA[79]	ACCP[80]
Extracranial carotid artery disease			
• Hemodynamically significant stenosis ≥70%, or 50%–69% depending on patient-specific factors			
○ Carotid endarterectomy*	Class I, level A	Category 1	No recommendations
• Non–hemodynamically significant stenosis; stenosis <50%			
○ Carotid endarterectomy not indicated	Class III, level A	Category 1	No recommendations
Atrial fibrillation			
• Long-term anticoagulation (adjusted-dose warfarin)	Class I, level A	Category 1	Grade 1A
• Aspirin (325 mg/day), if anticoagulants contraindicated	Class I, level A	Category 1	Grade 1A
Mitral valve prolapse			
• Long-term antiplatelet therapy	Class IIa, level C	Category 3	Grade 1C+
Prosthetic heart valves			
• Anticoagulants	Class I, level B	Category 1	Grade 1C+
• Plus antiplatelets (if anticoagulants inadequate)	Class IIa, level B	Category 3	Grade 1C

AHA, American Heart Association; ASA, American Stroke Association; NSA, National Stroke Association; ACCP, American College of Chest Physicians; *recommended by surgeon with perioperative morbidity and mortality rates <6%.

with carotid or vertebral dissection. The use of anticoagulation in patients with cerebral hemorrhage is influenced by several factors, such as type of hemorrhage, patient age, risk factors for recurrent hemorrhage, and indication for anticoagulation. The risk of recurrent hemorrhage must be weighed against the risk of ischemic cerebrovascular event. The AHA/ASA guidelines recommend that in patients with intracranial hemorrhage, subarachnoid hemorrhage, or subdural hematoma, all anticoagulants and antiplatelets should be discontinued during the acute period of at least 1–2 weeks posthemorrhage and that the anticoagulant effect should be reversed immediately with appropriate agents.[5]

FUTURE DEVELOPMENTS

One of the largest stroke prevention trials currently ongoing is the Prevention Regimen for Effectively avoiding Second Strokes (PRoFESS) study. The PRoFESS trial is a large (N = 20,333), randomized, double-blind, placebo-controlled, multinational study comparing the efficacy and safety of aspirin plus ER-DP with that of clopidogrel and the efficacy of telmisartan versus placebo in the presence of background blood pressure treatments in preventing recurrent stroke.[86] The primary outcome of the study is time to first recurrent stroke. Recently, the baseline demographics were published.[86] The mean age of patients was 66.1 years at enrollment, 36% of patients were women, and mean time from event to randomization was 15 days (40% randomized within 10 days). Most participants had had a stroke of arterial origin (29% large vessel disease and 52% small vessel disease), whereas 2% had had a stroke due to cardioembolism and 18% due to other causes. These baseline data suggest that the trial involves a representative international population of patients with stroke. The PRoFESS trial will provide additional insight into the benefits of the combination of aspirin plus ER-DP for secondary prevention of stroke in addition to providing direct comparison of efficacy with clopidogrel. The latest information on this and other ongoing stroke prevention trials can be accessed at http://www.strokecenter.org/trials/.

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Received 2 November 2007; revision received 24 March 2008; accepted 26 March 2008.

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