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Secondary Stroke Prevention and Management: An Evidence-Based Update for Managed Care

An examination of guideline-recommended treatment strategies for optimal individualized care and improvement of outcomes in the prevention of secondary stroke

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Secondary Stroke Prevention and Management: An Evidence-based Update for Managed Care

By Howard S. Kirshner, MD, Professor and Vice Chair, Department of Neurology, Vanderbilt University Medical Center, Director, Vanderbilt Stroke Center, Stroke Program Director, Stallworth Rehabilitation Hospital, Nashville, Tennessee

Stroke, comprised of hemorrhagic and ischemic subtypes, is the third leading cause of death in the United States and is the primary cause of neurologic disability in adults.[1] Of the estimated 780,000 strokes that occur annually in the United States, approximately 15% are preceded by a transient ischemic attack (TIA) and nearly 25% are recurrent events,[1] meaning that about 75% of patients who experience a stroke or TIA will suffer a secondary stroke.[2-5] Of additional concern is the high risk of death from events following the initial stroke event; cardiovascular death is the most common ultimate cause of death in stroke survivors.[6-8]

Because of the high rate of recurrence, prevention of secondary stroke is a primary goal for patients who have suffered a stroke or TIA. Attention must also be directed to cardioprotection, as patients who have experienced a stroke are also at an increased risk of other vascular events, such as myocardial infarction (MI), in the years following the initial stroke.[6,9] In an effort to assist clinicians in appropriate management of stroke patients, the American Heart Association (AHA) and the American Stroke Association (ASA) have published joint recommendations for the prevention of secondary stroke in patients with stroke and TIA.[10] The complete guidelines were last updated in 2006; however, a partial update to the guidelines was published in early 2008 to include revised recommendations particular to the use of antithrombotic agents in patients with a history of noncardioembolic stroke.[11]

The prevention and management of secondary stroke is based largely on the subtype of ischemic stroke, therefore clinicians require an understanding of the appropriate treatment strategies for patients with varying ischemic stroke subtypes to effectively apply and implement available treatment options. To improve stroke management strategies, clinicians must recognize the characteristics of each stroke subtype, appropriately manage modifiable risk factors, implement timely and efficacious prophylactic management of secondary stroke risk via pharmacologic and invasive treatment, and remain up-to-date on the available guidelines for secondary stroke prevention.

UNDERSTANDING STROKE SUBTYPES

Stroke can be divided into 2 main categories: hemorrhagic stroke and ischemic stroke. Hemorrhagic stroke, which comprises approximately 17% of stroke cases, occurs when a weakened blood vessel within the brain ruptures, resulting in accumulation of blood within the brain.[12] In most cases, the rupture of a small cerebral artery—usually related to hypertension—is the cause of the hemorrhage; however, approximately 5% of strokes are linked to the rupture of an aneurysm or arteriovenous malformation.[12] Ischemic strokes, which account for about 83% of all strokes, are the result of an obstructed blood vessel.[12] Four primary causes of obstruction comprise the majority of ischemic strokes: (1) large vessel occlusions related to atherosclerosis, such as in the internal carotid artery; (2) small vessel occlusions related to hypertension and diabetes; (3) embolic strokes, in which the clot originates from a distant source, usually the heart; and (4) a large category of stroke of either unknown (cryptogenic) or other known cause, such as vascular dissections, vasculitis, or hypercoagulable states.[13,14] Some embolic strokes, caused by so-called "artery-to-artery" emboli, occur due to plaques in the aortic arch or the carotid arteries. These subtypes are associated with varying risks of recurrence, as well as different degrees of severity and resulting impairment.[15] Small vessel disease (SVD) has been associated with lower 30-day risk of recurrence, lower 5-year mortality, and better functional outcomes than the other subgroups,[15] whereas large vessel disease (LVD) has demonstrated the highest 30-day recurrence among ischemic stroke subtypes, and cardioembolic stroke the highest 5-year mortality, at over 80%.[15] Approximately 60% to 70% of recurrent strokes are of the same subtype as the initial stroke.[15-17]

In addition to ischemic and hemorrhagic stroke, patients may also experience a TIA, a brief period of symptoms indicative of an ischemic stroke.[12] Unlike the effects of a stroke, these symptoms dissipate within 24 hours; however, in many cases, symptoms subside within minutes.[12] Despite the quick resolution of these symptoms, a TIA is a strong indicator of a possible future stroke and requires careful attention.[12]

Stroke is commonly linked to atherosclerotic disease in the coronary and peripheral vascular circulations,[18] but it is more heterogeneous in its vascular pathophysiology, as seen in the common subtypes of ischemic stroke enumerated earlier. These different subtypes of ischemic stroke may have varied risk profiles from those of large artery atherosclerosis in the cerebral, coronary, or peripheral circulations. For example, although the largest single risk factor for stroke is hypertension, the association of dyslipidemia with stroke is not as well established, in contrast with the close association of dyslipidemia with coronary artery disease.[19] Stroke is a unique vascular disease, requiring different preventive treatments than coronary heart disease or peripheral artery disease (PAD).[20] For example, patients with ischemic stroke appear to benefit from either aspirin or clopidogrel, but they do not derive significant additional benefit from the concurrent administration of both agents, whereas patients with acute coronary syndrome benefit from combination therapy.[21,22] Another difference between patients with stroke and those with other vascular disorders is that stroke patients appear more susceptible to bleeding caused by antithrombotic agents than, for example, patients with MI or PAD.[20] In a recent trial examining acute coronary syndrome, major bleeding occurred more often in patients with a history of stroke or TIA, likely due to microvascular damage to the brain sustained during the previous event.[23]

MODIFIABLE RISK FACTORS FOR SECONDARY STROKE

Available evidence suggests that the majority of strokes could potentially be prevented by the control of a collection of common risk factors

that include smoking, excessive alcohol consumption, obesity, low physical activity level, hypertension, hyperlipidemia, and diabetes.[24] The effect of these factors on stroke probability differ somewhat according to ischemic stroke subtypes—stronger risk factors for SVD include hypertension, smoking, and diabetes,[10,25,26] while risk factors for LVD include smoking,[10,26] abdominal obesity,[27] and dyslipidemia,[28] although the differences between the risks associated with these subtypes may not be as great as previously suspected.[29]

All stroke/TIA patients should be counseled not to smoke and to avoid environmental tobacco smoke, as meta-analysis data indicate that smoking has the potential to double stroke risk.[30] In addition to counseling, the AHA/ASA guidelines have found direct medical assistance to help patients quit smoking, including nicotine products and medications such as bupropion or varenicline, to be proven effective.[13]

Small quantities of alcohol (≤2 alcoholic drinks/day for men and 1 drink/day for women) may protect against ischemic stroke,[31] but any quantity of alcohol increases the risk of hemorrhagic stroke.[32] Excessive alcohol intake (>2 drinks/day) increases both ischemic and hemorrhagic stroke risk.[31,32] Based on these data, the AHA/ASA guidelines recommend that heavy drinkers reduce or cease their alcohol consumption; light to moderate alcohol consumption (≤2 drinks in men, 1 drink in women) may be considered.[13]

Obesity appears to be an indirect risk factor for stroke, as it impacts several major stroke risk factors, including hypertension, dyslipidemia, and diabetes.[13] AHA/ASA recommendations to reduce the effects of obesity on stroke risk include weight management through caloric limitation, physical activity, and behavioral counseling.[13] The goals of treatment for patients with a history of stroke are body mass index of 18.5 kg/m^2 to 24.9 kg/m^2 and waist circumference less than 35 inches for women or less than 40 inches for men.[13]

In an effort to further improve outcomes for a variety of cardiovascular risk factors, such as weight, blood pressure, glucose tolerance, and vascular health, the AHA/ASA has also made recommendations for increasing physical activity.[13] For ischemic stroke/TIA patients who are able to engage in physical activity, moderate exercise for 30 minutes or longer on most days is encouraged.[13] For those in whom a disability precludes independent exercise, a supervised therapeutic regimen is recommended.[13]

Control of blood pressure is one of the most powerful treatments in the secondary stroke prevention armamentarium. Studies have shown that lowering blood pressure levels can reduce the risk of stroke by as much as 30% to 40%.[33,34] A variety of hypertension treatment options exist, including angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta-blockers, diuretics, and calcium channel blockers. Clinicians should take into consideration not only the latest clinical data regarding each treatment option, but remain up-to-date with the latest recommendations from the Seventh Report of the Joint National Committee (JNC 7) guidelines for hypertension and the recommendations set forth by the AHA/ASA secondary stroke prevention guidelines.[13] Finally, the individual needs of each patient should be carefully weighed when making individualized treatment decisions.

Several studies have documented the positive effects of hypertensive therapies in secondary stroke prevention.[35-37] In the Perindopril Protection Against Recurrent Stroke Study, treatment with the ACE inhibitor perindopril, most frequently in combination with the diuretic indapamide, produced a 28% relative risk reduction (RRR) in recurrent stroke over a 4-year period.[35] Two trials involving ARBs, Acute Candesartan Cilexetil Evaluation in Stroke Survivors (ACCESS) and Morbidity and Mortality After Stroke (MOSES),[36,37] also showed efficacy in secondary stroke prevention. The ACCESS study randomized 342 patients to either candesartan or placebo; the study was ended before recruitment was complete, because of a significant difference in 12-month mortality in favor of candesartan (2.9% vs 7.2%; P=.07).[36] In the MOSES trial, 1405 patients with hypertension and a documented cerebral event during the past 24 months were randomized to receive either the ARB eprosartan or the calcium channel blocker nitrendipine; mean follow-up was 2.5 years.[37] Patients on eprosartan experienced significantly fewer cerebrovascular events compared with nitrendipine (102 vs 134; P=.03), and with regard to the primary composite end point of total mortality and all cardiovascular and cerebrovascular events, patients on eprosartan experienced fewer events overall.[37]

Calcium channel blockers have also been shown to effectively prevent recurrent stroke.[38] In the Valsartan Antihypertensive Long-term Use Evaluation trial, a randomized, double-blind, parallel-group study, 15,245 patients with hypertension and high risk of cardiovascular events were randomized to receive the calcium channel blocker valsartan or amlodipine, with a mean follow-up of 4.2 years.[38] The cardiovascular outcomes, including stroke, were 10.6% in the valsartan group, versus 10.4% in the amlodipine group; stroke rates were also not significantly higher in the valsartan group.[38] In the Intervention for End Point Reduction in Hypertension trial,[39] the beta-blocker atenolol was found to be less effective in stroke prevention than the ARB losartan.[39] The study randomized 9193 patients 55 to 80 years of age with essential hypertension and left ventricular hypertrophy to once-daily losartan-based or atenolol-based therapy.[39] Patients were treated for at least 4 years and until 1040 patients had a primary cardiovascular event (death, MI, or stroke).[39] With regard to stroke outcomes, 232 patients in the losartan group and 309 patients in the atenolol group experienced a fatal or nonfatal stroke (P=.001).[39]

The AHA/ASA guidelines recommend antihypertensive treatment for all ischemic stroke/TIA patients, although controversy still remains with regard to how soon after the initial stroke to initiate therapy.[13] Recent studies suggest that initiation of treatment before discharge from the hospital improves adherence to antihypertensive therapy.[40] The Implementation of Prevention After a Cerebrovascular Event study prospectively assessed 240 consecutive stroke/TIA patients for risk factors such as blood pressure and low-density lipoprotein cholesterol (LDL-C).[40] At 6 months, 41% of patients had a target blood pressure of less than 140/90 mm Hg and 55% of patients achieved a target LDL-C (<100 mg/dL).[40] Analysis indicated that initiation or reinforcement of appropriate treatment during hospitalization was a primary factor in lowering blood pressure and LDL-C, prompting investigators to conclude that in-hospital initiation of preventive therapy could improve long-term outcomes in secondary stroke prevention.[40]

The JNC 7 guidelines for hypertension[41] should generally be followed by clinicians in choosing appropriate antihypertensive agents, although the clinical trial evidence from studies such as MOSES and ACCESS,[36,37] which supports the use of diuretics with or without ACE inhibitors or ARBs, should also be considered. The only caveat to the ACE inhibitor recommendation is the lesser efficacy of these agents in African

American patients in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial.[42,43] For this group, diuretics and calcium channel blockers may be more effective, along with ACE inhibitors or ARBs.[43]

Evidence favoring lipid-lowering therapy for stroke prevention has accumulated only in the past few years. The National Cholesterol Education Panel (NCEP) III guidelines for lifestyle modification, diet, and medications, which are endorsed by the AHA/ASA guidelines, apply mainly to those ischemic stroke/TIA patients with elevated cholesterol, comorbid coronary artery disease, or evidence of large vessel atherosclerotic disease such as carotid stenosis.[44] Lipid-lowering therapy, especially with 3-hydroxy-3-methyl-glutaryl coenzyme A-reductase inhibitors, or statins, is recommended, with a goal LDL-C of less than 100 mg/dL and less than 70 mg/dL for very high-risk patients.[13,44] Patients with low HDL-C may be treated with niacin or gemfibrozil.[44]

Three randomized, placebo-controlled trials of patients with acute MI have shown that statins prevent stroke as well as recurrent MIs.[45-48] In the Scandinavian "4S" study,[45] 4444 patients with angina pectoris or MI and elevated serum cholesterol were randomized to receive simvastatin or placebo.[45] While the resulting reduction in lipid levels was anticipated, the 28% reduction in cerebrovascular events was not a preconceived end point.[46] In the later CARE and LIPID trials, there was a reduction in stroke as a planned end point (31%, *P*=.03; 19%, *P*=.048; respectively), regardless of whether patient LDL-C was elevated when initiating pravastatin treatment.[47,48] The Heart Protection Study (HPS), an investigation of "high risk" patients with either MI, stroke, or other risk factors such as diabetes, also demonstrated a significant reduction in the risk of initial stroke in patients treated with simvastatin (*P*<.0001).[49] Simvastatin was approved for secondary stroke prevention based on results of the HPS, as one of the study entry groups was patients with cerebrovascular disease.[49] However, a subsequent analysis of the stroke subgroup failed to show a significant secondary stroke preventive effect.[50] Most recently, the Stroke Prevention by Aggressive Reduction in Cholesterol Levels trial has shown that statin therapy can reduce the risk of recurrent stroke in patients with a history of stroke or TIA.[19] Based on these findings, the AHA/ASA 2008 guideline update recommends statin therapy for all ischemic stroke or TIA patients with an LDL-C higher than 100 mg/dL.[11]

In stroke patients with concomitant diabetes, strict glycemic control

Table 1. AHA/ASA Guidelines for Antithrombotic Therapy for Prevention of Stroke in Patients with Cardioembolism[13]

Risk Factor	Recommendation
AF	▪ Ischemic stroke or TIA patients with persistent or intermittent AF should receive oral anticoagulants, starting within 2 weeks of ischemic stroke/TIA and continuing long term; initiation may be later with large infarcts or uncontrolled hypertension ▪ Warfarin targeted to INR intensity 2.5 (range, 2.0-3.0) is recommended ▪ Aspirin 325 mg/day is recommended for patients who cannot tolerate oral anticoagulants
Acute MI and left ventricular thrombus	▪ If ischemic stroke/TIA is caused by acute MI and left ventricular mural thrombus is identified by cardiac imaging, oral anticoagulants are reasonable ▪ Target INR should be 2.0-3.0 and treatment should continue 3 months to 1 year ▪ Concurrent use of aspirin (≤162 mg/day, preferably enteric coated) is recommended for ischemic coronary artery disease
Cardiomyopathy	▪ Either warfarin (INR, 2.0-3.0) or antiplatelet therapy may be considered for prevention of recurrence in ischemic stroke/TIA patients with dilated cardiomyopathy
Rheumatic mitral valve disease	▪ Long-term oral anticoagulants are recommended in ischemic stroke/TIA patients with rheumatic mitral valve disease, whether or not AF is present ▪ Target warfarin to INR 2.5 (range, 2.0-3.0) ▪ To avoid bleeding risk, antiplatelet agents should not be added routinely ▪ Adding aspirin 81 mg/day is suggested if recurrent embolism occurs while receiving warfarin
Mitral valve prolapse	▪ Long-term antiplatelet therapy is reasonable for patients with mitral valve prolapse who have ischemic stroke/TIA
MAC	▪ Antiplatelet therapy may be considered for patients with ischemic stroke/TIA and MAC not documented to be calcific ▪ Either antiplatelet agents or warfarin may be considered in patients with mitral regurgitation resulting from MAC without AF
Aortic valve disease	▪ Antiplatelet therapy may be considered for patients with ischemic stroke/TIA and aortic valve disease in the absence of AF
Prosthetic heart valves	▪ Oral anticoagulants are recommended for ischemic stroke/TIA patients with modern mechanical prosthetic heart valves ▪ Target INR should be 3.0 (range, 2.5-3.5) ▪ If ischemic stroke or systemic embolism occurs despite adequate oral anticoagulant therapy, it is reasonable to add aspirin 75-100 mg/day, while maintaining target INR 3.0 (range, 2.5-3.5) ▪ For ischemic stroke/TIA patients with bioprosthetic heart valves and no other source of thromboembolism, warfarin to INR 2.0-3.0 may be considered

AF = atrial fibrillation; AHA/ASA = American Heart Association/American Stroke Association; INR = international normalized ratio; MAC = mitral annular calcification; MI = myocardial infarction; TIA = transient ischemic attack.

should target near-normal glucose levels and HbA1c less than or equal to 7%, although excessively tight glucose control may result in hypoglycemia and increased mortality.[51] With regard to cardiovascular management in patients with diabetes, the AHA/ASA recommends strict control of lipid levels and blood pressure, with ACE inhibitors and ARBs preferred as first-line antihypertensives in this patient population.[13]

PREVENTION OF SECONDARY STROKE

Aside from modification of risk factors such as hypertension, diabetes, hyperlipidemia, and smoking, prevention of secondary stroke depends largely on antithrombotic therapy, the 2 principal forms of which are anticoagulation and antiplatelet therapy. Anticoagulation is designed to block the cascade of clotting proteins, and is best for preventing red blood cell clots—or red clots—in low-flow vessels, including venous clots in deep vein thrombophlebitis.[51] Similar low-flow clotting occurs in the left atrial appendage in patients with atrial fibrillation, in dilated cardiomyopathies, and with prosthetic valves.[51] Clots that form on plaques in high-flow arteries—often referred to as white clots—are better prevented by inhibitors of platelet aggregation, such as aspirin, aspirin plus dipyridamole, and clopidogrel.[51]

Anticoagulant Therapy in Cardioembolic Stroke. Cardiogenic embolism, which is caused by a variety of cardiac disorders, accounts for approximately 20% of ischemic strokes.[13] In patients with cardioembolic stroke, the principal secondary stroke prevention treatment is anticoagulation.[13] Due to the high risk of recurrent stroke associated with cardioembolic disease, the ASA/AHA guidelines indicate that patients with a history of cardioembolic stroke should receive anticoagulant therapy to prevent recurrence, with additional attention paid to coexisting AHA guidelines on the management of any concomitant cardiac conditions.[13]

In the absence of a clear contraindication, atrial fibrillation (AF) patients with recent stroke or TIA should receive oral anticoagulation with adjusted-dose warfarin, a vitamin K antagonist; 6 primary prevention trials and 1 secondary prevention trial have supported the efficacy of warfarin in preventing embolic strokes secondary to AF,[52-58] indicating that in primary prevention, approximately 3 strokes can be prevented per 100 patients treated per year,[52-57] and in secondary prevention, about 9 strokes per 100 patients treated per year can be avoided.[58] In 2 of these trials—the Danish Atrial Fibrillation, Aspirin, Anticoagulation trial and the Stroke Prevention in Atrial Fibrillation trial—aspirin was either ineffective or less effective than warfarin.[53,54] A recent trial called Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events-Warfarin also illustrated that warfarin was superior to combined antiplatelet therapy with aspirin and clopidogrel in patients with AF.[59] A recent subgroup analysis also found that aspirin and clopidogrel was not superior to aspirin alone in preventing stroke in AF patients.[60] Parenteral anticoagulants such as intravenous heparin or subcutaneous low- molecular-weight heparins, such as enoxaparin, are at present the only therapeutic alternatives, but new direct thrombin inhibitors/oral factor Xa inhibitors are currently under investigation in clinical trials. At present, warfarin with optimal international normalized ratio intensity of 2.0 to 3.0 is recommended, while 325 mg per day of aspirin is suggested in patients who cannot take oral anticoagulants.[13] Oral anticoagulants are also recommended for secondary stroke prevention in stroke patients with acute MI and left ventricular thrombus, rheumatic mitral valve disease, and prosthetic heart valves (**Table 1**).[13]

Antiplatelet Treatment in Noncardioembolic Stroke. In patients with noncardioembolic ischemic stroke or TIA, the AHA/ASA guidelines recommend the use of antiplatelet agents rather than oral anticoagulation to reduce the risk of recurrent stroke and other cardiovascular events (**Table 2**).[11,13] Oral anticoagulants are generally not recommended for patients with noncardioembolic stroke because of a lack of evidence of greater efficacy and a documented increased risk of bleeding.[13]

Four antiplatelet regimens have been approved by the US Food and Drug Administration (FDA) for secondary ischemic stroke prevention: aspirin, ticlopidine, clopidogrel, and combination aspirin plus extended-release (ER) dipyridamole.[13] Ticlopidine is no longer widely used due to toxicity issues and is not recommended for first-line use by the AHA/ASA guidelines; aspirin, clopidogrel, and aspirin plus ER dipyridamole are all currently recommended for first-line secondary stroke prevention for noncardioembolic stroke.[11,13]

Aspirin prevents clot formation by inhibiting platelet function after irreversibly binding to the cyclooxygenase enzyme in the platelet, which reduces the generation of prostaglandins such as thromboxane-A2, a stimulator of vasoconstriction and platelet aggregation.61 Aspirin has been shown to be modestly effective for stroke prevention in many studies, with a recurrent-event risk reduction of approximately 13% to 22%.[62-64] This represents a limited degree of efficacy, and many patients with stroke/TIA will fail aspirin therapy, justifying the investigation of other antiplatelet agents. Other issues associated with aspirin treatment include the interference with its function by nonsteroidal anti-inflammatory drugs such as ibuprofen, gastrointestinal bleeding risk, and occasional aspirin allergy.

Two trials comparing aspirin dosing regimens demonstrated no additional benefit and a greater risk of nonfatal major gastrointestinal hemorrhage with increased doses.[65,66] In the United Kingdom Transient Ischaemic Attack trial (UK-TIA), patients with minor ischemic stroke or TIA (n=2435) were randomized to 600 mg aspirin twice daily, 300 mg aspirin once daily, or placebo.[65] The risk of major stroke, MI, or vascular death was reduced by 15% with aspirin compared with placebo, but the 2 aspirin doses were equal in efficacy.[65] Gastrointestinal hemorrhage was more common with the 1200-mg dose than the 300-mg dose.[65] In the Dutch TIA trial of patients with TIA or nondisabling stroke (n=3131), 30-mg aspirin was compared with 283 mg in outcomes of vascular death, nonfatal stroke, or nonfatal MI.[66] Again, there was no difference in stroke prevention between the 2 doses of aspirin, but the group receiving 30 mg experienced fewer bleeding complications than the high-dose group.[66]

For patients who experience a stroke while receiving aspirin, no evidence supports increasing the aspirin dose, and alternative antiplatelet agents have not been studied in this patient group.[13]

Clopidogrel prevents secondary stroke via inhibition of platelet aggregation by binding to the adenosine diphosphate site on the platelet.[61] Clopidogrel utilizes a mechanism of action similar to ticlopidine and the investigational prasugrel, which is currently under review by the FDA.[23] The Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) study was a major factor influencing the use of clopidogrel in stroke patients.[4] CAPRIE is a large trial of 19,185 patients with recent stroke, recent MI, or PAD randomized to receive aspirin 325 mg daily or clopidogrel 75 mg daily.[4] In the combined groups, clopidogrel monotherapy was more effective than aspirin (8.7% overall RRR;

Table 2. AHA/ASA Guidelines for Antithrombotic Therapy for Prevention of Stroke in Patients with Noncardioembolic Stroke or TIA[11,13]

Agent	Type	Recommendation
Aspirin	Antiplatelet, FDA approved for secondary ischemic stroke prevention	▪ Recommended as an acceptable option for initial therapy at doses of 50-325 mg/day ▪ For patients who experience ischemic stroke while on aspirin, no evidence supports increasing the aspirin dose, and no other antiplatelet agent or combination has been well studied under this circumstance
Ticlopidine	Antiplatelet, FDA approved for secondary ischemic stroke prevention	▪ No specific recommendations for use as initial antiplatelet therapy
Clopidogrel (monotherapy)	Antiplatelet, FDA approved for secondary ischemic stroke prevention	▪ Recommended as an acceptable option for initial therapy ▪ May be considered instead of aspirin monotherapy especially for patients who cannot tolerate aspirin ▪ Data are not yet sufficient to make evidence-based recommendations of one non-aspirin antiplatelet agent over another, and antiplatelet choices should be individualized for each patient
Aspirin plus ER-dipyridamole	Antiplatelet combination, FDA approved for secondary ischemic stroke prevention	▪ Recommended as an acceptable option for initial therapy ▪ Combination aspirin plus ER-dipyridamole is recommended instead of aspirin alone ▪ Data are not yet sufficient to make evidence-based recommendations of one non-aspirin antiplatelet agent over another, and antiplatelet choices should be individualized for each patient
Aspirin plus clopidogrel	Antiplatelet combination	▪ Not routinely recommended for ischemic stroke and TIA patients due to the increased risk of hemorrhage, unless a specific indication for this therapy exists (acute coronary syndrome or coronary stent)
Warfarin	Oral anticoagulant	▪ Not recommended due to the increased risk of bleeding and cost of monitoring

AHA/ASA = American Heart Association/American Stroke Association; ER = extended-release; FDA = US Food and Drug Administration; TIA = transient ischemic attack.

P=.043) in reducing the risk of stroke, MI, or vascular death.[4] The difference did not reach statistical significance in the subgroup of stroke patients.[4] The greatest benefit was seen in the PAD subgroup (RRR, 23.8%; *P*=.0028), whereas the RRR in stroke patients was 7.3% (nonsignificant, *P*=.26).[4]

Dual therapy with clopidogrel and aspirin for up to 12 months has been shown to be more effective than aspirin monotherapy in patients with acute coronary syndrome,[67] acute ST-segment elevation MI,[68,69] and patients with coronary stents.[70] Even in acute coronary syndrome, however, combined aspirin plus clopidogrel carried a higher risk of major bleeding, especially when the aspirin dose was 325 mg.[67] These studies of coronary disease patients created speculation that combined aspirin plus clopidogrel therapy would be effective in stroke patients. However, 2 trials have compared the effect of combination clopidogrel plus aspirin with monotherapy for prevention of vascular events in stroke/TIA patients and indicate that stroke patients appear to differ from acute coronary syndrome patients in response to antiplatelet agents with regard to this combined treatment regimen. The Management of Atherothrombosis with Clopidogrel in High-Risk Patients with Recent Transient Ischemic Attack or Ischemic Stroke (MATCH) trial compared clopidogrel alone versus aspirin plus clopidogrel,[21] whereas the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial compared aspirin alone versus aspirin plus clopidogrel.[22] In the MATCH trial, the combination of clopidogrel plus aspirin did not demonstrate significantly greater efficacy in prevention of the primary composite end point (ischemic stroke, MI, vascular death, or rehospitalization secondary to ischemic event) than clopidogrel alone (15.7% vs 16.7%), but major bleeding was almost twice as common (2.6% vs 1.3%).[21] It should be noted that more than 50% of enrolled subjects were SVD patients, who might benefit less from antiatherothrombotic effects and might be more susceptible to bleeding.[21] The CHARISMA trial compared clopidogrel (75 mg/day) plus aspirin (75-162 mg/day) with aspirin alone in 15,603 patients with cardiovascular disease or multiple risk factors, including about 3000 individuals without an index vascular event.[22] Overall, clopidogrel plus aspirin was not significantly more effective than aspirin in reducing incidence of the primary composite end point of ischemic stroke, MI, or cardiovascular death.[22] In a prespecified subgroup analysis of 12,153 patients with documented coronary disease, PAD, or ischemic stroke/TIA within the previous 5 years, the combination was slightly more effective than aspirin alone in reducing the primary end point (6.9% vs 7.9%; relative risk [RR] 0.88; *P*=.046).[22] In patients with previous cerebrovascular events, secondary prevention benefit with the combination therapy did not reach statistical significance.[22] Among all patients, moderate bleeding increased significantly with the combination therapy (2.1% vs 1.3%; RR, 1.62; *P*<.001).[22] In a post-hoc secondary prevention analysis of 9478 CHARISMA patients with previous MI, ischemic stroke, or symptomatic PAD, the composite end point rate was 7.3% with clopidogrel plus aspirin versus 8.8% with aspirin (hazard ratio [HR], 0.83; *P*=.01).[22] Moderate bleeding again increased significantly with the combination regimen (2.0% vs 1.3%; P=.004).[22]

ASPIRIN PLUS ER DIPYRIDAMOLE

Dipyridamole, a phosphodiesterase inhibitor, has a unique mechanism of action among antiplatelet therapies. Whereas aspirin inhibits thromboxane-A2 formation and clopidogrel binds to the adenosine

diphosphate site, dipyridamole raises intracellular levels of cyclic adenosine monophosphate and cyclic guanosine monophosphate (cAMP and cGMP), producing a weak antiplatelet effect.[71] The drug also increases cGMP, augmenting downstream signaling pathways of nitric oxide.[71] This may, in effect, produce an endothelial effect, including vasodilation, which can help prevent clot formation in stroke patients.[5]

ER dipyridamole has advantages over immediate-release (IR) dipyridamole. IR dipyridamole has a half-life of 40 minutes, which results in rapidly declining plasma concentrations. In contrast with single-agent IR or ER dipyridamole, the aspirin plus ER dipyridamole capsule also contains tartaric acid, which results in better gastrointestinal absorption.[5]

The Second European Stroke Prevention Study (ESPS-2) trial showed that aspirin plus ER dipyridamole was significantly more effective than aspirin alone in secondary stroke prevention, with a similarly low risk of severe bleeding.[5] ESPS-2 randomized 6602 patients with a recent ischemic stroke or TIA to aspirin 25 mg twice daily, ER dipyridamole 200 mg twice daily, fixed-dose combination aspirin plus ER dipyridamole, or placebo and followed patients for 2 years.[5] Primary end points were stroke, death, and a combined end point of stroke or death.[5] Compared with placebo, risk of stroke was reduced 18% with aspirin monotherapy (*P*=.013), 16% with ER dipyridamole monotherapy (*P*=.039), and 37% with aspirin plus ER dipyridamole (*P*<.001).[5] With combination therapy, the RR of stroke was reduced by 23% versus aspirin alone (P=.006).[5] The combination therapy also reduced the risk of the combined end point of stroke or death by 24% (*P*<.001).[5] The most common adverse event with ER dipyridamole was headache (37% ER dipyridamole alone and 38% aspirin plus ER dipyridamole vs 33% aspirin alone and 32% placebo).[5] All-site bleeding and gastrointestinal bleeding were significantly more common in patients who received aspirin alone or in combination (*P*<.001), but dipyridamole did not significantly increase bleeding over aspirin.[5] In patients receiving the combination, the incidence of severe or fatal bleeding was similar to that in patients receiving aspirin alone (aspirin 1.2%, aspirin plus ER dipyridamole 1.6%).[5] A post-hoc analysis of ESPS-2 data showed no increase in risk for MI, angina, or mortality among cardiac patients in the study who received ER dipyridamole.[22]

A recent open-label study—the European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT)—confirmed the findings of ESPS-2. ESPRIT randomized 2739 patients with recent TIA or minor ischemic stroke to aspirin or aspirin plus ER dipyridamole, separately or as a fixed-dose combination.[72] The aspirin dosage, determined by each patient's physician, was 30 mg to 325 mg (median 75 mg/day) daily, and the ER dipyridamole dosage was 200 mg twice daily; mean follow-up was 3.5 years.[72] On intention-to-treat analysis, the incidence of composite primary outcome (nonfatal MI, nonfatal stroke, vascular death, or major bleeding complication) was significantly lower with aspirin plus ER dipyridamole than with aspirin alone (13%vs 16%; HR, 0.80; 95% confidence interval [CI], 0.66-0.98).[72] Additionally, there were 35 major bleeding complications with aspirin plus dipyridamole versus 53 with aspirin alone (HR, 0.67; 95% CI, 0.44-1.02).[72] More patients discontinued the combination therapy than aspirin alone, primarily due to adverse effects, of which headache was the most common.[72] A revised meta-analysis including these data and all 6 studies comparing aspirin with aspirin plus ER dipyridamole or aspirin plus IR dipyridamole demonstrated an overall risk ratio for composite stroke, MI, or vascular death of 0.82 (95% CI, 0.74-0.91) with the combination versus aspirin alone, a RRR of 18%.[72]

Results of the Prevention Regimen for Effectively Avoiding Second Strokes trial were presented in May 2008 at the 17th European Stroke Conference.[73] This randomized, double-blind trial (N=20,332) compared efficacy of aspirin plus ER dipyridamole versus clopidogrel for prevention of recurrent stroke.[73] Recurrent stroke rates were similar with aspirin plus ER dipyridamole and clopidogrel therapy (9.0% vs 8.8%), and no significant differences in the incidence of the composite event—stroke, MI or vascular death—were reported.[73] Ischemic stroke occurred less often with aspirin plus ER dipyridamole (7.7% vs 7.9%), whereas hemorrhagic strokes occurred more often (0.8% vs 0.4%) in patients on this regimen.[73] More major hemorrhagic events occurred in patients receiving aspirin plus ER dipyridamole (4.1% vs 3.6%; HR, 1.15; 95% CI, 1.00-1.32), but no significant difference was found in the benefit-to-risk ratio expressed as combined recurrent stroke and major hemorrhage (11.7% vs 11.4%; HR, 1.03; 95% CI, 0.95-1.11).[73] Evidence to date does not support differential effectiveness of antiplatelet therapies among the different noncardioembolic subtypes.

The current AHA/ASA guidelines recommend aspirin, aspirin plus ER dipyridamole, or clopidogrel in secondary stroke prevention of noncardioembolic strokes.[11,13] The combination of aspirin plus ER dipyridamole is recommended over aspirin alone; evidence from the ESPRIT trial and meta-analysis of previous data motivated the AHA/ASA, in the 2008 guidelines update,[11] to upgrade this recommendation within the guidelines' classification structure.[11] New guidelines are expected to be published by the end of 2008, but for the present, the available evidence on antiplatelet therapies is not yet sufficient to make evidence-based recommendations of one agent over another, and choices should be individualized for each patient, considering allergies and adverse effects, cost, comorbidities, and adherence.[11,13]

AHA/ASA-Recommended Invasive Procedures. In addition to pharmacologic treatment, the AHA/ASA guidelines also make recommendations for invasive procedures when appropriate.[13] Carotid endarterectomy (CEA) is recommended for patients with TIA or ischemic stroke within the previous 6 months and ipsilateral severe (≥70%) carotid artery stenosis.[13,74] CEA is also recommended for those with ipsilateral moderate (50%-69%) carotid stenosis depending on patient age, sex, comorbidities, and severity of initial symptoms.[13,75] Carotid artery balloon angioplasty and stenting may be considered for symptomatic severe carotid stenosis in high-risk patients, such as those with inaccessible stenosis, severe comorbid conditions, radiation-induced stenosis, and restenosis after previous CEA.[76]

Endovascular therapy, such as angioplasty or stenting, can be performed on patients with symptomatic extracranial vertebral stenosis who have stroke or TIA symptoms, but this treatment is still investigational.[77]

Surgical intervention in patients with intracranial atherosclerosis is also under investigation due to a high risk of stroke in this population. The Warfarin-Aspirin Symptomatic Intracranial Disease study[78] showed that patients with TIA or stroke symptoms related to greater than 50% stenosis of the intracranial internal carotid, middle cerebral, distal vertebral, or basilar arteries had an approximately 20% risk of stroke over a 2-year period, but there was no significant difference between aspirin and warfarin in this group.[78] Endovascular therapy such as balloon angioplasty or stenting is considered investigational in patients with

hemodynamically significant intracranial stenosis.

CONCLUSION

In ischemic stroke and TIA patients, prevention of recurrent cerebrovascular events is the primary treatment goal; however, prevention of other long-term complications such as MI and cardiac death is also integral to overall patient management due to the high prevalence of cardiovascular death in stroke survivors. A number of lifestyle and risk factor modifications can significantly reduce the risk of stroke—if these modifications are implemented in combination with pharmacologic regimens clinically proven to drastically impact the risk of secondary stroke, the vast majority of stroke cases can be prevented. ■

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Clinical Commentary

Philip B. Gorelick, MD, FACP, John S. Garvin Professor and Head, Department of Neurology and Rehabilitation, University of Illinois College of Medicine at Chicago, Director, Center for Stroke Research, Chicago, Illinois

While recurrent stroke has long been a common health problem, the therapeutic armamentarium for secondary stroke prevention has expanded substantially only during the past 10 to 20 years. Whereas 20 years ago aspirin was the primary antiplatelet therapy for recurrent stroke prevention and statin agents were not yet utilized, recent clinical trials have shown the value of aspirin plus extended-release dipyridamole, clopidogrel, and statin agents in recurrent stroke prevention.[1] Furthermore, our approach to correcting high-grade carotid stenosis has been bolstered by the recent approval of angioplasty and stenting of the carotid artery.[2] Despite the wide availability of clinical guidelines and clearly defined evidence-based treatment recommendations, successful implementation of recurrent stroke prevention guidelines within the community at large is still a significant challenge. It is still difficult to ensure that each patient receives the appropriate stroke prevention management and adheres to the provided pharmacologic regimen.

There have been several key advances in recent years that have improved the field of stroke management, including the organization of stroke care via national guidelines and practice measures. This paradigm shift has provided a framework by which practice systems and individual practitioners can ensure that stroke patients receive best stroke care practices. Programs such as the Joint Commission's Primary

Stroke Center Certification,[3] which is aimed at providing benchmarks for care through quality indicators, and the American Heart Association's Get With The Guidelines program[4]—aimed at tracking critical treatment and outcome data for stroke patients—provide road maps that promise to heighten stroke care and improve outcomes. Published results have shown that organized stroke care may lead to a higher percentage of patients meeting best practice standards.[5]

Primary care providers are challenged by the number and complexity of disease states which they must correctly diagnose and properly treat, and thus may be unable to keep up with the nuances of all the available best practice guidelines for each disease state or risk group. Use of a hand-held device containing easy-to-reference key guideline statements may provide a necessary safety net for providers with concerns regarding their understanding of the latest guideline updates. Application of practice guidelines—when summarized in a simple, user friendly format—may be lifesaving. Although time consuming, it is essential for all clinicians treating patients at risk for recurrent stroke to remain up-to-date with the latest guidelines in an attempt to improve quality of care and optimize patient outcomes. ■

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Managed Care Commentary

William J. Cardarelli, PharmD, Director of Pharmacy, Atrius Health, Harvard Vanguard Medical Associates, Watertown, Massachusetts

Each year approximately 780,000 individuals experience a stroke, 180,000 of which are recurrent events.[1] At younger ages, men suffer strokes more frequently than women, but this statistic reverses itself at older ages.1 In terms of mortality, stroke ranks third among all causes of death, behind heart disease and cancer.[1]

Recently, the American Heart Association (AHA)/American Stroke Association (ASA) published updated recommendations for the treatment of stroke,[2] focusing on 2 areas of treatment—the use of specific antiplatelet agents, and the use of statins—for secondary stroke prevention. With treatment guidelines so rapidly changing, the challenge for managed care is how best to provide the prescribing community with the most updated clinical recommendations for effective patient management. Managed care organizations should become more directional in providing strategies that will assist clinicians in the treatment of their patients, an effort that begins with clinician education and timely dissemination of the revised AHA/ASA guidelines. In addition, the incorporation of risk stratification algorithms to the standard of care would further reduce the overall risk of a secondary stroke event. Due to the precise changes recommended in the guidelines, managed care should be focused on identifying those risk factors that contribute to the development and progression of atherosclerotic cerebrovascular disease.

Although the importance of stroke awareness and prevention are well understood by most clinicians, the challenge of educating patients on the importance of adherence to prescribed therapy has been a very difficult and often unsuccessful task. Managed care organizations have traditionally relied on directing members to publicly available Web sites for patient information on various diseases. Although these provide effective general education, there is a need for very specific patient instruction; a role that managed care organizations can fill given the information and communication infrastructure at their disposal. Many managed care organizations publish member newsletters several times each year, which could be utilized to educate members on stroke risk and the importance of medication adherence for the prevention of secondary stroke. Managed care organizations also participate in health fairs and marketing events at employer groups, which can provide an additional opportunity to disseminate information to members on this and other disease states.

It is widely accepted that the most effective means of secondary stroke prevention is via reduction of risk factors and adherence to the latest guideline recommendations. Many managed care plans have the capability to provide clinicians with the latest studies as well as published guidelines, and should utilize this avenue to enhance clinician education for the benefit of both the performance of managed care organizations and patient outcomes. It is crucial for managed care organizations to acquire a complete understanding of the diseases that affect their members, educate both clinicians and patients on the importance of disease management, and encourage treatment approaches consistent with the latest evidence, particularly with a condition as prevalent and devastating as stroke. ■

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