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Update to the AHA/ASA Recommendations for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack

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The American Heart Association/American Stroke Association (AHA/ASA) Writing Committee for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack (TIA) has reviewed the results of recent trials that were published after our previous recommendations were issued.[1] Our intention in the present statement is to provide a brief review of the new data, to update specific recommendations, and to provide the reasons for any modifications. The 2 areas in which major new clinical trials have been published are (1) the use of specific antiplatelet agents for stroke prevention in patients with a history of noncardioembolic ischemic stroke or TIA and (2) the use of statins in the prevention of recurrent stroke.

Antithrombotic Use for Prevention of Ischemic Stroke in Patients With History of Noncardioembolic Ischemic Stroke

Recently published trials have added to the evidence of the benefit of the use of specific antiplatelet agents for stroke prevention in patients with a history of noncardioembolic

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ischemic stroke or TIA. The secondary prevention guidelines[1] have been updated to reflect this new evidence.

Addition of Clopidogrel to Aspirin for Prevention of Vascular Events

The Clopidogrel and Aspirin Versus Aspirin Alone for the Prevention of Atherothrombotic Events (CHARISMA) trial[2] was a double-blinded study that randomized 15 603 subjects with cardiovascular disease or multiple risk factors for cardiovascular disease to either clopidogrel 75 mg plus low-dose aspirin (75 to 162 mg) or placebo plus aspirin (75 to 162 mg). Roughly 35% of subjects (n=4320) qualified on the basis of the presence of cerebrovascular disease within 5 years of enrollment; approximately a third experienced TIA. The median follow-up was 28 months.

No significant differences were seen in the rates of nonfatal ischemic stroke between the 2 groups (1.7% versus 2.1%, *P*=0.07). The placebo plus aspirin group showed a higher rate of nonfatal stroke than did the clopidogrel group (1.9% versus 2.4%, *P*=0.03). The 2 groups experienced no differences in the rate of intracerebral hemorrhage (0.3%). The combination therapy did not significantly increase the risk of severe or fatal bleeding; however, patients had a higher rate of moderate bleeding in the combination therapy arm. Patients in the combination therapy arm experienced a reduction in a secondary end point, hospitalization for unstable angina, TIA, or revascularization (11.1% versus 12.3%, *P*=0.02). In a prespecified subgroup analysis, the combination therapy was marginally superior to aspirin alone in symptomatic patients (6.9% versus 7.9%, *P*=0.046). In the subgroup of patients with a history of stroke, a trend was seen toward a benefit from combination therapy, but it was not significant (hazard ratio [HR] point estimate not provided). Subgroup analyses, which are subject to both type I and type II error, should be interpreted cautiously.

Initiation of study drug up to 5 years after the index event is significantly beyond the high-risk period for stroke recurrence. At this time, the Management of Atherothrombosis With Clopidogrel in High-Risk Patients (MATCH) study remains a more relevant trial of these therapies in patients with cerebrovascular disease.[3] The CHARISMA trial showed no benefit for combined use of aspirin and clopidogrel for stroke prevention in patients with prior history of ischemic stroke. Limited-duration combination clopidogrel and aspirin therapy is indicated in patients with recent coronary events and/or prior vascular stenting, however, and the reader is referred to the latest American College of Cardiology/AHA guidelines for information on aspirin and clopidogrel for coronary indications.

Aspirin With and Without Dipyridamole

The European/Australasian Stroke Prevention in Reversible Ischemia Trial (ESPRIT) was a randomized, open-label study comparing aspirin 30 to 325 mg with or without dipyridamole 200 mg bid in 2763 subjects with TIA, transient monocular blindness, or minor stroke (modified Rankin score ≤3) within 6 months of enrollment.[4] Eighty-three percent of the dipyridamole used was extended release, the formulation used in the European Stroke Prevention Study (ESPS)-2 study, and the remainder was conventional dipyridamole. The median dose of aspirin was 75 mg. Approximately 70% of patients were enrolled beyond a month of the index event. Patients with a cardioembolic source of embolism, high-grade

stenosis requiring intervention, or coagulation disorder were excluded. Subjects were followed up for a mean of 3.5 years. The primary outcome was death from all vascular causes, nonfatal stroke, nonfatal myocardial infarction, or major bleeding complication. Outcomes were blinded. The onprotocol therapy analysis of ESPRIT did not reach statistical significance, whereas the intention-to-treat analysis did. The risk for the primary outcome was significantly lower in the dipyridamole plus aspirin arm (HR, 0.80; 95% confidence interval, 0.66 to 0.98). The survival curves began to diverge after the second year, which appeared to be related to deceleration in the aspirin arm. The use of combined dipyridamole and aspirin conferred an absolute risk reduction of 1% per year. Although there has been concern about the effect of dipyridamole on risk of myocardial infarction, particularly with low-dose aspirin therapy, no significant difference in time to first cardiac event was seen between the 2 treatment arms.

There was a high rate of medication intolerance in the aspirin plus dipyridamole arm. Thirty-four percent of subjects randomized to aspirin plus dipyridamole discontinued therapy, compared with 13% of subjects in the aspirin-only group. The dose of aspirin in ESPRIT was variable and included 30 mg/d, which is lower than the ≥50-mg dose recommended in consensus guidelines and conventionally used in the United States. ESPRIT, a nonblinded study, provided additional evidence of an incremental benefit of combination aspirin and extended-release dipyridamole compared with aspirin monotherapy for stroke prevention in patients with noncardioembolic ischemic stroke, as supported by a meta-analysis that included the ESPRIT data.[4] The impact of the study on the recommendation is lessened by the open-label design, the variable nonstandard aspirin doses, and the divergence of significance between the on-treatment and intention-to-treat analyses. The additional evidence from ESPRIT, however, was considered sufficient to raise the previous recommendation from a Class II grade A evidence to a Class I recommendation supported by grade B evidence (Table 1). The combination of aspirin and extended-release dipyridamole is recommended over aspirin alone.

Individual patient characteristics continue to play a role in selection of antiplatelet agents for recurrent stroke prevention. Side effects, costs, and comorbid illnesses influence decisions regarding antiplatelet therapy. Dipyridamole is not tolerated by some patients because it can cause persistent headache. Upward tapering of the dipyridamole dose may be helpful,[5,6] although this therapy requires further study. Adherence to medication use is an important factor to consider and is affected by costs, side effects, and frequency of dosing.[7] Some patients have allergy or gastrointestinal intolerance to aspirin therapy, and in these patients, clopidogrel is reasonable.

Aspirin monotherapy, clopidogrel monotherapy, and aspirin combined with extended-release dipyridamole all remain accepted options for initial therapy for patients with noncardioembolic ischemic stroke and TIA. Data from ongoing clinical trials will provide a direct comparison of the efficacy of clopidogrel with that of extended-release dipyridamole plus aspirin for secondary prevention in patients with acute ischemic stroke.

Statin Therapy in Recurrent Stroke Prevention

The use of 3-hydroxy-3-methyglutaryl coenzyme A reductase inhibitors (statins) has been approved by regulatory agencies for prevention of ischemic stroke in patients with coronary heart disease (CHD).[8] It is uncertain, however, whether this class of drugs is indicated for recurrent stroke prevention.[9] This advisory reviews new data relating to the use of atorvastatin in recurrent stroke prevention on the basis of the results of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial.[10]

The SPARCL trial was a randomized, double-blind study designed to determine whether atorvastatin 80 mg/d or placebo would reduce the risk of fatal or nonfatal stroke in patients with no known coronary disease who had experienced a stroke or TIA within the previous 6 months.[10] Eligible patients included men and women over 18 years of age who had ischemic or hemorrhagic stroke or TIA 1 to 6 months before randomization. Patients had to be ambulatory with a modified Rankin score of ≤3 and a low-density lipoprotein cholesterol level 100 mg/dL (2.6 mmol/L) to 190 mg/dL (4.9 mmol/L). Study exclusion criteria included atrial fibrillation, other cardiac sources of embolism, subarachnoid hemorrhage, and other criteria. The prespecified secondary composite outcomes were stroke or TIA; major coronary event (death from cardiac causes, nonfatal myocardial infarction, or resuscitation after cardiac arrest); major cardiovascular event (stroke plus any major coronary event); acute coronary event (major coronary event or unstable angina); any coronary event (acute coronary event plus a coronary revascularization procedure, unstable angina, or angina or ischemia requiring emergency hospitalization); revascularization procedure (coronary, carotid, or peripheral); and any cardiovascular event. The study was designed to have a statistical power of 90% for the primary end point and continue until 540 primary events had occurred. Intention-totreat analyses of primary and secondary outcomes included prespecified adjustments for geographic region, entry event (stroke or TIA), time since entry event, sex, and baseline age.

Overall, 2365 patients were randomized to atorvastatin and 2366 to placebo. Standard cardiovascular preventive medications (eg, antiplatelet drugs, antihypertensives, and warfarin) were used frequently in the 2 treatment groups. The baseline low-density lipoprotein cholesterol levels were 132.7 mg/dL (3.43 mmol/L) and 133.7 mg/dL (3.46 mmol/L) in the atorvastatin and placebo treatment groups, respectively. The net difference in use of a statin drug between the 2 treatment groups was 78.1%. During the treatment phase of the study, the mean low-density lipoprotein cholesterol level was 73 mg/dL (1.9 mmol/L) in the atorvastatin treatment arm and 129 mg/dL (3.3 mmol/L) in the placebo treatment arm.[10] During a median follow-up of 4.9 years, 11.2% (265 patients) receiving atorvastatin and 13.1% (311 patients) receiving placebo reached the primary end point of fatal or nonfatal stroke (5-year absolute reduction in risk, 2.2%; adjusted HR, 0.84; 95% confidence interval, 0.71, 0.99; P=0.03 and unadjusted P=0.05). The 5-year absolute reduction in risk of major cardiovascular events was 3.5% (HR, 0.80; 95% confidence interval, 0.69, 0.92; P=0.002). Other secondary outcomes that achieved statistically significant reductions favoring the atorvastatin treatment arm were stroke or TIA (P<0.001), major coronary event (P=0.003), acute coronary event (P=0.001), any coronary event (P<0.001), revascularization (P<0.001), and any cardiovascular event (P<0.001). No

statistically significant differences were seen in the rates of nonfatal stroke (*P*=0.11) or death (*P*=0.98).

The 2 treatment groups had no significant differences in the incidence of serious adverse events.[10] The atorvastatin treatment group, however, experienced 55 hemorrhagic strokes, compared with 33 in the placebo treatment group. Incidence of myalgia (5.5% versus 6.0%), myopathy (0.3% versus 0.3%), and rhabdomyolysis (0.1% versus 0.1%) did not differ between the atorvastatin or placebo treatment groups, respectively. Elevation (>3 times) in liver enzymes was more common in the atorvastatin treatment group (2.2% versus 0.5%), and elevation of creatine kinase (>10 times) was more frequent with atorvastatin (0.1% versus 0%) treatment.

The 16% reduction in the HR favoring atorvastatin in the SPARCL trial was less than expected; however, a prespecified analysis of 4162 patients according to the protocol showed an 18% relative reduction in the risk of stroke in the atorvastatin treatment group compared with controls (HR, 0.82; 95% confidence interval, 0.69, 0.98; *P*=0.03). A somewhat surprising finding in SPARCL was the reduction of different types of CHD events that exceeded that of stroke events, although study patients did not have a history of overt CHD. This finding supports the concept that atherosclerosis is a systemic disease and that CHD may be an important occult comorbid condition in stroke patients whether or not there is a medical history of CHD.

The new recommendations are shown in Table 2. On the basis of the SPARCL trial, statin therapy with intensive lipid-lowering effects is recommended for patients with atherosclerotic ischemic stroke or TIA and without known CHD to reduce the risk of stroke and cardiovascular events[10] (*Class I, Level of Evidence B*).[1] For those patients with atherosclerotic ischemic stroke or TIA and a history of CHD, it is recommended that clinicians follow the current 2006 AHA/ASA guidelines for lipid management, which emphasize utilization of National Cholesterol Education Panel III guidelines.[1]

The SPARCL trial leaves a number of important questions unanswered in relation to statin therapy in prevention of recurrent stroke. For example, in the SPARCL trial, is the beneficial effect observed on recurrent stroke prevention a drug-class effect or an atorvastatin-specific effect? This recommendation conforms with AHA Guideline Development policy that assumes a class effect in the absence of data to the contrary.

Appendix

Disclosure

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This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10 000 or more during any 12 month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

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Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and Metabolism Council; Quality of Care and Outcomes Research Interdisciplinary Working Group; American Academy of Neurology. PPrimary prevention of ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council: cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and Metabolism Council; and the Quality of Care and Outcomes Research Interdisciplinary Working Group [published correction appears in *Stroke*. 2007; 38:207]. Stroke. 2006; 37:1583–1633. [PubMed: 16675728]

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Table 1

Recommendations for Antiplatelet Therapy

Class I Recommendations	
1	For patients with noncardioembolic ischemic stroke or TIA, antiplatelet agents rather than oral anticoagulation are recommended to reduce the risk of recurrent stroke and other cardiovascular events (*Class I, Level of Evidence A*).
2	Old recommendation: Aspirin (50 to 325 mg/d), the combination of aspirin and extended-release dipyridamole, and clopidogrel are all acceptable options for initial therapy (*Class IIa, Level of Evidence A*). New recommendation: Aspirin (50 to 325 mg/d) monotherapy, the combination of aspirin and extended-release dipyridamole, and clopidogrel monotherapy are all acceptable options for initial therapy (*Class I, Level of Evidence A*).*
3	Old recommendation: Compared with aspirin alone, both the combination of aspirin and extended-release dipyridamole and clopidogrel are safe. The combination of aspirin and extended-release dipyridamole is suggested over aspirin alone (*Class IIa, Level of Evidence A*). New recommendation: The combination of aspirin and extended-release dipyridamole is recommended over aspirin alone (*Class I, Level of Evidence B*).
Class II Recommendations	
1	Clopidogrel may be considered over aspirin alone on the basis of direct-comparison trials (*Class IIb, Level of Evidence B*).
2	For patients allergic to aspirin, clopidogrel is reasonable (*Class IIa, Level of Evidence B*).
Class III Recommendation	
	The addition of aspirin to clopidogrel increases the risk of hemorrhage. Combination therapy of aspirin and clopidogrel is not routinely recommended for ischemic stroke or TIA patients unless they have a specific indication for this therapy (ie, coronary stent or acute coronary syndrome) (*Class III, Level of Evidence A*).

* For patients who have an ischemic cerebrovascular event while taking aspirin, there is no evidence that increasing the dose of aspirin provides additional benefit. Although alternative antiplatelet agents are often considered for noncardioembolic patients, no single agent or combination has been well studied in patients who have had an event while receiving aspirin.

Table 2

Recommendations for Lipid Management

Recommendations	Class, Level of Evidence
Class I Recommendations	
Ischemic stroke or TIA patients with elevated cholesterol, comorbid coronary artery disease, or evidence of an atherosclerotic origin should be managed according to NCEP III guidelines, which include lifestyle modification, dietary guidelines, and medication recommendations.	*Class I, Level A*
Statin agents are recommended, and the target goal for cholesterol lowering for those with CHD or symptomatic atherosclerotic disease is an LDL-C level of <100 mg/dL. An LDL-C <70 mg/dL is recommended for very high-risk persons with multiple risk factors.	*Class I, Level A*
New Recommendation	
On the basis of the SPARCL trial, administration of statin therapy with intensive lipid-lowering effects is recommended for patients with atherosclerotic ischemic stroke or TIA and without known CHD to reduce the risk of stroke and cardiovascular events.	*Class I, Level B*
Class II Recommendation	
Ischemic stroke or TIA patients with low HDL cholesterol may be considered for treatment with niacin or gemfibrozil.	*Class IIb, Level B*

NCEP indicates National Cholesterol Education Panel; LDL-C, low-density lipoprotein cholesterol; and HDL, high-density lipoprotein.