Guidelines for Prevention of Stroke in Patients With Ischemic Stroke or Transient Ischemic Attack

A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association Council on Stroke

Co-Sponsored by the Council on Cardiovascular Radiology and Intervention

The American Academy of Neurology affirms the value of this guideline.

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Abstract—The aim of this new statement is to provide comprehensive and timely evidence-based recommendations on the prevention of ischemic stroke among survivors of ischemic stroke or transient ischemic attack. Evidence-based recommendations are included for the control of risk factors, interventional approaches for atherosclerotic disease, antithrombotic treatments for cardioembolism, and the use of antiplatelet agents for noncardioembolic stroke. Further recommendations are provided for the prevention of recurrent stroke in a variety of other specific circumstances, including arterial dissections; patent foramen ovale; hyperhomocysteinemia; hypercoagulable states; sickle cell disease; cerebral venous sinus thrombosis; stroke among women, particularly with regard to pregnancy and the use of postmenopausal hormones; the use of anticoagulation after cerebral hemorrhage; and special approaches for the implementation of guidelines and their use in high-risk populations. (***Circulation.*** **2006;113:e409-e449.)**

Key Words: AHA Scientific Statements ■ ischemia ■ ischemia attack, transient ■ stroke

Survivors of a transient ischemic attack (TIA) or stroke have an increased risk of another stroke, which is a major source of increased mortality and morbidity. Among the estimated 700 000 people with stroke in the United States each year, 200 000 of them are among persons with a recurrent stroke. The number of people with TIA, and therefore at risk for stroke, is estimated to be much greater. Epidemiological studies have helped to identify the risk and determinants of recurrent stroke, and clinical trials have provided the data to generate evidence-based recommendations to reduce this risk. Prior statements from the American Heart Association (AHA) have dealt with primary[1] and secondary stroke prevention.[2,3] Because most strokes are cerebral infarcts, these recommendations focus

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TABLE 1. Definition of Classes and Levels of Evidence Used in AHA Recommendations

Class I	Conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful and effective
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment
Class IIa	Weight of evidence or opinion is in favor of the procedure or treatment.
Class IIb	Usefulness/efficacy is less well established by evidence or opinion
Class III	Conditions for which there is evidence and/or general agreement that the procedure or treatment is not useful/effective and in some cases may be harmful
Level of Evidence A	Data derived from multiple randomized clinical trials
Level of Evidence B	Data derived from a single randomized trial or nonrandomized studies
Level of Evidence C	Expert opinion or case studies

primarily on the prevention of stroke among the ischemic stroke or TIA group. Other statements from the AHA have dealt with acute ischemic stroke,[4] subarachnoid hemorrhage (SAH),[5] and intracerebral hemorrhage (ICH).[6] Recommendations follow the AHA and the American College of Cardiology (ACC) methods of classifying the level of certainty of the treatment effect and the class of evidence (see Table 1).[7]

The aim of this new statement is to provide comprehensive and timely evidence-based recommendations on the prevention of ischemic stroke among survivors of ischemic stroke or TIA. A writing committee chair and vice chair were designated by the Stroke Council Manuscript Oversight Committee. A writing committee roster was developed and approved by the Stroke Council with representatives from neurology, cardiology, radiology, surgery, nursing, and health services research. The committee met in person and had a number of teleconferences to develop the outline and text of the recommendations. The writing group conducted a comprehensive review of the relevant literature. Although the complete list of keywords is beyond the scope of this section, the committee reviewed all compiled reports from computerized searches and conducted additional searching by hand. Searches were limited to English language sources and to human subjects. Literature citations were generally restricted to published manuscripts appearing in journals listed in Index Medicus and reflected literature published as of December 31, 2004. Because of the scope and importance of certain ongoing clinical trials and other emerging information, published abstracts were cited when they were the only published information available. The references selected for this document are exclusively for peer-reviewed papers that are representative but not all inclusive. All members of the committee had frequent opportunities to review drafts of the document, comment in writing or during teleconference discussions, and reach consensus with the final recommendations.

Although prevention of stroke is the primary outcome of interest, many of the grades for the recommendations were chosen to reflect the existing evidence on the reduction of all vascular outcomes after stroke, including stroke, myocardial infarction (MI), and vascular death. We have organized our recommendations in this statement to aid the clinician who has arrived at a potential explanation of the cause of the ischemic stroke in an individual patient and is embarking on therapy to reduce the risk of a recurrent event and other vascular outcomes. Our intention is to have these statements updated every 3 years, with additional interval updates as needed, to reflect the changing state of knowledge on the approaches to prevention of a recurrent stroke.

Definition of TIA and Ischemic Stroke Subtypes

The distinction between TIA and ischemic stroke has become less important in recent years because many of the preventive approaches are applicable to both groups. They share pathogenetic mechanisms; prognosis may vary, depending on their severity and cause; and definitions are dependent on the timing and degree of the diagnostic evaluation. By conventional clinical definitions, if the neurological symptoms continue for >24 hours, a person has been diagnosed with stroke; otherwise, a focal neurological deficit lasting <24 hours has been defined as a TIA. With the more widespread use of modern brain imaging, many patients with symptoms lasting <24 hours are found to have an infarction. The most recent definition of stroke for clinical trials has required either symptoms lasting >24 hours or imaging of an acute clinically relevant brain lesion in patients with rapidly vanishing symptoms. The proposed new definition of TIA is a "brief episode of neurological dysfunction caused by a focal disturbance of brain or retinal ischemia, with clinical symptoms typically lasting less than 1 hour, and without evidence of infarction."[8] TIAs are an important determinant of stroke, with 90-day risks of stroke reported as high as 10.5% and the greatest stroke risk apparent in the first week.[9,10]

Ischemic stroke is classified into various categories according to the presumed mechanism of the focal brain injury and the type and localization of the vascular lesion. The classic categories have been defined as large-artery atherosclerotic infarction, which may be extracranial or intracranial; embolism from a cardiac source; small-vessel disease; other determined cause such as dissection, hypercoagulable states, or sickle cell disease; and infarcts of undetermined cause.[11] The certainty of the classification of the ischemic stroke mechanism is far from ideal and reflects the inadequacy or timing of the diagnostic workup in some cases to visualize the occluded artery or to localize the source of the embolism. Recommendations for the timing and type of diagnostic workup for TIA and stroke patients are beyond the scope of this guideline statement.

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I. Risk Factor Control for All Patients With TIA or Ischemic Stroke

A. Hypertension

It is estimated that ≈50 000 000 Americans have hypertension.[12] There is a continuous association between both systolic and diastolic blood pressures (BPs) and the risk of ischemic stroke.[13,14] Meta-analyses of randomized controlled trials confirm an approximate 30% to 40% stroke risk reduction with BP lowering.[14,15] Detailed evidence-based recommendations for the BP screening and treatment of persons with hypertension are summarized in the American Stroke Association Scientific Statement on the Primary Prevention of Ischemic Stroke[1] and the AHA Guidelines for Primary Prevention of Cardiovascular Disease and Stroke: 2002 Update[16] and are detailed in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7).[17] JNC-7 stresses the importance of lifestyle modifications in the overall management of hypertension.[17] Systolic BP reductions have been associated with weight loss; the consumption of a diet rich in fruits, vegetables, and low-fat dairy products; regular aerobic physical activity; and limited alcohol consumption.[17]

Although a wealth of data from a variety of sources support the importance of treatment of hypertension for primary cardiovascular disease prevention in general and in stroke in particular, only limited data directly address the role of BP treatment in secondary prevention among persons with stroke or TIA.[15] There is a general lack of definitive data to help guide the immediate management of elevated BP in the setting of acute ischemic stroke; a cautious approach has been recommended, and the optimal time to initiate therapy remains uncertain.[18]

A systematic review focused on the relationship between BP reduction and the secondary prevention of stroke and other vascular events.[19] The analysis included 7 published, nonconfounded, randomized controlled trials with a combined sample size of 15 527 participants with ischemic stroke, TIA, or ICH randomized from 3 weeks to 14 months after the index event and followed up for 2 to 5 years. No relevant trials tested the effects of nonpharmacological interventions. Treatment with antihypertensive drugs has been associated with significant reductions in all recurrent strokes, nonfatal recurrent stroke, MI, and all vascular events with similar, albeit nonsignificant, trends toward a reduction in fatal stroke and vascular death. These results were seen in studies that recruited patients regardless of whether they had hypertension.

Data on the relative benefits of specific antihypertensive regimens for secondary stroke prevention are largely lacking. A meta-analysis showed a significant reduction in recurrent stroke with diuretics and diuretics and ACE inhibitors (ACEIs) combined but not with β-blockers (BBs) or ACEIs used alone.[19] Similar effects were found when all vascular events were considered as the outcome. The analysis included patients with ischemic stroke, TIA, or hemorrhagic stroke. The overall reductions in stroke and all vascular events were related to the degree of BP lowering achieved, and as pointed out in the meta-analysis, comparisons, "although internally consistent, are limited by the small numbers of trials, patients, and events for each drug class . . . especially for the β-receptor antagonists for which the findings might be falsely neutral."[19]

Given these considerations, whether a particular class of antihypertensive drug or a particular drug within a given class offers a particular advantage for use in patients after ischemic stroke remains uncertain. Much discussion has focused on the role of ACEIs. The Heart Outcomes Prevention Evaluation (HOPE) Study compared the effects of the ACEI ramipril with placebo in high-risk persons and found a 24% risk reduction (95% CI, 5 to 40) for stroke, MI, or vascular death among the 1013 patients with a history of stroke or TIA.[14] Although the BP-lowering effect as measured during the study was minimal (average, 3/2 mm Hg), it may have been related to the methodology used to measure BP. A substudy using ambulatory BP monitoring found a substantial 10/4 mm Hg reduction over 24 hours and a 17/8 mm Hg reduction during the nighttime.[20]

The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) was specifically designed to test the effects of a BP-lowering regimen, including an ACEI, in 6105 patients with stroke or TIA within the previous 5 years.[21] Randomization was stratified by intention to use single (ACEI) or combination (ACEI plus the diuretic indapamide) therapy in both hypertensive (>160 mm Hg systolic or >90 mm Hg diastolic) and nonhypertensive patients. The combination (reducing BP by an average of 12/5 mm Hg) resulted in a 43% (95% CI, 30 to 54) reduction in the risk of recurrent stroke and a 40% (95% CI, 29 to 49) reduction in the risk of major vascular events (coronary heart disease [CHD]), with the effect present in both the hypertensive and normotensive groups. However, there was no significant benefit when the ACEI was given alone. Those given combination therapy were younger, were more likely to be men, were more likely to be hypertensive, had a higher mean BP at entry, were more likely to have CHD, and were recruited sooner after the event. The JNC-7 report concluded that "recurrent stroke rates are lowered by the combination of an ACEI and thiazide-type diuretic."[17]

A preliminary phase II study randomized 342 hypertensive patients with acute ischemic stroke to an angiotensin receptor blocker (ARB) or placebo over the first week.[22] There were no significant differences in blood pressures between the active treatment and placebo patients, with both groups receiving the ARB after the first week. Although the number of vascular events among the ARB group was significantly reduced over the first week (OR, 0.475; 95% CI, 0.252 to 0.895), there were no differences in outcome at 3 months. At 12 months, a significant reduction in mortality was observed in the ARB group. The mechanisms by which an acute treatment led to this difference at 12 months, but no difference at 3 months, are uncertain; further studies are needed.

Recommendations

1. **Antihypertensive treatment is recommended for both prevention of recurrent stroke and prevention of other vascular events in persons who have had an ischemic stroke or TIA and are beyond the hyperacute period (Class I, Level of Evidence A). Because this benefit extends to persons with and without a history of hypertension, this recommendation should be considered for all ischemic stroke and TIA patients (Class IIa, Level of Evidence B). An absolute target BP level and reduction are uncertain and**

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should be individualized, but benefit has been associated with an average reduction of ≈10/5 mm Hg, and normal BP levels have been defined as <120/80 mm Hg by JNC-7 (Class IIa, Level of Evidence B).

2. **Several lifestyle modifications have been associated with blood pressure reductions and should be included as part of a comprehensive antihypertensive therapy (Class IIb, Level of Evidence C). The optimal drug regimen remains uncertain; however, the available data support the use of diuretics and the combination of diuretics and an ACEI (Class I, Level of Evidence A). The choice of specific drugs and targets should be individualized on the basis of reviewed data and consideration of specific patient characteristics (eg, extracranial cerebrovascular occlusive disease, renal impairment, cardiac disease, and diabetes) (Class IIb, Level of Evidence C).**

B. Diabetes

Diabetes is estimated to affect 8% of the adult population.[23] It is frequently encountered in stroke care, being present in 15%,[24] 21%,[25] and 33%[26] of patients with ischemic stroke. Diabetes is a clear risk factor for stroke.[27–31] The data supporting diabetes as a risk factor for recurrent stroke, however, are more sparse. Diabetes mellitus (DM) and age were the only significant independent predictors of recurrent stroke in a population-based study of stroke from Rochester, Minn.[32] In another community-based stroke study, the Oxfordshire Stroke Project, diabetes was 1 of 2 factors independently associated with stroke recurrence (hazard ratio [HR] 1.85; 95% CI, 1.18 to 2.90; $P<0.01$), and investigators estimated that 9.1% (95% CI, 2.0 to 20.2) of the recurrent strokes were attributable to diabetes.[33] In the evaluation of 2-year stroke recurrence in the Stroke Data Bank, patients at the lowest risk had no history of diabetes.[34] Furthermore, diabetes has been shown to be a strong determinant for the presence of multiple lacunar infarcts in 2 different stroke cohorts.[35,36]

Most of the available data on stroke prevention in patients with diabetes are on the primary rather than secondary prevention of stroke. Multifactorial approaches with intensive treatments to control hyperglycemia, hypertension, dyslipidemia, and microalbuminuria have demonstrated reductions in the risk of cardiovascular events.[37] These intensive approaches included behavioral measures and the use of a statin, ACEI, ARB, and antiplatelet drug as appropriate. Primary stroke prevention guidelines have emphasized the more rigorous control of BP among both type 1 and type 2 diabetics[1] with lower targets of 130/80 mm Hg.[16,17] Tight control of BP in diabetics has been shown to reduce the incidence of stroke significantly.[38–40] In the United Kingdom Prospective Diabetes Study (UKPDS), diabetic patients with controlled BP (mean BP, 144/82 mm Hg) had a 44% reduced relative risk (RR) of stroke compared with diabetics with poorer BP control (mean BP, 154/87 mm Hg; 95% CI, 11 to 65; $P=0.013$).[38] Intensive treatment of hypertension also significantly reduced the risk of the combined end point of MI, sudden death, stroke, and peripheral vascular disease by 34% ($P=0.019$). Additional clinical trials have corroborated the risk reduction in stroke and/or cardiovascular events with BP control in diabetics.[39,41–43] Although most of these studies did not reach the goal BP of 130/80 mm Hg, epidemiological analyses suggest a continual reduction in cardiovascular events to a BP of 120/80 mm Hg.[43–45]

Thiazide diuretics, BBs, ACEIs, and ARBs are beneficial in reducing cardiovascular events and stroke incidence in patients with diabetes[43,46–50] and are therefore preferred for the initial treatment of hypertension. ACEIs have a favorable effect on stroke and other cardiovascular outcomes.[21,41,51] ACEI- and ARB-based treatments have been shown to favorably affect the progression of diabetic nephropathy and to reduce albuminuria, and ARBs have been shown to reduce the progression to macroalbuminuria.[23,38,52–56] The American Diabetes Association (ADA) now recommends that all patients with diabetes and hypertension should be treated with a regimen that includes either an ACEI or an ARB.[23] Some studies have shown an excess of selected cardiac events in patients treated with calcium channel blockers (CCBs) compared with ACEIs.[57,58] The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study, which included >12 000 diabetic patients, demonstrated no difference between these 2 classes in the primary end point of coronary events regardless of diabetic status, although the diuretic chlorthalidone was found to be superior to both an ACEI (lisinopril) and a CCB (amlodipine) for selected secondary vascular end points.[47] Both diabetic and nondiabetic patients had similar vascular event rates treated with CCBs or ARBs in the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trial.[59] In the Hypertension Optimal Treatment (HOT) study and the Systolic Hypertension in Europe (Syst-Eur) Trial, CCBs in combination with ACEIs, BBs, and diuretics did not appear to be associated with increased cardiovascular morbidity.[43,49] However, because of lingering concerns about a potential increase in cardiovascular events and in the ability to reduce progression of renal disease with CCBs, the ADA has suggested that this class of medications should be considered add-on agents in patients with diabetes.[23] It is important to note that polytherapy is usually needed to reach BP targets among diabetics and that the benefits of antihypertensive therapy depend more on BP achieved than the regimen used.[23]

More rigorous control of lipids is now also recommended among diabetics with LDL cholesterol (LDL-C) targets as low as 70 mg/dL.[60] The Heart Protection Study (HPS) comparing simvastatin to placebo demonstrated the beneficial effect of lipid-lowering statin use in diabetic patients. In this randomized clinical trial (RCT), which included 5963 people with diabetes who were >40 years of age with a total cholesterol >135 mg/dL, simvastatin was associated with a 28% (95% CI, 8 to 44) reduction in ischemic strokes (3.4% simvastatin versus 4.7% placebo; $P=0.01$) and a 22% (95% CI, 13 to 30; $P<0.0001$) reduction in the first-event rate for vascular events, including major coronary artery events, strokes, and revascularizations. These results were independent of baseline LDL, preexisting vascular disease, type or duration of diabetes, or adequacy of glycemic control.[61] Several other clinical trials of statin agents that have included smaller numbers of patients with diabetes have found similar reductions in both cardiovascular and cerebrovascular events.[62–64]

Glycemic control, shown to reduce the occurrence of microvascular complications (nephropathy, retinopathy, and peripheral neuropathy) in several clinical trials,[62,65,66] is recommended in multiple guidelines of both primary and

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secondary prevention of stroke and cardiovascular disease.[1,16,23,67–69] Data on the efficacy of glycemic control on macrovascular complications, including stroke, are more limited. RCTs of intensive glycemic control in patients with type 1 and type 2 diabetes have shown trends in reducing the risk of cardiovascular events, although they did not reach statistical significance.[30,70] Analysis of data from randomized trials suggests a continual reduction in vascular events with the progressive control of glucose to normal levels.[71]

Normal fasting glucose is defined as glucose <100 mg/dL (5.6 mmol/L), and impaired fasting glucose has been defined at levels between 100 and 126 mg/dL (5.6 and 6.9 mmol/L). A fasting plasma glucose level >126 mg/dL (7.0 mmol/L) or a casual plasma glucose >200 mg/dL (11.1 mmol/L) meets the threshold for the diagnosis of diabetes.[23] Hemoglobin A_{1c} level >7% is defined as inadequate control of hyperglycemia. Diet and exercise, oral hypoglycemic drugs, and insulin are recommended to obtain glycemic control.[23] Although the focus here is on the treatment of stroke patients with diabetes, there is growing recognition of the high prevalence of insulin resistance. Ongoing trials are addressing the use of rosiglitazone agents in secondary stroke prevention among those with insulin resistance.

Recommendations

1. **More rigorous control of blood pressure and lipids should be considered in patients with diabetes (Class IIa, Level of Evidence B). Although all major classes of antihypertensives are suitable for BP control, most patients will require >1 agent. ACEIs and ARBs are more effective in reducing the progression of renal disease and are recommended as first-choice medications for patients with DM (Class I, Level of Evidence A).**
2. **Glucose control is recommended to near-normoglycemic levels among diabetics with ischemic stroke or TIA to reduce microvascular complications (Class I, Level of Evidence A) and possibly macrovascular complications (Class IIb, Level of Evidence B). The goal for hemoglobin A_{1c} should be ≤7% (Class IIa, Level of Evidence B).**

C. Lipids

Hypercholesterolemia and hyperlipidemia are not as well established as risk factors for first or recurrent stroke in contrast to what is seen in cardiac disease.[72,73] Overall, prior observational cohort studies have shown only a weakly positive association for cholesterol level and risk of ischemic stroke or no clear relationship between plasma cholesterol and total stroke, and stroke risk reduction in statin trials may be primarily for nonfatal stroke.[72,74] Recent clinical trial data suggest, however, that stroke may be reduced by the administration of statin agents in persons with CHD.[75–77] The risk reductions with statins were beyond that expected solely through cholesterol reductions and have led to the consideration of other potential beneficial mechanisms. These findings led to approval of simvastatin and pravastatin for the prevention of stroke in those with CHD.[78]

The Medical Research Council/British Heart Foundation HPS addressed the issue of stroke prevention with simvastatin administration in those with or without prior cerebrovascular disease.[79] In this study, 20 536 patients were identified who had coronary artery disease, occlusive vascular disease in other beds (including cerebrovascular disease), diabetes, or hypertension with other vascular risk factors. A patient was required to have a total cholesterol level of ≥135 mg/dL to qualify for the study. Patients were then assigned to either simvastatin 40 mg/d or placebo. Overall, there was a 25% RR reduction for the end point of stroke ($P<0.0001$). HPS showed that among those with preexisting cerebrovascular disease, the addition of statin therapy resulted in a significant reduction of coronary events and fewer revascularization procedures regardless of baseline cholesterol levels. However, among those with preexisting cerebrovascular disease, the incidence of stroke was not significantly reduced. Although many stroke patients with a history of CHD or DM may qualify for statin therapy, it remains uncertain whether those without CHD will benefit from statin therapy to reduce the risk of recurrent stroke according to HPS findings. This important question is being addressed in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels Study (SPARCL).[80]

A review of recent prevention guidelines concerning cholesterol lowering by statin use in stroke prevention[16,68] suggests that the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Cholesterol in Adults (Adult Treatment Panel III)[81,82] is the most comprehensive guide for management of lipids in persons at risk for or who have cerebrovascular disease. NCEP emphasizes LDL-C lowering and 2 major modalities for LDL-C lowering: therapeutic lifestyle change and drug-specific therapy. Therapeutic lifestyle change stresses a reduction in saturated fats and cholesterol intake, weight reduction, and an increase in physical activity. LDL-C goals and cutpoints for initiation of therapeutic lifestyle change and drug therapy are based on 3 categories of risk: CHD and CHD risk equivalents (the latter category includes diabetes and symptomatic carotid artery disease), ≥2 cardiovascular risk factors stratified by 10-year risk of 10% to 20% for CHD and <10% for CHD according to the Framingham risk score, and 0 to 1 cardiovascular risk factor. When there is a history of CHD and CHD risk equivalents, the target LDL-C goal is <100 mg/dL.[81,82] Drug therapy options and management of metabolic syndrome and other dyslipidemias are addressed in the NCEP guideline. LDL-C lowering results in a reduction of total mortality, coronary mortality, major coronary events, coronary procedures, and stroke in persons with CHD.[81,82]

Since the publication of ATP III, 5 major trials of statin therapy have been published that provide new insights for cholesterol lowering therapy in cardiovascular disease. On the basis of the results of these new studies, an addendum to the ATP III algorithm has been published.[60] The recommendation in very-high-risk persons is to aim for an LDL-C of <70 mg/dL.[60] Very-high-risk patients are those who have established cardiovascular disease plus (1) multiple major risk factors (especially diabetes), (2) severe and poorly controlled risk factors (especially continued cigarette smoking), (3) multiple risk factors of the metabolic syndrome

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TABLE 2. Recommendations for Treatable Vascular Risk Factors

Risk Factor	Recommendation	Class/Level of Evidence*
Hypertension	Antihypertensive treatment is recommended for prevention of recurrent stroke and other vascular events in persons who have had an ischemic stroke and are beyond the hyperacute period.	Class I, Level A
	Because this benefit extends to persons with and without a history of hypertension, this recommendation should be considered for all ischemic stroke and TIA patients.	Class IIa, Level B
	An absolute target BP Level And reduction are uncertain and should be individualized, but benefit has been associated with an average reduction of ≈10/5 mm Hg and normal BP levels have been defined as <120/80 by JNC-7.	Class IIa, Level B
	Several lifestyle modifications have been associated with BP reductions and should be included as part of a comprehensive approach antihypertensive therapy.	Class IIb, Level C
	Optimal drug regimen remains uncertain; however, available data support the use of diuretics and the combination of diuretics and an ACEI. Choice of specific drugs and targets should be individualized on the basis of reviewed data and consideration, as well as specific patient characteristics (eg, extracranial cerebrovascular occlusive disease, renal impairment, cardiac disease, and DM).	Class I, Level A
Diabetes	More rigorous control of blood pressure and lipids should be considered in patients with diabetes.	Class IIa, Level B
	Although all major classes of antihypertensives are suitable for the control of BP, most patients will require >1 agent. ACEIs and ARBs are more effective in reducing the progression of renal disease and are recommended as first-choice medications for patients with DM.	Class I, Level A
	Glucose control is recommended to near-normoglycemic levels among diabetics with ischemic stroke or TIA to reduce microvascular complications.	Class I, Level A
	The goal for Hb A_{1c} should be ≤7%.	Class IIa, Level B
Cholesterol	Ischemic stroke or TIA patients with elevated cholesterol, comorbid CAD, 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 of <100 mg/dL and LDL-C <70 mg/dL for very-high-risk persons with multiple risk factors.	Class I, Level A
	Patients with ischemic stroke or TIA presumed to be due to an atherosclerotic origin but with no preexisting indications for statins (normal cholesterol levels, no comorbid CAD, or no evidence of atherosclerosis) are reasonable to consider for treatment with a statin agent to reduce the risk of vascular events.	Class IIa, Level B
	Ischemic stroke or TIA patients with low HDL-C may be considered for treatment with niacin or gemfibrozil.	Class IIb, Level B

CAD indicates coronary artery disease; Hb, hemoglobin.
*See Table 1 for explanation of class and level of evidence.

(especially high triglycerides ≥200 mg/dL with low HDL cholesterol [<40 mg/dL]), and (4) patients with acute coronary syndromes.

Other medications also used to treat dyslipidemia include niacin, fibrates, and cholesterol absorption inhibitors. These agents can be used in stroke or TIA patients who cannot tolerate statins, but data demonstrating their efficacy for prevention of stroke recurrence are scant. Niacin was associated with a reduction in cerebrovascular events in the Coronary Drug Project.[83] Gemfibrozil reduced the rate of unadjudicated total strokes among men with coronary artery disease and low levels of HDL-C (≤40 mg/dL) in the Veterans Administration HDL Intervention Trial (VA-HIT).[84] However, the results were not significant when only adjudicated events were analyzed.

Recommendations

1. **Patients with ischemic stroke or TIA 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 of Evidence A) (Table 2). Statin agents are recommended, and the target goal for cholesterol lowering for those with CHD or symptomatic atherosclerotic disease is an LDL-C of <100 mg/dL and LDL-C of <70 mg/dL for very-high-risk persons with multiple risk factors (Class I, Level of Evidence A).**
2. **Patients with ischemic stroke or TIA presumed to be due to an atherosclerotic origin but with no preexisting indications for statins (normal cholesterol levels, no comorbid coronary artery disease, or no evidence of atherosclerosis) are reasonable candidates for treatment with a statin agent to reduce the risk of vascular events (Class IIa, Level of Evidence B).**
3. **Patients with ischemic stroke or TIA with low HDL cholesterol may be considered for treatment with niacin or gemfibrozil (Class IIb, Level of Evidence B) (Table 2).**

D. Cigarette Smoking

There is strong and convincing evidence that cigarette smoking is a major independent risk factor for ischemic stroke.[85–89] The risk associated with smoking is present at all ages, in both sexes, and among different racial/ethnic groups.[88,90] In a meta-analysis, smoking has been shown to be associated with a doubling of risk among smokers compared with nonsmokers.[88] The pathological pathway contributing to increased risk

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TABLE 3. Recommendations for Modifiable Behavioral Risk Factors

Risk Factor	Recommendation	Class/Level of Evidence*
Smoking	All ischemic stroke or TIA patients who have smoked in the past year should be strongly encouraged not to smoke.	Class I, Level C
	Avoid environmental smoke.	Class IIa, Level C
	Counseling, nicotine products, and oral smoking cessation medications have been found to be effective for smokers.	Class IIa, Level B
Alcohol	Patients with prior ischemic stroke or TIA who are heavy drinkers should eliminate or reduce their consumption of alcohol.	Class I, Level A
	Light to moderate levels of ≤2 drinks per day for men and 1 drink per day for nonpregnant women may be considered.	Class IIb, Level C
Obesity	Weight reduction may be considered for all overweight ischemic stroke or TIA patients to maintain the goal of a BMI of 18.5 to 24.9 kg/m^2 and a waist circumference of <35 in for women and <40 in for men. Clinicians should encourage weight management through an appropriate balance of caloric intake, physical activity, and behavioral counseling.	Class IIb, Level C
Physical activity	For those with ischemic stroke or TIA who are capable of engaging in physical activity, at least 30 minutes of moderate-intensity physical exercise most days may be considered to reduce risk factors and comorbid conditions that increase the likelihood of recurrence of stroke. For those with disability after ischemic stroke, a supervised therapeutic exercise regimen is recommended.	Class IIb, Level C

*See Table 1 for explanation of class and level of evidence.

includes changes in blood dynamics[91,92] and vascular stenosis.[86,93,94] Because ethical issues preclude conducting RCTs for smoking after stroke, RCTs of quitting after stroke are not available. However, from observational studies, we know that risk of stroke decreases after quitting and that the elevated risk disappears after 5 years.[85,89,90] In addition, smoking cessation has been associated with a reduction in stroke-related hospitalizations[95,96] and therefore supports secondary prevention efforts.

There is growing evidence that exposure to environmental tobacco smoke (or passive smoke) increases the risk of cardiovascular disease, including stroke.[97–99] Given the high prevalence of smoking, exposure to environmental smoke needs consideration in overall risk assessment.

Tobacco dependence is a chronic condition for which there are now effective behavioral and pharmacotherapy treatments.[100–103] A combination of nicotine replacement therapy, social support, and skills training has been proved to be the most effective approach for quitting.[100,104] Updated information on how to treat tobacco dependence is available in the 2004 report, *The Health Consequences of Smoking: a Report of the Surgeon General*.[105]

Recommendation

All healthcare providers should strongly advise every patient with stroke or TIA who has smoked in the last year to quit (Class I, Level of Evidence C). Avoidance of environmental tobacco smoke is recommended (Class IIa, Level of Evidence C). Counseling, nicotine products, and oral smoking cessation medications have been found to be effective in helping smokers to quit (Class IIa, Level of Evidence B) (Table 3).

E. Alcohol Consumption

The effect of alcohol on stroke risk is controversial. There is strong evidence that chronic alcoholism and heavy drinking are risk factors for all stroke subtypes.[106–110] For ischemic stroke, studies have demonstrated an association between alcohol and stroke, ranging from a definite independent effect to no effect. Most studies have suggested a J-shaped association between alcohol and ischemic stroke, with a protective effect in light or moderate drinkers and an elevated stroke risk with heavy alcohol consumption.[93,106,107,111–116] In a recent meta-analysis of 35 observational studies of the association between alcohol and stroke, alcohol consumption was categorized into 0, <1, 1 to 2, 2 to 5, >5 drinks per day; an average drink contained about 12 g, 15 mL, or 0.5 oz of alcohol, which was found in 1 bottle (12 oz) of beer, 1 small glass (4 oz) of wine, or 1 alcoholic (1.5 oz liquor) cocktail. Compared with nondrinkers, those who consumed >5 drinks per day had a 69% increased stroke risk (RR, 1.69).[117] Consumption of <1 drink per day was associated with a reduced risk (RR, 0.80), and consumption of 1 to 2 drinks per day was associated with a reduced risk of 0.72. Although few studies have evaluated the association between alcohol consumption and recurrent stroke, stroke recurrence was significantly increased among those ischemic stroke patients with prior heavy alcohol use in the Northern Manhattan cohort.[118] No studies have demonstrated that reduction of alcohol intake decreases stroke recurrence risk.

The mechanism for reduced risk of ischemic stroke with light to moderate alcohol consumption may be related to an increase in HDL,[119,120] decreases in platelet aggregation,[121,122] and lower plasma fibrinogen concentration.[123,124] The deleterious risk mechanisms for those who are heavy alcohol consumers include alcohol-induced hypertension, hypercoagulable state, reduced cerebral blood flow, and atrial fibrillation (AF).[106,115,125] In addition, the brain that has been subjected to heavy alcohol consumption is more vulnerable because of an increase in the presence of brain atrophy.[126,127]

It has been well established that alcohol can induce dependence and that alcoholism is a major public health problem. When advising a patient about behaviors to reduce recurrent stroke risk, clinicians need to take into consideration the interrelationship between other risk factors and

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alcohol consumption. A primary goal for secondary stroke prevention is to eliminate or reduce alcohol consumption in heavy drinkers through established screening and counseling methods as outlined in the US Preventive Services Task Force Update 2004.[128]

Recommendation

Patients with ischemic stroke or TIA who are heavy drinkers should eliminate or reduce their consumption of alcohol (Class I, Level of Evidence A). Light to moderate levels of no more than 2 drinks per day for men and 1 drink per day for nonpregnant women may be considered (Class IIb, Level of Evidence C) (Table 3).

F. Obesity

Obesity, defined as a body mass index (BMI) of >30 kg/m^2, has been established as an independent risk factor for CHD and premature mortality.[129–131] The prevalence of obesity in the United States has increased dramatically over the past several decades, with current estimates of 63% of men and 55% of women considered overweight and 30% considered obese.[132,133] For individuals with disabling conditions with associated physical disabilities, obesity is even more prevalent.[134]

The relationship of obesity and weight gain in adult years to stroke is complex. Obesity is strongly related to several major risk factors, including hypertension, diabetes, and dyslipidemia.[135,136] Studies documenting the specific impact of obesity to stroke have varied.[136–142] In men, findings from the Physicians' Health Study have shown that an increasing BMI is associated with a steady increase in ischemic stroke, independently of the effects of hypertension, diabetes, and cholesterol.[143] Among women, data are inconsistent, with some positive[138] and others with no association.[140–142]

Several studies have suggested that abdominal obesity, rather than general obesity, is more related to stroke risk.[144,145] Clinically, abdominal obesity is defined by a waist circumference >102 cm (40 in) in men and 88 cm (35 in) in women. Temporal trends in waist circumference among adults in the United States show a rapid increase in obesity, especially abdominal obesity.[146] For stroke, a significant and independent association between abdominal obesity and ischemic stroke was found in all racial/ethnic groups in the Northern Manhattan Study.[144] Comparing the first quartile of waist-to-hip ratio with the third and fourth quartiles gave ORs of 2.4 (95% CI, 1.5 to 3.9) and 3.0 (95% CI, 1.8 to 4.8), respectively, after adjustment for other risk factors and BMI.

No study has demonstrated that weight reduction will reduce stroke recurrence. Losing weight, however, significantly improves BP, fasting glucose values, serum lipids, and physical endurance.[147] Because obesity is a contributing factor to other risk factors associated with recurrent stroke, promoting weight loss and the maintenance of a healthy weight is a high priority. Diets rich in fruits and vegetables, such as the Mediterranean diet, can help with weight control and have been shown to reduce the risk of stroke, MI, and death.[148,149]

Dietary guidelines are more adequately addressed in other AHA statements, including the primary prevention guideline (Primary Prevention of Ischemic Stroke), which is currently being updated.[1,150]

Recommendation

Weight reduction may be considered for all overweight ischemic stroke and TIA patients to maintain the goal of a BMI of between 18.5 and 24.9 kg/m^2 and a waist circumference of <35 in for women and <40 in for men (Class IIb, Level of Evidence C). Clinicians should encourage weight management through an appropriate balance of calorie intake, physical activity, and behavioral counseling (Table 3).

G. Physical Activity

Substantial evidence exists that physical activity exerts a beneficial effect on multiple cardiovascular disease risk factors, including those for stroke.[16,151–155] In a recent review of existing studies on physical activity and stroke, overall moderately or highly active individuals had a lower risk of stroke incidence or mortality than did low-activity individuals.[154] Moderately active men and women had a 20% lower risk, and those who were highly active had a 27% lower risk. A plausible explanation for these observed reductions is that physical activity tends to lower BP and weight,[151,156] enhance vasodilation,[157] improve glucose tolerance,[158,159] and promote cardiovascular health.[130] Through lifestyle modification, exercise can minimize the need for more intensive medical and pharmacological interventions or enhance treatment end points.

Despite the established benefits of an active lifestyle, sedentary behaviors continue to be the national trends.[160,161] For those at risk for recurrent stroke and TIA, these sedentary behaviors complicate the recovery process and affect recurrent risk status. Because disability after stroke is substantial[12] and because neurological deficits predispose to activity intolerance and physical deconditioning,[162] the challenge for clinicians is to establish a safe therapeutic exercise regimen that allows the patient to regain prestroke levels of activity and then to attain sufficient physical activity and exercise to reduce stroke recurrence. Several studies support the implementation of aerobic exercise and strength training to improve cardiovascular fitness after stroke.[162–165] Structured programs of therapeutic exercise have been shown to improve mobility, balance, and endurance.[163] Beneficial effects have been demonstrated in different ethnic groups and in both older and younger groups.[166] Encouragement of physical activity and exercise can optimize physical performance and functional capacity, thus reducing the risk for recurrent stroke. Recommendations on the benefits of physical activity for stroke survivors are reviewed more extensively in other AHA Scientific Statements.[157]

Recommendation

For patients with ischemic stroke or TIA who are capable of engaging in physical activity, at least 30 minutes of moderate-intensity physical exercise most days may be considered to reduce the risk factors and comorbid conditions that increase the likelihood of recurrence of stroke (Class IIb, Level of Evidence C). For those individuals with disability after ischemic stroke, a supervised therapeutic exercise regimen is recommended (Table 3).

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II. Interventional Approaches for the Patient With Large-Artery Atherosclerosis

A. Extracranial Carotid Disease

Among patients with TIA or stroke and documented carotid stenosis, a number of randomized trials have compared endarterectomy plus medical therapy with medical therapy alone. For patients with symptomatic atherosclerotic carotid stenosis >70%, as defined using the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria, the value of carotid endarterectomy (CEA) has been clearly established from the results of 3 major prospective randomized trials: the NASCET, the European Carotid Surgery Trial (ECST), and the Veterans Affairs Cooperative Study Program.[167–169] Among symptomatic patients with TIAs or minor strokes and high-grade carotid stenosis, each trial showed impressive relative and absolute risk reductions for those randomized to surgery.

For patients with carotid stenosis <50%, these trials showed that there was no significant benefit of surgery. In ECST, no benefit of surgery was demonstrated among those with <50% ipsilateral carotid stenosis.[168] Among those patients with <50% stenosis in NASCET, there was no significant reduction in the ipsilateral stroke risk among those treated with endarterectomy compared with those treated medically.[170] Although not specifically addressed by these trials, patients with nonstenosing ulcerative plaque generally would have been included in the groups with carotid stenosis <50% and would not have been found to benefit from endarterectomy.

For those with symptomatic carotid stenosis in the moderate category (50% to 69% stenosis), there is some uncertainty. The results from NASCET and ECST demonstrated less impressive benefits for CEA in this moderate group compared with medical therapy.[170,171] In NASCET, the 5-year risk of fatal or nonfatal ipsilateral stroke over the 5-year period was 22.2% in the medically treated group and 15.7% in patients treated surgically ($P=0.045$).[170] The relative and absolute risk reductions for surgery were less impressive than those observed for more severe degrees of stenosis.

Various comorbid features altered the benefit-to-risk ratio for CEA for moderate carotid stenosis. Benefits were greatest among those with more severe stenosis, those ≥75 years of age, men, patients with recent stroke (rather than TIA), and patients with hemispheric symptoms rather than transient monocular blindness.[170,172] Other radiographic factors found to predict better outcomes after CEA included the presence of intracranial stenosis, the absence of leukoaraiosis, and the presence of collaterals.[170,173,174] Gender and age differences, as well as comorbidity, must be considered when treatment options are evaluated in patients with stenosis between 50% and 69%, because the absolute benefit of surgery is less than that for more severe degrees of stenosis. Pooled analyses from endarterectomy trials have shown that early surgery is associated with increased benefits compared with delayed surgery. Benefit from surgery was greatest in men, patients ≥75 years of age, and those randomized within 2 weeks after their last ischemic event and fell rapidly with increasing delay.[175]

Studies documenting the benefit of endarterectomy were conducted before the widespread use of medical treatments that have been demonstrated to reduce stroke risk in patients with vascular disease such as clopidogrel, extended-release dipyridamole and aspirin, statins, and more aggressive BP control. In NASCET, aspirin was the recommended antithrombotic agent, and only 14.5% of patients were on lipid-lowering therapy at the beginning of the study. During the NASCET study, although BP was monitored at regular office visits, there was not a recommended BP treatment algorithm across centers, and there was not consistent involvement by hypertension or vascular medicine specialists at each center. Whether the use of more aggressive medical therapy will alter the benefit of CEA plus best medical care over best medical care alone remains to be determined; however, it would be expected to reduce the stroke rates in both groups, leading to lower absolute risk reductions. Therefore, stroke or TIA patients who undergo interventional procedures also need to be treated with maximal medical therapies, as reviewed in the other recommendations in this document.

Extracranial-intracranial (EC/IC) bypass surgery was not found to provide any benefit for patients with carotid occlusion or those with carotid artery narrowing distal to the carotid bifurcation.[176] New efforts using more sensitive imaging to select patients with the greatest hemodynamic compromise for RCTs using EC/IC bypass surgery are ongoing.[177,178]

Data on carotid artery balloon angioplasty and stenting (CAS) for symptomatic patients with internal carotid artery stenosis in stroke prevention consist primarily of a number of individual published case series but few controlled randomized multicenter comparisons of CEA and CAS.[179–181] The Wallstent Trial randomized 219 symptomatic patients with 60% to 90% stenosis to CEA or CAS. CAS was performed without distal protection and currently accepted antiplatelet prophylaxis. Study design allowed operators with limited experience to participate. The risk of perioperative stroke or death was 4.5% for CEA and 12.1% for CAS, and the risk of major stroke or death at 1 year was 0.9% for CEA and 3.7% for CAS. The trial was halted because of poor results from CAS.[182]

The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) trial randomly compared angioplasty with surgical therapy among 504 symptomatic carotid patients, in whom only 26% received stents.[183] Major outcome events within 30 days did not differ between endovascular treatment and surgery groups, with a 30-day risk of stroke or death of 10.0% and 9.9%, respectively. Despite the increased risk of severe ipsilateral carotid stenosis in the endovascular group at 1 year, no substantial difference in the rate of ipsilateral stroke was noted up to 3 years after randomization.

The Stenting and Angioplasty With Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial randomized 334 patients to endarterectomy or stenting with the use of an emboli-protection device, testing the hypothesis that

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TABLE 4. Recommendations for Interventional Approaches to Patients With Stroke Caused by Large-Artery Atherosclerotic Disease

Risk Factor	Recommendation	Class/Level of Evidence*
Extracranial carotid disease	For patients with recent TIA or ischemic stroke within the last 6 mo and ipsilateral severe (70% to 99%) carotid artery stenosis, CEA is recommended by a surgeon with a perioperative morbidity and mortality of <6%.	Class I, Level A
	For patients with recent TIA or ischemic stroke and ipsilateral moderate (50% to 69%) carotid stenosis, CEA is recommended, depending on patient-specific factors such as age, gender, comorbidities, and severity of initial symptoms.	Class I, Level A
	When degree of stenosis is <50%, there is no indication for CEA.	Class III, Level A
	When CEA is indicated, surgery within 2 wk rather than delayed surgery is suggested.	Class IIa, Level B
	Among patients with symptomatic severe stenosis (>70%) in whom the stenosis is difficult to access surgically, medical conditions are present that greatly increase the risk for surgery, or when other specific circumstances exist such as radiation-induced stenosis or restenosis after CEA, CAS is not inferior to endarterectomy and may be considered.	Class IIb, Level B
	CAS is reasonable when performed by operators with established periprocedural morbidity and mortality rates of 4% to 6%, similar to that observed in trials of CEA and CAS.	Class IIa, Level B
	Among patients with symptomatic carotid occlusion, EC/IC bypass surgery is not routinely recommended.	Class III, Level A
Extracranial vertebrobasilar disease	Endovascular treatment of patients with symptomatic extracranial vertebral stenosis may be considered when patients are having symptoms despite medical therapies (antithrombotics, statins, and other treatments for risk factors).	Class IIb, Level C
Intracranial arterial disease	The usefulness of endovascular therapy (angioplasty and/or stent placement) is uncertain for patients with hemodynamically significant intracranial stenoses who have symptoms despite medical therapies (antithrombotics, statins, and other treatments for risk factors) and is considered investigational.	Class IIb, Level C

*See Table 1 for explanation of class and level of evidence.

stenting was not inferior to endarterectomy. Only 30% of the study population was symptomatic. Qualified CAS operators had a periprocedural stroke, death or MI complication rate of 4%. The primary end point of the study (the cumulative incidence of death, stroke, or MI within 30 days after the intervention, or death or ipsilateral stroke between 31 days and 1 year) occurred in 20 stent patients and 32 endarterectomy patients (30-day risk, 5.8% versus 12.6%; $P=0.004$ for noninferiority).[184] Most of the benefit was detected in the lower risk of MI for the stent compared with the high-surgical risk endarterectomy cases.

The National Institute of Neurological Diseases and Stroke (NINDS)–funded Carotid Revascularization With Endarterectomy or Stent Trial (CREST) is currently comparing CEA and CAS in patients with symptomatic severe stenosis (≥70% by ultrasonography or ≥50% by NASCET angiography criteria). The primary objective is to compare the efficacy of CAS versus CEA in preventing stroke over a follow-up period of up to 4 years. Other randomized trials are ongoing in Europe and Australia.

At present, CAS has been used in selected patients in whom stenosis is difficult to access surgically, medical conditions that greatly increase the risk for surgery are present, or other specific circumstances exist such as radiation-induced stenosis or restenosis after CEA. CAS has also been used in selected cases after arterial dissection, fibromuscular hyperplasia, or Takayasu's arteritis. More definitive evidence is needed before we can advocate the widespread use of angioplasty plus stent as routine care for patients with extracranial carotid stenosis.

Recommendations

1. **For patients with recent TIA or ischemic stroke within the last 6 months and ipsilateral severe (70% to 99%) carotid artery stenosis, CEA by a surgeon with a perioperative morbidity and mortality of <6% (Class I, Level of Evidence A) is recommended. For patients with recent TIA or ischemic stroke and ipsilateral moderate (50% to 69%) carotid stenosis, CEA is recommended, depending on patient-specific factors such as age, gender, comorbidities, and severity of initial symptoms (Class I, Level of Evidence A). When the degree of stenosis is <50%, there is no indication for CEA (Class III, Level of Evidence A) (Table 4).**
2. **When CEA is indicated for patients with TIA or stroke, surgery within 2 weeks is suggested rather than delaying surgery (Class IIa, Level of Evidence B).**
3. **Among patients with symptomatic severe stenosis (>70%) in whom the stenosis is difficult to access surgically, medical conditions are present that greatly increase the risk for surgery, or other specific circumstances exist such as radiation-induced stenosis or restenosis after CEA, CAS is not inferior to endarterectomy and may be considered (Class IIb, Level of Evidence B). CAS is reasonable when performed by operators with established periprocedural morbidity and mortality rates of 4% to 6%, similar to that observed in trials of CEA and CAS (Class IIa, Level of Evidence B).**
4. **Among patients with symptomatic carotid occlusion, EC/IC bypass surgery is not routinely recommended (Class III, Level of Evidence A).**

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B. Extracranial Vertebrobasilar Disease

Revascularization procedures can be performed on patients with extracranial vertebral artery stenosis who are having repeated vertebrobasilar TIAs or strokes despite medical therapy. Atherosclerotic plaques of both the vertebral and carotid arteries that are concentric, smooth, fibrous lesions without ulceration are amenable to endovascular therapy, which has generally moved from simple angioplasty to stenting to prevent recoil and restenosis.[185,186] Retrospective case series have shown that the procedure can be performed with a high degree of technical success.[187–190] Long-term follow-up data are limited, and further randomized studies are needed to more clearly define evidence-based recommendations in this setting.

Recommendation

Endovascular treatment of patients with symptomatic extracranial vertebral stenosis may be considered when patients are having symptoms despite medical therapies (antithrombotics, statins, and other treatments for risk factors) (Class IIb, Level of Evidence C) (Table 4).

C. Intracranial Atherosclerosis

Data from prospective studies show that patients with symptomatic intracranial atherosclerosis have a relatively high risk of recurrent stroke. The EC/IC bypass study randomized 352 patients with atherosclerotic disease of the middle cerebral artery to bypass surgery or medical treatment with aspirin.[191] The medically treated patients were followed up for a mean of 42 months and had an overall stroke rate of 9.5% and an ipsilateral stroke rate of 7.8%. The Warfarin Aspirin Symptomatic Intracranial Disease (WASID) study evaluated 569 patients with symptomatic intracranial stenoses who were prospectively randomized to aspirin or warfarin.[192] This study, which was stopped for safety reasons, showed no significant difference between groups in terms of the primary end point (ischemic stroke, brain hemorrhage, and nonstroke vascular death). In addition, retrospective data indicate that patients with symptomatic intracranial stenosis who fail antithrombotic therapy may have even greater rates of recurrent stroke.[193]

Intracranial angioplasty and/or stenting provide an opportunity to rapidly improve cerebral blood flow. Results from single-center experiences suggest that the procedure can be performed with a high degree of technical success.[194–198] These studies have generally been performed among patients who have hemodynamically significant intracranial stenoses and symptoms despite medical therapy. More long-term follow-up has been lacking, but available data raise the possibility that angioplasty may improve the natural history compared with medical therapy.[194]

It is not clear that stenting confers any improvement in the long-term clinical or angiographic outcome compared with angioplasty alone in this setting. One prospective trial has evaluated stenting in a mixed group of patients with intracranial and/or extracranial disease. The Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries (SSYLVIA) Trial, a corporate-sponsored multicenter, nonrandomized, prospective feasibility study, evaluated 1 stent for treatment of vertebral or intracranial artery stenosis.[199] Forty-three intracranial arteries (70.5%) and 18 extracranial vertebral arteries (29.5%) were treated. Successful stent placement was achieved in 58 of 61 cases (95%). Thirty-day stroke incidence was 6.6%, with no deaths. Four of 55 patients (7.3%) had strokes later than 30 days, 1 of which was in the only patient not stented. Recurrent stenosis >50% within 6 months occurred in 12 of 37 intracranial arteries (32.4%) and 6 of 14 extracranial vertebral arteries (42.9%). Seven recurrent stenoses (39%) were symptomatic. Although a few different stents have been approved by the Food and Drug Administration (FDA) for use in patients with arterial stenoses, further studies are necessary to determine whether these interventional procedures have short-term and long-term efficacy.

Recommendation

For patients with hemodynamically significant intracranial stenosis who have symptoms despite medical therapies (antithrombotics, statins, and other treatments for risk factors), the usefulness of endovascular therapy (angioplasty and/or stent placement) is uncertain and is considered investigational (Class IIb, Level of Evidence C) (Table 4).

III. Medical Treatments for the Patient With Cardiogenic Embolism

Cardiogenic cerebral embolism derived from a diversity of cardiac disorders is responsible for ≈20% of ischemic strokes. There is a history of nonvalvular AF in about one half the cases, of valvular heart disease in one fourth, and of left ventricular (LV) mural thrombus in almost one third.[200] Sixty percent of emboli of LV origin have been associated with acute MI.[200] Intracavitary thrombus occurs in about one third of patients in the first 2 weeks after anterior MI and in an even greater proportion of those with large infarcts involving the LV apex.[201] Ventricular thrombi also occur in patients with chronic ventricular dysfunction resulting from coronary disease, hypertension, or other forms of dilated cardiomyopathy. Congestive heart failure affects >4 000 000 Americans and increases stroke risk by a factor of 2 to 3, accounting for ≈10% of ischemic stroke events.[202]

In general, patients with cardiac disease and cerebral infarction face a high risk of recurrent stroke. Because it is often difficult to determine the precise mechanism, the choice of a platelet inhibitor or anticoagulant drug may be difficult. Patients who have suffered an ischemic stroke who have a high-risk source of cardiogenic embolism should generally be treated with anticoagulant drugs to prevent recurrence.

The reader should review other AHA statements on the recommendations for the management of cardiac disease when planning treatments for patients with stroke or TIA who have other cardiac conditions.[203–208]

A. Atrial Fibrillation

Both persistent AF and paroxysmal AF are potent predictors of first and recurrent stroke. More than 75 000 cases of stroke per year are attributed to AF. It has been estimated that AF affects >2 000 000 Americans and becomes more frequent

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with age, ranking as the leading cardiac arrhythmia in the elderly. Data from the AF clinical trials show that age, recent congestive heart failure, hypertension, diabetes, and prior thromboembolism have been found to identify high-risk groups for arterial thromboembolism among patients with AF. LV dysfunction, left atrial size, mitral annular calcification (MAC), spontaneous echo contrast, and left atrial thrombus by echocardiography have also been shown to predict increased thromboembolic risk. Overall, patients with prior stroke or TIA carry the highest stroke risk (RR, 2.5).

Multiple clinical trials have demonstrated the superior therapeutic effect of warfarin compared with placebo in the prevention of thromboembolic events among patients with nonvalvular AF. Pooled data from 5 primary prevention trials of warfarin versus control have been reported.[209] The efficacy of warfarin has been shown to be consistent across studies, with an overall RR reduction of 68% (95% CI, 50 to 79) and an absolute reduction in annual stroke rate from 4.5% for the control patients to 1.4% in patients assigned to adjusted-dose warfarin. This absolute risk reduction indicates that 31 ischemic strokes will be prevented each year for every 1000 patients treated. Overall, warfarin use has been shown to be relatively safe, with an annual rate of major bleeding of 1.3% for patients on warfarin compared with 1% for patients on placebo or aspirin.

The optimal intensity of oral anticoagulation for stroke prevention in patients with AF appears to be 2.0 to 3.0. Results from a large case-control study[210] and two RCTs[211,212] suggest that the efficacy of oral anticoagulation declines significantly below an international normalized ratio (INR) of 2.0. Unfortunately, a high percentage of AF patients have subtherapeutic levels of anticoagulation and therefore are inadequately protected from stroke.

Evidence supporting the efficacy of aspirin is substantially weaker than that for warfarin. A pooled analysis of data from 3 trials resulted in an estimated RR reduction of 21% compared with placebo (95% CI, 0 to 38). At present, data are sparse with regard to the efficacy of alternative antiplatelet agents for stroke prevention in AF patients who are allergic to aspirin.[213] An ongoing study, Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE), is evaluating the safety and efficacy of the combination of clopidogrel and aspirin in AF patients.

The superior efficacy of anticoagulation over aspirin for stroke prevention in patients with AF and a recent TIA or minor stroke was demonstrated in the European Atrial Fibrillation Trial.[214] Therefore, unless a clear contraindication exists, AF patients with a recent stroke or TIA should receive long-term anticoagulation rather than antiplatelet therapy. There is no evidence that combining anticoagulation with an antiplatelet agent reduces the risk of stroke compared with anticoagulant therapy alone.

The narrow therapeutic margin of warfarin in conjunction with numerous associated food and drug interactions requires frequent INR testing and dose adjustments. These liabilities of warfarin contribute to significant underutilization, even in high-risk patients. Therefore, alternative therapies that are easier to use are needed.

Ximelagatran is a direct thrombin inhibitor that is orally administered, has stable pharmacokinetics independent of the hepatic P_{450} enzyme system, and has a low potential for food or drug interactions. Two large studies, Stroke Prevention Using the Oral Direct Thrombin Inhibitor Ximelagatran in Patients With Atrial Fibrillation (SPORTIF) -III and -V,[215] compared ximelagatran with dose-adjusted warfarin (INR, 2 to 3) in high-risk patients with AF. A total of 7329 patients were included in these trials. Ximelagatran was administered at a fixed dose of 36 mg twice daily without coagulation monitoring. SPORTIF-III was an open-label study, involving 3407 patients randomized in 23 countries in Europe, Asia, and Australasia. SPORTIF-V was a double-blind trial otherwise identical in design that randomized 3922 patients in North America. About 25% of the patients in these trials had a history of stroke or TIA. In both trials, ximelagatran was noninferior to warfarin and was associated with fewer bleeding complications. In a pooled analysis of SPORTIF-III and -V, the rate of primary events (combined ischemic stroke, hemorrhagic stroke, and systemic embolic event) was 1.62% per year with ximelagatran and 1.65% per year with warfarin (difference, −0.03; 95% CI, −0.50 to 0.44; $P=0.94$) over 11 346 patient-years (mean, 18.5 months). The primary outcome event rate in patients with prior stroke was 2.83% per year in the ximelagatran group (n=786) and 3.27% per year in the warfarin group (n=753; $P=0.63$). There were no significant differences between treatments in rates of hemorrhagic stroke, fatal bleeding, or other major bleeding, but combined rates of minor and major bleeding were significantly lower with ximelagatran (31.7% versus 38.7% per year; $P<0.0001$). Serum alanine-aminotransferase levels rose transiently >3 times above normal in ≈6% of patients with ximelagatran, usually within 6 months.

The results of SPORTIF-III and -V provide evidence that ximelagatran 36 mg twice daily is essentially equivalent to well-controlled, dose-adjusted warfarin at INRs of 2.0 to 3.0. Because ximelagatran does not need anticoagulation monitoring or dose adjustment, it was developed to be an easier drug to administer than adjusted-dose warfarin; however, the need for monitoring hepatic enzymes may lessen its advantage in ease of use. At the time these guidelines were written, the FDA and certain European regulatory authorities have not approved ximelagatran; therefore, it will not be included in the recommendations.

Available data do not show greater efficacy of the acute administration of anticoagulants over antiplatelet agents in the setting of cardioembolic stroke.[18] More studies are required to clarify whether certain subgroups of patients who are perceived to be at high risk of recurrent embolism may benefit from urgent anticoagulation.

No data are available to address the question of when to initiate oral anticoagulation in a patient with AF after a stroke or TIA. In the European Atrial Fibrillation Trial (EAFT),[214] oral anticoagulation was initiated within 14 days of symptom onset in about one half of the patients. Patients in this trial had minor strokes or TIAs and AF. In general, we recommend initiation of oral anticoagulation within 2 weeks of an ischemic stroke or TIA; however, for patients with large

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infarcts or uncontrolled hypertension, further delays may be appropriate.

For patients with AF who suffer an ischemic stroke or TIA despite therapeutic anticoagulation, no data indicate that either increasing the intensity of anticoagulation or adding an antiplatelet agent provides additional protection against future ischemic events. In addition, both strategies are associated with an increase in bleeding risk.

About one third of patients who present with AF and an ischemic stroke will be found to have other potential causes for the stroke such as carotid stenosis. For these patients, treatment decisions should focus on the presumed most likely stroke origin. In many cases, it will be appropriate to initiate anticoagulation, because of the AF, and additional therapy (such as CEA).

Recommendations

1. **For patients with ischemic stroke or TIA with persistent or paroxysmal (intermittent) AF, anticoagulation with adjusted-dose warfarin (target INR, 2.5; range, 2.0 to 3.0) is recommended (Class I, Level of Evidence A) (Table 5).**
2. **For patients unable to take oral anticoagulants, aspirin 325 mg/d is recommended (Class I, Level of Evidence A).**

B. Acute MI and Left Ventricular Thrombus

Stroke or systemic embolism is less common among uncomplicated MI patients but can occur in up to 12% of patients with acute MI complicated by a LV thrombus. The rate is higher in those with anterior than inferior infarcts and may reach 20% of those with the large anteroapical infarcts.[216] The incidence of embolism is highest during the period of active thrombus formation in the first 1 to 3 months, yet the embolic risk remains substantial even beyond the acute phase in patients with persistent myocardial dysfunction, congestive heart failure, or AF. Although thrombus remains echocardiographically apparent for 1 year after MI in more than one third of patients in whom the diagnosis is initially made and evidence of thrombus persists for 2 years in about one fourth of cases, relatively few of these persistent thrombi are associated with late embolic events. The concurrent use of aspirin with oral anticoagulation is based on ACC/AHA guidelines for patients with ST-segment elevation MI.[206]

Recommendations

1. **For patients with an ischemic stroke or TIA caused by an acute MI in whom LV mural thrombus is identified by echocardiography or another form of cardiac imaging, oral anticoagulation is reasonable, aiming for an INR of 2.0 to 3.0 for at least 3 months and up to 1 year (Class IIa, Level of Evidence B).**
2. **Aspirin should be used concurrently for ischemic coronary artery disease during oral anticoagulant therapy in doses up to 162 mg/d (Class IIa, Level of Evidence A).**

C. Cardiomyopathy

When LV systolic function is impaired, the reduced stroke volume creates a condition of relative stasis within the left ventricle that may activate coagulation processes and increase the risk of thromboembolic events. The cause of cardiomyopathy may be ischemia or infarction based on coronary artery disease or nonischemic as a result of genetic or acquired defects of myocardial cell structure or metabolism. Although stroke rate was not found to be related to the severity of heart failure, 2 large studies did find the incidence of stroke to be inversely proportional to ejection fraction (EF).[217,218] In the Survival and Ventricular Enlargement (SAVE) study,[217,218] patients with an EF of 29% to 35% (mean, 32%) had a stroke rate of 0.8% per year; the rate in patients with EF ≤28% (mean, 23%) was 1.7% per year. There was an 18% increment in the risk of stroke for every 5% decline in EF. These findings apply mainly to men, who represented >80% of trial participants. A retrospective analysis of data from the Studies of Left Ventricular Dysfunction (SOLVD) trial,[51] which excluded patients with AF, found a 58% increase in risk of thromboembolic events for every 10% decrease in EF among women ($P=0.01$). There was no significant increase in stroke risk among men.

In patients with nonischemic dilated cardiomyopathy, the rate of stroke appears similar to that associated with cardiomyopathy resulting from ischemic heart disease. An estimated 72 000 initial stroke events per year have been associated with LV systolic dysfunction, and the 5-year recurrent stroke rate in patients with cardiac failure has been reported to be as high as 45%.[118] Warfarin is sometimes prescribed to prevent cardioembolic events in patients with cardiomyopathy; however, no randomized clinical studies have demonstrated the efficacy of anticoagulation, and considerable controversy surrounds the use of warfarin in patients with cardiac failure or reduced LV EF.[219,220] Several trials have been initiated to address this issue.[221–223] The primary objective of the Warfarin/Aspirin Study in Heart Failure (WASH) was to demonstrate feasibility and aid in the design of a larger outcome study.[217] The study showed no significant differences in the primary outcome (death, nonfatal MI, or nonfatal stroke) between the groups, with 26%, 32%, and 26% of patients randomized to no antithrombotic treatment, aspirin, and warfarin, respectively. The Warfarin and Antiplatelet Therapy in Chronic Heart Failure Trial (WATCH) was designed to evaluate the efficacy of antithrombotic strategies among symptomatic heart failure patients in sinus rhythm with EFs ≤35%.[218] Patients were randomized to open-label warfarin (target INR, 2.5 to 3.0) or double-blind antiplatelet therapy with aspirin 162 mg or clopidogrel 75 mg. The trial was terminated early for poor recruitment after 1587 patients among the 4500 planned were enrolled, with a resulting reduction of its power to achieve its original objective.

Two studies of patients with MI, involving a total of 4618 patients,[224,225] found that warfarin (INR, 2.8 to 4.8) reduced the risk of stroke compared with placebo by 55%[224] and 40%[225] over 37 months. In the SAVE study, both warfarin and aspirin (given separately) were associated with a lower risk for stroke than no antithrombotic therapy.[218] Warfarin appears to exert a similar effect on the reduction of stroke both in patients with nonischemic cardiomyopathy and in those with ischemic heart disease.[226] Aspirin reduces the stroke rate by ≈20%.[227] Potential antiplatelet therapies used

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TABLE 5. Recommendations for Patients With Cardioembolic Stroke Types

Risk Factor	Recommendation	Class/Level of Evidence*
AF	For patients with ischemic stroke or TIA with persistent or paroxysmal (intermittent) AF, anticoagulation with adjusted-dose warfarin (target INR, 2.5; range, 2.0–3.0) is recommended.	Class I, Level A
	In patients unable to take oral anticoagulants, aspirin 325 mg/d is recommended.	Class I, Level A
Acute MI and LV thrombus	For patients with an ischemic stroke caused by an acute MI in whom LV mural thrombus is identified by echocardiography or another form of cardiac imaging, oral anticoagulation is reasonable, aiming for an INR of 2.0 to 3.0 for at least 3 mo and up to 1 y.	Class IIa, Level B
	Aspirin should be used concurrently for the ischemic CAD patient during oral anticoagulant therapy in doses up to 162 mg/d, preferably in the enteric-coated form.	Class IIa, Level A
Cardiomyopathy	For patients with ischemic stroke or TIA who have dilated cardiomyopathy, either warfarin (INR, 2.0 to 3.0) or antiplatelet therapy may be considered for prevention of recurrent events.	Class IIb, Level C
Valvular heart disease		
Rheumatic mitral valve disease	For patients with ischemic stroke or TIA who have rheumatic mitral valve disease, whether or not AF is present, long-term warfarin therapy is reasonable, with a target INR of 2.5 (range, 2.0–3.0).	Class IIa, Level C
	Antiplatelet agents should not be routinely added to warfarin in the interest of avoiding additional bleeding risk.	Class III, Level C
	For ischemic stroke or TIA patients with rheumatic mitral valve disease, whether or not AF is present, who have a recurrent embolism while receiving warfarin, adding aspirin (81 mg/d) is suggested.	Class IIa, Level C
MVP	For patients with MVP who have ischemic stroke or TIAs, long-term antiplatelet therapy is reasonable.	Class IIa, Level C
MAC	For patients with ischemic stroke or TIA and MAC not documented to be calcific antiplatelet therapy may be considered.	Class IIb, Level C
	Among patients with mitral regurgitation resulting from MAC without AF, antiplatelet or warfarin therapy may be considered.	Class IIb, Level C
Aortic valve disease	For patients with ischemic stroke or TIA and aortic valve disease who do not have AF, antiplatelet therapy may be considered.	Class IIa, Level C
Prosthetic heart valves	For patients with ischemic stroke or TIA who have modern mechanical prosthetic heart valves, oral anticoagulants are recommended, with an INR target of 3.0 (range, 2.5–3.5).	Class I, Level B
	For patients with mechanical prosthetic heart valves who have an ischemic stroke or systemic embolism despite adequate therapy with oral anticoagulants, aspirin 75 to 100 mg/d, in addition to oral anticoagulants, and maintenance of the INR at a target of 3.0 (range, 2.5–3.5) is reasonable.	Class IIa, Level B
	For patients with ischemic stroke or TIA who have bioprosthetic heart valves with no other source of thromboembolism, anticoagulation with warfarin (INR, 2.0–3.0) may be considered.	Class IIb, Level C

CAD indicates coronary artery disease; MAC, mitral annular calcification; and MVP, mitral valve prolapse.
*See Table 1 for explanation of class and level of evidence.

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to prevent recurrent stroke include aspirin (50 to 325 mg/d), the combination of aspirin (25 mg twice daily) and extended-release dipyridamole (200 mg twice daily), and clopidogrel (75 mg daily).

In the ongoing Warfarin Versus Aspirin for Reduced Cardiac Ejection Fraction (WARCEF) study, the primary end point includes both stroke and death, and patients with and without prior stroke are enrolled. This trial is not statistically powerful enough to determine whether warfarin has an effect on stroke risk reduction; however, by pooling results with those of other trials, we may be able to draw some conclusions about this issue. Despite the hemorrhagic risk associated with chronic anticoagulation, retrospective data suggest that warfarin may reduce mortality and both initial and recurrent ischemic stroke rates in patients with impaired LV function.

Recommendation

For patients with ischemic stroke or TIA who have dilated cardiomyopathy, either warfarin (INR, 2.0 to 3.0) or antiplatelet therapy may be considered for prevention of recurrent events (Class IIb, Level of Evidence C) (Table 5).

D. Valvular Heart Disease

Antithrombotic therapy can reduce, but not eliminate, the likelihood of stroke and systemic embolism in patients with valvular heart disease. As in all situations involving antithrombotic therapy, the risks of thromboembolism in various forms of native valvular heart disease and in patients with mechanical and biological heart valve prostheses must be balanced against the risk of bleeding. Because the frequency and permanent consequences of thromboembolic events usually are greater than the outcome of hemorrhagic complications, anticoagulant therapy is generally recommended, particularly when these conditions are associated with AF.[228]

1. Rheumatic Mitral Valve Disease

Recurrent embolism occurs in 30% to 65% of patients with rheumatic mitral valve disease who have a history of a previous embolic event.[229–232] Between 60% and 65% of these recurrences develop within the first year,[229,230] most within 6 months. Mitral valvuloplasty does not seem to eliminate the risk of thromboembolism[233,234]; therefore, successful valvuloplasty does not eliminate the need for anticoagulation in patients requiring long-term anticoagulation preoperatively. Although not evaluated in randomized trials, multiple observational studies have reported that long-term anticoagulant therapy effectively reduces the risk of systemic embolism in patients with rheumatic mitral valve disease.[235–238] Long-term anticoagulant therapy in patients with mitral stenosis who had left atrial thrombus identified by transesophageal echocardiography has been shown to result in the disappearance of the left atrial thrombus.[239] Smaller thrombus and a lower New York Heart Association functional class were independent predictors of thrombus resolution.[239] ACC/AHA statements are available for the management of patients with valvular heart disease.[240]

Recommendations

1. **For patients with ischemic stroke or TIA who have rheumatic mitral valve disease, whether or not AF is present, long-term warfarin therapy is reasonable, with a target INR of 2.5 (range, 2.0 to 3.0) (Class IIa, Level of Evidence C). Antiplatelet agents should not routinely be added to warfarin to avoid the additional bleeding risk (Class III, Level of Evidence C).**
2. **For patients with ischemic stroke or TIA with rheumatic mitral valve disease, whether or not AF is present, who have a recurrent embolism while receiving warfarin, adding aspirin (81 mg/d) is suggested (Class IIa, Level of Evidence C) (Table 5).**

2. Mitral Valve Prolapse

Mitral valve prolapse is the most common form of valve disease in adults.[241] Although generally innocuous, it is sometimes symptomatic, and serious complications can occur. Thromboembolic phenomena have been reported in patients with mitral valve prolapse in whom no other source could be found.[242–246] No randomized trials have addressed the efficacy of selected antithrombotic therapies for this specific subgroup of stroke or TIA patients. The evidence with regard to the efficacy of antiplatelet agents for general stroke and TIA patients was used to reach these recommendations.

Recommendation

For patients with mitral valve prolapse who have ischemic stroke or TIAs, antiplatelet therapy is reasonable (Class IIa, Level of Evidence C) (Table 5).

3. Mitral Annular Calcification

MAC[247] predominates in women, is sometimes associated with significant mitral regurgitation, and is an uncommon nonrheumatic cause of mitral stenosis. Patients with MAC are also predisposed to endocarditis, conduction disturbances, arrhythmias, embolic phenomena, and calcific aortic stenosis.[247–253] Although the incidence of systemic and cerebral embolism is not clear,[249–251,254–256] thrombus has been found at autopsy on heavily calcified annular tissue, and echogenic densities have been identified in the LV outflow tract in patients with MAC who experience cerebral ischemic events.[250,254] Aside from the risk of thromboembolism, spicules of fibrocalcific material may embolize from the calcified mitral annulus.[249,251,255] The relative frequencies of calcific and thrombotic embolism are unknown.[249,256] Because there is little reason to believe that anticoagulant therapy would effectively prevent calcific embolism, the rationale for antithrombotic therapy in patients with MAC is related mainly to the frequency of thromboembolism.

From these observations and in the absence of randomized trials, anticoagulant therapy may be considered for patients with MAC and a history of thromboembolism. However, if the mitral lesion is mild or if an embolic event is clearly identified as calcific rather than thrombotic, the risks from anticoagulation may outweigh the benefit of warfarin therapy in patients without AF. Most uncomplicated MAC patients with stroke or TIA may be managed best by antiplatelet therapy. For patients with repeated embolic events despite

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antiplatelet or warfarin therapy or in whom multiple calcific emboli are recognized, valve replacement surgery should be considered.

Recommendations

1. **For patients with ischemic stroke or TIA and MAC not documented to be calcific, antiplatelet therapy may be considered (Class IIb, Level of Evidence C).**
2. **Among patients with mitral regurgitation caused by MAC without AF, antiplatelet or warfarin therapy may be considered (Class IIb, Level of Evidence C) (Table 5).**

4. Aortic Valve Disease

Clinically detectable systemic embolism in isolated aortic valve disease is increasingly recognized because of microthrombi or calcific emboli.[257] In an autopsy study of 165 patients with calcific aortic stenosis, systemic embolism was found in 31 patients (19%); the heart and kidneys were affected most often, but most embolisms were not associated with clinically detected events.[258] Therefore, it appears that calcific microemboli from heavily calcified, stenotic aortic valves, because of their small size, are not readily detected unless they can be visualized in the retinal artery. In the absence of associated mitral valve disease or AF, systemic embolism in patients with aortic valve disease is uncommon. No randomized trials on selected patients with stroke and aortic valve disease exist, so recommendations were based on evidence from larger antiplatelet trials of stroke and TIA patients.

Recommendation

For patients with ischemic stroke or TIA and aortic valve disease who do not have AF, antiplatelet therapy may be considered (Class IIb, Level of Evidence C) (Table 5).

5. Prosthetic Heart Valves

A variety of mechanical heart valve prostheses are available for clinical use, all of which require antithrombotic prophylaxis. Detailed information on the older types of prosthetic valves is beyond the scope of this review. The most convincing evidence that oral anticoagulants are effective in patients with prosthetic heart valves comes from patients randomized to treatment for 6 months with either warfarin in uncertain intensity or 1 of 2 aspirin-containing platelet-inhibitor drug regimens.[259] Thromboembolic complications occurred more frequently in the antiplatelet group (RR, 60% to 79%), but the incidence of bleeding was highest in the warfarin group. Other studies yielded variable results, depending on the type and location of the prosthesis, the intensity of anticoagulation, and the addition of platelet inhibitor medication; none specifically addressed secondary stroke prevention.

In 2 randomized studies, concurrent treatment with dipyridamole and warfarin reduced the incidence of systemic embolism,[260,261] and the combination of dipyridamole (450 mg/d) and aspirin (3.0 g/d) reduced the incidence of thromboembolism in patients with prosthetic heart valves.[262] A randomized study of aspirin (1.0 g/d) plus warfarin versus warfarin alone in 148 patients with prosthetic heart valves found a significant reduction of embolism in the aspirin-treated group.[213] Another trial showed that the addition of aspirin 100 mg/d to warfarin (INR, 3.0 to 4.5) improved efficacy compared with warfarin alone.[263] This combination of low-dose aspirin and high-intensity warfarin was associated with reduced all-cause mortality, cardiovascular mortality, and stroke at the expense of increased minor bleeding; the difference in major bleeding, including cerebral hemorrhage, did not reach statistical significance.

Guidelines developed by the European Society of Cardiology[264] called for anticoagulant intensity in proportion to the thromboembolic risk associated with specific types of prosthetic heart valves. For first-generation valves, an INR of 3.0 to 4.5 was recommended; an INR of 3.0 to 3.5 was recommended for second-generation valves in the mitral position, whereas an INR of 2.5 to 3.0 was advised for second-generation valves in the aortic position. The ACCP guidelines of 2004 recommended an INR of 2.5 to 3.5 for patients with mechanical prosthetic valves and 2.0 to 3.0 for those with bioprosthetic valves and low-risk patients with bileaflet mechanical valves (such as the St Jude Medical device) in the aortic position.[265] Similar guidelines have been promulgated conjointly by the ACC and the AHA.[204,240]

Recommendations

1. **For patients with ischemic stroke or TIA who have modern mechanical prosthetic heart valves, oral anticoagulants are recommended, with an INR target of 3.0 (range, 2.5 to 3.5) (Class I, Level of Evidence B).**
2. **For patients with mechanical prosthetic heart valves who have an ischemic stroke or systemic embolism despite adequate therapy with oral anticoagulants, aspirin 75 to 100 mg/d in addition to oral anticoagulants and maintenance of the INR at a target of 3.0 (range 2.5 to 3.5) are reasonable (Class IIa, Level of Evidence B).**
3. **For patients with ischemic stroke or TIA who have bioprosthetic heart valves with no other source of thromboembolism, anticoagulation with warfarin (INR 2.0 to 3.0) may be considered (Class IIb, Level of Evidence C).**

IV. Antithrombotic Therapy for Noncardioembolic Stroke or TIA (Specifically Atherosclerosis, Lacunar, or Cryptogenic Infarcts)

A. Antiplatelet Agents

Four antiplatelet agents have been shown to reduce the risk of ischemic stroke after a stroke or TIA and are currently approved by the FDA for this indication. In a meta-analysis of results of 21 randomized trials comparing antiplatelet therapy with placebo in 18 270 patients with prior stroke or TIA, antiplatelet therapy was associated with a 28% relative odds reduction in nonfatal strokes and a 16% reduction in fatal strokes.[266]

1. Aspirin

Aspirin in doses ranging from 50 to 1300 mg/d is efficacious for preventing ischemic stroke after stroke or TIA.[214,267,268] Two RCTs compared different doses of aspirin in TIA or

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stroke patients (1200 versus 300 mg/d and 283 versus 30 mg/d).[269,270] In both trials, high- and low-dose aspirin had similar efficacy in preventing vascular events. However, higher doses of aspirin have been associated with a greater risk of gastrointestinal hemorrhage.[43,266]

2. Ticlopidine

Ticlopidine, a thienopyridine, has been evaluated in 3 randomized trials of patients with cerebrovascular disease. The Canadian American Ticlopidine Study (CATS) compared ticlopidine (250 mg twice a day) with placebo for prevention of stroke, MI, or vascular death in 1053 patients with ischemic stroke and found that ticlopidine was associated with a 23% relative reduction in risk of the composite outcome.[271] The Ticlopidine Aspirin Stroke Study (TASS) compared ticlopidine 250 mg twice a day with aspirin 650 mg twice a day in 3069 patients with recent minor stroke or TIA.[272] In that study, ticlopidine was associated with a 21% RR reduction in stroke during a 3-year follow-up and produced a more modest and nonsignificant 9% reduction in risk of the combined outcome of stroke, MI, or vascular death. Finally, the African American Aspirin Stroke Prevention Study (AAASPS) enrolled 1800 black patients with recent noncardioembolic ischemic stroke who were allocated to receive ticlopidine 250 mg twice a day or aspirin 650 mg/d.[273] The study found no difference in the risk of the combination of stroke, MI, or vascular death at 2 years.

The most common side effects of ticlopidine are diarrhea (≈12%), other gastrointestinal symptoms, and rash, with a frequency of hemorrhagic complications similar to that of aspirin. Neutropenia occurred in ≈2% of patients treated with ticlopidine in CATS and TASS; however, it was severe in <1% and was almost always reversible with discontinuation. Thrombotic thrombocytopenic purpura has also been described.

3. Clopidogrel

The efficacy of clopidogrel was compared with that of aspirin in the Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial.[274] More than 19 000 patients with stroke, MI, or peripheral vascular disease were randomized to aspirin 325 mg/d or clopidogrel 75 mg/d. The primary end point, a composite outcome of ischemic stroke, MI, or vascular death, occurred in 8.7% fewer patients treated with clopidogrel compared with aspirin ($P=0.043$). However, in a subgroup analysis of those patients with prior stroke, the risk reduction with clopidogrel was slightly smaller and nonsignificant. Two post-hoc analyses indicated that diabetics and those with preexisting ischemic stroke or MI (before the index event) received relatively more benefit from clopidogrel than aspirin.[275,276]

Overall, the safety of clopidogrel is comparable to that of aspirin, and it has clear advantages over ticlopidine. As with ticlopidine, diarrhea and rash are more frequent than with aspirin, but gastrointestinal symptoms and hemorrhages are less frequent. Neutropenia is not a problem with clopidogrel, but a few cases of thrombotic thrombocytopenic purpura have been described.[277]

4. Dipyridamole and Aspirin

The combination of dipyridamole and aspirin was evaluated in several small trials that included patients with cerebral ischemia. The French Toulouse Study enrolled 440 patients with prior TIA. No significant differences were observed in outcomes among groups assigned to aspirin 900 mg/d, aspirin plus dihydroergotamine, aspirin plus dipyridamole, or dihydroergotamine alone.[278]

The Accidents ischemiques cerebraux lies a l'atherosclerose (AICLA) trial randomized 604 patients with TIA and ischemic stroke to placebo, aspirin 1000 mg/d, or aspirin 1000 mg/d plus dipyridamole 225 mg/d.[279] Compared with placebo, aspirin and the combination of aspirin and dipyridamole reduced the risk of ischemic stroke by a similar amount. Thus, there was no apparent benefit of adding dipyridamole to aspirin. The European Stroke Prevention Study (ESPS-1) included 2500 patients randomized to either placebo or the combination of aspirin plus dipyridamole (225 mg/d dipyridamole and 975 mg aspirin).[280] Compared with placebo, combination therapy reduced the risk of combined stroke and death by 33% and the risk of stroke alone by 38%. ESPS-1 did not include an aspirin arm, so it was not possible to evaluate the added benefit of dipyridamole.

ESPS-2 randomized 6602 patients with prior stroke or TIA in a factorial design using a different dipyridamole formulation and aspirin dose compared with ESPS-1. The treatment groups were as follows: (1) aspirin 50 mg/d plus extended-release dipyridamole at a dose of 400 mg/d, (2) aspirin alone, (3) extended-release dipyridamole alone, and (4) placebo. The risk of stroke was significantly reduced, by 18% on aspirin alone, 16% with dipyridamole alone, and 37% with a combination of aspirin plus dipyridamole. The outcome of death alone was not reduced by any of the interventions. The combination was superior to aspirin in reducing recurrence of stroke (by 23%), and 25% superior to dipyridamole alone.[267]

Headache is the most common side effect of extended-release dipyridamole. Bleeding was not significantly increased by dipyridamole. Although there are concerns about the use of immediate-release dipyridamole in patients with stable angina, a post hoc analysis from ESPS-2 that used extended-release dipyridamole showed no excess of adverse cardiac events compared with placebo or aspirin.[203,281] Although the daily dose of aspirin in extended-release dipyridamole plus aspirin is only 50 mg and below the recommended dose of 75 mg used for cardiac patients, no clinical data suggest that additional aspirin could alter the safety and efficacy of this combination antiplatelet agent.

5. Combination Clopidogrel and Aspirin

Recently, the results of the Management of Atherothrombosis With Clopidogrel in High-Risk Patients With TIA or Stroke (MATCH) trial were reported.[282] Patients with a prior stroke or TIA plus additional risk factors (n=7599) were allocated to clopidogrel 75 mg or combination therapy with clopidogrel 75 mg plus aspirin 75 mg per day. 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 or any of

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the secondary outcomes. The risk of major hemorrhage was significantly increased in the combination group compared with clopidogrel alone, with a 1.3% absolute increase in life-threatening bleeding. Although clopidogrel plus aspirin is recommended over aspirin for acute coronary syndromes, with most guidelines advocating for up to 12 months of treatment, the results of MATCH do not suggest a similar risk benefit ratio for stroke and TIA survivors.

6. Selection of Oral Antiplatelet Therapy

Several factors may guide the decision to select a specific antiplatelet agent to initiate first after TIA or ischemic stroke. Comorbid illnesses, side effects, and costs may influence the decision to initiate aspirin, combination aspirin and dipyridamole, or clopidogrel. Aspirin is less expensive, which may affect long-term adherence.[283,284] However, even small reductions in vascular events compared with aspirin may make combination dipyridamole and aspirin or clopidogrel cost-effective from a broader societal perspective.[285] For patients intolerant to aspirin because of allergy or gastrointestinal side effects, clopidogrel is an appropriate choice. Dipyridamole is not tolerated by some patients because of persistent headache. The combination of aspirin and clopidogrel may be appropriate for patients with recent presentation with acute coronary syndromes or after vascular stenting.[286] Ongoing trials are evaluating direct comparisons between clopidogrel and aspirin and extended-release dipyridamole, as well as the efficacy of the combination of aspirin plus clopidogrel among patients with stroke. At present, the selection of antiplatelet therapy after stroke and TIA should be individualized.

B. Oral Anticoagulants

Randomized trials have addressed the use of oral anticoagulants to prevent recurrent stroke among patients with noncardioembolic stroke, including strokes caused by large-artery EC or IC atherostenosis, small penetrating artery disease, and cryptogenic infarcts. The Stroke Prevention in Reversible Ischemia Trial (SPIRIT) was stopped early because of increased bleeding among those treated with high-intensity oral anticoagulation (INR, 3.0 to 4.5) compared with aspirin (30 mg/d) in 1316 patients.[287,288] This trial was reformulated as the European-Australian Stroke Prevention in Reversible Ischemia Trial (ESPRIT) and is continuing with a lower dose of warfarin (INR, 2 to 3) versus either aspirin (30 to 325 mg) or aspirin plus extended-release dipyridamole 200 mg BID.

The Warfarin Aspirin Recurrent Stroke Study (WARSS) compared the efficacy of warfarin (INR, 1.4 to 2.8) with aspirin (325 mg) for the prevention of recurrent ischemic stroke among 2206 patients with a noncardioembolic stroke.[289] This randomized, double-blind, multicenter trial found no significant difference between the treatments for the prevention of recurrent stroke or death (warfarin, 17.8%; aspirin, 16.0%). Rates of major bleeding were not significantly different between the warfarin and aspirin groups (2.2% and 1.5% per year, respectively). A variety of subgroups were evaluated, with no evidence of efficacy observed across baseline stroke subtypes, including large-artery atherosclerotic and cryptogenic categories. Although there was no difference in the 2 treatments, the potential increased bleeding risk in the community setting and cost of monitoring were considered in the recommendation to choose antiplatelets over anticoagulants in the setting of noncardioembolic stroke.

WASID was stopped prematurely for safety concerns among those treated with warfarin. This trial was designed to test the efficacy of warfarin with a target INR of 2 to 3 (mean, 2.5) versus aspirin for those with angiographically documented >50% intracranial stenosis. At the time of termination, warfarin was associated with significantly higher rates of adverse events and provided no benefit over aspirin. During a mean follow-up of 1.8 years, adverse events in the 2 groups were death (aspirin, 4.3%; warfarin, 9.7%; HR, 0.46; 95% CI, 0.23 to 0.90; $P=0.02$), major hemorrhage (aspirin, 3.2%; warfarin, 8.3%; HR, 0.39; 95% CI, 0.18 to 0.84; $P=0.01$), and MI or sudden death (aspirin, 2.9%; warfarin, 7.3%; HR, 0.40; 95% CI, 0.18 to 0.91; $P=0.02$). The primary end point (ischemic stroke, brain hemorrhage, and nonstroke vascular death) occurred in ≈22% of patients in both treatment arms (HR, 1.04; 95% CI, 0.73 to 1.48; $P=0.83$).[290]

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). 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).**
2. **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 instead of aspirin alone (Class IIa, Level of Evidence A), and clopidogrel may be considered instead of aspirin alone (Class IIb, Level of Evidence B) on the basis of direct-comparison trials. Insufficient data are available to make evidence-based recommendations about choices between antiplatelet options other than aspirin. The selection of an antiplatelet agent should be individualized on the basis of patient risk factor profiles, tolerance, and other clinical characteristics.**
3. **The addition of aspirin to clopidogrel increases the risk of hemorrhage and is not routinely recommended for ischemic stroke or TIA patients (Class III, Level of Evidence A).**
4. **For patients allergic to aspirin, clopidogrel is reasonable (Class IIa, Level of Evidence B).**
5. **For patients who have an ischemic stroke 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 studied in patients who have had an event while receiving aspirin (Table 6).**

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V. Treatments for Stroke Patients With Other Specific Conditions

A. Arterial Dissections

Dissections of the carotid and vertebral arteries are now recognized as relatively common causes of strokes, particularly among young patients. Although trauma to the neck and spine is commonly associated with such dissections, at least 50% of patients with dissections and stroke have no clear history of antecedent neck trauma.[291,292] Imaging studies such as MRI and magnetic resonance angiography with fat saturation protocols are now commonly used for the noninvasive detection of such dissections.[293,294] Dissections lead to ischemic strokes through artery-to-artery embolism or by causing significant stenosis and occlusion of the proximal vessel.[295] In some cases, dissections can lead to formation of a pseudoaneurysm, which can also serve as a source of thrombus formation. Intracranial dissections in the vertebrobasilar territory have a higher risk of rupture, leading to an SAH.[296,297] Hemorrhagic complications of dissections are not discussed further in this section.

The goals of therapy when treating patients with dissections and ischemic stroke are to prevent further ischemic strokes and to promote healing of the dissected vessel. Several therapeutic options currently are available, including anticoagulant therapy (typically intravenous heparin followed by oral Coumadin, antiplatelet therapy, endovascular treatment (usually stenting), surgical repair, and conservative management.

Studies have shown that the risk of recurrent stroke and dissection is low, typically in the range of 1% to 4% over the next 2 to 5 years.[298,299] A large study of >400 patients with carotid dissections found a stroke recurrence rate of 1% and a recurrent dissection rate of 1%.[299] A prospective study of 116 patients with cervical dissections found a recurrence rate of 4% for stroke after enrollment.[300] Many of these patients were treated with anticoagulants or antiplatelet agents for several months; therefore, it is difficult to determine the natural history rate of recurrence.

Anatomic healing of the dissection with recanalization occurs in 72% to 100% of patients.[294,301,302] Those dissections that do not fully heal do not appear to be associated with an increased risk of recurrent strokes.[299,303] Therefore, further treatment of currently asymptomatic lesions to achieve anatomic cure does not appear to be warranted in most cases.[301–303]

Although it is often stated that treatment with intravenous heparin, followed by 3 to 6 months of therapy with Coumadin, is routine care for patients with a carotid or vertebral dissection (with or without an ischemic stroke), there are no data from prospective randomized studies supporting such an approach. Some data suggest that intravenous heparin may be effective for preventing further arterial embolization in the setting of cervical dissections.[291,294,301,302] Heparin and similar agents may also promote or hasten the dissolution of the intramural thrombus found in many patients with dissections, thereby promoting healing of the dissection.[294] The risk of heparin causing hemorrhagic transformation in these patients appears to be low (<5%).[301] Use of heparin or other anticoagulants in patients with an SAH related to a dissection is contraindicated.

Small case series have used antiplatelet agents in patients with dissections, with results generally comparable to those for anticoagulants.[301,304] Aspirin often is used in such cases, although other antiplatelet agents may also be considered. A case series of 116 consecutive patients treated with anticoagulation (n=71) and antiplatelet agents (n=23) found no significant difference in outcomes (eg, TIA, stroke, or death) of 8.3% versus 12.4%, respectively.[300] Meta-analyses comparing rates of death and disability have not found any significant differences between treatment with anticoagulants and antiplatelet agents.[304]

Endovascular therapy, particularly stent placement, is emerging as an increasingly popular option to treat dissec-

TABLE 6. Recommendations for Antithrombotic Therapy for Noncardioembolic Stroke or TIA (Oral Anticoagulant and Antiplatelet Therapies)

Recommendation	Class/Level of Evidence*
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 A
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 A
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 A
Clopidogrel may be considered over aspirin alone on the basis of direct-comparison trials. Insufficient data are available to make evidence-based recommendations with regard to choices between antiplatelet options other than aspirin. Selection of an antiplatelet agent should be individualized based on patient risk factor profiles, tolerance, and other clinical characteristics.	Class IIb, Level B
Addition of aspirin to clopidogrel increases the risk of hemorrhage and is not routinely recommended for ischemic stroke or TIA patients.	Class III, Level A
For patients allergic to aspirin, clopidogrel is reasonable.	Class IIa, Level B
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.	

*See Table 1 for explanation of class and level of evidence.

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tions that fail standard medical therapy. Stent placement will often reduce the degree of vessel stenosis and may prevent extension of the dissection[305–308]; it may be useful for preventing pseudoaneurysm formation. As with the various medical therapies, endovascular therapy has not been studied within randomized trials.

Surgical therapy involves repairing the damaged vessel by direct replacement with a new vessel or by a patch-graft approach. Such treatments have been associated with complication rates of at least 10% to 12% (stroke and death combined), which are higher than those reported with medical therapy alone.[308–310] However, some of these patients may have failed standard medical therapy.

Most experts advise patients who experience a cervical arterial dissection to avoid future activities that may lead to neck injury, extreme straining, or excessive force and motion on the neck,[311,312] including contact sports, activities causing hyperextension of the neck, weight lifting, labor related to child birth, other strenuous exercises, and chiropractic manipulation of the neck region.

Recommendations

1. **For patients with ischemic stroke or TIA and extracranial arterial dissection, use of warfarin for 3 to 6 months or use of antiplatelet agents is reasonable (Class IIa, Level of Evidence B). Beyond 3 to 6 months, long-term antiplatelet therapy is reasonable for most stroke or TIA patients. Anticoagulant therapy beyond 3 to 6 months may be considered among patients with recurrent ischemic events (Class IIb, Level of Evidence C) (Table 7).**
2. **For patients who have definite recurrent ischemic events despite adequate antithrombotic therapy, endovascular therapy (stenting) may be considered (Class IIb, Level of Evidence C). Patients who fail or are not candidates for endovascular therapy may be considered for surgical treatment (Class IIb, Level of Evidence C) (Table 7).**

B. Patent Foramen Ovale

Patent foramen ovale (PFO), a persistence of an embryonic defect in the interatrial septum, is present in up to 27% of the general population. Atrial septal aneurysms, defined as >10-mm excursions of the interatrial septum, are less common, affecting ≈2% of the population. The prevalence of PFOs and atrial septal aneurysms does not appear to vary by race/ethnicity.[313] The presence of an atrial septal aneurysm or a large right-to-left shunt has been reported to increase the risk of stroke in patients with PFO.[314–322]

Studies have found an association between PFO and cryptogenic stroke.[323–327] In a study of 581 patients <55 years of age with cryptogenic stroke, the prevalence of PFO was reported to be 46%.[328] In the Patent Foramen Ovale in Cryptogenic Stroke Study (PICSS), a substudy of WARSS, which randomized patients between 30 and 85 years of age with noncardioembolic stroke to either warfarin or aspirin, the prevalence of PFO was 34%.[327] PFOs were identified in 39% of patients with cryptogenic stroke compared with 29% in those with a defined mechanism ($P<0.02$).[327]

Estimates for the rate of annual stroke recurrence in cryptogenic stroke patients with PFO vary widely, ranging from 1.5% to 12%, depending on the study population.[314,315,317,323,327,329] In the Lausanne Study, 140 patients representing 41% of a population-based cohort with stroke or TIA were found to have a PFO (mean age, 44±14 years) and were followed up for an average of 3 years. Venous thrombus was detected in 5.5%. An alternative cause of stroke was identified in 16%. PFO was not a significant predictor of 2-year risk of stroke recurrence in PICSS.

In another study from France, recurrent stroke risks were evaluated among patients 18 to 55 years of age with ischemic cryptogenic stroke and PFO on transesophageal echocardiography treated with aspirin.[315] After 4 years, the rates of recurrent stroke were 2.3% for PFO alone, 15.2% for PFO with atrial septal aneurysm, and 4.2% with neither. Although the increased risk associated with PFO and atrial septal aneurysms is supported by some studies, this finding remains controversial because other studies have failed to show a higher risk.[314,316,323,327]

1. Medical Therapy

In the Lausanne Study, the annual infarction rate on conventional therapies (66% aspirin, 26% anticoagulation, 8% PFO closure) was 1.9%. The rate of stroke and death was 2.4%. There were no ICHs.[323] Cujec et al[329] analyzed a cohort of 90 cryptogenic stroke patients <60 years of age, more than one half of whom had a PFO, and reported that warfarin was more effective than antiplatelet therapy for secondary stroke prevention. PICSS provides the only randomized comparison of warfarin and aspirin in patients with PFO. Because this was a substudy of WARSS, it was not designed to evaluate the superiority of an antithrombotic strategy among those with stroke and a PFO.[327] In PICSS, 33.8% of 630 patients found to have a PFO on transesophageal echocardiography and randomized to either aspirin 325 mg or warfarin (target INR range, 1.4 to 2.8) were followed up for 2 years. There was no significant difference in rates of recurrent stroke or death in patients with PFO versus those with no PFO. Event rates among the cryptogenic stroke patients with PFO treated with aspirin (17.9%, n=56) and warfarin (9.5%, n=42) were not statistically significant (HR, 0.52; 95%CI, 0.16 to 1.67; $P=0.28$) and similar to those cryptogenic stroke patients without PFO (HR, 0.50; 95% CI, 0.19 to 1.31; $P=0.16$).

2. Surgical Closure

There are conflicting reports concerning the safety and efficacy of surgical PFO closure. After 19 months of follow-up, there were no major complications or recurrent vascular events found among a series of 32 young patients with PFO and cryptogenic embolism or TIA and PFO who underwent surgical closure.[330] Similar results were reported in another independent series of 30 patients.[331] In a 2-year follow-up of a cohort of 91 patients with cryptogenic stroke or TIA who underwent surgical closure, 7 TIAs but no major complications were reported.[332] Another series found poorer outcomes, with a recurrence rate of 19.5% at 13 months after surgical closure.[333]

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TABLE 7. Recommendations for Stroke Patients With Other Specific Conditions

Risk Factor	Recommendation	Class/Level of Evidence*
Arterial dissection	For patients with ischemic stroke or TIA and arterial dissection, warfarin for 3 to 6 mo or antiplatelet agents are reasonable.	Class IIa, Level B
	Beyond 3 to 6 mo, long-term antiplatelet therapy is reasonable for most ischemic stroke or TIA patients. Anticoagulant therapy beyond 3 to 6 mo may be considered among patients with recurrent ischemic events.	Class IIb, Level C
	For patients who have definite recurrent ischemic events despite antithrombotic therapy, endovascular therapy (stenting) may be considered.	Class IIb, Level C
	Patients who fail or are not candidates for endovascular therapy may be considered for surgical treatment.	Class IIb, Level C
Patent foramen ovale	For patients with an ischemic stroke or TIA and a PFO, antiplatelet therapy is reasonable to prevent a recurrent event.	Class IIa, Level B
	Warfarin is reasonable for high-risk patients who have other indications for oral anticoagulation such as those with an underlying hypercoagulable state or evidence of venous thrombosis.	Class IIa, Level C
	Insufficient data exist to make a recommendation about PFO closure in patients with a first stroke and a PFO. PFO closure may be considered for patients with recurrent cryptogenic stroke despite medical therapy.	Class IIb, Level C
Hyperhomocysteinemia	For patients with an ischemic stroke or TIA and hyperhomocysteinemia (levels >10 μmol/L), daily standard multivitamin preparations are reasonable to reduce the level of homocysteine, given their safety and low cost. However, there is no evidence that reducing homocysteine levels will lead to a reduction of stroke occurrence.	Class I, Level A
Hypercoagulable states		
Inherited thrombophilias	Patients with an ischemic stroke or TIA with an established inherited thrombophilia should be evaluated for deep venous thrombosis, which is an indication for short- or long-term anticoagulant therapy, depending on the clinical and hematologic circumstances.	Class IIa, Level A
	Patients should be fully evaluated for alternative mechanisms of stroke.	Class IIa, Level C
	In the absence of venous thrombosis, long-term anticoagulation or antiplatelet therapy is reasonable.	
	Patients with a history of recurrent thrombotic events may be considered for long-term anticoagulation.	Class IIb, Level C
Antiphospholipid antibody syndrome	For cases of cryptogenic ischemic stroke or TIA and positive APL antibodies, antiplatelet therapy is reasonable.	Class IIa, Level B
	For patients with ischemic stroke or TIA who meet the criteria for the APL antibody syndrome with venous and arterial occlusive disease in multiple organs, miscarriages, and livedo reticularis, oral anticoagulation with a target INR of 2 to 3 is reasonable.	Class IIa, Level B
Sickle-cell disease	For adults with SCD and ischemic stroke or TIA, general treatment recommendations cited above are applicable with regard to the control of risk factors and use of antiplatelet agents.	Class IIa, Level B
	Additional therapies that may be added include regular blood transfusion to reduce Hb S to $<30\%$ to 50% of total Hb, hydroxyurea, or bypass surgery in cases of advanced occlusive disease.	Class IIb, Level C
Cerebral venous sinus thrombosis	For patients with cerebral venous sinus thrombosis, UFH or LMWH is reasonable even in the presence of hemorrhagic infarction.	Class IIa, Level B
	Continuation of anticoagulation with an oral anticoagulant agent is reasonable for 3 to 6 mo, followed by antiplatelet therapy.	Class IIa, Level C

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TABLE 7. Continued

Risk Factor	Recommendation	Class/Level of Evidence*
Pregnancy	For pregnant women with an ischemic stroke or TIA and high-risk thromboembolic conditions such as known coagulopathy or mechanical heart valves, the following options may be considered:	Class IIb, Level C
	Adjusted-dose UFH throughout pregnancy such as a subcutaneous dose every 12 h with APTT monitoring; Adjusted-dose LMWH with factor Xa monitoring throughout pregnancy; or UFH or LMWH until week 13, followed by warfarin until the middle of the third trimester, when UFH or LMWH is then reinstituted until delivery.	
	Pregnant women with lower-risk conditions may be considered for treatment with UFH or LMWH in the first trimester, followed by low-dose aspirin for the remainder of the pregnancy.	Class IIb, Level C
Postmenopausal HRT	For women with stroke or TIA, postmenopausal HRT is not recommended.	Class III, Level A
Cerebral hemorrhage	For patients who develop an ICH, SAH, or SDH, all anticoagulants and antiplatelets should be discontinued during the acute period for at least 1 to 2 wk after the hemorrhage and the anticoagulant effect reversed immediately with appropriate agents (ie, vitamin K, FFP).	Class III, Level B
	For patients who require anticoagulation soon after a cerebral hemorrhage, intravenous heparin may be safer than oral anticoagulation. Oral anticoagulants may be resumed after 3 to 4 wk, with rigorous monitoring and maintenance of INRs in the lower end of the therapeutic range.	Class IIb, Level C
	Special circumstances:	
	Anticoagulation should not be resumed after an SAH until the ruptured aneurysm is definitively secured.	Class III, Level C
	Patients with lobar ICHs or microbleeds and suspected CAA on MRI may be at a higher risk for recurrent ICH if anticoagulation needs to be resumed.	Class IIb, Level C
	For patients with hemorrhagic infarction, anticoagulation may be continued, depending on the specific clinical scenario and underlying indication for anticoagulant therapy.	Class IIb, Level C

APTT indicates activated partial thromboplastin time; CAA, cerebral amyloid angiopathy; FFP, fast frozen plasma; Hb, hemoglobin; and SDH, subdural hematoma.
*See Table 1 for explanation of class and level of evidence.

3. Transcatheter Closure

A recent review of 10 nonrandomized unblinded transcatheter closure studies for secondary prevention reported a 1-year rate of recurrent neurological events of 0% to 4.9% in patients undergoing transcatheter closure compared with 3.8% to 12.0% in medically treated patients.[334] The incidence of major and minor procedural complications was 1.45% and 7.9%, respectively.[334] Other randomized trials evaluating the efficacy of transcatheter closure devices are ongoing.

Our recommendations are consistent with those of other organizations that have also published recommendations with regard to the management of stroke and TIA patients with PFO.[335]

Recommendations

1. **For patients with an ischemic stroke or TIA and a PFO, antiplatelet therapy is reasonable to prevent a recurrent event (Class IIa, Level of Evidence B). Warfarin is reasonable for high-risk patients who have other indications for oral anticoagulation such as those with an underlying hypercoagulable state or evidence of venous thrombosis (Class IIa, Level of Evidence C).**
2. **Insufficient data exist to make a recommendation about PFO closure in patients with a first stroke and a PFO. PFO closure may be considered for patients with recurrent cryptogenic stroke despite optimal medical therapy (Class IIb, Level of Evidence C) (Table 7).**

C. Hyperhomocysteinemia

Cohort and case-control studies have consistently demonstrated a 2-fold-greater risk of stroke associated with hyperhomocysteinemia.[336–341] The Vitamin Intervention for Stroke Prevention (VISP) study randomized patients with a noncardioembolic stroke and mild to moderate hyperhomocysteinemia (>9.5 μmol/L for men, ≥8.5 μmol/L for women) to receive either a high- or low-dose vitamin therapy (eg, folate, B6, or B12) for 2 years.[342] The risk of stroke was related to level of homocysteine; the mean reduction in homocysteine was greater in the high-dose group, but there was no reduction in stroke rates in the patients given high-dose vitamin. The 2-year stroke rates were 9.2% in the high-dose and 8.8% in the low-dose arms. Although there is no proven clinical benefit to high-dose vitamin therapy for mild to moderate hyperhomocysteinemia, patients should be encouraged to take a daily standard multivitamin preparation, given the low risk and cost associated with vitamin therapy. Additional research is needed to determine whether there are subgroups that might benefit from more aggressive vitamin therapy, particularly over the long term.

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Recommendation

For patients with ischemic stroke or TIA and hyperhomocysteinemia (levels >10 μmol/L), daily standard multivitamin preparations with adequate B6 (1.7 mg/d), B12 (2.4 μg/d), and folate (400 μg/d) are reasonable to reduce the level of homocysteine, given their safety and low cost (Class IIa, Level of Evidence B). However, there is no evidence that reducing homocysteine levels will lead to a reduction in stroke recurrence (Table 7).

D. Hypercoagulable States

1. Inherited Thrombophilias

Inherited thrombophilias (such as protein C, protein S, or antithrombin III deficiency; factor V Leiden (FVL); or the prothrombin G20210A mutation) rarely contribute to adult stroke but may play a larger role in pediatric stroke.[343,344] Activated protein C resistance, caused by a defect in factor V, is the most common inherited coagulation disorder. More commonly a cause of venous thromboembolism, case reports have linked activated protein C resistance to ischemic stroke.[345–347] The link between activated protein C resistance and arterial stroke is tenuous in adults, but it may play a larger role in juvenile stroke.[348,349] FVL, a mutation causing activated protein C resistance, and the G20210A polymorphism in the prothrombin gene have similarly been linked to venous thrombosis, but their role in ischemic stroke remains controversial.[334,341,350–360]

Studies in younger patients have shown an association between these prothrombotic genetic variants and ischemic stroke, but this finding remains controversial in an older population with vascular risk factors and competing high-risk stroke mechanisms. Even in the young, results have been inconsistent. In 1 small study of cryptogenic stroke patients <50 years of age, there was an increased risk (odds ratio [OR], 3.75; 95% CI, 1.05 to 13.34) associated with the PT G20210A mutation but no significant association with FVL.[361] In contrast, 2 other studies of young (<50 years of age) patients found no association between ischemic stroke and the FVL, PT G20210A, or the methylenetetrahydrofolate reductase (MTHFR) C677T mutations.[341,362] Genetic factors associated with venous thromboembolism were compared in a study of young stroke patients (<45 years of age) to determine whether there was a higher prevalence of prothrombotic tendencies in those with PFO, which could reflect a susceptibility to paradoxical embolism. The prothrombin G20210A mutation, but not FVL, was significantly more common in the PFO+ group compared with PFO− or nonstroke controls.[359]

Three meta-analyses have examined the most commonly studied prothrombotic mutations in FVL, MTHFR, and PT G20210A. The first pooled ischemic stroke candidate gene association studies involving white adults and found statistically significant associations between stroke and FVL Arg506Gln (OR, 1.33; 95% CI, 1.12 to 1.58), MTHFR C677T (OR, 1.24; 95% CI, 1.08 to 1.42), and PT G20210A (OR, 1.44; 95% CI, 1.11 to 1.86).[363] A second meta-analysis explored the association between FVL, PT G20210A, and MTHFR C677T and arterial thrombotic events (MI, ischemic stroke, or peripheral vascular disease) and found no significant link to FVL mutation and modest associations with PT G20210A (OR 1.32; 95% CI 1.03 to 1.69) and MTHFR C677T (OR 1.20; 95% CI 1.02 to 1.41). These associations were stronger in the young (<55 years of age).[364] A third meta-analysis focused on the MTHFR C677T polymorphism, which is associated with high levels of homocysteine. The OR for stroke was 1.26 (95% CI, 1.14 to 1.40) for TT versus CC homozygotes.[363] Thus, although there appears to be a weak association between these prothrombotic mutations and ischemic stroke, particularly in the young, major questions remain as to the mechanism of risk (eg, potential for paradoxical venous thromboembolism), the effect of gene-environment interaction, and the optimal strategies for stroke prevention.

The presence of venous thrombosis is an indication for short- or long-term therapy, depending on the clinical and hematologic circumstances.[365,366] Although there are guidelines for the general management of acquired hypercoagulable states such as heparin-induced thrombocytopenia, disseminated intravascular coagulation, or cancer-related thrombosis, none are specific for the secondary prevention of stroke.[367–370]

Recommendation

Patients with ischemic stroke or TIA with an established inherited thrombophilia should be evaluated for deep vein thrombosis, which is an indication for short- or long-term anticoagulant therapy, depending on the clinical and hematologic circumstances (Class I, Level of Evidence A). Patients should be fully evaluated for alternative mechanisms of stroke. In the absence of venous thrombosis, long-term anticoagulants or antiplatelet therapy is reasonable (Class IIa, Level of Evidence C). Patients with a history of recurrent thrombotic events may be considered for long-term anticoagulation (Class IIb, Level of Evidence C) (Table 7).

2. Antiphospholipid Antibodies

Antiphospholipid (APL) antibody prevalence ranges from 1% to 6.5%, higher in the elderly and in patients with lupus.[371] Less commonly, the APL antibody syndrome consists of venous and arterial occlusive disease in multiple organs, miscarriages, and livedo reticularis.[372] The association between APL antibodies and stroke is strongest for young adults (<50 years of age).[373,374] In the Antiphospholipid Antibodies in Stroke Study (APASS), 9.7% of ischemic stroke patients and 4.3% of control subjects were anticardiolipin positive.[375] In the Antiphospholipid Antibodies in Stroke substudy of WARSS (WARSS/APASS), APL antibodies were detected in 40.7% of stroke patients, but they had no significant effect on the risk of stroke recurrence.[376]

Multiple studies have shown high recurrence rates in patients with APL antibodies in the young.[377–379] In 1 study of patients with arterial or venous thrombotic events (76% with venous thrombosis and only 32% with a history of thromboembolism in the prior 6 months) and 2 positive anticardiolipin antibodies separated by 3 months, higher intensities of oral anticoagulation were more beneficial than conventional pro-

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grams in preventing recurrent events.[380] However, there are conflicting data on the association between APL antibodies and stroke recurrence in the elderly.[377,381–383]

The WARSS/APASS collaboration was the first study to compare randomly assigned warfarin (INR, 1.4 to 2.8) with aspirin (325 mg) for the prevention of a second stroke in patients with APL antibodies. APASS enrolled 720 APL antibody–positive WARSS participants.[376] The overall event rate was 22.2% among APL-positive patients and 21.8% among APL-negative patients. Patients with both lupus anticoagulant and anticardiolipin antibodies had a higher event rate (31.7%) than patients negative for both antibodies (24.0%), but this was not statistically significant. There was no difference between the risk of the composite end point of death from any cause, ischemic stroke, TIA, MI, deep vein thrombosis, pulmonary embolism, and other systemic thrombo-occlusive events in patients treated with either warfarin (RR, 0.99; 95% CI, 0.75 to 1.31; $P=0.94$) or aspirin (RR, 0.94; 95% CI, 0.70 to 1.28; $P=0.71$).

Recommendations

1. **For cases of cryptogenic ischemic stroke or TIA and positive APL antibodies, antiplatelet therapy is reasonable (Class IIa, Level of Evidence B).**
2. **For patients with ischemic stroke or TIA who meet the criteria for the APL antibody syndrome with venous and arterial occlusive disease in multiple organs, miscarriages, and livedo reticularis, oral anticoagulation with a target INR of 2 to 3 is reasonable (Class IIa, Level of Evidence B) (Table 7).**

E. Sickle Cell Disease

Stroke is a common complication of sickle cell disease (SCD). The risk of stroke depends on the genotype; it is highest with homozygous SS and less pronounced with variants such as hemoglobin SC, whereas patients with sickle trait hemoglobin AS have little or no elevation of stroke rate.[384,385] Although there are few direct data and no animal model for stroke in SCD, a large-artery arteriopathy, fibrous in nature, presumably resulting from repeated endothelial injury, is usually cited as the most common SCD-specific cause for brain infarction.[386] In adults with SCD and brain or retinal ischemia, other potential stroke mechanisms should be considered and an appropriate diagnostic workup undertaken. There has been only 1 randomized trial for stroke prevention in SCD, and that was in children for primary prevention based on risk stratification by transcranial Doppler.[387] These data are not applicable to this guideline and are summarized in the Primary Prevention statement.[1]

Although SCD is considered a hypercoagulable state, with evidence of increased thrombin generation, platelet activation,[388] and inflammatory markers,[389] there has been no systematic experience with antiplatelet agents, anticoagulation, or antiinflammatory agents for stroke prevention. Elevation of systolic BP has been linked to stroke in SCD, whereas lipid elevation and coronary artery disease are not commonly reported in SCD.[390] Cardiac disease causing cerebral embolus is either rare or underreported. Despite the absence of data on how SCD-specific risk factors might interact with traditional stroke risk factors (such as hypertension, diabetes, and abnormal lipids), risk factor identification and reduction can be recommended on the basis of its importance in the general population. Markers of hypercoagulable state, anticardiolipin antibodies, and elevated homocysteine levels have all been reported and in some cases linked to adverse events, not necessarily stroke[391]; for these reasons, other mechanisms or risk factors associated with stroke in young adults should be considered.

Although no randomized controlled trial has been performed, a retrospective multicenter review of SCD patients with stroke, either observed or transfused, suggested that regular blood transfusion sufficient to suppress native hemoglobin S formation reduces recurrent stroke risk. The transfusion target most often used is the percentage of hemoglobin S as a fraction of total hemoglobin assessed just before transfusion. Reduction of hemoglobin S to $<30\%$ (from a typical baseline of 90% before initiating regular transfusions) was associated with a reduction in the rate of recurrence at 3 years from $>50\%$ to $\approx 10\%$.[392] Most of the patients in this series were children, and it is not clear whether adults have the same untreated risk or benefit from treatment. Regular transfusions are associated with long-term complications, especially iron overload, making its long-term use problematic. Some experts recommend using transfusion for 1 to 3 years after stroke, a presumed period of higher risk for recurrence, then switching to other therapies. A small number of patients treated with bypass operations used in moyamoya have been reported to have good outcomes, but no randomized or controlled data are available.[393]

Two small studies of secondary stroke prevention in children and young adults with stroke reported encouraging results using hydroxyurea to replace regular blood transfusion after ≥ 3 years of transfusion therapy.[394,395] For a small number of patients with a suitable donor and access to expert care, bone marrow transplantation can be curative from a hematologic perspective but is usually undertaken in young children, not adults, with SCD. Stroke and other brain-related concerns are frequently cited as reasons for undertaking transplant. Experience is limited, but both clinical and subclinical infarctions have been reported to be arrested by this procedure.[396]

Recommendation

For adults with SCD and ischemic stroke or TIA, general treatment recommendations cited above are applicable with regard to the control of risk factors and the use of antiplatelet agents (Class IIa, Level of Evidence B). Additional therapies that may be considered include regular blood transfusion to reduce hemoglobin S to <30% to 50% of total hemoglobin, hydroxyurea, or bypass surgery in cases of advanced occlusive disease (Class IIb, Level of Evidence C) (Table 7).

F. Cerebral Venous Sinus Thrombosis

Cerebral venous sinus thrombosis is frequently a challenging diagnosis because patients can present with a variety of signs and symptoms, including headache, focal neurological deficits, seizures, alterations of consciousness, and papillede-

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ma.[397] Routine neuroimaging studies such as CT or MRI may produce subtle findings that can be missed if there is not a high index of suspicion. MR venography can confirm the diagnosis, and conventional angiography is rarely needed now that MR venography is widely available.[398] Cerebral venous infarctions are frequently hemorrhagic and are associated with considerable vasogenic edema. Both high and low apparent diffusion coefficient values can be present on diffusion-weighted imaging.[399] Risk factors include factor V gene mutations and other hypercoagulable states, pregnancy/postpartum, oral contraceptives, and infections located near cerebral sinuses.

Two small randomized trials of anticoagulant therapy have been performed.[400,401] The first trial compared dose-adjusted unfractionated heparin (UFH) (partial thromboplastin time at least 2 times control) with placebo. The study was terminated early, after only 20 patents had been enrolled, because of the superiority of heparin therapy ($P<0.01$). Eight of the 10 patients randomized to heparin recovered completely, and the other 2 had only mild neurological deficits. In the placebo group, only 1 patient had a complete recovery, and 3 died.[400] The same research group also reported a retrospective study of 43 patients with cerebral venous sinus thrombosis associated with intracranial bleeding; 27 of these patients were treated with dose-adjusted heparin. The mortality rate in the heparin group was considerably lower than in the nonanticoagulated group.[400]

In a more recent and slightly larger randomized study of cerebral venous sinus thrombosis (n=59), nadroparin (90 anti-Xa units/kg twice daily) was compared with placebo.[401] After 3 months of follow-up, 13% of the patients in the anticoagulation group and 21% in the placebo group had poor outcomes (RR reduction, 38%; P=NS). Two patients in the nadroparin group died versus 4 in the placebo group. Patients with intracranial bleeding were included, and no new symptomatic cerebral hemorrhages occurred in either group.

From the results of these 2 small trials and observational data, it appears that both UFH and low-molecular-weight heparin (LMWH) are safe and probably effective in cerebral venous sinus thrombosis. Anticoagulation is recommended, even in patients with hemorrhagic venous infarcts. No adequate studies are available to address the optimal duration of anticoagulation. We recommend continuation of anticoagulation with an oral agent for 3 to 6 months. For patients who demonstrate continued neurological deterioration despite anticoagulation, local intrathrombus infusion of a thrombolytic agent has been reported to produce effective clot dissolution.[398,402] Further investigation of this option is needed.

Recommendation

For patients with cerebral venous sinus thrombosis, UFH or LMWH is reasonable even in the presence of hemorrhagic infarction (Class IIa, Level of Evidence B). Continuation of anticoagulation with an oral anticoagulant agent is reasonable for 3 to 6 months, followed by antiplatelet therapy (Class IIa, Level of Evidence C) (Table 7).

VI. Stroke Among Women

A. Pregnancy

Pregnancy increases the risk for several types of stroke and complicates the selection of preventive treatments.[403] There are no direct randomized data for stroke prevention in pregnant women; therefore, the choice of agents for prevention has to be made by inference from other studies, primarily prevention of deep vein thrombosis and the use of anticoagulants in women with high-risk cardiac conditions. Even in these situations, specific RCT data are lacking. For stroke prevention treatment during pregnancy, recommendations will be based on 2 scenarios: (1) the clinical situation reveals a condition that in nonpregnant women would require anticoagulation with warfarin, or (2) no such condition is present and antiplatelet therapy would be the treatment recommendation if pregnancy were not present. The first can be considered a high-risk and the second a lower- or uncertain-risk situation.

A full review of this complex topic is beyond the scope of this guideline; however, a recent detailed discussion of options is available from a writing group of the ACCP.[404] From their review, the following guidance can be offered.

1. Although warfarin may be safe for the fetus after a certain early period (6 to 12 weeks) and approaches to its use are varied, in the US, warfarin is not usually recommended during pregnancy primarily because of concerns of fetal safety, but it is an option identified by the ACCP.
2. Low-dose aspirin (<150 mg/d) appears safe after the first trimester.
3. LMWH is an acceptable option to UFH and may avoid the problem of osteoporosis associated with long-term heparin therapy.

Recommendations

1. **For pregnant women with ischemic stroke or TIA and high-risk thromboembolic conditions such as known coagulopathy or mechanical heart valves, the following options may be considered: adjusted-dose UFH throughout pregnancy, eg, a subcutaneous dose every 12 hours with activated partial thromboplastin time monitoring; adjusted-dose LMWH with factor Xa monitoring throughout pregnancy; or UFH or LMWH until week 13, followed by warfarin until the middle of the third trimester, when UFH or LMWH is then reinstituted until delivery (Class IIb, Level of Evidence C).**
2. **Pregnant women with lower-risk conditions may be considered for treatment with UFH or LMWH in the first trimester, followed by low-dose aspirin for the remainder of the pregnancy (Class IIb, Level of Evidence C) (Table 7).**

B. Postmenopausal Hormone Therapy

Despite the prior suggestions from observational studies that postmenopausal hormone therapy may be beneficial for the prevention of heart disease and stroke, randomized trials of heart disease and stroke survivors and primary prevention trials have failed to demonstrate any significant benefits. Three randomized trials have addressed this subject. The Women's Estrogen for Stroke Trial (WEST) failed to show

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any reduction in the risk of stroke recurrence or death with estradiol.[405] Within the first 6 months, the risk of stroke was higher among those randomized to estradiol (RR, 2.3; 95% CI, 1.1 to 5.0). Moreover, those who had a recurrent stroke and were randomized to hormonal therapy were less likely to recover. The Heart and Estrogen/Progesterone Replacement Study (HERS) Trial did not demonstrate any benefit of hormone therapy among postmenopausal women who had a MI.[406,407] The Women's Health Initiative (WHI), which examined the role of hormonal therapy for the primary prevention of cardiovascular disease and stroke among postmenopausal women, was stopped early because of an increase in vascular events.[408] An increased stroke risk among women with a previous hysterectomy who were randomized to hormonal therapy was also observed in a separate parallel trial.[409]

Recommendation

For women with ischemic stroke or TIA, postmenopausal hormone therapy (with estrogen with or without a progestin) is not recommended (Class III, Level of Evidence A) (Table 7).

VII. Use of Anticoagulation After Cerebral Hemorrhage

One of the most difficult problems that clinicians face is how to handle anticoagulation therapy in patients who have had a cerebral hemorrhage. In such a setting, there are several key variables to consider, including the type of cerebral hemorrhage, patient age, risk factors for recurrent hemorrhage, and the indication for anticoagulation. Most studies or case series have focused on patients with an ICH or subdural hematoma who are receiving anticoagulants because of a mechanical heart valve or AF. There are very few case series that focus on SAH. The risks of recurrent hemorrhage must be weighed against the risk of an ischemic cerebrovascular event. There is a paucity of data from large, prospective, randomized studies to answer these important management questions.

In the acute setting of a patient with an ICH or subdural hematoma and a therapeutic or supratherapeutic INR, it is imperative that the INR be normalized as soon as possible through the use of vitamin K, fresh frozen plasma, or other agents.[410,411] Studies have shown that 30% to 40% of ICHs will expand during the first 12 to 36 hours of their formation.[412] Such expansions are usually associated with neurological worsening.[6] Elevated INRs are presumed to enhance such expansions and are unlikely to be beneficial in this setting. Therefore, rapid normalization of the coagulation status is mandatory for any anticoagulated patient with an ICH or subdural hematoma, although there are no data demonstrating the efficacy of reversal of oral anticoagulation. The general consensus is that rebleeding is so common after an SAH that all anticoagulation should be reversed until the aneurysm is clipped or coiled.[413,414]

The appropriate duration of the period off anticoagulation among high-risk patients is unknown. Several case series have followed up patients off of anticoagulants for several days and weeks, with few reported instances of ischemic stroke. One study found that among 35 patients with hemorrhages followed up for up to 19 days off of Coumadin, there were no recurrent ischemic strokes.[411] In a study of 141 patients with an ICH while taking warfarin, warfarin was reversed and stopped for a median of 10 days. The risk of an ischemic event was 2.1% within 30 days. The risk of an ischemic stroke during cessation of warfarin was 2.9% in patients with a prosthetic heart valve, 2.6% in those with AF and a prior embolic stroke, and 4.8% for those with a prior TIA or ischemic stroke.[415] None of the 35 patients in whom warfarin was restarted had another ICH during the hospitalization.[415] Another study of 28 patients with prosthetic heart valves found that during a mean period of 15 days of no anticoagulation, no patient had an embolic event.[416] A study of 35 patients with an ICH or spinal hemorrhage reported no recurrent ischemic events among the 14 patients with prosthetic valves after a median of 7 days without anticoagulation.[411] One study of 100 patients who underwent intracranial surgery for treatment of a cerebral aneurysm found that 14% developed evidence of deep vein thrombosis postoperatively. These patients were treated with systemic anticoagulation without any bleeding complications.[417]

Bleed location and MR findings appear to be important variables in determining the risk of a new or recurrent ICH. Bleeds in a lobar location may pose a higher risk of recurrence when anticoagulation is reinstituted, perhaps because of the presence of cerebral amyloid angiopathy in some of these patients. A decision analysis recommended against restarting anticoagulation in patients with lobar ICH and AF.[418] Several other risk factors for new or recurrent ICH have been identified and include advanced age, hypertension, degree of anticoagulation, dialysis, leukoaraiosis, and the presence of microbleeds on MRI.[419–422] The presence of microbleeds on MRI (often seen on gradient echo images) may signify an underlying microangiopathy or the presence of cerebral amyloid angiopathy. One study found the risk of ICH in patients receiving anticoagulation to be 9.3% in patients with such microbleeds compared with 1.3% in those without such MRI findings.[419]

In patients with compelling indications for early reinstitution of anticoagulation, some studies suggest that intravenous heparin (with partial thromboplastin time 1.5 to 2.0 times normal) or LMWH may be safer options for acute therapy than restarting oral warfarin.[410] Failure to reverse the warfarin and achieve a normal INR has been associated with an increased risk of rebleeding, and failure to achieve a therapeutic partial thromboplastin time using IV heparin has been associated with an increased risk of ischemic stroke.[410] An advantage of intravenous heparin is that it can be easily titrated, discontinued, and rapidly reversed should bleeding recur. We do not recommend heparin boluses on the basis of studies showing that bolus therapy may increase the risk of bleeding.[423] There are few data from prospective, randomized studies with regard to the use of other agents for emergent anticoagulation in this setting.

Hemorrhagic transformation within an ischemic stroke appears to have a different course and natural history compared with an ICH. In general, such bleeds are often asymptomatic or cause minimal symptoms, rarely progress in size or extent, and are relatively common occurrences.[424,425] Some

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case series suggest continuing anticoagulation even in the presence of hemorrhagic transformation as long as there is a compelling indication and the patient is not symptomatic from the hemorrhagic transformation.[426] Each case must be assessed individually on the basis of variables such as size of the hemorrhagic transformation, patient status, and indication for anticoagulation.

Recommendations

1. **For patients who develop an ICH, SAH, or subdural hematoma, all anticoagulants and antiplatelets should be discontinued during the acute period for at least 1 to 2 weeks after the hemorrhage, and the anticoagulant effect should be reversed immediately with appropriate agents (ie, vitamin K, fresh frozen plasma) (Class III, Level of Evidence B).**
2. **For patients who require anticoagulation soon after a cerebral hemorrhage, intravenous heparin may be safer than oral anticoagulation. Oral anticoagulants may be resumed after 3 to 4 weeks, with rigorous monitoring and maintenance of INRs in the lower end of the therapeutic range (Class IIb, Level of Evidence C).**
3. **Special circumstances: anticoagulation should not be resumed after an SAH until the ruptured aneurysm is definitively secured (Class III, Level of Evidence C). Patients with lobar ICHs or microbleeds and suspected cerebral amyloid angiopathy on MRI may be at a higher risk for recurrent ICH if anticoagulation needs to be resumed (Class IIb, Level of Evidence C). For patients with hemorrhagic infarction, anticoagulation may be continued, depending on the specific clinical scenario and underlying indication for anticoagulant therapy (Class IIb, Level of Evidence C) (Table 7).**

VIII. Special Approaches for Implementing Guidelines and Their Use in High-Risk Populations

National consensus guidelines are published to increase provider awareness of evidence-based approaches to disease management. This assumes that increased awareness of guideline content alone will lead to changes in physician behavior and ultimately patient behavior and outcomes. Experience with previously published guidelines suggests otherwise, and compliance with secondary stroke and coronary artery disease prevention strategies has not increased dramatically.[427–431] For example, hypertension treatment to reduce stroke risk has been the subject of many guidelines and public education campaigns. Among adults with hypertension, 60% are on therapy, but only half of those are actually at their target goal, whereas another 30% are unaware that they even have the disease.[432] In a survey among physicians who were highly knowledgeable about target cholesterol goals for therapy, few were successful in achieving these goals for patients in their own practices.[433] The use of retrospective performance data to improve compliance has produced small changes in adherence to guideline-derived measures in coronary artery disease prevention.[429]

Systematic approaches to guideline implementation are needed to overcome the barriers to effective use by healthcare professionals. This was recognized by the authors of the Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) who stated[82]: Although traditional CME programs that use lectures and conferences to teach physicians rarely change professional practice, they can increase awareness and motivate physicians to learn more specific approaches to therapy. Moreover, when physician-training programs supply important background material (ie, science) and guidance on ways to implement treatment guidelines into everyday practice, they are more likely to influence practice. For example, when training programs provide the physician with enabling strategies (eg, office reminders), reinforcing strategies (eg, feedback), and predisposing strategies (eg, practice guidelines), improvements in the quality of practice are more commonly seen.

An AHA pilot program to improve post-MI implementation of coronary artery disease secondary prevention (Get With the Guidelines–CAD) demonstrated substantial improvements in care.[434] The program uses a collaborative model embedded in a systems approach that includes online access to relevant guidelines, preprinted and discharge order sets, and physician reminders to achieve increases in smoking cessation counseling from 53% to 88% ($P<0.05$), lipid therapy at discharge from 54% to 78% ($P<0.05$), and referral to cardiac rehabilitation from 33% to 73% ($P<0.05$) over a 1-year period.

The National Institutes of Health (NIH) has recognized the treatment gap between clinically proven therapies and actual treatment rates in the community and has created a new Roadmap for Medical Research to reengineer clinical research and "remove some of the biggest roadblocks that are keeping research findings from reaching the public as swiftly as possible."[435] To ensure that scientific knowledge is translated effectively into practice and that healthcare disparities are addressed, the Institute of Medicine of the National Academy of Sciences has recommended the establishment of coordinated systems of care that integrate preventive and treatment services and promote patient access to evidence-based care.[436]

Guideline recommendations should be defined as explicitly as possible, with an eye toward how they will be interpreted in the care-delivery setting and in populations that differ from the original study populations. To remain relevant, these guidelines should be updated frequently so that they reflect the latest evidence-based consensus among experts. This process of updating guidelines should take into account information about levels of compliance with previously published guidelines and challenges to implementation. Implementation of guidelines offers a unique opportunity to identify and help address disparities in healthcare delivery. The science of guideline implementation and the methods available to facilitate behavior change among patients and physicians should be the subject of formal study by organizations that promulgate guidelines.

Identifying and Responding to Populations at Highest Risk

Substantial evidence from observational epidemiological studies, clinical trials, and published data indicates that

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recurrent ischemic stroke can be prevented.[428] These studies highlight the need for special approaches for populations at high risk for recurrent stroke and TIA. Those at high risk have been identified as the aged, socially disadvantaged, and specific ethnic groups.[437–439]

The elderly are at a greater risk of stroke but also at the highest risk of complications from treatments such as oral anticoagulants and carotid endarterectomy.[209,440] Despite the need to consider different interventional approaches, some trials do not include a sufficient number of subjects >80 years of age to fully evaluate the efficacy of a therapy within this important subgroup. In SAPPHIRE, only 11% (85 of 776 CEA patients) were >80 years of age, and comparison of high-risk and low-risk CEAs demonstrated no difference in stroke rates.[441] However, other medical therapies such as the statin trials have included large numbers of elderly patients with coronary artery disease and uniformly support safety and event reduction in these groups.[442–444]

The socially disadvantaged constitute that population at high risk for stroke primarily because of limited access to care.[445,446] As indicated in the report of the American Academy of Neurology Task Force on Access to Healthcare in 1996, access to medical care in general and neurological conditions such as stroke remains limited. Hospitalized stroke patients with little or no insurance receive fewer angiograms and endarterectomies. Disparities in health care need to be addressed by the federal government and organizations such as the AHA and the American Stroke Association with the long-term goal of reducing the incidence and mortality of stroke.[447,448]

Equally socially disadvantaged for stroke care are those residing in rural America. Many rural institutions lack the resources for adequate emergency stroke treatment and the extensive community and professional educational services that address stroke awareness and prevention compared with urban areas. Telemedicine is emerging as a tool to support improved rural health care and the acute treatment and primary and secondary prevention of stroke.[449,450] The feasibility and reliability studies of the interpretation of brain CT and the administration of the NIH Stroke Scale and intravenous thrombolytic therapy have demonstrated the potential for telemedicine to address some of these resource disparities.[451–455] Larger studies are needed to validate these preliminary findings.

Stroke prevention efforts are of particular concern in those ethnic groups identified to be at the highest risk.[456] Although death rates attributed to stroke have declined by 11% in the United States from 1990 through 1998, not all groups have benefited equally, and substantial differences among ethnic groups persist.[457] Gender disparities remain, as evidenced by the fact that although the 3 leading causes of death for black men are heart disease, cancer, and HIV infection/AIDS, stroke replaces HIV infection as the third leading cause in black women.[458] Black women are particularly vulnerable to obesity, with a prevalence rate of >50%, and their higher morbidity and mortality from heart disease, diabetes, and stroke have been attributed in part to this increased BMI. The Basic Project notes the similarities in both Mexican Americans and non-Hispanic whites in that biological and social variables are associated with stroke rates in both groups to a similar extent.[459] The role of hypertension in blacks and its disproportionate impact on stroke risk have been clearly identified,[460–462] yet studies indicate that risk factors differ between different ethnic groups within the worldwide black population.[463]

For the aged, socially disadvantaged, and specific ethnic groups, inadequate implementation of guidelines and noncompliance with prevention recommendations are critical problems. Expert panels have indicated the need for a multilevel approach to include the patient, provider, and organization delivering health care. The evidence for such is well documented, yet further research is sorely needed.[464] The NINDS Stroke Disparities Planning Panel, convened in June 2002, is developing strategies that include establishing data collection systems and exploring effective community impact programs and instruments in stroke prevention.[465] Alliances with the federal government through the NINDS, nonprofit organizations such as the AHA/American Stroke Association, and medical specialty groups such as the American Academy of Neurology and the Brain Attack Coalition to coordinate, develop, and enhance such strategies are continuing in a more focused fashion. Finally, patients are becoming more effective advocates for stroke prevention through community awareness programs. The NINDS report of the Stroke Progress Review Group serves as a framework for stroke research over this decade and joins the federal government's Healthy People 2010 and the AHA/American Stroke Association strategic goal to significantly reduce stroke and those at risk for stroke by the year 2010.[466]

Recommendations

1. **To prevent underutilization or disparities in the use of therapies recommended in national guidelines, the guideline development and distribution process should recognize and incorporate strategies for increased implementation (Class I, Level of Evidence B).**
2. **It is reasonable that intervention strategies emphasize improved access to care for the aged, underserved, and ethnic populations by addressing economic barriers (eg, coverage for services required), geographic barriers (eg, expanded use of telemedicine), and a multidisciplinary approach to increase patient and healthcare provider compliance with guidelines and practice parameters (Class IIa, Level of Evidence B).**

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