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Guidelines for the Prevention of Stroke in Patients With Stroke or Transient Ischemic Attack: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

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

A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists.

The American Association of Neurological Surgeons and Congress of Neurological Surgeons have reviewed this document and affirm its educational content.

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Abstract**—**The aim of this updated 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 to the implementation of guidelines and their use in high-risk populations. **(*Stroke*. 2011;42:227-276.)**

Key Words: AHA Scientific Statements ■ ischemia ■ transient ischemic attack ■ stroke ■ stroke prevention

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Stroke is a major source of mortality and morbidity in the United States. Survivors of a transient ischemic attack (TIA) or stroke represent a population at increased risk of subsequent stroke. Approximately one quarter of the 795 000 strokes that occur each year are recurrent events. The true prevalence of TIA is difficult to gauge because a large proportion of patients who experience a TIA fail to report it to a healthcare provider.[1] On the basis of epidemiological data defining the determinants of recurrent stroke and the results of clinical trials, it is possible to derive evidence-based recommendations to reduce stroke risk. Notably, much of the existing data come from studies with limited numbers of older adults, women, and diverse ethnic groups, and additional research is needed to confirm the generalizability of the published findings.

The aim of this statement is to provide clinicians with the most up-to-date evidence-based recommendations for 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, pharmacy, and epidemiology/biostatistics. The writing group conducted a comprehensive review and synthesis of the relevant literature. The committee reviewed all compiled reports from computerized searches and conducted additional searches by hand. These searches are available on request. Searches were limited to English-language sources and human subjects. Literature citations were generally restricted to published manuscripts appearing in journals listed in Index Medicus and reflected literature published as of August 1, 2009. Because of the scope and importance of certain ongoing clinical trials and other emerging information, published abstracts were cited for informational purposes when they were the only published information available, but recommendations were not based on abstracts alone. The references selected for this document are exclusively for peer-reviewed papers that are representative but not all-inclusive, with priority given to references with higher levels of evidence. All members of the committee had frequent opportunities to review drafts of the document and reach a consensus with the final recommendations. Recommendations follow the American Heart Association (AHA) and the American College of Cardiology (ACC) methods of classifying the level of certainty of the treatment effect and the class of evidence (Tables 1 and 2).[2]

Although prevention of ischemic 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 or TIA, including subsequent stroke, myocardial infarction (MI), and vascular death. The recommendations in this statement are organized to help the clinician who has arrived at a potential explanation of the cause of ischemic stroke in an individual patient and is embarking on selection of a therapy to reduce the risk of a recurrent event and other vascular outcomes. Our intention is to update these statements every 3 years, with additional interval updates as needed, to reflect the changing state of knowledge on the approaches to prevent a recurrent stroke.

Definition of TIA and Ischemic Stroke Subtypes

A TIA is an important predictor of stroke. The 90-day risk of stroke after a TIA has been reported as being as high as 17%, with the greatest risk apparent in the first week.[3,4] The distinction between TIA and ischemic stroke has become less important in recent years because many of the preventive approaches are applicable to both.[5] TIA and ischemic stroke share pathophysiologic mechanisms, but prognosis may vary depending on severity and cause, and definitions are dependent on the timing and extent of the diagnostic evaluation. By conventional clinical definitions, the presence of focal neurological symptoms or signs lasting <24 hours has been defined as a TIA. With more widespread use of modern imaging techniques for the brain, up to one third of patients with symptoms lasting <24 hours have been found to have an infarction.[5,6] This has led to a new tissue-based definition of TIA: a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction.[5] Notably, the majority of studies described in this guideline used the older definition. Recommendations provided by this guideline are believed to apply to both stroke and TIA regardless of which definition is used.

The classification of ischemic stroke is based on 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.[7] The certainty of classification of the ischemic stroke mechanism is far from ideal and reflects the inadequacy of the diagnostic workup in some cases to visualize the occluded artery or localize the source of the embolism. The setting of specific recommendations for the timing and type of diagnostic workup for patients with TIA or stroke is beyond the scope of these guidelines; at a bare minimum, all stroke patients should have brain imaging with computed tomography or magnetic resonance imaging (MRI) to distinguish between ischemic and hemorrhagic events, and both TIA and ischemic stroke patients should have an evaluation sufficient to exclude high-risk modifiable conditions such as carotid stenosis or atrial fibrillation (AF) as the cause of ischemic symptoms.

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

A. Hypertension

An estimated 72 million Americans have hypertension, defined as a systolic blood pressure (BP) ≥140 mm Hg or diastolic BP ≥90 mm Hg.[8] Overall, there is an association between both systolic and diastolic BP and risk of stroke without a clear threshold even at a systolic BP of 115 mm Hg.[9] Meta-analyses of randomized controlled trials have shown that BP lowering is associated with a 30% to 40% reduction in risk of stroke.[10–12] Risk reduction is greater with larger reductions in BP without clear evidence of a drug class–specific treatment effect.[12] Evidence-based recommen-

Table 1. Applying Classification of Recommendations and Level of Evidence

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT ↓ / SIZE OF TREATMENT EFFECT →	CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/administered	CLASS IIa *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	CLASS IIb *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	CLASS III *Risk ≥ Benefit* Procedure/Treatment should **NOT** be performed/administered **SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL**
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations†	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	is not recommended is not indicated should not is not useful/effective/beneficial may be harmful

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as gender, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use. A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Even though randomized trials are not available, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

†For recommendations (Class I and IIa; Level of Evidence A and B only) regarding the comparative effectiveness of one treatment with respect to another, these words or phrases may be accompanied by the additional terms "in preference to" or "to choose" to indicate the favored intervention. For example, "Treatment A is recommended in preference to Treatment B for …" or "It is reasonable to choose Treatment A over Treatment B for …." Studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

dations for BP screening and treatment of persons with hypertension are summarized in the American Stroke Association (ASA) Guidelines on the Primary Prevention of Ischemic Stroke[13] and are detailed in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7).[14] JNC 7 stresses the importance of lifestyle modifications in the management of hypertension. Lifestyle interventions associated with reduction of BP include weight loss (including salt restriction); the consumption of a diet rich in fruits, vegetables, and low-fat dairy products; regular aerobic physical activity; and limited alcohol consumption.[14]

Although numerous randomized trials and meta-analyses support the importance of treatment of hypertension for prevention of primary cardiovascular disease in general and stroke in particular, few trials directly address the role of BP treatment in secondary prevention among persons with stroke or TIA.[10,15] 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.[16]

A meta-analysis of randomized trials showed that antihypertensive medications reduced the risk of recurrent stroke after stroke or TIA.[15] The meta-analysis included 7 randomized trials performed through 2002: the Dutch TIA trial (atenolol, a β-blocker),[17] Poststroke Antihypertensive Treatment Study (PATS; indapamide, a diuretic),[18] Heart Outcomes Prevention Evaluation (HOPE; ramipril, an angiotensin-converting enzyme inhibitor [ACEI]),[19] and Perindopril Protection Against Recurrent Stroke Study (PROGRESS; perindopril, an ACEI, with or without indapamide),[20] as well as 3 other smaller trials.[21–23] Together these trials included 15 527

Table 2. 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	The 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
Therapeutic recommendations	
Level of Evidence A	Data derived from multiple randomized clinical trials or meta-analyses
Level of Evidence B	Data derived from a single randomized trial or nonrandomized studies
Level of Evidence C	Consensus opinion of experts, case studies, or standard of care
Diagnostic recommendations	
Level of Evidence A	Data derived from multiple prospective cohort studies using a reference standard applied by a masked evaluator
Level of Evidence B	Data derived from a single grade A study, or one or more case-control studies, or studies using a reference standard applied by an unmasked evaluator
Level of Evidence C	Consensus opinion of experts

participants with transient ischemic stroke, TIA, or intracerebral hemorrhage (ICH) randomized from 3 weeks to 14 months after the index event and followed up for 2 to 5 years. No trials tested the effects of nonpharmacological interventions.

Overall, treatment with antihypertensive drugs was associated with significant reductions in recurrent strokes (relative risk [RR], 0.76; 95% confidence interval [CI], 0.63 to 0.92), MI (RR, 0.79; 95% CI, 0.63 to 0.98), and all vascular events (RR, 0.79; 95% CI, 0.66 to 0.95).[15] The impact of BP reduction was similar in the restricted group of subjects with hypertension and when all subjects, including those with and without hypertension, were analyzed. Larger reductions in systolic BP were associated with greater reduction in risk of recurrent stroke. The small number of trials limited comparisons between antihypertensive medications. Significant reductions in recurrent stroke were seen with diuretics alone and in combination with ACEIs but not with β-blockers or ACEIs used alone; nonetheless, statistical power was limited, particularly for the assessment of β-blockers, and calcium channel blockers and angiotensin receptor blockers were not evaluated in any of the included trials.

Since this meta-analysis, 2 additional large-scale randomized trials of antihypertensive medications after stroke have been published: Morbidity and Mortality After Stroke, Eprosartan Compared with Nitrendipine for Secondary Prevention (MOSES),[24] and Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS).[25] In MOSES, 1405 subjects with hypertension and a stroke or TIA within the prior 2 years were randomized to eprosartan (an angiotensin receptor blocker) or nitrendipine (a calcium channel blocker).[24] BP reductions were similar with the 2 agents. Total strokes and TIAs (counting recurrent events) were less frequent among those randomized to eprosartan (incidence density ratio, 0.75; 95% CI, 0.58 to 0.97), and there was a reduction in the risk of primary composite events (death, cardiovascular event, or cerebrovascular event; incidence density ratio, 0.79; 95% CI, 0.66 to 0.96). A reduction in TIAs accounted for most of the benefit in cerebrovascular events, with no significant difference in ischemic strokes, and a more traditional analysis of time to first cerebrovascular event did not show a benefit of eprosartan. In PRoFESS, 20 332 subjects with ischemic stroke were randomly assigned to telmisartan or placebo within 90 days of an ischemic stroke.[25] Telmisartan was not associated with a reduction in recurrent stroke (hazard ratio [HR], 0.95; 95% CI, 0.86 to 1.04) or major cardiovascular events (HR, 0.94; 95% CI, 0.87 to 1.01) during mean 2.5-year follow-up. The BP-lowering arm in PRoFESS was statistically underpowered. Nonadherence to telmisartan and more aggressive treatment with other antihypertensive medications in the placebo group reduced the difference in BP between the treatment groups (systolic BP differed by 5.4 mm Hg at 1 month and 4.0 mm Hg at 1 year) and may have reduced the impact of treatment on stroke recurrence. Taken together, a particular role for angiotensin receptor blockers after stroke has not been confirmed.

Recommendations

1. **BP reduction 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 first 24 hours (*Class I; Level of Evidence A*).**
2. **Because this benefit extends to persons with and without a documented history of hypertension, this recommendation is reasonable for all patients with ischemic stroke or TIA who are considered appropriate for BP reduction (*Class IIa; Level of Evidence B*).**
3. **An absolute target BP level and reduction are uncertain and should be individualized, but benefit has been associated with an average reduction of approximately 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*).**
4. **Several lifestyle modifications have been associated with BP reduction and are a reasonable part of a comprehensive antihypertensive therapy (*Class IIa; Level of Evidence C*). These modifications include salt restriction; weight loss; consumption of a diet rich in fruits, vegetables, and low-fat dairy products; regular**

Table 3. Recommendations for Treatable Vascular Risk Factors

Risk Factor	Recommendations	Class/Level of Evidence*
Hypertension	BP reduction 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 first 24 hours *(Class I; Level of Evidence A).*	Class I; Level A
	Because this benefit extends to persons with and without a documented history of hypertension, this recommendation is reasonable for all patients with ischemic stroke or TIA who are considered appropriate for BP reduction *(Class IIa; Level of Evidence B).*	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 approximately 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).*	Class IIa; Level B
	Several lifestyle modifications have been associated with BP reduction and are a reasonable part of a comprehensive antihypertensive therapy *(Class IIa; Level of Evidence C).* These modifications include salt restriction; weight loss; consumption of a diet rich in fruits, vegetables, and low-fat dairy products; regular aerobic physical activity; and limited alcohol consumption.	Class IIa; Level C
	The optimal drug regimen to achieve the recommended level of reduction is uncertain because direct comparisons between regimens are limited. The available data indicate that diuretics or the combination of diuretics and an ACEI are useful *(Class I; Level of Evidence A).*	Class I; Level A
	The choice of specific drugs and targets should be individualized on the basis of pharmacological properties, mechanism of action, and consideration of specific patient characteristics for which specific agents are probably indicated (eg, extracranial cerebrovascular occlusive disease, renal impairment, cardiac disease, and diabetes) *(Class IIa; Level of Evidence B).* (New recommendation)	Class IIa; Level B
Diabetes	Use of existing guidelines for glycemic control and BP targets in patients with diabetes is recommended for patients who have had a stroke or TIA *(Class I; Level of Evidence B).* (New recommendation)	Class I; Level B
Lipids	Statin therapy with intensive lipid-lowering effects is recommended to reduce risk of stroke and cardiovascular events among patients with ischemic stroke or TIA who have evidence of atherosclerosis, an LDL-C level ≥100 mg/dL, and who are without known CHD *(Class I; Level of Evidence B).*	Class I; Level B
	For patients with atherosclerotic ischemic stroke or TIA and without known CHD, it is reasonable to target a reduction of at least 50% in LDL-C or a target LDL-C level of <70 mg/dL to obtain maximum benefit *(Class IIa; Level of Evidence B).* (New recommendation)	Class IIa; Level B
	Patients with ischemic stroke or TIA with elevated cholesterol or comorbid coronary artery disease should be otherwise managed according to NCEP III guidelines, which include lifestyle modification, dietary guidelines, and medication recommendations *(Class I; Level of Evidence A).*	Class I; Level A
	Patients with ischemic stroke or TIA with low HDL-C may be considered for treatment with niacin or gemfibrozil *(Class IIb; Level of Evidence B).*	Class IIb; Level B

CHD indicates coronary heart disease; HDL, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NCEP III, *The Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Cholesterol in Adults*; and SPARCL, Stroke Prevention by Aggressive Reduction in Cholesterol.

*See Tables 1 and 2 for explanation of class and level of evidence.

aerobic physical activity; and limited alcohol consumption.

5. **The optimal drug regimen to achieve the recommended level of reduction is uncertain because direct comparisons between regimens are limited. The available data indicate that diuretics or the combination of diuretics and an ACEI are useful (*Class I; Level of Evidence A*). The choice of specific drugs and targets should be individualized on the basis of pharmacological properties, mechanism of action, and consideration of specific patient characteristics for which specific agents are probably indicated (eg, extracranial cerebrovascular occlusive disease, renal impairment, cardiac disease, and diabetes) (*Class IIa; Level of Evidence B*).** (New recommendation; Table 3)

B. Diabetes

Diabetes is estimated to affect 8% of the adult population in the United States.[26] Prevalence is 15% to 33% in patients with ischemic stroke.[27–29] Diabetes is a clear risk factor for first stroke,[30–34] but the data supporting diabetes as a risk factor for recurrent stroke are more sparse. Diabetes mellitus appears to be an independent predictor of recurrent stroke in population-based studies,[35] and 9.1% of recurrent strokes have been estimated to be attributable to diabetes.[36,37] Diabetes was a predictor of the presence of multiple lacunar infarcts in 2 stroke cohorts.[38,39]

Normal fasting glucose is defined as glucose <100 mg/dL (5.6 mmol/L), and impaired fasting glucose has been defined as a fasting plasma glucose of 100 mg/dL to 125 mg/dL (5.6 mmol/L to 6.9 mmol/L).[26] A fasting plasma glucose level ≥126 mg/dL (7.0 mmol/L), or A1C ≥6.5%, or a casual plasma glucose >200 mg/dL (11.1 mmol/L) in the setting of symptoms attributable to hyperglycemia meets the threshold for the diagnosis of diabetes.[26] A hemoglobin A_{1c} (HbA_{1c}) level >7% is defined as inadequate control of hyperglycemia. Diet, exercise, oral hypoglycemic drugs, and insulin are recommended to gain glycemic control.[26]

Three major randomized clinical trials of intensive glucose management in persons with diabetes with a history of cardiovascular disease, stroke, or additional vascular risk

factors have all failed to demonstrate a reduction in cardiovascular events or death in the groups receiving intensive glucose therapy. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, 10 251 patients with type 2 diabetes and vascular disease or multiple risk factors were randomly assigned to an intensive treatment program targeting a glycohemoglobin level of <6% versus a standard program with a goal HbA_{1c} level of 7% to 7.9%.[39] The trial was halted after a mean of 3.5 years of follow-up because of an increased risk of death in patients randomized to the intensive treatment program (HR, 1.22; 95% CI, 1.01 to 1.46). There was no significant difference in the rate of nonfatal stroke (HR, 1.06; 95% CI, 0.75 to 1.50; $P=0.72$) or in the primary end point, which was a composite of nonfatal heart attack, nonfatal stroke, and death due to a cardiovascular cause (HR, 0.90; 95% CI, 0.78 to 1.04; $P=0.16$). The Action in Diabetes and Vascular Disease (ADVANCE) trial also failed to show a benefit in secondary prevention of cardiovascular events. In this trial 11 140 patients with type 2 diabetes and a history of macrovascular disease or another risk factor were randomly assigned to intensive glucose control (target ≤6.5%) or standard glucose control (target HbA_{1c} ≤7%).[40] Thirty-two percent of subjects had a history of major macrovascular disease, including 9% with a history of stroke. There was no significant reduction in the occurrence of macrovascular events alone (HR, 0.94; 95% CI, 0.84 to 1.06; $P=0.32$) or nonfatal stroke (3.8% in both treatment arms). In contrast to the ACCORD trial, there were no significant differences in the rate of deaths between the study groups. Finally, the Veterans Affairs Diabetes Trial, consisting of 1791 veterans with type 2 diabetes assigned to intensive blood glucose treatment or standard treatment, found no significant difference between the 2 groups in any component of the primary outcome, which consisted of time to occurrence of a major cardiovascular event, or in the rate of death due to any cause (HR, 1.07; 95% CI, 0.81 to 1.42; $P=0.62$).[40] The results of these trials indicate the glycemic targets should not be lowered to HbA_{1c} <6.5% in patients with a history of cardiovascular disease or the presence of vascular risk factors.

Among patients who have had a stroke or TIA and have diabetes, guidelines have been established for glycemic control[41] and BP management.[14]

Recently the use of pioglitazone has been evaluated in 5238 patients with type 2 diabetes and macrovascular disease. In the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive), there was no significant reduction in the primary end point of all-cause death or cardiovascular events in patients randomly assigned to pioglitazone compared with placebo (HR, 0.78; 95% CI, 0.60 to 1.02).[42,43] Remarkably, among patients who entered PROactive with a history of stroke, pioglitazone therapy was associated with a 47% relative risk reduction in recurrent stroke (HR, 0.53; 95% CI, 0.34 to 0.85), and a 28% relative risk reduction in stroke, MI, or vascular death (HR, 0.72; 95% CI, 0.53 to 1.00). Conversely, rosiglitazone, another of the thiazolidinedione class of drugs, has been linked to the occurrence of heart failure and possible fluid retention, which led to the US Food and Drug Administration (FDA) requiring a boxed warning for this class of drugs in 2007. An increased risk of MI or cardiovascular death with the use of rosiglitazone has been suspected but not conclusively proven. The Insulin Resistance Intervention after Stroke (IRIS) trial is an ongoing study funded by the National Institute for Neurological Disorders and Stroke (NINDS) in which patients with TIA or stroke are randomly assigned to pioglitazone or placebo for a primary outcome of stroke and MI.

Recommendation

1. **Use of existing guidelines for glycemic control and BP targets in patients with diabetes is recommended for patients who have had a stroke or TIA (*Class I; Level of Evidence B*).** (New recommendation; Table 3)

C. Lipids

Large epidemiological studies in which ischemic and hemorrhagic strokes were distinguishable have shown a modest association of elevated total cholesterol or low-density lipoprotein cholesterol (LDL-C) with increased risk of ischemic stroke and a relationship between low LDL-C and greater risk of ICH.[44–46] With regard to other lipid subfractions, recent studies have independently linked higher serum triglyceride levels with occurrence of ischemic stroke[47,48] and large-artery atherosclerotic stroke,[49] as well as associating low high-density lipoprotein cholesterol (HDL-C) with risk of ischemic stroke.[50] A meta-analysis of >90 000 patients included in statin trials showed that the larger the reduction in LDL-C, the greater the reduction in stroke risk.[51] It was unclear, however, up until recently what beneficial role, if any, that statins played in stroke patients without established coronary heart disease (CHD), with regard to vascular risk reduction, particularly prevention of recurrent stroke.[52]

A retrospective subset analysis of 3280 subjects in the Medical Research Council/British Heart Foundation Heart Protection Study (HPS) with a remote (mean, 4.3 years) history of symptomatic ischemic cerebrovascular disease showed that simvastatin therapy yielded a 20% reduction in major vascular events (HR, 0.80; 95% CI, 0.71 to 0.92).[53] For the end point of recurrent strokes, simvastatin exerted no net benefit (HR, 0.98; 95% CI, 0.79 to 1.22), being associated with both a nonsignificant 19% reduction in ischemic stroke and a nonsignificant doubling of hemorrhagic stroke (1.3% simvastatin, 0.7% placebo; HR, 1.91; 95% CI, 0.92 to 3.96; 4.3% simvastatin versus 5.7% placebo; $P<0.0001$). Given the exploratory nature of this post hoc subgroup analysis of HPS, it remained unclear whether stroke patients would definitively benefit from statin treatment to lessen future vascular risk (including recurrent stroke), especially those without known CHD.[54]

In the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study, 4731 persons with stroke or TIA, LDL-C levels between 100 mg/dL and 190 mg/dL, and no known history of CHD were randomly assigned to 80 mg of atorvastatin daily versus placebo.[55] During a median follow-up of 4.9 years, fatal or nonfatal stroke occurred in 11.2% who received atorvastatin versus 13.1% who received placebo (5-year absolute reduction in risk, 2.2%; HR, 0.84; 95% CI, 0.71 to 0.99; $P=0.03$). The

5-year absolute reduction in risk of major cardiovascular events was 3.5% (HR, 0.80; 95% CI, 0.69 to 0.92; $P=0.002$).

Statin therapy was generally well tolerated, with a mildly increased rate of elevated liver enzymes and elevation of creatine kinase but no cases of liver failure nor significant excess in cases of myopathy, myalgia, or rhabdomyolysis.[55] There was a higher incidence of hemorrhagic stroke in the atorvastatin treatment arm (n=55 [2.3%] for active treatment versus n=33 [1.4%] for placebo; HR, 1.66; 95% CI, 1.08 to 2.55) but no difference in the incidence of fatal hemorrhagic stroke between the groups (17 in the atorvastatin group and 18 in the placebo group).[55]

The SPARCL results may understate the magnitude of the true treatment effect in fully compliant patients because of high rates of discontinuation of assigned therapy and crossovers to open-label, nonstudy statin therapy in the placebo group. A prespecified on-treatment analysis of 4162 patients revealed an 18% relative reduction in risk of stroke in the atorvastatin treatment group versus controls (HR, 0.82; 95% CI, 0.69 to 0.98; $P=0.03$).[56]

On the basis of SPARCL, the number needed to treat (NNT) to prevent a first recurrent stroke over 1 year is 258; to prevent 1 nonfatal MI, the NNT is 288. Despite the exclusion of subjects with CHD from the trial, the reduction of various CHD events surpassed that of stroke events, suggesting that asymptomatic CHD is often a comorbid condition in stroke patients even in the absence of a medical history of CHD. SPARCL assessed the benefits and risks associated with achieving a degree of LDL-C lowering and national guideline–recommended nominal targets. Patients with ≥50% reduction in LDL-C had a 35% reduction in combined risk of nonfatal and fatal stroke. Although ischemic strokes were reduced by 37% (HR, 0.63; 95% CI, 0.49 to 0.81), there was no increase in hemorrhagic stroke (HR, 1.02; 95% CI, 0.60 to 1.75). Achieving an LDL-C level of <70 mg/dL was associated with a 28% reduction in risk of stroke (HR, 0.72; 95% CI, 0.59 to 0.89; $P=0.0018$) without an increase in risk of hemorrhagic stroke (HR, 1.28; 95% CI, 0.78 to 2.09; $P=0.3358$), but again the confidence intervals around the latter point estimate were wide.[57] A post hoc analysis of the small number of ICHs in SPARCL (n=55 for active treatment versus n=33 for placebo) found an increased risk of hemorrhagic stroke associated with hemorrhagic stroke as the entry event (HR, 5.65; 95% CI, 2.82 to 11.30, $P<0.001$), male sex (HR, 1.79, 95% CI, 1.13 to 2.84, $P=0.01$), age (10-year increments; HR, 1.42; 95% CI, 1.16 to 1.74, $P=0.001$), and having stage 2 (JNC 7) hypertension at the last study visit (HR, 6.19; 95% CI, 1.47 to 26.11, $P=0.01$).[58]

The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Cholesterol in Adults (Adult Treatment Panel III [ATP III]) is the most comprehensive guide for management of dyslipidemia in persons with or at risk for vascular disease, including stroke.[59,60] The NCEP recommends LDL-C lowering as the primary lipid target. Therapeutic lifestyle modification emphasizes a reduction in saturated fat and cholesterol intake, weight reduction to achieve ideal body weight, and a boost in physical activity. LDL-C goals and cutpoints for implementing 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.[59] When there is a history of CHD and CHD risk equivalents, the target LDL-C goal is <100 mg/dL. Drug therapy options and management of 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.[59]

Other medications used to treat dyslipidemia include niacin, fibrates, and cholesterol absorption inhibitors. These agents can be used by stroke or TIA patients who cannot tolerate statins, but data demonstrating their efficacy for prevention of stroke recurrence are sparse. Niacin has been associated with a reduction in cerebrovascular events,[61] whereas 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 Affairs HDL Intervention Trial (VA-HIT), but the latter result lost significance when adjudicated events alone were analyzed.[62]

Recommendations

1. **Statin therapy with intensive lipid-lowering effects is recommended to reduce risk of stroke and cardiovascular events among patients with ischemic stroke or TIA who have evidence of atherosclerosis, an LDL-C level ≥100 mg/dL, and who are without known CHD (*Class I; Level of Evidence B*).**
2. **For patients with atherosclerotic ischemic stroke or TIA and without known CHD, it is reasonable to target a reduction of at least 50% in LDL-C or a target LDL-C level of <70 mg/dL to obtain maximum benefit[51,57] (*Class IIa; Level of Evidence B*).** (New recommendation)
3. **Patients with ischemic stroke or TIA with elevated cholesterol or comorbid coronary artery disease should be otherwise managed according to the NCEP III guidelines, which include lifestyle modification, dietary guidelines, and medication recommendations[59,60] (*Class I; Level of Evidence A*).**
4. **Patients with ischemic stroke or TIA with low HDL-C may be considered for treatment with niacin or gemfibrozil[61,62] (*Class IIb; Level of Evidence B*)** (Table 3).

D. Cigarette Smoking

There is strong and consistent evidence that cigarette smoking is a major independent risk factor for ischemic stroke.[63–67] There is also growing evidence that exposure to environmental tobacco smoke or passive smoke increases the risk of cardiovascular disease, including stroke.[68–73] All of the data available pertain to primary prevention and are extensively discussed in the AHA/ASA guideline statement on primary prevention of ischemic stroke.[13] These data broadly support smoking cessation and are applicable to people who have already had a stroke or TIA.

Tobacco dependence is a chronic condition for which there are effective behavioral and pharmacotherapeutic treatments (Table 4).[74–80] Current information on how to treat tobacco dependence is available in *Treating Tobacco Use and Dependence: 2008 Update*.[81]

Table 4. Recommendations for Modifiable Behavioral Risk Factors

Risk Factor	Recommendations	Class/Level of Evidence*
Cigarette smoking	Healthcare providers should strongly advise every patient with stroke or TIA who has smoked in the past year to quit *(Class I; Level of Evidence C).*	Class I; Level C
	It is reasonable to avoid environmental (passive) tobacco smoke *(Class IIa; Level of Evidence C).*	Class IIa; Level C
	Counseling, nicotine products, and oral smoking cessation medications are effective for helping smokers to quit *(Class I; Level of Evidence A).*	Class I; Level A
Alcohol consumption	Patients with ischemic stroke or TIA who are heavy drinkers should eliminate or reduce their consumption of alcohol *(Class I; Level of Evidence C).*	Class I; Level C
	Light to moderate levels of alcohol consumption (no more than 2 drinks per day for men and 1 drink per day for nonpregnant women) may be reasonable; nondrinkers should not be counseled to start drinking *(Class IIb; Level of Evidence B).*	Class IIb; Level B
Physical activity	For patients with ischemic stroke or TIA who are capable of engaging in physical activity, at least 30 minutes of moderate-intensity physical exercise, typically defined as vigorous activity sufficient to break a sweat or noticeably raise heart rate, 1 to 3 times a week (eg, walking briskly, using an exercise bicycle) may be considered to reduce risk factors and comorbid conditions that increase the likelihood of recurrent stroke *(Class IIb; Level of Evidence C).*	Class IIb; Level C
	For those individuals with a disability following ischemic stroke, supervision by a healthcare professional, such as a physical therapist or cardiac rehabilitation professional, at least on initiation of an exercise regimen, may be considered *(Class IIb; Level of Evidence C).*	Class IIb; Level C
Metabolic syndrome	At this time, the utility of screening patients for the metabolic syndrome after stroke has not been established *(Class IIb; Level of Evidence C).* (New recommendation)	Class IIb; Level C
	For patients who are screened and classified as having the metabolic syndrome, management should include counseling for lifestyle modification (diet, exercise, and weight loss) for vascular risk reduction *(Class I; Level of Evidence C).* (New recommendation)	Class I; Level C
	Preventive care for patients with the metabolic syndrome should include appropriate treatment for individual components of the syndrome that are also stroke risk factors, particularly dyslipidemia and hypertension *(Class I; Level of Evidence A).* (New recommendation)	Class I; Level A

*See Tables 1 and 2 for explanation of class and level of evidence.

Recommendations

1. **Healthcare providers should strongly advise every patient with stroke or TIA who has smoked in the past year to quit *(Class I; Level of Evidence C)*.**
2. **It is reasonable to avoid environmental (passive) tobacco smoke *(Class IIa; Level of Evidence C)*.**
3. **Counseling, nicotine products, and oral smoking cessation medications are effective for helping smokers quit *(Class I; Level of Evidence A)*** (Table 4).

E. Alcohol Consumption

There is strong evidence that chronic alcoholism and heavy drinking are risk factors for all stroke subtypes.[82–86] Studies have demonstrated an association between alcohol and ischemic 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 from light or moderate consumption and an elevated risk of stroke with heavy consumption of alcohol.[82,83,87–96]

The majority of the data on the risk of alcohol are related to primary prevention, which is discussed extensively in the AHA/ASA guideline statement on primary prevention of ischemic stroke.[13]

Few studies have evaluated the association between alcohol consumption and recurrent stroke. Stroke recurrence was significantly increased among ischemic stroke patients with prior heavy alcohol use in the Northern Manhattan cohort.[89] No studies have demonstrated that reduction of alcohol intake decreases risk of recurrent stroke. The mechanism for reduced risk of ischemic stroke with light to moderate alcohol consumption may be related to an increase in HDL,[97,98] a decrease in platelet aggregation,[99,100] and a lower concentration of plasma fibrinogen.[101,102] The mechanism of risk in heavy alcohol users includes alcohol-induced hypertension, hypercoagulable state, reduced cerebral blood flow, and AF or cardioembolism due to cardiomyopathy.[83,89,103] In addition, alcohol consumption has been associated with insulin resistance and the metabolic syndrome.[104]

It is well established that alcohol can cause dependence and that alcoholism is a major public health problem. When advising a patient about behaviors to reduce risk of recurrent stroke, clinicians should consider the interrelationship between other risk factors and alcohol consumption. Nondrinkers should not be counseled to start drinking. 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.[105]

Recommendations

1. **Patients with ischemic stroke or TIA who are heavy drinkers should eliminate or reduce their consumption of alcohol *(Class I; Level of Evidence C)*.**
2. **Light to moderate levels of alcohol consumption (no more than 2 drinks per day for men and 1 drink per day for women who are not pregnant) may be reasonable; nondrinkers should not be counseled to start drinking *(Class IIb; Level of Evidence B)*** (Table 4).

F. Obesity

Obesity, defined as a body mass index of >30 kg/m^2, has been established as an independent risk factor for CHD and premature mortality.[106–108] The relationship of obesity and weight to stroke is complex but has been studied mostly in relation to primary prevention.[109–118]

Among African-American stroke survivors in the African American Antiplatelet Stroke Prevention Study, cardiovascular risk factor profiles increased with increasing weight,[119] although a relationship with risk of recurrent stroke was not established.

No study has demonstrated that weight reduction reduces risk of stroke recurrence.

G. Physical Activity

Physical activity exerts a beneficial effect on multiple stroke risk factors.[108,120–125] In a recent review of existing studies on physical activity and stroke, moderately or highly active persons had a lower risk of stroke incidence or mortality than did persons with a low level of activity.[121] Moderately active men and women had a 20% lower risk, and those who were highly active had a 27% lower risk. Physical activity tends to lower BP and weight,[125,126] enhance vasodilation,[127] improve glucose tolerance,[128,129] and promote cardiovascular health.[108]

Despite the established benefits of an active lifestyle, sedentary behaviors continue to be the national trends.[130,131] Disability after stroke is substantial,[132] and neurological deficits can predispose an individual to activity intolerance and physical deconditioning.[133] Therefore, 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 a level of sufficient physical activity and exercise to optimize secondary prevention. Several studies support the implementation of aerobic exercise and strength training to improve cardiovascular fitness after stroke.[133–136] Structured programs of therapeutic exercise have been shown to improve mobility, balance, and endurance.[134] Beneficial effects have been demonstrated in different ethnic groups and in both older and younger groups.[137] Although these studies have shown that structured exercise programs are not harmful after stroke, no controlled studies have determined whether therapeutic exercise reduces the incidence of subsequent stroke. Physical activity was not measured in any of the recent international studies of recurrent stroke and risk factors.[138–140]

A few studies have investigated stroke survivors' awareness of exercise as a potential preventive measure. A survey using the 1999 Behavioral Risk Factor Surveillance System (BRFSS) showed that overall, 62.9% of those who reported having been told they had had a stroke were exercising to reduce their risk of heart attack or another stroke. Most importantly, a much larger percentage of stroke survivors who had received advice to exercise reported actually doing so (75.6%) than stroke survivors who did not receive such advice (38.5%). Stroke survivors who reported engaging in more exercise had fewer days when their activity was limited, fewer days when their physical health was not good, and healthier days than survivors who did not report exercising after stroke.[141] This study highlights the importance of provider advice about exercise, diet, and other lifestyle risk factors. It did not investigate the incidence of recurrent stroke.

Studies have shown that encouragement of physical activity and exercise can optimize physical performance, functional capacity, and quality of life after stroke. Recommendations on the benefits of physical activity for stroke survivors are reviewed more extensively in other publications.[108,125,127]

Recommendations

1. **For patients with ischemic stroke or TIA who are capable of engaging in physical activity, at least 30 minutes of moderate-intensity physical exercise, typically defined as vigorous activity sufficient to break a sweat or noticeably raise heart rate, 1 to 3 times a week (eg, walking briskly, using an exercise bicycle) may be considered to reduce the risk factors and comorbid conditions that increase the likelihood of recurrent stroke *(Class IIb; Level of Evidence C)*.**
2. **For those individuals with a disability after ischemic stroke, supervision by a healthcare professional, such as a physical therapist or cardiac rehabilitation professional, at least on initiation of an exercise regimen, may be considered *(Class IIb; Level of Evidence C)*** (Table 4).

H. Metabolic Syndrome

The metabolic syndrome refers to the confluence of several physiological abnormalities that increase risk for vascular disease.[142] Those abnormalities are variably counted in different definitions of the metabolic syndrome and include hypertriglyceridemia, low HDL-C, high BP, and hyperglycemia.[143–145] Research over the past decade has expanded the syndrome to include subclinical inflammation and disorders of thrombosis, fibrinolysis, and endothelial function, and has demonstrated that it may be transmitted genetically.[142,146,147] The metabolic syndrome is commonly diagnosed with criteria proposed by the NCEP Adult Treatment Panel, the World Health Organization, or the AHA (adopted from the NCEP). According to the AHA criteria, the metabolic syndrome is recognized when 3 of the following 5 features are present: increased waist circumference (≥102 cm in men; ≥88 cm in women); elevated triglycerides (≥150 mg/dL); reduced HDL-C (<40 mg/dL in women; <50 mg/dL in men); elevated BP (systolic ≥130 mm Hg or diastolic ≥85 mm Hg); and elevated fasting glucose (≥100 mg/dL).[148] Insulin resistance is usually described as a pathophysiologic state in which a normal amount of insulin produces a subnormal physiological response. Selected consequences include reduced peripheral glucose uptake (into muscle and fat), increased hepatic glucose production, and increased pancreatic insulin secretion (compensatory).[149] Diet, exercise, and use of drugs that enhance insulin sensitivity have also been shown to produce many of these improvements in persons with the metabolic syndrome.[150–155] The metabolic syndrome affects approximately 22% of US adults >20 years of age.[156] Among patients with ischemic stroke, the prevalence is 40% to 50%.[157–159]

Considerable controversy surrounds the metabolic syndrome, largely because of uncertainty regarding its etiology and clinical usefulness. The metabolic syndrome is related to an increased risk for diabetes, cardiovascular disease, and all-cause mortality.[160] It remains uncertain, however, whether

the metabolic syndrome has value in characterizing risk for individual patients; simpler risk stratification instruments, such as the Framingham risk score, perform as well or better in this regard.[157,158] Furthermore, the metabolic syndrome has not been associated with risk of developing cardiovascular disease in the elderly (70 to 82 years of age), limiting its generalizability in a typical stroke population.[161]

The association between the metabolic syndrome and risk for first ischemic stroke has been examined in several recent studies,[158,162–170] all but one of which have confirmed the association.[168] The predictive value of the metabolic syndrome relative to its individual components or simpler composite risk scores has not been adequately examined. One recent analysis supports the view that classification of patients according to the metabolic syndrome does not significantly improve estimation of stroke risk beyond what can be accomplished with traditional risk factors.[170,171]

Only 1 study has examined the association between the metabolic syndrome and risk for stroke recurrence. In the Warfarin Aspirin Symptomatic Intracranial Disease (WASID) trial,[206] participants with the metabolic syndrome were more likely to have a stroke, MI, or vascular death during 1.8 years of follow-up than participants without the metabolic syndrome (HR, 1.6; 95% CI, 1.1 to 2.4; $P=0.0097$). Patients with the metabolic syndrome were also at increased risk for ischemic stroke alone (HR, 1.7; 95% CI, 1.1 to 2.6; $P=0.012$). Adjustment for components of the metabolic syndrome attenuated the association for the composite outcome and stroke alone, rendering the hazards ratio not statistically significant. In addition, in a study of the impact of obesity and metabolic syndrome on risk factors in African American stroke survivors in the African American Antiplatelet Stroke Prevention Study, there were increasing cardiovascular risk factor profiles with increasing weight.[119]

The cardinal features of the metabolic syndrome all improve with weight loss. In particular, weight loss among men and women with the metabolic syndrome or obesity has been shown to improve insulin sensitivity, lower plasma glucose, lower plasma LDL-C, lower plasma triglycerides, raise HDL-C, lower BP, reduce inflammation, improve fibrinolysis, and improve endothelial function.[154,172,173]

No adequately powered randomized clinical trials have tested the effectiveness of weight loss, diet, or exercise for primary prevention of stroke or other vascular clinical events among patients with the metabolic syndrome, although several are under way.[174] No randomized trial of secondary prevention therapy has been conducted among stroke patients with the metabolic syndrome. Until such trials are completed, preventive therapy for patients with the metabolic syndrome should be driven by the same characteristics that guide therapy for patients without the metabolic syndrome, such as BP, age, weight, presence of diabetes, prior symptomatic vascular disease, LDL-C value, HDL-C value, renal function, and family history.

Recommendations

1. **At this time, the utility of screening patients for the metabolic syndrome after stroke has not been established *(Class IIb; Level of Evidence C)*.** (New recommendation)

Table 5. Prospective Trials Comparing Carotid Endarterectomy and Medical Therapy

Trial	Mean Follow-Up	Surgical Arm, %*	Medical Arm, %*
ECST	3 y	2.8	16.8
NASCET	2.7 y	9	26
VACS	11.9 mo	7.9	25.6

ECST indicates European Carotid Surgery Trial; NASCET, North American Symptomatic Carotid Endarterectomy Trial; and VACS, Veterans Affairs Cooperative Study Program.

*Risk of fatal or nonfatal ipsilateral stroke.

2. **For patients who are screened and classified as having the metabolic syndrome, management should include counseling for lifestyle modification (diet, exercise, and weight loss) for vascular risk reduction *(Class I; Level of Evidence C)*.** (New recommendation)
3. **Preventive care for patients with the metabolic syndrome should include appropriate treatment for individual components of the syndrome that are also stroke risk factors, particularly dyslipidemia and hypertension *(Class I; Level of Evidence A)*.** (New recommendation; Table 4)

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

A. Symptomatic Extracranial Carotid Disease

Many clinical trials, randomized and nonrandomized, comparing surgical intervention (carotid endarterectomy [CEA]) plus medical therapy with medical therapy alone, have been performed and published over the past 50 years. In these studies, several of which are described below, best medical therapy did not include aggressive atherosclerotic medical management, including use of HMG-CoA reductase inhibitors (statins), alternative antiplatelet agents such as clopidogrel or combination sustained-release dipyridamole-aspirin, optimized BP control, and smoking cessation therapy. Surgical techniques have evolved as well. Furthermore, in the past few years, carotid angioplasty and stenting (CAS) has emerged as an alternative treatment for stroke prevention in patients deemed at high risk for conventional endarterectomy. Ongoing clinical trials are comparing the efficacy of CAS with the gold standard CEA.

Carotid Endarterectomy

Three major prospective randomized trials have demonstrated the superiority of CEA plus medical therapy over medical therapy alone for symptomatic patients with a high-grade (>70% on angiography) atherosclerotic carotid stenosis.[175–177] The European Carotid Surgery trial (ECST), the North American Symptomatic Carotid Endarterectomy Trial (NASCET), and the Veterans Affairs Cooperative Study Program (VACS) each showed outcomes supporting CEA with moderate-term follow-up (Table 5). Symptomatic patients included those who had both >70% ipsilateral carotid stenosis and TIAs, transient monocular blindness, or nondisabling strokes. Pooled analysis of the 3 largest randomized trials involving >3000 symptomatic patients (VACS, NASCET, and ECST) found a 30-day stroke and death rate of 7.1% in surgically treated patients.[178] Additionally, each

of these major trials showed that for patients with stenoses of <50%, surgical intervention did not offer benefit in terms of reduction of stroke risk.

Controversy exists for patients with symptomatic stenoses in the range of 50% to 69%. Among symptomatic NASCET patients with a stenosis of 50% to 69%, the 5-year rate of any ipsilateral stroke was 15.7% in patients treated surgically compared with 22.2% in those treated medically ($P=0.045$).[179] Thus, to prevent 1 ipsilateral stroke during the 5-year follow-up, 15 patients would have to undergo CEA.[179] The conclusions justify use of CEA only with appropriate case selection when the risk-benefit ratio is favorable for the patient. Patients with a moderate (50% to 69%) stenosis who are at reasonable surgical and anesthetic risk may benefit from an intervention performed by a surgeon with excellent operative skills and a perioperative morbidity and mortality rate of <6%.[180]

Patient Selection Criteria Influencing Surgical Risk

The effect of sex on CEA results has been controversial. Some studies have identified a clear gender effect on perioperative stroke and death rates, though many such series combine both asymptomatic and symptomatic patients. Subgroup analyses of the NASCET trial questions the benefit of CEA in symptomatic women, although women were not well represented and the effect of sex was not overwhelming.[179,181] These data suggest that women are more likely to have less favorable outcomes, including surgical mortality, neurological morbidity, and recurrent carotid stenosis (14% in women versus 3.9% in men, $P=0.008$).[182] It has also been hypothesized that women are more prone to develop recurrent stenosis due to smaller-caliber vessels, particularly with patching, although this remains controversial. Of course, outcome differences in age and sex, along with medical comorbidities, must be considered when deciding whether or not to proceed with carotid revascularization.

With modern perioperative care and anesthetic techniques, the effects of age and controlled medical comorbidities on outcomes following CEA are also ambiguous. Though octogenarians were excluded from the NASCET, case series have documented the safety of CEA in those ≥80 years of age.[183]

Timing of Carotid Revascularization

The timing of CEA after an acute neurological event remains controversial, with experts advocating waiting anywhere from 2 to 6 weeks. The optimal timing for CEA after a minor or nondisabling stroke with stabilized or improving neurological deficits has been a subject of much debate. Those recommending early CEA (within 6 weeks) report excellent results without an increased risk of recurrent stroke. Early intervention may be beneficial in those without initial evidence of intraparenchymal brain hemorrhage. Very early intervention (<3 weeks) may also be performed safely in low-risk patients with TIAs or minor strokes.[184,185] 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 ≥75 years of age and those randomized within 2 weeks after their last ischemic event; benefit fell rapidly with increasing delay.[186]

Carotid Angioplasty and Stenting

CAS has emerged as a therapeutic alternative to CEA for treatment of extracranial carotid artery occlusive disease. Carotid artery angioplasty is a less invasive percutaneous procedure that was first reported by Kerber et al in 1980.[187] The expansion of this technique to include stenting has been under investigation in the United States since 1994.[188] Advances in endovascular technology, including embolic protection devices and improved stent design, have resulted in improvements in the technical aspects of CAS and improved outcomes. Existing available data suggest success and complication rates comparable to CEA.[189,190] The proposed advantages of CAS are its less invasive nature, decreased patient discomfort, and a shorter recuperation period, but its durability remains unproven. Clinical equipoise exists with respect to its comparison with CEA. Currently, CAS is mainly offered to those patients considered *high risk* for open endarterectomy based on the available data from large, multicenter, prospective, randomized studies. High risk is defined as (1) patients with severe comorbidities (class III/IV congestive heart failure, class III/IV angina, left main coronary artery disease, ≥2-vessel coronary artery disease, left ventricular ejection fraction [LVEF] ≤30%, recent MI, severe lung disease, or severe renal disease), or (2) challenging technical or anatomic factors, such as prior neck operation (ie, radical neck dissection) or neck irradiation, postendarterectomy restenosis, surgically inaccessible lesions (ie, above C2, below the clavicle), contralateral carotid occlusion, contralateral vocal cord palsy, or the presence of a tracheostomy. Anatomic high risk has generally been accepted, but several recent studies have called medical high risk into question, given improved anesthetic and critical care management.[191]

Most reported trials have been industry sponsored and evaluated the efficacy of a single stent/neuroprotection system. The first large randomized trial was the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS).[192] In this trial, published in 2001, symptomatic patients suitable for surgery were randomly assigned to either stenting or surgery. Patients unsuitable for surgery were randomized to either stenting or medical management. CAVATAS showed CAS to have comparable outcomes to surgery (30-day rate of stroke or death, 6% in both groups); however, only 55 of the 251 patients in the endovascular group were treated with a stent, and embolic protection devices were not used. Preliminary long-term data showed no difference in the rate of stroke in patients up to 3 years after randomization.

Embolic protection devices have reduced periprocedural stroke rates and are required in procedures reimbursed by the Centers for Medicare and Medicaid. The SAPPHIRE trial (Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy) had the primary objective of comparing the safety and efficacy of CAS with an embolic protection device with CEA in 334 symptomatic and asymptomatic high-risk patients.[193] The perioperative 30-day combined stroke, death, and MI rates were 9.9% for surgery versus 4.4% for stenting. The 1-year primary end point of death, stroke, or MI at 30 days plus ipsilateral stroke or death due to neurological causes within 31 days to 1 year was 20.1% for surgery and 12.0% for stenting ($P=0.05$). Despite the fact

Table 6. Hazard Ratio for CAS Versus CEA in 1321 Symptomatic Patients by Treatment Group

	Periprocedural HR (95% CI)	4-Year Study Period HR (95% CI)
MI	0.45 (0.18–1.11)	…
Any periprocedural stroke or postprocedural ipsilateral stroke	1.74 (1.02–2.98)	1.29 (0.84–1.98)
Any periprocedural stroke, death, or postprocedural ipsilateral stroke	1.89 (1.11–3.21)	1.37 (0.90–2.09)
Any periprocedural stroke, MI, death, or postprocedural ipsilateral stroke	1.26 (0.81–1.96)	1.08 (0.74–1.59)

that these differences primarily represented differences in periprocedural MI rates, the major conclusion from this trial was that CAS was not inferior to CEA in this specific *high-risk* patient cohort. However, only 30% of the study population was symptomatic, and no subset analyses were performed.

Other randomized trials, EVA-3S (Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis) and SPACE (Stent-supported Percutaneous Angioplasty of the Carotid artery versus Endarterectomy), had a noninferiority design comparing CAS to CEA in symptomatic patients.[194,195] Both trials were stopped prematurely for reasons of safety and futility because of a higher 30-day stroke and death rate in the CAS group. In the EVA-3S trial, the 30-day combined stroke and death rate for CAS was 9.6% compared with 3.9% for CEA, with a relative risk of 2.5 for any stroke or death for CAS.[194] Furthermore, at 6 months, the risk for any stroke or death with CAS was 11.7% compared with 6.1% with CEA. Both trials have been criticized for inadequate and nonuniform operator experience, which may have had a negative impact on CAS.

The Carotid Revascularization Endarterectomy versus Stent Trial (CREST) was a prospective, randomized trial comparing the efficacy of CAS with CEA. Results of the CREST lead-in period demonstrated 30-day stroke and death rates for symptomatic patients comparable to CEA.[196] Interim outcomes from the lead-in data, however, showed an increasing risk of stroke and death with increasing age ($P=0.0006$): 1.7% of patients <60 years of age, 1.3% of patients 60 to 69 years of age, 5.3% of patients 70 to 79 years of age, and 12.1% of patients ≥80 years of age.[196] CREST randomized 2502 symptomatic and asymptomatic patients with carotid stenosis (>70% by ultrasonography or >50% by angiography) at 117 centers in the United States and Canada. There was no significant difference in the composite primary outcome (30-day rate of stroke, death, MI, and 4-year ipsilateral stroke) in patients treated with CAS (n=1262) versus CEA (n=1240; 7.2% versus 6.8%; HR for stenting, 1.1; 95% CI, 0.81 to 1.51, $P=0.51$) at a median follow-up of 2.5 years. In symptomatic patients the 4-year rate of stroke or death was 8% with CAS versus 6.4% with CEA (HR, 1.37; $P=0.14$). In the first 30 days, in symptomatic patients the rate of any periprocedural stroke or postprocedural ipsilateral stroke was significantly higher in the CAS group than in the CEA group (5.5±0.9% versus 3.2±0.7%; $P=0.04$). However, in symptomatic patients the rate of MI was higher in the CEA group (2.3±0.6% with CEA versus 1.0±0.4% with CAS; $P=0.08$). Periprocedural and 4-year event hazard ratios are summarized in Table 6. When all patients were analyzed (symptomatic and asymptomatic), there was an interaction between age and treatment efficacy ($P=0.02$). For patients <70 years of age, CAS showed greater efficacy, whereas for patients >70 years, CEA results were superior. There was no difference by sex.[197]

Extracranial-Intracranial Bypass Surgery

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.[198] New efforts are ongoing, using more sensitive imaging, such as $^{15}O_2/H_2{}^{15}O$ positron emission tomography (PET), to select patients with the greatest hemodynamic compromise for a randomized controlled trial using EC/IC bypass surgery (Carotid Occlusion Surgery Study [COSS]).[198–200]

Recommendations

1. **For patients with recent TIA or ischemic stroke within the past 6 months and ipsilateral severe (70% to 99%) carotid artery stenosis, CEA is recommended if the perioperative morbidity and mortality risk is estimated to be <6% *(Class I; Level of Evidence A)*.**
2. **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, sex, and comorbidities, if the perioperative morbidity and mortality risk is estimated to be <6% *(Class I; Level of Evidence B)*.**
3. **When the degree of stenosis is <50%, there is no indication for carotid revascularization by either CEA or CAS *(Class III; Level of Evidence A)*.**
4. **When CEA is indicated for patients with TIA or stroke, surgery within 2 weeks is reasonable rather than delaying surgery if there are no contraindications to early revascularization *(Class IIa; Level of Evidence B)*.**
5. **CAS is indicated as an alternative to CEA for symptomatic patients at average or low risk of complications associated with endovascular intervention when the diameter of the lumen of the internal carotid artery is reduced by >70% by noninvasive imaging or >50% by catheter angiography *(Class I; Level of Evidence B)*.**
6. **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 may be considered *(Class IIb; Level of Evidence B)*.**
7. **CAS in the above setting is reasonable when performed by operators with established periprocedural morbidity and mortality rates of 4% to 6%, similar to those observed in trials of CEA and CAS *(Class IIa; Level of Evidence B)*.**

Table 7. Recommendations for Interventional Approaches to Patients With Stroke Caused by Large-Artery Atherosclerotic Disease

Risk Factor	Recommendations	Class/Level of Evidence*
Symptomatic extracranial carotid disease	For patients with recent TIA or ischemic stroke within the past 6 months and ipsilateral severe (70% to 99%) carotid artery stenosis, CEA is recommended if the perioperative morbidity and mortality risk is estimated to be <6% *(Class I; Level of Evidence A).*	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, sex, and comorbidities if the perioperative morbidity and mortality risk is estimated to be <6% *(Class I; Level of Evidence B).*	Class I; Level B
	When the degree of stenosis is <50%, there is no indication for carotid revascularization by either CEA or CAS *(Class III; Level of Evidence A).*	Class III; Level A
	When CEA is indicated for patients with TIA or stroke, surgery within 2 weeks is reasonable rather than delaying surgery if there are no contraindications to early revascularization *(Class IIa; Level of Evidence B).*	Class IIa; Level B
	CAS is indicated as an alternative to CEA for symptomatic patients at average or low risk of complications associated with endovascular intervention when the diameter of the lumen of the internal carotid artery is reduced by >70% by noninvasive imaging or >50% by catheter angiography *(Class I; Level of Evidence B).*	Class I; 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 may be considered *(Class IIb; Level of Evidence B).*	Class IIb; Level B
	CAS in the above setting is reasonable when performed by operators with established periprocedural morbidity and mortality rates of 4% to 6%, similar to those observed in trials of CEA and CAS *(Class IIa; Level of Evidence B).*	Class IIa; Level B
	For patients with symptomatic extracranial carotid occlusion, EC/IC bypass surgery is not routinely recommended *(Class III; Level of Evidence A).*	Class III; Level A
	Optimal medical therapy, which should include antiplatelet therapy, statin therapy, and risk factor modification, is recommended for all patients with carotid artery stenosis and a TIA or stroke as outlined elsewhere in this guideline *(Class I; Level of Evidence B).* (New recommendation)	Class I; Level B
Extracranial vertebrobasilar disease	Optimal medical therapy, which should include antiplatelet therapy, statin therapy, and risk factor modification, is recommended for all patients with vertebral artery stenosis and a TIA or stroke as outlined elsewhere in this guideline *(Class I; Level of Evidence B).* (New recommendation)	Class I; Level B
	Endovascular and surgical treatment of patients with extracranial vertebral stenosis may be considered when patients are having symptoms despite optimal medical treatment (including antithrombotics, statins, and relevant risk factor control) *(Class IIb; Level of Evidence C).*	Class IIb; Level C
Intracranial atherosclerosis	For patients with a stroke or TIA due to 50% to 99% stenosis of a major intracranial artery, aspirin is recommended in preference to warfarin *(Class I; Level of Evidence B).* Patients in the WASID trial were treated with aspirin 1300 mg/d, but the optimal dose of aspirin in this population has not been determined. On the basis of the data on general safety and efficacy, aspirin doses of 50 mg/d to 325 mg/d are recommended *(Class I; Level of Evidence B).* (New recommendation)	Class I; Level B
	For patients with stroke or TIA due to 50% to 99% stenosis of a major intracranial artery, long-term maintenance of BP <140/90 mm Hg and total cholesterol level <200 mg/dL may be reasonable *(Class IIb; Level of Evidence B).* (New recommendation)	Class IIb; Level B
	For patients with stroke or TIA due to 50% to 99% stenosis of a major intracranial artery, the usefulness of angioplasty and/or stent placement is unknown and is considered investigational *(Class IIb; Level of Evidence C).* (New recommendation).	Class IIb; Level C
	For patients with stroke or TIA due to 50% to 99% stenosis of a major intracranial artery, EC/IC bypass surgery is not recommended *(Class III; Level of Evidence B).* (New recommendation)	Class III; Level B

*See Tables 1 and 2 for explanation of class and level of evidence.

8. **For patients with symptomatic extracranial carotid occlusion, EC/IC bypass surgery is not routinely recommended *(Class III; Level of Evidence A)*.**
9. **Optimal medical therapy, which should include antiplatelet therapy, statin therapy, and risk factor modification, is recommended for all patients with carotid artery stenosis and a TIA or stroke as outlined elsewhere in this guideline *(Class I; Level of Evidence B)*.** (New recommendation; Table 7)

B. Extracranial Vertebrobasilar Disease

Individuals with occlusive disease of the proximal and cervical portions of the vertebral artery are at relatively high risk for posterior or vertebrobasilar circulation ischemia.[201] Indeed, a systematic review suggested that patients with symptomatic vertebral artery stenosis may have a greater recurrent stroke risk in the first 7 days after symptom onset than patients with recently symptomatic carotid stenosis.[202]

Nevertheless, the best medical therapy for these patients is unclear, and the precise role of invasive treatment remains uncertain.

Medical therapy has generally been the mainstay of treatment for this condition because of the high rate of morbidity associated with surgical correction (endarterectomy or reconstruction), but several case series have indicated that revascularization procedures can be performed on patients with extracranial vertebral artery stenosis who are having repeated vertebrobasilar TIAs or strokes despite medical therapy.[203]

To date, the only randomized study to compare outcomes after endovascular treatment versus optimal medical treatment alone among patients with vertebral artery stenosis was CAVATAS.[204] In this small trial, 16 subjects with symptoms in the vascular territory supplied by a stenosed vertebral artery were randomized to receive either endovascular therapy (with medical treatment) or medical management alone and followed for 4.7 years. The primary outcome was the risk of fatal and nonfatal vertebrobasilar territory strokes during follow-up in the 2 treatment groups. Secondary end points included the risk of vertebrobasilar TIA, fatal and nonfatal carotid territory stroke, and fatal MI.[204]

In the endovascular group, 6 patients underwent percutaneous transluminal angioplasty alone and 2 had primary stenting. There was no difference in the 30-day risk of cerebrovascular symptoms between the treatment groups ($P=0.47$), and beyond the initial 30-day periprocedural or postrandomization period, no patient experienced the primary trial outcome.[204] The trial was underpowered, and the relatively long interval (mean, 92 days) between the index event and randomization excluded patients at high risk of recurrence.[204] Larger randomized trials will be necessary to better define evidence-based recommendations for these patients and assess whether vertebral artery stenting is of relevance in patients at higher risk of vertebrobasilar stroke.

Recommendations

1. **Optimal medical therapy, which should include antiplatelet therapy, statin therapy, and risk factor modification, is recommended for all patients with vertebral artery stenosis and a TIA or stroke as outlined elsewhere in this guideline *(Class I; Level of Evidence B)*.** (New recommendation)
2. **Endovascular and surgical treatment of patients with extracranial vertebral stenosis may be considered when patients are having symptoms despite optimal medical treatment (including antithrombotics, statins, and relevant risk factor control) *(Class IIb; Level of Evidence C)*** (Table 7).

C. Intracranial Atherosclerosis

Patients with symptomatic intracranial atherosclerotic stenosis are at high risk of subsequent stroke. The natural history is known predominantly from studies designed to measure the effect of 1 or more treatments, so the natural history of the disease without treatment presumably is even more ominous than it appears in treatment trials. In the EC/IC Bypass Study, 189 patients with stenosis of the middle cerebral artery were randomly assigned to undergo bypass surgery or medical treatment with aspirin.[198,205] The medically treated patients were followed up for a mean of 44 months and had an annual stroke rate of 9.5% and an ipsilateral stroke rate of 7.8%. The surgically treated patients had worse outcomes than those treated medically, so this procedure has largely been abandoned as a treatment for intracranial stenosis.

In the WASID study, 569 patients with stroke or TIA resulting from intracranial stenoses of the middle cerebral artery, intracranial internal carotid artery, intracranial vertebral artery, or basilar artery were randomly assigned to receive aspirin 1300 mg or warfarin (target international normalized ratio [INR] 2.0 to 3.0).[206] This study, which was stopped early due to safety concerns in the warfarin arm, showed no significant difference between groups in terms of the primary end point (ischemic stroke, brain hemorrhage, and vascular death; HR, warfarin versus aspirin, 0.96; 95% CI, 0.68 to 1.37), but there was more bleeding with warfarin. In the first year after the initial event the overall risk of recurrent stroke was 15% and the risk of stroke in the territory of the stenosis was 12%. For patients with a stenosis ≥70%, the 1-year risk of stroke in the territory of the stenotic artery was 19%.[207] Multivariate analysis showed that risk for stroke in the symptomatic vascular territory was highest for a severe stenosis (≥70%), and patients enrolled early (≤17 days) after the initial event. Women also appeared to be at increased risk. Although the type of initial cerebrovascular event (stroke or TIA) was not significantly associated with the risk of stroke in the territory, those presenting with a TIA and an intracranial arterial stenosis of <70% had a low rate of same-territory stroke at 1 year (3%), whereas those presenting with a stroke and an intracranial arterial stenosis ≥70% had a very high rate of a recurrent stroke in the same territory at 1 year (23%). Patients presenting with a TIA and an intracranial arterial stenosis ≥70% and those presenting with a stroke and an intracranial arterial stenosis of 50% to 69% had an intermediate risk.

In the Groupe d'Etude des Stenoses Intra-Craniennes Atheromateuses symptomatiques (GESICA) study,[208] a prospective cohort of 102 patients with symptomatic intracranial arterial stenosis received medical treatment at the discretion of their physicians and were followed up for a mean of 23 months. The risk of subsequent stroke was 13.7%. Notably, 27% of patients had hemodynamic symptoms, defined as those "related to the stenosis that occurred during a change or position (supine to prone), an effort, or the introduction or increase or an antihypertensive medication," and if the stenosis was deemed hemodynamically symptomatic, the subsequent risk of cerebrovascular events increased substantially.

Intracranial angioplasty or stenting or both provide an opportunity to alleviate the stenosis, improve cerebral blood flow, and hopefully reduce the risk of subsequent stroke, particularly in those patients with the risk factors described above. Several published series,[209–218] both retrospective and prospective, suggest that the procedure can be performed with a high degree of technical success. The Wingspan stent (Boston Scientific) is approved for clinical use under a humanitarian device exemption from the FDA for "improving cerebral artery lumen diameter in patients with intracranial atherosclerotic disease, refractory to medical therapy, in intracranial vessels with ≥50% stenosis that are accessible to

the system," but the effectiveness of this approach has not been established.[219,220] In the largest prospective registry involving this stent, 129 patients with symptomatic intracranial stenosis of 70% to 99% were followed.[218] The technical success rate was 97%. The frequency of any stroke, ICH, or death within 30 days or ipsilateral stroke beyond 30 days was 14% at 6 months, and 25% of patients had recurrent stenosis of >50% on follow-up angiography. It therefore remains possible that stenting could be associated with a substantial relative risk reduction, but superiority over medical management has not been proved. It is also not clear that stenting, compared with angioplasty alone, confers any benefit in long-term clinical or angiographic outcome. A randomized clinical trial (Stenting and Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis [SAMMPRIS]) is under way to determine whether intracranial stenting is superior to medical therapy.

Aggressive medical treatment of vascular risk factors for patients with intracranial stenosis may also reduce the risk of subsequent stroke. Although there had been concern that BP lowering might impair cerebral blood flow and thereby increase stroke risk in patients with large-vessel stenosis,[221] post hoc analysis of the WASID trial data suggested that patients with intracranial stenosis had fewer strokes and other vascular events (HR, 0.59; 95% CI, 0.40 to 0.79) when long-term BP was <140/90 mm Hg.[222,223] Patients also had lower subsequent stroke risk (HR, 0.69; 95% CI, 0.48 to 0.99) if the total cholesterol level was <200 mg/dL.[223] This BP target does not necessarily apply in the acute setting.

Recommendations

1. **For patients with stroke or TIA due to 50% to 99% stenosis of a major intracranial artery, aspirin is recommended in preference to warfarin *(Class I; Level of Evidence B)*. Patients in the WASID trial were treated with aspirin 1300 mg/d, but the optimal dose of aspirin in this population has not been determined. On the basis of the data on general safety and efficacy, aspirin doses of 50 mg to 325 mg of aspirin daily are recommended *(Class I; Level of Evidence B)*.** (New recommendation)
2. **For patients with stroke or TIA due to 50% to 99% stenosis of a major intracranial artery, long-term maintenance of BP <140/90 mm Hg and total cholesterol level <200 mg/dL may be reasonable *(Class IIb; Level of Evidence B)*.** (New recommendation)
3. **For patients with stroke or TIA due to 50% to 99% stenosis of a major intracranial artery, the usefulness of angioplasty and/or stent placement is unknown and is considered investigational *(Class IIb; Level of Evidence C)*.** (New recommendation)
4. **For patients with stroke or TIA due to 50% to 99% stenosis of a major intracranial artery, EC-IC bypass surgery is not recommended *(Class III; Level of Evidence B)*.** (New recommendation; Table 7)

III. Medical Treatments for Patients With Cardiogenic Embolism

Cardiogenic cerebral embolism is responsible for approximately 20% of ischemic strokes. There is a history of nonvalvular AF in about one half of cases, valvular heart disease in one fourth, and LV mural thrombus in almost one third.[224]

A. Atrial Fibrillation

Both persistent and paroxysmal AF are potent predictors of first as well as recurrent stroke. In the United States, >75 000 cases of stroke per year are attributed to AF. It has been estimated that AF affects >2 million Americans and becomes more frequent with age, ranking as the leading cardiac arrhythmia in the elderly. Of all AF patients, those with a prior stroke or TIA have the highest relative risk (2.5) of stroke. A number of other clinical features also influence stroke risk in patients with AF; age, recent congestive heart failure, hypertension, diabetes, and prior thromboembolism have all been associated with increased stroke risk in these patients. LV dysfunction, left atrial size, mitral annular calcification (MAC), spontaneous echo contrast, and left atrial thrombus by echocardiography have also been found to be predictors of increased thromboembolic risk.

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.[225] The efficacy of warfarin has been shown to be consistent across studies, with an overall relative risk reduction of 68% (95% CI, 50% to 79%) and an absolute reduction in annual stroke rate from 4.5% for 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 an INR of 2.0 to 3.0. Results from 1 large case-control study[226] and 2 randomized controlled trials[227,228] suggest that the efficacy of oral anticoagulation declines significantly below an INR of 2.0. Unfortunately, a high percentage of AF patients have subtherapeutic levels of anticoagulation and therefore are inadequately protected from stroke. For patients with AF who suffer an ischemic stroke or TIA despite therapeutic anticoagulation, there are no data to indicate that increasing the intensity of anticoagulation provides additional protection against future ischemic events. Higher INRs are associated with increased risk of bleeding.

Evidence supporting the efficacy of aspirin is substantially weaker than for warfarin. A pooled analysis of data from 3 trials resulted in an estimated relative risk reduction of 21% compared with placebo (95% CI, 0 to 38%).[229] The largest aspirin effect was seen in the Stroke Prevention in Atrial Fibrillation (SPAF 1) Trial, which used aspirin 325 mg/d. However, on the basis of results of studies performed in multiple vascular indications, the best balance of the efficacy and safety of aspirin appears to be approximately 75 mg/d to 100 mg/d.[229]

At present there are sparse data regarding the efficacy of alternative antiplatelet agents or combinations for stroke

prevention in AF patients who are allergic to aspirin.[230] The Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE W) evaluated the safety and efficacy of the combination of clopidogrel and aspirin versus warfarin in AF patients with at least 1 risk factor for stroke. This study was stopped prematurely by the safety monitoring committee after 3371 patients were enrolled because of the clear superiority of warfarin (INR 2.0 to 3.0) over the antiplatelet combination (RR, 1.44; 95% CI 1.18 to 1.76; $P=0.0003$).[231]

An additional arm of this study (ACTIVE A) compared aspirin versus clopidogrel plus aspirin in AF patients who were considered "unsuitable for vitamin K antagonist therapy" and reported a reduction in the rate of stroke with clopidogrel plus aspirin. Stroke occurred in 296 patients receiving clopidogrel plus aspirin (2.4% per year) and 408 patients receiving aspirin monotherapy (3.3% per year; RR, 0.72; 95% CI, 0.62 to 0.83; $P<0.001$). Major bleeding occurred in 251 patients receiving clopidogrel plus aspirin (2.0% per year) and in 162 patients receiving aspirin alone (1.3% per year; RR, 1.57; 95% CI, 1.29 to 1.92; $P<0.001$).[232] An analysis of major vascular events combined with major hemorrhage showed no difference between the 2 treatment options (RR, 0.97; 95% CI, 0.89 to 1.06; $P=0.54$). The majority of patients enrolled in this study were deemed to be unsuitable for warfarin based on physician judgment or patient preference; only 23% had increased bleeding risk or inability to comply with monitoring as the reason for enrollment. Therefore, on the basis of uncertainty of how to identify patients who are "unsuitable" for anticoagulation, as well as the lack of benefit in the analysis of vascular events plus major hemorrhage, aspirin remains the treatment of choice for AF patients who have a clear contraindication to vitamin K antagonist therapy but are able to tolerate antiplatelet therapy.

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 (EAFT).[233] 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 or MI compared with anticoagulant therapy alone in AF patients, but there is clear evidence of increased bleeding risk.[234] Therefore, in general, addition of aspirin to anticoagulation therapy should be avoided in AF patients.

The narrow therapeutic margin of warfarin in conjunction with numerous associated food and drug interactions requires frequent INR testing and dose adjustments. These liabilities contribute to significant underutilization of warfarin even in high-risk patients. Therefore, alternative therapies that are easier to use are needed. A number of recent and ongoing trials are evaluating alternative antithrombotic strategies in AF patients, including direct thrombin inhibitors and factor Xa inhibitors. To date, the most successful alternative anticoagulant evaluated is the oral antithrombin dabigatran, which was tested in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) study.[235] RE-LY, a randomized open-label trial of >18 000 AF patients, demonstrated that at a dose of 150 mg twice daily, dabigatran was associated with lower rates of stroke or systemic embolism and rates of major hemorrhage similar to those of dose-adjusted warfarin. The absolute reduction in stroke or systemic embolism was small (1.69% in the warfarin group versus 1.11% in the dabigatran 150 mg twice-daily group; RR, 0.66 [0.53 to 0.82]; $P<0.001$). No significant safety concerns were noted with dabigatran other than a small but statistically significant increase in MI (0.74% per year versus 0.53% per year). No recommendation will be provided for dabigatran in the current version of these guidelines because regulatory evaluation and approval has not yet occurred. However, the availability of a highly effective oral agent without significant drug or food interactions that does not require coagulation monitoring would represent a major advance for this patient population.

An alternative strategy for preventing stroke in AF patients is percutaneous implantation of a device to occlude the left atrial appendage. The PROTECT AF (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) study demonstrated that use of an occlusion device is feasible in AF patients and has the potential to reduce stroke risk.[236] In this open-label trial, 707 warfarin-eligible AF patients were randomly assigned to receive either the WATCHMAN left atrial appendage occlusion device (n=463) or dose-adjusted warfarin (n=244). Forty-five days after successful device implantation, warfarin was discontinued. The primary efficacy rate (combination of stroke, cardiovascular or unexplained death, or systemic embolism) was low in both the device versus the warfarin group and satisfied the noninferiority criteria established for the study. The most common periprocedural complication was serious pericardial effusion in 22 patients (5%; 15 were treated with pericardiocentesis and 7 with surgery). Five patients (1%) had a procedure-related ischemic stroke and 3 had embolization of the device. This approach is likely to have greatest clinical utility for AF patients at high stroke risk who are poor candidates for oral anticoagulation; however, more data are required in these patient populations before a recommendation can be made.

Available data do not show greater efficacy of the acute administration of anticoagulants over antiplatelet agents in the setting of cardioembolic stroke.[237] 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 (eg, AF patients for whom transesophageal echocardiography [TEE] shows a left atrial appendage thrombus).

No data are available to address the question of optimal timing for initiation of oral anticoagulation in a patient with AF after a stroke or TIA. In the EAFT trial,[233] oral anticoagulation was initiated within 14 days of symptom onset in about one half of patients. Patients in this trial had minor strokes or TIAs and AF. However, for patients with large infarcts, extensive hemorrhagic transformation, or uncontrolled hypertension, further delays may be appropriate.

For patients with AF who suffer an ischemic stroke or TIA despite therapeutic anticoagulation, there are no data to

indicate that either increasing the intensity of anticoagulation or adding an antiplatelet agent provides additional protection against future ischemic events. In addition, both of these strategies are associated with an increase in bleeding risk. For example, in the Stroke Prevention using an ORal Thrombin inhibitor in Atrial Fibrillation study (SPORTIF), AF patients with prior stroke or TIA who were treated with the combination of aspirin and warfarin were at considerably higher risk of major bleeding (1.5% per year with warfarin and 4.95% per year with warfarin plus aspirin; $P=0.004$) and no reduction in ischemic events.[234] High INR values are clearly associated with increased risk of hemorrhage; risk of ICH increases dramatically at INR values >4.0.[229]

Patients with AF and prior stroke or TIA have increased stroke risk when oral anticoagulant therapy is temporarily interrupted (typically for surgical procedures). The issue of whether to use bridging therapy with intravenous heparin or a low-molecular-weight heparin (LMWH) in these situations is complex and has been recently reviewed.[238] In general, bridging anticoagulation is recommended for AF patients assessed to be at particularly high risk (stroke or TIA within 3 months, $CHADS_2$ score of 5 or 6, or mechanical or rheumatic valve disease). The preferred method for bridging is typically LMWH administered in an outpatient setting in full treatment doses (as opposed to low prophylactic doses).[238]

About one quarter of patients who present with AF and ischemic stroke will be found to have other potential causes of the stroke, such as carotid stenosis.[239] For these patients, treatment decisions should focus on the presumed most likely stroke etiology. In many cases it will be appropriate to initiate anticoagulation because of the AF, as well as an additional therapy (such as CEA).

Recommendations

1. **For patients with ischemic stroke or TIA with paroxysmal (intermittent) or permanent AF, anticoagulation with a vitamin K antagonist (target INR 2.5; range, 2.0 to 3.0) is recommended *(Class I; Level of Evidence A)*.**
2. **For patients unable to take oral anticoagulants, aspirin alone *(Class I; Level of Evidence A)* is recommended. The combination of clopidogrel plus aspirin carries a risk of bleeding similar to that of warfarin and therefore is not recommended for patients with a hemorrhagic contraindication to warfarin *(Class III; Level of Evidence B)*.** (New recommendation)
3. **For patients with AF at high risk for stroke (stroke or TIA within 3 months, $CHADS_2$ score of 5 or 6, mechanical or rheumatic valve disease) who require temporary interruption of oral anticoagulation, bridging therapy with an LMWH administered subcutaneously is reasonable *(Class IIa; Level of Evidence C)*.** (New recommendation; Table 8)

B. Acute MI and LV Thrombus

Without acute reperfusion therapy, intracardiac 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.[224,240–243] In the absence of anticoagulant therapy, clinically evident cerebral infarction occurs in approximately 10% of patients with LV thrombus following MI.[241] Thrombolytic therapy may result in a lower incidence of LV thrombus formation,[242,244,245] but the magnitude of risk reduction is controversial.[246] The remainder of ventricular mural thrombi occur in patients with chronic ventricular dysfunction resulting from coronary disease, hypertension, or other forms of dilated cardiomyopathy, who face a persistent risk of stroke and systemic embolism whether or not AF is documented.

Over the past 20 years, 3 large trials involving patients with acute inferior and anterior MIs concluded that initial treatment with heparin followed by administration of warfarin reduced the occurrence of cerebral embolism from 3% to 1% compared with no anticoagulation. Differences were statistically significant in 2 of the 3 studies, with a concordant trend in the third.[242,244,245] Four randomized studies involving patients with acute MI have addressed the relationship of echocardiographically detected LV thrombus and cerebral embolism.[247–250] In aggregate, thrombus formation was reduced by >50% with anticoagulation; individually, however, each trial had insufficient sample size to detect significant differences in embolism.

On the basis of available clinical trial results, Class I recommendations have been promulgated for oral anticoagulant treatment of patients with echocardiographically detected LV thrombi after anterior MI. There is no consensus regarding the duration of anticoagulant treatment.[251] The persistence of stroke risk for several months after infarction in these patients is suggested by aggregate results of a number of studies, but alternative antithrombotic regimens have not been systematically evaluated. The risk of thromboembolism seems to decrease after the first 3 months, and in patients with chronic ventricular aneurysm, the risk of embolism is comparatively low, even though intracardiac thrombi occur frequently in this condition.

Recommendation

1. **Patients with ischemic stroke or TIA in the setting of acute MI complicated by LV mural thrombus formation identified by echocardiography or another cardiac imaging technique should be treated with oral anticoagulation (target INR 2.5, range 2.0 to 3.0) for at least 3 months *(Class I; Level of Evidence B)*** (Table 8).

C. Cardiomyopathy

Although numeric estimates are difficult to verify, approximately 10% of patients with ischemic stroke have an LVEF ≤30%.[252] The first randomized trial to study warfarin in patients with heart failure in the era of modern heart failure management, the Warfarin and Antiplatelet Therapy in Chronic Heart Failure trial (WATCH) was terminated without adequate power to define the effect of warfarin compared with aspirin or clopidogrel on stroke.[253]

Similarly, no adequately powered randomized studies of aspirin or other platelet inhibitor drugs have been carried out in patients with chronic heart failure. An ongoing trial, Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF), is designed to compare the efficacy of warfarin (INR 2.5 to 3.0) and aspirin (325 mg daily) with regard to the composite end point of death or stroke (ischemic or hemor-

Table 8. Recommendations for Patients With Cardioembolic Stroke Types

Risk Factor	Recommendations	Class/Level of Evidence*
Atrial fibrillation	For patients with ischemic stroke or TIA with paroxysmal (intermittent) or permanent AF, anticoagulation with a vitamin K antagonist (target INR 2.5; range, 2.0 to 3.0) is recommended *(Class I; Level of Evidence A).*	Class I; Level A
	For patients unable to take oral anticoagulants, aspirin alone *(Class I; Level of Evidence A)* is recommended.	Class I; Level A
	The combination of clopidogrel plus aspirin carries a risk of bleeding similar to that of warfarin and therefore is not recommended for patients with a hemorrhagic contraindication to warfarin *(Class III; Level of Evidence B).* (New recommendation)	Class III; Level B
	For patients with AF at high risk for stroke (stroke or TIA within 3 months, $CHADS_2$ score of 5 or 6, mechanical valve or rheumatic valve disease) who require temporary interruption of oral anticoagulation, bridging therapy with an LMWH administered subcutaneously is reasonable *(Class IIa; Level of Evidence C).* (New recommendation)	Class IIa; Level C
Acute MI and LV thrombus	Patients with ischemic stroke or TIA in the setting of acute MI complicated by LV mural thrombus formation identified by echocardiography or another cardiac imaging technique should be treated with oral anticoagulation (target INR 2.5; range 2.0 to 3.0) for at least 3 months *(Class I; Level of Evidence B).*	Class I; Level B
Cardiomyopathy	In patients with prior stroke or transient cerebral ischemic attack in sinus rhythm who have cardiomyopathy characterized by systolic dysfunction (LVEF ≤35%), the benefit of warfarin has not been established *(Class IIb; Level of Evidence B).* (New recommendation)	Class IIb; Level B
	Warfarin (INR 2.0 to 3.0), aspirin (81 mg daily), clopidogrel (75 mg daily), or the combination of aspirin (25 mg twice daily) plus extended-release dipyridamole (200 mg twice daily) may be considered to prevent recurrent ischemic events in patients with previous ischemic stroke or TIA and cardiomyopathy *(Class IIb; Level of Evidence B).*	Class IIb; Level B
Native valvular heart 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 an INR target range of 2.5 (range, 2.0 to 3.0) *(Class IIa; Level of Evidence C).*	Class IIa; Level C
	To avoid additional bleeding risk, antiplatelet agents should not be routinely added to warfarin *(Class III; Level of Evidence C).*	Class III; Level C
	For patients with ischemic stroke or TIA and native aortic or nonrheumatic mitral valve disease who do not have AF, antiplatelet therapy may be reasonable *(Class IIb; Level of Evidence C).*	Class IIb; Level C
	For patients with ischemic stroke or TIA and mitral annular calcification, antiplatelet therapy may be considered *(Class IIb; Level of Evidence C).*	Class IIb; Level C
	For patients with MVP who have ischemic stroke or TIA, long-term antiplatelet therapy may be considered *(Class IIb; Level of Evidence C).*	Class IIb; Level C
Prosthetic heart valves	For patients with ischemic stroke or TIA who have mechanical prosthetic heart valves, warfarin is recommended with an INR target of 3.0 (range, 2.5 to 3.5) *(Class I; Level of Evidence B).*	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 mg/d 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) is reasonable if the patient is not at high bleeding risk (eg, history of hemorrhage, varices, or other known vascular anomalies conveying increased risk of hemorrhage, coagulopathy) *(Class IIa; Level of Evidence B).*	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 to 3.0) may be considered *(Class IIb; Level of Evidence C).*	Class IIb, Level C

LV indicates left ventricular; and MVP, mitral valve prolapse.
*See Tables 1 and 2 for explanation of class and level of evidence.

rhagic) among patients with LVEF ≤35% without documented AF, mechanical prosthetic heart valve, or other indication for anticoagulant therapy.[254] The trial is not designed to address questions of which antithrombotic strategy is superior for prevention of initial or recurrent stroke in this population,[255] whether clopidogrel or another thienopyridine platelet inhibitor provides results comparable or superior to aspirin, or whether combination therapy with a platelet inhibitor plus an anticoagulant is superior to treatment with either agent alone.

Recommendations

1. **In patients with prior stroke or transient cerebral ischemic attack in sinus rhythm who have cardiomyopathy characterized by systolic dysfunction (LVEF ≤35%), the benefit of warfarin has not been established *(Class IIb; Level of Evidence B).*** (New recommendation)
2. **Warfarin (INR 2.0 to 3.0), aspirin (81 mg daily), clopidogrel (75 mg daily), or the combination of aspirin (25 mg twice daily) plus extended-release dipyridamole (200 mg twice daily) may be considered to prevent recurrent ischemic events in patients with previous ischemic stroke or TIA and cardiomyopathy *(Class IIb; Level of Evidence B)*** (Table 8).

D. Native 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.

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.[256–259] Between 60% and 65% of these recurrences develop within the first year,[256,257] most within 6 months. Mitral valvuloplasty does not seem to eliminate the risk of thromboembolism[260,261]; 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.[262–265] Long-term anticoagulant therapy in patients with mitral stenosis who had left atrial thrombus identified by TEE has been shown to result in the disappearance of the left atrial thrombus.[266] The ACC/AHA Task Force on Practice Guidelines has published guidelines for the management of patients with valvular heart disease.[267]

The safety and efficacy of combining antiplatelet and anticoagulant therapy have not been evaluated in patients with rheumatic valve disease. On the basis of extrapolation from similar patient populations, it is clear that combination therapy increases bleeding risk.[268,269]

Mitral Valve Prolapse

Mitral valve prolapse (MVP) is the most common form of valve disease in adults.[270] Although generally innocuous, it is sometimes symptomatic, and thromboembolic phenomena have been reported in patients with MVP in whom no other source could be found.[271–275] However, more recent population-based prospective studies, such as the Framingham Heart Study, have failed to clearly identify an increased risk of stroke.[276,277]

No randomized trials have addressed the efficacy of antithrombotic therapies for this specific subgroup of stroke or TIA patients.

Mitral Annular Calcification

MAC,[278] which is predominantly found in women, is sometimes associated with significant mitral regurgitation and is an uncommon nonrheumatic cause of mitral stenosis. Although the incidence of systemic and cerebral embolism is not clear,[279–284] 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.[280,282] Aside from the risk of thromboembolism, spicules of fibrocalcific material may embolize from the calcified mitral annulus.[279,281,283] The relative frequencies of calcific and thrombotic embolism are unknown.[279,284]

There has been uncertainty whether MAC is an independent risk factor for stroke. In a recent cohort study of American Indians, MAC was found to be a strong risk factor for stroke, even after adjustment for other risk factors.[273] A cross-sectional study of patients referred for TEE for evaluation of cerebral ischemia found that MAC was significantly associated with proximal and distal complex aortic atheroma.[285]

There are no relevant data comparing the safety and efficacy of anticoagulant therapy versus antiplatelet therapy in patients with TIA or stroke.

Aortic Valve Disease

Clinically detectable systemic embolism in isolated aortic valve disease is increasingly recognized as due to microthrombi or calcific emboli.[286] In the absence of associated mitral valve disease or AF, systemic embolism in patients with aortic valve disease is uncommon. No randomized trials of selected patients with stroke and aortic valve disease exist, so recommendations are based on the evidence from larger antiplatelet trials of stroke and TIA patients.

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 an INR target range of 2.5 (range, 2.0 to 3.0) *(Class IIa; Level of Evidence C)*.**
2. **To avoid additional bleeding risk, antiplatelet agents should not be routinely added to warfarin *(Class III; Level of Evidence C)*.**
3. **For patients with ischemic stroke or TIA and native aortic or nonrheumatic mitral valve disease who do not have AF, antiplatelet therapy may be reasonable *(Class IIb; Level of Evidence C)*.**
4. **For patients with ischemic stroke or TIA and mitral annular calcification, antiplatelet therapy may be considered *(Class IIb; Level of Evidence C)*.**
5. **For patients with MVP who have ischemic stroke or TIAs, long-term antiplatelet therapy may be considered *(Class IIb; Level of Evidence C)*** (Table 8).

E. Prosthetic Heart Valves

Evidence that oral anticoagulants are effective in preventing thromboembolism in patients with prosthetic heart valves comes from a trial that randomized patients to either 6 months with warfarin of uncertain intensity versus 2 different aspirin-containing platelet-inhibitor drug regimens.[287] Thromboembolic complications occurred significantly more frequently in the antiplatelet groups than in the anticoagulation group (event rates were 8% to 10% per patient-year in the antiplatelet groups versus 2% per year in the anticoagulation group). The incidence of bleeding was higher 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 in patients with prosthetic heart valves.[288,289] 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.[290] This combination of low-dose aspirin and high-intensity warfarin was associated with a 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.

Bioprosthetic valves are associated with a lower rate of thromboembolism than mechanical valves. In patients with bioprosthetic valves who have an otherwise unexplained ischemic stroke or TIA, oral anticoagulation (INR 2.0 to 3.0) is suggested.

Recommendations

1. **For patients with ischemic stroke or TIA who have mechanical prosthetic heart valves, warfarin is 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 mg/d 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) is reasonable if the patient is not at high bleeding risk (eg, history of hemorrhage, varices, or other known vascular anomalies conveying increased risk of hemorrhage, coagulopathy) (*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)*** (Table 8).

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

A. Antiplatelet Agents

Four antiplatelet drugs have been approved by the FDA for prevention of vascular events among patients with a stroke or TIA: aspirin, combination aspirin/dipyridamole, clopidogrel, and ticlopidine. On average, these agents reduce the relative risk of stroke, MI, or death by about 22%,[291] but important differences exist between agents that have direct implications for therapeutic selection.

Aspirin

Aspirin prevents stroke among patients with a recent stroke or TIA.[233,292–294] In a meta-regression analysis of placebo-controlled trials of aspirin therapy for secondary stroke prevention, the relative risk reduction for any type of stroke (hemorrhagic or ischemic) was estimated at 15% (95% CI, 6% to 23%).[295] The magnitude of the benefit is similar for doses ranging from 50 mg to 1500 mg,[233,291,292,294–296] although the data for doses <75 mg are limited.[291] In contrast, toxicity does vary by dose; the principal toxicity of aspirin is gastrointestinal hemorrhage, and higher doses of aspirin are associated with greater risk.[292,294] For patients who use low-dose aspirin (≤325 mg) for prolonged intervals, the annual risk of serious gastrointestinal hemorrhage is about 0.4%, which is 2.5 times the risk for nonusers.[292,294,297,298] Aspirin therapy is associated with an increased risk of hemorrhagic stroke that is smaller than the risk for ischemic stroke, resulting in a net benefit.[299]

Ticlopidine

Ticlopidine is a platelet adenosine diphosphate (ADP) receptor antagonist that has been evaluated in 3 randomized trials of patients with cerebrovascular disease.[300–302] 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.[302] After a mean follow-up duration of 2 years, patients assigned to ticlopidine therapy had fewer outcomes per year (11.3% compared with 14.8%; relative risk reduction [RRR], 23%; 95% CI, 1% to 41%). 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.[301] After 3 years, patients assigned to ticlopidine had a lower rate for the primary outcome of stroke or death (17% compared with 19%; RRR, 12%; 95% CI, 2% to 26%; $P=0.048$ by Kaplan-Meier estimates). Finally, the African American Antiplatelet Stroke Prevention Study enrolled 1809 black patients with recent noncardioembolic ischemic stroke who were allocated to receive ticlopidine 250 mg twice a day or aspirin 325 mg twice a day.[300] The study found no difference in risk of the combination of stroke, MI, or vascular death at 2 years. Side effects of ticlopidine include diarrhea and rash. Rates of gastrointestinal bleeding are comparable or less than with aspirin. Neutropenia occurred in <2% of patients treated with ticlopidine in CATS and TASS; however, it was severe in about 1% and was almost always reversible with discontinuation. Thrombotic thrombocytopenic purpura has also been described.[303]

Clopidogrel

Another platelet ADP receptor antagonist, clopidogrel, became available after aspirin, combination aspirin/dipyridamole, and ticlopidine were each shown to be effective for secondary stroke prevention. As a single agent, clopidogrel has been tested for secondary stroke prevention in 2 trials, one comparing it with aspirin[298] alone and one comparing it with combination aspirin/dipyridamole.[304] In each trial, rates of primary outcomes were similar between the treatment groups. Clopidogrel has not been compared with placebo for secondary stroke prevention.[305]

Clopidogrel was compared with aspirin alone in the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial.[298] More than 19 000 patients with stroke, MI, or peripheral vascular disease were randomly assigned to aspirin 325 mg/d or clopidogrel 75 mg/d. The annual rate of ischemic stroke, MI, or vascular death was 5.32% among patients assigned to clopidogrel compared with 5.83% among patients assigned to aspirin (RRR, 8.7%; 95% CI, 0.3 to 16.5; $P=0.043$). Notably, in a subgroup analysis of patients who entered CAPRIE after a stroke, the effect of clopidogrel was smaller and did not reach statistical significance. In this subgroup the annual rate of stroke, MI, or vascular death was 7.15% in the clopidogrel group compared with 7.71% in the aspirin group (RRR, 7.3%; 95% CI, −6% to 19%; $P=0.26$). CAPRIE was not designed to determine if clopidogrel was equivalent to aspirin among stroke patients.

Clopidogrel was compared with combination aspirin and extended-release dipyridamole in the PRoFESS trial, which

was designed as a noninferiority study. Among 20 332 patients with ischemic stroke who were followed for a mean of 2.5 years, recurrent stroke occurred among 9.0% of participants assigned to aspirin/dipyridamole compared with 8.8% assigned to clopidogrel (HR, 1.01; 95% CI, 0.92 to 1.11). Because the upper bound of the confidence interval crossed the noninferiority margin (HR, 1.075), the investigators concluded that the results failed to show that aspirin/dipyridamole was not inferior to clopidogrel.

Overall the safety of clopidogrel is comparable to that of aspirin with only minor differences.[298] As with ticlopidine, diarrhea and rash are more frequent than with aspirin, but aside from diarrhea, gastrointestinal symptoms and hemorrhages are less frequent. Neutropenia did not occur more frequently among patients assigned to clopidogrel, compared with aspirin or placebo, in published trials,[298,306] but a few cases of thrombotic thrombocytopenic purpura have been described.[303] Recently, evidence has emerged that proton pump inhibitors (PPIs), such as esomeprazole, reduce the effectiveness of clopidogrel.[307] Coadministration of clopidogrel with a PPI may lead to increased risk for major cardiovascular events, including stroke and MI. When antacid therapy is required in a patient on clopidogrel, an H2 blocker may be preferable to a PPI if the PPI is metabolized at the CYP2C19 P-450 cytochrome site.[308] In addition, functional genetic variants in CYP genes can affect the effectiveness of platelet inhibition in patients taking clopidogrel. Carriers of at least 1 CYP2C19 reduced-function allele had a relative reduction of 32% in plasma exposure to the active metabolite of clopidogrel compared with noncarriers ($P<0.001$).[309]

Dipyridamole and Aspirin

Dipyridamole inhibits phosphodiesterase and augments prostacyclin-related platelet aggregation inhibition. The effect of dipyridamole combined with aspirin among patients with TIA or stroke has been examined in 4 large randomized clinical trials. Together these trials indicate that the combination is at least as effective as aspirin alone for secondary stroke prevention but less well tolerated by patients.

The first of the large trials was the European Stroke Prevention Study (ESPS-1),[310] which randomly assigned 2500 patients to placebo or the combination of 325 mg aspirin plus 75 mg immediate-release dipyridamole 3 times a day. After 24 months the rate of stroke or death was 16% among patients assigned to aspirin/dipyridamole compared with 25% among patients assigned to placebo (RRR, 33%; $P<0.001$).

The next large study was ESPS-2, which randomized 6602 patients with prior stroke or TIA in a factorial design to 4 groups: (1) aspirin 25 mg twice a day plus extended-release dipyridamole 200 mg twice a day, (2) aspirin 25 mg twice daily, (3) extended-release dipyridamole alone, and (4) placebo.[311] Compared with placebo, risk of stroke was reduced by 18% with aspirin ($P=0.013$), 16% with dipyridamole ($P=0.039$), and 37% with the combination ($P<0.001$). Compared with aspirin alone, combination therapy reduced the risk of stroke by 23% ($P=0.006$) and stroke or death by 13% ($P=0.056$). Bleeding was not significantly increased by dipyridamole, but headache and gastrointestinal symptoms were more common among the combination group. The interpretation of this study was complicated by problems in data quality reported by the investigators, a relatively low dose of aspirin, and the choice of a placebo at a time when aspirin was standard therapy in many countries.

The third large trial, European/Australasian Stroke Prevention in Reversible Ischemia Trial (ESPRIT), used a prospective, randomized, open-label, blinded end point evaluation design to compare aspirin alone with aspirin plus dipyridamole for prevention of stroke, MI, vascular death, or major bleeding among men and women with a TIA or ischemic stroke within 6 months.[312] Although the dose of aspirin could vary at the discretion of the treating physician from 30 mg to 325 mg daily, the mean dose in each group was 75 mg. Among patients assigned to dipyridamole, 83% took the extended-release form and the rest took the immediate-release form. After 3.5 years the primary end point was observed in 13% of patients assigned to combination therapy compared with 16% among those assigned to aspirin alone (HR, 0.80; 95% CI, 0.66 to 0.98; absolute risk reduction [ARR], 1.0% per year; 95% CI, 0.1 to 1.8). In this open-label trial, bias in reporting of potential outcome events might have occurred if either patients or field researchers differentially reported potential vascular events to the coordinating center. The unexpected finding of a reduced rate of major bleeding in the combination group (35 compared with 53 events) may be an indication of this bias. Finally, the investigators did not report postrandomization risk factor management, which, if differential, could partially explain differing outcome rates.

The fourth trial was the PRoFESS study described above,[304] which showed no difference in stroke recurrence rates among patients assigned to clopidogrel compared with patients assigned to combination dipyridamole and aspirin. Major hemorrhagic events were more common among patients assigned to aspirin and extended-release dipyridamole (4.1% compared with 3.6%) but did not meet statistical significance. Adverse events leading to drug discontinuation (16.4% compared with 10.6%) were more common among patients assigned to aspirin and extended-release dipyridamole. The combination therapy was shown to be less well tolerated than single antiplatelet therapy.

Combination of Clopidogrel and Aspirin

The effectiveness of clopidogrel 75 mg plus aspirin 75 mg, compared with clopidogrel 75 mg alone for prevention of vascular events among patients with a recent TIA or ischemic stroke, was examined in the Management of Atherothrombosis with Clopidogrel in High-Risk Patients with Recent Transient Ischemic Attacks or Ischemic Stroke (MATCH) trial.[313] A total of 7599 patients were followed for 3.5 years for the occurrence of the primary composite outcome of ischemic stroke, MI, vascular death, or rehospitalization for any central or peripheral ischemic event. There was no significant benefit of combination therapy compared with clopidogrel alone in reducing the primary outcome or any of 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, the

results of MATCH do not suggest a similar risk-benefit ratio for patients with stroke and TIA who start therapy beyond the acute period.

Combination clopidogrel and aspirin has been compared with aspirin alone in 2 secondary prevention trials: 1 small[314] and 1 large.[315] Neither demonstrated a benefit from combination therapy. The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial[315] enrolled 15 603 patients with clinically evident cardiovascular disease or multiple risk factors. After a median of 28 months the primary outcome (MI, stroke, or death due to cardiovascular causes) was observed in 6.8% of patients assigned to combination therapy compared with 7.3% assigned to aspirin (RR, 0.93; 95% CI, 0.83 to 1.05; $P=0.22$). An analysis among the subgroup of patients who entered after a stroke showed increased bleeding risk but no statistically significant benefit of combination therapy compared with aspirin alone. The Fast Assessment of Stroke and Transient ischemic attack to prevent Early Recurrence (FASTER) trial[314] was designed to test the effectiveness of combination therapy compared with aspirin alone for preventing stroke among patients with a TIA or minor stroke within the previous 24 hours. The trial was stopped early because of slow recruitment. Results were inconclusive.

Selection of Oral Antiplatelet Therapy

The evidence described above indicates that aspirin, ticlopidine, and the combination of aspirin and dipyridamole are each effective for secondary stroke prevention. No studies have compared clopidogrel with placebo, and studies comparing it with other antiplatelet agents have not clearly established that it is superior to or even equivalent to any one of them. Observation of the survival curves from CAPRIE and PRoFESS indicate that it is probably as effective as aspirin and combination aspirin/dipyridamole, respectively.

Selection among these 4 agents should be based on relative effectiveness, safety, cost, patient characteristics, and patient preference. The combination of aspirin and dipyridamole may be more effective than aspirin alone for prevention of recurrent stroke[311] and the combination of stroke, MI, death, or major bleeding.[312] On average, compared with aspirin alone, the combination may prevent 1 event among 100 patients treated for 1 year.[312] Ticlopidine may be more effective than aspirin for secondary prevention,[301] but safety concerns limit its clinical value.

Risk for gastrointestinal hemorrhage or other major hemorrhage may be greater for aspirin or combination aspirin/dipyridamole than for clopidogrel.[298,304] The difference is small, however, amounting to 1 major hemorrhage event per 500 patient-years.[304] The risk appears to be similar for aspirin at doses of 50 mg to 75 mg compared with the combination of aspirin/dipyridamole. However, the combination of aspirin/dipyridamole is less well tolerated than either aspirin or clopidogrel, primarily because of headache. Ticlopidine is associated with thrombotic thrombocytopenic purpura and should be used only cautiously in patients who cannot tolerate other agents.

In terms of cost, aspirin is by far the least expensive agent. The cost of aspirin at acquisition is at least 20 times less than any of the other 3 options.

Patient characteristics that may affect choice of agent include tolerance of specific agents and comorbid illness. For patients who cannot tolerate aspirin because of allergy or gastrointestinal side effects, clopidogrel is an appropriate choice. For patients who do not tolerate dipyridamole because of headache, either aspirin or clopidogrel is appropriate. The combination of aspirin and clopidogrel may be appropriate for patients with acute coronary syndromes[306] or recent vascular stenting.[306,316]

Selection of Antiplatelet Agents for Patients Who Experience a Stroke While on Therapy

Patients who present with a first or recurrent stroke are commonly already on antiplatelet therapy. Unfortunately, there have been no clinical trials to indicate that switching antiplatelet agents reduces the risk for subsequent events.

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 extracranial or intracranial atherosclerosis, 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.[317,318] The trial was then reformulated as ESPRIT, using a medium-intensity warfarin dose (INR 2.0 to 3.0) compared with either aspirin alone (30 mg to 325 mg daily) or aspirin plus extended-release dipyridamole 200 mg twice daily. The trial was again ended early due to the superiority demonstrated by the combination of aspirin and dipyridamole over aspirin alone.[312] Mean follow-up was 4.6 years and mean INR achieved was 2.57. Patients treated with warfarin experienced a significantly higher rate of major bleeding (HR, 2.56; 95% CI, 1.48 to 4.43) but lower rate, albeit not statistically significant, in ischemic events (HR, 0.73; 95% CI, 0.52 to 1.01)[319] compared with aspirin alone.

The ESPRIT results confirmed those reported earlier by the Warfarin Aspirin Recurrent Stroke Study (WARSS), in which warfarin (INR 1.4 to 2.8) was compared with aspirin (325 mg daily) among 2206 patients with a noncardioembolic stroke.[320] This randomized, double-blind, multicenter trial found no significant difference between treatments for prevention of recurrent stroke or death (warfarin, 17.8%; aspirin, 16.0%). In contrast to ESPRIT, 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 clear evidence of efficacy observed across baseline stroke subtypes, including large-artery atherosclerotic and cryptogenic categories. The aforementioned WASID trial compared warfarin with aspirin in patients with intracranial stenoses and found no significant benefit and a higher risk of hemorrhage with warfarin therapy (see "Intracranial Atherosclerosis").

The role of anticoagulation for specific stroke etiologies is described elsewhere in this document.

Table 9. Recommendations for Antithrombotic Therapy for Noncardioembolic Stroke or TIA (Oral Anticoagulant and Antiplatelet Therapies)

Recommendations	Class/Level of Evidence*
For patients with noncardioembolic ischemic stroke or TIA, the use of antiplatelet agents rather than oral anticoagulation is recommended to reduce risk of recurrent stroke and other cardiovascular events *(Class I; Level of Evidence A).*	Class I; Level A
Aspirin (50 mg/d to 325 mg/d) monotherapy *(Class I; Level of Evidence A)*, the combination of aspirin 25 mg and extended-release dipyridamole 200 mg twice daily *(Class I; Level of Evidence B)*, and clopidogrel 75 mg monotherapy *(Class IIa; Level of Evidence B)* are all acceptable options for initial therapy. The selection of an antiplatelet agent should be individualized on the basis of patient risk factor profiles, cost, tolerance, and other clinical characteristics.	Class I; Level A; Class I; Level B; Class IIa; Level B
The addition of aspirin to clopidogrel increases risk of hemorrhage and is not recommended for routine secondary prevention after ischemic stroke or TIA *(Class III; Level of Evidence A).*	Class III; Level A
For patients allergic to aspirin, clopidogrel is reasonable *(Class IIa; Level of Evidence C).*	Class IIa; Level C
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, no single agent or combination has been studied in patients who have had an event while receiving aspirin *(Class IIb; Level of Evidence C).*	Class IIb; Level C

*See Tables 1 and 2 for explanation of class and level of evidence.

Newer Agents

At least 3 additional antiplatelet agents have recently been investigated for their potential effectiveness in secondary stroke prevention: triflusal, cilostazol, and sarpogrelate.[321–323] A recent noninferiority trial failed to show that sarpogrelate was not inferior to aspirin.[321] Triflusal has been examined only in a pilot trial.[323] Cilostazol is currently FDA approved for treatment of intermittent claudication and is further along in development as a stroke treatment. The effectiveness of cilostazol (dose not specified) compared with aspirin (dose not specified) was recently examined in a randomized, double-blind pilot study that enrolled 720 patients with a recent ischemic stroke.[322] During 12 to 18 months of follow-up, stroke was observed in 3.26 patients assigned to cilostazol per year compared with 5.27 patients assigned to aspirin per year ($P=0.18$). Headache, dizziness, and tachycardia, but not hemorrhage, were more common in the cilostazol group. Thus far, none of these newer agents have been approved by the FDA for prevention of recurrent stroke.

Recommendations

1. **For patients with noncardioembolic ischemic stroke or TIA, the use of antiplatelet agents rather than oral anticoagulation is recommended to reduce the risk of recurrent stroke and other cardiovascular events *(Class I; Level of Evidence A)*.**
2. **Aspirin (50 mg/d to 325 mg/d) monotherapy *(Class I; Level of Evidence A)*, the combination of aspirin 25 mg and extended-release dipyridamole 200 mg twice daily *(Class I; Level of Evidence B),* and clopidogrel 75 mg monotherapy *(Class IIa; Level of Evidence B)* are all acceptable options for initial therapy. The selection of an antiplatelet agent should be individualized on the basis of patient risk factor profiles, cost, tolerance, and other clinical characteristics.**
3. **The addition of aspirin to clopidogrel increases the risk of hemorrhage and is not recommended for routine secondary prevention after ischemic stroke or TIA *(Class III; Level of Evidence A)*.**
4. **For patients allergic to aspirin, clopidogrel is reasonable *(Class IIa; Level of Evidence C)*.**
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, no single agent or combination has been studied in patients who have had an event while receiving aspirin *(Class IIb; Level of Evidence C)*** (Table 9).

V. Treatments for Stroke Patients With Other Specific Conditions

A. Arterial Dissections

Dissections of the carotid and vertebral arteries are relatively common causes of TIA and stroke, particularly among young patients. Dissections may occur as a result of significant head and neck trauma, but about half occur spontaneously or after a trivial injury.[324] A number of underlying connective tissue disorders appear to be risk factors for spontaneous dissection, including fibromuscular dysplasia, Marfan syndrome, Ehlers-Danlos syndrome (type IV), osteogenesis imperfecta, and genetic conditions in which collagen is abnormally formed.[325–327] At present none of these underlying conditions are amenable to treatment. Noninvasive imaging studies such as MRI and magnetic resonance angiography with fat saturation protocols or computed tomography angiography are commonly used for diagnosis of extracranial dissection,[328] although conventional angiography is often necessary for the diagnosis of intracranial dissection. Ischemic stroke related to dissection may be a result of thromboembolism or hemodynamic compromise, although the former seems to be the dominant mechanism.[328–330] In some cases, dissections can lead to formation of a dissecting aneurysm, which can also serve as a source of thrombus formation. Intracranial dissections, particularly in the vertebrobasilar territory pose a risk of subarachnoid hemorrhage (SAH), as well as cerebral infarction.[331] Hemorrhagic complications of dissections are not discussed further in this guideline.

The optimal strategy for prevention of stroke in patients with arterial dissection is controversial. Options include anticoagulation, antiplatelet therapy, angioplasty with or without stenting, or conservative observation without specific medical therapy. Surgical approaches are unconventional. Early anticoagulation with heparin or LMWH has long been recommended at the time of diagnosis,[332–334] particularly

since the risk of stroke is greatest in the first few days after the initial vascular injury.[332,334–337] There have been no controlled trials supporting the use of any particular antithrombotic regimen. A Cochrane systematic review of 327 patients with carotid dissection in 26 case series reported no statistically significant difference in death or disability between antiplatelet and anticoagulant therapy (23.7% with antiplatelet versus 14.3% with anticoagulant; odds ratio [OR] 1.94; 95% CI, 0.76 to 4.91).[338] Recurrent stroke was seen in 1.7% of patients receiving anticoagulation, 3.8% receiving antiplatelet therapy, and 3.3% receiving no therapy. Another systematic review that included 762 patients with carotid or vertebral artery dissection from 34 case series showed no significant difference in risk of death (antiplatelet, 5/268 [1.8%]; anticoagulation, 9/494 [1.8%]; $P=0.88$), stroke (antiplatelet, 5/268 [1.9%]; anticoagulant, 10/494 [2.0%]; $P=0.66$), or stroke and death.[339] These pooled data from small studies must be considered severely limited and likely subject to publication bias. Two larger studies, including a retrospective cohort of 432 patients with carotid or vertebral artery dissection[340] and a prospective cohort of 298 subjects with only carotid dissection,[341] reported a much lower risk of subsequent stroke: 0.3% over the 3- to 12-month period after dissection. The latter study also included a nonrandomized comparison of anticoagulation versus antiplatelet therapy and found no difference in risk of recurrent stroke (0.5% versus 0%, $P=1.0$), and major bleeding events occurred numerically more often than recurrent stroke with both interventions (2% versus 1%). These observational data suggest that antiplatelet therapy and anticoagulation are associated with similar risk of subsequent stroke but that the former is likely safer. A randomized trial comparing these strategies is under way in the United Kingdom.

Dissections usually heal over time, and patients are commonly maintained on antithrombotic therapy for at least 3 to 6 months. This duration of therapy is arbitrary, and some authors suggest that imaging studies be repeated to confirm recanalization of the dissected vessel before a change in therapy.[336,342,343] Anatomic healing of the dissection with recanalization occurs in the majority of patients.[344] Those dissections that do not fully heal do not appear to be associated with an increased risk of recurrent strokes.[340,345] A dissecting aneurysm may also persist, but these appear to pose a low risk for subsequent stroke or rupture and therefore do not usually warrant aggressive intervention.[345]

Although most ischemic strokes due to dissection are a result of early thromboembolism, a minority are attributed to hemodynamic compromise.[346,347] The prognosis may be worse in these cases, and revascularization procedures such as stenting or bypass surgery have been proposed in this setting,[346,348–350] although prospective studies do not currently exist.

Many experts advise patients who experience a cervical arterial dissection to avoid activities that may cause sudden or excessive rotation or extension of the neck, such as contact sports, activities that cause hyperextension of the neck, weight lifting, labor in childbirth, strenuous exercise, and chiropractic manipulation of the neck,[351] but no real data exist to define the limits of activity for these patients. There is no established reason to manage their physical therapy differently during rehabilitation after stroke because of the dissection.

Recommendations

1. **For patients with ischemic stroke or TIA and extracranial carotid or vertebral arterial dissection, antithrombotic treatment for at least 3 to 6 months is reasonable *(Class IIa; Level of Evidence B)*.**
2. **The relative efficacy of antiplatelet therapy compared with anticoagulation is unknown for patients with ischemic stroke or TIA and extracranial carotid or vertebral arterial dissection *(Class IIb; Level of Evidence B)*.** (New recommendation)
3. **For patients with stroke or TIA and extracranial carotid or vertebral arterial dissection who have definite recurrent cerebral ischemic events despite optimal medical therapy, endovascular therapy (stenting) may be considered *(Class IIb; Level of Evidence C)*.**
4. **Patients with stroke or TIA and extracranial carotid or vertebral arterial dissection who fail or are not candidates for endovascular therapy may be considered for surgical treatment *(Class IIb; Level of Evidence C)*** (Table 10).

B. Patent Foramen Ovale

Causes of right to left passage of embolic material to the brain include patent foramen ovale (PFO) and pulmonary arteriovenous malformations. A PFO is an embryonic defect in the interatrial septum. It may or may not be associated with an atrial septal aneurysm, defined as a >10 mm excursion in the septum. PFO is common in up to 15% to 25% of the adult population according to data from Olmstead County, Minnesota,[352,353] and the Northern Manhattan Study (NOMAS)[354] in New York. The prevalence of isolated atrial septal aneurysm, estimated at 2% to 3%, is much lower than PFO.[352–354]

The meta-analysis of Overell et al[355] published in 2000 concluded that PFO and atrial septal aneurysm were significantly associated with increased risk of stroke in patients <55 years of age. For those >55 years, the data were less compelling but indicated some increased risk, with an OR of 1.27 (95% CI, 0.8 to 2.01) for PFO; 3.43 (95% CI, 1.89 to 6.22) for atrial septal aneurysm; and 5.09 (95% CI, 1.25 to 20.74) for both PFO and atrial septal aneurysm. The reported ORs for ischemic stroke in patients <55 years of age were 3.1 (95% CI, 2.29 to 4.21) for PFO; 6.14 (95% CI, 2.47 to 15.22) for atrial septal aneurysm, and 15.59 (95% CI, 2.83 to 85.87) for both PFO and atrial septal aneurysm, all compared with those with neither PFO nor atrial septal aneurysm.[355]

Older data are reviewed in detail in the 2006 statement,[355a] but 2 studies that provided information important to the recommendations are summarized here. The Patent Foramen Ovale in Cryptogenic Stroke (PICSS) substudy of WARSS provided data on both the contribution of PFO and atrial septal aneurysm to risk of recurrent stroke in a randomized clinical trial setting and comparative treatment data. In that study, 630 patients underwent TEE. In this subgroup, selected on the basis of their willingness to undergo TEE, about 34% had PFO. After 2 years of follow-up, there were no differences (HR, 0.96; $P=0.84$) in rates of recurrent stroke in those with (2-year event rate, 14.8%) or without PFO (15.4%), as well as no demonstrated effect on outcomes based on PFO

Table 10. Recommendations for Stroke Patients With Other Specific Conditions

Risk Factor	Recommendations	Class/Level of Evidence*
Arterial dissections	For patients with ischemic stroke or TIA and extracranial carotid or vertebral arterial dissection, antithrombotic treatment for at least 3 to 6 months is reasonable *(Class IIa; Level of Evidence B).*	Class IIa; Level B
	The relative efficacy of antiplatelet therapy compared with anticoagulation is unknown for patients with ischemic stroke or TIA and extracranial carotid or vertebral arterial dissection *(Class IIb; Level of Evidence B).* (New recommendation)	Class IIb; Level B
	For patients with stroke or TIA and extracranial carotid or vertebral arterial dissection who have definite recurrent cerebral ischemic events despite optimal medical therapy, endovascular therapy (stenting) may be considered *(Class IIb; Level of Evidence C).*	Class IIb; Level C
	Patients with stroke or TIA and extracranial carotid or vertebral arterial dissection who fail or are not candidates for endovascular therapy may be considered for surgical treatment *(Class IIb; Level of Evidence C).*	Class IIb; Level C
Patent foramen ovale	For patients with an ischemic stroke or TIA and a PFO, antiplatelet therapy is reasonable *(Class IIa; Level of Evidence B).*	Class IIa; Level B
	There are insufficient data to establish whether anticoagulation is equivalent or superior to aspirin for secondary stroke prevention in patients with PFO *(Class IIb; Level of Evidence B).* (New recommendation)	Class IIb; Level B
	There are insufficient data to make a recommendation regarding PFO closure in patients with stroke and PFO *(Class IIb; Level of Evidence C).*	Class IIb; Level C
Hyperhomocysteinemia	Although folate supplementation reduces levels of homocysteine and may be considered for patients with ischemic stroke and hyperhomocysteinemia *(Class IIb; Level of Evidence B)*, there is no evidence that reducing homocysteine levels prevents stroke recurrence.	Class IIb; Level B
Inherited thrombophilias	Patients with arterial ischemic stroke or TIA with an established inherited thrombophilia should be evaluated for DVT, which is an indication for short- or long-term anticoagulant therapy depending on the clinical and hematologic circumstances *(Class I; Level of Evidence A).*	Class I; Level A
	Patients should be fully evaluated for alternative mechanisms of stroke. In the absence of venous thrombosis in patients with arterial stroke or TIA and a proven thrombophilia, either anticoagulant or antiplatelet therapy is reasonable *(Class IIa; Level of Evidence C).*	Class IIa; Level C
	For patients with spontaneous cerebral venous thrombosis and/or a history of recurrent thrombotic events and an inherited thrombophilia, long-term anticoagulation is probably indicated *(Class IIa; Level of Evidence C).*	Class IIa; Level C
APL antibodies	For patients with cryptogenic ischemic stroke or TIA in whom an APL antibody is detected, antiplatelet therapy is reasonable *(Class IIa; Level of Evidence B).*	Class IIa; Level B
	For patients with ischemic stroke or TIA who meet the criteria for the APL antibody syndrome, oral anticoagulation with a target INR of 2.0 to 3.0 is reasonable *(Class IIa; Level of Evidence B).*	Class IIa; Level B
Sickle cell disease	For adults with SCD and ischemic stroke or TIA, the general treatment recommendations cited above are reasonable with regard to control of risk factors and the use of antiplatelet agents *(Class IIa; Level of Evidence B).*	Class IIa; Level B
	Additional therapies that may be considered to prevent recurrent cerebral ischemic events in patients with SCD include regular blood transfusions 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).*	Class IIb; Level C
Cerebral venous sinus thrombosis	Anticoagulation is probably effective for patients with acute CVT *(Class IIa; Level of Evidence B).*	Class IIa; Level B
	In the absence of trial data to define the optimal duration of anticoagulation for acute CVT, it is reasonable to administer anticoagulation for at least 3 months followed by antiplatelet therapy *(Class IIa; Level of Evidence C).*	Class IIa; Level C
Fabry disease	For patients with ischemic stroke or TIA and Fabry disease, alpha-galactosidase enzyme replacement therapy is recommended *(Class I; Level of Evidence B).* (New recommendation)	Class I; Level B
	Other secondary prevention measures as outlined elsewhere in this guideline are recommended for patients with ischemic stroke or TIA and Fabry disease *(Class I; Level of Evidence C).* (New recommendation)	Class I; Level C
Pregnancy	For pregnant women with ischemic stroke or TIA and high-risk thromboembolic conditions such as hypercoagulable state or mechanical heart valves, the following options may be considered: adjusted-dose UFH throughout pregnancy, for example, a subcutaneous dose every 12 hours with monitoring of activated partial thromboplastin time; adjusted-dose LMWH with monitoring of anti-factor Xa throughout pregnancy; or UFH or LMWH until week 13, followed by warfarin until the middle of the third trimester and reinstatement of UFH or LMWH until delivery *(Class IIb; Level of Evidence C).*	Class IIb; Level C
	In the absence of a high-risk thromboembolic condition, pregnant women with stroke or TIA may be considered for treatment with UFH or LMWH throughout the first trimester, followed by low-dose aspirin for the remainder of the pregnancy *(Class IIb; Level of Evidence C).*	Class IIb; Level C

(Continued)

Table 10. Continued

Risk Factor	Recommendations	Class/Level of Evidence*
Postmenopausal hormone replacement therapy	For women who have had ischemic stroke or TIA, postmenopausal hormone therapy (with estrogen with or without a progestin) is not recommended *(Class III; Level of Evidence A).*	Class III; Level A
Use of anticoagulation after intracranial hemorrhage	For patients who develop ICH, SAH, or SDH, it is reasonable to discontinue all anticoagulants and antiplatelets during the acute period for at least 1 to 2 weeks and reverse any warfarin effect with fresh frozen plasma or prothrombin complex concentrate and vitamin K immediately *(Class IIa; Level of Evidence B).*	Class IIa; Level B
	Protamine sulfate should be used to reverse heparin-associated ICH, with the dose depending on the time from cessation of heparin *(Class I; Level of Evidence B).* (New recommendation)	Class I; Level B
	The decision to restart antithrombotic therapy after ICH related to antithrombotic therapy depends on the risk of subsequent arterial or venous thromboembolism, risk of recurrent ICH, and overall status of the patient. For patients with a comparatively lower risk of cerebral infarction (eg, AF without prior ischemic stroke) and a higher risk of amyloid angiopathy (eg, elderly patients with lobar ICH) or with very poor overall neurological function, an antiplatelet agent may be considered for prevention of ischemic stroke. In patients with a very high risk of thromboembolism in whom restarting warfarin is considered, it may be reasonable to restart warfarin at 7 to 10 days after onset of the original ICH *(Class IIb; Level of Evidence B).* (New recommendation)	Class IIb; Level B
	For patients with hemorrhagic cerebral infarction, it may be reasonable to continue anticoagulation, depending on the specific clinical scenario and underlying indication for anticoagulant therapy *(Class IIb; Level of Evidence C).*	Class IIb; Level C
Special approaches to implementing guidelines and their use in high-risk populations	It can be beneficial to embed strategies for implementation within the process of guideline development and distribution to improve utilization of the recommendations *(Class IIa; Level of Evidence B).* (New recommendation)	Class IIa; Level B
	Intervention strategies can be useful to address economic and geographic barriers to achieving compliance with guidelines and to emphasize the need for improved access to care for the aged, underserved, and high-risk ethnic populations *(Class IIa; Level of Evidence B).* (New recommendation)	Class IIa; Level B

APL indicates antiphospholipid; CVT, cerebral venous thrombosis; DVT, deep vein thrombosis; SCD, sickle cell disease; SDH, subdural hematoma; and UFH, unfractionated heparin.

*See Tables 1 and 2 for explanation of class and level of evidence.

size or presence of atrial septal aneurysm. No differences (HR, 1.17; $P=0.65$) were seen in outcome in patients with cryptogenic stroke and PFO between those treated with aspirin (2-year event rates, 13.2%) versus warfarin (16.5%). Although these data are from a randomized clinical trial, this substudy was not designed specifically to test the superiority of one medical treatment in this subset.[356]

In contrast, the European PFO-ASA study reported by Mas et al[357] in 2002 reported recurrence rates of stroke on 4-year follow-up of 581 stroke patients with stroke of unknown cause. The patients were 18 to 55 years of age, and all were treated with 300 mg of aspirin. The rate of recurrence was 2.3% (0.3 to 4.3) in those with PFO alone, 15.2% (1.8 to 28.6) in patients with PFO and atrial septal aneurysm, and 4.2% (1.8 to 6.6) in patients with neither cardiac finding. The importance of PFO with or without atrial septal aneurysm and its optimal treatment remain in question.[357] Three large prospective studies have examined the risk of first stroke with PFO and cast doubt on the strength of the relationship between PFO and stroke risk.[13,252,352,354]

More recently, Handke et al[358] examined 503 consecutive patients with stroke, including 227 patients with cryptogenic stroke and 276 patients with stroke of known cause. TEE was performed after stroke classification. PFO was detected more often in cryptogenic stroke for both younger patients (43.9% versus 14%; OR, 4.7; 95% CI, 1.89 to 11.68; $P<0.001$) and older patients (28.3% versus 11.9%; OR, 2.92; 95% CI, 1.70 to 5.01; $P<0.001$). An atrial septal aneurysm was present with a PFO in 13.4% versus 2.0% of younger patients (cryptogenic versus known; OR, 7.36; 95% CI, 1.01 to 326) and in older patients (15.2% versus 4.4%; OR, 3.88; 95% CI, 1.78 to 8.49; $P<0.001$).[358] The Prospective Spanish Multicenter (CODICIA) Study examined 486 patients with cryptogenic stoke and quantified the magnitude of right-to-left shunt using contrast transcranial Doppler ultrasonography. Massive right-to-left shunt was detected in 200 patients (41%). Stroke recurrence was low (5.8%) and was not associated with the degree of the shunt.[359]

Given these data, overall, the importance of PFO with or without atrial septal aneurysm for a first stroke or recurrent cryptogenic stroke remains in question. No randomized controlled clinical trials comparing different medical therapies, medical versus surgical closure, or medical versus transcatheter closure have been reported, although several studies are ongoing. Nonrandomized comparisons of various closure techniques with medical therapy have generally shown reasonable complication rates and recurrence risk with closure at or below those reported with medical therapy.[360–370] One study suggested a particular benefit in patients with >1 stroke at baseline.[370]

In summary, these studies provide new information on options for closure of PFO and generally indicate that short-term complications with these procedures are rare and for the most part minor. Unfortunately, long-term follow-up is lacking. Event rates over 1 to 2 years after transcatheter closure ranged from 0% to 3.4%. Studies in which closure

was compared with medical treatment alone indicate trends toward better outcomes with closure.[361,362,370] Windecker et al reported a very high 3-year event rate of 33.2% in 44 medically treated patients compared with 7.3% in 59 similar patients treated with PFO closure.[370] The generally low rates of stroke in the closure series, the lack of robust outcome differences in the 3 nonrandomized comparison studies, and the overall absence of controlled comparisons of closure strategies with medical treatment alone, reinforce the need to complete randomized clinical trials comparing closure with medical therapy. A 2009 statement from the AHA/ASA/ACC strongly encourages all clinicians involved in the care of appropriate patients with cryptogenic stroke and PFO—cardiologists, neurologists, internists, radiologists, and surgeons—to consider referral for enrollment in these landmark trials to expedite their completion and help resolve the uncertainty regarding optimal care for this condition.[371]

Recommendations

1. **For patients with an ischemic stroke or TIA and a PFO, antiplatelet therapy is reasonable *(Class IIa; Level of Evidence B)*.**
2. **There are insufficient data to establish whether anticoagulation is equivalent or superior to aspirin for secondary stroke prevention in patients with PFO *(Class IIb; Level of Evidence B)*.** (New recommendation)
3. **There are insufficient data to make a recommendation regarding PFO closure in patients with stroke and PFO *(Class IIb; Level of Evidence C)*** (Table 10).

C. Hyperhomocysteinemia

Cohort and case-control studies have consistently demonstrated a 2-fold greater risk of stroke associated with hyperhomocysteinemia.[372–377] In a meta-analysis of clinical trials evaluating the efficacy of folate supplementation for stroke prevention, folate was associated with an 18% reduction (RR, 0.82; 95% CI, 0.68 to 1.00; $P=0.045$) in primary stroke risk.[378] Supplementation also appeared to be beneficial for stroke prevention in patients receiving folate for >36 months, cases with ≥20% reduction in homocysteine, and in populations without folate grain supplementation. Despite this, clinical trials focusing on secondary prevention in patients with cardiovascular disease or stroke have failed to demonstrate a benefit for homocysteine-reducing vitamins. The Heart Outcomes Prevention Evaluation (HOPE-2) trial was a randomized, placebo-controlled trial comparing homocysteine-lowering vitamins (2.5 mg of folic acid, 50 mg of vitamin B_6, 2 mg of vitamin B_{12}) or placebo in 5522 patients >55 years of age with vascular disease or diabetes, irrespective of baseline homocysteine.[379] Approximately 12% of the population had a TIA or stroke at study entry. Subjects were followed up for 5 years. The primary outcome was the composite of death due to cardiovascular causes, MI, or stroke. Vitamin therapy did not reduce the risk of the primary end point, but there was a lower risk of stroke (4.0% versus 5.3%; RR, 0.75; 95% CI, 0.59 to 0.97; $P=0.03$) in the active therapy group. The Vitamin Intervention for Stroke Prevention (VISP) study randomly assigned patients with a noncardioembolic stroke and mild to moderate hyperhomocysteinemia (>9.5 μmol/L for men and ≥8.5 μmol/L for women) to receive either a high- or low-dose vitamin therapy (eg, folate, B_6, or B_{12}) for 2 years.[380] 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 patients treated with the high-dose vitamins. Two-year stroke rates were 9.2% in the high-dose and 8.8% in the low-dose arms. At present there is no proven clinical benefit for high-dose vitamin therapy for mild to moderate hyperhomocysteinemia.

Recommendation

1. **Although folate supplementation reduces levels of homocysteine and may be considered for patients with ischemic stroke and hyperhomocysteinemia *(Class IIb; Level of Evidence B)*, there is no evidence that reducing homocysteine levels prevents stroke recurrence** (Table 10).

D. Hypercoagulable States

Inherited Thrombophilias

Little is known about the effect of inherited thrombophilias on the risk of recurrent stroke after stroke or TIA. Studies reported in the literature have been limited to case reports, case series, and small case-control studies in patients with initial stroke. There are inconsistent data on the relative risk associated with a homozygous, as opposed to heterozygous, state and the subsequent risk of stroke. This is likely a result of heterogeneity in the patient populations and varied outcome definitions. No clinical stroke trial has compared the efficacy of different antithrombotic approaches based on genotype.

Inherited thrombophilias (eg, protein C, protein S, or antithrombin III deficiency; factor V Leiden; or the prothrombin G20210A mutation), and the methylenetetrahydrofolate reductase (MTHFR) C677T mutation rarely contribute to adult stroke but may play a larger role in pediatric stroke.[381,382] The most prevalent inherited coagulation disorder is activated protein C (APC) resistance, caused by a mutation in factor V (most commonly the factor V Leiden mutation, Arg506Gln). More commonly a cause of venous thromboembolism, APC resistance has been linked to ischemic stroke in case reports.[383–385] The link between APC resistance and arterial stroke is tenuous in adult stroke but may be more significant in pediatric stroke.[225,386] Both the factor V Leiden (FVL) and the G20210A polymorphism in the prothrombin gene (PT G20210A) have been similarly linked to venous thrombosis, but their role in ischemic stroke remains controversial.[377,387–398]

Studies in younger patients (<55 years of age) have shown an association between these prothrombotic genetic variants and ischemic stroke, but this association 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 a small study of cryptogenic stroke patients <50 years of age, there was an increased risk (OR, 3.75; 95% CI, 1.05 to 13.34) associated with the PT G20210A mutation, but no significant association with FVL.[399] In contrast, 2 other studies of young (<50 years) patients found no association between ischemic stroke and the FVL, PT G20210A, or the MTHFR C677T mutations.[377,400] Genetic factors associated with venous thrombo-

embolism 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 PT G20210A mutation, but not FVL, was significantly more common in the PFO plus group than in PFO minus or nonstroke controls.[397]

Three meta-analyses have examined the most commonly studied prothrombotic mutations in FVL, MTHFR, and PT. The first pooled ischemic stroke candidate gene association studies involving Caucasian adults found statistically significant associations between stroke and FVL (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).[401] 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).[402] 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 the homozygous mutation (TT) versus the common alleles.[401] Thus, although there appears to be a weak association between these prothrombotic mutations and ischemic stroke, particularly in the young, major questions remain about the mechanism of risk (eg, potential for paradoxical venous thromboembolism), effect of gene-environment interaction, and optimal strategies for stroke prevention.

The presence of venous thrombosis is an indication for short- or long-term anticoagulant therapy depending on the clinical and hematologic circumstances.[403,404] Although there are guidelines for the general management of acquired hypercoagulable states such as protein C, S, and ATIII deficiencies, heparin-induced thrombocytopenia, disseminated intravascular coagulation, or cancer-related thrombosis, none are specific for the secondary prevention of stroke.[405–408]

Recommendations

1. **Patients with arterial ischemic stroke or TIA with an established inherited thrombophilia should be evaluated for deep vein thrombosis (DVT), which is an indication for short- or long-term anticoagulant therapy depending on the clinical and hematologic circumstances *(Class I; Level of Evidence A)*.**
2. **Patients should be fully evaluated for alternative mechanisms of stroke. In the absence of venous thrombosis in patients with arterial stroke or TIA and a proven thrombophilia, either anticoagulant or antiplatelet therapy is reasonable *(Class IIa; Level of Evidence C)*.**
3. **For patients with spontaneous cerebral venous thrombosis and/or a history of recurrent thrombotic events and an inherited thrombophilia, long-term anticoagulation is probably indicated *(Class IIa; Level of Evidence C)*** (Table 10).

Antiphospholipid Antibodies

Antiphospholipid (APL) antibody prevalence ranges from 1% to 6.5%; it is higher in the elderly and patients with lupus.[409] Less commonly the APL antibody syndrome consists of venous and arterial occlusive disease in multiple organs and fetal loss.[410] In addition to having a thrombotic episode or fetal loss, anticardiolipin antibody of IgG and/or IgM isotype or lupus anticoagulant must be present in the blood in medium or high titers on ≥2 occasions at least 6 weeks apart.[411] The association between APL antibodies and stroke is strongest for young adults (<50 years of age).[412,413] In the Antiphospholipid Antibodies in Stroke Study (APASS), 9.7% of ischemic stroke patients and 4.3% of controls had demonstrable anticardiolipin antibodies.[414] In the Antiphospholipid Antibodies in Stroke substudy of the Warfarin Aspirin Recurrent Stroke Study (WARSS/APASS), APL antibodies were detected in 40.7% of stroke patients, were low titer, and had no significant effect on risk of stroke recurrence.[415]

Multiple studies have shown high recurrence rates in patients with APL antibodies in the young.[416–418] In 1 study of patients with arterial or venous thrombotic events, high-intensity warfarin (INR 3.1 to 4.0) therapy was not more effective than moderate-intensity warfarin (INR 2.0 to 3.0) for prevention of recurrent thrombosis in patients with APL antibodies.[419] There are conflicting data on the association between APL antibodies and stroke recurrence in the elderly.[416,420–422]

The WARSS/APASS collaboration was the first study to compare randomly assigned warfarin (INR 1.4 to 2.8) with aspirin (325 mg) for prevention of a second stroke in patients with APL antibodies. APASS enrolled 720 APL antibody–positive WARSS participants.[415] 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 risk of the composite end point of death due to any cause, ischemic stroke, TIA, MI, DVT, 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 patients with cryptogenic ischemic stroke or TIA in whom an APL antibody is detected, 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, oral anticoagulation with a target INR of 2.0 to 3.0 is reasonable *(Class IIa; Level of Evidence B)*** (Table 10).

E. Sickle Cell Disease

Stroke is a common complication of sickle cell disease (SCD). The highest risk of stroke is in patients with SS genotype, but stroke can occur in patients with other genotypes.[423] For adults with SCD, the risk of having a first stroke can be as high as 11% by age 20, 15% by age 30, and 24% by age 45.[423] In SCD patients who had their first stroke as an adult (age ≥20 years), the recurrent stroke rate has been reported at 1.6 events per 100 patient-years,[423] and most recurrent events in adults occur within the first few years.[423,424] The character-

istics of patients with SCD that have been associated with increased risk of ischemic stroke include prior TIA (RR, 56; 95% CI, 12 to 285, $P<0.001$),[423] greater degree of anemia (RR, 1.85 per 1 g/dL decrease in steady-state hemoglobin; 95% CI, 1.32 to 2.59; $P<0.001$),[423,425] prior acute chest syndrome (a *new* infiltrate on chest x-ray associated with 1 or more new symptoms: fever, cough, sputum production, dyspnea, or hypoxia) within 2 weeks (RR, 7.03; 95% CI, 1.27 to 4.48; $P=0.001$),[423] annual rate of acute chest syndrome (RR, 2.39 per event per year; 95% CI, 1.27 to 4.48; $P=0.005$),[423] increased leukocyte count at age 1 year (20.79×10^9/L in stroke group versus 17.21×10^9/L in those without stroke; $P<0.05$),[425] nocturnal hypoxemia (HR, mean Sao_2 <96%, 5.6; 95% CI, 1.8 to 16.9; $P=0.0026$),[426] and higher systolic BP (RR, 1.31/10-mm Hg increase; 95% CI, 1.03 to 1.67; $P=0.33$).[423,424]

The most common mechanism of ischemic stroke in SCD patients appears to be large-artery arteriopathy,[427,428] which is believed to be due to intimal hyperplasia related to repeated endothelial injury,[429] but other mechanisms of stroke can occur. Low protein C and S levels have been associated with ischemic stroke,[430] and other markers of hypercoagulability have been reported in SCD patients, albeit not directly linked to stroke.[431,432] Cerebral venous sinus thrombosis is another mechanism of brain ischemia reported in SCD patients.[433] Cardiac disease causing cerebral embolus is either rare or underreported. Because mechanisms other than large-artery arteriopathy can result in stroke in SCD patients, and data on the possible interaction between SCD-specific risk factors and vascular risk factors (eg, diabetes or hyperlipidemia) are not available, identification and treatment of other potential stroke mechanisms and traditional risk factors should be considered and an appropriate diagnostic workup undertaken.

Recommendations for treatment of SCD patients with large-artery arteriopathy are largely based on stroke prevention studies performed in a pediatric population. The Stroke Prevention Trial in Sickle Cell Anemia (STOP) trial was a randomized, placebo-controlled trial that showed transfusion was effective for primary prevention of stroke in children with SCD and high transcranial Doppler velocities.[434] The STOP results are not directly applicable to these guidelines and are summarized in the AHA statements on primary prevention[13] and management of stroke in infants and children.[435] For secondary stroke prevention there are no randomized controlled trials to support transfusion in adults or children. 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 reduced 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 significant reduction in the rate of recurrent stroke during a mean follow-up of 3 years compared with historical controls followed for an unknown duration (13.3% versus 67% to 90%; $P<0.001$).[436] 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. In addition to the effects of transfusion therapy on clinical events, transfusion has been associated with less progression of large-vessel stenoses on angiography ($P<0.001$)[437] and decreased incidence of silent infarcts seen on MRI in SCD patients with elevated transcranial Doppler velocities ($P<0.001$) compared with patients who did not receive transfusions.[438] Regular transfusions are associated with long-term complications, especially iron overload, making 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.

Other therapies for secondary stroke prevention in adult SCD patients also have limited evidence to support their efficacy. Several small studies of secondary stroke prevention in children and young adults with SCD and stroke reported encouraging results using hydroxyurea to replace regular blood transfusion after ≥3 years of transfusion therapy.[439–441] Hydroxyurea has been reported to decrease transcranial Doppler velocities from baseline in SCD patients ($P<0.001$)[442] and may improve cerebral vasculopathy[443] as well. A phase III randomized clinical trial comparing long-term transfusion with transfusion followed by hydroxyurea in children with SCD (Stroke With Transfusions Changing to Hydroxyurea [SWiTCH]) is currently under way. Bone marrow transplantation can be curative from a hematologic perspective for a small number of SCD patients with a suitable donor and access to expert care but is usually undertaken in young children, not adults. Stroke and other brain-related concerns are frequently cited as reasons for undertaking bone marrow transplantation. Experience is limited, but both clinical and subclinical infarctions have been reported to be arrested by this procedure.[444] Surgical bypass operations have also been reported to have successfully improved outcomes in a few small series of SCD patients with moyamoya vasculopathy, but no randomized or controlled data are available.[445,446] Given the lack of systematic experience with antiplatelet agents, anticoagulants, and anti-inflammatory agents for secondary stroke prevention in SCD patients, specific stroke prevention medications cannot be recommended outside of general treatment recommendations. Preliminary data from animal studies suggest that statins may decrease endothelial tissue factor expression in SCD,[447] but until further evidence of the benefit of statins in SCD patients has been demonstrated, risk factor reduction with statins and antihypertensives can only be recommended on the basis of their importance in the general population.

Recommendations

1. **For adults with SCD and ischemic stroke or TIA, the general treatment recommendations cited above are reasonable with regard to control of risk factors and the use of antiplatelet agents *(Class IIa; Level of Evidence B)*.**
2. **Additional therapies that may be considered to prevent recurrent cerebral ischemic events in patients with SCD include regular blood transfusions 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 10).

F. Cerebral Venous Sinus Thrombosis

The estimated annual incidence of cerebral venous thrombosis (CVT) is 3 to 4 cases per 1 million population.[448] Although CVT accounts for <1% of all strokes, it is an important diagnostic consideration because of the differences in its management from that of arterial strokes.[448]

Early anticoagulation is often considered as both treatment and early secondary prophylaxis for patients with CVT, although controlled trial data remain limited to 2 studies.[449,450] 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 patients had been enrolled, because of the superiority of heparin therapy ($P<0.01$). Eight of the 10 patients randomly assigned to heparin recovered completely, and the other 2 patients had only mild neurological deficits. In the placebo group, only 1 patient had a complete recovery; 3 patients died.[449] 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 nonanticoagulation group.[449]

A more recent and slightly larger randomized study of cerebral venous sinus thrombosis (n=59) compared nadroparin (90 anti–Xa U/kg twice daily) with placebo.[450] After 3 months of follow-up, 13% of patients in the anticoagulation group and 21% in the placebo group had poor outcomes (RRR, 38%; P=NS). Two patients in the nadroparin group died, compared with 4 patients in the placebo group. Patients with intracranial bleeding were included, and no new symptomatic cerebral hemorrhages occurred in either group.

In a Cochrane meta-analysis of these 2 trials, anticoagulant therapy was associated with a pooled relative risk of death of 0.33 (95% CI, 0.08 to 1.21) and death or dependency of 0.46 (95% CI, 0.16 to 1.31). No new symptomatic ICHs were observed in either study. One major gastrointestinal hemorrhage occurred after anticoagulant treatment. Two control patients (on placebo) had a diagnosis of probable pulmonary embolism (one fatal).[451] On the basis of these 2 trials, the use of anticoagulation with heparin or LMWH given acutely in the setting of CVT is recommended, regardless of the presence of hemorrhagic conversion.

No randomized trial data exist to guide duration of anticoagulation therapy. For an initial event, periods between 3 and 12 months have been reported. Patients with inherited thrombophilia often undergo anticoagulation for longer periods than someone with a transient (reversible) risk factor such as oral contraceptive use. Given the absence of data on duration of anticoagulation in patients with CVT, it is reasonable to follow the externally established guidelines set for patients with extracerebral DVT, which includes anticoagulation treatment for 3 months for first-time DVT in patients with transient risk factors and at least 3 months for an unprovoked first-time DVT and anticoagulation for an indefinite period in patients with a second unprovoked DVT.[452] Antiplatelet therapy is generally given indefinitely after discontinuation of warfarin.

Given the relatively high proportion of pregnancy-related CVT, which ranges from 15% to 31%,[453] the risk for recurrent CVT during subsequent pregnancies is a commonly encountered question. Sixty-three pregnancies in patients with prior CVT have been reported in the literature, including 21 with pregnancy-related CVT, with normal delivery and no recurrence of CVT. Although this suggests that future pregnancies are not an absolute contraindication, given the scarcity of available data, decisions about future pregnancies must be individualized.[454]

Recommendations

1. **Anticoagulation is probably effective for patients with acute CVT *(Class IIa; Level of Evidence B)*.**
2. **In the absence of trial data to define the optimal duration of anticoagulation for acute CVT, it is reasonable to administer anticoagulation for at least 3 months, followed by antiplatelet therapy *(Class IIa; Level of Evidence C)*** (Table 10).

G. Fabry Disease

Fabry disease is a rare X-linked inherited deficiency of the lysosomal enzyme α-galactosidase, which causes lipid deposition in the vascular endothelium and results in progressive vascular disease of the brain, heart, skin, and kidneys.[455] Stroke may occur due to dolichoectasia of the vertebral and basilar arteries, cardioembolism, or small-vessel occlusive disease.[455–457] Fabry disease may be underdiagnosed as a cause of seemingly cryptogenic stroke in the young.[458] Antiplatelet agents are believed to be useful in preventing ischemic events related to existing vascular disease,[458] but the disease itself was untreatable and the prognosis quite poor until recombinant α-galactosidase A became available. In randomized controlled trials, administration of intravenous α-galactosidase (also known as agalsidase beta) at a dose of 1 mg/kg every other week reduced new and cleared old microvascular endothelial deposits in the kidneys, heart, and skin[459] and modestly reduced the composite of renal, cardiac, or cerebrovascular events or death (HR, 0.47; 95% CI, 0.21 to 1.03).[460] Enzyme replacement therapy also leads to clinical improvements in kidney function,[460,461] but the impact on cardiac function has been inconsistent.[462,463] Enzyme replacement therapy has been shown to have a favorable effect on cerebral blood flow,[464] but the risk of stroke appears substantial despite therapy.[465] Earlier intervention or higher enzyme doses or both may be needed for stroke prevention, and this is an area of active research.[466] The major adverse effects of recombinant α-galactosidase A infusions are fever and rigors, which may occur in 25% to 50% of treated patients but may be minimized with slow infusion rates and premedication with acetaminophen and hydroxyzine. An expert panel recommended enzyme replacement therapy for all male patients starting at age 16 and all other patients if there is evidence of symptoms or progressive organ involvement.[467]

Recommendations

1. **For patients with ischemic stroke or TIA and Fabry disease, α-galactosidase enzyme replacement ther-**

apy is recommended *(Class I; Level of Evidence B)*. (New recommendation)

2. **Other secondary prevention measures as outlined elsewhere in this guideline are recommended for patients with ischemic stroke or TIA and Fabry disease *(Class I; Level of Evidence C)*.** (New recommendation; Table 10)

VI. Stroke in Women

A. Pregnancy

Stroke can occur during pregnancy, the puerperium, or postpartum. Incidence of pregnancy-related stroke varies between 11 and 26 per 100 000 deliveries, with the greatest risk in the postpartum period and the 3 days surrounding birth.[468–470] Pregnancy also complicates the selection of antithrombotic treatments among women who have had a prior TIA or stroke mainly because of potential teratogenic effects on the fetus or increasing risk of bleeding.

For stroke prevention treatment during pregnancy, recommendations are based on 2 scenarios: (1) the presence of a high-risk condition that would require anticoagulation with warfarin, or (2) a lower or uncertain risk situation exists and antiplatelet therapy would be the treatment recommendation if pregnancy were not present. A full review of this complex topic is beyond the scope of these guidelines; however, a recent detailed discussion of options is available from a writing group of the American College of Chest Physicians.[471]

There are no randomized clinical trials regarding stroke prevention among pregnant women; therefore, the choice of agents must be made by inference from other studies, primarily prevention of DVT and the use of anticoagulants in women with high-risk cardiac conditions. In cases where anticoagulation is required, for example, because of the existence of a known thrombophilia or prosthetic cardiac valve, vitamin K antagonists, UFH, or LMWH has been used during pregnancy. Because warfarin crosses the placenta and can have potential deleterious fetal effects, UFH or LMWH is usually substituted throughout pregnancy. In some high-risk cases with concerns about the efficacy of UFH or LMWH, warfarin has been used after the 13th week of pregnancy and replaced by UFH or LMWH at the time of delivery.[471] LMWH is an acceptable option to UFH and may avoid the problem of heparin-induced thrombocytopenia and osteoporosis associated with long-term heparin therapy. Pharmacokinetic changes have been observed among pregnant women taking LMWH, so doses must be normalized for body weight changes and anti-Xa levels need to be monitored more closely.[472]

An expert survey on treatment of pregnant women with the APL antibody syndrome concluded that such women should be treated with LMWH and low-dose aspirin.[473] Women at high risk and with prior stroke or severe arterial thromboses were thought to be acceptable candidates for warfarin from 14 to 34 weeks' gestation. They also suggested that intravenous immunoglobulin be restricted to patients with pregnancy losses despite treatment.

Among lower-risk pregnant women, low-dose aspirin (50 mg/d to 150 mg/d) appears safe after the first trimester. A large meta-analysis of randomized trials among women at risk for pre-eclampsia has not shown any significant risk of teratogenicity or long-term adverse effects of low-dose aspirin during the second and third trimesters of pregnancy.[474] Low-dose aspirin was used in a randomized study among women with pre-eclampsia after the second trimester and was not found to increase adverse effects in the mother or fetus except for a higher risk of transfusion after delivery among those assigned to aspirin.[475] The use of aspirin during the first trimester remains uncertain. Although there was no overall increase in congenital anomalies associated with aspirin use in another meta-analysis, there was an increase in a rare congenital defect in the risk of gastroschisis.[476] Use of alternative antiplatelet agents has not been investigated during pregnancy.

Recommendations

1. **For pregnant women with ischemic stroke or TIA and high-risk thromboembolic conditions such as hypercoagulable state or mechanical heart valves, the following options may be considered: adjusted-dose UFH throughout pregnancy, for example, a subcutaneous dose every 12 hours with monitoring of activated partial thromboplastin time; adjusted-dose LMWH with monitoring of anti-factor Xa throughout pregnancy; or UFH or LMWH until week 13, followed by warfarin until the middle of the third trimester and reinstatement of UFH or LMWH until delivery *(Class IIb; Level of Evidence C)*.**
2. **In the absence of a high-risk thromboembolic condition, pregnant women with stroke or TIA may be considered for treatment with UFH or LMWH throughout the first trimester, followed by low-dose aspirin for the remainder of the pregnancy *(Class IIb; Level of Evidence C)*** (Table 10).

B. Postmenopausal Hormone Therapy

Despite prior suggestions from observational studies that postmenopausal hormone therapy may be beneficial for the prevention of cardiovascular disease, randomized trials in stroke survivors and primary prevention trials have failed to demonstrate any significant benefits and have found increased risk for stroke among women who use hormones. The Women's Estrogen for Stroke Trial (WEST), conducted among 664 women with a prior stroke or TIA, failed to show any reduction in risk of stroke recurrence or death with estradiol over a 2.8-year follow-up period.[477] The women in the estrogen therapy arm had a higher risk of fatal stroke (HR, 2.9; 95% CI, 0.9 to 9.0). Moreover, those who had a recurrent stroke and were randomized to hormone therapy were less likely to recover. The Heart and Estrogen/progestin Replacement Study (HERS) Trial of 2763 postmenopausal women with heart disease did not demonstrate any reduction in stroke risk or any cardiovascular benefit of hormone therapy.[478] The Women's Health Initiative (WHI) randomized, primary prevention, placebo-controlled clinical trial of estrogen plus progestin among 16 608 postmenopausal women 50 to 79 years of age found a 44% increase in all stroke (HR, 1.44; 95% CI, 1.09 to 1.90).[479,480] The parallel trial of estrogen alone among 10 739 women found a similar increase in risk (HR, 1.53; 95% CI, 1.16 to 2.02).[480] Because animal studies appeared to show a protective effect of estrogen on the brain, the possibility was raised that hormone therapy given to

younger postmenopausal or perimenopausal women might be protective, sometimes referred to as taking advantage of the "window of opportunity."[481] Despite this, neither observational studies nor the WHI clinical trials have supported such a hypothesis. The Nurses' Health Study indicated that the increased risk of stroke was not associated with timing of initiation of hormone therapy.[482] In the WHI trial, stroke risk was elevated regardless of years since menopause when hormone therapy was started.[483]

Recommendation

1. **For women who have had ischemic stroke or TIA, postmenopausal hormone therapy (with estrogen with or without a progestin) is not recommended *(Class III; Level of Evidence A)*** (Table 10).

VII. Use of Anticoagulation After Intracranial Hemorrhage

One of the most difficult problems that clinicians face is the management of antithrombotic therapy in patients who suffer an intracranial hemorrhage. There are several key variables to consider, including the type of hemorrhage, patient age, risk factors for recurrent hemorrhage, and indication for antithrombotic therapy. Most studies or case series have focused on patients receiving anticoagulants for a mechanical heart valve or AF who develop an ICH or subdural hematoma (SDH). There are very few case series addressing SAH. In all cases, the risk of recurrent hemorrhage must be weighed against the risk of an ischemic cerebrovascular event. Overall 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 SDH and an elevated INR, it is generally thought that the INR should be reduced as soon as possible through the use of clotting factors, vitamin K, and/or fresh frozen plasma.[484,485] Studies have shown that 30% to 40% of ICHs expand during the first 12 to 36 hours of formation,[486] and this may be prolonged when the patient is receiving anticoagulation.[487] Such expansions are usually associated with neurological worsening.[488] Elevated INRs have been shown to be associated with larger hematoma volumes when corrected for age, sex, race, antiplatelet use, hemorrhage location, and time from onset to scan.[489] In this retrospective study of 258 patients, hematoma volume was significantly higher in patients with an INR >3.0 (compared with those with an INR <1.2; $P=0.02$). Rapid reversal of anticoagulation is generally recommended for any patient with an ICH or subdural hematoma,[490,491] but there are no data on the preferred methods or consequences of this practice. Prothrombin complex concentrate normalizes the INR within 15 minutes of administration and is preferred over fresh frozen plasma in most national guidelines for the treatment of serious bleeding because of its ease of administration and fast action.[492] Vitamin K should be administered in combination with either product to maintain the beneficial effect. It is possible that rapid reversal to a normal INR will put high-risk patients at risk for thromboembolic events. Any reversal should be undertaken with a careful weighing of the risks and benefits of the treatment.

The appropriate duration of interruption of anticoagulation among high-risk patients is unknown. Several case series have followed up patients who were off anticoagulants for several days and weeks, with few reported instances of ischemic stroke. One study found that among 35 patients with hemorrhages followed for up to 19 days off warfarin, there were no recurrent ischemic strokes.[485] 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 event during cessation of warfarin was 2.9% in patients with a prosthetic heart valve, 2.6% in those with AF and prior embolic stroke, and 4.8% for those with a prior TIA or ischemic stroke.[493] None of the 35 patients in whom warfarin was restarted had another ICH during hospitalization.[493] 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.[494] 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.[485] One study of 100 patients who underwent intracranial surgery for treatment of cerebral aneurysm found that 14% developed evidence of DVT postoperatively. These patients were treated with systemic anticoagulation without any bleeding complications.[495]

The relative risks of recurrent ICH versus ischemia must be considered when deciding whether to reinstitute antithrombotic therapy after ICH. In a recent large study of 768 ICH patients followed for up to 8 years, the risk of recurrent ICH was higher than that of ischemic stroke in the first year (2.1% versus 1.3%), but there was no difference beyond that period (1.2% versus 1.3%). In this largely Caucasian population, it appeared that reinstitution of antithrombotic therapy soon after ICH was not beneficial, particularly in lobar ICH, where recurrence rates were highest.[496] Lobar hemorrhage poses a greater risk of recurrence when anticoagulation is reinstituted, possibly because of underlying cerebral amyloid angiopathy. A decision analysis study recommended against restarting anticoagulation in patients with lobar ICH and AF.[497] Several other risk factors for new or recurrent ICH have been identified, including advanced age, hypertension, degree of anticoagulation, dialysis, leukoaraiosis, and the presence of microbleeds on MRI.[498–501] The presence of microbleeds on MRI (often seen on gradient echocardiographic 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 microbleeds compared with 1.3% in those without MRI evidence of prior hemorrhage.[499]

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.[484] Failure to reverse the warfarin and achieve a normal INR has been associated with an increased risk of rebleeding, and failure to achieve a thera-

peutic partial thromboplastin time using intravenous heparin has been associated with increased risk of ischemic stroke.[484] Intravenous heparin can be easily titrated, discontinued, and rapidly reversed with protamine sulfate should bleeding recur. Heparin boluses are not recommended because studies have shown that bolus therapy increases the risk of bleeding.[502] There is a paucity of data from prospective, randomized studies with regard to the use of other agents for anticoagulation in this setting.

Hemorrhagic transformation within an ischemic stroke appears to have a different course and natural history compared with ICH. In general, these hemorrhages are often asymptomatic or cause minimal symptoms, rarely progress in size or extent, and are relatively common occurrences.[503,504] Some 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.[505] Each case must be assessed individually on the basis of variables such as size of hemorrhagic transformation, patient status, and indication for anticoagulation.

Recommendations

1. **For patients who develop ICH, SAH, or SDH, it is reasonable to discontinue all anticoagulants and antiplatelets during the acute period for at least 1 to 2 weeks and reverse any warfarin effect with fresh frozen plasma or prothrombin complex concentrate and vitamin K immediately *(Class IIa; Level of Evidence B)*.**
2. **Protamine sulfate should be used to reverse heparin-associated ICH, with the dose depending on the time from cessation of heparin *(Class I; Level of Evidence B)*.** (New recommendation)
3. **The decision to restart antithrombotic therapy after ICH related to antithrombotic therapy depends on the risk of subsequent arterial or venous thromboembolism, risk of recurrent ICH, and overall status of the patient. For patients with a comparatively lower risk of cerebral infarction (eg, AF without prior ischemic stroke) and a higher risk of amyloid angiopathy (eg, elderly patients with lobar ICH) or with very poor overall neurological function, an antiplatelet agent may be considered for prevention of ischemic stroke. In patients with a very high risk of thromboembolism in whom restart of warfarin is considered, it may be reasonable to restart warfarin therapy at 7 to 10 days after onset of the original ICH *(Class IIb; Level of Evidence B)*.** (New recommendation)
4. **For patients with hemorrhagic cerebral infarction, it may be reasonable to continue anticoagulation, depending on the specific clinical scenario and underlying indication for anticoagulant therapy *(Class IIb; Level of Evidence C)*** (Table 10).

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

National consensus guidelines are published by many professional societies and government agencies to increase healthcare providers' awareness of evidence-based approaches to disease management. This method of knowledge delivery assumes that increased awareness of guideline content alone can lead to substantial changes in physician behavior and ultimately patient behavior and health outcomes. Experience with previously published guidelines suggests otherwise, and compliance with secondary stroke and coronary artery disease prevention strategies based on guideline dissemination has not increased dramatically.[506–510] For example, treatment of hypertension 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 BP goal, whereas another 30% are unaware that they even have the disease.[511] In a survey of physicians who were highly knowledgeable about target cholesterol goals for therapy, few were successful in achieving these goals for patients in their own practice.[512] The use of retrospective performance data to improve compliance has produced small changes in adherence to guideline-derived measures in prevention of coronary artery disease.[506]

Systematic implementation strategies must be coupled with guideline dissemination to change healthcare provider practice. *The Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults*[513] identified the need for enabling strategies (eg, office reminders), reinforcing strategies (eg, feedback), and predisposing strategies (eg, practice guidelines) to improve the quality of practice. One such example is the AHA voluntary quality improvement program, Get With The Guidelines (GWTG), which has 3 individual modules on secondary prevention of coronary heart disease, heart failure, and stroke. The GWTG–Stroke program was implemented nationally in 2003; as of 2008, >1000 hospitals are participating in the program. Participation was associated with improvements in the following measures related to secondary stroke prevention from baseline to the fifth year[514]: discharge antithrombotics, anticoagulation for AF, lipid treatment for LDL-C >100 mg/dL, and smoking cessation. GWTG–Stroke was associated with a 1.18-fold yearly increase in the odds of adherence to guidelines, independent of secular trends.

Other organizations have also recognized the need for systematic approaches. The National Institutes of Health Roadmap for Medical Research was implemented to address treatment gaps between clinically proven therapies and actual treatment rates in the community.[515] 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.[516]

Although data link guideline compliance with improved health and cost outcomes in acute stroke, secondary prevention has been less well studied. The Italian Guideline Application for Decision Making in Ischemic Stroke (GLADIS) Study demonstrated better outcomes, reduced length of stay, and lower costs for patients with acute stroke who were treated according to guidelines. Guideline compliance and stroke severity were independent predictors of cost.[517,518] The

Stroke PROTECT (Preventing Recurrence Of Thromboembolic Events through Coordinated Treatment) program examined 8 medication/behavioral secondary prevention measures during hospitalization and found good but variable compliance with guidelines at 90 days. There was no analysis of recurrence rates, quality of life, or healthcare costs in this population.[519] It has been proposed that linking financial reimbursement to compliance might improve the quality of care for stroke survivors. A UK study examined the relationship between the Quality and Outcomes Framework (QOF), which calculated "quality points" for stroke using computer codes and reimbursed physicians accordingly. Higher-quality points did not correlate with better adherence to national guidelines, however, indicating that additional research is needed to determine how best to effect and measure these practices.[520]

Identifying and Responding to Populations at Highest Risk

Studies highlight the need for special approaches for populations at high risk for recurrent stroke and TIA, either because of increased predisposition or reduced health literacy and awareness. Those at high risk have been identified as the aged, socioeconomically disadvantaged, and specific ethnic groups.[521–523]

The elderly are at greater risk of stroke and at the highest risk of complications from treatments such as oral anticoagulants and carotid endarterectomy.[524,525] Despite the need to consider different approaches in these vulnerable populations, 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 and ever-growing subgroup. In SAPPHIRE, only 11% (85 of 776 CEA patients) were >80 years of age, and comparison of high- and low-risk CEAs demonstrated no difference in stroke rates.[526] By contrast, trials of medical therapies such as statins have included relatively large numbers of elderly patients with coronary artery disease and support safety and event reduction in these groups, although further study in the elderly may still be needed.[527–530]

The socioeconomically disadvantaged constitute that population at high risk for stroke primarily because of limited access to care.[531,532] 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 for neurological conditions such as stroke remains limited. These limitations to access may be due to limited personal resources such as lack of health insurance, geographic differences in available facilities or expertise, as is often the case in rural areas, or arrival at a hospital after hours. Hospitalized stroke patients with little or no insurance receive fewer angiograms and endarterectomies.[533–536]

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.[537] Stroke prevention efforts are of particular concern in those ethnic groups identified as being at the highest risk.[132] 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.[538] Even within minority ethnic populations, gender disparities remain, as evidenced by the fact that although the top 3 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.[539] black women are particularly vulnerable to obesity, with a prevalence rate of >50%, and their higher morbidity and mortality rates from heart disease, diabetes, and stroke have been attributed in part to increased body mass index. In the Michigan Coverdell Registry,[540] African Americans were less likely to receive smoking cessation counseling (OR, 0.27; CI, 0.17 to 0.42). The BASIC Project noted the similarities in stroke risk factor profiles in Mexican Americans and non-Hispanic whites.[541] The role of hypertension in blacks and its disproportionate impact on stroke risk has been clearly identified,[542–544] yet studies indicate that risk factors differ between different ethnic groups within the worldwide black population.[545]

For the aged, socioeconomically 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 this approach is well documented, but further research is sorely needed.[546] The NINDS Stroke Disparities Planning Panel, convened in June 2002, developed strategies and program goals that include establishing data collection systems and exploring effective community impact programs and instruments in stroke prevention.[547] The panel encouraged projects aimed at stroke surveillance projects in multiethnic communities such as those in southern Texas,[541] northern Manhattan,[544] Illinois,[548] and suburban Washington,[549] and stroke awareness programs targeted directly at minority communities.

Alliances with the federal government through the NINDS, Centers for Disease Control and Prevention, nonprofit organizations such as the AHA/ASA, and medical specialty groups such as the American Academy of Neurology and the Brain Attack Coalition are needed to coordinate, develop, and optimize implementation of evidence-based stroke prevention recommendations.[550]

Recommendations

1. **It can be beneficial to embed strategies for implementation within the process of guideline development and distribution to improve utilization of the recommendations *(Class IIa; Level of Evidence B)*.** (New recommendation)
2. **Intervention strategies can be useful to address economic and geographic barriers to achieving compliance with guidelines and to emphasize the need for improved access to care for the aged, underserved, and high-risk ethnic populations *(Class IIa; Level of Evidence B)*.** (New recommendation; Table 10)

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This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (1) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (2) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

Reviewer Disclosures

Reviewer	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
Oscar Benavente	University of Texas Health Science Center	NIH/NINDS†	Sanofi/BMS†	None	None	None	None	None
Larry B. Goldstein	Duke University	None	None	None	None	None	None	None
Philip B. Gorelick	University of Illinois	None	None	Boehringer-Ingelheim†	None	None	Genentech,* Boehringer Ingelheim†; BMS Sanofi*; Pfizer*; Daiichi Sankyo*	None
Elaine L. Miller	University of Cincinnati	None	None	None	None	None	None	None
Barney Stern	University of Maryland	NIH/NINDS†; NIH/NINDS†; NIH/NINDS*	None	AAN*	None	None	None	None

This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (1) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (2) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

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