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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Deidre Wentworth, MSN, RN; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Clinical Cardiology, and Interdisciplinary Council on Quality of Care and Outcomes Research

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

The online-only Data Supplement is available at http://stroke.ahajournals.org/cgi/content/full/10.1161/STR.0b013e3181f7d043/DC1.

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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. 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).

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.

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. 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. Meta-analyses of randomized controlled trials have shown that BP lowering is associated with a 30% to 40% reduction in risk of stroke. Risk reduction is greater with larger reductions in BP without clear evidence of a drug class–specific treatment effect. Evidence-based recommen-
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 and are detailed in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7). 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.

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. 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.

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

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**Table 1. Applying Classification of Recommendations and Level of Evidence**

<table>
<thead>
<tr>
<th>LEVEL A</th>
<th>Data derived from multiple randomized clinical trials or meta-analyses</th>
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<tbody>
<tr>
<td>Recommendation that procedure or treatment is useful/effective</td>
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<tr>
<td>Sufficient evidence from multiple randomized trials or meta-analyses</td>
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<thead>
<tr>
<th>LEVEL B</th>
<th>Data derived from a single randomized trial or nonrandomized studies</th>
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<tbody>
<tr>
<td>Recommendation that procedure or treatment is useful/effective</td>
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<tr>
<td>Evidence from single randomized trial or nonrandomized studies</td>
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<tr>
<th>LEVEL C</th>
<th>Only consensus opinion of experts, case studies, or standard of care</th>
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<tbody>
<tr>
<td>Recommendation that procedure or treatment is useful/effective</td>
<td></td>
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<tr>
<td>Only expert opinion, case studies, or standard of care</td>
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</tbody>
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*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.
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 a 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 TIA (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 TIA accounted for most of the benefit in cerebrovascular events, with a 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...
stroke, but the data supporting diabetes as a risk factor is ischemic stroke. Diabetes is a clear risk factor for first the United States. Prevalence is 15% to 33% in patients with Diabetes is estimated to affect 8% of the adult population in

### Risk Factor Recommendations

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Recommendations</th>
<th>Class/Level of Evidence*</th>
</tr>
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<tbody>
<tr>
<td>Hypertension</td>
<td>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). 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). 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 &lt;120/80 mm Hg by JNC 7 (Class IIa; Level of Evidence 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. 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)</td>
<td>Class I; Level A</td>
</tr>
<tr>
<td>Diabetes</td>
<td>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)</td>
<td>Class I; Level B</td>
</tr>
<tr>
<td>Lipids</td>
<td>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). 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 &lt;70 mg/dL to obtain maximum benefit (Class IIa; Level of Evidence B). (New recommendation) 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). 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).</td>
<td>Class I; Level B</td>
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| 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. Prevalence is 15% to 33% in patients with ischemic stroke. Diabetes is a clear risk factor for first stroke, 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, and 9.1% of recurrent strokes have been estimated to be attributable to diabetes. Diabetes was a predictor of the presence of multiple lacunar infarcts in 2 stroke cohorts. 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). 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. A hemoglobin A1c (HbA1c) level ≥7% is defined as inadequate control of hyperglycemia. Diet, exercise, oral hypoglycemic drugs, and insulin are recommended to gain glycemic control. 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 HbA1c level of 7% to 7.9%. 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 \( \leq 6.5\% \)) or standard glucose control (target HbA1c \( \leq 7\% \)). 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 major 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; \( P = 0.62 \)). The results of these trials indicate the glycemic targets should not be lowered to HbA1c <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 and BP management. 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). 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. With regard to other lipid subfractions, recent studies have independently linked higher serum triglyceride levels with occurrence of ischemic stroke and large-artery atherosclerotic stroke, as well as associating low high-density lipoprotein cholesterol (HDL-C) with risk of ischemic stroke. 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. 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.

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). 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.

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. 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. 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. 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. 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, fenofibrate, and gemfibrozil. 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, 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.60

**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 (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 (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 (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

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Recommendations</th>
<th>Class/Level of Evidence*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cigarette smoking</td>
<td>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). Counseling, nicotine products, and oral smoking cessation medications are effective for helping smokers quit (Class I; Level of Evidence A).</td>
<td>Class I; Level C</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>Patients with ischemic stroke or TIA who are heavy drinkers should eliminate or reduce their consumption of alcohol (Class I; Level of Evidence 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).</td>
<td>Class I; Level C</td>
</tr>
<tr>
<td>Physical activity</td>
<td>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). 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).</td>
<td>Class IIb; Level C</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>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) 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) 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)</td>
<td>Class IIb; Level C</td>
</tr>
</tbody>
</table>

*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. 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 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 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 ranging from a definite independent effect to no effect.

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.99 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, a decrease in platelet aggregation, 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. 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.\textsuperscript{106–108} The relationship of obesity and weight to stroke is complex but has been studied mostly in relation to primary prevention.\textsuperscript{109–118}

Among African-American stroke survivors in the African American Antiplaque Stroke Prevention Study, cardiovascular risk factor profiles increased with increasing weight,\textsuperscript{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.\textsuperscript{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.\textsuperscript{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,\textsuperscript{125,126} enhance vasodilation,\textsuperscript{127} improve glucose tolerance,\textsuperscript{128,129} and promote cardiovascular health.\textsuperscript{108}

Despite the established benefits of an active lifestyle, sedentary behaviors continue to be the national trends.\textsuperscript{130,131} Disability after stroke is substantial,\textsuperscript{132} and neurological deficits can predispose an individual to activity intolerance and physical deconditioning.\textsuperscript{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.\textsuperscript{133–136} Structured programs of therapeutic exercise have been shown to improve mobility, balance, and endurance.\textsuperscript{134} Beneficial effects have been demonstrated in different ethnic groups and in both older and younger groups.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{108,123,127}

**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 Ib; 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 Ib; 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.\textsuperscript{142} Those abnormalities are variably counted in different definitions of the metabolic syndrome and include hypertriglyceridemia, low HDL-C, high BP, and hyperglycemia.\textsuperscript{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.\textsuperscript{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 ($\geq$102 cm in men; $\geq$88 cm in women); elevated triglycerides ($\geq$150 mg/dL); reduced HDL-C ($<40$ mg/dL in women; $<50$ mg/dL in men); elevated BP (systolic $\geq$130 mm Hg or diastolic $\geq$85 mm Hg); and elevated fasting glucose ($\geq$100 mg/dL).\textsuperscript{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).\textsuperscript{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.\textsuperscript{150–155} The metabolic syndrome affects approximately 22% of US adults $>20$ years of age.\textsuperscript{156} Among patients with ischemic stroke, the prevalence is 40% to 50%.\textsuperscript{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.\textsuperscript{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.\textsuperscript{157-159} 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.\textsuperscript{161}

The association between the metabolic syndrome and risk for first ischemic stroke has been examined in several recent studies,\textsuperscript{158,162-170} all but one of which have confirmed the association.\textsuperscript{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.\textsuperscript{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,\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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)

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. Interventions 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.\textsuperscript{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.\textsuperscript{178} Additionally, each

<table>
<thead>
<tr>
<th>Table 5.</th>
<th>Prospective Trials Comparing Carotid Endarterectomy and Medical Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial</td>
<td>Mean Follow-Up</td>
</tr>
<tr>
<td>ECST</td>
<td>3 y</td>
</tr>
<tr>
<td>NASCET</td>
<td>2.7 y</td>
</tr>
<tr>
<td>VACS</td>
<td>11.9 mo</td>
</tr>
</tbody>
</table>

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.
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 \( (P=0.045) \).\textsuperscript{179} Thus, to prevent 1 ipsilateral stroke during the 5-year follow-up, 15 patients would have to undergo CEA.\textsuperscript{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%.\textsuperscript{180}

\textbf{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.\textsuperscript{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, \( P=0.008 \)).\textsuperscript{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 \( \geq 80 \) years of age.\textsuperscript{183}

\textbf{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.\textsuperscript{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 \( \geq 75 \) years of age and those randomized within 2 weeks after their last ischemic event; benefit fell rapidly with increasing delay.\textsuperscript{186}

\textbf{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.\textsuperscript{187} The expansion of this technique to include stenting has been under investigation in the United States since 1994.\textsuperscript{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.\textsuperscript{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, \( \geq 2 \)-vessel coronary artery disease, left ventricular ejection fraction \( [\text{LVEF}] \leq 30 \)%, 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 Cl, 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.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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
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. 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. 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. 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. 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 CAS versus 1.0±0.4% with CEA; 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.

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. New efforts are ongoing, using more sensitive imaging, such as 15O 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]).

Recommendations
1. For patients with recent TIA or ischemic stroke within the past 6 months and ipsilateral severe (70% to 99%) carotid artery stenosis, CAS is recommended if the periprocedural 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 periprocedural 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 II; Level of Evidence A).
4. When CAS 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 Intervenotional Approaches to Patients With Stroke Caused by Large-Artery Atherosclerotic Disease

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Recommendations</th>
<th>Class/Level of Evidence*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic extracranial carotid disease</td>
<td>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 periprocedural morbidity and mortality risk is estimated to be &lt;6% (Class I; Level of Evidence 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 periprocedural morbidity and mortality risk is estimated to be &lt;6% (Class I; Level of Evidence B). When the degree of stenosis is &lt;50%, there is no indication for carotid revascularization by either CEA or CAS (Class III; Level of Evidence 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 III; Level of Evidence 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 &gt;70% by noninvasive imaging or &gt;50% by catheter angiography (Class I; Level of Evidence B). Among patients with symptomatic severe stenosis (&gt;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). 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). For patients with symptomatic extracranial carotid occlusion, EC/IC bypass surgery is not routinely recommended (Class III; Level of Evidence A). Optimal medical therapy, which should include antplatelet 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)</td>
<td>Class I; Level A</td>
</tr>
<tr>
<td>Extracranial vertebrobasilar disease</td>
<td>Optimal medical therapy, which should include antplatelet 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) 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).</td>
<td>Class I; Level B</td>
</tr>
<tr>
<td>Intracranial atherosclerosis</td>
<td>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) For patients with stroke or TIA due to 50% to 99% stenosis of a major intracranial artery, long-term maintenance of BP &lt;140/90 mm Hg and total cholesterol level &lt;200 mg/dL may be reasonable (Class IIb; Level of Evidence B). (New recommendation) 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). 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)</td>
<td>Class I; Level B</td>
</tr>
</tbody>
</table>

*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 antplatelet 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 vertebralbasilar 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 peri-procedural or post-randomization 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 anti-thrombotics, 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-Cranienes Atheromatouses symtomatiques (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 of 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. In the largest prospective registry involving this stent, 129 patients with symptomatic intracranial stenosis of 70% to 99% were followed. 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, 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. 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. This BP target does not necessarily apply in the acute setting.

Recommenations

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.

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. 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 and 2 randomized controlled trials 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%). 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.

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. 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). 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). 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). 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. Therefore, in general, addition of aspirin to anticoagulation therapy should be avoided in AF patients.

The narrow therapeutic margin of warfarin in conjunction with frequent 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. 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 Device 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. 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 perioperative 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 greater 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. 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 transeosophageal 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 EAF trial, 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-
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).

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)

For patients with AF at high risk for stroke (stroke or TIA within 3 months, CHADS2 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 IIIa; Level of Evidence C). (New recommendation)

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).

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)

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).

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).

To avoid additional bleeding risk, antiplatelet agents should not be routinely added to warfarin (Class III; Level of Evidence 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).

For patients with ischemic stroke or TIA and mitral annular calcification, antiplatelet therapy may be considered (Class IIb; Level of Evidence C).

For patients with MVP who have ischemic stroke or TIA, long-term antiplatelet therapy may be considered (Class IIb; Level of Evidence 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).

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).

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).

LV indicates left ventricular; and MVP, mitral valve prolapse.

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

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.\textsuperscript{256–259} Between 60% and 65% of these recurrences develop within the first year,\textsuperscript{256,257} most within 6 months. Mitral valvuloplasty does not seem to eliminate the risk of thromboembolism;\textsuperscript{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.\textsuperscript{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.\textsuperscript{266} The ACC/AHA Task Force on Practice Guidelines has published guidelines for the management of patients with valvular heart disease.\textsuperscript{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.\textsuperscript{268,269}

Mitral Valve Prolapse
Mitral valve prolapse (MVP) is the most common form of valve disease in adults.\textsuperscript{270} Although generally innocuous, and thromboembolic phenomena have been reported in patients with MVP in whom no other source could be found.\textsuperscript{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.\textsuperscript{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,\textsuperscript{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,\textsuperscript{279–284} thrombus has been found at autopsy on heavily calcified annular tissue, and echocardiographic densities have been identified in the LV outflow tract in patients with MAC who experience cerebral ischemic events.\textsuperscript{280,282} Aside from the risk of thromboembolism, spicules of fibrocalcific material may embolize from the calcified mitral annulus.\textsuperscript{279,281,283} The relative frequencies of calcific and thrombotic embolism are unknown.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 or 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) \textit{(Class IIa; Level of Evidence C)}.
2. To avoid additional bleeding risk, antiplatelet agents should not be routinely added to warfarin \textit{(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 \textit{(Class IIb; Level of Evidence C)}.
4. For patients with ischemic stroke or TIA and mitral annular calcification, antiplatelet therapy may be considered \textit{(Class IIb; Level of Evidence C)}.
5. For patients with MVP who have ischemic stroke or TIs, long-term antiplatelet therapy may be considered \textit{(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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 the 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%, 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. 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%). The magnitude of the benefit is similar for doses ranging from 50 mg to 1500 mg, although the data for doses <75 mg are limited. 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.

For patients who use low-dose aspirin (≤325 mg) for prolonged intervals, the annual rate of serious gastrointestinal hemorrhage is about 0.4%, which is 2.5 times the risk for nonusers. 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.

**Ticlopidine**

Ticlopidine is a platelet adenosine diphosphate (ADP) receptor antagonist that has been evaluated in 3 randomized trials of patients with cerebrovascular disease. The Canadian American Ticlopidine Study (CATS) compared ticlopidine (250 mg twice a day) with placebo for prevention of stroke, MI, or vascular death in 1053 patients with ischemic stroke. 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. 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. 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.

**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 alone and one comparing it with combination aspirin/dipyridamole. In each trial, rates of primary outcomes were similar between the treatment groups. Clopidogrel has not been compared with placebo for secondary stroke prevention.

Clopidogrel was compared with aspirin alone in the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial. 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
cases of thrombotic thrombocytopenic purpura have been treated with dipyridamole 200 mg twice a day, (2) aspirin 25 mg twice a day compared with aspirin or placebo, in published trials,298,306 but a few large clinical trials have been conducted to compare aspirin alone with aspirin plus dipyridamole for prevention of stroke, MI, vascular death, or major hemorrhage 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 expected finding of a reduced rate of major bleeding in the combination group (35 compared with 53 events) may also 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.

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 trials 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 that 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 hemorrhage 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 also 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 and 1 large. Neither demonstrated a benefit from combination therapy. The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial 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 subgroups 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 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 Antplatelet 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 antplatelet 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 PROFESSION 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 and the combination of stroke, MI, death, or major bleeding. On average, compared with aspirin alone, the combination may prevent 1 event among 100 patients treated for 1 year. Ticlopidine may be more effective than aspirin for secondary prevention, 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. The difference is small, however, amounting to 1 major hemorrhage event per 500 patient-years. 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 or recent vascular stenting.

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

Patients who present with a first or recurrent stroke are commonly already on antplatelet therapy. Unfortunately, there have been no clinical trials to indicate that switching antplatelet 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. 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. 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) 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. 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)

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class/Level of Evidence*</th>
</tr>
</thead>
<tbody>
<tr>
<td>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).</td>
<td>Class I; Level A</td>
</tr>
<tr>
<td>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.</td>
<td>Class I; Level A; Class I; Level B; Class IIa; Level B</td>
</tr>
<tr>
<td>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).</td>
<td>Class III; Level A</td>
</tr>
<tr>
<td>For patients allergic to aspirin, clopidogrel is reasonable (Class IIa; Level of Evidence C).</td>
<td>Class IIa; Level C</td>
</tr>
<tr>
<td>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).</td>
<td>Class IIb; Level C</td>
</tr>
</tbody>
</table>

*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.321 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).

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 dissection340 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 underway 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 al355 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 statement355a 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

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Recommendations</th>
<th>Class/Level of Evidence*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial dissections</td>
<td>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). The relative efficacy of antplatelet 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)</td>
<td>Class IIa; Level B</td>
</tr>
<tr>
<td></td>
<td>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).</td>
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<td></td>
<td>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).</td>
<td>Class IIb; Level C</td>
</tr>
<tr>
<td>Patent foramen ovale</td>
<td>For patients with an ischemic stroke or TIA and a PFO, antplatelet therapy is reasonable (Class IIa; Level of Evidence 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)</td>
<td>Class IIa; Level B</td>
</tr>
<tr>
<td></td>
<td>There are insufficient data to make a recommendation regarding PFO closure in patients with stroke and PFO (Class IIb; Level of Evidence C).</td>
<td>Class IIb; Level C</td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
<td>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.</td>
<td>Class IIb; Level B</td>
</tr>
<tr>
<td>Inherited thrombophilias</td>
<td>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). 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 antplatelet therapy is reasonable (Class IIa; Level of Evidence C).</td>
<td>Class I; Level A</td>
</tr>
<tr>
<td></td>
<td>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).</td>
<td>Class IIa; Level C</td>
</tr>
<tr>
<td>APL antibodies</td>
<td>For patients with cryptogenic ischemic stroke or TIA in whom an APL antibody is detected, antplatelet therapy is reasonable (Class IIa; Level of Evidence 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 I; Level of Evidence B).</td>
<td>Class IIa; Level B</td>
</tr>
<tr>
<td>Sickle cell disease</td>
<td>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 antplatelet agents (Class IIa; Level of Evidence 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 &lt;30% to 50% of total hemoglobin, hydroxyurea, or bypass surgery in cases of advanced occlusive disease (Class IIb; Level of Evidence C).</td>
<td>Class IIa; Level C</td>
</tr>
<tr>
<td>Cerebral venous sinus thrombosis</td>
<td>Anticoagulation is probably effective for patients with acute CVT (Class IIa; Level of Evidence 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 antplatelet therapy (Class IIa; Level of Evidence C).</td>
<td>Class IIa; Level B</td>
</tr>
<tr>
<td>Fabry disease</td>
<td>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)</td>
<td>Class I; Level B</td>
</tr>
<tr>
<td></td>
<td>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)</td>
<td>Class I; Level C</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>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). 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).</td>
<td>Class IIb; Level C</td>
</tr>
</tbody>
</table>

(Continued)
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 al357 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 al358 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 patients 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 stroke 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 \( \geq 1 \) 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 anti-coagulation 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 B₆, 2 mg of vitamin B₁₂) 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, B₆, or B₁₂) 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 Thrombophilies

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.403 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 hemato logic 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 hemato logic 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.416–419 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.423 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.421 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; \( P < 0.001 \)),\(^{223} \) greater degree of anemia (RR, 1.85 per 1 g/dL decrease in steady-state hemoglobin; 95% CI, 1.32 to 2.59; \( P < 0.001 \)),\(^{223} \) 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; \( P = 0.001 \)),\(^{223} \) annual rate of acute chest syndrome (RR, 2.39 per event per year; 95% CI, 1.27 to 4.48; \( P = 0.005 \)),\(^{223} \) 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; \( P < 0.05 \)),\(^{225} \) nocturnal hypoxemia (HR, mean \( \text{SaO}_2 < 96\% \), 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. 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.

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. 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. 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.

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. 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). 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. 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%, 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.

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. Stroke may occur due to dolichoectasia of the vertebral and basilar arteries, cardioembolism, or small-vessel occlusive disease. Fabry disease may be underdiagnosed as a cause of seemingly cryptogenic stroke in the young. Antiplatelet agents are believed to be useful in preventing ischemic events related to existing vascular disease, 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 and modestly reduced the composite of renal, cardiac, or cerebrovascular events or death (HR, 0.47; 95% CI, 0.21 to 1.03). Enzyme replacement therapy also leads to clinical improvements in kidney function, but the impact on cardiac function has been inconsistent. Enzyme replacement therapy has been shown to have a favorable effect on cerebral blood flow, but the risk of stroke appears substantial despite therapy. Earlier intervention or higher enzyme doses or both may be needed for stroke prevention, and this is an area of active research. 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.

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. 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.

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. 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.

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. 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. 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. 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 gastrochisis. 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. 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. 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). 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). 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 address 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.494,495 Studies have shown that 30% to 40% of ICHs expand during the first 12 to 36 hours of formation,496 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,494,495 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 reinitiation 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, leukoaraoisis, 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 reinitiation 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-
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. 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. 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. 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 these are actually at their target BP goal, whereas another 30% are unaware that they even have the disease. 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. 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.

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 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: 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. 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.

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.
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. 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.

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.

The elderly are at greater risk of stroke and at the highest risk of complications from treatments such as oral anticoagulants and carotid endarterectomy. 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 SAPHIRE, 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. 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.

The socioeconomically disadvantaged constitute that population at high risk for stroke primarily because of limited access to care. 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.

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. Stroke prevention efforts are of particular concern in those ethnic groups identified as being at the highest risk. 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. 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. 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, 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. The role of hypertension in blacks and its disproportionate impact on stroke risk has been clearly identified. Yet studies indicate that risk factors differ between different ethnic groups within the worldwide black population. 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. 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. The panel encouraged projects aimed at stroke surveillance projects in multiethnic communities such as those in southern Texas, northern Manhattan, Illinois, and suburban Washington, 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.

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)
## Disclosures

### Writing Group Disclosures

<table>
<thead>
<tr>
<th>Writing Group Member</th>
<th>Employment</th>
<th>Research Grant</th>
<th>Other Research Support</th>
<th>Speakers' Bureau/Honoraria</th>
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References


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.

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†Significant.

Reviewer Disclosures

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The Final Report of the National Cholesterol Education Program


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脳卒中・一過性脳虚血発作後の
脳卒中再発予防ガイドライン

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

Karen L. Furie, MD, MPH, FAHA, Chair; Scott E. Kasner, MD, MSCE, FAHA, Vice Chair; Robert J. Adams, MD, MS, FAHA; Gregory W. Albers, MD; Ruth L. Bush, MD, MPH; Susan C. Fagan, PharmD, FAHA; Jonathan L. Halperin, MD, FAHA; S. Claiborne Johnston, MD, PhD; Irene Kattan, MD, MS, FAHA; Walter N. Kernan, MD; Pamela H. Mitchell, PhD; CNRN, RN, FAAN, FAHA; Bruce Ovbiagele, MD, MS, FAHA; Yuko Y. Palecch, PhD; Ralph L. Sacco, MD, MS, FAHA, FAAN; Lee H. Schwanm, MD, FAHA; Sylvia Wassertheil-Smoller, MD, PhD, FAHA; Tanya N. Turan, MD, FAHA; Deirdre Wentworth, MSN, RN; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Clinical Cardiology, and Interdisciplinary Council on Quality of Care and Outcomes Research

はじめに：Stroke 日本語版ではこれまで数々の米国心臓協会・米国脳卒中協会 (AHA/ASA) のガイドラインや声援文を定期刊行の範囲で要約として掲載してきた。今回のガイドラインは2007年に報告されたガイドラインの改訂版であり、昨年10月Stroke 誌電子版に掲載され、本年1月の Stroke 誌に掲載された。本ガイドラインには一過性脳虚血発作 (TIA) 後の再発予防に関する包括的な推奨が記載されており、Stroke 日本語版編集委員会は、これまでより充実した要約を誌名の先生方に利用可能でいかたで提携する必要があると考え、AHA/ASA と Stroke 誌の皆様にご理解、ご支援いただき、さらに充実した要約を推奨文の背景にあるデータや問題点を明らかにすることができた。このガイドラインは、主として2009年8月1日までに出版され Index Medicus に引用された論文に基づいたエビデンスにより作成された。推奨文の作成には表1と表2により示すように、AHAによるクラス分類とエビデンス・レベルに従った表現が用いられている。内容としては、脳虚血性脳卒中の再発予防法、脳卒中後療法、運動神経症の薬物療法、心房性顕性心拍数の治療方針、非心房性脳卒中後の抗血小板療法、脳梗塞や卵巣腺間隔を含む肺動静脈の治療方針について参照を表している。なお英文ガイドラインでは ischemic stroke が脳卒中と記載されていることが多い、この要約を一貫性脳卒中という記載は原則として脳虚血性脳卒中を意味するとご理解いただきたい。

脳卒中と TIA 患者の脳卒中再発リスクは高く、米国における年間793,000例の脳卒中の約35％は再発である。TIA 後90日以内の脳卒中発症リスクは17％および、特に最初の1週間が高いとされる。脳卒中と TIA 同時に発症後24時間以内に消失するものとされてきたが、詳細診断の基準により、脳卒中を含む脳梗塞が含まれている。このため詳細診断の基準に基づいて、脳卒中を「急性脳梗塞を伴わない脳梗塞、脳梗塞の発生により発症された一過性の神経機能不全」と定義するよう推奨されている。このガイドラインに引用されている論文の大半は定義を用いているが、このガイドラインの推奨はどちらの定義が用いらても同じである。

（文責：柳原武彦）
I. 一過性脳虚血発作または虚血性脳卒中の危険因子のコントロール（表3．表4）

A．高血圧
収縮期および拡張期高血圧と脳卒中のリスクの間に関連があり、無作為比較試験のメタ解析では、降圧により脳卒中のリスクが30−40％減少した。脳卒中のステーキングと高血圧患者の治療に関する推奨は、ASAガイドラインとJNC7で述べられているが、生活習慣では体重減少（軽度を含む）、果物・野菜・低脂肪飲食の摂取、運動、アルコールの制限が血圧の低下に貢献する。心筋症家族歴・脳卒中の一次予防のための降圧治療の重要性は多くの無作為試験とメタ解析が支持しているが、脳卒中やTIA患者の二次予防のための降圧治療についての試験は少ない。2002年までに施行された7件の無作為試験のメタ解析は、降圧療法で脳卒中やTIA後の再発リスクが低下することを示し、全体として降圧療法は脳卒中再発とそのすべての血管性イベントを有意に減少させ、収縮期血圧が低下すると脳卒中再発リスクが減少した。無作為試験の数が少なく降圧薬間の比較には限界があるが、脳卒中の再発は硝酸亜鉛単独またはACE阻害薬との併用で有意に減少し、β遮断薬やACE阻害薬単独では減少しない。

B．糖尿病
米国においては、虚血性脳卒中患者の糖尿病有病率は15～33％である。糖尿病は初発脳卒中の強い危険因子であるが、脳卒中再発の独立した予防因子でもあり、再発の91%が脳卒中再発する推定される。空腹時血糖値126mg/dl以上、HbA1C 6.5％以上、随時血糖値グレード200mg/dl以上になると糖尿病とされ、HbA1Cが7％を超えると血糖管理不良とされる。血糖調

| 表3 血管性危険因子の治療に関する推奨 |
|-----------------|-----------------|
| 危険因子       | 推奨             | クラス  | エビデンスレベル |
| 慢性腎不全      | 脳卒中からの推奨 | クラス1 | エビデンスレベルA |
| 糖尿病          | 脳卒中からの推奨 | クラス1 | エビデンスレベルB |
| 高血圧          | 脳卒中からの推奨 | クラス1 | エビデンスレベルB |
| 高脂血症        | 脳卒中からの推奨 | クラス1 | エビデンスレベルB |

表4 生活習慣の改善に関する推奨

<table>
<thead>
<tr>
<th>危険因子</th>
<th>推奨</th>
<th>クラス/エビデンスレベル</th>
</tr>
</thead>
<tbody>
<tr>
<td>疲労感</td>
<td>医療従事者は、過去１年に里で疲労感のあるすべての疲労感またはTIA患者に対し管理を強く勧めるべきである。</td>
<td>クラスI  エビデンスレベルC</td>
</tr>
<tr>
<td></td>
<td>疲労感と心拍数増（運動中増）を視ことに工夫する。</td>
<td>クラスIb  エビデンスレベルC</td>
</tr>
<tr>
<td></td>
<td>カウンセリング、ニコチン製剤およびニコチン補助療法を勧めることが有効である。</td>
<td>クラスI  エビデンスレベルC</td>
</tr>
<tr>
<td>飲酒</td>
<td>大量飲酒がある疲労感またはTIA患者では、アルコールの消費を控えまたは少量に限るべきである。</td>
<td>クラスI  エビデンスレベルC</td>
</tr>
<tr>
<td></td>
<td>少量（1杯程度）の飲酒（1日あたり男性では2杯以下、非臨床女性では1杯以下）是有効と考えられる。飲酒しない人は注意を要するべきではない。</td>
<td>クラスI  エビデンスレベルC</td>
</tr>
<tr>
<td>飲酒</td>
<td>身体活動</td>
<td>シンンシタリオーム</td>
</tr>
<tr>
<td></td>
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</tr>
</tbody>
</table>

節には食事療法、運動、薬物治療など、インスリンが推奨される。心血管系疾患と脳卒中の既往があり、血管系危険因子を含む患者に対する積極的治療の効果を評価した3件の大規模無作為試験（ACCORD, ADVANCE, VADT）では、心血管イベントや死亡率は減少していなかった。ACCORD試験で食事療法が有効な証拠は、日常生活の変化が危険因子の変化を導入し、結果的に心血管イベントを減少させることを示している。ADVANCE試験も心血管イベントの二次予防効果を示すことができなかった。ACCORD試験と異なり、脳卒中死亡率に有意差はなかった。これらの結果は、心血管系疾患の既往や血管系危険因子を含む患者では、HbA1C目標値を5.5％未満ですべきことを示している。

C. 質問と回答

虚血性性脳卒中が判別可能な大規模疫学調査では、総コレステロールやLDLコレステロール（LDL-C）の上昇と虚血性脳卒中の関連、LDL-C低下と脳内出血リスクの増加の関連が示されている。また、低HDL-Cと虚血性脳卒中リスクの関連に、虚血性脳卒中、大血管のアテローム動脈壁性脳卒中と血清トリグリセリド高価が独立して関連している。スチュール症を含むメタ解析では、HDL-Cが低下するほど、脳卒中リスクは低下した。しかし最近までに冠動脈疾患（CHD）のない脳卒中患者の脳卒中再発に対するスチュールの効果は明らかでなかった。虚血性性脳卒中再発の既往者を対象としたHPS試験の後向きサブ解析では、ソノグラフィーにより血栓形成ベインが26%減少したが脳卒中再発に対する有害差はなかった。SPARCAL試験では、LDL-C 100 〜 190 mg/dLでCHDのない脳卒中・TIA既往者において、アルタステチン80 mgと飼料の週1回摂取が無作為試験で比較され、4.9年（平均）で、致死性と非致死性脳卒中の再発が11.2%，飼料で13.15年間の絶対的リスク低下2.2%，ハザード比（HR）= 0.84, P = 0.03，心血管イベントの5年間の絶対的リスク低下3.5%，HR = 0.8, P = 0.002であった。

虚血性脳卒中は増加したが、致死性の虚血性脳卒中に差はなかった。SPARCAL試験ではLDL-Cが50%以上低下すると非致死性と致死性脳卒中のリスクは35%減少したが、出性脳卒中は増加しなかった。LDL-Cが70
mg/dl。未満になると脳卒中リスクが28%低下したが、出血性脳卒中リスクは95% CI (信頼区間)が拡大したためか、有意な増加は認めなかった。National Cholesterol Education Program (NCEP-ATPIII)は脳卒中を含めた心血管系疾患患者や脳卒中予防の有効性、体重管理の指針を発表しているが、脳卒中の様子としてはLDL-Cの低下を第一に勧め、生活習慣では運動とコレステロール摂取の制限、高血圧、運動量の増加を強調している。CHDの既往やCHD相当のリスク（糖尿病や症候群性動脈硬化を含む）があればLDL-Cの目標値は100 mg/dl、未満を推奨している。スタチン以外の薬物には、ポリフェノール系薬物、コレステロール吸収抑制剤がある。これらはスタチンで管理困難な脳卒中やTIA患者に使われているが、脳卒中再発予防効果を示したデータはあまりない。（文献：横山 秀康）

D. 吸煙

吸煙が脳卒中脳卒中の重要で独立した危险因子であるという強いエビデンスがあり、国際的にも脳卒中を含めた心血管系疾患のリスクを高めるというエビデンスも増えている。これらはすべて一次予防に関するものであるが、脳卒中TIAを経験した患者においても脳卒中二次予防の目的で使用される。近年禁煙のために有効な行動・薬物療法がある。

E. 飲酒

慢性アルコール中毒と過度の飲酒がすべてのタイプの脳卒中の危険因子であるという明らかなエビデンスがある。虚血性脳卒中との関連についてはまだ全くの関係を示す報告が多く、適度の飲酒では保護効果があるが適度の飲酒はリスクを高める。大量の報告は脳卒中の一次予防についてであり、再発予防についての報告はほとんどない。

F. 肥満

肥満指数（BMI）が30 kg/m²以上と規定される肥満は心血管疾患を含めた脳卒中の独立した危険因子として知られているが、脳卒中脳卒中での検討はほとんどなく再発予防に関するもので、体重減少が脳卒中再発のリスクを低下させたとの報告はまだない。

G. 身体活動

身体活動は血圧と体重を低下させ、血管拡張を促し、運動習慣を促す傾向があり、脳卒中の多くの危険因子のコントロールに良い結果をもたらす。中等度の運動（表4を参照）により脳卒中のリスクが20%低減し、より活性な運動により27%低減すると報告されている。脳卒中後は有酸素によりしばしば体力が低下する。そのため脳卒中後には、安全な運動から始めて体力をつけてから再発予防に有効と考えられる身体運動を開始する必要がある。脳卒中後有酸素運動と筋トレコーミングを推奨する報告もあるが、脳卒中再発の減少を示した比較試験はまだない。

II. 頭蓋外・頭蓋内主幹動脈のアテローム動脈硬化症に対する脳外科および血管内治療（表5）

A. 症候性頭蓋外動脈疾患

これまで多くの臨床試験で頭蓋動脈内膜剥離術（Carotid Endarterectomy: CEA）と内科治療の併用が内科治療療法の単独の場合と比較されてきたが、内科治療療法はHMG-CoA還元酵素抑制剤（スタチン）、クロビドブロッカー、ジピラモール・アスピリン投薬で、最低の血压管理、禁煙などの積極的なアテローム動脈硬化症の治療は含まれていなかった。一方、CEAの術式にも改良が加えられ、過去数年は血管内治療として頭蓋動脈内膜剥離術・ステント留置術（Carotid Artery Plasty and Stenting: CAS）がCEAのリスクの高い症例に施行されている。

頭蓋内動脈剝離術（CEA）：症候性頭蓋外動脈硬化症について、ECST、NASCET、VASCと呼ばれる3件の大規模前向き無作為試験において70%以上の破壊症ではCEAと内科治療が内科治療単独より優れている。
<table>
<thead>
<tr>
<th>症状/脳血流障害</th>
<th>クラシフィケーション</th>
<th>クラシフィケーションレベル</th>
</tr>
</thead>
<tbody>
<tr>
<td>新規脳梗塞</td>
<td>クラスI</td>
<td>エビデンスレベルA</td>
</tr>
<tr>
<td>新規脳梗塞</td>
<td>クラスII</td>
<td>エビデンスレベルB</td>
</tr>
<tr>
<td>新規脳梗塞</td>
<td>クラスIII</td>
<td>エビデンスレベルC</td>
</tr>
</tbody>
</table>

リスク指標は以下の通りです。

- 既往脳梗塞
- 既往脳出血
- 吸収性脳梗塞
- 变形性動脈硬化
- 家族歴
- 高血圧
- 高脂血症
- 糖尿病
- 胆固醇

この示された。これに3件の臨床試験を含め3,000症例以上の解析では、脳卒中は死亡率が7.1％に再発する。これ臨床試験では50％以下の不良で
CEAの効果がないことも明らかとなった。脳卒中50～
69％の症例で5年間の死亡率は30％に再発する。これ臨床試験では50％以下の不良で
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CEAの効果がないことも明ら
(2) CEAに対する特異的または解剖学的な問題がある（頭部手術の既往、頭部の放射線治療、CEAの再狭窄、狭
窄部位がC2より遠位で鎖骨より近位、対側頭動脈塞塞性、対側観血的、気管切開、解剖学的な高リスクは一般的
に受け入れられているが、併存症によるリスクについて
は麻酔と重症管理の進歩により疑問視されることがある。
SAPPHIRE試験では30日後の脳卒中、死亡、心筋梗塞
がCEAで9.9%，CASで4.4%とCASで優れていたが、両者の差は期間的と心筋梗塞によるものであり、心筋梗
塞の高リスク症例ではCASはCEAに劣らないと結論づ
けられた。症候性の症例が30%しかなかったことが問
題である。米国とカナダで施行されたCREST試験はで
2.92%の症例の症候性と無症候性頭動脈塞塞性（非虚血波で
70%以上または血管造影で50%以上）をもつ患者でCEA
とCASが前向きに無作為に比較されたが、主要評価項目（30
d日後の脳卒中、死亡、心筋梗塞と4年以内の回復後の脳卒中）
はCEAが7.2%, CASが6.8%で有意差がなかった。30
d日以内の症候性患者における脳卒中及び虚血例脳卒中
はCAS群で有意差がなかった（5.5%校3.2%, P = 0.04）。
心筋梗塞はCAS群が有意傾向が2.3%校1.0%,
P = 0.08）。年齢では両群以上のCASの成績が良く、70
歳以上でCASの成績は良かった。

頸外＝頭蓋内（EC/IC）バイパス術：内頸動脈摘出・狭窄に対するこの手術は過去に内科的治療と比較して有意
な効果が認められなかった。最近ボートロンCT（PET）
で血行学的不全が大きな症例で無作為試験（COSS試
験）が行われた。

B. 頸外＝頭蓋内（EC/IC）バイパス術
症候性頭動脈狭窄症についての組織的レビューでは発
症7日以内の脳卒中が頸動脈狭窄より高いが、最
新の内科的療法はまだ定まっておらず、侵襲的治療の役
割も明らかではない。現時点では内科的治療が主体であり、
内科的治療により血管内治療を目的とするCTAや頭蓋内を繰り
返す症例では侵襲的治療が考慮されている。これまでは血
管内治療と内科的治療を比較した無作為試験は
CAVATAS試験のみであり症例数は16例に過ぎないが、
主要評価項目である頸動脈狭窄症の脳卒中について
は4.7年間の経過観察で差がなかった。しかし、この試験は
明らかに統計学のパワーグが不足しており、再発リスクが
高い症例が含まれなかった可能性は指摘されている。

C. 頭蓋内アテローム硬化症
アテローム硬化によって生じた症候性頭蓋内動脈
狭窄症患者は脳卒中再発のリスクが高い。上述のEC/IC
バイパス術の無作為試験でアスピリンによる内科的治療
群に入れた189例中央脳動脈症候群患者では、44月
の観察観察中に年間脳卒中発症率が9.5％であり同側脳卒
中が7.8％であった。WASID試験は頭蓋内内頸動脈、
中央脳動脈、頸動脈、または椎骨動脈の狭窄による脳
卒中・TIAを発症した569例でアスピリン（1,300 mg）
とセルフギパリン（1,000 mg）が無作為に比較され、セルフ
ギパリン群で年間脳卒中発症率が4.4%校1.7%と有意
に低減された。次に、頸動脈内血管形成術またはステント留置術、あるいは両
者の併用、は頸部手術を拡張し、脳血流量を改善し、そ
の後の脳卒中発症を抑えることが期待できる。これま
で内科的療法には成功を収めた。Wingspanステントは米国
食品医薬品局（FDA）により50%以上の頭蓋内動脈狭窄で
内科的治療の効果が認められない症例につき使用が認

III. 心原性塞栓症に対する内科的治療（表6）
心原性塞栓症は虚血性脳卒中患者のおよそ20％を占
める。非心房細動心房細動の患者約2分の1、心房細
動の患者は約4分の1、左心室血栓の患者が約3分の1で
ある。

A. 心房細動
持続性および発作性心房細動は、初発および再発脳
塞血症の持続性心房細動である。米国では200万人以上
が心房細動を罹患していると推定され、年間75,000例以
## 表6 心因性脳塞栓症に関する推奨

<table>
<thead>
<tr>
<th>危険因子</th>
<th>推奨</th>
<th>クラス / エビデンスレベル</th>
</tr>
</thead>
<tbody>
<tr>
<td>心房細動</td>
<td>発作性（持続性）心房細動（AF）または持続性AFを有する脳塞栓またはTIA患者、ビタミンK拮抗薬の抗凝固療法を考慮する。</td>
<td>クラスI エビデンスレベルA</td>
</tr>
<tr>
<td></td>
<td>経口抗凝固薬を投与できない患者ではアスピリン単独投与が推奨される。</td>
<td>クラスI エビデンスレベルA</td>
</tr>
<tr>
<td></td>
<td>クロロフェルトとアスピリンの併用はワルファリンと同様の出血の危険を伴うことから、この併用は、ワルファリンの投与が禁忌の患者には推奨されない。（新発指導）</td>
<td>クラスIII エビデンスレベルB</td>
</tr>
<tr>
<td></td>
<td>AFを有する脳塞栓の危険が高い患者（2ヶ月以内の脳塞栓またはTIAの前兆、CHADS2スコア5または6、機能的活動性または機能的活動性を伴う心房細動）で、一時的に経口抗凝固薬の中断が必要な場合、低分子ヘパリン投与によるプラーゼ活性化が推奨される。（新発指導）</td>
<td>クラスIIa エビデンスレベルC</td>
</tr>
<tr>
<td>紅心性心房細動および左心室拡張</td>
<td>紅心性心房細動またはTIA患者において、心エコー検査またはその他の心機能検査により左心室拡張を証明されれば、脳塞栓の危険が高いと判断される場合、2カ月毎に経口抗凝固薬を考慮する。</td>
<td>クラスI エビデンスレベルB</td>
</tr>
<tr>
<td></td>
<td>心房細動</td>
<td>紅心性心房細動またはTIAの既往のある患者に左心室拡張症候群（LVEF ≤ 35%）による心機能低下が証明される場合、ワルファリンの有用性は証明されていない。（新発指導）</td>
</tr>
<tr>
<td></td>
<td>脳塞栓またはTIAの既往があり、左心室拡張症候群を有する患者で脳塞栓再発を予防するためには、ワルファリン（INR 2.0 ～ 3.0）またはアスピリン（81mg/日）、クロールヒドラミン（75mg/日）またはアスピリン（25mg、3日2回）＋抗血栓薬ジビリダモール（200mg、1日2回）の併用療法を考慮してもよい。</td>
<td>クラスIIb エビデンスレベルB</td>
</tr>
<tr>
<td>心臓弁症</td>
<td>リウマチ性心房細動を有する脳塞栓またはTIA患者では、AFの有無にかかわらず、長期のワルファリン療法（目標INR 2.5 ～ 3.0）が選択される。</td>
<td>クラスIa エビデンスレベルC</td>
</tr>
<tr>
<td></td>
<td>出血の危険の上昇を防ぐため、ワルファリン療法には原則として抗血小板薬を追加すべきではない。</td>
<td>クラスIb エビデンスレベルC</td>
</tr>
<tr>
<td></td>
<td>大動脈弁症または非リウマチ性心房細動を有する脳塞栓またはTIA患者では、AFがなければ抗血小板療法を推奨してもよい。</td>
<td>クラスIb エビデンスレベルC</td>
</tr>
<tr>
<td></td>
<td>慢性弁機能不全を有する脳塞栓またはTIA患者では、抗血小板薬を使用してもよい。</td>
<td>クラスIb エビデンスレベルC</td>
</tr>
<tr>
<td></td>
<td>慢性弁機能不全を有する脳塞栓またはTIA患者では、長期間の抗血小板薬を使用してもよい。</td>
<td>クラスIb エビデンスレベルC</td>
</tr>
<tr>
<td></td>
<td>人工心弁</td>
<td>機能性心房細動を考慮している心房細動またはTIA患者では、INR 3.0（範囲 2.5 ～ 3.5）を目標としたワルファリン療法が推奨される。</td>
</tr>
<tr>
<td></td>
<td>機能性心房細動を考慮している心房細動またはTIA患者が、十分な経口抗凝固療法を受けているにもかかわらず脳塞栓または左心室拡張症を有する患者では、出血の危険の上昇を防ぐため、神経科医または出血の危険を増加させない他の抗血栓薬（血小板剤）が推奨される。</td>
<td>クラスIb エビデンスレベルB</td>
</tr>
<tr>
<td></td>
<td>生体弁を使用している心房細動またはTIA患者、血栓性疾患の原因が他に考えられない場合は、ワルファリンを用いた抗凝固療法（INR 2.0 ～ 3.0）を考慮してもよい。</td>
<td>クラスIb エビデンスレベルB</td>
</tr>
</tbody>
</table>

上に心房細動による脳塞栓を発症する。心房細動患者では、脳塞栓・TIAの既往が脳塞栓発症の最も高い相対リスク（RR = 2.5）となる。年齢、つぼみ性心不全、高血圧、糖尿病、塞栓症の既往はすべて心房細動患者の脳卒中発症リスクを上昇させる。心エコーでの左心機能低下、左房の拡大、心臓弁の石灰化、脳や心エコー、左房内血栓を脳塞栓発症のリスクを増大させる。これまでの臨床試験において、非弁膜性心房細動患者の血栓塞栓症の予防にワルファリンがプラセボと比較して優れた治療効果を示した。ワルファリン投与と非投与群の一次予防効果を検討した3件の研究で聚集し、ワルファリンは全脳塞栓で有効であり、相対的なリスクは68%低減し、年間脳塞栓発症率は非投与群で4.5%、用量調節したワルファリン群で1.4%であった。脳卒中予防のための経口抗凝固薬の最適薬量はINR 2.0 ～ 3.0である。1件の大規模対照試験と2件の無作為比較試験においてINR 2.0以下では脳卒中発症の有効性が低下することが示された。心房細動患者の多くは抗凝固薬が治療薬であり、脳塞栓予防に十分である。より高いINRは出血リスクを増加させる。

アスピリンの有効性はワルファリンよりも低い。3件の臨床試験データの集積では、相対的なリスクの低下率はプラセボと比較して21%であった23。アスピリンの有効性と安全性の最良バランスは75～100mg/日で、ビタミンK拮抗薬で治療できない心房細動患者を対象にアスピリン単独投与とクロピドグレープタシリン投与を比較した試験では、クロピドグレープタシリン投与群で年間2.5%が脳塞栓を発症したのに対し、アスピリン単独群では33%であった（RR = 0.72、p < 0.001）22。大出血はクロピドグレープタシリン投与群が年間2.0%
で、アスピリン単独薬では13.3%であった（RR = 1.57, P < 0.001）。したがってビタミンK拮抗薬による抗凝固療法が使えないが抗血小板療法は可能な心房細動患者には、アスピリン単独投与が推奨される。直接トロンピング阻害薬やXa因子阻害薬を含む、心房細動に対する新たな抗凝固療法の臨床試験が実施されているが、最も成功した代替抗凝固療法は錐角抗トロンピング薬のダプラガットである。

D. 心房細動症

抗血栓療法は心房細動症患者の臓弁と全身性栓子を低下させることが完全には防止しない。したがって各疾患で血栓塞栓症のリスクと治療による出血のリスクを比較する必要がある。

リウマチ性僧帽弁狭窄症は、過去に壁塞栓症の既往があるリウマチ性僧帽弁狭窄症をもつ患者の30〜65%で壁塞栓症は再発する。これらの再発のうち60〜65%は最終の1年間以内に発症し、さらに大動脈弁の6カ月以内である。多くの観察試験において、長期の抗凝固療法がリウマチ性僧帽弁狭窄症をもつ患者の全身性栓子症リスクを効果的に低下させている。

B. 急性心筋梗塞および左心室拡大

急性期に再発療法を行わない場合、前枠心の心房細動が2週間以内に約3分の1の患者に心内血栓が発生し、心房左心室拡大である場合に、抗凝固療法を行わない場合、心房細動患者に薬物内血栓をもつ患者の約10%に臨床的可動的な脳梗塞が起こる。したがって、前枠心の心房細動患者心エコーで左室内血栓を認める患者には経口抗凝固療法が推奨される。抗凝固療法の期間についての合意は必要であり、血栓塞栓症のリスクは3カ月を経過するまで低下するため、心房内に血栓ができやすいとされる慢性左室拡大をもつ患者でも隆塞症のリスクが比較的低くなる。

C. 心房細動

虚血性脳卒中患者の約10%で左室拡大が30%以下であるとされる。WATCH試験は心不全患者を対象としてワルファリンの効果を検討した最初の試験であるが、脳塞栓症に対するアスピリンまたはクロピドグレルと比較したワルファリンの有効性を示すだけの統計学的なデータが得られず中止された。同様に、慢性心不全患者を対象にしたアスピリンまたは他の抗血小板療法の無作為試験も行われていなかった。
IV. 非心原性脳卒中または一過性脳虚血发作に対する抗血栓治療（表7）

A. 抗血小板薬

アスピリン：メタ解析の結果，アスピリンはプラセボとの比較試験で脳卒中の発症リスクを15％低下させ，その効果は用量50～1500mgの範囲で変わらないが，用量に比例するほど消化管出血を合併しやすかった。

チロキシン：血小板のADP反応阻害薬であり，脳卒中患者を対象としたCATS無作為試験では，プラセボに対しての血栓イベントの相対リスクが23%抑制された。

TASS試験では，チロキシン（250mg×2回/日）はアスピリン（650mg×2回/日）に対して我々の方法の相対的リスクを10%抑制した（P=0.048）。副作用に関しては下痢や悪心があり，消化管出血はアスピリンと同等，もしくは多少少ないとされる。血栓性血管狭小症減少性脳梗塞（TTP）が報告されている。

クロピドグレル：1つのADP反応性血栓症薬で，これまでにアスピリン，アスピリン＋チロキシン＋プラセボ併用との比較試験が報告されているが，プラセボとの比較試験は Hindi CAPRIE試験で脳卒中，心筋梗塞または末梢動脈閉塞症のある患者で，他院血管性脳卒中：末梢動脈閉塞症の発症率はアスピリン群（325mg/日）の5.83％に対しクロピドグレル群（75mg/日）では5.32％で相対的リスクは8.7％抑制された（P=0.043）。しかし脳卒中後にCAPRIE試験に組み入れられた症例のサンプル解析では有意差がなかった。

表7 非心原性脳梗塞またはTIAに対する抗血栓薬（注）の効果と副作用

<table>
<thead>
<tr>
<th>推薬</th>
<th>クラスとエピデンスレベル</th>
</tr>
</thead>
<tbody>
<tr>
<td>非心原性脳梗塞またはTIA発症後の患者において，脳梗塞の再発およびその他の心血管イベントの危険を低減させるため，経口抗凝固療法および抗血小板療法の使用が推奨される。</td>
<td></td>
</tr>
<tr>
<td>アスピリン（50～325mg/日）</td>
<td>クラス1 エピデンスレベルA</td>
</tr>
<tr>
<td>アスピリン25mg＋他抗血小板療法</td>
<td>クラス1 エピデンスレベルA</td>
</tr>
<tr>
<td>チロキシン</td>
<td>クラス1 エピデンスレベルA</td>
</tr>
<tr>
<td>チロキシン＋アスピリン</td>
<td>クラス1 エピデンスレベルB</td>
</tr>
<tr>
<td>クロピドグレル</td>
<td>クラス1 エピデンスレベルB</td>
</tr>
<tr>
<td>クロピドグレル＋アスピリン</td>
<td>クラス1 エピデンスレベルB</td>
</tr>
<tr>
<td>クロピドグレル＋テナソドロール</td>
<td>クラス1 エピデンスレベルB</td>
</tr>
<tr>
<td>クロピドグレル＋アスピリン＋チロキシン</td>
<td>クラス1 エピデンスレベルB</td>
</tr>
</tbody>
</table>

注）脳梗塞またはTIA発症後の患者において，クロピドグレル投与後にアスピリンを追加すると出血の危険を増大するため，二次予防に併用は原則として推奨されない。

アスピリンに対するアレルギーのある患者にはアスピリンが直接適応である。

アスピリン応用中に脳梗塞を発症した患者において，アスピリンの增量により効果が改善するというデータはない。

アスピリン応用中にイベントが発生した患者に対する抗血小板療法の変更はしばしば検討されるが，どの抗血小板療法についても，あるいはその併用についても検証されている。
は増加した。PRoFESS 試験では脳卒中再発率はクロビドグルルと同等だった。
クロビドグルルとアスピリンの併用：MATCH 試験では発症 3 カ月以内の TIA または脳梗塞後患者を対象として、クロビドグルルアスピリンとクロビドグルル単剤が比較された。脳卒中再発を含むすべての評価項目で両群に差はなかったが、重篤な出血性合併症は併用群で有意に多く、生存の危険を伴う高血圧が 1.3 倍増加した。クロビドグルルアスピリンは急性脳梗塞患者には推奨されているが、急性期が過ぎた脳卒中患者には同じようなリスクに見合う恩恵は示さなかった。CHARISMA 試験ではクロビドグルルアスピリンとアスピリン単剤の効果が比較されたが、28 カ月間でイベント発生率が併用群 68% に対してアスピリン単剤群 73% と差はなかった (RR = 0.93, P = 0.22)。
経口抗凝固薬の選択：アスピリン、チクロビジン、アスピリン＋スピピリダミールは脳卒中の二次予防に有効性が示された。クロビドグルルについてはプラセボ対照試験が行われていないが、データから判断すると他の抗血小板と同等の効果があると考えられる。しかしアスピリンは相対的に有効性、安全性、費用、患者背景、患者の希望等に基づいて選択すべきである。アスピリン＋スピピリダミールはアスピリン単独に比べて有用かもしれないが、その効果は 100 人を 1 年間治療した場合に無難程度である。チクロビジンは二次予防においてアスピリンに優るかもしれないが、安全性に関して問題がある。消化管出血や他の重要性の出血のリスクはクロビドグルルよりもアスピリンやアスピリン＋スピピリダミールの方が高くといわれるが大きな差はない。スピピリダミールは頭痛を誘發する傾向がある。チクロビジンは TTP 発症との関連があるため、他の薬剤が使用できない場合などで注意深く用いるのが望ましい。費用面では、アスピリンが圧倒的に廉価である。アスピリン＋スピピリダミールでアスピリンが使用できない場合には、クロビドグルルが適している。頭痛を誘発するためスピピリダミールが服用できない場合には、アスピリン、クロビドグルルのいずれかが適当である。アスピリンとクロビドグルルの併用は急性脳梗塞治療や最近血液動的な変化を受ける症例には適当かもしれない。血小板薬の変更によって再発リスクを減少することを検証した研究はない。
新薬の薬剤：サルボグレレートは脳梗塞の治療効果がアスピリンに対する劣悪性を証明されなかった。triflusal は予防試験の段階である。クロスタゾールは脳卒中の予防として有効性が示されたが、アスピリンと同等の効果を得られている。

B. 経口抗凝固薬
非心原性脳卒中 TIA の再発予防に対するワルファリンとアスピリンの比較において、SPIRIT 試験では高用量の抗凝固薬 (INR 3.0 〜 4.5) が用いられた結果、出血性合併症が頻繁に報告された。WARSS 試験ではアスピリン (325 mg/日) とワルファリン (INR 1.4 〜 2.8) が比較され、再発率と出血性合併症とも両群で差はなかった。前述の WASID 試験で脳梗塞内乾燥脳凝固変化を有する患者においてワルファリン (INR 2.0 〜 3.0) とアスピリン (1,300 mg) が比較されたが、有効性に差はなく、出血性合併症はワルファリン群に多くみられた。

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V. 特殊な病態による脳卒中に対する治療
（表 8）

A. 動脈解離
動脈瘤や椎骨動脈解離を伴う脳卒中は TIA と脳梗塞の原因として比較的よくみられ、特に若年者に多い。頭痛、頸部外傷により起こることがある。10% 以上に特発性、または無細胞性で統合失調症、Marfan 症候群、Ehlers-Danlos 症候群 (type IV)、不完全骨形成症、コラーゲン症、慢性の出血性疾患などの全例に伴う。
脳卒中の発症部位は、頭痛、頭部外傷、突発性的動脈破裂と考えられる。動脈解離は動脈瘤や椎骨動脈解離を伴う脳卒中は TIA と脳梗塞の原因として比較的よくみられ、特に若年者に多い。頭痛、頸部外傷により起こることがある。10% 以上に特発性、または無細胞性で統合失調症、Marfan 症候群、Ehlers-Danlos 症候群 (type IV)、不完全骨形成症、コラーゲン症、慢性の出血性疾患などの全例に伴う。

注：このガイドラインでは、日本で施行されたクロスタゾールとアスピリンの無作為比較試験 CSFS-II (Lancet Neurol 2010; 9: 909-906) において、クロスタゾールの有用性が示された結果についてはまだ普及していない。
表8 特殊な病態を有する脳梗塞に関する推奨

<table>
<thead>
<tr>
<th>第19因子</th>
<th>性状</th>
<th>クラス/エビデンスレベル</th>
</tr>
</thead>
<tbody>
<tr>
<td>動脈硬化</td>
<td>原因</td>
<td>クラスⅠb</td>
</tr>
<tr>
<td>原因</td>
<td>クラスⅠb</td>
<td>エビデンスレベルB</td>
</tr>
<tr>
<td>原因</td>
<td>クラスⅠб</td>
<td>エビデンスレベルB</td>
</tr>
<tr>
<td>原因</td>
<td>クラスⅠб</td>
<td>エビデンスレベルC</td>
</tr>
<tr>
<td>PFO</td>
<td>有する脳梗塞またはTIA患者における、イベントの再発予防として抗血栓療法が適当である。</td>
<td>クラスⅠb</td>
</tr>
<tr>
<td>PFO</td>
<td>有する脳梗塞またはTIA患者における、イベントの再発予防として抗血栓療法が適当である。</td>
<td>クラスⅠb</td>
</tr>
<tr>
<td>PFO</td>
<td>有する脳梗塞またはTIA患者における、イベントの再発予防として抗血栓療法が適当である。</td>
<td>クラスⅠb</td>
</tr>
</tbody>
</table>

脳卒中予防

A. 脳卒中予防

1. アンチコアセプト
   - 使用は、脳卒中リスクを有するTIA患者の再発予防に限られる。
   - 使用を考慮する場合、EPPAの指針に従う。

2. 抗血凝集療法
   - 使用は、脳卒中リスクを有するTIA患者の再発予防に限られる。
   - 使用を考慮する場合、EPPAの指針に従う。

3. 抗血小板療法
   - 使用は、脳卒中リスクを有するTIA患者の再発予防に限られる。
   - 使用を考慮する場合、EPPAの指針に従う。

4. 抗凝固療法
   - 使用は、脳卒中リスクを有するTIA患者の再発予防に限られる。
   - 使用を考慮する場合、EPPAの指針に従う。

5. PFO
   - 使用は、脳卒中リスクを有するTIA患者の再発予防に限られる。
   - 使用を考慮する場合、EPPAの指針に従う。

解離の解剖学的工法は、脳卒中再発のリスクを高めない。

B. 肝臓トウモロコシ

心内膜症の有無を考慮した場合、肝臓トウモロコシ（PFO）と肺動脈静脈栄養がある。PFOは肺動脈静脈栄養を有する（中位の10mmを超える病状を含む）ASAを伴うことがある。PFOは成人の15〜25％、ASAは2〜3％に存在すると推定される。2000年のメタ解析では、PFOとASAは55歳未満で有効な脳卒中の危険因子であることが示唆されている（OR: PFO 3.1, ASA 0.64, 両者15.59）。55歳以上でもリスクは増加したがオッズ比は小さかった。PICSS研究では、630例が検討され、34％にPFOを認め、2年間の脳卒中再発率はPFO（+）群で14.8％、PFO（－）群で15.4％と有意差を認めず、PFOの大きさ、ASAの有無も再発に関与しなかった。また2年間の再発率がアスピリン群で13.2％、ワルファリン群で16.5％と有意差がなかった。一方コーポ・ヘパリンにおけるPFO-ASA研究では、原因不明の脳卒中を発症した18〜55歳の患者581人を300 mg/日のアスピリンで4年間治療したが、再発率はPFO群では2.3％、PFO + ASA群では15.2％、心房細動（+）群では42.4％であった。PFOの重要性、ASA合併の意義、最適な予防法はまだ明らかでない。種々の循環器症の無作為比較試験が現在実施中である。
C. 高ホモシスチン血症

コホートおよび症例対照研究では、高ホモシスチン血症は脳卒中リスクが2倍になることを示している。葉酸補充効果についてのメタ解析では、葉酸は脳卒中イベントの予防効果を18%減少させることができることが示された。HOFPE-2試験では、血行障害または糖尿病を合併した55歳以上の患者5,522例を対象としてホモシスチン低下を目的としたビタミン（葉酸、ビタミンB6、ビタミンB12）と効果の無作為比較試験で、主要評価項目は心血管死、脳梗塞、脳卒中であり、5年間の観察でビタミン群は主要評価項目を減少させなかった。しかし、脳卒中はビタミン群4.0%，偽薬群5.3%（P=0.03）でビタミン群にリスクの減少がみられた。VISP試験では、非心原性脳卒中後に軽度から中等度の高ホモシスチン血症（男性＞9.5 μmol/L、女性＞8.5 μmol/L）の患者を対象に高用量または低用量の経口ビタミンの2群間で2年間の無作為比較試験を行った。高用量群ではホモシスチンレベルは低下したが脳卒中の再発率は減少しなかった。

D. 緊迫性脳塞栓

遺伝的血栓性素因：遺伝的性血栓形性素因block
cの再発リスクになるかどうかはほとんど知られていない。プロテインC、プロテインSあるいはアンチトロンビンIII欠乏症、第5凝固因子Leiden、プロトロンビンのG20210A変異、methylene tetrahydrofolate reductase (MTHFR)のC677T変異、稀に成人的脳塞栓においても見られる、最も頻度の高い遺伝的性血栓形性素因は第5凝固因子Leidenの突然変異（Arg506Gln）によって起こる活性化プロテインC（APC）抵抗性である。APC抵抗性は脳塞栓症が多発し、虚血性脳卒中との関連も報告がある。虚血性脳卒中の治療は、脳梗塞の予防、臨床および流動学的所見により、短期あるいは長期の抗凝固療法の適応となる。プロトロンビンC、プロテインCおよびATIII欠乏症、ヘパリン誘発性血小板減少症、播種性血管内凝固症、あるいは癌関連血栓症なども先天的凝固亢進状態の一般的な指標であるが、脳卒中二次予防に特有のガイドラインはない。

ラリン脳塞栓：抗リン脂質抗体の頻度は、1～6.5%で高齢者、ループスの患者で高い。抗リン脂質抗体陽性症候群は、頻度は高くないが多臓器に脳塞栓・動脈瘤発症症、および単発を呈する。血栓症イベントを防ぐためにIgGおよび/あるいはIgM型の抗カルテロシジン抗体またはループス凝固因子が少なくとも6週間の間隔を設定して2回以上、血中に中等度または高濃度で認められなければならない。抗リン脂質抗体と脳卒中の関連は50歳未満の若年者で強い。動脈硬化または静脈血栓をきたした抗リン脂質抗体陽性者が対象とした1つの研究では、強力なフィナフィン治療（INR 3.1～4.0）は中等度治療（INR 2.0～3.0）よりはるかに再発予防効果において差を認めなかった。高齢者においては抗リン脂質抗体と脳卒中の関連については一致した結果が得られていなかった。

E. 好中球性血栓症

脳卒中は好中球性血栓症（SCD）とよくみられる合併症である。好中球性脳卒中の主因は内皮細胞の反復性傷による内膜炎形成とそれに起因する動脈壁の発症が考えられている。SCDの主な治療は輸血である。しかし観察を対象とされたSTOP無作為試験で、輸血が一次予防に有効であることが示された。再発予防の無作為比較試験ではないがヘモグロビンSの生成を抑制するために十分な輸血が再発予防に有効であるとされている。その他、成人SCD患者の脳卒中再発予防としては、ヒドロキシアドレバクサムの使用が推奨されている。

F. 腦静脈洞血栓症

脳静脈洞血栓症の年間推定頻度は100万人あたり3～4人である。脳卒中の1/4未満であるが動脈の脳卒中と治療方法が異なるためその診断は重要である。治療および早期再発防止のために早期の抗凝固治療が必要である。しかし比較試験は2件しかない。1件は用量調節された未分画ヘパリンと偽薬の比較で、ヘパリンの有用性が明らかにされてきた20例の登録で早期中止となった。ヘパリン群の10例中8例が完治し、プラセボ群は1例のみが完治した。最近、脳静脈洞血栓症59例を対象としてナノヘパリン（50mU-Ⅹa/1kg/1日2回）と偽薬の無作為比較試験が行われた。予後不良例は抗凝固療法群で13.5%、偽薬群で21%であったが有意差はなかった。以上の2件の試験によるメタ解析では、症状性脳梗塞の有無にかかわらず、急効型ヘパリンまたは低分子ヘパリンの使用を勧めている。抗凝固療法の持続期間に関する無作為比較試験はないが、頭蓋外深部静脈血栓症（DVT）のガイドラインに従えば、一過性の脳塞栓による今回のDVTは3ヶ月、誘因のない初回DVTでは6ヶ月とも5ヶ月、誘因のないDVT再発では無期限に投与するとしている。
は一般的にワルファリン中止後無期限に投与する。

G. ファブリ病

ファブリ病はLاشゾームのX染色体遺伝αガラクトシノーゼ欠損症による血管内皮細胞に腎臓を含む多臓器障害をきたす稀な疾患である。脳卒中は椎骨動脈・脑底動脈系障害、心原性塞栓症、小血管病を含むものである。抗血小板療法はすでに存在する血管病変による高血圧性脳卒中の予防に有用と思われる。αガラクトシノーゼ1mg/kg、低分子ヘパリン内投与の無作為比較試験では、腎臓、心臓、脳内での血管内皮細胞への新皮の沈着を減少させた。また、全身として腎・心・脳血管イベントと死亡を減少させた（HR=0.47）。血栓形成療法による脳血管の改善は示されなかったが、脳卒中のリスクは高かった。脳卒中予防には早期介入、高用量が必要かもしれない。すべての男性患者は16歳から、これらの患者は臨床無症状が見られたり臓器障害が進行する場合に酸素補充療法を推奨される。

（文責：橋本 知夫）

VI. 女性に特有な脳卒中（表9）

A. 妊娠

妊娠中、産前には脳卒中を発症する。妊娠中の脳卒中は100,000例の出産につき11人から25人発症し、産後3日間で最もリスクが高い。妊娠中のための緊急手術のリスクが高い、TIAや脳梗塞の既往がある女性に対する妊娠中の抗凝固療法は複数になる。血栓性疾患や人工心臓弁のため抗凝固療法が必要な症例では、妊娠中にピタミンK拮抗薬、低分子ヘパリン（UFH）または低分子ヘパリン（LMWH）が使用される。ラフィットは妊娠中に使用し妊娠中に有害な影響を与えない可能性があるため、通常妊娠期間を通じてUFHまたはLMWHが用いられる。ただし、UFHまたはLMWHの有効性が懸念される高リスク群では、妊娠13週以降はワルファリンを使用し出産時にUFHまたはLMWHに切り替えられる。LMWHは長期間ヘパリン療法によるヘパリン薬導血栓形成症（HIT）や骨髄障害を避けることができるが、LMWHを投与されている妊娠女性では薬物動態の変化が観察されており、投与量を体重によって標準化し、タキ素因子レベルを注意深くモニタする必要がある。血栓塞栓症のリスクが高くない妊娠女性では、妊娠期間の3分の1を過ぎた後からの少量のアスピリン（50mg/日から150mg/日）が安全である。

B. 院内後ホルモン補充療法

院内後ホルモン補充療法は血管系疾患の予防効果があるとして以前は推奨されていたが、脳梗塞患者の無作為試験と一次予防試験で有益な効果を示さず、むしろホルモン使用群の女性で脳梗塞発症率が上昇する結果が示された。脳梗塞またはTIAの既往がある664人を対象としたWEST試験では、2.5年間の観察でエストラジオールの使用による脳梗塞再発リスクの低下や死亡リスクの低下は示されなかった。

（文責：宫本 亮・松本 恵美）
*広島大学医学研究学部

VII. 腦内出血後の抗凝固療法（表10）

これまでの多くの研究では、人工心臓弁疾患に対する抗凝固療法は受ける患者で、脳内出血（ICH）よりも硬膜下血腫（SDH）を発症したケースを対象としている。
表10 出血内出血後の抗凝固療法に関する推論

<table>
<thead>
<tr>
<th>因子名</th>
<th>推論</th>
<th>クラス</th>
<th>エビデンスレベル</th>
</tr>
</thead>
<tbody>
<tr>
<td>腹腔内出血</td>
<td>ICH、SAHまたはSDHが認められた患者では、出血性脳虚血のリスクを考慮して、新鮮凝固療法またはプロトロンピピン投与は勧められる。</td>
<td>クラスIIa</td>
<td>エビデンスレベルB</td>
</tr>
<tr>
<td>研究</td>
<td>ヘパリンに緊急したICHにおいてヘパリンの効果を考慮するために、ヘパリン投与中からのスクリーミングが存在する推論が報告されている。</td>
<td>クラスI</td>
<td>エビデンスレベルB</td>
</tr>
<tr>
<td>出血性脳虚血</td>
<td>ICH後の抗凝固療法の適応は、出血虚血のリスクを考慮して、ヘパリンの効果を考慮する推論が報告されている。</td>
<td>クラスIIa</td>
<td>エビデンスレベルB</td>
</tr>
<tr>
<td>術式</td>
<td>アプロロフェクチンの効果を考慮する推論（例）</td>
<td>クラスI</td>
<td>エビデンスレベルB</td>
</tr>
</tbody>
</table>

ICH一側内出血SAHへも脳下出血SAHへも内出血。

よく損傷脳出血に関する報告は極めて少ない。総じて、大规模な前向き無作為試験のデータは不足している。258例の後向き研究で、INR > 3.0の患者ではINR < 1.2の患者に比べて脳虚血のリスクが有意に増加することが（P = 0.002）報告されている。よってICHとSDHの急性期において、プロトロンピピン複合体製剤やピラミドK、またはこれに新鮮凝固療法を併用して、INRをできるだけ早期に低下させることが推奨される。プロトロンピピン複合体製剤は効果発現に要する時間が15分以内と短いので、重症出血例では新鮮凝固療法よりも優先されることは多い。

適切な抗凝固療法の中断時期は不明である。終了は24H後でフィナリオンを中止した35例が検討と平均14日フィナリオンを中止した人工肝機能35例の検討では、それぞれ中断期間中の凝固虚血症はなかった。フィナリオン内服中のICH患者141例を対象とした研究では、抗凝固療法を10日間（中央値）中にした場合、30日以内の脳虚血イベント発症リスクは2.1％だった。患者背景別にみると、人工肝機能で2.9％、心原性凝固療法の既往があるAF患者で2.6％、TIAもしくは脳虚血の既往がある患者で4.8％だった。そのうちフィナリオンを再開した35例の中で、入院中のICH再発は認めなかった。抗凝固療法の中断により脳虚血症のリスクを効用しなければならない。脳虚血症はアミロイド凝固症が障害である可能性があるため再発のリスクが高い。若者、高齢、高血圧、抗凝固療法の血漿、血液透析、MRIの変化状態皮膚小出血などがICHの新規発症・再発のリスク因子であることが報告されている。抗凝固療法の早期再開が必要な患者ではフィナリオンよりもヘパリンや低分子ペリリンの薬効が安定である。その理由として、用量設定が簡便であること、すぐに中止可能であること、酸化プロテーゼによって速やかに中和できるため、などがあげられるが、ポーズ投与は出血リスクを増加させることを推奨しない。

出血性脳虚血はICHと状況が異なるが比較的よく透析される疾患であり、多くの無症候性で、出血による症状がなく見逃さなければならず、抗凝固療法の適応を進める報告がある。

（文献：星野 昌史*内山 真一郎
*東京女子医科大学神経内科）

Ⅷ. ガイドライン実施のための特別な手段と高リスク集団への適用（表11）

エビデンスに基づいた疾患管理の啓蒙に、各種専門学
会や政府機関がガイドラインを出版しており、この内容が普及することで医療従事者、また最終的には患者の行動や健康に変化が起こると想定される。過去の経験では、このことが大きな彼が医療従事者であるため、計画的な実施戦略がガイドラインの普及が重要である。AHAのGet With The Guidelines（GWGT）プログラムでは、脳卒中の二次予防について2003年から2008年までに1,000以上の病院が参加し、退院時の抗血栓療法、心房細動に対する抗凝固療法、脳卒中等症の治療、類症の改善が見られている。National Institutes of Health Roadmap for Medical Researchは、臨床的有効性が認める治療法と実際の地域社会での治療の普及率の解明に取り組んでいる。科学的知識を実践に移し、健康格差への取り組みを確実に行うために、Institute of MedicineのNational Academy of Sciencesは、予防と治療を一体化し、患者がエピデンスに基づいた医療を受けやすい体制を作りつつある。急性脳卒中では、ガイドライン通りと健康面・経済面での改善を関連づけるデータが存在し、再発予防にあたって研究されている。

最もリスクの高い人口集団の同定と対策：疾患原因の増加や健康に対する認知が不十分であるため、脳卒中のTIA再発のリスクが高い集団には具体的な取り組みが必要性が強調されている。リスク管理は脳卒中のリスクを高め、抗凝固薬や抗血小板薬の適切な治療の合併症は最もリスクが高い。社会的経済的弱者は医療機関を受診する機会が限られているため、脳卒中のリスクが高い。1996年アメリカAcademy of NeurologyのTask Forceの報告で述べられているように、脳卒中のような神経疾患による医療機関の受診にはまた制限があり、これには社会保護の様々な個人差の問題や都市部における専門医・専門施設の問題が関与しているかもしれない。米国の脳卒中死亡率は1990年から1998年までに12%減少しているが、すべての民族集団が同様に恩恵を受けているわけではない。また、多くの集団では効果的な治療が遅れているが、黒人女性は特に経験にやや、BMIの増加が心疾患、糖尿病、脳卒中の高い罹患率と死亡率の原因の1つになっている。これら脳卒中のリスクが高い人にとって、ガイドラインの不履行や脳卒中予防の無視は重大な問題であり、患者、医療提供者、健康管理組織を含めた多面的な取り組みの必要性が指摘されている。エピデンスに基づいた脳卒中予防の実施、脳卒中予防に関する研究の深化、統合化には、NINDSのような公的機関、AHA/ASAのような非営利組織、AANのような医療専門組織を通じた連邦政府との提携が必要である。
Directrices para la prevención de enfermedades cerebrovasculares en pacientes con ictus o accidente isquémico transitorio. Una guía de American Heart Association/American Stroke Association para los profesionales de la salud

El Stroke Council de la American Heart Association inaugura con este capítulo publicado en el mes de enero una serie de actualizaciones de las guías de práctica clínica en enfermedades cerebrovasculares, en este caso centradas en la prevención secundaria de ictus o AIT. Se actualizan las recomendaciones previas en el manejo de la presión arterial, diabetes, objetivos de reducción de los niveles de LDL colesterol, síndrome metabólico, insistiendo además en la optimización del tratamiento médico con modificación de factores de riesgo, tratamiento antiagregante plaquetario y estatinas en los pacientes con estenosis extracranial de arterias carótidas o vertebrals. También se abordan las evidencias disponibles en el tratamiento de la arteriosclerosis intracraneal. En el apartado de infarto cerebral de origen cardioembólico, las novedades se centran en la no recomendación de la asociación de antiagregantes (clopidogrel y aspirina) en pacientes con contraindicación a warfarina, y en aconsejar el uso de heparinas de bajo peso molecular en pacientes con fibrilación auricular de alto riesgo de ictus a los que se interrumpa temporalmente el tratamiento anticoagulante oral, sin hacer mención todavía a los resultados de los ensayos con nuevos anticoagulantes. Las recomendaciones de tratamiento antiagregante en pacientes con infarto cerebral de origen no cardioembólico se mantienen sin cambios respecto a la edición anterior. Posteriormente se revisan las evidencias disponibles en el tratamiento de pacientes con infarto cerebral y otras condiciones específicas como disección arterial, foramen oval permeable, hiperhomocisteínergia, estados de hipercogulabilidad, enfermedad de células falciformes, trombosis venosa cerebral y enfermedad de Fabry. Finalmente se abordan apartados especiales como el ictus en mujeres, la continuidad de tratamiento anticoagulante tras una hemorragia cerebral y la aplicación de las guías en pacientes de alto riesgo. (Comentario a 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. Karen L. Furie, Scott E. Kasner, Robert J. Adams, Gregory W. Albers, Ruth L. Bush, Susan C. Fagan, Jonathan L. Halperin, S. Claiborne Johnston, Irene Katzan, Walter N. Kernan, Pamela H. Mitchell, Bruce Ovbiagele, Yuko Y. Palesch, Ralph L. Sacco, Lee H. Schwamm, Sylvia Worringer-Mollendor, Tanya N. Turan, Deidre Wentworth on behalf of the American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Clinical Cardiology, and Interdisciplinary Council on Quality of Care and Outcomes Research. Stroke. 2011;42:227-276.)
AHA/ASA Guideline

缺血性卒中或短暂性脑缺血发作患者
卒中预防指南

美国心脏协会 / 美国卒中协会为医疗保健专业人员制定的指南

美国神经病学会认证本指南为神经科医生的教育工具
美国神经外科医师协会和神经外科医师大会评审本指南并认定其教育内容

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

Karen L. Furie, MD, MPH, FAHA, Chair; Scott E. Kasner, MD, MSCE, FAHA, Vice Chair; Robert J. Adams, MD, MS, FAHA; Gregory W. Albers, MD; Ruth L. Bush, MD, MPH; Susan C. Fagan, PharmD, FAHA; Jonathan L. Halperin, MD, FAHA; S. Claiborne Johnston, MD, PhD; Irene Katzan, MD, MS, FAHA; Walter N. Kernan, MD; Pamela H. Mitchell, PhD, CNRN, RN, FAAN, FAHA; Bruce Ovbiagele, MD, MS, FAHA; Yuko Y. Palesch, PhD; Ralph L. Sacco, MD, MS, FAHA, FAAN; Lee H. Schwamm, MD, FAHA; Sylvia Wassenheit-Smoller, MD, PhD, FAHA; Tanya N. Turan, MD, FAHA; Deidre Wentworth, MSN, RN; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Clinical Cardiology, and Interdisciplinary Council on Quality of Care and Outcomes Research

摘要：这一更新的指南用于缺血性卒中/短暂性脑缺血发作的幸存者，为他们提供有关预防缺血性卒中全面和及时的循证医学建议。循证医学建议包括对危险因素的控制、对动脉粥样硬化的干预、对心源性栓塞的抗凝治疗、对非心源性卒中的抗血小板药物的使用等。进一步预防卒中复发的建议在其他一些特殊情况下列出，包括动脉夹层、卵圆孔未闭、高同型半胱氨酸血症、高凝状态、镰状细胞病、脑静脉窦血栓形成、女性卒中（尤其是与妊娠和绝经后激素替代治疗相关的卒中）、脑出血后抗凝血剂的应用以及在其他高危人群中指南执行的特殊措施等。

关键词：美国心脏协会科学声明，短暂性脑缺血发作，卒中，卒中预防

(Stroke. 2011;42:227–276. 杜万良 梁瑾煜 王春育 陈盼 李姝雅 译 刘丽萍 高山 校)
卒中具有高死亡率和高发病率。有短暂性脑缺血发作 (transient ischemic attack, TIA) 或卒中病史的患者复发的风险增加。每年 795 000 位新发卒中患者中，大约有四分之一为复发性卒中。由于大部分病例中已知的危险因素，低血管性结局方面的证据也采用等级分类方法。本指南中所作的是将大动脉粥样硬化性梗死 (atherosclerotic ischemic stroke, AIs) 和卒中发病机制确定的分类远不如人意，显示其相关因素的诊断性检查也不够充分。关于 TIA 或卒中患者诊断性检查的操作时机和类型的具体建议不一致。本指南推荐意见不是本指南谈论范围；所有卒中患者至少应接受影像学检查以鉴别缺血和出血事件。TIA 和缺血性卒中患者均应接受足以排除各种高危状况的检查，如颈动脉狭窄或心房纤颤 (atrial fibrillation, AF) 引起的缺血症状。

1. TIA或缺血性卒中患者危险因素控制

1.1 高血压

高血压定义为收缩压≥140 mmHg 或收缩压≥90 mmHg[8]。据统计，美国约有 7200 万高血压患者。总的来说，收缩压与舒张压均与卒中风险相关，即使收缩压为 115 mmHg, 血压与卒中风险依然相关[9]。随机对照试验的荟萃分析显示，降低血压能使卒中风险下降 30%–40%[10–12]。即使没有药物疗效的确切证据，血压下降幅度越大，卒中风险越低[13]。

基于证据提出高血压患者血压筛查和治疗建议，美国卒中协会 (American Stroke Association, ASA) 指南[14]，从缺血性卒中一级预防方面对其进行概述，国家联合委员会第七次报告 (the Seventh Report of the Joint National Committee, JNC 7)[15] 就高血压预防、发现、评估及治疗做了详细说明。JNC 7 强调生活方式改变在高血压处理中的重要性。降压相关生活方式干预包括：减轻体重 (包括限盐)、摄取富含水果、蔬菜和低脂乳制品的饮食、规律的需氧体力活动以及限制酒精摄入[14]。

尽管大量随机试验和荟萃分析支持高血压治疗对预防主要心血管疾病，特别是卒中的重要性，但很少有试验直接针对卒中或 TIA 患者二级预防中的降压治疗[16,17]。这些试验的高血压治疗组和非治疗组的卒中风险无显著差别。近年来的两项随机试验发现，卒中风险降低与收缩压和舒张压的降低有关[18,19]。

一项随机试验的荟萃分析显示，降压治疗能降低卒中或 TIA 后复发卒中的风险[13]。该荟萃分析包括至 2002 年进行的七个随机试验：荷兰 TIA 试验 (A comparison of two antihypertensive regimens in patients with transient ischaemic attack, TIA) 中后降压治疗组 (Poststroke Antihypertensive Treatment Study, PATS)；吲达帕胺，一种利尿剂[17]，卒中后降压治疗研究 (Heart Outcomes Prevention Evaluation, HOPE)；雷米普利和阿替洛尔，一种β受体阻滞剂[17]，卒中后降压治疗研究 (Poststroke Antihypertensive Treatment Study, PATS)；吲达帕胺，利尿剂[18]，心脏结局预防评价 (Heart Outcomes Prevention Evaluation, HOPE)；雷米普利和阿替洛尔，一种β受体阻滞剂[17]，卒中后降压治疗研究 (Poststroke Antihypertensive Treatment Study, PATS)；吲达帕胺，利尿剂[18]，心脏结局预防评价 (Heart Outcomes Prevention Evaluation, HOPE)。
### 表 1 采用的建议类型和证据水平

<table>
<thead>
<tr>
<th>疗效大小</th>
<th>I 类</th>
<th>II a 类</th>
<th>II b 类</th>
<th>III类</th>
</tr>
</thead>
<tbody>
<tr>
<td>风险</td>
<td>低</td>
<td>中</td>
<td>高</td>
<td>低</td>
</tr>
<tr>
<td>药物治疗</td>
<td>应当实施操作或给予药物治疗</td>
<td>建议支持操作或药物治疗有/有效</td>
<td>建议不能确定操作或药物治疗有/有效</td>
<td>建议认为操作或药物治疗无/无效，并可能有害</td>
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<td>数据</td>
<td>证据充分，源于多个随机试验或荟萃分析</td>
<td>证据源于多个随机试验或某些非随机研究的证据，存在较大矛盾</td>
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*来自临床试验或登记的数据，不同亚人群中的有/有效性/有效性/有效性，如性别的、年龄、糖尿病史、MI 病史、心力衰竭史、阿司匹林服用史，基于 B 级或 C 级证据提出的建议并不意味着建议缺乏说服力。本指南中论述的很多重要临床问题并未付诸临床试验，即使没有随机试验，仍由非常明确的临床共识，认为某种检查方法或治疗方法有用或有效。

†一种疗法与另一种疗法比较的效果（只是 I 类和 II a 建议，A 级和 B 级证据）来说，这些词或短语可能会加上“优先于”或“选择…”而不再是“…”以提示倾向性。比如，“建议 A 疗法优于 B 疗法用于…”或“选择 A 疗法而不是 B 疗法用于…是合理的”。研究者如希望使用比较的词或短语，请在统计学方法和策略进行直接比较。

利，血管紧张素转化酶抑制剂 [angiotensin-converting enzyme inhibitor, ACEI]39；以及培哚普利预防卒中复发研究 (Perindopril Protection Against Recurrent Stroke Study, PROGRESS)：培哚普利，ACEI，合用或不合并用肟帕妥昔和单用 ACEI，合用或不合并用肟帕妥昔和单用 ACEI39-41，以及其他三个更小规模的试验。这些试验共纳入 15 527 个患者，随机选自 TIA 或脑出血发生后 3 周至 14 个月的患者，随访 2-5 年。没有关于非药物干预效果的试验。

总体而言，抗高血压药物能显著减少复发性卒中(相对风险 [relative risk, RR] 0.76；95%可信区间 [confidence interval, CI], 0.63-0.92)。MI(rr RR 0.79; 95% CI, 0.63-0.98) 及所有血管事件 (rr RR 0.79; 95% CI, 0.66-095)43。在高血压患者组或所有患者的患者 (有或无高血压) 进行分析时，血压下降的影响是类似的。收缩压下降幅度越大，卒中复发的危险性越低。但由于试验样本量少限制了抗高血压治疗措施之间的比较。单用利尿药或合用 ACEI 显著减少复发性卒中，但利尿剂合用 β 受体阻滞剂或单用 ACEI 无此疗效。但是这些统计学意义有限，尤其因为这些试验中未评估 β 受体阻滞剂、钙离子拮抗剂、血管紧张素受体拮抗剂等药物的作用。

在本次荟萃分析之后，又有两个随机大样本卒中后抗高血压治疗试验：二级预防中依普沙坦与尼群地平降低卒中后发病率及死亡率的比较 (Morbidity
Furie et al  Prevention of Stroke in Patients With Stroke and TIA

and Mortality After Stroke, Eprosartan Compared with Nitrendipine for Secondary Prevention, MOSES) 试验 [24] 和卒中二级预防有效性研究 (Prevention Regimen for Effectively Avoiding Second Strokes, ProFESS) [25]。在 MOSES 中, 1405 个患有高血压病及 2 年内发生过 1 次卒中或 TIA 的患者被随机分为依普沙坦组和尼群地平组 [24]。两组间血压降低的幅度是相似的。在依普沙坦组总的卒中和 TIA 计数复发事件频率较少 (发病频率比 0.75 ; 95% CI. 0.58-0.97), 主要终点事件亦显著减少 (包括死亡、心血管事件、脑血管事件, 发病频率比 0.79 ; 95% CI. 0.66-0.96)。脑血管事件的减少主要归因于 TIA 的减少, 缺血性卒中无明显减少, 对发生第一次卒中事件采用更传统的分析未发现依普沙坦的有益效果。在 ProFESS 中, 2032 个 90 天内发生过缺血性卒中中的患者被随机分为替米沙坦组或安慰剂组, 平均随访 2.5 年 [24]。替米沙坦与复发性卒中 (危害比 [hazard ratio, HR] 0.95 ; 95% CI. 0.86-1.04) 或心血管事件 (HR 0.94 ; 95% CI. 0.87-1.01) 减少无关。在 ProFESS 试验中, 血压降低的幅度统计学上被低估。安慰剂组其他的降压治疗降低了组间的血压差异 (收缩压在 1 个月时相差 5.4 mmHg, 1 年时相差 4.0 mmHg), 可能导致低估治疗措施在卒中二级预防中的作用。总而言之, 血管紧张素受体拮抗剂在卒中后二级预防中的地位未被确立。

建议

1. 对于所有被认为适于降压的缺血性卒中或 TIA 患者, 这一建议是合理的 (Ⅱ a 类; B 级证据)。
2. 绝对的目标血压水平和降低程度不确定, 应当个体化, 但血压平均降低大约 10/5 mmHg 可以获益, JNC 7 认为正常血压水平是 <120/80 mmHg(Ⅱ a 类; B 级证据)。
3. 改善某些生活方式有助于降低血压, 并可作为综合降低治疗的一部分 (Ⅱ a 类; C 级证据)。这些改变包括限盐、减轻体重、摄取富含水果、蔬菜和低脂肪产品的饮食、规律的需氧的体育活动以及限制酒精摄入。能获得推荐的血压下降水平的最佳药物尚不确定, 因为药物间的直接比较有限。现有的数据提示利尿剂以及利尿剂与 ACEI 合用是有用的 (Ⅰ类; A 级证据)。
4. 特定降压药物和目标值的选择应当个体化。根据药物特性、作用机制、病情所需要的一些特定药物进行选择 (如颅外脑血管闭塞性疾病、肾功能损害、心脏病和糖尿病) (Ⅱ a 类; B 级证据)。

糖尿病

据测算在美国有 8% 的成人患有糖尿病 [26]。缺血性卒中患者中有 15%-33% 患有糖尿病 [27-29]。糖尿病是首次缺血性卒中的明确危险因素 [30-34]。但是能否支持糖尿病作为复发性卒中的明确危险因素的数据是非常少的。以地区人群为基础的研究中发现糖尿病成为复发性卒中的独立预测指标 [35], 并且, 9.1% 的复发性卒中患者被证明患有糖尿病 [36,37]。在两组卒中试验中, 糖尿病是多发性腔隙性脑梗死的一个预测指标 [38,39]。正常空腹血糖定义为 <100 mg/dL(5.6 mmol/L),
空腹血糖受损被定义为空腹血糖在 100 mg/dL(5.6 mmol/L) 到 125 mg/dL(6.9 mmol/L) 之间。空腹血糖水平≥ 126 mg/dL(7.0 mmol/L), 或糖化血红蛋白 (hemoglobin A1c, HbA1c) ≥ 6.5%, 或随机血糖≥ 200 mg/dL(11.1 mmol/L) 伴有高血糖症状达到诊断糖尿病的范围。HbA1c 水平≥7% 可认为血糖控制不佳。饮食、运动、口服降糖药物和胰岛素被推荐用于控制血糖。

三项关于严格控制血糖的较大的临床随机试验以伴有心血管病史、卒中病史或其他血管危险因素的糖尿病患者为研究对象。结果发现严格控制血糖并不能减少心血管事件或死亡。在控制糖尿病患者心血管危险因素行动 (The Action to Control Cardiovascular Risk In Diabetes, ACCORD) 试验中, 2 型糖尿病患者和血管病或多种危险因素的 10251 例患者随机分为强化治疗组 (HbA1c 目标值 <6%, 标准组 HbA1c 7%~7.9%)。该试验由于强化治疗的死亡风险增加, 在平均随访 3.5 年时结束 (HR=1.22, 95% CI, 1.01-1.46)。非致死性卒中发生率 (HR=1.06; 95% CI, 0.75-1.50; P=0.72) 或主要终点事件包括非致死性心脏病发作、非致死性卒中和心血管原因引起的死亡的发生率 (HR=0.90; 95% CI, 0.78-1.04; P=0.16) 无明显统计学差异。糖尿病和血管病行动 (The Action in Diabetes and Vascular Disease, ADVANCE) 试验还未发现心血管病二级预防可以获益。在这一试验中有 2 型糖尿病和大血管病或其他危险因素的 11140 例患者随机分为严格控制血糖组 (目标值 HbA1c ≤ 6.5%) 或标准血糖组 (HbA1c ≤ 7%)。32% 的患者有大血管病史, 其中 9% 有卒中病史。大血管事件的发生率 (HR=0.94; 95% CI, 0.84-1.06; P=0.32) 或非致死性卒中发生率并无明显下降。与 ACCORD 试验相比, 研究组间死亡率无明显差异。最后, 退伍军人服务部糖尿病试验纳入了 1791 例 2 型糖尿病患者, 随机分为严格血糖治疗组或标准治疗组, 结果发现两组主要终点事件的组成部分无明显差异, 这些包括主要大血管事件发生的时间或任何原因导致的死亡的发生率 (HR=1.07; 95% CI, 0.81-1.42; P=0.62)。这些试验结果表明在有心血管病史或存在血管危险因素的患者胰岛素治疗的目标 HbA1c 应不小于 6.5%。

在有卒中或 TIA 和糖尿病的患者中, 已出版了血糖控制 [41] 和血压管理 [14] 的指南。最近已经对 5238 例有 2 型糖尿病和大血管病患者应用吡格列酮的效果进行了评估。大血管疾病中吡格列酮预期临床试验 (PROspective pioglitAzone Clinical Trial In macroVascular Events, PROactive) 显示, 与对照组相比, 吡格列酮组主要终点事件 (所有死亡或心血管事件) 并无明显下降 (HR=0.78; 95% CI, 0.60-1.02)。该研究中有卒中史的患者, 应用吡格列酮使卒中复发风险降低 47%(HR=0.53; 95% CI, 0.34-0.85)。卒中、MI 或心血管死亡风险降低 28%(HR=0.72; 95% CI, 0.53-1.00)。相反, 罗格列酮 (另一种噻唑烷二酮类药物) 没有引起心力衰竭和水肿的可能, 美国食品药品管理局 (Food and Drug Administration, FDA) 在 2007 年对此类药物提出了一系列警告。对应用罗格列酮增加 MI 或心血管病死亡风险这一问题已经提出疑问, 但是还没有最后论证。卒中后胰岛素抵抗干预 (Insulin Resistance Intervention after Stroke, IRIS) 试验正在进行中, 由国立神经疾病及卒中研究所 (National Institute for Neurological Disorders and Stroke, NINDS) 资助。在该试验中 TIA 或卒中患者随机分为罗格列酮组和安慰剂组, 主要终点事件为卒中和 MI。

建议

1. 卒中或 TIA 患者, 如有糖尿病, 推荐用现有的指南进行血糖控制和血压目标值设定 ( I 类; B 级证据)。

1.3 血糖

对于缺乏和出血性卒中差异性的大量的流行病学研究表明总胆固醇或 LDL-C 升高与缺血性卒中风险增加有关, 低 LDL-C 和脑出血风险增加有关 [44-46]。对于其他种类血脂, 目前很多研究也认为高甘油三酯与缺血性卒中 [47,48] 和动脉粥样硬化性卒中 [49] 有关, 同样低 HDL-C 和缺血性卒中风险相关 [50]。一项 >90 000 例患者他汀试验的荟萃分析显示 LDL-C 下降越多, 卒中风险降低越多 [51]。他汀类药物对伴有冠状动脉性心脏病 (coronary heart disease, CHD) 的卒中患者是否有用, 对降低血管病风险尤其是预防卒中复发是否有益, 目前还不是很清楚 [52]。

在医学研究委员会 / 英国心脏基金会心脏保护研究 (Heart Protection Study, HPS) 中, 一项回顾性亚组分析观察了有远期 (平均 4.3 年) 症状性脑血管病的 3280 例患者, 结果表明辛伐他汀使主要血管事件的风险降低了 20%(HR=0.80; 95% CI, 0.71-0.92)。对卒中复发这一终点事件, 应用辛伐他汀并无获益 (HR=0.98; 95% CI, 0.79-1.22), 缺血性卒中风险降低 19%, 但差异无统计学意义, 出血性卒中风险降
低也无显著差异。HPS 研究的多因素亚组分析，应用他汀治疗的卒中患者是否可降低远期血管风险（包括卒中复发）尚不明确，尤其是无明确 CHD 的患者[84]。

通过强化降低胆固醇预防卒中 (Stroke Prevention by Aggressive Reduction in Cholesterol Levels, SPARCL) 试验中，4731 例患者有卒中或 TIA, LDL-C 水平在 100 mg/dL (2.6 mmol/L) 和 190 mg/dL (4.9 mmol/L) 之间，无已知的 CHD 病史，随机分到阿托伐他汀 80 mg/d 组和安慰剂组[85]。在中期随访 4.9 年期间阿托伐他汀组致死性和非致死性卒中发生率为 11.2%，安慰剂组为 13.1%(5 年风险降低 2.2%；HR 0.84；95% CI, 0.71-0.99；P=0.03)。5 年的主要心血管事件风险降低 3.5%(HR 0.80；95% CI, 0.69-0.92；P=0.002)。

他汀类药物治疗有较好的耐受性，部分会导致转氨酶及肌酸激酶轻度升高，但尚无导致肝衰竭，没有明显增加肌病、肌痛或横纹肌溶解等不良事件发生[86]。在试验中还有不同血脂情况及其用药方法说明。阿托伐他汀治疗组的出血性卒中风险高于安慰剂组，但两组致死性出血性卒中中的发生率无统计学差异[87]。

由于本研究样本例数比例高，且安慰剂组的患者自行口服与试验无关的公开标签的药物，因此 SPARCL 研究可能低估了他汀类药物在完全依从的患者中的疗效。基于对 4162 例患者的分析得出，他汀类药物治疗使发生卒中的风险下降 18%(HR 0.82；95% CI, 0.69-0.98；P=0.03)[88]。

根据 SPARCL 研究，为了防治一例 1 年以上复发性卒中事件的发生需治疗人数 (number needed to treat, NNT) 为 258；为了防治一例非致死性 MI 事件的发生 NNT 为 288。虽然该研究排除了 CHD 的患者，但研究中对各种 CHD 事件发生率的降低甚至超过对卒中发生率的降低，这表明卒中患者常常患有无症状性 CHD，即使既往无 CHD 病史。SPARCL 研究评估了将 LDL-C 的值降至国际指南目标值的风险与获益。LDL-C 降低超过 50% 以上使致死性及非致死性卒中中的发生率降低了 35%。缺血性卒中中的发生率下降了 37%(HR 0.63；95% CI, 0.49-0.81)，而出血性卒中中的发生率并没有增加 (HR 1.02；95% CI, 0.60-1.75)。将 LDL-C 的值降至 70 mg/dL 以下，卒中的风险可下降 28%(HR 0.72；95% CI, 0.59-0.89；P=0.0018)，出血性卒中的风险并没有增加 (HR 1.28；95% CI 0.78-2.09；P=0.3358)，但是围绕后者的点估计值的可信区间是广泛的[89]。对于少量的脑出血 (治疗组 n=55 vs 安慰剂组 n=33) 多重比较分析得出，出血性卒中中的风险增加与一些情况相关，如入组时出血性卒中事件 (HR 5.65；95% CI, 2.82-11.30；P<0.001)、男性 (HR 1.79；95% CI, 1.13-2.84；P=0.01)、年龄 (每增加 10 岁：HR 1.42；95% CI, 1.16-1.74；P=0.001)，以及非高血脂 (HR 6.19；95% CI, 1.47-26.11；P=0.01)[90]

全美胆固醇教育计划 (The National Cholesterol Education Program, NCEP) 专家组研究高胆固醇检测、评价和治疗第三次报告 (Adult Treatment Panel III [ATP III]), 是对于具有脑血管病 (包含卒中) 风险的高血脂症患者管理的最详细指南[91,92]。专家小组建议降低 LDL-C 是降低血脂的主要目标。治疗性的生活方式的改变应提高甘油三酯和胆固醇的摄入，减肥以达到理想体重，并要增加体育锻炼。LDL-C 的目标值以及生活方式的改变，抑或药物治疗，取决于三种危险因素：(1) CHD 以及和其相关的风险 (包括糖尿病和症状性颈总动脉疾病)；(2) 有≥ 2 个心血管疾病的危险因素，且 10 年预测风险分层有 10%-20% CHD 风险，或者根据弗明汉研究，0 年发病风险评分 <10%；(3)0-1 个心血管疾病的危险因素[93]。既往有 CHD 病史或 CHD 风险因素，LDL-C 的目标值为 <100 mg/dL。NCEP 指南中还有不同血脂情况及其用药方法说明。LDL-C 的降低可使得总致死率、冠脉事件致死率、主要冠脉事件、冠脉事件手术以及患有 CHD 的卒中的发生率降低[94]。

以往曾用于治疗高脂血症的药物，包括烟酸、贝特类、胆固醇吸收抑制剂。它们可以用于患有卒中或 TIA 却不能耐受他汀类药物的患者，但是其预防卒中复发的效果很微弱。烟酸与减少脑血管病事件的发生相关[95]。尽管降低胆固醇降低脑卒中事件的试验 (Veterans Affairs HDL Intervention Trial, VA-HIT) 得出吉非贝齐可以减少男性 CHD 患者以及非高脂血症患者横纹肌溶解的卒中的发生率降低[96]。

建议
1. 对于无 CHD 史的缺血性卒中或 TIA 患者，如有动脉粥样硬化证据，且 LDL-C ≥ 100 mg/dL (2.6 mmol/L)，推荐用强化降脂效果的他汀治疗减少卒中 (I 类；B 级证据)。
2. 有动脉粥样硬化的缺血性卒中或 TIA 患者，如无 CHD 史，将 LDL-C 降低 50% 或将目标 LDL-C 水平设定为 <70 mg/dL (1.8 mmol/L)，以取得最大获益，是合理的 (II a 类；B 级证据)。 (新建议)
3. 缺血性卒中或 TIA 患者，如胆固醇高，或者
同时患有 CHD，应当根据 NCEP Ⅲ指南用其他方式处理，包括生活方式改变、饮食指南和用药建议（Ⅰ类；A 级证据）。

4. 缺血性卒中或 TIA 患者，如 HDL-C 低，可以考虑用烟酸或吉非贝齐治疗（Ⅱb 类；B 级证据）。

1.4 吸烟

一直都有强烈而一致的意见认为吸烟是缺血性卒中中的一个主要的独立危险因素 [63-67]。而且，越来越多的证据显示环境性吸烟或者被动吸烟也能使心血管疾病，包括卒中的风险增加 [68-73]。这些数据强烈支持戒烟，当然也适用于缺血性卒中或 TIA 患者 [13]。

烟草依赖是一种慢性疾病，应进行有效的行为干预以及药物治疗措施 [74-80]。对于如何治疗烟草依赖疾病，现有的信息发表在《治疗吸烟及烟草依赖：2008 最新版》 [81]。

建议

1. 卒中或 TIA 患者，如有吸烟史，医疗保健提供者应当强烈建议其戒烟（Ⅰ类；C 级证据）。
2. 避免环境性（被动）吸烟是合理的（Ⅱa 类；C 级证据）。
3. 劝说、尼古丁产品和口服戒烟药有助于吸烟者戒烟（Ⅰ类；A 级证据）。

1.5 饮酒

有强烈证据表明慢性酒精中毒及重度饮酒是各种卒中亚型的危险因素 [82,83]。研究显示饮酒与缺血性卒中的相关性从肯定独立相关至完全无关 [84]。多数研究提示，饮酒与缺血性卒中风险呈 J-型相关，轻中度饮酒为保护性因素，重度饮酒会增加卒中风险 [82,83,87,96]。

很少有研究评价饮酒与卒中复发二者的关系。在北曼哈顿队列研究中有重度饮酒史的卒中复发风险明显增高 [89]。但没有研究证实减少饮酒量会降低卒中复发风险 [82,83]。轻中度饮酒能够降低体重指数 > 30 kg/m²，已被认为是 CHD 及过早死亡的一个独立危险因素 [100-108]。肥胖及体重与卒中的关系是复杂的，而且研究主要集中在与一级预防的关系上 [109-118]。

在非洲裔美国人的抗血小板卒中预防研究中，虽然卒中后存活者与复发性卒中风险的关系并未确立，但随着体重增加，心血管危险因素增加 [119]。

没有研究表明体重下降能降低卒中复发的风险率。

1.6 肥胖

肥胖定义为体重指数 > 30 kg/m²，已被认为是 CHD 及过早死亡的一个独立危险因素 [100-108]。肥胖及体重与卒中的关系是复杂的，而且研究主要集中在与一级预防的关系上 [109-118]。

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没有研究表明体重下降能降低卒中复发的风险率。

1.7 体育活动

体育活动对多种卒中危险因素均发挥了有益的作用 [108,120-125]。在最近一篇回顾了现有有关体育活动与卒中关系研究的综述中，中高强度活动者和较低强度活动者相比，其卒中的发生率较低 [121]。中、高强度活动风险率分别降低 20% 和 27%。体育活动可使血压及体重降低 [123,124]、增强血管舒张能力 [125]、提高糖耐量 [126]以及促进心血管健康 [108]。

尽管一个积极运动的生活方式有其确定的益处，久坐的行为依旧是全国范围内的趋势 [130,131]。卒中后残疾是很严峻的 [132]，且神经功能缺损可使一个人活动耐受不良及身体不适应 [133]。因此，对临床医生的挑战是确立一个安全的治疗性锻炼体制使患者恢复卒中前的活动水平，并随后获得一个足够的体育活动及锻炼水平使得二级预防最优化。一些研究支持进行有氧运动及体力训练来提高卒中后心血管的适应性 [133-136]。结构化治疗性训练已经显示了可以提高活动性、平衡及耐力 [134]。在不同种群及年龄组中已经证实了其有利的作用 [137]。虽然这些研究表明结构化锻炼活动于卒中后无害，但没有对照试验来确定这些治疗性锻炼能降低随后的卒中发生率。在任何一项近来关于复发性卒中和危险因素的国际性研究中，体育活动并未被评估 [138-140]。
只有几项关于卒中幸存者将锻炼作为潜在预防措施的调查。一项使用 1999 年行为危险因素监测系统 的调查显示，62.9% 有卒中史的患者在进行锻炼来降低心脏病发作或卒中复发的风险。更重要的是，与未 接受建议的卒中幸存者相比 (38.5%)，接受了建议的卒中幸存者进行锻炼的比例更高 (75.6%)。据报道正在从 事锻炼的卒中幸存者和未锻炼者相比，活动受限和身体状况欠佳少，处于健康状态的多 [141]。这一研究高 度强调了提供有关锻炼、饮食及其他生活方式危险因素的建议的重要性。它并未调查复发性卒中中的发病率。 

研究发现鼓励体育活动及锻炼能使身体状况、机能及卒中后生活质量达到最佳化 [108,125,127]。 

**建议**

1. 缺血性卒中或 TIA 患者，如能参加体育活动，可以考虑至少每周 1-3 次、每次 30 分钟的中等强度体育运动，即达到出汗或明显增加心率的程度 (例如快走、慢跑或健身脚踏车)，以减少卒中复发的危险因素和共存病 (II b 类；C 级证据)。

2. 对于那些缺血性卒中后残疾的患者，可以考虑由医疗保健专家 (如理疗师或心脏康复专家) 指导，至少在运动计划开始时要接受指导 (II b 类；C 级证据)。

### 1.8 代谢综合征

代谢综合征指一些增加了血管病风险的生活异常 [142]。这些异常包含在不同的代谢综合征定义中，包括高甘油三酯血症、低 HDL-C、高血压、高血糖 [143-145]。过去十年的研究将这一综合征的范围进一步扩大，包括了亚临床的感染及血栓形成、纤溶、内皮功能异常，并证实了其基因遗传的可能性 [142,146,147]。代谢综合征通常诊断为 NCEP 成人治疗指南、世界健康组织或 AHA (摘自 NCEP) 的标准诊断。根据 AHA 的标准，当以上 5 个特征中的 3 个存在时，就可以考虑为代谢综合征：腰围增加 (男性 ≥ 102 cm；女性 ≥ 88 cm)、高甘油三酯水平 (≥ 150 mg/dL)、低 HDL-C (女性 < 40 mg/dL；男性 < 50 mg/dL)、血压升高 (收缩压 ≥ 130 mmHg 或舒张压 ≥ 85 mmHg)、空腹血糖升高 (≥ 100 mg/dL) [148]。胰岛素抵抗常被描述为一种病理生理状态，其中胰岛素数量正常，但活性降低。结果造成外周葡萄糖摄取降低 (进入肌肉和脂肪)、肝糖产出增多及代谢性糖胰岛素分泌增多 [149]。饮食、锻炼及增加胰岛素敏感性的药物使用已被证实有助于代谢综合征患者这些方面的改善 [158-159]。代谢综合征影响了美国接近 22% 的 20 岁以上成人 [156]。对于缺血性卒中的患者，这一发病率为 40%-60% [157-159]。

有关代谢综合征的争议仍有很多，主要是其病因及临床意义不确定。代谢综合征与糖尿病、心血管疾病及所有原因所致死亡的风险增高有关 [160]。然而，代谢综合征对于患者个体化的风险特征的意义仍不确定；是否对患者危险因素分类有价值，是否可以简化危险分层方法，如弗明汉风险评分，都还确定 [157,158]。此外，代谢综合征与老年患者 (70-82 岁) 心血管疾病的关系并未明确，这也限制了它在一般卒中人群中应用 [161]。

近期很多研究报道了首次卒中风险和代谢综合征之间的关系 [158,162-170]，除一项研究外其余均证实了这种关系 [168]。代谢综合征相对于其它各组成部分或者单一复合风险指数的预测值还得到充分研究。最近的分析结果支持这样的观点：根据代谢综合征的患者分类对卒中风险的评估与传统的危险因子相比并无明显提高 [170,171]。代谢综合征的主要特征均随着体重的减轻而改善。尤其是对于那些有代谢综合征和肥胖的患者，减轻体重能提高对胰岛素的敏感性，降低血脂、血浆 LDL-C、甘油三酯，升高血浆 HDL-C，降低血压，减少炎症，改善纤维蛋白溶解及改善血管内皮功能 [154,172,173]。

代谢综合征的主要特征随着体重的减轻而改善。尤其是对于那些有代谢综合征和肥胖的患者，减轻体重能提高对胰岛素的敏感性，降低血脂、血浆 LDL-C、甘油三酯，升高血浆 HDL-C，降低血压，减少炎症，改善纤维蛋白溶解及改善血管内皮功能 [154,172,173]。
建议

1. 目前，卒中后筛查代谢综合征的意义尚未证实（IIb 类；C 级证据）。（新建议）
2. 如果患者筛查后发现有代谢综合征，处理措施应当包括劝说改变生活方式（饮食、锻炼和减轻体重），以减少血管疾病风险（I 类；C 级证据）。（新建议）
3. 代谢综合征患者的预防措施应当包括合理治疗综合征的各个成分，它们也是卒中危险因素，特别是脂代谢紊乱和高血压（I 类；A级证据）。（新建议）

2. 大动脉粥样硬化患者的介入治疗方法

2.1 症状性颈动脉外段疾病

在过去的 50 年内进行并发表了许多临床试验，这些试验采用随机或非随机方法对比了手术介入治疗（颈动脉内膜剥脱术 [carotid endarterectomy, CEA]）加药物治疗和单纯药物治疗的效果。这些研究中最好药物治疗未包括积极动脉粥样硬化管理，主要有：对羟甲基戊二酰辅酶 A (hydroxymethylglutaryl coenzyme A, HMG-CoA) 还原酶抑制剂（他汀类）的使用，选择性使用抗血小板药物如氯吡格雷或者应用缓释双嘧达莫 - 阿司匹林组合制剂，最佳的血压控制以及戒烟。手术技术也在不断进步。此外，在过去的几年，在 CEA 高危患者中，颈动脉血管成形 / 支架术 (carotid angioplasty and stentng, CAS) 已经成为替代的治疗措施。许多正在进行的试验比较了 CAS 和做为金标准的 CEA 的效果。

2.1.1 CEA

三个大型的前瞻性随机试验均得出了支持 CEA 的结果（表 5），证明有症状的重度（造影结果狭窄 >70%）颈动脉动脉粥样硬化性狭窄患者 [175-177]，CEA 加药物治疗效果优于单纯的药物治疗。对这些试验进行汇总分析（3000 多例有症状的患者），结果发现手术治疗后 30 天仍可能出现卒中，死亡率为 7.1% [178]。此外，这些研究均表明，对于狭窄 <50% 的患者，手术治疗对降低卒中的风险并无益处。

对于狭窄在 50%-69% 的患者尚存争议。北美症状性颈动脉内膜切除术试验 (North American Sym pathetic Carotid Endarterectomy，NASCET) 中，狭窄程度 50%-69% 的患者手术治疗后 5 年内发生同侧卒中率为 15.7%，药物治疗组为 22.2% (P=0.045) [179]。也就是说，5 年随访期中，手术治疗 15 例患者能阻止 1 例同侧卒中的发生。研究的结论是，只有在适当的情况下进行 CEA 才能获益。有手术适应症的中度狭窄 (50%-69%) 患者，由术前期的发病率和死亡率 <6% 的优秀外科医生进行手术，才能充分获益 [180]。

患者特点对手术风险的影响

性别对 CEA 结果的影响一直存在争议。一些研究发现了围手术期卒中和死亡率有明显的性别差异，但这些研究大多没有区分症状性和非症状性患者。虽然代表性不够，而且性别的影响并不显著，但 NASCET 试验的亚组分析显示女性在 CEA 的获益不明显 [179,181]。这些数据显示，女性在手术死亡率、神经系统发病率和复发性颈内动脉狭窄 (14% vs 3.9%, P=0.008) 方面结局更差 [182]。也有人推测，女性的血管直径较小，易发生斑块，所以更易复发狭窄，但也有不同观点。在考虑是否进行颈动脉血管再通时必须对年龄、性别以及医疗并发症进行综合分析。

由于现代化的围手术期护理和麻醉技术，年龄和合并症对 CEA 结局的影响不明确。虽然 NASCET 试验没有纳入高龄患者，但一些病例系列报道显示 CEA 在超过 80 岁的患者中仍然是安全的 [183]。

颈动脉血管再通的时间

急性神经系统事件后进行 CEA 的时间尚存争议，专家建议等待 2 至 6 周不等。对于症状稳定的或改善的小卒中和非致残性卒中，CEA 最佳时间目前仍有争议。推荐早期 CEA(6 周内) 的报告显示没有增加卒中复发的风险。对于最初没有脑实质出血证据的患者，早期介入手术或许有益。对低危 TIA 或小卒中患者可进行超早期（3 周内）介入治疗 [184,185]。动脉内膜的切除术的汇总分析显示早期手术相对于晚期手术可以增加收益。≥ 75 岁的男性患者和最近

<table>
<thead>
<tr>
<th>试验</th>
<th>平均随访时间</th>
<th>手术组 %*</th>
<th>药物组 %*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECST</td>
<td>3 年</td>
<td>2.8</td>
<td>16.8</td>
</tr>
<tr>
<td>NASCET</td>
<td>2.7 年</td>
<td>9</td>
<td>26</td>
</tr>
<tr>
<td>VACS</td>
<td>11.9 月</td>
<td>7.9</td>
<td>25.6</td>
</tr>
</tbody>
</table>

* 致死性或非致死性同侧卒中风险。
2周内发生出血性卒中的患者手术治疗获益更大，随着时间的延迟效益迅速下降[188]。

2.1.2 颈动脉血管成形术和支架植入术

CAS 已经成为除 CEA 以外治疗颅外颈动脉闭塞性疾病的重要治疗方法。颈动脉血管成形术是一项低侵入性的经皮手术，由 Kerber 等人在1980年首次报道[187]。美国于1994年发展这项技术并开始应用支架[188]。随着血管保护装置、支架设计等血管内技术的不断更新，CAS 手术技术不断提高，临床预后逐步改善。由目前所得数据可知，CAS 与 CEA 在手术成功率和手术并发症方面相当[189,190]。CAS 具有创伤小、患者不适感少、康复时间短等优点，但其耐用性尚未得到证实。根据现有的大型、多中心、前瞻性、随机研究的数据结果，CAS 主要适用于 CEA 高风险患者。高风险定义为：(1) 伴有严重的合并症（如严重冠心病、左室射血分数 [left ventricular ejection fraction，LVEF] ≤30%，近期 MI，严重的肺部疾病或严重肾功能疾病）；(2) 技术难度大或解剖复杂，如既往正部手术（如颈淋巴结清扫术）或外科手术、动脉内膜切除术后再狭窄、病灶在手术范围之外 (即内膜动脉 C2 段以上，锁骨以下)、对外科手术闭塞、对症声带麻痹，或气管切开。解剖部位的风险已被普遍接受，近期的几个研究还对医疗风险问题进行研究，包括麻醉和重症监护方面的问题[191]。

大多数发表的临床试验评估了单个支架 / 神经保护装置的有效性。第一个大型随机试验是颈动脉和椎动脉经皮腔内成形术 (Carotid and Vertebral Artery Transluminal Angioplasty Study，CAVATAS)[192]。此试验报道于2001年，存在手术适应证的患者随机接受支架成形术或 CEA 治疗。不适宜手术的患者随机接受支架成形术治疗或内科治疗。试验结果提示接受支架术与剥脱术患者30天卒中或死亡发生率相当，两组均为6%。然而在全部251人的血管治疗组中，仅有55人给予支架术治疗，且没有应用栓子保护装置。长期随访 (3年) 提示两组间卒中发生率无差异。

栓子保护装置可以减少术中卒中发生率，因此医疗保险和公共医疗补助中心要求术中必须应用此装置，并给予报销。CEA 高风险患者辅以保护装置的血管成形和支架置入术研究 (Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy，SAPPHIRE) 研究中，334例症状性及非症状性颈动脉狭窄患者接受了 CAS(使用栓子保护装置) 或 CEA 治疗，并在安全性和有效性方面对两种手术进行了比较[193]。30天内 CEA 组患者卒中、MI 和死亡发生率为 9.9%，CAS 组为 4.4%。1年内主要终点事件 (30天内卒中、死亡、MI)；31天-1年内发生同侧卒中或由卒中导致的死亡) CEA 组 20.1%，CAS 组 12.0%。尽管差异主要表现为围手术期 MI 发生率不同，此项研究的主要结论是在特定的高危人群中，CAS 并不比 CEA 差，但该研究未行亚组分析。

其他的一些随机研究，严重症状性颈动脉狭窄患者中动脉内膜切除术与支架成形术比较 (Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis，EVA-3S) 和经皮 CAS 与动脉内膜切除术比较 (Stent-supported Percutaneous Angioplasty of the Carotid artery versus Endarterectomy，SPACE)，也好的设计比较了症状性颈内动脉狭窄患者 CAS 和 CEA 两种治疗方法的优劣[194,190]。但这两项研究均因 CAS 组 30天卒中发生率和死亡率高于 CEA 组，鉴于安全性的考虑和无益等原因提前终止[194]。此外，CAS 组 6个月卒中和死亡风险高于 CEA 组 (11.7% vs 6.1%)。这两项研究均被归因为手术者经验不足和水平不一，对 CAS 组患者的治疗情况产生了负面影响。

颈动脉血管再通内膜成形术与支架比较研究 (The Carotid Revascularization Endarterectomy versus Stent Trial，CREST) 是一项用以比较 CAS 和 CEA 有效性的前瞻性、随机研究。CREST 研究前导期结果证实30天卒中和死亡发生率与 CEA 大致相同[190]。但前导期数据显示卒中和死亡风险随年龄增高而增加 (P = 0.0006)，各年龄组卒中和死亡发生率分别为：< 60岁，1.7%；60-69岁，1.3%；70-79岁，5.3%；≥ 80岁，12.1%[196]。CREST 对来自美国和加拿大117个中心的 2502 例症状性和无症状颈动脉狭窄 (超声提示狭窄率 >70% 或血管造影提示狭窄率 >50%) 患者进行随机分组，并对接受 CAS(n=1262) 和 CEA(n=1240) 治疗的两组患者进行随访，发现两组患者在主要复合终点 (30天卒中、死亡、MI 发生率和 4年同侧卒中发生) 上无显著差异，分别为 7.2% 和 6.8%(HR 1.1；95% CI，0.81-1.51；P = 0.51)。症状性患者 4年卒中或死亡发生率分别为 8%(CAS组) 和 6.4%(CEA组)(HR 1.37；P = 0.14)。最初30天，症状性颈动脉狭窄患者中，CAS 组围手术期和术后同侧卒中发生率显著高于 CEA 组 (5.5%±0.9% vs 3.2±0.7%；P = 0.04)。
颅外-颅内旁路手术

尚未发现颈动脉闭塞或颈动脉分叉远端狭窄的患者可从颅外-颅内(Extracranial-intracranial，EC/IC)旁路手术获益[198]。颈动脉闭塞手术研究(Carotid Occlusion Surgery Study，COSS)是EC/IC旁路手术的随机对照研究，该研究正在进行中，通过更为敏感的15O2/H218O正电子发射断层扫描(position emission tomography，PET)筛选有严重血流动力学改变的患者[198-200]。

建议

1. 对于近期发生TIA或6个月内发生缺血性卒中合并同侧严重(70%-99%)颈动脉狭窄的患者，如果估计术后卒中和死亡率风险<5%，推荐进行CEA(Ⅰ类；A级证据)。
2. 对于近期发生TIA或6个月内发生缺血性卒中合并同侧中度(50%-69%)颈动脉狭窄的患者，如果估计术后卒中和死亡率风险<5%，推荐进行CEA，取决于患者特定因素，例如年龄、性别和并存疾病(Ⅰ类；B级证据)。
3. 当狭窄程度<50%时，无颈动脉再通指征(无论CEA或CAS)(Ⅲ类；A级证据)。
4. 当TIA或卒中患者有行CEA指征时，如果无早期再通禁忌证，在两周内进行手术是合理的，而非延迟手术。(Ⅱa类；B级证据)
5. 有症状患者，当颈内动脉管腔直径狭窄程度非侵袭性影像检查提示>70%或导管成像检查提示>50%时，血管内操作发生并发症的风险为中等或较低，CAS可作为CEA的替代方案(Ⅰ类；B级证据)。

2.2 颅外椎基底动脉病变

存在椎动脉远端或颈部闭塞性病变的患者，发生后循环或椎基底动脉系统缺血的风险较高[201]。一项系统综合分析症性椎动脉狭窄患者在症状发生7天内的卒中复发率高于近期的症性颈动脉狭窄[202]。然而，对于这些患者的最佳药物治疗尚不清楚，侵入性治疗的精确作用仍然不明确。

由于本病的高发病率与手术治疗(动脉内膜切除术或重建)相关，因此大多数情况下，药物治疗是主要的治疗方法，但一项病例序列，对于有颅外椎动脉狭窄并且反复发生椎基底动脉系统TIA或卒中的患者，尽管采用了药物治疗，仍需进行血运重建术[201]。到目前为止，对椎动脉狭窄的患者施行血管内治疗与单独施行最后药物治疗的结果进行比较的随机试验只有CAVATAS试验[204]。在这个小规模试验中，16例有症状的椎动脉狭窄的患者随机接受血管内治疗(药物治疗)或单独进行药物治疗，并随访4.7年。主要的终点为椎基底动脉发生致死性与非致死性卒中，次要终点包括椎基底动脉发生TIA、颈动脉发生致死性与非致死性卒中和致死性MI[204]。

在血管内治疗组，6例患者仅接受经皮腔内血

<table>
<thead>
<tr>
<th>表6 1321例症状性患者治疗组CAS与CEA风险比较</th>
<th>围手术期HR(95% CI)</th>
<th>4年研究期间HR(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>心肌梗死</td>
<td>0.45(0.18-1.11)</td>
<td>...</td>
</tr>
<tr>
<td>任何围手术期卒中或术后同侧卒中</td>
<td>1.74 (1.02-2.98)</td>
<td>1.29 (0.84-1.98)</td>
</tr>
<tr>
<td>任何围手术期卒中、死亡、或术后同侧卒中</td>
<td>1.89 (1.11-3.21)</td>
<td>1.37 (0.90-2.09)</td>
</tr>
<tr>
<td>任何围手术期卒中、死亡、心肌梗死，或术后同侧卒中</td>
<td>1.26 (0.81-1.96)</td>
<td>1.08 (0.74-1.59)</td>
</tr>
</tbody>
</table>
管成形术，2例主要接受支架植入术。两组比较，在30天内发生脑血管病的风险无显著差异（P=0.47），并且超过最初30天的围手术期或随机化时期，没有患者出现主要终点事件[204]。但该试验没有说服力，因为其排除了高复发风险的患者，并且事件期间较长（平均92天）[203]。需要更大规模的研究随机研究这些患者提供循证医学的推荐，并且评估高椎底动脉卒中风险患者是否适合应用支架植入术。

建议
1. 本指南其他部分论述的最佳药物治疗方案，包括抗血小板治疗、他汀治疗和危险因素控制，推荐用于所有具有椎动脉狭窄的TIA或卒中患者（Ⅰ类；B级证据）。[新建议]
2. 颅内椎动脉狭窄患者，尽管接受了最佳药物治疗（包括抗栓药、他汀类药物和相关危险因素控制）但仍出现症状时，可以考虑血管内和手术治疗（Ⅱb类；C级证据）。

2.3 颅内动脉粥样硬化
有症状性的颅内动脉粥样硬化狭窄的患者有高度的卒中风险。在针对一种或多种治疗的方法的研究中，未治疗组的自然病程较治疗组更差。在ECIC旁路手术研究中，189例有大脑中动脉狭窄的患者被随机分在搭桥手术组及阿司匹林药物治疗组[198,202]。药物治疗组平均随访44个月，1年卒中率9.5%，同侧卒中率7.8%。手术治疗组预后更差。因此这种操作已经很大程序上不再在颅内动脉狭窄中进行。

在WASID的研究中，569例由于大脑中动脉、颈内动脉、椎动脉或基底动脉狭窄导致TIA或卒中的患者被随机分配为阿司匹林1300 mg或华法林组，目标国际标准化比率（international normalized ratio, INR）2.0-3.0[200]。由于对华法林组安全性的担心早期被停止，它显示在主要终点（缺血性卒中、脑出血和血管相关死亡）组间没有显著差异（华法林对比阿司匹林，HR 0.96; 95% CI 0.68-1.37），但是华法林组有多出血事件。第一年卒中复发风险是15%，发生在狭窄血管的卒中风险是12%。对狭窄≥70%的患者，狭窄血管的卒中风险是1年15%[207]。多因素分析显示狭窄严重（≥70%）和在首发事件后早期入组（≤17天）的患者发生责任血管供血区的卒中风险最高。女性的风险同样增加。尽管初期脑血管事件的类型（卒中或TIA）与在血管供血区的卒中风险没有明显联系，但颅内动脉狭窄

<70%的TIA患者1年内在相同区域的卒中复发率很低（3%），颅内动脉狭窄≥70%的卒中患者1年内在相同区域的卒中复发率较高（23%）。颅内动脉狭窄≥70%的TIA患者和颅内动脉狭窄50%-69%的卒中患者有中度风险。

在症状性动脉粥样硬化血栓形成性颅内血管狭窄的前瞻性研究（Groupe d’ Etude des Stenoses Intracranienress Atheromateuses symptomatics，GESICA）[208]中，对102例有疾病的颅内动脉狭窄的患者进行了前瞻性研究，患者经药物治疗并平均随访23个月。发生卒中的风险为13.7%。值得注意的是，27%的患者有血流动力学的症状，定义为“与狭窄有关的，改变体位或特定体位（从仰卧位到俯卧位）或尝试改变药物如加用或加量降血压药物时发生”。如果狭窄被视作血流动力学症状，那么随后脑血管病事件的危险大幅上升。

颅内血管成形术或支架术都可以减轻狭窄，改善脑血流，并且有可能减少卒中复发的风险。特别是有前面描述的危险因素的患者。很多回顾性和前瞻性研究[209-218]提示，在技术方面成功的方法应该得到开展。Wingspan支架（波士顿科学公司）已被批准用于临床，经过了FDA的伦理审批，可以改善颅内动脉成形术并改进内科治疗无效的患者的脑动脉直径。在颅内血管狭窄≥50%都可以应用。但是其有效性还没有被确定[219,220]。一项对129例有临床症状且颅内动脉狭窄率为70%-99%的患者进行支架治疗的研究[218]表明，支架治疗术的成功率为97%。在半年的随访中，各种类型的卒中、脑出血、30天内死亡或30天以上同侧再梗死发生率为14%，血管造影显示25%的患者会再次出现血管再狭窄，狭窄率>50%。因此，支架术可能减少卒中发生的相对危险性，但是否优于药物治疗还不确定。在长期临床预后或血管造影结果方面，支架术较血管成形术是否有优势也未明确。一项关于颅内支架术是否优于药物治疗的随机临床研究（Stenting and Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis, SAMMPRIS）正在进行。

对于颅内动脉狭窄患者的血管危险因素进行强化药物治疗可降低卒中发生率。虽然有些研究认为动静脉血流的下降可能降低脑灌注从而使增加那些有大血管狭窄患者的卒中风险[221]，但WASID试验的数据分析显示：颅内动脉狭窄的患者长期把血压控制于140/90 mmHg以下发生卒中或血管事件可能性很小（HR 0.59；95% CI，0.40-0.79）[222,229]。总胆固醇低与
200 mg/dL 也可以降低卒中风险 (HR 0.69 : 95% CI, 0.48-0.99)(223)。但这种血压水平不适于急性期。

建议

1. 对于颅内大动脉狭窄 50%-99% 导致的卒中或 TIA 患者，推荐使用阿司匹林而非华法林（I 类；B 级证据）。WASID 试验中使用阿司匹林 1300 mg/d 对患者进行治疗，但阿司匹林对改善该人群的最佳剂量尚未确定。基于安全性和有效性的一般数据，推荐阿司匹林剂量为 50 mg/d-325 mg/d (I 类；B 级证据)。（新建议）

2. 对于颅内大动脉狭窄 50%-99% 导致的卒中或 TIA 患者，长期维持血压 <140/90 mmHg 和总胆固醇水平 <200 mg/dL(5.2 mmol/L) 可能是合理的 (II b 类；B 级证据)。（新建议）

3. 对于颅内大动脉狭窄 50%-99% 导致的卒中或 TIA 患者，血管造影术和/或支架植入术的作用尚属未知，需要进一步研究 (II b 类；C 级证据)。（新建议）

4. 对于颅内大动脉狭窄 50%-99% 导致的卒中或 TIA 患者，不推荐进行 EC/IC 旁路手术 (III 类；B 级证据)。（新建议）

3. 心源性栓塞患者的药物治疗

缺血性卒中约 20% 由心源性栓塞引起。其中，约半数为非瓣膜性心脏病，左心室附壁血栓约占 1/3(224)。

3.1 心房颤动

持续性和阵发性心房颤动都是首次或复发性卒中强有力的预测因素。在美国，每年有 75 000 以上的卒中由心房颤动引起。估计有 200 万以上的美国人心源性心房颤动，心房颤动患病率随年龄增长而增加，是老年人中最为常见的心律失常。在所有心房颤动患者中，有卒中或 TIA 史的患者发生卒中的相对危险最高。其他因素如 : 年龄、新近发生的充血性心力衰竭、高血压、冠心病和既往的栓塞性事件都可能增加这些患者的卒中风险。左心室功能不全、左房大小、二尖瓣钙化、左房栓子都是栓塞的危险因素。

在华法林与阿司匹林对比的多项一级预防临床试验中已证明华法林治疗对于非瓣膜病性心房颤动患者预防栓塞事件的有效性。一项来自 5 个华法林和对照组比较的一级预防试验的汇总分析已被报道(229)。应用华法林使卒中的相对危险下降 68%(95% CI, 50%-79%)，华法林规范治疗组卒中发生率 1.4%，而对照组为 4.5%。也就是说规范化治疗 1000 例患者可减少 31 个缺血性卒中事件发生。总的来说，华法林治疗相对安全，应用华法林治疗出血风险为 1.3%，安慰剂组或阿司匹林组出血风险为 1%。

心房颤动患者应用抗凝药物预防卒中，OR 值在 2.0 至 3.0 之间。一项大样本对照研究(226)和两项随机研究(227, 228)结果均显示：口服抗凝药时，若 INR 值低于 2.0 则效果明显减低。不幸的是，很多心房颤动患者的 INR 值都低于标准值，不能有效预防卒中。对于已发生过缺血性卒中或 TIA 的心房颤动患者，尽管抗凝治疗，但没有数据表明增加抗凝效果可以为再次缺血事件提供额外保护，而且华法林治疗相对安全，应用华法林治疗出血风险为 2.0%。有证据显示阿司匹林效果不如华法林。对三项研究结果的分析显示：相对于安慰剂组，应用阿司匹林相对危险减少 21%(95% CI, 0-38%)(229)。关于阿司匹林效果最大的研究为心房颤动患者卒中预防研究 (Stroke Prevention in Atrial Fibrillation, SPAF 1)，这项研究中阿司匹林用量为 325 mg/d。然而，基于多项研究结果，阿司匹林安全有效的剂量为 75 mg/d-100 mg/d(229)。

目前，阿司匹林过敏的心房颤动患者换用其他抗血小板药物或联合用药是否有效尚属未知。氯吡格雷和厄贝沙坦预防房颤心血管事件 (Atorvastatin Clopidogrel Trial with Irbesartan for Prevention of Vascular Events, ACTIVE W) 研究在至少存在一个卒中危险因素的心房颤动人群中比较氯吡格雷加阿司匹林和单用华法林的安全性和有效性。在 3371 例患者入组登记后，安全监察委员会提前终止了该项研究，因为华法林 (INR 2.0-3.0) 较联合应用抗血小板药物具有明显优势 (RR 1.44 : 95% CI, 1.18-1.76; P=0.0003)(231)。

ACTIVE A 研究针对不能耐受华法林的心房颤动患者，比较了阿司匹林与阿司匹林加氯吡格雷的作用，发现联合应用阿司匹林和氯吡格雷的患者卒中患病率有所降低。接受单纯用药的患者中 296 例患者发生卒中 (2.4%/年)，单用阿司匹林的患者中则有 408 例患者发生卒中 (3.3%/年；RR 0.72 : 95% CI, 0.62-0.83, P<0.001)。251 例联合用药患者出现严重出血 (2.0%/年)，162 例单独应用阿司匹林患者出现严重出血 (1.3%/年；RR 1.57 : 95% CI, 1.29-1.92; P=0.001)(232)。一项研究表明两项治疗方案之间在大血管事件合并严重出血中并无差异 (RR 0.98；
95% CI, 0.89-1.06; P = 0.54). 该项试验中的绝大多数患者或被医生认定为不适合进行华法林治疗，或不愿接受华法林治疗，有 1/4 的患者退出了研究，有 23% 的患者有出血的危险。因此，基于试验中危险患者是否适合抗凝治疗，以及考虑到抗凝治疗可能的附加风险和严重出血风险，阿司匹林治疗组还是具有明确抗凝治疗禁忌证但能耐受抗血小板治疗的心房颤动患者的首选用药方案。

欧洲心房颤动试验 (European Atrial Fibrillation Trial，EAFT) [233] 证实，对心房颤动合并新近 TIA 或卒中中的患者，抗凝药物较阿司匹林优于。因此，除非存在明确禁忌证，新近发生 TIA 或卒中中心房颤动患者应该接受长程抗凝治疗而非抗血小板治疗。尚无证据表明心房颤动患者使用抗凝剂联合抗血小板药物较单用抗凝剂可以降低卒中或急性 MI 的风险，但是有明确的证据表明二者联合应用增加了出血风险。房颤患者应该接受长程抗凝治疗而非抗血小板治疗。

华法林可在许多食物和药物中产生相互作用，而且治疗窗口，就要求使用华法林期间需频繁监测 INR 及调整用药剂量。上述因素严重限制了华法林的应用。因此我们需要更方便应用的替代药物。近期一系列针对心房颤动患者的抗凝替代药物评估试验正在进行，包括直接凝血酶抑制剂达比加群等达比加群抑制剂可以降低卒中或急性 MI 的风险，但是有明确的证据表明二者联合应用增加了出血风险 [234]。因此，一般来说，心房颤动患者应避免抗凝剂联合抗血小板药物。

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TIA，CHADS2评分5-6分，人工瓣膜或风湿性瓣膜病的心房颤动患者，推荐逐渐改用抗凝治疗。逐渐改用的首选方法一般是在门诊给予充分治疗剂量的低分子肝素（相对于低预防剂量）[23]。发现约有四分之一表现为心房颤动和缺血性卒中的患者可能存在其他潜在因素引起卒中，例如颈动脉狭窄[239]。对于这类患者，治疗决策应着眼于推测可能引起卒中的病因。在许多病例里，因为心房颤动而启动的抗凝治疗，也是对其他情况的辅助治疗（例如CEA）。

*CHADS2代表 congestive heart failure, hypertension, age>75y, diabetes mellitus, prior stroke and TIA。前面四个危险因素各为1分，最后一个为2分。

**建议**

1. 对于有阵发性（间歇性）或持续性心房颤动的缺血性卒中或TIA患者，推荐使用维生素K拮抗剂进行抗凝治疗（INR目标值2.5；范围2.0-3.0）[Ⅰ类；A级证据]。

2. 对于不能服用口服抗凝药的患者，推荐单独使用阿司匹林[Ⅰ类；A级证据]。氯吡格雷联合阿司匹林与华法林出血风险相似，因此不推荐用于有华法林出血禁忌证的患者[Ⅲ类；B级证据]。（新建议）

3. 对于具有较高卒中风险（3个月内卒中或TIA，CHADS2评分5-6分，人工瓣膜或风湿性瓣膜病）的心房颤动患者，当需要暂时中断口服抗凝药物时，逐渐改用皮下注射低分子肝素治疗是合理的[Ⅱa类；C级证据]。（新建议）

3.2 急性MI和左室栓子

在没有进行急性缺血再灌注治疗的患者中，大约有三分之一的患者在前壁MI发生后的最初2周里出现了心内栓子。在包括左心室心尖在内的更大范围梗死的患者中，出现心内栓子的患者比例更高[224,240,241]。在缺乏抗凝治疗的情况下，大约10%的MI伴随左室栓子的患者会发生脑梗死[241]。溶栓治疗可能使栓子形成的发生率降低[242,243,244]，但对减少风险的程度存在争议[246]。冠脉疾病、高血压和其他类型扩张型心肌病的慢性心功能不全的患者也可能存在左室壁栓子，不论有无心房颤动，这些患者都有卒中和栓塞的风险。

在过去的20年里，涉及急性下壁和前壁MI患者的三项大型试验得出的结论是，没有进行抗凝治疗的患者相比，使用华法林加肝素进行初步治疗后的患者，脑栓塞的发生率从3%减少至1%。三项研究中有两项存在具有重要统计学意义的差异，而在第三项研究中存在一致的趋势[242,244,245]。四项涉及急性MI患者的随机研究探讨了超声心动图检测左室栓子和心房颤动的关系[247-249]。抗凝治疗使栓子形成减少了50%以上；但是，每项试验都没有能达到统计学差异的足够的样本量。

在现有临床试验结果的基础上，对前壁MI后使用超声心动图检测出左室微栓的患者发表了口服抗凝药物治疗的Ⅰ类建议。关于抗凝治疗的持续时间问题还没有一个共识[251]。大量研究的汇总结果表明，这些患者在梗死后存在数月的持续性的卒中风险，但是其他抗凝治疗方案还没有得到系统的评价。最初的3个月后，血栓塞的风险似乎有所减少，并且在慢性室壁瘤患者中，栓塞的风险相对较低，即使在这种情况下经常会发生心内栓子。

**建议**

1. 缺血性卒中或TIA患者，出现急性MI并有超声心动图或其他心脏影像检查证实的左室栓子形成时，应当进行口服抗凝治疗（INR目标值2.5；范围2.0 - 3.0）至少3个月[Ⅰ类；B级证据]。

3.3 心肌病

尽管数字估计难以证实，但是大约10%的缺血性卒中患者LVEF ≤ 30%[252]。第一个现代心力衰竭管理意义上的随机试验研究是华法林和抗血小板治疗慢性心力衰竭(Warfarin and Antiplatelet Therapy in Chronic Heart Failure trial, WATCH)试验，该试验没有证明华法林与阿司匹林或氯吡格雷相比更有效[253]。

同样，缺乏证实阿司匹林或其他血小板抑制剂对慢性心力衰竭治疗作用的有力的随机研究。一项正在进行的华法林与阿司匹林对心脏射血分数减少患者(Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction, WARCEF)的试验，在LVEF ≤ 35%的无心房颤动、机械人工心脏瓣膜、或其他指征而接受抗凝药物治疗的患者中，比较华法林(INR 2.0-3.0) 和阿司匹林 (325 mg，每日一次) 的作用，复合终点是死亡或卒中（缺血性或出血性）[254]。该试验的设计目的并不是针对下列问题的：哪种抗血栓疗法在预防该人群首次或复发性卒中方面是较好的选择[255]，氯吡格雷或其他噻吩吡啶类血小板抑制剂的疗效是否类似或优于阿司匹林，血小板抑制剂和抗凝剂的联合治疗是否优于二者单独治疗。
建议

1. 窦性心律的既往卒中或 TIA 患者，出现表现为收缩功能下降 (LVEF ≤ 35%) 的心肌病，应用华法林的获益尚未得到证实 (Ⅱb 类; B 级证据)。（新建议）

2. 可以考虑用华法林 (INR 2.0-3.0)、阿司匹林 (81 mg, 每日一次)、氯吡格雷 (75 mg, 每日一次) 或阿司匹林 (25 mg, 每日两次) - 缓释双嘧达莫 (200 mg, 每日两次) 联用预防有心肌病的既往缺血性卒中或 TIA 患者的复发事件 (Ⅱb 类; B 级证据)。

3. 自体瓣膜性心脏病

对于患有瓣膜性心脏病的患者，抗凝治疗可以降低但不能够消除卒中和全身栓塞的可能性。在心脏瓣膜病患者和人工或生物心脏瓣膜的患者中，进行抗血栓形成治疗时，需要平衡患者发生各种形式的血栓风险和避免出血的风险。

3.4 自体瓣膜性心脏病

对于患有瓣膜性心脏病的患者，抗凝治疗可以降低但不能够消除卒中和全身栓塞的可能性。在心脏瓣膜病患者和人工或生物心脏瓣膜的患者中，进行抗血栓形成治疗时，需要平衡患者发生各种形式的血栓风险和避免出血的风险。

3.4.1 风湿性二尖瓣膜病

曾发生过栓塞事件的风湿性二尖瓣膜病患者再发生栓塞的几率是 30%-65%[256-259]。其中 60%-65% 的栓塞发生在第一年内[256,257]，大部分在 6 个月之内。二尖瓣成形术并不能消除血栓栓塞的风险[260,261]。因此，成功的二尖瓣成形术并不能排除需长期接受抗凝治疗患者的抗凝需要。尽管没有随机试验评估，但是许多观察性研究发现，对于风湿性二尖瓣膜病患者，长期的抗凝治疗有效的减少了血栓栓塞的风险[262-265]。经食道超声心动图 (transesophageal echocardiography, TEE) 发现在左房栓子的二尖瓣狭窄的患者中，经长期的抗凝治疗后左房栓子可以消失[266]。ACC/AHA 实践指南已经出版了瓣膜心脏病患者的治疗指南[267]。

没有在风湿性瓣膜病患者中评估抗血小板聚集和抗凝联合治疗的安全性和有效性。如不伴有关节瓣膜疾病或心房颤动，系统性栓塞在主动脉瓣膜病的患者中是不常见的。因为没有对卒中和主动脉瓣膜病的患者的随机试验，因此推荐是基于卒中和 TIA 患者更大的抗血小板聚集治疗试验的证据。

3.4.2 二尖瓣脱垂

二尖瓣脱垂是成人瓣膜病最常见的一种[270]。尽管大部分无害，但有时是症状性的，在一些二尖瓣脱垂患者中被报道有血栓栓塞肺炎 (没有发现其他的栓子源)[271-273]。然而最近许多人群的回顾研究，如弗明汉心脏研究，并没有明确发现卒中风险的增高[276,277]。没有针对这些卒中或 TIA 患者抗栓治疗有效性的资料。

3.4.3 二尖瓣钙化

二尖瓣钙化[279]多见于女性，有时伴有二尖瓣反流，是二尖瓣狭窄的一个不常见的风湿性病因。尽管全身性栓塞和脑栓塞的发生率不明确[279-284]，但尸检中发现严重的二尖瓣钙化组织上存在血栓，超声检查发现在发生脑缺血事件的患者中心房室流出道有回声密度[280,282]。除了血栓栓塞风险外，二尖瓣环钙化后脱落的纤维钙化物也可能导致栓塞[279,281,283]。钙化和血栓栓塞的相对发生率还不明确[279,284]。

二尖瓣钙化是否是卒中的一个独立风险因子还不确定。最近的一项美国印第安人的研究发现，在调整其他的风险因素后，二尖瓣钙化仍是卒中中的一个强有力的危险因子[273]。一项有关患者通过经食道超声心动检查评价脑缺血的研究发现，二尖瓣钙化与近端和末端的复合主动脉瘤明显相关[285]。

对于卒中和 TIA 的患者，没有相关的数据对比抗血小板聚集和抗凝治疗的有效性和安全性。

3.4.4 主动脉瓣膜病

对于单独的主动脉瓣膜病，临床可发现的系统栓塞逐渐被认为是由于微血栓或钙化栓塞[286]。如不伴有二尖瓣膜疾病或心房颤动，系统性栓塞在主动脉瓣膜病的患者中是不常见的。因为没有对卒中和主动脉瓣膜病的患者的随机试验，因此推荐是基于卒中和 TIA 患者更大的抗血小板聚集治疗试验的证据。

建议

1. 对于有风湿性二尖瓣疾病的缺血性卒中或 TIA 患者，不论是否存在心房颤动，长期华法林治疗是合理的，INR 目标值为 2.5(范围 2.0-3.0)(Ⅱa 类; C 级证据)。

2. 为了避免额外出血风险，华法林不应常规联用抗血小板药物 (Ⅲ类; C 级证据)。

3. 对于有局部主动脉弓或非风湿性二尖瓣疾病而无心房颤动的缺血性卒中或 TIA 患者，抗血小板治疗可能是合理的 (Ⅱb 类; C 级证据)。

4. 对于有二尖瓣钙化的缺血性卒中或 TIA 患者，可以考虑抗血小板治疗 (Ⅱb 类; C 级证据)。

5. 对于有二尖瓣脱垂的缺血性卒中或 TIA 患者，可以考虑长期抗血小板治疗 (Ⅱb 类; C 级证据)。
3.5 人工心脏瓣膜

来自于临床试验的证据表明口服抗凝药物对于预防人工心脏瓣膜患者的血栓栓塞是有效的。这项临床试验将患者随机分为 6 个月不确定强度的华法林治疗组和包括阿司匹林的两种抗血小板药物治疗组。与抗凝药物治疗组相比，抗血小板药物组更易发生血栓栓塞 (每年 5%-10% vs 2%)。出血发生率在华法林组更高。其他的研究有些不同的结果，主要取决于人工心脏瓣膜的类型和部位。抗凝的强度以及联合的抗血小板药物使用。没有针对卒中二级预防的研究。

在两个随机研究中，双嘧达莫和华法林联合治疗减少了人工心脏瓣膜患者系统性栓塞的发生率[288,289]。另一项临床试验显示，单独使用华法林相比，阿司匹林 100 mg/d 加华法林 (INR 3.5-4.5) 提高了治疗效果[289]。低剂量的阿司匹林联合高强度的华法林减少了总死亡率、心血管死亡率以及卒中，但是增加了微量出血。大量出血 (包括脑出血) 的差异没有统计学意义。

生物心脏瓣膜与机械心脏瓣膜相比，血栓栓塞几率低。对于有生物心脏瓣膜而无其他血栓栓塞来源的卒中患者，建议口服抗凝治疗 (INR 2.0-3.0)。

建议

1. 对于人工心脏瓣膜的缺血性卒中或 TIA 患者，推荐使用华法林，INR 目标值为 3.0 (范围 2.5-3.5) (I 类; B 级证据)。
2. 对于尽管进行充分口服抗凝治疗但仍发生缺血性卒中或系统性栓塞的人工心脏瓣膜患者，如果患者没有较高出血风险 (例如，出血史、血管曲张、或其他已知导致出血风险增加的血管异常、凝血病)，在口服抗凝药基础上联合应用阿司匹林 75 mg/d-100 mg/d，维持 INR 目标值为 3.0 (范围 2.5-3.5) 是合理的 (IIa 类; B 级证据)。
3. 对于有生物心脏瓣膜而无其他血栓栓塞来源的缺血性卒中或 TIA 患者，可以考虑使用华法林抗凝治疗 (INR 2.0-3.0) (IIb 类; C 级证据)。

4. 非心源性栓塞所致卒中或 TIA(特别是动脉粥样硬化、腔隙性或隐源性梗死)的抗凝治疗

4.1 抗血小板制剂

FDA 批准可用于预防卒中或 TIA 患者发生心血管事件的四种抗血小板方案有：阿司匹林、阿司匹林 / 双嘧达莫联合用、氯吡格雷及噻氯吡啶。这些药物可以使卒中、MI 或死亡的相对风险降低 22%(291)，但这些药物也存在重要的差异，对治疗的选择产生直接的影响。

4.1.1 阿司匹林

阿司匹林可预防近期发生卒中或 TIA 的患者的卒中复发[233,292-294]。在应用阿司匹林治疗继发性卒中中的一项安慰剂对照试验中发现其可将任何类型的卒中[缺血性或出血性]的相对风险降低 15%(95% CI，6%-23%)[295]。虽然应用 <75 mg 治疗剂量的数据很少[291]，但研究显示治疗效益的大小与药物剂量相关 (范围在 50 mg-1500 mg 之间)[233,291,292,294-296]。副作用表现与药物剂量相关，阿司匹林的主要副作用是消化道出血，高剂量的阿司匹林具有更大的出血风险[292,294]。对于应用小剂量阿司匹林 (325 mg) 的患者，每年发生消化道出血的风险为 0.4%，是未服药患者的 2.5 倍[292,294,297,298]。阿司匹林增加的消化道出血的风险，仍比未服药发生缺血性卒中风险小，因此有正向获益[299]。

4.1.2 噻氯吡啶

噻氯吡啶是血小板腺苷二磷酸受体拮抗剂，已在三项脑血管疾病患者的随机试验中进行了评估[299-302]。加拿大和美国噻氯吡啶研究 (The Canadian American Ticlopidine Study, CATS) 比较了在 1053 例缺血性卒中患者中应用噻氯吡啶 (250 mg，一天两次 ) 与安慰剂预防卒中、MI 及血管性死亡的效果[300]。在平均 2 年的随访中，噻氯吡啶治疗的患者发生卒中事件较少(11.3% vs 14.8%)；相对风险降低 [relative risk reduction, RRR] 23%；95% CI，1%-41%)。噻氯吡啶阿司匹林卒中研究 (Ticlopidine Aspirin Stroke Study, TASS) 在 3069 例近期出现轻微卒中或 TIA 的患者中应用噻氯吡啶 250 mg 一天两次及应用阿司匹林 650 mg 一天两次的治疗效果进行比较[301]。3 年后，应用噻氯吡啶的患者发生继发性卒中或死亡的几率较低 (17% vs 19%；RRR 12%；95% CI，2%-26%)；使用 Kaplan-Meier 估算 P=0.048)。最后，非洲裔美国人阿司匹林卒中预防研究 (African American Antiplatelet Stroke Prevention Study, AAASPS) 调查了 1809 例近期发生的非心源性栓塞性缺血性卒中的黑人患者，这些患者都接受了噻氯吡啶 250 mg 一天两次或阿司匹林 325 mg 一天两次的治疗[300]。研究发现在 2 年内，卒中、MI 或血管性死亡的风险无差
异性。氯吡格雷的副作用包括腹泻和皮疹。而发生消化道出血的风险较阿司匹林低。在 CATS 和 TASS 的研究中，应用氯吡格雷治疗的患者发生中性粒细胞减少的比例 < 2%；其中有 1% 的患者可出现严重的中性粒细胞减少症，但停药后基本可逆。同时，也曾发现血栓性血小板减少性紫癜病例 [303]。

4.1.3 氯吡格雷

氯吡格雷是另一种血小板腺苷二磷酸受体拮抗剂，完全不同于阿司匹林。联合应用阿司匹林 / 双嘧达莫及氯吡格雷等方案，对卒中的二级预防也有效。作为一种独立制剂，氯吡格雷在两项卒中二级预防试验中得到证实，一项是与单独使用阿司匹林相比 [298]，一项是与联合使用阿司匹林 / 双嘧达莫相比较 [304]。两项试验治疗组的初始数据结果都很接近。目前尚没有证据表明质子泵抑制剂 (PPI) 如艾美拉唑，可降低氯吡格雷的作用 [307]。联合应用氯吡格雷和一种 PPI 可能导致包括卒中和 MI 在内的严重心血管事件的风险增加。服用氯吡格雷的患者需要抑酸治疗时，如 PPI 在 P-450 细胞色素酶 CYP2C19 位点代谢的，则最好选择 H2 阻断剂 [308]。此外，CYP 基因的功能性遗传变异可影响氯吡格雷抑制血小板的作用。与非携带者相比，携带 CYP2C19 功能性等位基因的患者疗效好于非携带者，而携带 CYP2C19 等位基因的患者疗效没有显著差异 [309]。

4.1.4 双嘧达莫联合阿司匹林

双嘧达莫抑制磷酸二酯酶，并增加前列环素抗血小板聚集作用。目前已有四项大型随机临床研究检测了双嘧达莫 / 阿司匹林对卒中卒中的疗效，这些研究共同指出该联合制剂对卒中二级预防的作用至少等同于阿司匹林单药治疗，但患者耐受性相对较差。

第一个大型试验是欧洲卒中预防研究 (European Stroke Prevention Study，ESPSTP)。2500 例患者随机分为安慰剂组或阿司匹林 325 mg 和快速释放双嘧达莫 75 mg 一天三次组。24 个月后阿司匹林 / 双嘧达莫组卒中或死亡率为 16%，安慰剂组为 25% (RRR 33% ; P < 0.001)。

第二个大型研究是 ESPS-2，核因设计将 6602 例中 / TIA 患者随机分为四组：(1) 阿司匹林 25 mg 一天两次加缓释双嘧达莫 200 mg 一天两次；(2) 阿司匹林 25 mg 一天两次；(3) 单用缓释双嘧达莫；(4) 安慰剂组。与安慰剂组相比，阿司匹林组卒中风险降低 18% (P < 0.013)，双嘧达莫组降低 16% (P = 0.039)，联合治疗组降低 37% (P < 0.001)。阿司匹林单药治疗比较，联合治疗降低卒中风险 23% (P < 0.006)，降低卒中或死亡 13% (P = 0.056)。双嘧达莫并没有明显增加出血，但头痛和胃肠道症状在联合治疗组更加常见。由于研究者报道的数据质量问题，许多国家使用较低剂量的阿司匹林，阿司匹林作为标准治疗的同时选择一种安慰剂等，使该项研究结果的判断变得复杂。

第三项大型研究是欧洲 - 澳大利亚可逆性缺血性卒中预防试验 (European/Australasian Stroke Prevention in Reversible Ischemia Trial，ESPRIT)，应用前瞻性、随机、公开、双盲、终点评估设计，比较近 6 个月 TIA/ 缺血性卒中患者阿司匹林单药和阿司匹林 / 双嘧达莫联合制剂预防卒中、MI、血管性死亡事件或严重出血情况 [312]。
由 30 mg/d 至 325 mg/d 不等，但每组的平均剂量均为 75 mg/d。双嘧达莫组患者中，83% 使用缓释剂型，其余 17% 为快速释放剂型。3.5 年后，联合治疗组有 13% 患者发生主要终点事件，阿司匹林组为 16%(HR 0.80; 95% CI, 0.66-0.98; 绝对风险降低 [ARR], 1.0% 每年; 95% CI, 0.1-1.8)。在这款公开试验中，如果患者或研究者向中心报告的潜在血管事件存在差别，那么该研究报道的潜在预后事件可能也存在偏倚。研究意外地发现联合治疗组严重出血事件的发生率降低 (35 例 vs 53 例)，可能就是这种偏倚的一个指征。最后，研究者没有报道随机化的风险因素管理，如果不同则可以部分解释预后的不同。

第四个试验是前面提到的 ProFESS 研究 [104]，研究显示氯吡格雷组和双嘧达莫/阿司匹林联合治疗组中复发率没有差别，严重出血事件在阿司匹林/双嘧达莫组较常见 (4.1% vs 3.6%)，但差异不具有统计学意义。不良事件致药物中断在阿司匹林/双嘧达莫组较常见 (16.4% vs 10.6%)。联合治疗的耐受性较抗血小板单药治疗差。

4.1.5 氯吡格雷与阿司匹林联合

氯吡格雷与近期 TIA/缺血性卒中高危患者的动脉粥样血栓形成管理研究 (Management of Atherothrombosis with Clopidogrel in High-Risk Patients with Recent Transient Ischemic Attacks or Ischemic Stroke, MATCH)。比较了氯吡格雷 75 mg 联合阿司匹林 75 mg 与单用氯吡格雷 75 mg 对新近 TIA/缺血性卒中患者的预防血管事件的作用 [113]。共入组 7599 例患者，随访 3.5 年，观察缺血性卒中、MI、血管性死亡或因任何中枢性或周围性血管事件再次住院等主要复合终点。与氯吡格雷单药治疗比较，联合治疗在降低主要终点或任何次要终点方面均无明显获益。联合治疗组的严重出血风险却明显增加，致死性出血事件绝对增加 1.3%。虽然对于急性冠脉综合征患者推荐氯吡格雷联合阿司匹林优于单用阿司匹林，但 MATCH 研究对 TIA/卒中患者 ( 急性期以后开始治疗 ) 并没有显示类似的风险—获益比。

联合服用氯吡格雷和阿司匹林与单独服用阿司匹林的疗效已经在两项预防试验 [114,115] 中进行了比较，均未证实联合用药的获益。氯吡格雷用于高动力粥样硬化血栓形成风险和稳定、处理和避免出血 (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance, CHARISMA) 的试验 [115] 中，有 15 603 例伴有明显心血管疾病或多重风险因素的患者参与。28 个月随访后，主要结局 (MI、卒中或血管性死亡) 在联合治疗组为 6.8%，单独服用阿司匹林组为 7.3%(RR 0.93; 95% CI, 0.83-1.05; P=0.22)。在卒中后患者亚组分析显示，联合治疗与单独服用阿司匹林相比，增加了出血危险但是无显著统计学意义。卒中和 TIA 发作快速评估以预防早期复发 (Fast Assessment of Stroke and Transient Ischemic Attack to prevent Early Recurrence, FASTER) 的试验 [116] 检测了在发病 24 小时内 TIA 或小卒中患者卒中预防方面，联合治疗和单独阿司匹林治疗相比的疗效。由于入组慢，这个试验早期就被停止了。结果是不确定的。

4.1.6 选择口服抗血小板药物治疗

上述的证据表明：阿司匹林、阿司匹林/双嘧达莫联合用药、氯吡格雷对二次卒中预防均有效。目前还没有氯吡格雷与安慰剂组比较的试验，它与其他抗血小板药物比较的研究还未确切表明它优于或等于它们中任何一个。CAPRIE 和 ProFESS 的生存曲线观察表明：阿司匹林和阿司匹林/双嘧达莫联合用药可能是同等有效的。

选择这四种药物应以有效性、安全性、成本、患者特征和患者的接受程度为基础。联合服用阿司匹林和双嘧达莫比单独服用阿司匹林可能更能有效预防卒中复发 [117] 和卒中、MI、死亡或大量出血终点 [118] 的发生。平均而言，与单独服用阿司匹林相比，联合用药在一年中能预防 100 个治疗患者中的 1 个发生脑血管意外 [119]。在二级预防中，氯吡格雷可能比阿司匹林更有效 [120]，但是安全顾虑限制了它的临床应用价值。

阿司匹林或阿司匹林/双嘧达莫联用发生消化道出血或其他大出血风险可能比氯吡格雷更大 [121,122]。虽然差异很小，但是每年每 500 例患者中会有 1 例发生大出血 [123]。50 mg-75 mg 剂量的阿司匹林与阿司匹林/双嘧达莫联用的风险似乎是相似的。然而，阿司匹林/双嘧达莫联用比单独使用阿司匹林或氯吡格雷耐受性差，主要副作用是头痛。噻氯匹啶与血栓性血小板减少性紫癜有关，应该只谨慎用于不能耐受其他药物的患者。

在成本方面，阿司匹林是目前最便宜的药物。成本比其他三种药物至少低 20 倍。
4.1.7 Treatment of Patients Who Have Had a Stroke or TIA

目前首次或再次出现卒中的患者一般已经开始抗血小板治疗。不幸的是,没有临床试验证实更换抗血小板药物能降低继发事件的风险。

4.2 Oral Anticoagulants

随机对照试验的结果已经证实,口服抗凝剂可预防非心源性栓塞性卒中患者卒中复发。不幸的是,没有临床试验证实更换抗血小板药物能降低继发事件的风险。

建议

4. 对于非心源性栓塞性缺血性卒中患者,推荐使用抗血小板药物而不是口服抗凝药来降低卒中复发及其他心血管事件的风险 (Ⅰ类 ; A级证据)。

5. 对于阿司匹林过敏的患者,使用氯吡格雷是合理的 (Ⅱa类 ; C级证据)。
动脉夹层还没有明确有效的治疗方法。虽然传统的血管成像是针对颅外夹层的必要检查，但非侵入性的影像学检查如 MRI 和应用脂肪饱和技术的 MRA 或 CTA 也常常用于颅外夹层的诊断 [426]。动脉夹层相关的出血性卒中可能是血栓栓塞或血流动力学障碍导致的，虽然前者是主要机制[428-430]，但在一些病例中，夹层所致的夹层动脉瘤是栓子的来源。颅内动脉夹层，尤其是椎基底动脉区有发生蛛网膜下腔出血 (SAH) 和脑栓塞的危险 [431]。本指南对不同夹层的出血并发症进行讨论。

对有动脉夹层的卒中患者的最佳预防策略仍然存在争议。可供选择的方法有抗凝、抗血小板治疗、有或无支架的血管成形术，或不用特定药物治疗的保守观察。外科治疗方法不常用。确诊后，特别是突然或过度的旋转或拉伸的活动，例如身体接触性运动、导致颈部过伸的活动、举重、分娩、剧烈运动和颈部推拿等 [431]，但没有明确限定这些患者活动的实际证据。还没有对动脉夹层所致卒中患者进行不同的康复治疗的充分理由。

建议

1. 对于有颅外颈动脉或椎动脉夹层的缺血性卒中或 TIA 患者，至少进行 3-6 个月的抗栓治疗是合理的 (I a 类；B 级证据)。

2. 与抗凝相比，抗血小板治疗对有颅外颈动脉或椎动脉夹层的缺血性卒中或 TIA 患者的相关性较小 [430]。新建议 (I b 类；B 级证据)

3. 对于有颅外颈动脉或椎动脉夹层的缺血性卒中或 TIA 患者，使用最佳药物治疗但仍出现复发的脑缺血事件，可以考虑血管内治疗 (支架) (II b 类；C 级证据)。

4. 对颅外颈动脉或椎动脉夹层的缺血性卒中或 TIA 患者，如果血管内治疗失败，或不具有血管内治疗指征，可以考虑手术治疗 (II b 类；C 级证据)。

5.2 卵圆孔未闭

右侧向左分流脑栓塞病因包括卵圆孔未闭 (patent foramen ovale, PFO) 和肺动脉 - 静脉畸形。卵圆孔未闭是房间隔的胚胎性的缺陷，伴有或不伴有房间隔动脉瘤，房间隔动脉瘤定义为卵圆孔部位的组织移动 >10 mm。根据明尼苏达州奥姆斯特德郡的研究 [432,433] 和纽约北曼哈顿研究 (Northern Manhattan Study, NOMAS) [434]，成人 PFO 的发生率多达 15%-25%。孤立的房间隔动脉瘤发生率为 2%-3%，远远低于 PFO [432,434]。

2000 年发表的 Overell 等人 [435] 的荟萃分析断定 PFO 和房间隔动脉瘤会导致显著增加 55 岁患者的卒中风险。对于 55 岁以上的患者，数据的说服力不
够但显示会增加卒中风险：PFO OR=1.27(95% CI，0.8-2.01)，房间隔动脉疾病 OR=3.43(95% CI, 1.86-6.22)，同时患有PFO和房间隔动脉疾病 OR=5.09(95% CI, 1.25-20.74)。研究中报道的 55 岁以下患者与不患有PFO 或房间隔动脉疾病的缺血性卒中患者相比 OR 值分别为：PFO OR=3.1(95% CI, 2.29-4.21)，房间隔动脉疾病 OR=6.14(95% CI, 2.47-15.22)，PFO 伴房间隔动脉疾病 OR=15.59(95% CI, 2.83-85.87) [355]。

2006 年的指南已经详细回顾了先前的数据 [359]，但有两项研究对预防提供了极其重要的信息，在此对其进行总结。WARSS 的研究—— 隐源性卒中 PFO 研究 The Patent Foramen Ovale in Cryptogenic Stroke，PICSS 为 PFO 和房间隔动脉疾病卒中复发风险提供了随机对照研究的数据并比较了治疗方法。该研究中 630 例患者接受了经食道超声心动检查。接受经食道超声心动检查亚组中约 34% 患有 PFO。经过 2 年的随访，卒中发生率在 PFO 患者 (2 年事件发生率 14.8%) 与无 PFO 者 (5.4%) 之间未见差异 (HR 0.96；P=0.84)，而且 PFO 的大小和是否伴有房间隔动脉疾病预后后也无明显影响。接受阿司匹林 (2 年事件发生率为 13.2%) 或华法林治疗 (2 年事件发生率为 16.5%) 的合并 PFO 的隐源性卒中患者临床结局未见差异 (HR 1.17；P=0.65)。尽管这些数据来自一项随机的临床试验，但是其研究并非专为比较两种治疗方法优劣而设计的 [356]。

2002 年 Mas 等 [357] 进行的欧洲 PFO-ASA 研究报道了 581 例隐源性卒中患者发病 4 年后的卒中发生率。该研究的患者年龄在 18 岁 -55 岁之间，均接受每天阿司匹林 300 mg 治疗。研究发现，单独 PFO 的患者、合并 PFO 及房间隔动脉疾病患者和无心脏病患者 4 年时卒中发生率分别为 2.3%(0.3-4.3)、15.2%(1.8-28.6) 和 4.2%(1.8-6.6)。PFO 是否合并房间隔动脉疾病的意义及其最佳治疗方法仍是未知 [357]。目前有三项关于 PFO 患者首次卒中风险的前瞻性研究研究并对 PFO 和卒中风险之间的关系提出了怀疑 [13,325,352,354]。

最近，Handke 等 [358] 的研究连续入选了 503 例卒中患者，其中 227 例患者卒中病因不明，另外 276 例患者病因明确。在对卒中病因进行分类之后，对患者进行经食道超声心动检查。年轻 (43.9% vs 14%；OR 4.7；95% CI，1.89-11.68；P<0.001) 与年老 (28.3% vs 11.9%；OR 2.92；95% CI，1.70-5.01；P<0.001) 的隐源性卒中患者发现 PFO 的比例均高于病因明确的卒中患者。另外，年轻 (13.4% vs 2.0%；OR 7.36；95% CI，1.01-326) 与年老 (15.2% vs 4.4%；OR 3.88；95% CI，1.78-8.49；P<0.001) 的隐源性卒中患者发现 PFO 合并房间隔动脉疾病的比例均高于病因明确的卒中患者 [358]。西班牙前瞻性多中心研究 (The Prospective Spanish Multicenter, CODICIA) 入组了 486 例隐源性卒中患者，应用经颅多普勒计算了患者右向左分流的程度，其中 200 例患者 (41%) 存在较大程度的右向左分流。该研究中，卒中的卒中复发率较低 (5.8%)，且与分流的程度无关 [359]。

在上述研究之后，PFO 合并/不合并房间隔动脉疾病对于卒中首发或复发的意义目前尚不明确。尽管目前一些相关研究正在进行，但尚无随机对照临床试验比较不同的药物治疗、药物治疗和外科手术，以及药物治疗和经导管 PFO 封堵术的差异。关于不同 PFO 封堵技术与药物治疗的非随机对照研究发现，PFO 封堵术的并发症风险和卒中复发风险并不高于药物治疗 [363,370]。一项研究发现，基线时发生 1 次或 1 次以上卒中的患者可能明显获益 [370]。

总言之，上述研究对选择 PFO 封堵提供了新的信息——PFO 封堵术的短期并发症很少，且大多数并发症很轻微。但不幸的是，目前尚无长期的随访信息。经导管 PFO 封堵术后 1-2 年的不良事件发生率为 0.3-4%。比较 PFO 封堵术与单纯药物治疗的相关研究发现，封堵术的预后较好 


doi:10.1161/JAHA.109.818933

### 建议

1. 对于有 PFO 的缺血性卒中或 TIA 患者，抗血小板治疗是合理的 (Ⅱa 类；B 级证据)。
2. 尚无充分证据能够证实 PFO 患者卒中二级预防中抗凝治疗与阿司匹林治疗相同或优于阿司匹林 ( Ⅱb 类；B 级证据)。建议(新建议)
3. 尚无对有 PFO 的卒中患者进行 PFO 封堵技术的充分证据 ( Ⅱb 类；C 级证据)。

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*Furie et al Prevention of Stroke in Patients With Stroke and TIA*


5.3 高Hcy血症

遗传性易栓症对于卒中或TIA后的复发风险的作用尚不得而知。已报道的研究多为病例报告、病例系列或小的首次发作卒中患者的病例对照研究。目前对纯合子和杂合子卒中的相对风险性的数据存在矛盾。这可能是由于人群中异质性以及对于预后定义不同而致。目前还没有根据基因型给予不同的抗血栓治疗的临床试验。


在年轻患者(年龄<55岁)的研究中发现，前血栓形成基因的变异与缺血性卒中相关，但在有心血管病危险因素的老年人中，这种相关性仍存在争议，而且其提高卒中风险的机制的观点相互矛盾。甚至与年轻患者的相关性也存在争议。在一项小样本的对<50岁、病因不明的卒中患者的研究中显示，PTG20210A突变使卒中的风险增加(OR 3.75；95% CI，1.05-13.34)，但FVL与卒中风险无关[399]。相反的，另外两项对年轻患者(<50岁)的研究发现，缺血性卒中与FVL、PTG20210A或MTHFR C677T基因突变均无相关性[377,400]。一项研究对比了青年卒中(<45岁)静脉血栓形成相关的遗传因素，发现PTG20210A突变在合并PFO的患者中比无PFO或非卒中患者更常见，而FVL无此趋势[397]。

有三项关于最常见的FVL、MTHFR、PT基因突变研究的荟萃分析。第一项是针对高加索成人中缺血性卒中相关候选基因研究，发现卒中与FVL(OR 1.33；95% CI，1.12-1.58)、MTHFR C677T(OR 1.24；95% CI，1.08-1.42)、PTG20210A(OR 1.44；95% CI，1.11-1.86)基因突变具有明显的相关性[401]。第二项探讨了FVL、PTG20210A、MTHFR C677T基因突变与动脉血栓事件(MI、缺血性卒中、外周血管疾病)的相关性，没有发现FVL突变与之明显相关，PTG20210A(OR 1.32；95% CI，1.03-1.69)、MTHFR C677T(OR 1.20；95% CI，1.02-1.41)基因突变与动脉血栓事件有轻度的相关性，而且在相对年轻的人群(<55岁)中更明显[402]。第三个荟萃分析主要探讨了MTHFR基因C677T位点的多态性，它
抗磷脂抗体

建议

1. 对患有遗传性易栓症的动脉性缺血性卒中或TIA患者，应进行深静脉血栓 (deep vein thrombosis, DVT) 形成评估，根据临床和血液学情况决定短期或长期抗凝治疗 (I 类; A级证据)。

2. 适当充分评估患者卒中的可能机制。对于有易栓症但没有静脉血栓的动脉性缺血性卒中或TIA患者，使用抗凝剂或抗血小板治疗均是合理的 (IIa 类; C级证据)。

3. 有自发性脑静脉血栓形成和/或复发性血栓事件的遗传性易栓症患者，可能具有长期抗凝治疗指征 (IIa 类; C级证据)。

5.4.2 抗磷脂抗体

抗磷脂 (Antiphospholipid，APL) 抗体阳性率在1%-6.5%之间，老年人及狼疮患者中更高 [409]。APL抗体综合征较少见，表现为多脏器的动静脉闭塞性疾病和血栓 [410]。除了血栓事件或流产外，诊断还需要间隔6周以上血抗心磷脂 IgG和/或IgM抗体或狼疮抗凝物有两次以上达到中等到高等滴度 [411]。APL抗体与卒中的相关性在年轻成人 (<50岁) 中显著 [412-414]。在APL抗体中研究 (Antiphospholipid Antibodies in Stroke Study, APASS) 中，9.7%的缺血性卒中患者和4.3%的对照者抗心磷脂抗体阳性 [415]。在APASS 子研究——WARSS/APASS 中，40.7%的卒中患者APL抗体阳性，但滴度很低，对卒中复发没有明显影响 [415]。

多项研究发现APL抗体阳性的年轻患者卒中复发的风险高 [416-418]。在一项对发生动脉或静脉血栓事件人群的研究中，高剂量的华法林 (INR 3.1-4.0) 并不比中等剂量华法林 (INR 2.0-3.0) 治疗能够更好的预防APL抗体阳性患者血栓事件的复发 [419]。但是老年人群中APL抗体与卒中复发相关性的结论相互矛盾 [416,420-422]。

WARSS/APASS 协作研究是首次比较华法林 (INR 1.4-2.8) 和阿司匹林 (325 mg) 预防APL抗体阳性患者卒中复发的随机对照研究。APASS 入组了720例APL抗体阳性的WARSS受试者 [415]。APL阳性和阴性患者卒中复发生发率分别为22.2%和21.8%。狼疮抗凝物和心磷脂抗体均阳性患者卒中复发率比二者均为阴性的高 (31.7% vs 24.0%)，但是差异没有统计学意义。两种治疗组间在包括任何原因所致死亡、缺血性卒中、TIA、MI、DVT及其他全身血栓闭塞性事件的联合终点事件方面没有差异 (华法林: RR 0.99; 95% CI, 0.75-1.31; P=0.94; 阿司匹林: RR 0.94; 95% CI, 0.70-1.28; P=0.71)。

建议

1. 对APL抗体阳性的隐源性缺血性卒中或TIA患者，抗血小板治疗是合理的 (IIa 类; B级证据)。

2. 对于符合APL抗体综合征诊断标准的缺血性卒中或TIA患者，口服抗凝治疗，目标 INR值为2.0-3.0是合理的 (IIa 类; B级证据)。

5.5 镰状细胞病

卒中是镰状细胞病 (sickle cell disease, SCD) 常见的合并症。SS基因型患者的卒中风险最高，但其他基因型也可能发生 [423]。SCD的成年患者到20岁、30岁和45岁时发生首次卒中的风险分别为11%、15%和24% [423]。首次卒中发生于成年后SCD患者 (年龄≥20岁)，卒中复发率每年1.6/100人 [423]，而且大多发生于首次卒中后几年内 [424,425]。导致SCD患者缺血性卒中风险增加的情况包括：既往TIA病史 (RR 56; 95% CI, 12.285; P<0.001) [423]，PCT 重贫血 (稳态血红蛋白每降低1 g/dL，RR 值为1.85; 95% CI, 1.32-2.59; P<0.001) [426,427]，2周内有急性胸痛综合征 (胸痛X光片显示新发的浸润病灶并伴有1个及以上新症状：发热、咳嗽、咳痰、呼吸困难、缺氧) (RR 7.03; 95% CI, 1.27-4.48; P=0.001) [421]，每年发生一次急性胸痛综合征 (RR 2.39/事件/年; 95% CI, 1.27-4.48; P=0.005) [423]，1岁时白细胞数增
内皮损伤后内膜增生

SCD 患者缺血性卒中最常见的发病机制为反复内皮损伤后内膜增生 [420] 所致大动脉病变 [427-428]。其他机制也可引起卒中。蛋白 C 和蛋白 S 的水平下降也和缺血性卒中相关 [430]，反映凝血状态的其他指标虽然和卒中没有直接关联，但是有报道显示 SCD 患者的这些指标升高 [431,432]。颅内静脉窦血栓形成是 SCD 患者发生脑缺血的另一机制 [433]。在这些患者中心脏疾病所致脑梗塞非常少见而且未见报道。除大动脉病变外，其他机制也可能导致 SCD 患者发生卒中，而且目前缺少 SCD 特异性危险因素和血管危险因素（如糖尿病、高血压）之间相互作用的资料，因此需要对其他可能的机制以及传统的卒中危险因素进行识别和治疗，并且这需要由一个合适的诊断小组实施。

对于伴有大动脉病变的 SCD 患者的治疗建议主要是基于对儿童卒中的预防研究。镰状细胞贫血患者的卒中预防研究 (Stroke Prevention Trial in Sickle Cell Anemia, STOP) 是一个随机、安慰剂对照的研究。该研究显示，对患有 SCD 和轻度多普勒 (TCD) 显示血流速度快的儿童进行输血有助于卒中的一级预防 [434]。STOP 的结果不适用于本指南，在 AHA 关于儿童和婴儿卒中一级预防 [435] 及治疗声明中对其进行了总结 [436]。目前还没有临床随机对照研究支持输血有利于儿童或成人的卒中二级预防。一项针对 SCD 卒中患者的回顾性、多中心研究对比了观察和输血治疗，结果显示定期输血足以抑制自身血红蛋白 S 的合成，从而降低卒中复发风险。最常用的输血的目标是输血前血红蛋白 S 占总血红蛋白的比例，血红蛋白 S 降至 30% 以下 ( 在开始定期输血前的基线水平常常为 90%) 能使卒中的 3 年复发率显著下降 (13.3% vs 67%-90%; P<0.001) [436]。该研究中的大部分患者为儿童，成人血红蛋白 S 是否增加卒中风险以及降低其水平的治疗是否可以获益目前尚不清楚。与对照组相比，输血治疗除了可以减少临床事件外，对于伴有 TCD 血流速度增加的 SCD 患者，还可以延缓大血管狭窄的进展 (P<0.001) [437]，减少 MRI 上的无症状梗死灶的发生率 (P<0.001) [438]。定期输血能导致一些远期并发症，尤其是铁超载，这使长期输血治疗受到质疑。一些专家建议在卒中后进行 1-3 年 ( 推测这段时期卒中复发风险较高 ) 的输血治疗，然后改用其他的治疗方案。

成人 SCD 患者的其他卒中二级预防措施缺少有效性的证据。一些对 SCD 的儿童和年轻患者进行的卒中二级预防的小样本研究显示，经 3 年以上的定期输血治疗后改用羟基脲治疗结果令人鼓舞 [439,441]。羟基脲可以降低 SCD 患者的 TCD 流速 (P<0.001) [442], 还可能改善脑血管病变 [443]。羟基脲替代输血治疗卒中研究 (Stroke With Transfusions Changing to Hydroxyurea, SWiITCH) 是一项正在进行的Ⅲ期随机临床研究, 对比了在患 SCD 的儿童中长期输血与输血后改用羟基脲两种方法的疗效。从血液学的角度看，对一小部分有适合供体并且有条件接收专业治疗的患者，骨髓移植能够治愈该病，但这一般是针对儿童而非成人。卒中以及其他脑相关疾病经常是骨髓移植的原因。虽然经验还很有限，但报道显示骨髓移植对于临床和亚临床梗死均起到抑制作用 [444]。在一些报道中，建立侧枝的外科手术能够成功改善具有 moyamoya 样血管病变的 SCD 患者的预后，但是还是无相关的随机或对照研究 [445,446]。考虑到目前对于 SCD 患者使用抗血小板药、抗凝剂和抗炎药进行卒中二级预防还缺乏足够的经验，因此除了遵循一般治疗指南外，不建议额外加用任何一种药物。动物研究结果显示，他汀类药物能降低 SCD 动物内皮组织因子的表达 [447]。但没有进一步的证据支持他汀类药物对 SCD 患者具有疗效前，仅建议在依据其对普通人群重要性的基础上使用他汀类或降压药来降低风险。

建议

1. 对于有 SCD 的成人缺血性卒中或 TIA 患者，给予控制危险因素和应用抗血小板药物的一般治疗是合理的（I b 类；B 级证据）。

2. 为预防脑缺血事件复发，可以考虑对有镰状细胞病的患者进行其他治疗，如定期输血使血红蛋白 S 降低至总血红蛋白的 30%-50% 以下、使用羟基脲、或对严重闭塞性疾病进行旁路手术（I b 类；C 级证据）。

5.6 脑静脉壁血栓

脑静脉血栓 (cerebral venous thrombosis, CVT) 的估计年发生率为 3-4/100 万。尽管 CVT 仅占所有卒中的 1%，但因为它的治疗不同于动脉性卒中，因此应引起重视 [448]。
7. Prevention of Stroke in Patients With Stroke and TIA

7.1 Acute and Chronic Anticoagulation

Anticoagulation is the primary treatment for patients with acute ischemic stroke, and it is recommended to begin as soon as possible after the onset of symptoms. The most common agents used are vitamin K antagonists (VKAs) such as warfarin and direct oral anticoagulants (DOACs) such as apixaban, rivaroxaban, and edoxaban. The duration of anticoagulation is typically 3 to 6 months, particularly for patients with atrial fibrillation or transient ischemic attack (TIA). For patients with acute ischemic stroke, the recommendation is to continue anticoagulation for at least 3 months, and in some cases, even longer, depending on the individual patient's risk factors and clinical course.

7.2 Risk Stratification

Risk stratification is crucial in determining the duration of anticoagulation. Patients with high-risk conditions such as atrial fibrillation, previous stroke, or congestive heart failure may require long-term anticoagulation. In contrast, patients with low-risk conditions such as a single TIA or minor stroke may be candidates for shorter durations of anticoagulation.

7.3 case study

A 65-year-old patient presented with a first-ever ischemic stroke. On imaging, it was determined that the patient had a left middle cerebral artery (MCA) territory infarct. The patient had a history of atrial fibrillation controlled with a VKA. The patient was started on apixaban for 3 months after the event, which was considered appropriate given the patient's age, lack of other complications, and low risk of bleeding.

7.4 Anticoagulation Management

Effective anticoagulation management requires close monitoring of the international normalized ratio (INR) or other relevant laboratory markers, adjustment of the anticoagulant dose as needed, and adequate patient education on the importance of consistent treatment. Regular follow-up appointments with a healthcare provider are necessary to ensure that the patient remains safely anticoagulated.

7.5 Conclusion

Anticoagulation is a crucial aspect of stroke prevention and management. Timely initiation, appropriate duration, and effective management are key to optimizing outcomes for patients. Patients and healthcare providers should work closely together to ensure the best possible care.

7.6 References

[Furie et al. Prevention of Stroke in Patients With Stroke and TIA]
关性卒中的发生率为11-26/100 000不等，最危险时期为产后和出生前后3天。因为对胎儿有潜在的致畸作用或增加出血的风险，所以对于曾有TIA或卒中病史的女性，妊娠期抗血栓治疗更加复杂。

对于妊娠期间的卒中预防性治疗，建议基于以下两种方案：(1) 存在高风险者需使用华法林抗凝治疗，或(2) 如果患者有较低或不确定风险状况存在，并非处于妊娠阶段，抗血小板治疗可推荐。对这个复杂话题的全面评价已经超过了本指南的范围，但美国胸科医师协会协作组近期已经对这个问题进行了详细讨论。

目前没有针对妊娠期卒中预防的随机临床试验，因此，必须根据其他研究的结果选择药物，主要是根据DVT的预防和高心脏病风险女性中抗凝剂的使用研究。一些患者需要抗凝治疗，如已有栓子形成或人工心脏瓣膜患者、维生素K抵抗、妊娠期间已经使用过普通肝素或低分子肝素者。由于华法林可以透过胎盘并对胎儿有潜在的有害影响，妊娠期间常用普通肝素或低分子肝素替代华法林。在一些高风险患者中应用普通肝素或低分子肝素疗效的研究中，华法林通常在妊娠13周后使用，分娩时换用普通肝素或低分子肝素 [42]。低分子肝素可以避免与长期使用肝素相关的肝素诱导的血小板减少症和骨质疏松症，因此可以替代普通肝素。妊娠期女性低分子肝素的药代动力学会改变，所以应对其剂量进行标准化，密切监测抗Xa水平 [43]。

一项有关患有APL抗体综合征的妊娠期女性调查的结论是，此类患者应该给予低分子肝素和低剂量阿司匹林治疗 [44]。高卒中风险、既往卒中病史或严重动脉血栓的患者妊娠14-34周时应考虑给予华法林治疗。对于治疗后仍然流产的患者建议静脉注射免疫球蛋白。低风险的妊娠女性，妊娠3个月后给予低剂量的阿司匹林（50 mg/d 至 150 mg/d）似乎是安全的。一项对有先兆子痫风险的妊娠期女性的大型荟萃分析并未显示在妊娠3-9个月内服用低剂量阿司匹林对胎儿有明显的致畸作用或长期的副作用 [45]。低剂量阿司匹林用于6个月后先兆子痫患者的随机研究显示，阿司匹林除了增加分娩后输血风险外，对母亲和婴儿无其他副作用 [46]。妊娠期前3个月使用阿司匹林还需进一步确认。尽管在另一项数据分析中还未发现和服用阿司匹林相关的先天性异常总体有所增加，但增加了一种罕见的先天性缺陷——腹裂畸形的风险 [47]。妊娠期间其他可选择的抗血小板药物的使用也还没有比较全面的研究。

建议

1. 对于有高危血栓栓塞状态或高凝状态或人工心脏瓣膜的妊娠期缺血性卒中或TIA患者，可以考虑以下用药方案：在整个妊娠期间调整普通肝素剂量，例如，根据部分凝血酶原时间（activated partial thromboplastin time, aPTT）的检测，每12小时皮下注射；在妊娠期间根据抗Xa因子监测情况调整低分子肝素剂量；或在妊娠13周之前使用普通肝素/低分子肝素，然后改用华法林直到妊娠9个月时，然后重新使用普通肝素/低分子肝素直到分娩(Ⅱb类；C级证据)。

2. 若不存在高危血栓栓塞状态、卒中或TIA的妊娠期女性可以考虑在妊娠前3个月使用普通肝素/低分子肝素，然后使用低剂量阿司匹林 (Ⅱb类；C级证据)。

6.2 绝经后激素治疗

以前根据观察性研究认为，绝经后给予激素治疗可能对心血管疾病的预防有益，但在心脏病和卒中幸存者中进行的随机试验和一级预防试验均未能证实有任何明显的获益，并且还发现使用激素治疗能增加卒中风险。女性雌激素卒中试验(Women’s Estrogen for Stroke Trial, WEST)纳入664例曾患有卒中或TIA的女性，在超过2.8年的随访后没有发现雌二醇能降低卒中复发死亡的风险 [48]。雌激素治疗组发生致死性卒中的风险更高(OR 2.9；95% CI，0.9-9.0)。而且，激素治疗组复发性卒中的患者恢复更差。包括2763例患有心脏病的绝经后女性心脏和雌激素/黄体酮替代研究(Heart and Estrogen/progestin Replacement Study, HERS)试验并未显示激素治疗能降低卒中风险，也未显示有任何心血管获益 [49]。女性健康促进研究(Women’s Health Initiative, WHI)对16 608例50-79岁的绝经后女性患者进行了安慰剂对照的随机研究，发现在一级预防中，卒中复发率增加44%(HR 1.44；95% CI，1.09-1.90) [50]。另一项包括10 739例女性的雌激素平行研究发现了相同的风险增加率 (HR 1.53；95% CI，1.16-2.02) [51]。因为动物试验显示雌激素对脑组织有保护作用，故对绝经后及围绝经期的妇女采取激素疗法或许可以提供保护作用。尽管如此，观察性研究及WHI临床研究均未证实这一假
说。护士健康研究 (Nurses’ Health Study) 指出，卒中风险的增加与激素治疗开始的时机并无相关性。在 WHI 研究中，无论绝经后激素治疗开始的早晚，卒中风险均提高 [483]。

建议

1. 对于女性缺血性卒中或 TIA 患者，不推荐进行绝经后激素治疗 (雌激素和 / 或孕激素) (II类；A级证据)。

7. 颅内出血后抗凝药物的使用

临床医师面临的最困难的问题之一是对颅内出血患者抗血栓治疗的管理。有几个关键问题需要考虑：出血类型、患者年龄、复发性出血的危险因素及抗栓治疗的指征。大部分研究或病例系列报道都集中于人工瓣膜或心房颤动者接受抗凝治疗后出现脑出血或硬膜下血肿的患者。在所有的病例中，都要权衡复发出血的风险及缺血性脑血管事件的风险。总之，目前缺乏能回答这些问题的大型前瞻性随机研究资料。

对于 INR 升高的急性脑出血或硬膜下血肿患者，应使用凝血因子、维生素 K、和 / 或新鲜冷冻血浆尽快降低 INR 值 [484,485]。目前已经证实，30%-40% 的脑出血在发病后 12-36 小时会出现脑肿扩大 [486]，如果患者使用抗凝剂，脑肿扩大的时间还会延长 [487]。这种脑肿扩大常伴随神经功能恶化 [488]。校正年龄、性别、种族、抗血小板药物应用、血肿位置、发病到扫描时间等因素，INR 升高与脑肿扩大有关 [489]。在这项 258 例患者的回顾性研究中，INR>3 的患者血肿体积增大更明显 (与 INR<1.2 者相比；P=0.02)。一般情况下，快速的抗凝逆转推荐用于脑出血或者硬膜下出血的患者 [490,491]。但是目前并没有关于这种治疗和结局的资料。在大部分国家指南中，对严重出血患者推荐应用凝血酶原复合物并在 15 分钟内使 INR 达标，优于应用新鲜冻血浆，因为其更易于管理且起效迅速 [492]。维生素 K 应与其他药物联合应用。迅速逆转 INR 值至正常会使高危患者面临血栓事件的风险。任何一项治疗都将严格衡量风险与获益后再实施。在有强烈指征早期抗凝的患者中，一些研究提示静脉肝素 (PTT [partial thromboplastin time] 在正常值的 1.5-2.0 倍) 或低分子肝素或许是比口服华法林更为安全的选择 [484]。未能逆转华法林或者未能达到正常 INR 值将带来再出血的风险，未能用静脉肝素达到治疗的 PTT 值将带来缺血性卒中的风险 [484]。如果复发出血，静脉注射肝素的优点是很容易调整剂量和停药，并可很快被硫酸鱼精蛋白纠正。不推荐静脉推注肝素，因为研究表明这可能增加出血风险 [502]。在这项研究中，缺乏关于低分子肝素的前瞻性、随机性试验的证据。很少有在这种情况下应用其他抗凝药物的随机对照研究数据。

缺血性卒中的出血转化似乎与脑出血的病程和自然史不同。在有强烈指征早期抗凝的患者中，一些研究提示静脉肝素 (PTT [partial thromboplastin time] 在正常值的 1.5-2.0 倍) 或低分子肝素或许是比口服华法林更为安全的选择 [484]。未能逆转华法林或者未能达到正常 INR 值将带来再出血的风险，未能用静脉肝素达到治疗的 PTT 值将带来缺血性卒中的风险 [484]。如果复发出血，静脉注射肝素的优点是很容易调整剂量和停药，并可很快被硫酸鱼精蛋白纠正。不推荐静脉推注肝素，因为研究表明这可能增加出血风险 [502]。在这项研究中，缺乏关于低分子肝素的前瞻性、随机性试验的证据。很少有在这种情况下应用其他抗凝药物的随机对照研究数据。
状轻微，病灶大小及范围很少进展，相对常见[503,504]。一些病例系列研究提示，即使出现了出血转化，只要不是症状性出血且有适应证，仍可以继续抗凝治疗[500]。每一个病例都应该根据例如出血转化大小、患者状态、抗凝治疗的适应证等情况进行个体化评估。

建议

1. 对于脑出血、SAH 或硬膜下出血的患者，急性期停止使用所有抗凝药物和抗血小板药物至少 1-2 周，并立即使用新鲜冰冻血浆或凝血酶原复合物和维生素 K 逆转华法林作用是合理的（Ⅱ a 类；B 级证据）。

2. 应使用硫酸鱼精蛋白对抗肝素相关颅内出血，使用剂量取决于肝素停止的时间（Ⅰ类；B 级证据）。（新建议）

3. 抗栓治疗相关脑出血发生后是否应再次开始抗栓治疗，取决于随后发生动脉或静脉血栓栓塞的风险、脑出血复发风险和患者的总体情况。脑梗死风险较低的患者（例如，既往无缺血性卒中的心房颤动患者）和淀粉样血管病风险较高的患者（例如，脑叶出血的老年人）或整体神经功能非常差的患者，可以考虑使用抗血小板药物预防缺血性卒中。对于具有较高血栓栓塞风险、应考虑再次使用华法林的患者，在最初脑出血发生后 7-10 天内重新启用华法林治疗是合理的（Ⅱ b 类；B 级证据）。（新建议）

4. 对于出血性脑梗死患者，根据具体临床情况和潜在的抗凝治疗指征，继续进行抗凝治疗可能是合理的（Ⅱ b 类；C 级证据）。

8. 贯彻指南的具体措施及其在高危人群中使用的应用

全国共识指南已经由许多专业协会及政府机构出版，目的是增加医疗保健提供者对于循证方法治疗疾病的认识。

这一知识传递的方法假定，仅仅对指南内容认识增加即可导致医生行为的巨大改变，最终改变患者的行为及健康的结局。但之前出版指南的经验提示事实并非如此，基于指南普及在后续卒中与冠脉疾病预防策略的依从性并未显著性地提高[508-510]。例如，治疗高血压可以降低卒中发病风险，这一认识被认为是对许多指南及公共教育活动的主题。在患高血压的成年人中，60% 接受治疗，但只有其中一半真正达到目标血压值，另外 30% 甚至还未认识到他们患有高血压[511]。

系统实施策略必须与指南的普及相辅，来改变医疗卫生提供者的实践行为。《专家组检测、评估及治疗成人高血浆胆固醇水平的第三次报告》(The Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults)[512] 证明了实施策略（例如，诊所提醒者），加强策略（例如，反馈）及趋向策略（例如，实践指南）来提高卫生实践的必要性。一项这样的例子是 AHA 自发质量提高项目 - 跟着指南走(GWTG)，在 CHD、心力衰竭和卒中二级预防方面有三个单独的模块。跟着指南走 - 卒中项目于 2003 年在全国范围内实施；2008 年，超过 1000 所医院参加了此次项目。参与项目和之后的措施提高有关[514]，这一措施与从基线至第 5 年预防继发性卒中相关：为心房颤动患者发放抗血栓药物和抗凝药物，对 LDL-C 水平超过 100 mg/dL 的患者进行降脂治疗及戒烟。跟着指南走 - 卒中与每年 1.18 倍的遵循指南的几率增长有关，与长期趋势无关。

其他组织也认识到系统方法的必要性。国家医疗研究指示机构表明临床证实有效的治疗与社区实际治疗率间的差距[515]。为保证科学知识有效地转化为临床实践，以及解决医疗卫生差距，国家科学研究院医学所提倡建立协调的、融合预防与治疗措施的系统，来促进患者达到循证治疗[516]。
质量与医生收入构成关系的研究用电脑代码对卒中的治疗质量进行评分，并据此给予医生相应的报酬，发现高质量评分并非与对国际指南的良好依从性相关。这意味着我们需要更多的研究来决定如何能最好地实践和衡量这些预防措施[520]。

高危人群的识别和反馈

各项研究均强调了为卒中及TIA复发高危人群制定特殊预防措施的重要性，原因包括增加的复发倾向和下降的健康素质和意识。老年人、社会经济地位低者和特殊种族均被视为高危人群[521-523]。

老年人具有更高的卒中风险，且发生治疗(如口服抗凝药和颈动脉内膜切除术)相关并发症的风险也最高[524-525]。尽管为这些易患人群制定不同的预防措施很有必要，但一些临床试验并没有包含足以全面评价80岁以上研究对象治疗效果的完整数据，而这个年龄段的人群是一个日益增长的重要亚组。在SAPPHIRE中，只有11%(776例行CEA的患者中有85例)的患者年龄在80岁以上，而在所有行CEA的患者中卒中高危组和卒中低危组的对比研究显示两组的卒中发生率无差异[526]。相反，一些药物治疗(如抑制素)试验的研究对象中则包含了相对较多的患有CHD的老年人，并保障这群人的治疗安全性及减少不良反应的发生。因此，我们还需要对老年人进行进一步研究[527-530]。

社会经济地位低者之所以成为卒中高危人群主要是由于治疗途径有限[531,532]。美国科学院神经病学专家小组1996年的报告指出，全科及神经系统疾病(如卒中)的治疗途径仍然有限。这些限制可能要归咎于有限的人力资源，如健康保险的缺乏、可利用的设备及专业知识的地理差异(农村经常出现这种情况)、或到达医院的时间太长。几乎没有医疗保险的住院卒中患者所得到的血管造影及颈动脉内膜切除术的机会更少[533-534]。

与城市地区相比，很多农村医疗机构缺乏足够的卒中急救治疗资源，广泛的社区和专业教育服务，而这些资源影响着对卒中的认识和预防。远程医学作为一种工具，正显现其支持改善的农村医疗、卒中的急救治疗、卒中的一级及二级预防的作用[537]。那些卒中风险较高的种族的预防效果受到格外的关注[538]。虽然从1991年到1998年美国的卒中死亡率已下降了11%，但不是所有人都平等受益，不同种族间的显著差分持续存在[539]。即使在少数种族中，性别差异也依然存在。事实证明黑人男性的三大死因是心脏病、癌症和HIV感染(艾滋病)，而黑人女性的第三大死因则被卒中取代，而不是HIV感染[540]。黑人女性尤其易患肥胖，发病率大于50%，而体重指数(BMI)的增加则是他们心脏病、糖尿病及卒中患病率及死亡率高的部分原因。在密歇根科弗代尔登记(Michigan Coverdell Registry)中[541]，非洲裔美国人较少得到戒烟咨询服务(OR0.27;95%CI,0.17-0.42)。

BASIC项目记录了墨西哥裔美国人和非西班牙裔白人卒中危险因素概况的相似性[542]。虽然高血压在黑人健康中的角色及其对卒中风险的不成比例的作用已被清楚认识[542-544]，但各国报告分析显示在全球范围内，不同种族的黑人危险因素也是不同的[545]。对于老年人、社会经济地位低者和特殊种族，关键问题是对指南的落实不充分和对预防建议的不依从。专家小组已经指出卒中的预防需要包含患者、家属及医疗服务机构的多层次方法。虽然这种方法已具备了充分的依据，但仍迫切需要进一步研究[546]。

成立于2002年的NINDS卒中差异计划小组，制订了包括建立数据收集系统以及开发在卒中预防中有效的社区治疗方案和设备的策略和目标[547]，并支持以多种族地区(如德克萨斯州南部[541]、曼哈顿北部[544]、伊利诺伊州[548]和华盛顿郊区[549])卒中监督计划为宗旨的项目和直接针对少数种族社区的卒中宣传项目。与联邦政府通过NINDS组成的联盟，即疾病预防控制中心、非营利组织(如AHA/ASA)以及医学专业团体(如美国神经病学会和卒中联盟)，需要共同努力、发展并优化循证卒中预防建议的落实[548]。

建议

1. 为增加建议的使用，在指南制定及推广过程中国增加实施策略可能是有益的(IIa类；B级证据)。(新建议)

2. 干预策略对于克服经济和地理上的障碍、提高指南依从性并重视改善年长者、缺少医疗服务的高危人群的需求可能是有用的(IIa类；B级证据)。(新建议，表10)

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Stroke January 2011


AHA/ASA Guideline

Executive Summary: 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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Survivors of a transient ischemic attack (TIA) or stroke represent a population at increased risk of subsequent stroke. 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, although 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. 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).

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.

Recommendations

Hypertension

1. Blood pressure (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

The full-text version is available online at http://stroke.ahajournals.org/cgi/reprint/STR.0b013e3181f7d043.


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Stroke is available at http://stroke.ahajournals.org
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 reductions 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.

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 angiotensin-converting enzyme inhibitor (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)

### Diabetes

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)
Lipids

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, a low-density lipoprotein cholesterol (LDL-C) level ≥100 mg/dL, and who are without known coronary heart disease (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 (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 National Cholesterol Education Program (NCEP) III guidelines, which include lifestyle modification, dietary guidelines, and medication recommendations (Class I; Level of Evidence A).

4. Patients with ischemic stroke or TIA with low high-density lipoprotein (HDL) cholesterol may be considered for treatment with niacin or gemfibrozil (Class IIb; Level of Evidence B).

Cigarette Smoking

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).

Alcohol Consumption

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).

Physical Activity

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).

Metabolic Syndrome

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)

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)

Symptomatic Extracranial Carotid Disease

1. For patients with recent TIA or ischemic stroke within the past 6 months and ipsilateral severe (70% to 99%) carotid artery stenosis, carotid endarterectomy (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 carotid angioplasty and stenting (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).

8. For patients with symptomatic extracranial carotid occlusion, extracranial/intracranial (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)

Extracranial Vertebrobasilar Disease

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 antiplatelet therapy, statins, and relevant risk factor control) (Class IIb; Level of Evidence C).

Intracranial Atherosclerosis

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 (Warfarin Aspirin Symptomatic Intracranial Disease) 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 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)

Atrial Fibrillation

1. For patients with ischemic stroke or TIA with paroxysmal (intermittent) or permanent atrial fibrillation (AF), anticoagulation with a vitamin K antagonist (target international normalized ratio [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, CHADS2 score of 5 or 6, mechanical or rheumatic valve disease) who require temporary interruption of oral anticoagulation, bridging therapy with a low-molecular-weight heparin (LMWH) administered subcutaneously is reasonable (Class IIa; Level of Evidence C). (New recommendation)

Acute MI and Left Ventricular Thrombus

1. Patients with ischemic stroke or TIA in the setting of acute MI complicated by left ventricular (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).

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).

Cardiomyopathy

1. In patients with prior stroke or transient cerebral ischemic attack in sinus rhythm who have cardiomyopathy characterized by systolic dysfunction (left ventricular ejection fraction [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).

Native Valvular Heart Disease (Rheumatic Mitral Valve Disease, Mitral Valve Prolapse, Mitral Annular Calcification, and Aortic Valve Disease)

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 mitral valve prolapse (MVP) who have ischemic stroke or TIs, long-term antiplatelet therapy may be considered (Class IIb; Level of Evidence C).

Prosthetic Heart Valves

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).

Antiplatelet Agents and Oral Anticoagulants

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).

Arterial Dissections

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).

Patent Foramen Ovale
1. For patients with an ischemic stroke or TIA and a patent foramen ovale (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).

Hyperhomocysteinemia
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.

Inherited Thrombophilias
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).

Antiphospholipid Antibodies
1. For patients with cryptogenic ischemic stroke or TIA in whom an antiphospholipid (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).

Sickle Cell Disease
1. For adults with sickle cell disease (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).

Cerebral Venous Sinus Thrombosis
1. Anticoagulation is probably effective for patients with acute cerebral venous thrombosis (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).

Fabry Disease
1. For patients with ischemic stroke or TIA and Fabry disease, α-galactosidase enzyme replacement therapy 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)

Pregnancy
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 unfractionated heparin (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).

Postmenopausal Hormone Therapy

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).

Use of Anticoagulation After Intracranial Hemorrhage

1. For patients who develop intracranial hemorrhage (ICH), subarachnoid hemorrhage (SAH), or subdural hematoma (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).

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

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)

References

References are available in the full text of this guideline: http://stroke.ahajournals.org/cgi/reprint/STR.0b013e3181f7d043.