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

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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

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

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

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

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

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Abstract—The aim of this updated statement is to provide comprehensive and timely evidence-based recommendations on the prevention of ischemic stroke among survivors of ischemic stroke or transient ischemic attack. Evidence-based recommendations are included for the control of risk factors, interventional approaches for atherosclerotic disease, antithrombotic treatments for cardioembolism, and the use of antiplatelet agents for noncardioembolic stroke. Further recommendations are provided for the prevention of recurrent stroke in a variety of other specific circumstances, including arterial dissections; patent foramen ovale; hyperhomocysteinemia; hypercoagulable states; sickle cell disease; cerebral venous sinus thrombosis; stroke among women, particularly with regard to pregnancy and the use of postmenopausal hormones; the use of anticoagulation after cerebral hemorrhage; and special approaches to the implementation of guidelines and their use in high-risk populations. **(*Stroke*. 2011;42:227-276.)**

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

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

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

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

Definition of TIA and Ischemic Stroke Subtypes

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

The classification of ischemic stroke is based on the presumed mechanism of the focal brain injury and the type and localization of the vascular lesion. The classic categories have been defined as large-artery atherosclerotic infarction, which may be extracranial or intracranial; embolism from a cardiac source; small-vessel disease; other determined cause such as dissection, hypercoagulable states, or sickle cell disease; and infarcts of undetermined cause.[7] The certainty of classification of the ischemic stroke mechanism is far from ideal and reflects the inadequacy of the diagnostic workup in some cases to visualize the occluded artery or localize the source of the embolism. The setting of specific recommendations for the timing and type of diagnostic workup for patients with TIA or stroke is beyond the scope of these guidelines; at a bare minimum, all stroke patients should have brain imaging with computed tomography or magnetic resonance imaging (MRI) to distinguish between ischemic and hemorrhagic events, and both TIA and ischemic stroke patients should have an evaluation sufficient to exclude high-risk modifiable conditions such as carotid stenosis or atrial fibrillation (AF) as the cause of ischemic symptoms.

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

A. Hypertension

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

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Table 1. Applying Classification of Recommendations and Level of Evidence

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

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

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

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

Although numerous randomized trials and meta-analyses support the importance of treatment of hypertension for prevention of primary cardiovascular disease in general and stroke in particular, few trials directly address the role of BP treatment in secondary prevention among persons with stroke or TIA.[10,15] There is a general lack of definitive data to help guide the immediate management of elevated BP in the setting of acute ischemic stroke; a cautious approach has been recommended, and the optimal time to initiate therapy remains uncertain.[16]

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

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Table 2. Definition of Classes and Levels of Evidence Used in AHA Recommendations

Class I	Conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful and effective
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment
Class IIa	The weight of evidence or opinion is in favor of the procedure or treatment
Class IIb	Usefulness/efficacy is less well established by evidence or opinion
Class III	Conditions for which there is evidence and/or general agreement that the procedure or treatment is not useful/effective and in some cases may be harmful
Therapeutic recommendations	
Level of Evidence A	Data derived from multiple randomized clinical trials or meta-analyses
Level of Evidence B	Data derived from a single randomized trial or nonrandomized studies
Level of Evidence C	Consensus opinion of experts, case studies, or standard of care
Diagnostic recommendations	
Level of Evidence A	Data derived from multiple prospective cohort studies using a reference standard applied by a masked evaluator
Level of Evidence B	Data derived from a single grade A study, or one or more case-control studies, or studies using a reference standard applied by an unmasked evaluator
Level of Evidence C	Consensus opinion of experts

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

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

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

Recommendations

1. **BP reduction is recommended for both prevention of recurrent stroke and prevention of other vascular events in persons who have had an ischemic stroke or TIA and are beyond the first 24 hours (*Class I; Level of Evidence A*).**
2. **Because this benefit extends to persons with and without a documented history of hypertension, this recommendation is reasonable for all patients with ischemic stroke or TIA who are considered appropriate for BP reduction (*Class IIa; Level of Evidence B*).**
3. **An absolute target BP level and reduction are uncertain and should be individualized, but benefit has been associated with an average reduction of approximately 10/5 mm Hg, and normal BP levels have been defined as <120/80 mm Hg by JNC 7 (*Class IIa; Level of Evidence B*).**
4. **Several lifestyle modifications have been associated with BP reduction and are a reasonable part of a comprehensive antihypertensive therapy (*Class IIa; Level of Evidence C*). These modifications include salt restriction; weight loss; consumption of a diet rich in fruits, vegetables, and low-fat dairy products; regular**

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Table 3. Recommendations for Treatable Vascular Risk Factors

Risk Factor	Recommendations	Class/Level of Evidence*
Hypertension	BP reduction is recommended for both prevention of recurrent stroke and prevention of other vascular events in persons who have had an ischemic stroke or TIA and are beyond the first 24 hours *(Class I; Level of Evidence A).*	Class I; Level A
	Because this benefit extends to persons with and without a documented history of hypertension, this recommendation is reasonable for all patients with ischemic stroke or TIA who are considered appropriate for BP reduction *(Class IIa; Level of Evidence B).*	Class IIa; Level B
	An absolute target BP level and reduction are uncertain and should be individualized, but benefit has been associated with an average reduction of approximately 10/5 mm Hg, and normal BP levels have been defined as <120/80 mm Hg by JNC 7 *(Class IIa; Level of Evidence B).*	Class IIa; Level B
	Several lifestyle modifications have been associated with BP reduction and are a reasonable part of a comprehensive antihypertensive therapy *(Class IIa; Level of Evidence C).* These modifications include salt restriction; weight loss; consumption of a diet rich in fruits, vegetables, and low-fat dairy products; regular aerobic physical activity; and limited alcohol consumption.	Class IIa; Level C
	The optimal drug regimen to achieve the recommended level of reduction is uncertain because direct comparisons between regimens are limited. The available data indicate that diuretics or the combination of diuretics and an ACEI are useful *(Class I; Level of Evidence A).*	Class I; Level A
	The choice of specific drugs and targets should be individualized on the basis of pharmacological properties, mechanism of action, and consideration of specific patient characteristics for which specific agents are probably indicated (eg, extracranial cerebrovascular occlusive disease, renal impairment, cardiac disease, and diabetes) *(Class IIa; Level of Evidence B).* (New recommendation)	Class IIa; Level B
Diabetes	Use of existing guidelines for glycemic control and BP targets in patients with diabetes is recommended for patients who have had a stroke or TIA *(Class I; Level of Evidence B).* (New recommendation)	Class I; Level B
Lipids	Statin therapy with intensive lipid-lowering effects is recommended to reduce risk of stroke and cardiovascular events among patients with ischemic stroke or TIA who have evidence of atherosclerosis, an LDL-C level ≥100 mg/dL, and who are without known CHD *(Class I; Level of Evidence B).*	Class I; Level B
	For patients with atherosclerotic ischemic stroke or TIA and without known CHD, it is reasonable to target a reduction of at least 50% in LDL-C or a target LDL-C level of <70 mg/dL to obtain maximum benefit *(Class IIa; Level of Evidence B).* (New recommendation)	Class IIa; Level B
	Patients with ischemic stroke or TIA with elevated cholesterol or comorbid coronary artery disease should be otherwise managed according to NCEP III guidelines, which include lifestyle modification, dietary guidelines, and medication recommendations *(Class I; Level of Evidence A).*	Class I; Level A
	Patients with ischemic stroke or TIA with low HDL-C may be considered for treatment with niacin or gemfibrozil *(Class IIb; Level of Evidence B).*	Class IIb; Level B

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

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

aerobic physical activity; and limited alcohol consumption.

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

B. Diabetes

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

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

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

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

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

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

Recommendation

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

C. Lipids

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

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

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

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

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

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

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

The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Cholesterol in Adults (Adult Treatment Panel III [ATP III]) is the most comprehensive guide for management of dyslipidemia in persons with or at risk for vascular disease, including stroke.[59,60] The NCEP recommends LDL-C lowering as the primary lipid target. Therapeutic lifestyle modification emphasizes a reduction in saturated fat and cholesterol intake, weight reduction to achieve ideal body weight, and a boost in physical activity. LDL-C goals and cutpoints for implementing therapeutic lifestyle change and drug therapy are based on 3 categories of risk: CHD and CHD risk equivalents (the latter category includes diabetes and symptomatic carotid artery disease), ≥2 cardiovascular risk factors stratified by 10-year risk of 10% to 20% for CHD and <10% for CHD according to the Framingham risk score, and 0 to 1 cardiovascular risk factor.[59] When there is a history of CHD and CHD risk equivalents, the target LDL-C goal is <100 mg/dL. Drug therapy options and management of other dyslipidemias are addressed in the NCEP guideline. LDL-C lowering results in a reduction of total mortality, coronary mortality, major coronary events, coronary procedures, and stroke in persons with CHD.[59]

Other medications used to treat dyslipidemia include niacin, fibrates, and cholesterol absorption inhibitors. These agents can be used by stroke or TIA patients who cannot tolerate statins, but data demonstrating their efficacy for prevention of stroke recurrence are sparse. Niacin has been associated with a reduction in cerebrovascular events,[61] whereas gemfibrozil reduced the rate of unadjudicated total strokes among men with coronary artery disease and low levels of HDL-C (≤40 mg/dL) in the Veterans Affairs HDL Intervention Trial (VA-HIT), but the latter result lost significance when adjudicated events alone were analyzed.[62]

Recommendations

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

D. Cigarette Smoking

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

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

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Table 4. Recommendations for Modifiable Behavioral Risk Factors

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

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

Recommendations

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

E. Alcohol Consumption

There is strong evidence that chronic alcoholism and heavy drinking are risk factors for all stroke subtypes.[82–86] Studies have demonstrated an association between alcohol and ischemic stroke, ranging from a definite independent effect to no effect. Most studies have suggested a J-shaped association between alcohol and ischemic stroke, with a protective effect from light or moderate consumption and an elevated risk of stroke with heavy consumption of alcohol.[82,83,87–96]

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

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

It is well established that alcohol can cause dependence and that alcoholism is a major public health problem. When advising a patient about behaviors to reduce risk of recurrent stroke, clinicians should consider the interrelationship between other risk factors and alcohol consumption. Nondrinkers should not be counseled to start drinking. A primary goal for secondary stroke prevention is to eliminate or reduce alcohol consumption in heavy drinkers through established screening and counseling methods as outlined in the US Preventive Services Task Force Update 2004.[105]

Recommendations

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

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F. Obesity

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

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

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

G. Physical Activity

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

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

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

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

Recommendations

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

H. Metabolic Syndrome

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

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

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

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

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

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

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

Recommendations

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

Table 5. Prospective Trials Comparing Carotid Endarterectomy and Medical Therapy

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

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

*Risk of fatal or nonfatal ipsilateral stroke.

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

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

A. Symptomatic Extracranial Carotid Disease

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

Carotid Endarterectomy

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

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

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

Patient Selection Criteria Influencing Surgical Risk

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

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

Timing of Carotid Revascularization

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

Carotid Angioplasty and Stenting

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

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

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

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

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

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

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

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

Extracranial-Intracranial Bypass Surgery

Extracranial-intracranial (EC/IC) bypass surgery was not found to provide any benefit for patients with carotid occlusion or those with carotid artery narrowing distal to the carotid bifurcation.[198] New efforts are ongoing, using more sensitive imaging, such as $^{15}O_2/H_2{}^{15}O$ positron emission tomography (PET), to select patients with the greatest hemodynamic compromise for a randomized controlled trial using EC/IC bypass surgery (Carotid Occlusion Surgery Study [COSS]).[198–200]

Recommendations

1. **For patients with recent TIA or ischemic stroke within the past 6 months and ipsilateral severe (70% to 99%) carotid artery stenosis, CEA is recommended if the perioperative morbidity and mortality risk is estimated to be <6% *(Class I; Level of Evidence A)*.**
2. **For patients with recent TIA or ischemic stroke and ipsilateral moderate (50% to 69%) carotid stenosis, CEA is recommended depending on patient-specific factors, such as age, sex, and comorbidities, if the perioperative morbidity and mortality risk is estimated to be <6% *(Class I; Level of Evidence B)*.**
3. **When the degree of stenosis is <50%, there is no indication for carotid revascularization by either CEA or CAS *(Class III; Level of Evidence A)*.**
4. **When CEA is indicated for patients with TIA or stroke, surgery within 2 weeks is reasonable rather than delaying surgery if there are no contraindications to early revascularization *(Class IIa; Level of Evidence B)*.**
5. **CAS is indicated as an alternative to CEA for symptomatic patients at average or low risk of complications associated with endovascular intervention when the diameter of the lumen of the internal carotid artery is reduced by >70% by noninvasive imaging or >50% by catheter angiography *(Class I; Level of Evidence B)*.**
6. **Among patients with symptomatic severe stenosis (>70%) in whom the stenosis is difficult to access surgically, medical conditions are present that greatly increase the risk for surgery, or when other specific circumstances exist, such as radiation-induced stenosis or restenosis after CEA, CAS may be considered *(Class IIb; Level of Evidence B)*.**
7. **CAS in the above setting is reasonable when performed by operators with established periprocedural morbidity and mortality rates of 4% to 6%, similar to those observed in trials of CEA and CAS *(Class IIa; Level of Evidence B)*.**

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

Risk Factor	Recommendations	Class/Level of Evidence*
Symptomatic extracranial carotid disease	For patients with recent TIA or ischemic stroke within the past 6 months and ipsilateral severe (70% to 99%) carotid artery stenosis, CEA is recommended if the perioperative morbidity and mortality risk is estimated to be <6% *(Class I; Level of Evidence A).*	Class I; Level A
	For patients with recent TIA or ischemic stroke and ipsilateral moderate (50% to 69%) carotid stenosis, CEA is recommended depending on patient-specific factors such as age, sex, and comorbidities if the perioperative morbidity and mortality risk is estimated to be <6% *(Class I; Level of Evidence B).*	Class I; Level B
	When the degree of stenosis is <50%, there is no indication for carotid revascularization by either CEA or CAS *(Class III; Level of Evidence A).*	Class III; Level A
	When CEA is indicated for patients with TIA or stroke, surgery within 2 weeks is reasonable rather than delaying surgery if there are no contraindications to early revascularization *(Class IIa; Level of Evidence B).*	Class IIa; Level B
	CAS is indicated as an alternative to CEA for symptomatic patients at average or low risk of complications associated with endovascular intervention when the diameter of the lumen of the internal carotid artery is reduced by >70% by noninvasive imaging or >50% by catheter angiography *(Class I; Level of Evidence B).*	Class I; Level B
	Among patients with symptomatic severe stenosis (>70%) in whom the stenosis is difficult to access surgically, medical conditions are present that greatly increase the risk for surgery, or when other specific circumstances exist, such as radiation-induced stenosis or restenosis after CEA, CAS may be considered *(Class IIb; Level of Evidence B).*	Class IIb; Level B
	CAS in the above setting is reasonable when performed by operators with established periprocedural morbidity and mortality rates of 4% to 6%, similar to those observed in trials of CEA and CAS *(Class IIa; Level of Evidence B).*	Class IIa; Level B
	For patients with symptomatic extracranial carotid occlusion, EC/IC bypass surgery is not routinely recommended *(Class III; Level of Evidence A).*	Class III; Level A
	Optimal medical therapy, which should include antiplatelet therapy, statin therapy, and risk factor modification, is recommended for all patients with carotid artery stenosis and a TIA or stroke as outlined elsewhere in this guideline *(Class I; Level of Evidence B).* (New recommendation)	Class I; Level B
Extracranial vertebrobasilar disease	Optimal medical therapy, which should include antiplatelet therapy, statin therapy, and risk factor modification, is recommended for all patients with vertebral artery stenosis and a TIA or stroke as outlined elsewhere in this guideline *(Class I; Level of Evidence B).* (New recommendation)	Class I; Level B
	Endovascular and surgical treatment of patients with extracranial vertebral stenosis may be considered when patients are having symptoms despite optimal medical treatment (including antithrombotics, statins, and relevant risk factor control) *(Class IIb; Level of Evidence C).*	Class IIb; Level C
Intracranial atherosclerosis	For patients with a stroke or TIA due to 50% to 99% stenosis of a major intracranial artery, aspirin is recommended in preference to warfarin *(Class I; Level of Evidence B).* Patients in the WASID trial were treated with aspirin 1300 mg/d, but the optimal dose of aspirin in this population has not been determined. On the basis of the data on general safety and efficacy, aspirin doses of 50 mg/d to 325 mg/d are recommended *(Class I; Level of Evidence B).* (New recommendation)	Class I; Level B
	For patients with stroke or TIA due to 50% to 99% stenosis of a major intracranial artery, long-term maintenance of BP <140/90 mm Hg and total cholesterol level <200 mg/dL may be reasonable *(Class IIb; Level of Evidence B).* (New recommendation)	Class IIb; Level B
	For patients with stroke or TIA due to 50% to 99% stenosis of a major intracranial artery, the usefulness of angioplasty and/or stent placement is unknown and is considered investigational *(Class IIb; Level of Evidence C).* (New recommendation).	Class IIb; Level C
	For patients with stroke or TIA due to 50% to 99% stenosis of a major intracranial artery, EC/IC bypass surgery is not recommended *(Class III; Level of Evidence B).* (New recommendation)	Class III; Level B

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

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

B. Extracranial Vertebrobasilar Disease

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

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

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

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

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

Recommendations

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

C. Intracranial Atherosclerosis

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

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

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

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

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

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

Recommendations

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

III. Medical Treatments for Patients With Cardiogenic Embolism

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

A. Atrial Fibrillation

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

Multiple clinical trials have demonstrated the superior therapeutic effect of warfarin compared with placebo in the prevention of thromboembolic events among patients with nonvalvular AF. Pooled data from 5 primary prevention trials of warfarin versus control have been reported.[225] The efficacy of warfarin has been shown to be consistent across studies, with an overall relative risk reduction of 68% (95% CI, 50% to 79%) and an absolute reduction in annual stroke rate from 4.5% for control patients to 1.4% in patients assigned to adjusted-dose warfarin. This absolute risk reduction indicates that 31 ischemic strokes will be prevented each year for every 1000 patients treated. Overall, warfarin use has been shown to be relatively safe, with an annual rate of major bleeding of 1.3% for patients on warfarin compared with 1% for patients on placebo or aspirin.

The optimal intensity of oral anticoagulation for stroke prevention in patients with AF appears to be an INR of 2.0 to 3.0. Results from 1 large case-control study[226] and 2 randomized controlled trials[227,228] suggest that the efficacy of oral anticoagulation declines significantly below an INR of 2.0. Unfortunately, a high percentage of AF patients have subtherapeutic levels of anticoagulation and therefore are inadequately protected from stroke. For patients with AF who suffer an ischemic stroke or TIA despite therapeutic anticoagulation, there are no data to indicate that increasing the intensity of anticoagulation provides additional protection against future ischemic events. Higher INRs are associated with increased risk of bleeding.

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

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

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

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

The superior efficacy of anticoagulation over aspirin for stroke prevention in patients with AF and a recent TIA or minor stroke was demonstrated in the European Atrial Fibrillation Trial (EAFT).[233] Therefore, unless a clear contraindication exists, AF patients with a recent stroke or TIA should receive long-term anticoagulation rather than antiplatelet therapy. There is no evidence that combining anticoagulation with an antiplatelet agent reduces the risk of stroke or MI compared with anticoagulant therapy alone in AF patients, but there is clear evidence of increased bleeding risk.[234] Therefore, in general, addition of aspirin to anticoagulation therapy should be avoided in AF patients.

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

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

Available data do not show greater efficacy of the acute administration of anticoagulants over antiplatelet agents in the setting of cardioembolic stroke.[237] More studies are required to clarify whether certain subgroups of patients who are perceived to be at high risk of recurrent embolism may benefit from urgent anticoagulation (eg, AF patients for whom transesophageal echocardiography [TEE] shows a left atrial appendage thrombus).

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

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

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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-

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Table 8. Recommendations for Patients With Cardioembolic Stroke Types

Risk Factor	Recommendations	Class/Level of Evidence*
Atrial fibrillation	For patients with ischemic stroke or TIA with paroxysmal (intermittent) or permanent AF, anticoagulation with a vitamin K antagonist (target INR 2.5; range, 2.0 to 3.0) is recommended *(Class I; Level of Evidence A).*	Class I; Level A
	For patients unable to take oral anticoagulants, aspirin alone *(Class I; Level of Evidence A)* is recommended.	Class I; Level A
	The combination of clopidogrel plus aspirin carries a risk of bleeding similar to that of warfarin and therefore is not recommended for patients with a hemorrhagic contraindication to warfarin *(Class III; Level of Evidence B).* (New recommendation)	Class III; Level B
	For patients with AF at high risk for stroke (stroke or TIA within 3 months, $CHADS_2$ score of 5 or 6, mechanical valve or rheumatic valve disease) who require temporary interruption of oral anticoagulation, bridging therapy with an LMWH administered subcutaneously is reasonable *(Class IIa; Level of Evidence C).* (New recommendation)	Class IIa; Level C
Acute MI and LV thrombus	Patients with ischemic stroke or TIA in the setting of acute MI complicated by LV mural thrombus formation identified by echocardiography or another cardiac imaging technique should be treated with oral anticoagulation (target INR 2.5; range 2.0 to 3.0) for at least 3 months *(Class I; Level of Evidence B).*	Class I; Level B
Cardiomyopathy	In patients with prior stroke or transient cerebral ischemic attack in sinus rhythm who have cardiomyopathy characterized by systolic dysfunction (LVEF ≤35%), the benefit of warfarin has not been established *(Class IIb; Level of Evidence B).* (New recommendation)	Class IIb; Level B
	Warfarin (INR 2.0 to 3.0), aspirin (81 mg daily), clopidogrel (75 mg daily), or the combination of aspirin (25 mg twice daily) plus extended-release dipyridamole (200 mg twice daily) may be considered to prevent recurrent ischemic events in patients with previous ischemic stroke or TIA and cardiomyopathy *(Class IIb; Level of Evidence B).*	Class IIb; Level B
Native valvular heart disease	For patients with ischemic stroke or TIA who have rheumatic mitral valve disease, whether or not AF is present, long-term warfarin therapy is reasonable with an INR target range of 2.5 (range, 2.0 to 3.0) *(Class IIa; Level of Evidence C).*	Class IIa; Level C
	To avoid additional bleeding risk, antiplatelet agents should not be routinely added to warfarin *(Class III; Level of Evidence C).*	Class III; Level C
	For patients with ischemic stroke or TIA and native aortic or nonrheumatic mitral valve disease who do not have AF, antiplatelet therapy may be reasonable *(Class IIb; Level of Evidence C).*	Class IIb; Level C
	For patients with ischemic stroke or TIA and mitral annular calcification, antiplatelet therapy may be considered *(Class IIb; Level of Evidence C).*	Class IIb; Level C
	For patients with MVP who have ischemic stroke or TIA, long-term antiplatelet therapy may be considered *(Class IIb; Level of Evidence C).*	Class IIb; Level C
Prosthetic heart valves	For patients with ischemic stroke or TIA who have mechanical prosthetic heart valves, warfarin is recommended with an INR target of 3.0 (range, 2.5 to 3.5) *(Class I; Level of Evidence B).*	Class I; Level B
	For patients with mechanical prosthetic heart valves who have an ischemic stroke or systemic embolism despite adequate therapy with oral anticoagulants, aspirin 75 mg/d to 100 mg/d in addition to oral anticoagulants and maintenance of the INR at a target of 3.0 (range, 2.5 to 3.5) is reasonable if the patient is not at high bleeding risk (eg, history of hemorrhage, varices, or other known vascular anomalies conveying increased risk of hemorrhage, coagulopathy) *(Class IIa; Level of Evidence B).*	Class IIa; Level B
	For patients with ischemic stroke or TIA who have bioprosthetic heart valves with no other source of thromboembolism, anticoagulation with warfarin (INR 2.0 to 3.0) may be considered *(Class IIb; Level of Evidence C).*	Class IIb, Level C

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

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

Recommendations

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

D. Native Valvular Heart Disease

Antithrombotic therapy can reduce, but not eliminate, the likelihood of stroke and systemic embolism in patients with valvular heart disease. As in all situations involving antithrombotic therapy, the risks of thromboembolism in various

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forms of native valvular heart disease and in patients with mechanical and biological heart valve prostheses must be balanced against the risk of bleeding.

Rheumatic Mitral Valve Disease

Recurrent embolism occurs in 30% to 65% of patients with rheumatic mitral valve disease who have a history of a previous embolic event.[256–259] Between 60% and 65% of these recurrences develop within the first year,[256,257] most within 6 months. Mitral valvuloplasty does not seem to eliminate the risk of thromboembolism[260,261]; therefore, successful valvuloplasty does not eliminate the need for anticoagulation in patients requiring long-term anticoagulation preoperatively. Although not evaluated in randomized trials, multiple observational studies have reported that long-term anticoagulant therapy effectively reduces the risk of systemic embolism in patients with rheumatic mitral valve disease.[262–265] Long-term anticoagulant therapy in patients with mitral stenosis who had left atrial thrombus identified by TEE has been shown to result in the disappearance of the left atrial thrombus.[266] The ACC/AHA Task Force on Practice Guidelines has published guidelines for the management of patients with valvular heart disease.[267]

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

Mitral Valve Prolapse

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

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

Mitral Annular Calcification

MAC,[278] which is predominantly found in women, is sometimes associated with significant mitral regurgitation and is an uncommon nonrheumatic cause of mitral stenosis. Although the incidence of systemic and cerebral embolism is not clear,[279–284] thrombus has been found at autopsy on heavily calcified annular tissue, and echogenic densities have been identified in the LV outflow tract in patients with MAC who experience cerebral ischemic events.[280,282] Aside from the risk of thromboembolism, spicules of fibrocalcific material may embolize from the calcified mitral annulus.[279,281,283] The relative frequencies of calcific and thrombotic embolism are unknown.[279,284]

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

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

Aortic Valve Disease

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

Recommendations

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

E. Prosthetic Heart Valves

Evidence that oral anticoagulants are effective in preventing thromboembolism in patients with prosthetic heart valves comes from a trial that randomized patients to either 6 months with warfarin of uncertain intensity versus 2 different aspirin-containing platelet-inhibitor drug regimens.[287] Thromboembolic complications occurred significantly more frequently in the antiplatelet groups than in the anticoagulation group (event rates were 8% to 10% per patient-year in the antiplatelet groups versus 2% per year in the anticoagulation group). The incidence of bleeding was higher in the warfarin group. Other studies yielded variable results depending on the type and location of the prosthesis, the intensity of anticoagulation, and the addition of platelet inhibitor medication; none specifically addressed secondary stroke prevention.

In 2 randomized studies, concurrent treatment with dipyridamole and warfarin reduced the incidence of systemic embolism in patients with prosthetic heart valves.[288,289] Another trial showed that the addition of aspirin 100 mg/d to warfarin (INR 3.0 to 4.5) improved efficacy compared with warfarin alone.[290] This combination of low-dose aspirin and high-intensity warfarin was associated with a reduced all-cause mortality, cardiovascular mortality, and stroke at the expense of increased minor bleeding; the difference in major

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bleeding, including cerebral hemorrhage, did not reach statistical significance.

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

Recommendations

1. **For patients with ischemic stroke or TIA who have mechanical prosthetic heart valves, warfarin is recommended with an INR target of 3.0 (range, 2.5 to 3.5) *(Class I; Level of Evidence B)*.**
2. **For patients with mechanical prosthetic heart valves who have an ischemic stroke or systemic embolism despite adequate therapy with oral anticoagulants, aspirin 75 mg/d to 100 mg/d in addition to oral anticoagulants and maintenance of the INR at a target of 3.0 (range, 2.5 to 3.5) is reasonable if the patient is not at high bleeding risk (eg, history of hemorrhage, varices, or other known vascular anomalies conveying increased risk of hemorrhage, coagulopathy) (*Class IIa; Level of Evidence B*).**
3. **For patients with ischemic stroke or TIA who have bioprosthetic heart valves with no other source of thromboembolism, anticoagulation with warfarin (INR 2.0 to 3.0) may be considered *(Class IIb; Level of Evidence C)*** (Table 8).

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

A. Antiplatelet Agents

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

Aspirin

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

Ticlopidine

Ticlopidine is a platelet adenosine diphosphate (ADP) receptor antagonist that has been evaluated in 3 randomized trials of patients with cerebrovascular disease.[300–302] The Canadian American Ticlopidine Study (CATS) compared ticlopidine (250 mg twice a day) with placebo for prevention of stroke, MI, or vascular death in 1053 patients with ischemic stroke.[302] After a mean follow-up duration of 2 years, patients assigned to ticlopidine therapy had fewer outcomes per year (11.3% compared with 14.8%; relative risk reduction [RRR], 23%; 95% CI, 1% to 41%). The Ticlopidine Aspirin Stroke Study (TASS) compared ticlopidine 250 mg twice a day with aspirin 650 mg twice a day in 3069 patients with recent minor stroke or TIA.[301] After 3 years, patients assigned to ticlopidine had a lower rate for the primary outcome of stroke or death (17% compared with 19%; RRR, 12%; 95% CI, 2% to 26%; $P=0.048$ by Kaplan-Meier estimates). Finally, the African American Antiplatelet Stroke Prevention Study enrolled 1809 black patients with recent noncardioembolic ischemic stroke who were allocated to receive ticlopidine 250 mg twice a day or aspirin 325 mg twice a day.[300] The study found no difference in risk of the combination of stroke, MI, or vascular death at 2 years. Side effects of ticlopidine include diarrhea and rash. Rates of gastrointestinal bleeding are comparable or less than with aspirin. Neutropenia occurred in <2% of patients treated with ticlopidine in CATS and TASS; however, it was severe in about 1% and was almost always reversible with discontinuation. Thrombotic thrombocytopenic purpura has also been described.[303]

Clopidogrel

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

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

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

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

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

Dipyridamole and Aspirin

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

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

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

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

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

Combination of Clopidogrel and Aspirin

The effectiveness of clopidogrel 75 mg plus aspirin 75 mg, compared with clopidogrel 75 mg alone for prevention of vascular events among patients with a recent TIA or ischemic stroke, was examined in the Management of Atherothrombosis with Clopidogrel in High-Risk Patients with Recent Transient Ischemic Attacks or Ischemic Stroke (MATCH) trial.[313] A total of 7599 patients were followed for 3.5 years for the occurrence of the primary composite outcome of ischemic stroke, MI, vascular death, or rehospitalization for any central or peripheral ischemic event. There was no significant benefit of combination therapy compared with clopidogrel alone in reducing the primary outcome or any of the secondary outcomes. The risk of major hemorrhage was significantly increased in the combination group compared with clopidogrel alone, with a 1.3% absolute increase in life-threatening bleeding. Although clopidogrel plus aspirin is recommended over aspirin for acute coronary syndromes, the

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

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

Selection of Oral Antiplatelet Therapy

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

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

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

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

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

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

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

B. Oral Anticoagulants

Randomized trials have addressed the use of oral anticoagulants to prevent recurrent stroke among patients with noncardioembolic stroke, including strokes caused by large-artery extracranial or intracranial atherosclerosis, small penetrating artery disease, and cryptogenic infarcts. The Stroke Prevention in Reversible Ischemia Trial (SPIRIT) was stopped early because of increased bleeding among those treated with high-intensity oral anticoagulation (INR 3.0 to 4.5) compared with aspirin (30 mg/d) in 1316 patients.[317,318] The trial was then reformulated as ESPRIT, using a medium-intensity warfarin dose (INR 2.0 to 3.0) compared with either aspirin alone (30 mg to 325 mg daily) or aspirin plus extended-release dipyridamole 200 mg twice daily. The trial was again ended early due to the superiority demonstrated by the combination of aspirin and dipyridamole over aspirin alone.[312] Mean follow-up was 4.6 years and mean INR achieved was 2.57. Patients treated with warfarin experienced a significantly higher rate of major bleeding (HR, 2.56; 95% CI, 1.48 to 4.43) but lower rate, albeit not statistically significant, in ischemic events (HR, 0.73; 95% CI, 0.52 to 1.01)[319] compared with aspirin alone.

The ESPRIT results confirmed those reported earlier by the Warfarin Aspirin Recurrent Stroke Study (WARSS), in which warfarin (INR 1.4 to 2.8) was compared with aspirin (325 mg daily) among 2206 patients with a noncardioembolic stroke.[320] This randomized, double-blind, multicenter trial found no significant difference between treatments for prevention of recurrent stroke or death (warfarin, 17.8%; aspirin, 16.0%). In contrast to ESPRIT, rates of major bleeding were not significantly different between the warfarin and aspirin groups (2.2% and 1.5% per year, respectively). A variety of subgroups were evaluated, with no clear evidence of efficacy observed across baseline stroke subtypes, including large-artery atherosclerotic and cryptogenic categories. The aforementioned WASID trial compared warfarin with aspirin in patients with intracranial stenoses and found no significant benefit and a higher risk of hemorrhage with warfarin therapy (see "Intracranial Atherosclerosis").

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

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

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

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

Newer Agents

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

Recommendations

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

V. Treatments for Stroke Patients With Other Specific Conditions

A. Arterial Dissections

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

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

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

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

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

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

Recommendations

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

B. Patent Foramen Ovale

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

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

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

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Table 10. Recommendations for Stroke Patients With Other Specific Conditions

Risk Factor	Recommendations	Class/Level of Evidence*
Arterial dissections	For patients with ischemic stroke or TIA and extracranial carotid or vertebral arterial dissection, antithrombotic treatment for at least 3 to 6 months is reasonable *(Class IIa; Level of Evidence B).*	Class IIa; Level B
	The relative efficacy of antiplatelet therapy compared with anticoagulation is unknown for patients with ischemic stroke or TIA and extracranial carotid or vertebral arterial dissection *(Class IIb; Level of Evidence B).* (New recommendation)	Class IIb; Level B
	For patients with stroke or TIA and extracranial carotid or vertebral arterial dissection who have definite recurrent cerebral ischemic events despite optimal medical therapy, endovascular therapy (stenting) may be considered *(Class IIb; Level of Evidence C).*	Class IIb; Level C
	Patients with stroke or TIA and extracranial carotid or vertebral arterial dissection who fail or are not candidates for endovascular therapy may be considered for surgical treatment *(Class IIb; Level of Evidence C).*	Class IIb; Level C
Patent foramen ovale	For patients with an ischemic stroke or TIA and a PFO, antiplatelet therapy is reasonable *(Class IIa; Level of Evidence B).*	Class IIa; Level B
	There are insufficient data to establish whether anticoagulation is equivalent or superior to aspirin for secondary stroke prevention in patients with PFO *(Class IIb; Level of Evidence B).* (New recommendation)	Class IIb; Level B
	There are insufficient data to make a recommendation regarding PFO closure in patients with stroke and PFO *(Class IIb; Level of Evidence C).*	Class IIb; Level C
Hyperhomocysteinemia	Although folate supplementation reduces levels of homocysteine and may be considered for patients with ischemic stroke and hyperhomocysteinemia *(Class IIb; Level of Evidence B)*, there is no evidence that reducing homocysteine levels prevents stroke recurrence.	Class IIb; Level B
Inherited thrombophilias	Patients with arterial ischemic stroke or TIA with an established inherited thrombophilia should be evaluated for DVT, which is an indication for short- or long-term anticoagulant therapy depending on the clinical and hematologic circumstances *(Class I; Level of Evidence A).*	Class I; Level A
	Patients should be fully evaluated for alternative mechanisms of stroke. In the absence of venous thrombosis in patients with arterial stroke or TIA and a proven thrombophilia, either anticoagulant or antiplatelet therapy is reasonable *(Class IIa; Level of Evidence C).*	Class IIa; Level C
	For patients with spontaneous cerebral venous thrombosis and/or a history of recurrent thrombotic events and an inherited thrombophilia, long-term anticoagulation is probably indicated *(Class IIa; Level of Evidence C).*	Class IIa; Level C
APL antibodies	For patients with cryptogenic ischemic stroke or TIA in whom an APL antibody is detected, antiplatelet therapy is reasonable *(Class IIa; Level of Evidence B).*	Class IIa; Level B
	For patients with ischemic stroke or TIA who meet the criteria for the APL antibody syndrome, oral anticoagulation with a target INR of 2.0 to 3.0 is reasonable *(Class IIa; Level of Evidence B).*	Class IIa; Level B
Sickle cell disease	For adults with SCD and ischemic stroke or TIA, the general treatment recommendations cited above are reasonable with regard to control of risk factors and the use of antiplatelet agents *(Class IIa; Level of Evidence B).*	Class IIa; Level B
	Additional therapies that may be considered to prevent recurrent cerebral ischemic events in patients with SCD include regular blood transfusions to reduce hemoglobin S to $<$30% to 50% of total hemoglobin, hydroxyurea, or bypass surgery in cases of advanced occlusive disease *(Class IIb; Level of Evidence C).*	Class IIb; Level C
Cerebral venous sinus thrombosis	Anticoagulation is probably effective for patients with acute CVT *(Class IIa; Level of Evidence B).*	Class IIa; Level B
	In the absence of trial data to define the optimal duration of anticoagulation for acute CVT, it is reasonable to administer anticoagulation for at least 3 months followed by antiplatelet therapy *(Class IIa; Level of Evidence C).*	Class IIa; Level C
Fabry disease	For patients with ischemic stroke or TIA and Fabry disease, alpha-galactosidase enzyme replacement therapy is recommended *(Class I; Level of Evidence B).* (New recommendation)	Class I; Level B
	Other secondary prevention measures as outlined elsewhere in this guideline are recommended for patients with ischemic stroke or TIA and Fabry disease *(Class I; Level of Evidence C).* (New recommendation)	Class I; Level C
Pregnancy	For pregnant women with ischemic stroke or TIA and high-risk thromboembolic conditions such as hypercoagulable state or mechanical heart valves, the following options may be considered: adjusted-dose UFH throughout pregnancy, for example, a subcutaneous dose every 12 hours with monitoring of activated partial thromboplastin time; adjusted-dose LMWH with monitoring of anti-factor Xa throughout pregnancy; or UFH or LMWH until week 13, followed by warfarin until the middle of the third trimester and reinstatement of UFH or LMWH until delivery *(Class IIb; Level of Evidence C).*	Class IIb; Level C
	In the absence of a high-risk thromboembolic condition, pregnant women with stroke or TIA may be considered for treatment with UFH or LMWH throughout the first trimester, followed by low-dose aspirin for the remainder of the pregnancy *(Class IIb; Level of Evidence C).*	Class IIb; Level C

(Continued)

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Table 10. Continued

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

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

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

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

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

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

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

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

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

Recommendations

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

C. Hyperhomocysteinemia

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

Recommendation

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

D. Hypercoagulable States

Inherited Thrombophilias

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

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

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

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embolism were compared in a study of young stroke patients (<45 years of age) to determine whether there was a higher prevalence of prothrombotic tendencies in those with PFO, which could reflect a susceptibility to paradoxical embolism. The PT G20210A mutation, but not FVL, was significantly more common in the PFO plus group than in PFO minus or nonstroke controls.[397]

Three meta-analyses have examined the most commonly studied prothrombotic mutations in FVL, MTHFR, and PT. The first pooled ischemic stroke candidate gene association studies involving Caucasian adults found statistically significant associations between stroke and FVL (OR, 1.33; 95% CI, 1.12 to 1.58), MTHFR C677T (OR, 1.24; 95% CI, 1.08 to 1.42), and PT G20210A (OR, 1.44; 95% CI, 1.11 to 1.86).[401] A second meta-analysis explored the association between FVL, PT G20210A, and MTHFR C677T and arterial thrombotic events (MI, ischemic stroke, or peripheral vascular disease) and found no significant link to FVL mutation and modest associations with PT G20210A (OR, 1.32; 95% CI, 1.03 to 1.69) and MTHFR C677T (OR, 1.20; 95% CI, 1.02 to 1.41). These associations were stronger in the young (<55 years of age).[402] A third meta-analysis focused on the MTHFR C677T polymorphism, which is associated with high levels of homocysteine. The OR for stroke was 1.26 (95% CI, 1.14 to 1.40) for the homozygous mutation (TT) versus the common alleles.[401] Thus, although there appears to be a weak association between these prothrombotic mutations and ischemic stroke, particularly in the young, major questions remain about the mechanism of risk (eg, potential for paradoxical venous thromboembolism), effect of gene-environment interaction, and optimal strategies for stroke prevention.

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

Recommendations

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

Antiphospholipid Antibodies

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

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

The WARSS/APASS collaboration was the first study to compare randomly assigned warfarin (INR 1.4 to 2.8) with aspirin (325 mg) for prevention of a second stroke in patients with APL antibodies. APASS enrolled 720 APL antibody–positive WARSS participants.[415] The overall event rate was 22.2% among APL-positive patients and 21.8% among APL-negative patients. Patients with both lupus anticoagulant and anticardiolipin antibodies had a higher event rate (31.7%) than patients negative for both antibodies (24.0%), but this was not statistically significant. There was no difference between risk of the composite end point of death due to any cause, ischemic stroke, TIA, MI, DVT, pulmonary embolism, and other systemic thrombo-occlusive events in patients treated with either warfarin (RR, 0.99; 95% CI, 0.75 to 1.31; $P=0.94$) or aspirin (RR, 0.94; 95% CI, 0.70 to 1.28; $P=0.71$).

Recommendations

1. **For patients with cryptogenic ischemic stroke or TIA in whom an APL antibody is detected, antiplatelet therapy is reasonable *(Class IIa; Level of Evidence B)*.**
2. **For patients with ischemic stroke or TIA who meet the criteria for the APL antibody syndrome, oral anticoagulation with a target INR of 2.0 to 3.0 is reasonable *(Class IIa; Level of Evidence B)*** (Table 10).

E. Sickle Cell Disease

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

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

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

Recommendations for treatment of SCD patients with large-artery arteriopathy are largely based on stroke prevention studies performed in a pediatric population. The Stroke Prevention Trial in Sickle Cell Anemia (STOP) trial was a randomized, placebo-controlled trial that showed transfusion was effective for primary prevention of stroke in children with SCD and high transcranial Doppler velocities.[434] The STOP results are not directly applicable to these guidelines and are summarized in the AHA statements on primary prevention[13] and management of stroke in infants and children.[435] For secondary stroke prevention there are no randomized controlled trials to support transfusion in adults or children. A retrospective multicenter review of SCD patients with stroke, either observed or transfused, suggested that regular blood transfusion sufficient to suppress native hemoglobin S formation reduced recurrent stroke risk. The transfusion target most often used is the percentage of hemoglobin S as a fraction of total hemoglobin assessed just before transfusion. Reduction of hemoglobin S to <30% (from a typical baseline of 90% before initiating regular transfusions) was associated with a significant reduction in the rate of recurrent stroke during a mean follow-up of 3 years compared with historical controls followed for an unknown duration (13.3% versus 67% to 90%; $P<0.001$).[436] Most of the patients in this series were children, and it is not clear whether adults have the same untreated risk or benefit from treatment. In addition to the effects of transfusion therapy on clinical events, transfusion has been associated with less progression of large-vessel stenoses on angiography ($P<0.001$)[437] and decreased incidence of silent infarcts seen on MRI in SCD patients with elevated transcranial Doppler velocities ($P<0.001$) compared with patients who did not receive transfusions.[438] Regular transfusions are associated with long-term complications, especially iron overload, making long-term use problematic. Some experts recommend using transfusion for 1 to 3 years after stroke, a presumed period of higher risk for recurrence, then switching to other therapies.

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

Recommendations

1. **For adults with SCD and ischemic stroke or TIA, the general treatment recommendations cited above are reasonable with regard to control of risk factors and the use of antiplatelet agents *(Class IIa; Level of Evidence B)*.**
2. **Additional therapies that may be considered to prevent recurrent cerebral ischemic events in patients with SCD include regular blood transfusions to reduce hemoglobin S to <30% to 50% of total**

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hemoglobin, hydroxyurea, or bypass surgery in cases of advanced occlusive disease *(Class IIb; Level of Evidence C)* (Table 10).

F. Cerebral Venous Sinus Thrombosis

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

Early anticoagulation is often considered as both treatment and early secondary prophylaxis for patients with CVT, although controlled trial data remain limited to 2 studies.[449,450] The first trial compared dose-adjusted unfractionated heparin (UFH; partial thromboplastin time at least 2 times control) with placebo. The study was terminated early after only 20 patients had been enrolled, because of the superiority of heparin therapy ($P<0.01$). Eight of the 10 patients randomly assigned to heparin recovered completely, and the other 2 patients had only mild neurological deficits. In the placebo group, only 1 patient had a complete recovery; 3 patients died.[449] The same research group also reported a retrospective study of 43 patients with cerebral venous sinus thrombosis associated with intracranial bleeding; 27 of these patients were treated with dose-adjusted heparin. The mortality rate in the heparin group was considerably lower than in the nonanticoagulation group.[449]

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

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

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

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

Recommendations

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

G. Fabry Disease

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

Recommendations

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

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

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

VI. Stroke in Women

A. Pregnancy

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

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

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

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

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

Recommendations

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

B. Postmenopausal Hormone Therapy

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

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

Recommendation

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

VII. Use of Anticoagulation After Intracranial Hemorrhage

One of the most difficult problems that clinicians face is the management of antithrombotic therapy in patients who suffer an intracranial hemorrhage. There are several key variables to consider, including the type of hemorrhage, patient age, risk factors for recurrent hemorrhage, and indication for antithrombotic therapy. Most studies or case series have focused on patients receiving anticoagulants for a mechanical heart valve or AF who develop an ICH or subdural hematoma (SDH). There are very few case series addressing SAH. In all cases, the risk of recurrent hemorrhage must be weighed against the risk of an ischemic cerebrovascular event. Overall there is a paucity of data from large, prospective, randomized studies to answer these important management questions.

In the acute setting of a patient with an ICH or SDH and an elevated INR, it is generally thought that the INR should be reduced as soon as possible through the use of clotting factors, vitamin K, and/or fresh frozen plasma.[484,485] Studies have shown that 30% to 40% of ICHs expand during the first 12 to 36 hours of formation,[486] and this may be prolonged when the patient is receiving anticoagulation.[487] Such expansions are usually associated with neurological worsening.[488] Elevated INRs have been shown to be associated with larger hematoma volumes when corrected for age, sex, race, antiplatelet use, hemorrhage location, and time from onset to scan.[489] In this retrospective study of 258 patients, hematoma volume was significantly higher in patients with an INR >3.0 (compared with those with an INR <1.2; $P=0.02$). Rapid reversal of anticoagulation is generally recommended for any patient with an ICH or subdural hematoma,[490,491] but there are no data on the preferred methods or consequences of this practice. Prothrombin complex concentrate normalizes the INR within 15 minutes of administration and is preferred over fresh frozen plasma in most national guidelines for the treatment of serious bleeding because of its ease of administration and fast action.[492] Vitamin K should be administered in combination with either product to maintain the beneficial effect. It is possible that rapid reversal to a normal INR will put high-risk patients at risk for thromboembolic events. Any reversal should be undertaken with a careful weighing of the risks and benefits of the treatment.

The appropriate duration of interruption of anticoagulation among high-risk patients is unknown. Several case series have followed up patients who were off anticoagulants for several days and weeks, with few reported instances of ischemic stroke. One study found that among 35 patients with hemorrhages followed for up to 19 days off warfarin, there were no recurrent ischemic strokes.[485] In a study of 141 patients with an ICH while taking warfarin, warfarin was reversed and stopped for a median of 10 days. The risk of an ischemic event was 2.1% within 30 days. The risk of an ischemic event during cessation of warfarin was 2.9% in patients with a prosthetic heart valve, 2.6% in those with AF and prior embolic stroke, and 4.8% for those with a prior TIA or ischemic stroke.[493] None of the 35 patients in whom warfarin was restarted had another ICH during hospitalization.[493] Another study of 28 patients with prosthetic heart valves found that during a mean period of 15 days of no anticoagulation, no patient had an embolic event.[494] A study of 35 patients with an ICH or spinal hemorrhage reported no recurrent ischemic events among the 14 patients with prosthetic valves after a median of 7 days without anticoagulation.[485] One study of 100 patients who underwent intracranial surgery for treatment of cerebral aneurysm found that 14% developed evidence of DVT postoperatively. These patients were treated with systemic anticoagulation without any bleeding complications.[495]

The relative risks of recurrent ICH versus ischemia must be considered when deciding whether to reinstitute antithrombotic therapy after ICH. In a recent large study of 768 ICH patients followed for up to 8 years, the risk of recurrent ICH was higher than that of ischemic stroke in the first year (2.1% versus 1.3%), but there was no difference beyond that period (1.2% versus 1.3%). In this largely Caucasian population, it appeared that reinstitution of antithrombotic therapy soon after ICH was not beneficial, particularly in lobar ICH, where recurrence rates were highest.[496] Lobar hemorrhage poses a greater risk of recurrence when anticoagulation is reinstituted, possibly because of underlying cerebral amyloid angiopathy. A decision analysis study recommended against restarting anticoagulation in patients with lobar ICH and AF.[497] Several other risk factors for new or recurrent ICH have been identified, including advanced age, hypertension, degree of anticoagulation, dialysis, leukoaraiosis, and the presence of microbleeds on MRI.[498–501] The presence of microbleeds on MRI (often seen on gradient echocardiographic images) may signify an underlying microangiopathy or the presence of cerebral amyloid angiopathy. One study found the risk of ICH in patients receiving anticoagulation to be 9.3% in patients with microbleeds compared with 1.3% in those without MRI evidence of prior hemorrhage.[499]

In patients with compelling indications for early reinstitution of anticoagulation, some studies suggest that intravenous heparin (with partial thromboplastin time 1.5 to 2.0 times normal) or LMWH may be safer options for acute therapy than restarting oral warfarin.[484] Failure to reverse the warfarin and achieve a normal INR has been associated with an increased risk of rebleeding, and failure to achieve a thera-

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

Hemorrhagic transformation within an ischemic stroke appears to have a different course and natural history compared with ICH. In general, these hemorrhages are often asymptomatic or cause minimal symptoms, rarely progress in size or extent, and are relatively common occurrences.[503,504] Some case series suggest continuing anticoagulation even in the presence of hemorrhagic transformation as long as there is a compelling indication and the patient is not symptomatic from the hemorrhagic transformation.[505] Each case must be assessed individually on the basis of variables such as size of hemorrhagic transformation, patient status, and indication for anticoagulation.

Recommendations

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

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

National consensus guidelines are published by many professional societies and government agencies to increase healthcare providers' awareness of evidence-based approaches to disease management. This method of knowledge delivery assumes that increased awareness of guideline content alone can lead to substantial changes in physician behavior and ultimately patient behavior and health outcomes. Experience with previously published guidelines suggests otherwise, and compliance with secondary stroke and coronary artery disease prevention strategies based on guideline dissemination has not increased dramatically.[506–510] For example, treatment of hypertension to reduce stroke risk has been the subject of many guidelines and public education campaigns. Among adults with hypertension, 60% are on therapy, but only half of those are actually at their target BP goal, whereas another 30% are unaware that they even have the disease.[511] In a survey of physicians who were highly knowledgeable about target cholesterol goals for therapy, few were successful in achieving these goals for patients in their own practice.[512] The use of retrospective performance data to improve compliance has produced small changes in adherence to guideline-derived measures in prevention of coronary artery disease.[506]

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

Other organizations have also recognized the need for systematic approaches. The National Institutes of Health Roadmap for Medical Research was implemented to address treatment gaps between clinically proven therapies and actual treatment rates in the community.[515] To ensure that scientific knowledge is translated effectively into practice and that healthcare disparities are addressed, the Institute of Medicine of the National Academy of Sciences has recommended the establishment of coordinated systems of care that integrate preventive and treatment services and promote patient access to evidence-based care.[516]

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

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

Identifying and Responding to Populations at Highest Risk

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

The elderly are at greater risk of stroke and at the highest risk of complications from treatments such as oral anticoagulants and carotid endarterectomy.[524,525] Despite the need to consider different approaches in these vulnerable populations, some trials do not include a sufficient number of subjects >80 years of age to fully evaluate the efficacy of a therapy within this important and ever-growing subgroup. In SAPPHIRE, only 11% (85 of 776 CEA patients) were >80 years of age, and comparison of high- and low-risk CEAs demonstrated no difference in stroke rates.[526] By contrast, trials of medical therapies such as statins have included relatively large numbers of elderly patients with coronary artery disease and support safety and event reduction in these groups, although further study in the elderly may still be needed.[527–530]

The socioeconomically disadvantaged constitute that population at high risk for stroke primarily because of limited access to care.[531,532] As indicated in the report of the American Academy of Neurology Task Force on Access to Healthcare in 1996, access to medical care in general and for neurological conditions such as stroke remains limited. These limitations to access may be due to limited personal resources such as lack of health insurance, geographic differences in available facilities or expertise, as is often the case in rural areas, or arrival at a hospital after hours. Hospitalized stroke patients with little or no insurance receive fewer angiograms and endarterectomies.[533–536]

Many rural institutions lack the resources for adequate emergency stroke treatment and the extensive community and professional educational services that address stroke awareness and prevention compared with urban areas. Telemedicine is emerging as a tool to support improved rural health care and the acute treatment and primary and secondary prevention of stroke.[537] Stroke prevention efforts are of particular concern in those ethnic groups identified as being at the highest risk.[132] Although death rates attributed to stroke have declined by 11% in the United States from 1990 through 1998, not all groups have benefited equally, and substantial differences among ethnic groups persist.[538] Even within minority ethnic populations, gender disparities remain, as evidenced by the fact that although the top 3 causes of death for black men are heart disease, cancer, and HIV infection/AIDS, stroke replaces HIV infection as the third leading cause in black women.[539] black women are particularly vulnerable to obesity, with a prevalence rate of >50%, and their higher morbidity and mortality rates from heart disease, diabetes, and stroke have been attributed in part to increased body mass index. In the Michigan Coverdell Registry,[540] African Americans were less likely to receive smoking cessation counseling (OR, 0.27; CI, 0.17 to 0.42). The BASIC Project noted the similarities in stroke risk factor profiles in Mexican Americans and non-Hispanic whites.[541] The role of hypertension in blacks and its disproportionate impact on stroke risk has been clearly identified,[542–544] yet studies indicate that risk factors differ between different ethnic groups within the worldwide black population.[545]

For the aged, socioeconomically disadvantaged, and specific ethnic groups, inadequate implementation of guidelines and noncompliance with prevention recommendations are critical problems. Expert panels have indicated the need for a multilevel approach to include the patient, provider, and organization delivering health care. The evidence for this approach is well documented, but further research is sorely needed.[546] The NINDS Stroke Disparities Planning Panel, convened in June 2002, developed strategies and program goals that include establishing data collection systems and exploring effective community impact programs and instruments in stroke prevention.[547] The panel encouraged projects aimed at stroke surveillance projects in multiethnic communities such as those in southern Texas,[541] northern Manhattan,[544] Illinois,[548] and suburban Washington,[549] and stroke awareness programs targeted directly at minority communities.

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

Recommendations

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

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Disclosures

Writing Group Disclosures

Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
Karen L. Furie	Massachusetts General Hospital	ASA-Bugher†; NINDS†	None	None	None	None	None	Cardiovascular Events Committee member (Quintiles sponsored) supporting Biosante's Multi-Center Study of the Safety of LibigeL for the Treatment of HSDD in Menopausal Women* EAC Member for InChoir (through MSSM) for NHLBI supported trials* Chair, NINDS NSD-K study section* Chair, NINDS ARUBA DSMB* Member, NINDS SPS3 DSMB*
Scott E. Kasner	University of Pennsylvania Medical Center	Gore Associates†; NIH†	None	None	None	None	AstraZeneca*; Cardionet*	None
Robert J. Adams	Medical University of South Carolina	NHLBI†	None	Boehringer Ingelheim†; Genentech*; Novartis*; Sanofi-Aventis*	None	None	Novartis*; Penumbra Corporation*	None
Gregory W. Albers	Stanford University	Boehringer Ingelheim†; NMT†	None	None	None	None	Boehringer Ingelheim*; Lundbeck*	None
Ruth L. Bush	Scott & White Hospital, Texas A&M University Health Science Center	None	None	None	None	None	None	None
Susan C. Fagan	University of Georgia College of Pharmacy	Pfizer, Inc†	None	Boehringer Ingelheim*	None	None	Boehringer Ingelheim*; Pfizer*	None
Jonathan L. Halperin	Mt. Sinai Hospital	NIH-NHLBI†	None	None	None	None	Astellas Pharma*; Bayer HealthCare*; Biotronik, Inc†; Boehringer Ingelheim*; Daiichi Sankyo Pharma*; Johnson & Johnson*; Portola*; Sanofi-Aventis*	Member of DSMB for Phase II trial of an oral anticoagulant for stroke prevention in patients with atrial fibrillation*
S. Claiborne Johnston	UCSF Medical Center/Dept of Neurology	Boehringer Ingelheim†; Boston Scientific†; NINDS†; On behalf of NINDS/NIH, received drug and placebo for the POINT trial from Sanofi-Aventis†	None	None	None	None	Daiichi Sankyo*	National Stroke Association*
Irene Katzan	Cleveland Clinic	CDC and the Ohio Department of Health*; NINDS†; Schering-Plough*	None	None	None	None	None	Novartis (End point adjudication committee)†
Walter N. Kernan	Yale University School of Medicine	NINDS†; Takeda Pharmaceuticals†	None	None	None	None	None	None
Pamela H. Mitchell	University of Washington	NIH†	None	None	None	None	None	None
Bruce Ovbiagele	University of California at Los Angeles (UCLA)	None	None	None	None	None	None	None
Yuko Y. Palesch	Medical University of South Carolina	Boehringer Ingelheim*	None	None	None	None	None	None
Ralph L. Sacco	University of Miami	NHLBI; Evelyn A. McKnight Foundation*; NINDS†		None	None	None	Boehringer Ingelheim*; Sanofi-Aventis*	Member of DSMB sponsored by Population Health Research Institute (McMaster University in Ontario)–Clinical trial on stroke prevention in AF–support received from Bristol-Myers Squibb and Pfizer and goes to University of Miami)*

(Continued)

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

*Modest.

†Significant.

Reviewer Disclosures

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Philip B. Gorelick	University of Illinois	None	None	Boehringer-Ingelheim†	None	None	Genentech,* Boehringer Ingelheim†; BMS Sanofi*; Pfizer*; Daiichi Sankyo*	None
Elaine L. Miller	University of Cincinnati	None	None	None	None	None	None	None
Barney Stern	University of Maryland	NIH/NINDS†; NIH/NINDS†; NIH/NINDS*	None	AAN*	None	None	None	None

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

*Modest.

†Significant.

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AHA/ASA Guideline

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 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 Wassertheil-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

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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明書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虚血性脳卒中と一過性脳虚血発作（TIA）後の虚血性脳卒中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読者の先生方が利用しやすいかたちで提供する必要があると考え，AHA/ASA と *Stroke* 誌の賛同を得て，*Stroke* 日本語版の分冊として刊行することになった。要約の本文は *Stroke* 日本語版編集委員が分担して翻訳・執筆したものであり，充実した要約によって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可能となった。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，虚血性脳卒中の再発予防につき，危険因子，アテローム動脈硬化症の脳外科・血管内治療，心原性塞栓症の抗血栓療法，非心原性脳卒中後の抗血小板療法，動脈解離や卵円孔開存を含む特殊な病態の治療などについて指針を表明している。なお英文ガイドラインでは ischemic stroke が単に stroke と記載されていることが多いため，この要約でも単に脳卒中という記載は原則として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795,000例の脳卒中の約25％は再発である。TIA 後90日以内の脳卒中発症リスクは17％におよび，特に最初の1週間に高いとされる。TIA は脳虚血徴候が発症後24時間以内に消失するものとされてきたが，画像診断法の進歩によりほぼ3分の1の症例で脳梗塞がみられている。このため組織障害の有無に基づいて，最近 TIA を「急性梗塞を伴わない脳，脊髄，網膜の虚血により惹起された一過性の神経系機能不全」と定義するよう提唱されている[1]。このガイドラインに引用されている論文の大半は古い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れても同じである。

（文責：柳原武彦）

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表1 推奨のクラス分類とエビデンスレベルの実際的な使用法

治療効果の確実性（的確性）の評価 ＼ 治療効果の程度 →	クラスI *ベネフィット>>>危険* 検査・治療が実施・投与されるべきである	クラスIIa *ベネフィット>>危険* *対象を絞った追加試験が必要である* 検査・治療を行うことは適当である	クラスIIb *ベネフィット≧危険* *幅広い対象での追加試験が必要である；追加登録データは有用と考えられる* 検査・治療が考慮されても良い	クラスIII 危険≧ベネフィット 有用ではなく有害かもしれないので，検査・治療は実施／投与されるべきでない
レベルA 評価対象は複数の集団* 複数の無作為化臨床試験またはメタ解析より得られたデータがある	■検査・治療が有用／有効であると推奨 ■複数の無作為化試験またはメタ解析による十分なエビデンスがある	■検査・治療の有用性／有効性を支持して推奨 ■複数の無作為化試験またはメタ解析の一部に相反するエビデンスがある	■推奨する有用性／有効性はあまり確立されていない ■複数の無作為化試験またはメタ解析の中に相反するエビデンスが多い	■検査・治療は有用／有効でなく有害かもしれない ■複数の無作為化試験またはメタ解析による十分なエビデンスがある
レベルB 評価対象は限られた集団* 1つの無作為化試験または複数の非無作為化試験より得られたデータがある	■検査・治療が有用／有効であると推奨 ■1つの無作為化試験または複数の非無作為化試験によるエビデンスがある	■検査・治療の有用性／有効性を支持して推奨 ■1つの無作為化試験または複数の非無作為化試験の中に相反するエビデンスがある	■推奨する有用性／有効性はあまり確立されていない ■1つの無作為化試験または複数の非無作為化試験の中に相反するエビデンスが多い	■検査・治療は有用／有効でなく有害かもしれない ■1つの無作為化試験または複数の非無作為化試験によるエビデンスがある
レベルC 評価対象は非常に限られた集団* 専門家の合意した見解のみ，症例研究，あるいは標準治療法	■検査・治療が有用／有効であると推奨 ■専門家の見解のみ，症例研究，あるいは標準治療法	■検査・治療の有用性／有効性を支持して推奨 ■専門家の異なる見解のみ，症例研究，あるいは標準治療法	■推奨する有用性／有効性はあまり確立されていない ■専門家の異なる見解のみ，症例研究，あるいは標準治療法	■検査・治療は有用／有効でなく有害かもしれない ■専門家の見解のみ，症例研究，あるいは標準治療法
推奨事項を示唆する表現†	べきである 推奨される 適応がある 有用／有効／有益である	適当である 有用／有効／有益と思われる おそらく推奨される，または適応があるだろう	考慮されてもよい 適当かもしれない 有用性／有効性は不明である／明瞭でない／不確実である，または確立されていない	推奨されない 適応がない べきでない 有用／有効／有益でない おそらく有害であろう

*種々のサブグループ（性別，年齢，糖尿病歴，心筋梗塞歴，心不全歴，アスピリン服用歴など）での有用性／有効性に関する臨床試験あるいは登録データがある。エビデンスレベルBまたはCの推奨は推奨が弱いということを意味するものではない。ガイドラインで取り上げている多くの重要な臨床上の課題は，臨床試験に適しているものではない。たとえ無作為化試験がなくても，特別な検査や治療が有用または有効であるという非常に明白な臨床上の合意が得られている場合もある。
†ある治療が他の治療に対して有効性が高いことに関し推奨を行う場合（クラスIおよびIIa；エビデンスレベルAおよびBのみ），好ましい介入を示すために「～よりむしろ」や「選択するほうが」という用語や表現を使う場合がある。例えば，「～には治療法Bよりむしろ治療法Aが推奨される」または「～には治療法Bより治療法Aを選択するほうが適当である」。比較を示す動詞を使用する研究には，評価される治療法が直接比較されているものを含むべきである。

表2 AHAガイドラインにおける各推奨のクラスとエビデンスレベルの定義

クラスI	検査や治療法の有用性および有効性を示すエビデンスまたは一般的合意がある。
クラスII	検査や治療法の有用性および有効性に関して相反するエビデンスまたは見解の相違が認められる。
クラスIIa	検査や治療法の有用性および有効性を支持するエビデンスまたは見解が多数を占める。
クラスIIb	有用性および有効性を支持するエビデンスや見解は十分ではない。
クラスIII	検査や治療法が有用または有効でなく，場合によっては有害となり得ることを示すエビデンスまたは一般的合意がある。
治療の推奨	
エビデンスレベルA	複数の無作為化試験またはメタ解析により得られたデータがある。
エビデンスレベルB	1つの無作為化試験または複数の非無作為化試験より得られたデータがある。
エビデンスレベルC	専門家の合意した見解，症例研究，または標準治療法。
診断の推奨	
エビデンスレベルA	参照基準を用いてマスクされた評価者により施行された複数の前向きコホート研究のデータがある。
エビデンスレベルB	1つのグレードAの研究，または1つ以上の症例対照研究のデータ，あるいは参照基準を使ってマスクされていない評価者により施行された研究のデータがある。
エビデンスレベルC	専門家の合意した見解。

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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，降圧により脳卒中リスクが 30～40％減少した。血圧のスクリーニ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[2]と JNC 7[3]に述べられているが，生活習慣では体重減量（減塩を含む），果物・野菜・低脂肪食品の摂取，運動，アルコールの制限が血圧の低下に貢献する。心血管系疾患全般と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 後の再発リスクが下がることを示し，全体として降圧薬治療は脳卒中再発と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ほど脳卒中再発リスクは減少した[4]。無作為試験の数が少なく降圧薬間の比較には限度があるが，脳卒中の再発は利尿薬単独または 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かった。これらの試験にはアンジオテンシン受容体阻害薬（ARB）は含まれなかったが，その後，脳卒中後の降圧薬について 2 件の大規模無作為試験が報告された。MOSES 試験では，eprosartan（ARB）と nitrendipine（カルシウム拮抗薬）が比較されたが，脳卒中と TIA の合計再発イベント数は ARB で低く，死亡率・心血管イベント・脳血管イベントの低下を認めた。しかし TIA の減少が脳血管イベント減少の大部分であり，脳梗塞には十分な効果がなかった。PRoFESS 試験[5]では発症 90 日以内にテルミサルタン（ARB）と偽薬が比較されたが，テルミサルタンは脳卒中再発や心大血管イベントを減少させなかったため，ARB の効果はまだ未確定である。

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明らかな危険因子であるが，脳卒中再発の独立した予測因子でもあり，再発の 9.1％が糖尿病に起因すると推定される。空腹時血糖レベル 126 mg/dL 以上，HbA1C 6.5％以上，随時血漿グルコース 200 mg/dL 以上になると糖尿病となり，HbA1C が 7％を超えると血糖管理不良とされる。血糖調

表３ 血管系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
高血圧症	発症から 24 時間を過ぎた脳梗塞または TIA の患者では，脳梗塞の再発およびその他の血管イベントの予防として降圧療法が推奨される。	クラス I エビデンスレベル A
	降圧療法による予防効果は高血圧症の既往の有無に関係なく得られるため，この推奨は降圧療法が適切と考えられるすべての脳梗塞または TIA 患者に妥当である。	クラス IIa エビデンスレベル B
	目標とすべき血圧や降圧の程度は明白になっておらず，個々の患者で設定すべきであるが，降圧が平均 10/5 mmHg 程度であれば有効であると考えられる。また JNC-7 では，正常血圧は 120/80 mmHg 未満と定義している。	クラス IIa エビデンスレベル B
	生活習慣を改善することによって血圧の低下が勧められており，総合的な降圧療法の一環として生活習慣の改善は適切である。これらの改善には，塩分摂取の制限，体重の減量，果物・野菜・低脂肪乳製品を多く含む食事の摂取，規則的な有酸素運動，およびアルコール摂取の制限が挙げられる。	クラス IIa エビデンスレベル C
	薬物療法間の直接比較が限られているため，推奨血圧レベルを達成するための最適な薬物療法は確立されていない。現在得られているデータによると，利尿薬単独療法または利尿薬＋ACE 阻害薬併用療法が有用である。	クラス I エビデンスレベル A
	薬物の選択や治療目標は，薬理学的特性，作用機序，および処方される特定の薬物に対する患者の特性の検討（例えば，頭蓋外脳血管の閉塞性疾患，腎障害，心疾患，糖尿病）を基に，個々の患者で決定されるべきである。（新規推奨）	クラス IIa エビデンスレベル B
糖尿病	脳梗塞または TIA の既往がある糖尿病患者では，血糖コントロールおよび血圧目標に関する現行のガイドラインを使用することが推奨される。（新規推奨）	クラス I エビデンスレベル B
脂質異常症	アテローム硬化症があり LDL コレステロール値≧ 100 mg/dL かつ CHD の併存がない脳梗塞または TIA 患者において，脳梗塞や心血管イベントの危険を低減するためには，強力な脂質低下作用のあるスタチン系薬が推奨される。	クラス I エビデンスレベル B
	アテローム血栓による脳梗塞または TIA の患者で CHD の併存がなければ，最良の成果を得るためには LDL コレステロールの 50％以上の低下，または LDL コレステロール値＜ 70 mg/dL を目標とするのが適切である。（新規推奨）	クラス IIa エビデンスレベル B
	高コレステロール血症または冠動脈疾患が併存している脳梗塞もしくは TIA 患者では，NCEP の ATPIII ガイドラインに従った管理（生活習慣の改善，食事療法，薬物治療に関する推奨など）を行うべきである。	クラス I エビデンスレベル A
	HDL コレステロール値が低い脳梗塞または TIA 患者では，ナイアシンまたはゲムフィブロジルによる治療が適当と考えられる。	クラス IIb エビデンスレベル B

CHD＝冠動脈心疾患；HDL-C＝高比重リポ蛋白コレステロール；LDL-C＝低比重リポ蛋白コレステロール；JNC-7＝*The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure*；NCEPIII＝*The Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Cholesterol in Adults*。

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表4 生活習慣の改善に関する推奨

危険因子	推　奨	クラス/エビデンスレベル
喫煙	医療従事者は，過去1年間に喫煙歴のあるすべての脳梗塞またはTIA患者に対し禁煙を強く勧めるべきである。	クラスI エビデンスレベルC
	環境タバコ煙（受動喫煙）を避けることは適切である。	クラスIIa エビデンスレベルC
	カウンセリング，ニコチン製剤および経口禁煙治療薬は禁煙を助けるのに有効である。	クラスI エビデンスレベルA
飲酒	大量飲酒歴がある脳梗塞またはTIA患者では，アルコールの消費をゼロまたは少量に抑えるべきである。	クラスI エビデンスレベルC
	少量～中等量の飲酒（1日あたり男性では2杯以下，非妊娠女性では1杯以下）は適当と考えられる。飲酒しない人に飲酒を勧めるべきではない。	クラスIIb エビデンスレベルB
身体活動	身体活動が可能な脳梗塞またはTIA患者では，脳梗塞再発を高める危険因子や併存症を抑制することを目的として，汗をかいたり明らかに心拍数が上がる程度の活発な運動（足早のウォーキング，運動用自転車の使用など）として一般的に定義される中程度の運動を30分以上，週に1～3回行うことが考慮されてもよい。	クラスIIb エビデンスレベルC
	脳梗塞による身体障害が認められる個々の患者に対しては，少なくとも運動療法開始時に，理学療法士や心臓リハビリテーション専門医など医療専門家による監督指導が考慮されてもよい。	クラスIIb エビデンスレベルC
メタボリックシンドローム	現時点では，脳梗塞後の患者をメタボリックシンドロームでスクリーニングする有用性は確立していない。（新規推奨）	クラスIIb エビデンスレベルC
	メタボリックシンドロームとしてスクリーニングされ分類された患者では，血管リスク低減のために生活習慣の改善（食事療法，運動療法および体重の減量）のカウンセリングを含めた管理が行われるべきである。（新規推奨）	クラスI エビデンスレベルC
	メタボリックシンドローム患者に対する予防措置として，特に脂質異常症や高血圧症など，脳梗塞の危険因子でもあるシンドロームの個々の要素に対し適切な治療をするべきである。（新規推奨）	クラスI エビデンスレベルA

節には食事療法，運動，経口血糖降下薬，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，血管系危険因子をもつ糖尿病患者への積極的血糖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なかった[6,7]。ACCORD試験は積極的血糖治療群で死亡リスクが高まったため平均3.5年間で中止となったが，非致死性脳卒中の発症率にも主要評価項目である非致死性心臓発作・非致死性脳卒中・心血管系疾患死にも有意差はなかった[6]。ADVANCE試験も心血管イベントの二次予防効果を示さなかったが，ACCORD試験と異なり，群間の死亡率に有意差はなかった[7]。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もつ患者では，HbA1C目標値を6.5%未満にすべきでないことを示唆している。PROactive試験では，大血管の疾患がある2型糖尿病患者で，心血管イベントと死亡率の低下を主要評価項目としてピオグリタゾンの効果が評価されたが，主要評価項目に有意差はなかった。しかし脳卒中既往のある症例で脳卒中再発の相対的リスクと脳卒中・心筋梗塞・血管死の相対的リスクがそれぞれ47%と28%減少した。一方，同じチアゾリジンジオン系薬物であるrosiglitazoneでは心不全の出現や体液貯留疑いから，FDAは2007年にこの系列の薬物に対して警告を出している。

C. 脂質異常症

虚血性と出血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と同様に，虚血性脳卒中，大血管のアテローム動脈硬化性脳卒中と血清トリグリセリド高値が独立して関連している。スタチン試験のメタ解析ではLDL-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タチンの効果は明らかでなかった。症候性虚血性脳卒中の既往者を対象としたHPS試験の後向きサブ解析では，シンバスタチンにより大血管イベントが20%減少したが，脳卒中再発に対する有意差はなかった[8]。SPARCL試験では，LDL-C 100～190 mg/dLでCHDのない脳卒中・TIA既往患者において，アトルバスタチン80 mgと偽薬の連日投与が無作為試験で比較され，4.9年間（中央値）で，致死性と非致死性脳卒中の再発は11.2%，偽薬で13.1[5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[9]。出血性脳卒中は増加したが，致死性の出血性脳卒中に差はなかった。SPARCL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，出血性脳卒中は増加しなかった。LDL-Cが70

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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）が広かったためか，有意な増加は認めなかった。National Cholesterol Education Program（NCEP-ATPIII）は脳卒中を含めた血管系疾患患者や危険因子の保有者への脂質異常症の管理に対する包括的指針[10]を発表しているが，脂質の標的としては LDL-C の低下を第一に勧めて，生活習慣では飽和脂肪とコレステロール摂取の減量，理想体重，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（糖尿病や症候性頸動脈疾患を含む）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，ナイアシン，フィブラート系薬剤，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。　（文責：福山　秀直）

D. 喫煙

喫煙が虚血性脳卒中の重要で独立した危険因子であるという強いエビデンスがあり[11]，受動喫煙が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ンスも増えている。これらのデータはすべて一次予防に関するものであるが，既に脳卒中・TIA を罹患した患者にもあてはまる。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確なエビデンスがある[12]。虚血性脳卒中との関連については J 字型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過度の飲酒はリスクを高める。大半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/m^2 以上と規定される肥満は冠動脈疾患と若年死の独立した危険因子として知られているが，肥満と脳卒中についての検討はほとんどが一次予防に関するもので，体重減量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，耐糖能を改善させ，健全な心血管系を促す傾向があり，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[13]。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，より活発な運動により 27％低減すると報告されている。脳卒中後は後遺症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。脳卒中後の有酸素運動と筋力トレーニ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。

H. メタボリックシンドローム

メタボリックシンドロームは心血管系疾患の危険を高める生理的異常の集団を指すが，生理的異常は定義の仕方により異なっており，AHA の基準では腹囲（男子≧ 102 cm，女子≧ 88 cm），高トリグリセリド血症（≧ 150 mg/dL），低 HDL-コレステロール血症（男子＜ 50 mg/dL，女子＜ 40 mg/dL），高血圧（収縮期≧ 130 mmHg または拡張期≧ 85 mmHg），空腹時高血糖（≧ 100 mg/dL）のうち 3 項目を満たす場合に認められる[14]。この症候群と初発脳卒中の関連について最近数篇の研究が報告されて，ほとんどの論文で関連が確認された。脳卒中の二次予防については，これまで WASID 試験[15]において，本症候群の存在により虚血性脳卒中の再発が多くなる（HR＝1.7, P＝0.012）ことが報告されているが，個々の危険因子で補正すると有意差が消失した。本症候群を構成する主な危険因子は体重の減量により改善するが，本症候群の患者が体重減量，食事療法，運動療法によって，脳卒中その他の血管系疾患の発症を予防することは統計学的パワーのある無作為試験で示されておらず，本症候群を伴った脳卒中患者の再発が予防できるという無作為試験もない。

（文責：柳原　武彦）

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. 症候性頭蓋外頸動脈疾患

これまで多くの臨床試験で頸動脈内膜剥離術（Carotid Endarterectomy: CEA）と内科的療法の併用が内科的療法単独の場合と比較されてきたが，内科的治療には HMG-CoA 還元酵素抑制剤（スタチン），クロピドグレル，ジピリダモール・アスピリン徐放合剤，最適な血圧管理，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頸動脈血管形成術・ステント留置術（Carotid Angioplasty and Stenting: CAS）が CEA のリスクの高い症例に施行されている。

頸動脈内膜剥離術（CEA）：症候性頭蓋外頸動脈高度狭窄症について，ECST，NASCET[16]，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％以上の狭窄症では CEA と内科的治療が内科的治療単独より優れている

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表5 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に関する推奨

危険因子	推　奨	クラス / エビデンスレベル
症候性頭蓋外頸動脈病変	発症後6ヵ月以内のTIAまたは脳梗塞患者で，同側頸動脈の高度（70～90%）狭窄が認められる症例では，周術期死亡および合併症の危険が＜6%と推定される場合にはCEAが推奨される。	クラスI エビデンスレベルA
	最近TIAまたは脳梗塞を発症した患者で，同側頸動脈の中等度（50～69%）狭窄が認められる症例では，周術期死亡および合併症の危険が＜6%と推定される場合には年齢，性別，併存症など患者の背景因子に応じてCEAが推奨される。	クラスI エビデンスレベルB
	狭窄度が＜50%の症例ではCEAまたはCASによる頸動脈血行再建術の適応はない。	クラスIII エビデンスレベルA
	TIAまたは脳梗塞患者にCEAが適応となる場合，早期の頸動脈血行再建術に対する幕易がなければ，時期を遅らせることなく2週間以内にCEAを実施することが適当である。	クラスIIa エビデンスレベルB
	血管内治療に伴う合併症の危険が平均的あるいは低い症候性患者で，内頸動脈の内腔径が非侵襲性画像検査で＞70%あるいはカテーテル血管造影で＞50%減少している場合，CEAの代替としてCASが有用である。	クラスI エビデンスレベルB
	高度（＞70%）狭窄が認められる症候性患者のうち，狭窄部位への外科的なアクセスが困難な患者，外科手術による危険を大きく高めるような医学的問題を有する患者，放射線誘発性狭窄やCEA後の再狭窄など特殊な状態を有する患者では，CASが考慮されてもよい。	クラスIIb エビデンスレベルB
	CASに関する上記の状況下では，CEAおよびCASの臨床試験で認められたように，周術期合併症および死亡率が4～6%の治療成績をもつ外科医が行うCASは適当である。	クラスIIa エビデンスレベルB
	症候性頭蓋外頸動脈閉塞が認められる患者では，EC/ICバイパス手術は原則的には推奨されない。	クラスIII エビデンスレベルA
	頸動脈狭窄を有するTIAまたは脳梗塞患者に対しては，本ガイドラインの他項でも概説されているように，最適な内科的治療（抗血小板療法，スタチン療法，危険因子の改善など）が推奨される。（新規推奨）	クラスI エビデンスレベルB
頭蓋外椎骨動脈病変	椎骨動脈狭窄を有するTIAまたは脳梗塞患者に対しては，本ガイドラインの他項でも概説されているように，最適な内科的治療（抗血小板療法，スタチン療法，危険因子の改善など）が推奨される。（新規推奨）	クラスI エビデンスレベルB
	頭蓋外椎骨動脈狭窄が存在し，最適な内科的治療（抗血栓療，スタチン系薬，関連する危険因子のコントロール）を行っても症状が認められる患者では，血管内治療および外科的治療を考慮してもよい。	クラスIIb エビデンスレベルC
頭蓋内アテローム硬化症	頭蓋内主要動脈の50～99%狭窄により脳梗塞またはTIAを発症した患者には，ワルファリンよりアスピリンが推奨される。 WASID試験の患者ではアスピリン1,300 mg/日が投与されたが，アスピリンの至適用量は明らかになっていない。一般的な安全性と有効性に関するデータに基づくと，アスピリンの用量は50～325 mg/日が推奨される。（新規推奨）	クラスI エビデンスレベルB
	頭蓋内主要動脈の50～99%狭窄により脳梗塞またはTIAを発症した患者では，血圧＜140/90 mmHg，総コレステロール値＜200 mg/dLを長期間維持するのが適当であろう。（新規推奨）	クラスIIb エビデンスレベルB
	頭蓋内主要動脈の50～99%狭窄により脳梗塞またはTIAを発症した患者では，血管形成術あるいはステント留置術の有用性は確立されておらず，研究段階の治療法と考えられる。（新規推奨）	クラスIIb エビデンスレベルC
	頭蓋内主要動脈の50～99%狭窄により脳梗塞またはTIAを発症した患者では，EC/ICバイパス手術は推奨されない。（新規推奨）	クラスIII エビデンスレベルB

ことが示された。これら3件の臨床試験を集めた3,000症例以上の解析では術後30日以内の脳卒中と死亡が7.1%にみられた。これらの臨床試験では50%以下の狭窄でCEAの効果がないことも明らかになった。狭窄が50～69%の症例では5年間の手術側の脳卒中発症率が15.7%で，内科的治療単独では22.2%（$P = 0.045$）であるため，この範疇に入る症例ではリスクより恩恵が多い症例を選び，周術期死亡・罹病率が6%以下の外科医がCEAをすると恩恵が期待できる[17]。CEAのリスクに影響を与える因子として性別があげられており，NASCETのサブ解析では手術死亡率，神経系罹病率，再狭窄率が女性で14%に対し男性では3.9%（$P = 0.008$）であり，女性の転帰が良くないことが示されている。周術期の管理と麻酔技術が進歩したため，年齢の影響ははっきりしない。NASCETでは80歳以上の症例は除外されたが，この年齢層でのCEAの安全性も後に示されている。CEAの施行時期に関しては，脳卒中・TIA発症後2～6週目の手術で脳卒中再発リスクを高めずに好成績が得られるとされるが，TIAや軽度の脳卒中後であれば3週以内のCEAも安全であろう。CEAは75歳以上で2週以内に施行した場合に最も成績が良かったとの報告もある。

頸動脈血管形成術・ステント留置術（CAS）：頭蓋外頸動脈狭窄症においてCEAの代替治療法としてCASが用いられている。CASの利点は侵襲が少ないこと，患者の苦痛が少ないこと，回復が早いことがあげられるが，長期の有用性はまだ不明である。現在CASは以下のような高リスク患者に勧められている。(1) 重篤な併存症が存在する（クラスIII/IVうっ血性心不全，クラスIII/IV狭心症，左側主幹冠動脈疾患，≥2冠動脈疾患，左心室駆出率≤30%，最近の心筋梗塞，重篤な呼吸器疾患，重篤な腎疾患），

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(2) CEA に対する技術的または解剖学的な問題がある（頸部手術の既往，頸部の放射線治療，CEA 後の再狭窄，狭窄部位が C2 より遠位か鎖骨より近位，対側頸動脈閉塞，対側声帯麻痺，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ものがある。SAPPHIER 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，両者の差は周術期の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が，症候性の症例が 30% しかなかったことが問題点である。米国とカナダで施行された CREST 試験[18]では 2,502 症例の症候性と無症候性頸動脈狭窄（超音波で 70% 以上または血管造影で 50% 以上）をもつ患者で CEA と CAS が前向き無作為に比較されたが，主要評価項目（30 日以内の脳卒中，死亡，心筋梗塞と 4 年以内の同側梗塞）は CEA が 7.2%，CAS が 6.8% で有意差がなかった[注1]。30 日以内の症候性患者における脳卒中と術後同側脳卒中は CAS 群で有意に高かったが（5.5% 対 3.2%, $P = 0.04$），心筋梗塞は CEA 群で高い傾向があった（2.3% 対 1.0%, $P = 0.08$）。年齢では 70 歳以下で CAS の成績が良く，70 歳以上では CEA の成績が良かった。

頭蓋外―頭蓋内（EC/IC）バイパス術：内頸動脈閉塞・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。最近ポジトロン CT（PET）で血行力学的不全が大きな症例で無作為試験（COSS 試験）が始められた[注2]。

B. 頭蓋外椎骨動脈疾患

症候性椎骨動脈狭窄についての組織的レビューでは発症 7 日以内の脳卒中再発率が頸動脈狭窄より高いが，最善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ない。現状では内科的治療が主体であり，内科的治療により椎骨脳底動脈系の TIA や脳卒中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椎骨脳底動脈系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的パワーが不足しており，再発リスクが高い症例が含まれなかった可能性が指摘されている。

C. 頭蓋内アテローム動脈硬化症

アテローム動脈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。上記の 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った 189 例の中大脳動脈狭窄症患者では，44 カ月の経過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[15]は頭蓋内で内頸動脈，中大脳動脈，脳底動脈，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）とワルファリン（INR 2.0 ～ 3.0）が無作為に比較され，ワルファリン群で出血が多いため早期に中止されたが，両者で再発予防効果に差がなかった。最初の 1 年間の脳卒中再発率は全体で 15% であり，動脈狭窄が存在する領域の脳卒中は 12% であった。狭窄が 70% 以上ある動脈では脳卒中の再発率が 19% に及んだ。多変量解析では 70% 以上の狭窄と初発症状後 17 日以内の臨床試験への参加が当該動脈領域の脳卒中再発と最も関連を示し，女性もリスクが高い傾向があった。また血管系危険因子の積極的治療が頭蓋内動脈狭窄をもつ患者の脳卒中再発を軽減する可能性があり，WASID 試験の事後（post hoc）解析では，長期的に血圧を 140/90 mmHg 以下に保ち，総コレステロールを 200 mg/dL 以下に保つことにより脳卒中再発と他の血管性イベントが低減されることが示唆された。

頭蓋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，狭窄部位を拡張し，脳血流量を改善し，その後の脳卒中発症を抑制することが期待でき，これまで手技的には成功を収めている。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められているが，このステント治療の効果はまだ確立されていない。症候性頭蓋内動脈狭窄症（70 ～ 90%）の 129 例を対象とした前向き登録調査[19]ではステント留置成功率は 97% であったが，30 日以内の脳卒中，脳内出血，死亡と 30 日以上の同側脳卒中は 6 カ月で 14% に達し，25% の症例で 50% 以上の再狭窄がみられた。このステントは内科的治療に優ることは証明されておらず，ステントを用いない血管形成術の単独治療との比較もされていない。

（文責：柳原　武彦）

III. 心原性塞栓症に対する内科的治療（表 6）

心原性脳塞栓症は虚血性脳卒中患者のおよそ 20% を占める。非弁膜症性心房細動の患者が約 2 分の 1，心臓弁膜症の患者が約 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，初発および再発脳梗塞発症の強力な予測因子である。米国では 200 万人以上が心房細動に罹患していると推定され，年間 75,000 例以

注 1：欧州で施行された同様の ICCS 試験（Ederle J et al. *Lancet*. 2010; 375: 985-997）では CEA が優れていた。
注 2：COSS 試験は有意差を検出することが困難と判断され，昨年中止となった。

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表6 心原性脳塞栓症に関する推奨

危険因子	推　奨	クラス / エビデンスレベル
心房細動	発作性（間欠性）心房細動（AF）または持続性AFを有する脳梗塞またはTIA患者では，ビタミンK拮抗薬による抗凝固療法（目標INR 2.5：範囲2.0～3.0）が推奨される。	クラスI エビデンスレベルA
	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。	クラスI エビデンスレベルA
	クロピドグレル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困難の患者には推奨されない。（新規推奨）	クラスIII エビデンスレベルB
	AFを有する脳梗塞の危険が高い患者（3ヵ月以内の脳梗塞またはTIAの発症，$CHADS_2$スコアが5または6，機械的人工弁またはリウマチ性弁膜疾患）で，一時的に経口抗凝固薬の中断が必要な場合，低分子ヘパリンの皮下投与によるブリッジングが適当である。（新規推奨）	クラスIIa エビデンスレベルC
急性心筋梗塞および左心室血栓	急性心筋梗塞を伴う脳梗塞またはTIA患者において，心エコー検査またはその他の心臓画像検査により左心室壁在血栓が認められる場合は，少なくとも3ヵ月間，経口抗凝固薬（目標INR 2.5：範囲2.0～3.0）を投与するべきである。	クラスI エビデンスレベルB
心筋症	脳梗塞またはTIAの既往のある洞調律患者に左心室収縮機能障害（LVEF ≦ 35%）による心筋症が認められる場合，ワルファリンの有用性は確立していない。（新規推奨）	クラスIIb エビデンスレベルB
	脳梗塞またはTIAの既往があり心筋症を有する患者で脳梗塞再発を予防するには，ワルファリン（INR 2.0～3.0），アスピリン（81 mg/日），クロピドグレル（75 mg/日），またはアスピリン（25 mg，1日2回）＋徐放性ジピリダモール（200 mg，1日2回）の併用投与を考慮してもよい。	クラスIIb エビデンスレベルB
心臓弁膜症	リウマチ性僧帽弁疾患を有する脳梗塞または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：範囲2.0～3.0）が適当である。	クラスIIa エビデンスレベルC
	出血の危険の上昇を避けるため，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。	クラスIII エビデンスレベルC
	大動脈弁疾患または非リウマチ性僧帽弁疾患を有する脳梗塞またはTIA患者では，AFがなければ抗血小板療法が適当であろう。	クラスIIb エビデンスレベルC
	僧帽弁輪石灰化を有する脳梗塞またはTIA患者では，抗血小板療法を考慮してもよい。	クラスIIb エビデンスレベルC
	僧帽弁逸脱を有する脳梗塞またはTIA患者では，長期の抗血小板療法を考慮してもよい。	クラスIIb エビデンスレベルC
人工心臓弁	機械的人工心臓弁を使用している脳梗塞または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。	クラスI エビデンスレベルB
	機械的人工心臓弁を使用している患者で，十分な経口抗凝固療法を行っていたにもかかわらず脳梗塞または全身性塞栓症を発症した患者では，出血の危険の高い患者（例えば，出血の既往歴，脳新鮮，または出血の危険を増加させる他の血管異常，血液凝固障害）でなければ，アスピリン（75～100 mg/日）を経口抗凝固薬に追加し，INR（目標INR 3.0，範囲2.5～3.5）を維持することが適当である。	クラスIIa エビデンスレベルB
	生体心臓弁を使用している脳梗塞またはTIA患者で，血栓塞栓症の原因が他に考えられない場合，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。	クラスIIb エビデンスレベルC

上の心房細動による脳梗塞を発症する。心房細動患者では，脳梗塞・TIAの既往が脳梗塞発症の最も高い相対的リスク（RR＝2.5）となる。年齢，うっ血性心不全，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。心エコーでの左室機能低下，左房径の拡大，僧帽弁輪の石灰化，もやもやエコー，左房内血栓も塞栓症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，非弁膜症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。ワルファリン投与群と非投与群の一次予防効果を検討した5件の試験を集積すると[20]，ワルファリンは全試験で有効であり，相対的リスクは68%低下し，年間脳梗塞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強度は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以下では経口抗凝固薬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域以下であり，脳梗塞予防に不十分である。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低い。3件の臨床試験データの集積では，相対的リスクの低下率はプラセボと比較して21%であった[21]。アスピリンの有効性と安全性の最も良いバランスは75～100 mg/日であろう。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ル＋アスピリン投与を比較した試験では，クロピドグレル＋アスピリン投与群で年間2.4%が脳梗塞を発症したのに対し，アスピリン単独群では3.3%であった（RR＝0.72，$P < 0.001$）[22]。大出血はクロピドグレル＋アスピリン投与群が年間2.0%

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で，アスピリン単独群では1.3％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。直接トロンビン阻害薬やXa因子阻害薬を含み，心房細動に対する新たな抗凝固療法の臨床試験が施行されているが，最も成功した代替抗凝固療法は経口抗トロンビン薬のダビガトランである。RE-LY試験[23]では18,000人以上の心房細動患者に無作為非盲検下にダビガトラン1日2回150 mgの内服が用量調節したワルファリンに比較して脳梗塞や全身性塞栓症の発症率を下げ（RR＝0.66，$P<0.001$），大出血が同等であることが示された。薬剤や食物との相互作用が少なく，凝固モニタリングを必要としない経口薬が使えることは，患者にとって大きな前進であろう。

心房細動患者の脳卒中予防の代替療法として，左心耳を閉塞するデバイスの経皮的埋込み術がある。PROTECT AF試験において，心房細動患者に対する閉塞デバイスの使用は脳卒中発症率を下げる可能性が示された[24]。経口抗凝固療法が困難で脳梗塞発症リスクが高い心房細動患者にとって非常に有用であろう。心房細動を有し脳梗塞あるいはTIAの既往のある患者は，一時的に経口抗凝固療法を中断した時（典型的には外科的処置）に脳梗塞のリスクが高まる。一般的にリスクが高いと考えられる心房細動患者（3カ月以内の脳卒中またはTIAの既往，$CHADS_2$スコアが5または6，機械的人工弁あるいはリウマチ性弁膜疾患）では，ブリッジング抗凝固療法が推奨される。外来患者として適当なブリッジング療法は治療用量の低分子ヘパリンである。

B. 急性心筋梗塞および左心室血栓

急性期に再灌流療法を行わない場合，前方枝の心筋梗塞後2週間以内に約3分の1の患者に心内血栓が発生し，心尖部を含む大きな梗塞の場合はさらに高くなる。抗凝固療法を行わない場合，心筋梗塞後に左室内血栓をもつ患者の約10％に臨床的に明らかな脳梗塞が起こる。したがって，前方枝の心筋梗塞後に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ないが，血栓塞栓症のリスクは3カ月が経過すると低下するようであり，心腔内に血栓ができやすいとされる慢性左室瘤をもつ患者でも塞栓症のリスクが比較的低くなる。

C. 心筋症

虚血性脳卒中患者の約10％で左室駆出率が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，脳梗塞発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パワーが得られず中止された[25]。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薬の無作為試験も行われていない。

D. 心臓弁膜症

抗血栓療法は心臓弁膜症患者の脳卒中と全身性塞栓を低下させるが完全には予防しない。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べねばならない。

リウマチ性僧帽弁疾患：過去に塞栓症の既往があるリウマチ性僧帽弁疾患をもつ患者の30～65％で塞栓症は再発する。これらの再発のうち60～65％は最初の1年以内に発症し，さらに大部分は6カ月以内である。多くの観察試験において，長期間の抗凝固療法がリウマチ性僧帽弁疾患をもつ患者の全身性塞栓症リスクを効果的に低下させている。リウマチ性弁膜症患者における抗血小板薬と抗凝固薬の併用療法の安全性と有効性はまだ評価されていない。同じような患者集団による推定では，併用療法が出血のリスクを増大させることは明らかである。

僧帽弁逸脱症：僧帽弁逸脱症は成人の心臓弁膜症の中で最も多く，一般的に無害であるが，時々他に塞栓源のない僧帽弁逸脱症患者に症候性の血栓塞栓症を認める。僧帽弁逸脱症をもつ脳梗塞・TIA患者に対する抗血栓療法の有効性を示した無作為試験は存在しない。

僧帽弁輪石灰化：女性優位にみられる僧帽弁輪石灰化は時々僧帽弁逆流症と併存し，また稀に非リウマチ性僧帽弁狭窄症の原因となり得る。全身性または脳塞栓症の発症率は不明だが，剖検例において重度に石灰化した弁輪組織に血栓が認められている。脳梗塞・TIAを起こした患者に対する抗凝固療法と抗血小板療法の安全性と有効性の比較はまだされてない。

大動脈弁疾患：僧帽弁疾患や心房細動を合併しない場合，大動脈弁疾患をもつ患者の全身性塞栓症は稀である。脳梗塞と大動脈弁疾患をもつ患者を選んだ無作為試験は存在しないので，脳梗塞・TIA患者を対象とした抗血小板療法の臨床試験の結果に基づいた治療が推奨される。

E. 人工心臓弁

人工心臓弁をもつ患者を対象として，投与量を規定しないワルファリンと2種類のアスピリンを含む抗血小板薬の投与を6カ月間比較した無作為試験において，血栓塞栓症の予防に経口抗凝固薬が有効であることが示されている[26]。出血はワルファリン群で多かった。2件の無作為試験において，人工心臓弁をもつ患者に対してジピリ

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ダモールとワルファリンの併用により全身性塞栓症が減少した。また他の試験では，ワルファリン（INR 3.0 ～ 4.5）にアスピリン 100 mg/ 日を加えることによりワルファリン単独よりも塞栓症に対する有効性が上昇した。軽症の出血は増加したが有意差はなかった。生体弁は機械的人工弁と比較して血栓塞栓症との関連は低い。他に説明がつかない虚血性脳卒中や TIA を発症した生体弁患者では，経口抗凝固療法（INR 2.0 ～ 3.0）が勧められる。

（文責：青木　志郎*・松本　昌泰）

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IV. 非心原性脳卒中または一過性脳虚血発作に対する抗血栓薬治療（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再発リスクを 15％低下させ[27]，その効果は用量 50 ～ 1500 mg の範囲で変わらないが，高用量であるほど消化管出血を合併しやすかった。

チクロピジン：血小板の ADP 受容体阻害薬であり，脳卒中患者を対象とした CATS 無作為試験では，プラセボに対して心血管イベントの相対的リスクが 23％抑制された。TASS 試験では，チクロピジン（250 mg × 2 回 / 日）はアスピリン（650 mg × 2 回 / 日）に対して脳卒中発症＋死亡の相対的リスクを 12％抑制した（$P = 0.048$）。副作用には下痢や薬疹があり，消化管出血はアスピリンと同等，もしくは少ないとされる。血栓性血小板減少性紫斑病（TTP）が報告されている。

クロピドグレル：もう 1 つの ADP 受容体阻害薬で，これまでにアスピリン，アスピリン＋ジピリダモール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ない。CAPRIE 試験では脳卒中，心筋梗塞または末梢動脈閉塞症のある患者で，年間虚血性脳卒中・心筋梗塞・血管死の発生率はアスピリン群（325 mg/ 日）の 5.83％に対してクロピドグレル群（75 mg/ 日）では 5.32％で相対的リスクは 8.7％抑制された（$P = 0.043$）[28]。しかし脳卒中後に CAPRIE 試験に組み入れられた症例のサブ解析では有意差がなかった。PRoFESS 試験はアスピリン＋徐放型ジピリダモールのクロピドグレルに対する非劣性試験であったが，両者に差は認められなかった。クロピドグレルは下痢と薬疹はアスピリンよりも多いが，下痢以外の消化器症状や出血の頻度は少ない。TTP の報告は散見される。最近，チトクローム P-450（CYP2C19）で代謝されるプロトンポンプ阻害薬との併用によって，クロピドグレルの作用が減弱し，脳卒中と心筋梗塞を含む重篤な心血管イベントのリスクが増加することが明らかになった[29]。さらに CYP 遺伝子多型がクロピドグレルの作用に影響を与え，少なくとも CYP2C19 機能消失型アレルの保有者では非保有者に比べて 32％の活性低下（$P < 0.001$）が報告されている[30]。

ジピリダモール＋アスピリン：ジピリダモールはホスフォジエステラーゼ阻害作用を有する抗血小板薬である。アスピリンとの併用療法としては，プラセボと比較した ESPS-1 無作為試験で 2 年間のイベント発生率はアスピリン（325 mg/ 日）＋ジピリダモール（75 mg × 3 回 / 日）群で 16％，プラセボ群で 25％だった（$P < 0.001$）。ESPS-2 試験では，アスピリン（25 mg × 2 回 / 日）＋徐放型ジピリダモール（200 mg × 2 回 / 日）併用群は，アスピリン単独群と比較して脳卒中再発を 23％（$P = 0.006$），脳卒中＋死亡を 13％（$P = 0.056$）抑制した。ジピリダモール併用で出血性合併症は増加しなかったが，頭痛や消化器症状

表 7 非心原性脳梗塞または TIA に対する抗血栓薬治療（経口抗凝固薬および抗血小板薬）に関する推奨

推　奨	クラス / エビデンスレベル
非心原性脳梗塞または TIA 患者では，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，経口抗凝固療法よりも抗血小板療法の使用が推奨される。	クラス I エビデンスレベル A
アスピリン（50 ～ 325 mg/ 日）単独療法（①），アスピリン 25 mg ＋徐放性ジピリダモール 200 mg（1 日 2 回）の併用療法（②），およびクロピドグレル（75 mg/ 日）単独療法（③）は，いずれも初期治療としての選択が可能である。 抗血小板薬の選択は患者の危険因子のプロフィール，費用，忍容性，および他の臨床的特性に応じて個別に行われるべきである。	①クラス I エビデンスレベル A ②クラス I エビデンスレベル B ③クラス IIa エビデンスレベル B
脳梗塞または TIA 発症後の患者では，クロピドグレル投与にアスピリンを追加すると出血の危険を高めるため，二次予防に併用は原則的に推奨されない。	クラス III エビデンスレベル A
アスピリンに対するアレルギーがある患者にはクロピドグレルが適当である。	クラス IIa エビデンスレベル C
アスピリン服用中に脳梗塞を発症した患者において，アスピリンの増量により効果が改善するというデータはない。 アスピリン服用中にイベントが発生した患者では他の抗血小板薬への変更がしばしば検討されるが，どの抗血小板薬についても，あるいはその併用についても試験がされていない。	クラス IIb エビデンスレベル C

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は増加した。PRoFESS試験では脳卒中再発率はクロピドグレルと同等だった。

クロピドグレルとアスピリンの併用：MATCH試験では発症3カ月以内のTIAまたは脳梗塞患者を対象として，クロピドグレル＋アスピリンとクロピドグレル単剤が比較された[31]。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，生命の危険を伴う出血率が1.3％増加した。クロピドグレル＋アスピリンは急性冠症候群患者には推奨されているが，急性期を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[32]ではクロピドグレル＋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6.8％に対してアスピリン単独群7.3％と差はなかった（RR＝0.93，P＝0.22）。

経口抗血小板薬の選択：アスピリン，チクロピジン，アスピリン＋ジピリダモールは脳卒中の二次予防に有効性が示された。クロピドグレルについてはプラセボ対照試験が行われていないが，データから判断して他の抗血小板薬と同等の効果があると考えられる。したがって抗血小板薬は相対的な有効性，安全性，費用，患者背景，患者の希望などに基づいて選択されるべきである。アスピリン＋ジピリダモ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1例程度である。チクロピ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，安全性に問題がある。消化管出血や他の重篤な出血のリスクはクロピドグレルよりもアスピリンやアスピリン＋ジピリダモールの方が高いといえるが大きな差はない。ジピリダモールは頭痛を誘発する傾向がある。チクロピジンは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に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。アレルギーや消化管症状でアスピリンが使用できない場合には，クロピドグレルが適している。頭痛を誘発するためジピリダモールが服用できない場合には，アスピリン，クロピドグレルのいずれかが適当である。アスピリンとクロピドグレルの併用は急性冠動脈症候群や最近血管ステント留置術を受けた症例には適当かもしれない。抗血小板薬の変更によって再発リスクが減少することを検証した研究はない。

新規の薬剤：サルポグレラートは最近の報告でアスピリンに対する非劣性は証明されなかった。triflusalは予備試験の段階である。シロスタゾールは最近の予備的無作為比較試験[33]でアスピリンと同等の効果が得られている[注]。

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，出血性合併症が多く早期に中止された。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，出血性合併症ともに両群で差はなかった。前述のWASID試験[15]では頭蓋内主幹動脈病変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

頸動脈や椎骨動脈解離は，TIAや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。頭部・頸部外傷により起こるが，半数以上は特発性または些細な障害後にみられる。多くの結合織疾患，線維性筋異形成症，Marfan症候群，Ehlers-Danlos症候群（type IV），不完全骨形成症，コラーゲン形成の先天的異常症などが危険因子となる。解離に伴う脳虚血は，塞栓性機序と血行力学的機序があるが前者が主体である。時に動脈瘤が形成されるが，これもまた塞栓源となる。特に椎骨動脈領域の頭蓋内動脈解離ではくも膜下出血のリスクがある。動脈解離患者の脳卒中予防のための最適な治療は議論があり，抗凝固療法，抗血小板療法，ステント留置を含めた血管内治療，経過観察のみなどの選択枝がある。外科的治療は一般的ではない。血管損傷後，2～3日以内は脳卒中リスクが高いためヘパリンや低分子ヘパリンを用いた早期抗凝固療法が推奨されてきたが，特定の抗血栓療法を支持する比較試験はない。頸動脈解離327例を対象としたCochrane review[34]では，抗凝固療法と抗血小板療法の間で死亡または機能予後不良例に有意差を認めなかった。脳卒中再発は，抗凝固療法1.7％，抗血小板療法3.8％，無治療3.3％であった。頸動脈または椎骨動脈解離762例の組織的レビュー[35]でも，死亡・脳卒中再発は，抗血小板療法と抗凝固療法間に有意差を認めなかった。その他のデータも含め，これらの観察研究では抗血小板療法と抗凝固療法の脳卒中再発リスクがほぼ同等であることを示す。患者は通常少なくとも3～6カ月間は抗血栓療法を維持する。治療継続期間は決まっていないが，治療変更前に解離血管の再開通を確認する検査が推奨される。

注：このガイドラインでは，日本で施行されたシロスタゾールとアスピリンの無作為比較試験CSPS-II（*Lancet Neurol* 2010;9:959-968）において，シロスタゾールの有用性が示された結果についてはまだ言及していない。

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表8 特殊な病態を有する脳梗塞に関する推奨

危険因子	推　奨	クラス / エビデンスレベル
動脈解離	頭蓋外頸動脈または椎骨動脈解離を有する脳梗塞または TIA 患者では，3～6ヵ月間の抗血栓療法が適当である。	クラス IIa エビデンスレベル B
	頭蓋外頸動脈または椎骨動脈解離を有する脳梗塞または TIA 患者において，抗凝固薬と比較した抗血小板療法の相対的有効性は不明である。（新規推奨）	クラス IIb エビデンスレベル B
	頭蓋外頸動脈または椎骨動脈解離を有する脳梗塞または TIA 患者で，最適な内科的治療にもかかわらず明確な脳梗塞再発が認められた場合には，血管内治療（ステント留置術）を考慮してもよい。	クラス IIb エビデンスレベル C
	頭蓋外頸動脈または椎骨動脈解離を有する脳梗塞または TIA 患者で，血管内治療が失敗したか，または適応とならなかった場合は，外科的治療を考慮してもよい。	クラス IIb エビデンスレベル C
卵円孔開存	PFO を有する脳梗塞または TIA 患者では，イベントの再発予防として抗血小板療法が適当である。	クラス IIa エビデンスレベル B
	PFO 有する患者において，脳梗塞の再発予防として抗凝固療法がアスピリンと比べ同等または優れていることを示す十分なデータはない。（新規推奨）	クラス IIb エビデンスレベル B
	PFO を有する脳梗塞患者に対する PFO 閉鎖術の推奨に関しては，データが十分得られていない。	クラス IIb エビデンスレベル C
高ホモシステイン血症	葉酸の補充はホモシステイン値を低下させ，高ホモシステイン血症を有する脳梗塞患者に考慮してもよいが，ホモシステイン値の低下によって脳梗塞の再発を抑制できるというエビデンスはない。	クラス IIb エビデンスレベル B
先天性血栓性素因	先天性血栓性素因が確認されている動脈性脳梗塞または TIA 患者では，DVT の有無を評価すべきであり，DVT が認められる場合は，臨床的および血液学的な状態に応じて短期または長期の抗凝固療法の適応となる。	クラス I エビデンスレベル A
	先天性血栓性素因以外の機序も十分に評価すべきである。血栓性素因が確認されている動脈性脳梗塞または TIA 患者で静脈血栓症が認められない場合は，抗凝固療法または抗血小板療法が適当である。	クラス IIa エビデンスレベル C
	自然発症の脳静脈血栓症かつ / または反復性血栓性イベントの既往歴のある患者で先天性血栓性素因がある場合は，長期抗凝固療法の適応があるだろう。	クラス IIa エビデンスレベル C
抗リン脂質抗体陽性	APL 抗体が検出された原因不明の脳梗塞または TIA 患者では，抗血小板療法が適当である。	クラス IIa エビデンスレベル B
	APL 抗体症候群の診断基準を満たす脳梗塞または TIA 患者では，経口抗凝固療法（目標 INR 2.0～3.0）が適当である。	クラス IIa エビデンスレベル B
鎌状赤血球症	SCD を有する成人脳梗塞または TIA 患者では，危険因子のコントロールおよび抗血小板薬の使用に関する前述の一般的な治療が適当である。	クラス IIa エビデンスレベル B
	SCD 患者の脳虚血性イベントの再発予防には，全ヘモグロビン量に対するヘモグロビン S 量を＜30～50%に抑制するために定期的な輸血療法，ヒドロキシウレア，血管閉塞が進行した症例でのバイパス手術などの追加療法を考慮してもよい。	クラス II b エビデンスレベル C
脳静脈洞血栓症	急性 CVT 患者では，抗凝固療法が有効と思われる。	クラス IIa エビデンスレベル B
	急性 CVT 患者において抗凝固療法の至適施行期間を明らかにした臨床試験のデータはないが，抗凝固薬を少なくとも 3 ヵ月間投与し，その後，抗血小板療法に切り替えるのが適当である。	クラス IIa エビデンスレベル C
ファブリ病	ファブリ病を有する脳梗塞または TIA 患者では，α-ガラクトシダーゼ酵素補充療法が推奨される。（新規推奨）	クラス I エビデンスレベル B
	本ガイドライン中で概説されている他の二次予防法は，ファブリ病を有する脳梗塞または TIA 患者にも推奨される。（新規推奨）	クラス I エビデンスレベル C

APL ―抗リン脂質；CVT ―脳静脈洞血栓症；DVT ―深部静脈血栓，PFO ―卵円孔開存；SCD ―鎌状赤血球症。

解離の解剖学的治癒は大多数で認められる。完全に治癒しない例でも脳卒中再発のリスクは高くない。

B. 卵円孔開存

心腔内塞栓の右から左への通過の原因には，卵円孔開存（PFO）と肺動静脈奇形がある。PFO は心房中隔瘤（中隔の 10mm を超す偏移と定義される：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 歳未満で有意な脳卒中の危険因子であった［オッズ比（OR）；PFO 3.1，ASA 6.14，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[36]では，630 例が経食道心エコーを受け 34%に PFO を認めた。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。一方ヨーロッパにおける PFO-ASA 研究[37]では，原因不明の脳梗塞を発症した 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%，心所見（−）群では 4.2%であった。PFO の重要性，ASA 合併の意義，最適な予防治療はまだ明らかでない。種々の閉鎖テクニックの無作為比較試験が現在進行中である。

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C. 高ホモシステイン血症

コホートおよび症例対照研究では，高ホモシステイ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，葉酸は脳卒中の初回発症を18%減少させたが，心血管系疾患または脳卒中の二次予防の臨床試験では，ホモシステインを低下させるビタミンの効果は示されなかった。HOPE-2試験[38]は血管系疾患または糖尿病を有する55歳以上の患者5,522例を対象としたホモシステインを低下させるビタミン（葉酸，ビタミンB6，ビタミンB12）と偽薬の無作為比較試験で，主要評価項目は心血管死，心筋梗塞，脳卒中であったが，5年間の観察でビタミン治療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[39]は，非心原性脳卒中後に軽度から中等度の高ホモシステイン血症（男性＞9.5 μmol/L，女性＞8.5 μmol/L）のある患者を対象に高用量または低用量の上記ビタミンの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テイ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. 凝固亢進状態

遺伝的血栓性素因：遺伝的血栓性素因が脳梗塞やTIA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突然変異，methylenetetrahydrofolate reductase（MTHER）のC677T突然変異は，稀に成人の脳卒中に貢献するが，主に小児の脳卒中において重要である。最も頻度の高い遺伝的血栓性素因は第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抵抗性は静脈血栓症が多いが，虚血性脳卒中との関連も報告がある。静脈血栓の存在は，臨床的および血液学的所見により，短期あるいは長期の抗凝固療法の適応となる[40]。プロテインC，プロテインS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後天的凝固亢進状態の一般的管理のガイドラインはあるが，脳卒中二次予防に特定のガイドラインはない。

抗リン脂質抗体：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。抗リン脂質抗体症候群は，頻度は高くないが多臓器に静脈・動脈閉塞疾患，および流産を伴う。血栓性イベントや流産以外にIgGおよび/あるいはIgM型の抗カルジオジピン抗体またはループス抗凝固因子が少なくとも6週間の間隔をおいて2回以上，血中に中等度または高値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。動脈または静脈血栓をきたした抗リン脂質抗体陽性患者を対象とした1つの研究で，強力なワルファリン治療（INR 3.1～4.0）は中等度治療（INR 2.0～3.0）に比較し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再発の関連については一致した結果が得られていない。WARSS/APASS試験[41]では，抗リン脂質抗体陽性患者の脳卒中再発予防効果をワルファリン（INR 1.4～2.8）とアスピリン（325 mg）の無作為試験で検討したが，ワルファリン群とアスピリン群の間で，複合エンドポイント（あらゆる死亡，脳梗塞，TIA発作，心筋梗塞，深部静脈血栓症，肺塞栓症，その他の全身性血栓性イベント）に差を認めなかった。

E. 鎌状赤血球症

脳卒中は鎌状赤血球症（SCD）でよくみられる合併症である。虚血性脳卒中の主原因は内皮細胞の反復損傷による内膜過形成に起因する頭蓋内主幹動脈血管症と考えられる。SCDの主な治療は輸血である。小児を対象として行われた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。再発予防の無作為試験はないがヘモグロビンSの生成を抑制するの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治療として，ヒドロキシウレア，血管閉塞が進行した症例でのバイパス手術などがある。

F. 脳静脈洞血栓症

脳静脈血栓症の年間推定頻度は100万人あたり3～4人である。全脳卒中の1%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予防のために早期の抗凝固療法が考慮される。しかし比較試験は2件しかない。1件は用量調節し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たため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例を対象としてナドロパリン（90anti-Xa U/kg/1日2回）と偽薬の無作為試験が行われた。予後不良例は抗凝固療法群で13%，偽薬群で21%であったが有意差はなかった。上述の2件の試験によるメタ解析[42]では，症候性脳出血の有無にかかわらず，急性期の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，一過性の危険因子による初回DVTは3カ月，誘因のない初回DVTでは少なくとも3カ月，誘因のないDVT再発では無期限に投与するとしている。抗血小板薬

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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

ファブリ病はリソゾームのX染色体連鎖αガラクトシダーゼ遺伝子の欠損により血管内皮細胞に脂肪が沈着し，脳・心臓・皮膚・腎臓の進行性血管障害をきたす稀な疾患である。脳卒中は椎骨動脈・脳底動脈拡張症，心原性塞栓症，小血管病により起こる。抗血小板薬はすでに存在する血管病変による虚血性脳卒中の予防に有用と思われる。αガラクトシダーゼ1 mg/kg，隔週静脈内投与の無作為比較試験では，腎臓・心臓・皮膚の微小血管内皮細胞への新旧の沈着を減少させた[43]。また僅かであるが，全体として腎・心・脳血管イベントと死亡を減少させた（HR＝0.47）。酵素補充療法により脳血流の改善は示されたが，脳卒中のリスクはまだ高い。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，その他の患者は臨床徴候が現れたり臓器障害が進行する場合に酵素補充療法が推奨される。

（文責：棚橋　紀夫）

VI. 女性に特有な脳卒中（表9）

A. 妊娠

妊娠中，産褥期は脳卒中を発症しやすい。妊娠に関連した脳卒中は100,000例の出産につき11人から26人が発症し，産褥期と出産前後3日間で最もリスクが高い。胎児に対する催奇性や出血リスクが上昇するため，TIAや脳梗塞の既往がある女性に対する妊娠時の抗血栓療法は複雑になる[44]。血栓性素因や人工心臓弁のため抗凝固療法が必要な症例では，妊娠中にビタミンK拮抗薬，未分画ヘパリン（UFH）または低分子ヘパリン（LMWH）が使用される。ワルファリンは胎盤に移行し胎児に有害な影響を与える可能性があるため，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に切り替える。LMWHは長期間ヘパリン療法によるヘパリン誘導性血小板減少症（HIT）や骨粗鬆症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，抗Xa因子レベルを注意深くモニターする必要がある。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（50 mg/日から150 mg/日）が安全である。

B. 閉経後ホルモン補充療法

閉経後ホルモン補充療法は心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，脳梗塞生存者の無作為試験と一次予防試験で有意な効果を示さず，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，2.8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[45]。エストロゲン治療を受けている女性は致死的脳卒中発症のリスクがより高かった（HR＝2.9）。一方，WHI試験では50～79歳の閉経後女性16,608人を対象として，エストロゲン＋プロゲスチンによる一次予防効果がプラセボを対照に無作為に検討されたが，ホルモン補充療法はすべての脳卒中発症を44％増加させた（HR＝1.44）[46]。

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VII. 頭蓋内出血後の抗凝固療法（表10）

これまでの多くの研究は，人工弁か心房細動に対して抗凝固療法を受けている患者が，脳内出血（ICH）もしくは硬膜下血腫（SDH）を発症したケースを対象としている。

表9 女性に特有な脳卒中に関する推奨

危険因子	推　奨	クラス/エビデンスレベル
妊娠	妊娠中で，血栓塞栓に関して危険の高い状態（凝固亢進状態，機械的人工弁など）を有する脳梗塞またはTIA患者では，以下の選択肢が考慮されてもよい：妊娠期間を通じ，UFHを用量調節して投与する（例えば，活性化部分トロンボプラスチン時間をモニタリングしながら12時間毎に皮下投与する）；妊娠期間を通じ，第Xa因子のモニタリングをしながらLMWHを用量調節して投与する；あるいは，UFHまたはLMWHを妊娠13週目まで投与，その後ワルファリンを妊娠第3期の半ばまで投与，その後UFHまたはLMWHを再開して出産時まで継続投与する。	クラスIIb エビデンスレベルC
	妊娠中で，血栓塞栓の危険が著くない脳梗塞またはTIA患者では，妊娠第1期にUFHまたはLMWHを投与し，その後出産まで低用量アスピリンの投与が考慮されてもよい。	クラスIIb エビデンスレベルC
閉経後ホルモン補充療法	脳梗塞またはTIAを発症した女性患者には，閉経後ホルモン補充療法（エストロゲン単独投与またはエストロゲン＋プロゲスチン併用投与）は推奨されない。	クラスIII エビデンスレベルA

LMWH＝低分子ヘパリン；UFH＝未分画ヘパリン。

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表10 頭蓋内出血後の抗凝固療法に関する推奨

危険因子	推　奨	クラス/エビデンスレベル
頭蓋内出血	ICH，SAHまたはSDHが認められた患者では，出血急性期の少なくとも1～2週間はすべての抗凝固薬および抗血小板薬の投与を中止し，新鮮凍結血漿またはプロトロンビン複合体製剤とビタミンKにより直ちにワルファリンの作用を中和することが適当である。	クラスIIa エビデンスレベルB
	硫酸プロタミンは，ヘパリンに関連したICHにおいてヘパリンの効果を中和するために，ヘパリン投与中止からの時間に依存した用量で使用すべきである。（新規推奨）	クラスI エビデンスレベルB
	抗血栓療法に関連したICH後の抗血栓療法再開の決定は，それ以降の動脈または静脈血栓塞栓症の危険，ICH再発の危険，患者の全身状態に基づいて行う。脳梗塞の危険が比較的低い患者（例えば，脳梗塞の既往がない心房細動），アミロイド血管症の危険が高い患者（例えば，脳葉出血を有する高齢患者）あるいは全体的な神経機能が非常に低下した患者では，抗血小板薬が脳梗塞予防に考慮されてもよい。血栓塞栓症の危険が非常に高い患者にワルファリン治療再開が考慮される場合，ICH発症後7～10日でワルファリン治療を再開することは適当であろう。（新規推奨）	クラスIIb エビデンスレベルB
	出血性脳梗塞の患者では，個々の臨床状況や抗凝固療法の適応理由に基づき，抗凝固療法を継続することは適当かもしれない。	クラスIIb エビデンスレベルC

ICH＝脳内出血；SAH＝くも膜下出血；SDH＝硬膜下血腫。

くも膜下出血に関する報告は極めて少ない。総じて，大規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の患者に比べて血腫の体積が有意に増加すること（$P=0.002$）が報告されている[47]。よってICHとSDHの急性期においては，プロトロンビン複合体製剤とビタミンK，またはこれらに新鮮凍結血漿を併用して，INRをできるだけ早く低下させることが推奨される。プロトロンビン複合体製剤は効果発現に要する時間が15分以内と速いので，重症出血例では新鮮凍結血漿よりも優先されることが多い。

適切な抗凝固療法の中断期間は不明である。最長で19日ワルファリンを中止した35例の検討と平均15日ワルファリンを中止した人工弁患者35例の検討では，それぞれ中止期間中の脳梗塞発症はなかった。ワルファリン内服中のICH患者141例を対象とした研究[48]では，抗凝固療法を10日間（中央値）中止した結果，30日以内の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，人工弁患者で2.9%，心原性脳塞栓の既往があるAF患者で2.6%，TIAもしくは脳梗塞の既往がある患者で4.8%だった。そのうちワルファリンを再開した35例の中で，入院中のICH再発は認めなかった。抗凝固療法の再開にあたっては，ICH再発と虚血イベントそれぞれのリスクを勘案しなければならない。脳葉出血はアミロイド血管症が背景にある可能性があるため再発のリスクが高い。その他にも，高齢，高血圧，抗凝固療法の強度，血液透析，MRIの白質病変や微小出血などが，ICHの新規発症・再発の危険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ワルファリンよりもヘパリンや低分子ヘパリンの静注が安全である[49]。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，硫酸プロタミンによって速やかに中和できること，などがあげられるが，ボーラス投与は出血リスクを増加させるため推奨されない。

出血性梗塞はICHと状況が異なるが比較的よく遭遇する病態であり，多くは無症候である。出血による症状がなく是非必要であれば抗凝固療法の継続を勧める報告もあるが，梗塞のサイズ，患者の状態，抗凝固療法の適応に基づき，個々の症例ごとに判断しなければならない。

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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

表11 ガイドライン実施のための特別な手段とリスクの高い人口集団での適用に関する推奨

推　奨	クラス/エビデンスレベル
推奨の利用を向上させる目的で，ガイドラインの作成・普及の過程に，実践するための戦略を組み込むことは有用である。（新規推奨）	クラスIIa エビデンスレベルB
介入的戦略はガイドラインのコンプライアンス達成に対する経済的および地域的バリアに対処するために有用であり，また，高齢者，十分な社会的サービスを受けていない者および危険の高い人種・民族集団が医療を利用できるように改善する必要性を強調する意味でも有用と思われる。（新規推奨）	クラスIIa エビデンスレベルB

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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予想されるが，過去の経験ではそうならなかった。医療現場を変えるには，計画的な実施戦略とガイドラインの普及が一体になければならない。AHA の Get With The Guidelines（GWTG）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，脂質異常症の治療，禁煙療法の普及に改善がみられている[50]。National Institutes of Health Roadmap for Medical Research は，臨床的に有効性が認められた治療法と実際の地域社会での治療の普及率の解離に取り組んでいる。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 of the National Academy of Sciences は，予防と治療を一体化し，患者がエビデンスに基づいた医療を受けやすい体制の設立を勧めている。急性脳卒中では，ガイドライン遵守と健康面・経済面での改善を関連づけるデータはあるが，再発予防ではあまり研究されていない。

最もリスクの高い人口集団の同定と対応：疾病素因の増加や健康に対する認識が不充分であるため，脳卒中・TIA の再発のリスクが高い集団には特別な取り組みをする必要性が強調されている。高リスク集団としては高齢者，社会・経済的弱者，特殊な民族集団が確認されている。加齢は脳卒中のリスクを高め，抗凝固薬や頸動脈内膜剥離術のような治療の合併症に対して最もリスクが高い。社会・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 年の American Academy of Neurology (AAN) 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だ制限があり，これには健康保険のような個人資産の問題や非都市部における専門医・専門施設の問題が関連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 年にかけて 11％低下したが，すべての民族集団が平等に恩恵を受けているわけではない。また少数民族集団内でさえ性別による格差が残っている。黒人女性は特に肥満になりやすく，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々にとって，ガイドラインの不履行や脳卒中予防勧告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[51]。エビデンスに基づいた脳卒中予防勧告の実施，発展，最適化には，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した連邦政府との提携が必要である。（文責：福山　秀直）

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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 centrada 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 extracraneal de arterias carótidas o vertebrales. 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, hiperhomocisteinemia, estados de hipercoagulabilidad, 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 Wassertheil-Smoller, 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.**)

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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阅本指南并认证其教育内容

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 Wassertheil-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、对动脉粥样硬化性疾病的干预、对心源性栓塞的抗血栓治疗、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　栾璟煜　王春育　陈盼　李姝雅 译　刘丽萍　高山 校)

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

This guideline was approved by the American Heart Association Science Advisory and Coordinating Committee on July 13, 2010. A copy of the guideline is available at http://www.americanheart.org/presenter.jhtml?identifier3003999 by selecting either the "topic list" link or the "chronological list" link (No. KB-0102). To purchase additional reprints, call 843-216-2533 or e-mail kelle.ramsay@wolterskluwer.com.

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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 TIA 患者并不上报医疗保健中心，TIA 的真实患病率很难估计 [1]。流行病学研究帮助我们明确复发性卒中的决定因素，并与临床试验的结果一起，为降低卒中风险提供循证医学意见。值得注意的是，许多现有数据多来自于老年人、女性和不同种族的人群研究，且数量有限，目前公布的结论仍需要更多的研究予以验证。

本文的主旨是为缺血性卒中或 TIA 病史的患者预防卒中复发提供循证医学建议。建议遵循美国心脏协会 (American Heart Association，AHA) 和美国心脏病学院 (American College of Cardiology，ACC) 的疗效确定性和证据等级分类方法 (表 1 和表 2)[2]。

尽管卒中预防是关注的主要结局，但卒中或 TIA 后血管性结局亦应受到关注，包括卒中、心肌梗死 (myocardial infarction，MI) 和血管性死亡，降低血管性结局方面的证据也采用等级分类方法。本文是为有能力对缺血性卒中进行个体化病因诊断的临床医生提供建议，帮助他们选择可以降低复发性事件和其他血管性结局的治疗方法。

指南中TIA和缺血性卒中亚型的定义

TIA 是卒中的重要预警信号。TIA 发病 90 天内卒中风险高达 17%，发病一周内卒中风险最高 [3,4]。由于 TIA 和缺血性卒中的预防方法可通用，近年来二者的差别趋于弱化 [5]。TIA 和缺血性卒中发病机制相同，但因严重程度和病因不同预后可能不同。二者根据诊断评估的时间和病情程度区别定义。传统临床定义 TIA 为局灶性神经症状体征持续 <24 小时。随着现代脑影像技术的广泛应用，多达三分之一的患者症状持续 <24 小时，但影像表现仍有梗死灶 [5,6]。因此，提出了基于组织学的 TIA 定义：脑、脊髓或视网膜缺血引起的短暂性神经功能缺损，无急性脑梗死证据 [5]。值得注意的是，本指南提到的多数研究采用的是传统临床定义。不管采用哪种定义，本指南推荐意见对 TIA 和卒中患者均适用。

根据局灶性脑损伤的可能机制和血管损伤的类型和定位，缺血性卒中可分为不同类型。经典的分类方法是：大动脉粥样硬化性梗死 (颅内或颅外)、心源性脑栓塞、小血管病变、其他原因所致的缺血性卒中 (如动脉夹层分离、高凝状态或镰状红细胞病)、不明原因的缺血性卒中 [7]。根据缺血性卒中发病机制确定的分类远不如人意，显示闭塞动脉或定位栓塞来源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是本指南谈论范围；所有卒中患者至少应接受脑部影像学检查，包括计算机断层扫描 (computed tomography，CT) 或核磁共振 (magnetic resonance imaging，MRI) 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风险状况的检查，如颈动脉狭窄或心房颤动 (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]。据估计，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 [12]。

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 [13] 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)[14] 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 [10,15]。普遍缺乏明确的数据以指导急性缺血性卒中血压升高的即刻处理，推荐采用谨慎的方法，开始治疗的最佳时间尚未确定 [16]。

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 [15]。该荟萃分析包括至 2002 年进行的七个随机试验：荷兰 TIA 试验 (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

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表 1 采用的建议类型和证据水平

疗效肯定性（精确性）评价 ↓ / 疗效大小 →	Ⅰ类 获益 >>> 风险 应当实施操作 / 给予药物治疗	Ⅱa 类 获益 >> 风险 需要研究目的集中的进一步研究 实施操作 / 给予药物治疗是合理的	Ⅱb 类 获益≥风险 需要研究目的广泛的进一步研究。需要更多的登记数据 可以考虑实施操作 / 给予药物治疗	Ⅲ类 风险≥获益 由于无益并可能有害，不应实施操作 / 给予药物治疗
A 级证据 研究人群数量众多 * 数据源于多个随机临床试验或荟萃分析	■ 建议认为操作或药物治疗有用 / 有效 ■ 证据充分，源于多个随机试验或荟萃分析	■ 建议支持操作或药物治疗有用 / 有效 ■ 证据源于多个随机试验或荟萃分析，存在某些矛盾	■ 建议不能确定操作或药物治疗有用 / 有效 ■ 证据源于多个临床试验或荟萃分析，存在较大矛盾	■ 建议认为操作或药物治疗无用 / 无效，并可能有害 ■ 证据充分，源于多个临床试验或荟萃分析
B 级证据 研究人群数量有限 * 数据源于单个随机试验或某些非随机研究	■ 建议认为操作或药物治疗有用 / 有效 ■ 证据源于单个随机试验或某些非随机研究	■ 建议支持操作或药物治疗有用 / 有效 ■ 证据源于单个随机试验或某些非随机研究的证据，存在某些矛盾	■ 建议不能确定操作或药物治疗有用 / 有效 ■ 证据源于单个随机试验或某些非随机研究，存在较大矛盾	■ 建议认为操作或药物治疗无用 / 无效，并可能有害 ■ 证据源于单个随机试验或某些非随机研究
C 级证据 研究人群数量极其有限 * 仅依据专家共识意见，病例对照研究，或临床经验	■ 建议认为操作或药物治疗有用 / 有效 ■ 仅依据专家意见、病例对照研究或临床经验	■ 建议支持操作或药物治疗有用 / 有效 ■ 仅依据专家意见、病例对照研究或临床经验，其中存在分歧	■ 建议不能确定操作或药物治疗有用 / 有效 ■ 仅依据专家意见、病例对照研究或临床经验，其中存在分歧	■ 建议认为操作或药物治疗无用 / 无效，并可能有害 ■ 仅依据专家意见、病例对照研究或临床经验究
写建议采用的语句 †	应当 推荐 需要 有用 / 有效 / 有益	合理 可能有用 / 有效 / 有益 可能推荐或需要	可以考虑 可能合理 有用性 / 有效性 / 有益性未知 / 未明 / 未确定或未证实	不推荐 不需要 不应当 无用 / 无效 / 无益 可能有害

* 来自临床试验或登记的数据，不同亚人群中的有用性 / 有效性，如性别、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，仍有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

† 就一种疗法与另一种疗法比较的建议（只是Ⅰ类和Ⅱa建议、A 级和 B 级证据）来说，这些词或短语可能会附加上“优先于”或“选择…而不是…”以提示倾向性。比如，“推荐 A 疗法优先 B 疗法用于…”或“选择 A 疗法而不是 B 疗法用于…是合理的”。研究如支持使用比较动词，应当对评估的疗法或策略进行直接比较。

利，血管紧张素转化酶抑制剂 [angiotensin-converting enzyme inhibitor, ACEI])[19]；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，合用或不合用吲达帕胺)[20]，以及其他三个更小规模的试验 [21-23]。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 0.79；95% CI，0.63-0.98) 及所有的血管事件 (RR 0.79；95% CI，0.66-095)[15]。在高血压患者组或所有的患者 (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，尤其因为在这些试验中未评估 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

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表 2 AHA 建议中建议类型和证据水平的定义

建议类型	
Ⅰ类	有证据表明和 / 或普遍共识表明该措施或治疗有用、有效
Ⅱ类	关于该措施或治疗的有用性 / 有效性存在着证据冲突和 / 或意见分歧
Ⅱ a 类	大多数证据或意见支持该措施或治疗
Ⅱ b 类	有用性 / 有效性未能得到证据或意见的充分证实
Ⅲ类	有证据表明和 / 或普遍共识表明该措施或治疗无用 / 无效，而且某些情况下甚至可能有害
治疗建议	
A 级证据	资料来自于多个随机临床试验
B 级证据	资料来自于单个随机试验或非随机研究
C 级证据	专家共识、病例研究、治疗标准
诊断建议	
A 级证据	资料来自于多个采用参考标准进行盲法评价的前瞻性队列研究
B 级证据	资料来自于一个单独的 A 级研究或者一个或多个病例对照研究或者采用参考标准未进行盲法评价的的研究
C 级证据	专家共识

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 (发病频度比 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，发病频度比 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，20 332 个 90 天内发生过缺血性卒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[25]。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别 (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. **缺血性卒中或 TIA 患者，出于预防复发性卒中和预防其他血管事件的目的，推荐在发病 24 小时后开始降压 (Ⅰ类；A 级证据)。**
2. **因为有或无高血压病史的人都能获益，所以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)。**
3. **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)。**
4. **改善某些生活方式有助于降低血压，并可作为综合降压治疗的一部分 (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很有限。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)。**
5. **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、病情所需要的某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)。**

1.2 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)，

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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 [26]。空腹血糖水平≥ 126 mg/dL(7.0 mmol/L)，或糖化血红蛋白 (hemoglobin A1c，HbA_{1c}) ≥ 6.5%，或随机血糖 >200 mg/dL(11.1 mmol/L) 并伴有高血糖症状达到诊断糖尿病的范围 [26]。HbA_{1c} 水平 >7% 可认为高血糖控制不佳。饮食、运动、口服降糖药物和胰岛素被推荐用于控制血糖 [26]。

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 型糖尿病和血管病或多种危险因素的 10 251 例患者随机分为强化治疗组使 HbA_{1c} 目标值 <6%，标准组 HbA_{1c} 7%-7.9%[39]。该试验由于强化治疗组的死亡风险增加，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) 试验尚未发现心血管疾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 11 140 例患者随机分为严格控制血糖组 (目标值 $HbA_{1c} \leq 6.5\%$) 或标准血糖组 ($HbA_{1c} \leq 7\%$)[40]。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) 或非致死性卒中的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)[40]。这些试验结果表明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 HbA_{1c} 不应低于 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)[42,43]。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 或血管性死亡风险降低 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) 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 血脂

针对缺血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] 和大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]。他汀类药物对不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，目前还不是很明确 [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)[53]。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

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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 [54]。

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，随机分为阿托伐他汀 80 mg/d 组和安慰剂组 [55]。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 [55]。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的发生率无统计学差异 [55]。

由于本研究停药比例高，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)[56]。

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的发生率降低了 35%。缺血性卒中的发生率下降了 37%(HR 0.63；95% CI，0.49-0.81)，而出血性卒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)，而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 [57]。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Ⅱ级高血压 (HR 6.19；95% CI，1.47-26.11；*P*= 0.01)[58]。

全美胆固醇教育计划 (The National Cholesterol Education Program，NCEP) 专家组成人高胆固醇检测、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 (包括卒中) 风险的高脂血症患者管理的最详细指南 [59,60]。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强调减少饱和脂肪酸及胆固醇的摄入，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，抑或是药物治疗，取决于三种危险因素：(1)CHD 以及和其相当的风险 (后者包括糖尿病和症状性颈动脉疾病)；(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 [59]。既往有 CHD 病史或 CHD 危险因素，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 [59]。

既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 [61]，尽管退伍军人 HDL-C 干预试验 (Veterans Affairs HDL Intervention Trial，VA-HIT) 得出吉非贝齐可以减少男性 CHD 患者以及 HDL-C ≤ 30 mg/dL 患者的卒中发生率，但最后的数据分析却没有达到统计学意义 [62]。

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、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**

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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的一个主要的独立的危险因素[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[82-86]。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。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缺血性卒中患者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。轻中度饮酒能够降低缺血性卒中风险的机制可能与升高 HDL 水平[97,98]、减少血小板聚集[99,100]、降低血浆纤维蛋白原浓度[101,102]等有关。重度饮酒者的卒中风险发生机制包括酒精引起的高血压、高凝状态、脑血流减少以及由于心肌病引起的心房颤动或心源性栓塞[83,89,103]。另外，饮酒与胰岛素抵抗及代谢综合征相关[104]。

已明确的是，酒精可导致依赖，酒精中毒是一个重要的公众健康问题。当临床医师建议患者能够降低卒中复发风险的行为时，应该考虑到其他危险因素和饮酒的内在联系。不应当劝说不饮酒者开始饮酒。卒中二级预防基本目标，是通过已制定的筛查和咨询方法使重度饮酒者戒酒或减少饮酒[105]。

建议

1. 缺血性卒中或 TIA 患者，如为重度饮酒者，应当停止或减少酒精摄入（Ⅰ类；C 级证据）。

2. 轻到中度的酒精摄入（男性每天不超过 2 杯，非妊娠女性每天不超过 1 杯）可能是合理的；不应劝说不饮酒者开始饮酒（Ⅱb类;B级证据）。

1.6 肥胖

肥胖定义为体重指数 >30 kg/m^2，已经被认为是 CHD 及过早死亡的一个独立危险因素[106-108]。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。

1.7 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存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[125,126]、增强血管舒张能力[127]、提高糖耐量[128,129]并促进心血管健康[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]。

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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的发生率。

研究表明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、蹬健身脚踏车)，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理异常 [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]。代谢综合征通常依据 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，当以下 5 个特征中的 3 个存在时，就可以考虑为代谢综合征：腰围增大 (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 或者舒张压≥ 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)、肝糖产出增多及代偿性胰腺胰岛素分泌增多 [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 [150-155]。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%-50%[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，都还不确定 [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的应用 [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]。代谢综合征相对于它各个组成部分或者单一复合风险指数的预测值还没得到充分研究。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]。

只有一项研究报道了代谢综合征与卒中复发风险的关系。华法林阿司匹林对症状性颅内病变 (Warfarin Aspirin Symptomatic Intracranial Disease，WASID) 试验 [206] 中，随访 1.8 年中具有代谢综合征的人群更易发生卒中、MI 或血管性死亡 (HR 1.6；95% CI，1.1-2.4；*P*=0.0097)，而且单独缺血性卒中的风险也增加 (HR 1.7；95% CI，1.1-2.6；*P*=0.012)。调整代谢综合征组成部分后，卒中和复合终点的 HR 降低至没有统计学意义。此外，在对非洲裔美国人抗血小板预防卒中的研究中，肥胖和代谢综合征对幸存者危险因素影响的研究部分结果显示体重越大，患心血管疾病的风险越高 [119]。

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，降低血糖、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]。

尚无关于代谢综合征患者减轻体重、控制饮食、或体育锻炼等卒中一级预防效果的足够强有力的随机临床试验结果，尽管有几项研究正在进行 [174]。没有关于伴代谢综合征的卒中患者二级预防的随机试验。应参照无代谢综合征患者的针对不同 BP、年龄、体重、有无糖尿病、有无先前症状性血管疾病、

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LDL-C 值、HDL-C 值、肾功能以及家族史等的治疗指南，对有代谢综合征的患者进行预防性治疗，直到上述的临床试验得出结论。

建议

1. **目前，卒中后筛查代谢综合征的意义尚未证实 (Ⅱ b 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 症状性颈动脉颅外段疾病

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]) 加药物治疗和单纯的药物治疗的效果。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 stenting，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 Symptomatic 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，在 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，由围手术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 的获益不确定 [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

表 5 比较颈动脉内膜切除术和药物治疗的前瞻性试验

试验	平均随访时间	手术组 %*	药物组 %*
ECST	3 年	2.8	16.8
NASCET	2.7 年	9	26
VACS	11.9 月	7.9	25.6

ECST，欧洲颈动脉手术试验；NASCET，北美症状性颈动脉内膜切除术试验；VACS，退伍军人事务部合作研究项目。

* 致死性或非致死性同侧卒中风险。

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2 周内发生缺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 [186]。

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另一种重要治疗方法。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 (Ⅲ /Ⅳ 级充血性心力衰竭，Ⅲ /Ⅳ 级心绞痛，左冠状动脉主干疾病，两支及以上冠状动脉疾病，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，如既往颈部手术 (如颈淋巴结清扫术) 或颈部放疗、动脉内膜切除术后再狭窄、病灶在手术范围之外 (即颈内动脉 C2 段以上，锁骨以下)、对侧颈动脉闭塞、对侧声带麻痹，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价了单个支架 / 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血管成形术 (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，且给予报销。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血管成形术比较 (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)，也很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 [194,195]。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 [196]。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，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)，而 CEA 组 MI 发生率更高

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(2.3±0.6% vs 1.0±0.4%；*P*=0.08)。两组围手术期和4年事件发生风险比见表6。通过对所有患者(症状性和无症状性)进行分析，发现年龄和治疗有效性相关(*P*=0.02)。年龄<70岁的患者，CAS显示更有效，而在年龄>70岁的患者中，CEA为佳。未发现存在性别差异[197]。

2.1.3 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$^{15}O_2/H_2{}^{15}O$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，如果预计围手术期患病率和死亡率风险<6%，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，如果预计围手术期患病率和死亡率风险<6%，推荐进行CEA，取决于患者特异因素，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)。

6. 对于症状性严重狭窄(>70%)患者，当狭窄超出手术所能及、内科情况大大增加手术风险、或存在其他特殊情况，例如放射诱导的血管狭窄或CEA后再狭窄，可以考虑行CAS(Ⅱb类；B级证据)。

7. 当证实操作者的围操作期患病率和死亡率为4%-6%，与其他CEA和CAS试验观察到的相似时，在上述情况下行CAS是合理的(Ⅱa类；B级证据)。

8. 对于症状性颅外颈动脉闭塞患者，不推荐常规进行EC/IC旁路手术(Ⅲ类；A级证据)。

9. 在本指南其他地方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，推荐用于所有有颈动脉狭窄的TIA或卒中患者(Ⅰ类；B级证据)。(新建议)

2.2 颅外椎基底动脉病变

存在椎动脉近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]。一项系统综述提出症状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状性颈动脉狭窄[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确定。

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，但一些案例表明，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[203]。

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佳药物治疗的结果进行比较的随机研究只有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(加药物治疗)或者仅药物治疗，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

表6 1321例症状性患者治疗组CAS与CEA风险比较

	围手术期 HR(95% CI)	4年研究期间 HR(95% CI)
心肌梗死	0.45(0.18-1.11)	…
任何围手术期卒中或术后同侧卒中	1.74 (1.02–2.98)	1.29((0.84–1.98)
任何围手术期卒中、死亡，或术后同侧卒中	1.89 (1.11–3.21)	1.37 (0.90–2.09)
任何围手术期卒中、死亡、心肌梗死，或术后同侧卒中	1.26 (0.81–1.96)	1.08 (0.74–1.59)

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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明显差异 (*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，并且事件间期较长 (平均 92 天)[204]。需要更大规模的临床随机研究为这些患者提供循证医学的推荐，并且评估高椎基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，推荐用于所有患有椎动脉狭窄的 TIA 或卒中患者 (Ⅰ类；B 级证据)。(新建议)**
2. **颅外椎动脉狭窄患者，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 (Ⅱ b 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方法的研究中，未治疗组的自然病程较治疗组更差。在 EC/IC 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 [198,205]。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。所以这种操作已经很大程度上不再在颅内动脉狭窄的治疗中应用。

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为阿司匹林 1300 mg 或华法林组，目标国际标准化比值 (international normalized ratio，INR)2.0-3.0[206]。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) 组间没有明显差异 (华法林对比阿司匹林，HR 0.96；95% CI 0.68-1.37)，但是华法林组有更多出血事件。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，狭窄血管供血区 1 年的卒中风险是 19%[207]。多因素分析显示严重狭窄 (≥ 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 Intra-Craniennes Atheromateuses symptomatiques，GESICA)[208] 中，对 102 例有症状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”。如果狭窄被视为血流动力学症状，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，在技术方面的成功使该操作得以开展。Wingspan 支架 (波士顿科学公司) 已被批准用于临床，通过了 FDA 伦理审批，可以改善有颅内动脉粥样硬化疾病并对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。虽然有观点认为动脉血压的下降可能降低脑灌注从而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)[222,223]。总胆固醇低于

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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. **对由于颅内大动脉狭窄 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. **对由于颅内大动脉狭窄 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. **对由于颅内大动脉狭窄 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，需要继续研究 (Ⅱ b 类；C 级证据)。(新建议)**
4. **对由于颅内大动脉狭窄 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，约半数为非瓣膜病性心房颤动，1/4 为瓣膜性心脏病，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 万以上的美国人患有心房颤动，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、糖尿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。

在华法林与安慰剂对比的多项一级预防临床试验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 [225]。应用华法林使卒中的相对危险下降 68%(95% CI，50%-79%)，华法林规范治疗组年卒中发生率为 1.4%，而对照组为 4.5%。也就是说每规范化治疗 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，INR 值需控制在 2.0 至 3.0 之间。一项大型病例对照研究 [226] 和两项随机研究 [227,228] 结果显示：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，尽管仍抗凝治疗，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，而且高 INR 值增加出血风险。

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的数据还很稀缺 [230]。氯吡格雷和厄贝沙坦预防房颤心血管事件 (Atrial Fibrillation 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减少，接受联合用药的患者中 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 0.97；

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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，基于难于鉴别患者是否适合抗凝治疗，以及考虑到抗凝治疗伴随的血管事件和严重出血风险，阿司匹林始终还是具有明确抗凝治疗禁忌证但能耐受抗血小板治疗心房颤动患者的首选治疗方案。

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 或小卒中的患者，抗凝药物较阿司匹林优越。因此，除非存在明确禁忌证，新近发生 TIA 或小卒中的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 [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。

华法林可与许多食物和药物产生相互作用，而且治疗谱窄，这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和凝血因子 X 抑制剂。通过新型凝血酶直接抑制剂达比加群酯长期抗凝治疗的随机评价研究 (Randomized Evaluation of Long-Term Anticoagulation Therapy study，RE-LY)[235]，达比加群被认为是目前最成功的抗凝替代药物。超过 18 000 例心房颤动患者参加了该项试验，研究结果显示达比加群组 (150 mg，每日两次) 与华法林组相比更能降低卒中和全身栓塞事件的发生 (1.69% vs 1.11%；RR 0.66 [0.53-0.82]；*P*<0.001)，同时其发生大出血的风险与华法林组相近。除了略微增加急性 MI 发生率外 (0.53%/ 年 vs 0.74%/ 年)，服用达比加群无其他安全问题。因为尚未通过评审和审批，该药在本版指南中不做推荐。应用这种不与食品药品发生相互反应，且不需要监测凝血的高效口服抗凝药物，对心房颤动患者来说无疑是意义重大的。

另一个预防心房颤动患者卒中的替代策略是经皮植入装置封堵左心耳。WATCHMAN 左心耳封闭系统用于心房颤动患者栓塞预防 (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation，PROTECT AF) 试验 [236] 表明，心房颤动患者植入封堵器是可行的并且有可能降低卒中发生率，在这一试验中，707 例有华法林适应证的心房颤动患者随机分配至封堵治疗组 (n=463) 和华法林治疗组 (n=244)。成功置入封堵器的患者常规服用华法林 45 天。两组的主要有效率 (包括出血或缺血性卒中、心血管死亡或不能解释的死亡及全身性栓塞) 均较低，满足了该研究的既定非劣效性准则。围手术期最常见并发症是严重的心包积液，出现于 22 例患者中 (5%；15 例经心包穿刺术治疗，7 例经手术治疗)，5 例患者 (1%) 出现了因不当操作导致的缺血性卒中，3 例患者出现器械导致的栓塞。左心耳封闭这一方法可能对不适合口服抗凝药物的高卒中风险心房颤动患者有重要临床意义，但是，在这一方法获得推荐前，尚需要更多有关这类患病群体的数据。

现有资料不能表明在心源性卒中的急性药物治疗方面，抗凝药物比抗血小板药物更加有效 [237]。需要更多的研究以阐明具有反复发生卒中的高风险亚组患者是否可通过急性抗凝药获益 (例如通过经食道超声证实存在左心耳附壁血栓的心房颤动患者)。

目前尚无数据资料研究心房颤动患者卒中或 TIA 发作后开始服用抗凝药物的最佳时间。在 EAFT 试验 [233] 中，约一半心房颤动合并小卒中或 TIA 的患者在出现症状后 14 天开始口服抗凝药物。然而，对于存在大面积梗死、严重出血转化及未得到控制的高血压的患者来说，可适当延迟用药。

尽管对于发生缺血性卒中或 TIA 的心房颤动患者应使用抗凝治疗，但没有数据表明增加抗凝强度或联合应用抗血小板药物可对未来缺血性卒中事件提供额外保护。而且这些措施都与出血风险的增加相关。例如，口服凝血酶抑制剂预防卒中试验 (Stroke Prevention using an ORal Thrombin inhibitor in Atrial Fibrillation study，SPORTIF) 中，既往有卒中史或 TIA、并接受过阿司匹林和华法林联合治疗的心房颤动患者，存在相当高的严重出血的风险 (华法林：1.5%/ 年，华法林联合阿司匹林：4.95%/ 年；*P*=0.004)，同时缺血性事件没有减少 [234]。高 INR 值与出血风险的增加明显相关；当 INR 值 >4.0 时，脑出血的风险极大地增加 [229]。

当既往有卒中史或 TIA 的心房颤动患者暂时中断口服抗凝药物时，患卒中的风险增加 (一般用于外科手术)。在这些情况下，是否逐渐改用静脉肝素或低分子肝素 (low-molecular-weight heparin，LMWH) 治疗，这个问题很复杂而且最近被重新考虑 [238]。一般而言，对评估为具有特别高风险 (3 个月内卒中或

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TIA，$CHADS_2$* 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)[238]。

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最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)。

*$CHADS_2$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)**
4. **对于具有较高卒中风险 (3 个月内卒中或 TIA，$CHADS_2$ 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 (Ⅱ a 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 [224,240-243]。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 [242,244,245]，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，与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，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心室栓子和脑栓塞的关系 [247-250]。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血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，但是其他的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血药物治疗的患者中，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初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。

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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 (Ⅱ b 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 (Ⅱ b 类；B 级证据)。

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系统栓塞的风险 [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。基于来自相似患者的外推发现，联合治疗明显地增加了出血风险 [268,269]。

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)[271-275]。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 [278] 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非风湿性病因。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左心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的一个强有力的风险因子 [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)(Ⅱ a 类；C 级证据)。

2. 为避免额外出血风险，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 (Ⅱ b 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 (Ⅱ b 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 (Ⅱ b 类；C 级证据)。

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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 [287]。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 8%-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聚集药物。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，与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 [290]。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又不能解释的缺血性卒中或 TIA 患者，建议口服抗凝药治疗 (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 (Ⅱ a 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)(Ⅱ b 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)的抗栓治疗

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]。在应用阿司匹林防治继发性卒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]，但研究显示治疗收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，每年发生严重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的风险小，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 [300-302]。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 [302]。在平均 2 年的随访中，应用噻氯吡啶治疗的患者发生终点事件较少 (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及 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

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异性。噻氯吡啶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，应用噻氯吡啶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。晚于阿司匹林、联合应用阿司匹林 / 双嘧达莫及噻氯吡啶等方案，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较 [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。目前尚没有比较氯吡格雷与安慰剂在卒中二级预防中的作用 [305]。

缺血性事件高危患者氯吡格雷与阿司匹林 (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events，CAPRIE) 试验 [298] 比较了氯吡格雷与阿司匹林的效果。超过 19 000 例患有卒中、MI 或周围血管疾病的患者被随机地分配到阿司匹林 325 mg/d 或氯吡格雷 75 mg/d 组中，氯吡格雷组发生卒中、MI 或血管性死亡的几率为 5.32%，而阿司匹林组为 5.83%(RRR 8.7%；95% CI，0.3%-16.5%；*P*=0.043)。值得注意的是，在对发生卒中后加入 CAPRIE 的亚组患者的分析中，氯吡格雷组卒中、MI 或血管性死亡的年发生率为 7.15%，而阿司匹林组为 7.71%(RRR 7.3%；95% CI，–6%-19%；*P*=0.26)，差异没有达到统计学意义。但 CAPRIE 没有被设计来确定在卒中患者中，应用氯吡格雷与阿司匹林的效果是否相当。在非劣性研究的 PRoFESS 试验中，比较了氯吡格雷与联合应用阿司匹林和双嘧达莫缓释片的效果。20 332 例缺血性卒中患者平均随访 2.5 年，阿司匹林 / 双嘧达莫组卒中复发率为 9.0%，氯吡格雷组为 8.8%(HR 1.01；95% CI，0.92-1.11)。由于可信区间上限与非劣性边缘交叉 (HR 1.075)，得出结论该研究结果不能证实阿司匹林 / 双嘧达莫疗效不次于氯吡格雷。

总体来讲，氯吡格雷的安全性与阿司匹林比较只有很小的差别 [298]。与噻氯吡啶一样，腹泻和皮疹的发生比阿司匹林常见，但其它胃肠道症状和出血相对少见。已发表的研究显示，氯吡格雷组中性粒细胞减少症的发生并不多于阿司匹林组或安慰剂组 [298,306]，但有少数血栓性血小板减少性紫癜的报道 [303]。最近，有证据表明质子泵抑制剂 (proton pump inhibitors，PPIs)，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，如果 PPI 是在 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，携带至少 1 个 CYP2C19 功能降低等位基因可使血浆氯吡格雷活性代谢产物相对减少 32% (*P*<0.001)[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 / 阿司匹林合剂对 TIA/ 卒中患者的疗效，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，ESPS-1)[310]，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，析因设计将 6602 例卒中 /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 [311]。与安慰剂组对比，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)。与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读变得复杂。

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，比较新近 6 个月内 TIA/ 缺血性卒中患者应用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]。虽然阿司匹林治疗剂量

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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% 服用缓释剂型，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)。在这项公开试验中，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，研究者没有报到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。

第四项试验是前面提到的 PRoFESS 研究 [304]，研究显示氯吡格雷组和双嘧达莫 / 阿司匹林联合治疗组卒中复发率没有差别。严重出血事件在阿司匹林 / 缓释双嘧达莫组较常见 (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 / 缓释双嘧达莫组较常见 (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 [313]。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 [314,315] 中进行了比较，均未证实联合用药的获益。氯吡格雷用于高动脉粥样硬化血栓形成风险和稳定、处理和避免缺血 (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization，Management，and Avoidance，CHARISMA) 的试验 [315] 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、卒中或心血管性死亡) 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 [314] 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 / 双嘧达莫联用、噻氯吡啶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研究，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同于它们中任何一个。CAPRIE 和 PRoFESS 的生存曲线观察表明：阿司匹林和阿司匹林 / 双嘧达莫联用可能是同等有效的。

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 [311] 和卒中、MI、死亡或大量出血联合终点 [312] 的发生。平均而言，与单独服用阿司匹林相比，联合用药 1 年中能预防 100 个治疗患者中的 1 个发生脑血管意外 [312]。在二级预防中，噻氯匹啶可能比阿司匹林更有效 [301]，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 [298,304]。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 [304]。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。噻氯吡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。

可能会影响药物选择的患者特征包括特定药物耐受程度和合并的疾病。对于不能耐受过敏或胃肠道副作用的患者，选择氯吡格雷较合适。对于不能

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耐受双嘧达莫所致头痛的患者，选择阿司匹林或氯吡格雷比较合适。对于急性冠脉综合征[306]或近期计划血管支架患者[306,316]选择联合应用阿司匹林和氯吡格雷较合适。

4.1.7 治疗过程中出现卒中的患者抗血小板药物选择

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 口服抗凝剂

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卒中患者卒中复发，包括颅外大动脉或脑动脉粥样硬化性卒中、小穿支动脉病变及不明原因梗死。可逆性缺血的卒中预防研究 (The Stroke Prevention in Reversible Ischemia Trial，SPIRIT) 被早期停止，因为在 1316 例患者中口服高剂量抗凝剂 (INR 3.0-4.5) 与阿司匹林 (30 mg/d) 相比出血风险增加[317,318]。ESPRIT 试验比较了中等剂量华法林 (INR 2.0-3.0) 与单用阿司匹林 (30 mg-325 mg/d) 或阿司匹林联用双嘧达莫缓释片 200 mg 每日两次。因为联合用药的效果优于单独服用阿司匹林，所以此实验也早期就停止了[312]。该研究平均随访时间是 4.6 年，平均 INR 为 2.57。华法林与单用阿司匹林相比，出血风险显著增高 (HR 2.56；95% CI，1.48-4.43)，缺血事件发生概率虽然较低 (HR 0.73；95% CI，0.52-1.01)，但没有达到统计学意义。

ESPRIT 结果证实了华法林阿司匹林复发性卒中研究 (Warfarin Aspirin Recurrent Stroke Study，WARSS) 之前的研究结果[320]，WARSS 是随机、双盲、多中心研究，在 2206 例非心源性卒中患者中比较了华法林 (INR 1.4-2.8) 与阿司匹林 (325 mg/d) 的效果。并没有发现两种药物对预防卒中复发或死亡方面的差异 (华法林：17.8%；阿司匹林：16.0%)。与 ESPRIT 相反，华法林组和阿司匹林组的大出血的概率也没有明显差异 (每年分别是 2.2% 和 1.5%)。通过亚群分析，显示在包括大动脉粥样硬化和不明原因的卒中亚型中，没有明显的功效差异。

新药

至少三种其它抗血小板药物最近正在进行二级预防作用的研究，包括三氟柳、西洛他唑、沙格雷酯[321-323]。一项最近的非劣性研究未能证明沙格雷酯的疗效不差于阿司匹林[321]。对三氟柳只有一项前导性研究[323]。西洛他唑已被 FDA 批准用于间歇性跛行的治疗，作为卒中的治疗方法还需进一步的研究。最近一个随机的、双盲的研究比较了西洛他唑 (剂量不详) 与阿司匹林 (剂量不详) 的疗效，它纳入了 720 例近期发生过缺血性卒中的患者[322]。在 12-18 个月的随访中发现，阿司匹林组与西洛他唑组每年卒中复发的比例是 5.27:3.26 (*P*=0.18)。除了出血外，头痛、眩晕、心动过速在西洛他唑组中更常见。因此，目前为止，这些新药没有一个被 FDA 批准用于预防卒中复发。

建议

1. **对于非心源性栓塞性缺血性卒中或 TIA 患者，推荐使用抗血小板药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)。**
2. **单用阿司匹林 (50 mg/d-325 mg/d)(Ⅰ类；A 级证据)、阿司匹林 25 mg/ 缓释双嘧达莫 200 mg 联用，每日两次 (Ⅰ类；B 级证据) 和单用氯吡格雷 75 mg(Ⅱa 类；B 级证据)，均可作为基本治疗方案。选择抗血小板药物应当个体化，基于患者的危险因素、经济情况、耐受性及其他临床特征进行选择。**
3. **在氯吡格雷基础上联用阿司匹林增加出血风险，不推荐在缺血性卒中或 TIA 后二级预防中常规使用 (Ⅲ类；A 级证据)。**
4. **对于对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)。**
5. **对于在服用阿司匹林期间发生缺血性卒中的患者，没有证据表明增加阿司匹林剂量能够额外获益。尽管通常会考虑更换抗血小板药物，目前尚无针对在服用阿司匹林期间发生缺血事件的患者的单药或联合用药研究 (Ⅱb 类；C 级证据)。**

5. 对存在其他特殊情况的卒中患者的治疗

5.1 *动脉夹层*

颈动脉和椎动脉夹层是导致 TIA 和卒中的相对常见的原因，尤其是在年轻患者当中。严重的头颈部创伤可能导致动脉夹层，但是有大约一半是自发性的或由轻微的损伤所致[324]。许多结缔组织病都可能是自发夹层的危险因素，包括肌纤维发育不全、马凡氏综合征、Ehlers-Danlos 综合征 (IV 型)、成骨不全症和胶原形成异常基因病等[325-327]。目前，对

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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常常是诊断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 也经常用于颅外夹层的诊断 [328]。动脉夹层相关的缺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 [328-330]，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 [331]。本指南不对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，特别是在卒中风险最大的血管损伤后最初几天内 [332,334-337]，给予肝素或低分子肝素抗凝治疗是很久之前就有的推荐建议 [332-334]。尚无支持特定抗栓疗法的对照试验。一项包括 26 项病例观察研究 (327 例颈动脉夹层患者) 的 Cochrane 系统回顾显示，抗血小板和抗凝治疗的死亡率和残疾率没有明显差异 (抗血小板治疗：23.7%；抗凝治疗：14.3%；优势比 [odds ratio，OR] 1.94；95% CI，0.76-4.91)[338]。抗凝治疗、抗血小板治疗和未治疗患者卒中复发率分别为 1.7%、3.8% 和 3.3%。另一项包括 34 项病例观察 (762 例颈动脉或椎动脉夹层患者) 的系统回顾显示抗血小板治疗和抗凝治疗在死亡 (抗血小板治疗：1.8%；抗凝治疗：1.8%；*P*=0.88)、卒中 (抗血小板治疗：1.9%；抗凝治疗：2.0%；*P*=0.66) 及卒中和死亡总风险方面均没有明显差异 [339]。这些对小型研究进行的回顾易受发表偏倚影响。有两项大型研究分别对 432 例颈动脉或椎动脉夹层患者进行了回顾性队列研究 [340] 和对 298 例颈动脉夹层患者进行了前瞻性队列研究 [341]，显示动脉夹层继发卒中的风险较低：3-12 个月内为 0.3%。随后一项对抗血小板和抗凝治疗非随机对照的研究也显示两组的卒中复发的风险没有显著差异 (0.5% vs 1%，*P*=1.0)，两种干预措施的出血主要事件发生率都高于卒中复发率 (2% vs 1%)。这些观察数据显示抗血小板治疗和抗凝治疗继发性卒中的风险相当，但前者似乎更安全。一项对这些治疗方法的随机对照试验正在英国进行。

夹层常随时间愈合，患者通常维持抗栓治疗至少 3-6 个月。治疗持续时间并不确定，一些作者建议进行改变治疗方法前行影像学检查确定血管是否再通的研究 [336,342,343]。大部分患者可血管再通并达到解剖学愈合 [344]。没有完全愈合的夹层并不增加卒中复发的风险 [340,345]。夹层动脉瘤可能一直持续存在，但继发性卒中或破裂风险并不高，因此通常不进行积极干预 [345]。

尽管大部分夹层造成的缺血性卒中是早期血栓栓塞的结果，但小部分是由于血流动力学不足引起 [346,347]。这些情况预后可能较差，尽管目前还没有前瞻性研究，但需要考虑血流重建如支架或搭桥手术 [346,348-350]。

许多专家建议颈动脉夹层患者应避免导致颈部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 [351]，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 (Ⅱ 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 患者的相对有效性未知 (Ⅱ b 类；B 级证据)。(新建议)。**
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明确的复发脑缺血事件，可以考虑血管内治疗 (支架)(Ⅱ b 类；C 级证据)。**
4. **有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

右向左分流脑栓塞病因包括卵圆孔未闭 (patent foramen ovale，PFO) 和肺动 - 静脉畸形。卵圆孔未闭是房间隔的胚胎性的缺损，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数据 [352,353] 和纽约北曼哈顿研究 (Northern Manhattan Study，NOMAS)[354]，成人 PFO 的发生率多达 15%-25%。孤立的房间隔动脉瘤发生率约为 2%-3%，远远低于 PFO[352-354]。

2000 年发表的 Overell 等人 [355] 的荟萃分析断定 PFO 和房间隔动脉瘤会显著增加小于 55 岁的患者的卒中风险。对于 55 岁以上的患者，数据的说服力不

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够但也显示会增加卒中风险：PFO OR=1.27(95% CI，0.8-2.01)，房间隔动脉瘤 OR=3.43(95% CI，1.86-6.22)，同时患有 PFO 和房间隔动脉瘤 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 或房间隔动脉瘤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)，房间隔动脉瘤 OR=6.14(95% CI，2.47-15.22)，PFO 伴房间隔动脉瘤 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 [355]，但有两项研究对推荐提供了极其重要的信息，在此对其进行总结。WARSS 的子研究——隐源性卒中 PFO 研究 (The Patent Foramen Ovale in Cryptogenic Stroke，PICSS) 为 PFO 和房间隔动脉瘤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，卒中复发率在 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瘤对预后也无明显影响。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，但是其子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 年后的卒中复发率。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 及房间隔动脉瘤的患者和无心脏病变患者 4 年时卒中复发率分别为 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瘤的意义及其最佳治疗方法仍是未知 [357]。目前有三项关于 PFO 患者首发卒中风险的大型前瞻性研究也对 PFO 和卒中风险之间的关系提出了怀疑 [13,252,352,354]。

最近，Handke 等 [358] 的研究连续入组了 503 例卒中患者，其中 227 例患者的卒中病因不明，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 合并房间隔动脉瘤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，患者的卒中复发率较低 (5.8%)，且与分流的程度无关 [359]。

在上述研究之后，PFO 合并 / 不合并房间隔动脉瘤对于卒中首发或复发的意义仍未可知。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 [360-370]。一项研究发现，基线时发生 1 次或 1 次以上卒中的患者可有明显获益 [370]。

总而言之，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，目前尚没有长期的随访信息。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，前者的预后较好 [361,362,370]。Windecker 等报道，在 44 例接受药物治疗的 PFO 患者中，3 年内出现不良事件的发生率高达 33.2%，而在 59 例接受 PFO 封堵手术的患者中，其 3 年内出现不良事件的发生率仅为 7.3%[370]。但三项非随机对比的研究却没有发现接受封堵手术的患者卒中率显著降低。目前缺少封堵手术与单独药物治疗对比的试验，因此有关随机临床试验是很有必要的。2009 年来自于 AHA/ASA/ACC 的一项声明强烈鼓励所有与治疗病因不明的卒中以及 PFO 有关的临床医生，包括心内科、神经内科、内科、放射科以及外科医生，都要积极参与这些有标志性意义的临床试验，促进实验的完成，帮助确定最佳治疗方案 [371]。

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 (Ⅱ a 类；B 级证据)。**
2. **尚无充分证据能够证实在 PFO 患者卒中二级预防中抗凝治疗与阿司匹林疗效相同或优于阿司匹林 (Ⅱ b 类；B 级证据)。(新建议)**
3. **尚无对有 PFO 的卒中患者进行 PFO 封堵术的充分证据 (Ⅱ b 类；C 级证据)。**

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5.3 高Hcy血症

队列及病例对照研究中证实，伴有高 Hcy 血症的患者其卒中发生率的风险将增加两倍 [372-377]。在一项荟萃分析的临床试验中，发现叶酸补充能降低 18%(RR 0.82；95% CI，0.68-1.00；*P*=0.045) 的卒中发生风险 [378]。给予叶酸治疗超过 36 个月并将 Hcy 降低≥ 20% 的患者与未补充叶酸的患者相比，能更好的预防卒中。尽管如此，对心血管疾病或卒中二级预防的临床试验并没有发现补充维生素降低血 Hcy 能够获益。心脏结局预防评估 (Heart Outcomes Prevention Evaluation，HOPE-2) 试验是一项随机、安慰剂对照试验，共入组 5522 例年龄大于 55 岁且伴有血管疾病或糖尿病的患者，患者分为维生素 (2.5 mg 叶酸，50 mg 维生素 B6，2 mg 维生素 B12) 降低 Hcy 治疗组或安慰剂组，分组时不考虑基线 Hcy 水平。大约有 12% 的患者有 TIA 或卒中 [379]。随访 5 年，主要复合终点是心血管性死亡、MI 和卒中。结果显示维生素治疗不能减少主要终点事件，但能降低卒中的风险 (4.0% vs 5.3%；RR 0.75；95% CI，0.59-0.97；*P*=0.03)。维生素预防卒中 (The Vitamin Intervention for Stroke Prevention，VISP) 研究将 Hcy 轻中度升高的非心源性卒中患者 (男性，Hcy>9.5 μ mol/L; 女性，Hcy ≥ 8.5 μ mol/L) 随机分为维生素高剂量治疗组和低剂量治疗组 (如，叶酸、维生素 B6 或维生素 B12)[380]，治疗 2 年后结果显示卒中的风险与 Hcy 的水平相关；高剂量维生素组 Hcy 水平的平均降低幅度较大，但卒中发生率却并无减少。高剂量组和低剂量组，2 年内卒中发生率分别为 9.2% 和 8.8%。目前，尚无临床证据支持高剂量维生素治疗对轻到中度高 Hcy 血症患者有益。

建议

1. 尽管补充叶酸能够降低 Hcy 水平，并可以考虑在有高 Hcy 血症的缺血性卒中患者中使用 (Ⅱ b 类 ;B 级证据)，但尚无证据表明降低 Hcy 水平能够预防卒中复发。

5.4 高凝状态

5.4.1 遗传性易栓症

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。

遗传性易栓症 (如，蛋白 C、蛋白 S 或者抗凝血酶Ⅲ缺乏；V Leiden 因子；或者凝血因子 G20210A 突变) 和亚甲基四氢叶酸还原酶 (methylenetetrahydrofolate reductase，MTHFR)C677T 突变在成人卒中罕见，但却是儿童卒中的重要原因 [381,382]。最常见的遗传性凝血功能障碍是由于 V 因子基因突变 (最常见的是 V Leiden 因子突变，Arg506Gln) 所致的活化蛋白 C(activated protein，APC) 抵抗。APC 抵抗多导致静脉血栓，与卒中的联系仅见于病例报道 [383-385]，APC 抵抗所致卒中在成人中少见，而在儿童中更多 [225,386]。凝血因子基因 (PT G20210A) 中 V Leiden 因子 (factor V Leiden，FVL) 与 G20210A 的多态性同样与静脉血栓形成相关，但他们对于缺血性卒中的作用机制仍存在争议 [377,387-398]。

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，但在有血管病危险因素的老年患者中，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。在一项小样本量的对 <50 岁、病因不明的卒中患者的研究中显示，PT G20210A 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、PT G20210A 或者 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 PT G20210A 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)、PT G20210A(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、PT G20210A、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，PT G20210A(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

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主要与高 Hcy 相关。与最常见的等位基因对比，纯合突变 (TT) 卒中 OR 值为 1.26(95% CI，1.14-1.40)[401]。所以，尽管遗传性易栓症基因突变与卒中有着微弱相关性，在相对年轻人群中可能更大，但关于卒中风险的机制 (如反常的静脉血栓栓塞)、基因 - 环境相互作用的影响以及预防卒中的最佳策略仍然存在很大疑问。

静脉血栓形成后选择长期还是短期抗凝治疗要视临床及血液循环情况而定 [403,404]。虽然对于获得性高凝状态，如蛋白 C、蛋白 S 和抗凝血酶Ⅲ (AT Ⅲ) 缺乏、肝素诱导的血小板减少症、弥散性血管内凝血或肿瘤相关性血栓形成，已经有指南推荐了总体治疗原则，但是没有针对卒中二级预防制定具体措施 [405-408]。

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. **应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 (Ⅱ a 类；C 级证据)。**
3. **有自发性脑静脉血栓形成和 / 或复发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 (Ⅱ a 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流产 [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) 中最显著 [412,413]。在 APL 抗体卒中研究 (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 [414]。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]。但是在老年人群中 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 阳性和阴性患者总体卒中复发事件的发生率分别为 22.2% 和 21.8%。狼疮抗凝物和心磷脂抗体均阳性的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 (Ⅱ a 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 (Ⅱ a 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的 SCD 患者 (年龄≥ 20 岁)，卒中复发率达每年 1.6/100 人 [423]，而且大多发生在首次卒中后几年内 [423,424]。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]，严重贫血 (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)[423,425]，2 周内有急性胸痛综合征史 (胸部 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)[423]，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

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加 (卒中组 20.79×10^9/L vs 非卒中组 17.21×10^9/L ; *P*<0.05)[425]，夜间低氧血症 (HR，平均 Sao_2<96%，5.6 ; 95% CI，1.8-16.9 ; *P*=0.0026)[426]，收缩压升高 (每升高 10 mmHg，RR 值 1.31 ; 95% CI，1.03-1.67 ; *P*=0.33)[423,424]。

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 [429] 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]，反映高凝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栓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 和经颅多普勒 (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 [433]。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 [13] 及治疗声明中对其进行了总结 [435]。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值是输血前血红蛋白 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，SWiTCH) 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。从血液病学的角度看，对一小部分有适合供体并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临床和亚临床梗死均能起到抑制作用 [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，不建议额外加用其中任何一种药。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 (Ⅱ a 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 (Ⅱ b 类 ; C 级证据)。**

5.6 脑静脉窦血栓

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]。

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尽管目前仅有两项相关的对照试验，但早期的抗凝治疗通常被认为既是对 CVT 的治疗也是早期二级预防措施 [449,450]。第一项试验对剂量调整的普通肝素 (部分凝血活酶时间至少为对照的两倍) 和安慰剂进行了比较。因为肝素治疗明显优越 (P<0.01)，这项研究在仅仅 20 例患者入组后便提前终止了。10 例随机分到肝素治疗组的患者中，8 例完全康复，其他 2 例仅有轻微的神经系统损害。在安慰剂组，只有 1 例患者完全康复，3 例患者死亡 [449]。这个研究小组还报道了一项对 43 例伴有颅内出血的 CVT 患者的回顾性研究，其中 27 例患者用剂量调整的肝素治疗。肝素治疗组的死亡率显著低于非抗凝治疗组 [449]。

一项更近的而且规模略大的 CVT 的随机研究 (n=59) 对低分子量肝素 (90 抗 Xa U/kg，一天两次) 和安慰剂进行了比较 [450]。随访 3 个月后，抗凝治疗组和安慰剂组结局不良的比例分别为 13% 和 21%(RRR，38% ; P=NS)。低分子肝素组有 2 例患者死亡，而安慰剂组有 4 例患者死亡。伴有颅内出血的患者也纳入研究，两个组中都没有新的症状性脑出血发生。

对这两个试验进行 Cochrane 荟萃分析，抗凝治疗的死亡合并 RR 为 0.33(95% CI，0.08-1.21)，死亡或残疾的 RR 为 0.46(95% CI，0.16-1.31)。抗凝治疗有 1 例胃肠道大出血。2 例对照组患者 (安慰剂组) 诊断为可能的肺栓塞 (其中 1 例死亡)[451]。基于这两个试验，在 CVT 的情况下推荐立即应用肝素或低分子量肝素进行抗凝治疗，无论是否出现出血转化。

目前还没有随机试验数据来指导抗凝治疗的持续时间。对于初发静脉窦血栓患者，持续治疗 3 个月到 12 个月都有报道。有遗传性血栓形成倾向的患者通常比有短暂 (可逆的) 危险因素如口服避孕药的患者抗凝治疗的时间更长。由于目前没有关于 CVT 患者抗凝治疗持续时间的数据，因此遵循为颅外 DVT 患者制定的指南是合理的，包括对有短暂危险因素的患者初次 DVT 抗凝治疗 3 个月，对无原因的初次 DVT 抗凝治疗至少 3 个月，对无原因的再发 DVT 患者抗凝治疗则无明显期限 [452]。通常在华法林治疗结束后给予无明显期限的抗血小板治疗。

由于妊娠相关的 CVT 比例占 15% 到 31%[453]，再次妊娠时也可能 CVT 复发。有对 63 例有 CVT 史的妊娠女性 (其中 21 例是妊娠相关 CVT) 的报道显示，这些患者均正常分娩并且没有 CVT 的复发。尽管这表明再次妊娠并不是一个绝对禁忌证，但因为可用的数据不足，再次妊娠的决定必须个体化 [454]。

建议

1. **对于急性 CVT 患者，抗凝治疗可能有效 (Ⅱ a 类 ; B 级证据)。**
2. **鉴于尚无试验数据能够确定急性 CVT 进行抗凝治疗的最佳疗程，给予抗凝药物至少 3 个月，随后进行抗血小板治疗是合理的 (Ⅱ a 类；C 级证据)。**

5.7 Fabry病

Fabry 病是一种罕见的 X- 连锁遗传疾病，由于溶酶体酶 α- 半乳糖苷酶缺陷引起脂质在血管内皮沉积并导致脑、心、皮肤和肾的进行性血管病变。卒中的机制可能是椎动脉和基底动脉延长扩张、心源性栓塞或小血管闭塞 [455-457]。没有诊断出来的 Fabry 病可能是年轻患者隐源性卒中的一个原因 [458]。抗血小板药物被认为可以降低此类患者卒中的风险 [458]，但疾病本身是无法医治的，而且在重组 α- 半乳糖苷酶 A 可利用之前预后很差。在随机对照试验中，每 2 周静脉输注 1 mg/kg 的 α- 半乳糖苷酶减少了肾、心脏和皮肤微血管内皮上新的沉积物 [459] 并能清除旧的沉积物，适度降低了肾、心、脑血管事件或死亡 (HR 0.47 ; 95% CI，0.21-1.03)[460]。酶替代治疗还能改善肾脏功能 [460,461]，但对心功能的影响还没有统一的结论 [462,463]。酶替代治疗能改善脑血流 [464]，但卒中的风险看起来仍然很高 [465]。早期介入治疗或高剂量酶治疗或是两者联合对卒中的预防可能是必要的，此领域研究非常活跃 [466]。输注重组 α- 半乳糖苷酶 A 的主要副作用是发热和寒战，发生率 25%-50%，可以通过降低输注速率和输注前应用对乙酰氨基酚和安泰乐来减少这些副作用。一个专家组推荐对所有男性患者从 16 岁开始酶替代治疗，对所有其他有症状或器官受累的患者进行酶替代治疗 [467]。

建议

1. **对于有 Fabry 病的缺血性卒中或 TIA 患者，推荐进行 α- 半乳糖苷酶替代疗法 (Ⅰ类 ; B 级证据)。(新建议)**
2. **本指南其他部分的卒中二级预防措施也适用于有 Fabry 病的缺血性卒中或 TIA 患者 (Ⅰ类；C 级证据)。(新建议)**

6. 女性卒中

6.1 妊娠

孕期、分娩时或产后都可能发生卒中。妊娠相

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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 [468-470]。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 [471]。

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。由于华法林可以通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 [471]。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 [472]。

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 [473]。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，在妊娠 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 [474]。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 [475]。妊娠前 3 个月是否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 [476]。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如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，根据部分凝血活酶时间 (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 (Ⅱ b 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 (Ⅱ b 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 [477]。雌激素治疗组发生致死性卒中的风险更高 (HR 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 [478]。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)[479.480]。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)[480]。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，有时候要掌握利用好“时机窗”[481]。尽管如此，观察性研究及 WHI 临床研究均未证实这一假

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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 [482]。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)(Ⅲ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 小时会出现血肿扩大 [486]，如果患者使用抗凝剂，血肿扩大的时间还会延长 [487]。这种血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 升高与血肿扩大有关 [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，优于应用新鲜冰冻血浆，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。

高危患者中断抗凝治疗的最佳持续时间尚未确定。一些病例系列研究对中断抗凝治疗的患者随访数天到数周，发现很少有缺血性卒中发生。一项对 35 例出血患者停用华法林后随访 19 天的研究没有发现复发的缺血事件 [485]。在一项 141 例服用华法林期间发生脑出血的患者的研究中，逆转华法林作用并停用华法林 10 天，30 天后缺血性事件的风险为 2.1%。停用华法林后缺血性卒中风险在人工瓣膜的患者中是 2.9%，在心房颤动或有过栓塞卒中病史的患者中是 2.6%，在有过 TIA 或缺血性卒中的患者中是 4.8%[493]。35 例重新应用华法林的患者在住院期间均未出现新的脑出血 [493]。另一项对 28 例人工瓣膜患者的研究发现，平均中断抗凝治疗 15 天内没有出现栓塞事件 [494]。一项对 35 例脑出血或脊髓出血患者的研究报道，14 例人工瓣膜的患者在停止抗凝后 7 天均未复发缺血事件 [485]。一项对 100 例脑动脉瘤手术治疗后患者的研究发现，14% 的患者有术后 DVT 的证据。这些患者接受系统性抗凝治疗没有发生任何出血并发症 [495]。

脑出血后抗栓治疗的决策需要评估脑出血复发和缺血的相对风险。最近的一项大型研究纳入了 768 例脑出血患者，随访 8 年发现第一年颅内出血复发比缺血风险更高 (2.1% vs 1.3%)，但一年后两者间无差别 (1.2% vs 1.3%)。这项对高加索人的研究显示，脑出血后立即给予抗凝治疗不能获益，尤其是对脑叶出血，其再出血风险最高 [496]。脑叶出血后抗凝治疗再出血风险高是因为有潜在脑淀粉样变性可能。一项决策分析反对在脑叶出血和心房颤动患者中重新开始抗凝治疗。其他一些新发或复发脑出血的危险因素也已经确定，包括高龄、高血压、抗凝的程度、透析、脑白质疏松、MRI 上显示微出血 [498-501]。MRI 上显示的微出血 (常见于梯度自旋回波成像) 常提示存在微血管病变或脑淀粉样变性。一项研究发现脑出血患者接受抗凝治疗的风险在合并微出血的患者中为 9.3%，而在无 MRI 证据的患者中为 1.3%[499]。

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，缺乏关于其他药物抗凝的前瞻性、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。一般来说，这些出血通常无症状或症

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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而且有适应证，仍可以继续抗凝治疗[505]。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（Ⅱa 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，脑叶出血的老年患者）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。（Ⅱb 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（Ⅱb 类；C 级证据）。**

8. 贯彻指南的具体措施及其在高危人群中的应用

全国共识指南已经被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[506-510]。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]。在一项对有胆固醇水平治疗达标丰富经验的内科医生的调查表明，在医疗实践中很少患者能真正达到目标值[512]。在冠状动脉疾病预防方面，使用回顾性执行资料已经增加了一些遵循指南的依从性[506]。

系统实施策略必须与指南的普及相伴，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)[513] 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。国家医疗卫生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]。

尽管数据提示急性卒中对指南的依从性和改善的健康和成本效益相关，二级预防的研究却很少。意大利缺血性卒中决策指南 (GLADIS) 研究证明了更好的结果，减少了入院时间，降低了急性卒中患者按照指南治疗的花费。对指南的依从性和卒中严重程度是花费的独立危险因素[517,518]。卒中联合治疗预防血栓栓塞的复发 (Preventing Recurrence Of Thromboembolic Events through Coordinated Treatment，PROTECT) 项目对住院期间所应用的 8 种二级预防措施（包括药物和生活方式）进行 90 天的检查，发现医生对指南有良好但多变的依从性，但没有对这些患者的复发率、生活质量和医疗费用进行分析[519]。有人提出，把经济回报和依从性联系到一起可提高卒中患者的治疗质量。英国一项关于卒中治疗

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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必要性，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可足以全面评价 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，而对所有行 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，并保障这个人群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责小组 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 [533-536]。

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，正显现出其支持改良的农村医疗、卒中的急救治疗、卒中的一级及二级预防的作用 [537]。那些卒中风险最高的种族的预防效果受到格外的关注 [132]。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异持续存在 [538]。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 [539]。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 [540]，非洲裔美国人较少得到戒烟咨询服务 (OR 0.27；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 [541]。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]，但各项研究提示在全球范围内，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的种族，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]) 卒中监督计划为目标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)，需要共同合作、发展并优化循证卒中预防建议的落实 [550]。

建议

1. **为增加建议的使用，在指南制定及推广过程中增加实施策略可能是有益的 (Ⅱ a 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、缺少医疗者和高风险种族人群享受医疗服务的需求可能是有用的 (Ⅱ a 类；B 级证据)。(新建议，表 10)**

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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.

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 Wassertheil-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

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

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The American Heart Association requests that the full-text version of this document be used when cited: Furie KL, Kasner SE, Adams RJ, Albers GW, Bush RL, Fagan SC, Halperin JL, Johnston SC, Katzan I, Kernan WN, Mitchell PH, Ovbiagele B, Palesch YY, Sacco RL, Schwamm LH, Wassertheil-Smoller S, Turan TN, Wentworth D; 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. 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. *Stroke*. 2011;42:227–276.

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Table 1. Applying Classification of Recommendations and Level of Evidence

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

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

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

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)

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Table 2. Definition of Classes and Levels of Evidence Used in AHA Recommendations

Class I	Conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful and effective
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment
Class IIa	The weight of evidence or opinion is in favor of the procedure or treatment
Class IIb	Usefulness/efficacy is less well established by evidence or opinion
Class III	Conditions for which there is evidence and/or general agreement that the procedure or treatment is not useful/effective and in some cases may be harmful
Therapeutic recommendations	
Level of Evidence A	Data derived from multiple randomized clinical trials or meta-analyses
Level of Evidence B	Data derived from a single randomized trial or nonrandomized studies
Level of Evidence C	Consensus opinion of experts, case studies, or standard of care
Diagnostic recommendations	
Level of Evidence A	Data derived from multiple prospective cohort studies using a reference standard applied by a masked evaluator
Level of Evidence B	Data derived from a single grade A study, or one or more case-control studies, or studies using a reference standard applied by an unmasked evaluator
Level of Evidence C	Consensus opinion of experts

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)

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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 antithrombotics, 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

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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 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).*

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 TIAs, 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*).

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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 antifactor Xa throughout pregnancy; or UFH or LMWH until week 13, followed by warfarin until the middle of

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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.

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