Guidelines for the Prevention of Stroke in Patients With Stroke and 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.

Endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons

Walter N. Kernan, MD, Chair; Bruce Ovbiagele, MD, MSc, MAS, Vice Chair; Henry R. Black, MD; Dawn M. Bravata, MD; Marc I. Chimowitz, MBChB, FAHA; Michael D. Ezekowitz, MBChB, PhD; Margaret C. Fang, MD, MPH; Marc Fisher, MD, FAHA; Karen L. Furie, MD, MPH, FAHA; Donald V. Heck, MD; S. Claiborne (Clay) Johnston, MD, PhD; Scott E. Kasner, MD, FAHA; Steven J. Kittner, MD, MPH, FAHA; Pamela H. Mitchell, PhD, RN, FAHA; Michael W. Rich, MD; DeJuran Richardson, PhD; Lee H. Schwamm, MD, FAHA; John A. Wilson, MD; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease

Abstract—The aim of this updated guideline is to provide comprehensive and timely evidence-based recommendations on the prevention of future stroke among survivors of ischemic stroke or transient ischemic attack. The guideline is addressed to all clinicians who manage secondary prevention for these patients. Evidence-based recommendations are provided for control of risk factors, intervention for vascular obstruction, antithrombotic therapy for cardioembolism, and antiplatelet therapy for noncardioembolic stroke. Recommendations are also provided for the prevention of recurrent stroke in a variety of specific circumstances, including aortic arch atherosclerosis, arterial dissection, patent foramen ovale, hyperhomocysteinemia, hypercoagulable states, antiphospholipid antibody syndrome, sickle cell disease, cerebral venous sinus thrombosis, and pregnancy. Special sections address use of antithrombotic and anticoagulation therapy after an intracranial hemorrhage and implementation of guidelines. **(*Stroke*. 2014;45:00-00.)**

Key Words: AHA Scientific Statements ■ atrial fibrillation ■ carotid stenosis ■ hypertension ■ ischemia ■ ischemic attack, transient ■ prevention ■ stroke

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Each year in the United States, >690 000 adults experience an ischemic stroke.[1] The enormous morbidity of ischemic stroke is the result of interplay between the resulting neurological impairment, the emotional and social consequences of that impairment, and the high risk for recurrence. An additional large number of US adults, estimated at 240 000, will experience a transient ischemic attack (TIA).[2] Although a TIA leaves no immediate impairment, affected individuals have a

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high risk for future ischemic events, particularly in the days and weeks immediately after symptom resolution.[3] On average, the annual risk for future ischemic stroke after an initial ischemic stroke or TIA is ≈3% to 4%.[4] Recent clinical trials of patients with noncardioembolic ischemic stroke suggest the risk may be as low as 3%, but these data probably underestimate the community-based rate.[5–9] The estimated risk for an individual patient will be affected by specific characteristics of the event and the person, including age, event type, comorbid illness, and adherence to preventive therapy.[10–12]

In recognition of the morbidity of recurrent brain ischemia, the aim of the present statement is to provide clinicians with evidence-based recommendations for the prevention of future stroke among survivors of ischemic stroke or TIA. The current average annual rate of future stroke (≈3%–4%) represents a historical low that is the result of important discoveries in prevention science.[13] These include antiplatelet therapy and effective strategies for treatment of hypertension, atrial fibrillation (AF), arterial obstruction, and hyperlipidemia. Since the first of these therapies emerged in 1970,[14] when results of the Veterans Administration Cooperative Study Group trial of hypertension therapy were published, the pace of discovery has accelerated. New approaches and improvements in existing approaches are constantly emerging. To help clinicians safeguard past success and drive the rate of secondary stroke even lower, this guideline is updated every 2 to 3 years.

Important revisions since the last statement[15] are displayed in Table 1. New sections were added for sleep apnea and aortic arch atherosclerosis, in recognition of maturing literature to confirm these as prevalent risk factors for recurrent stroke. The section on diabetes mellitus (DM) has been expanded to include pre-DM. The revised statement gives somewhat greater emphasis to lifestyle and obesity as potential targets for risk reduction given mounting evidence to support a role for lifestyle modification in vascular risk reduction.[19,20] A section on nutrition was added. The sections on carotid stenosis, AF, and prosthetic heart valves have been revised substantially in a manner that is consistent with recently published American Heart Association (AHA) and American College of Chest Physicians (ACCP) guidelines.[21–22] Sections on pregnancy and intracranial atherosclerosis have also been rewritten substantially. One section was removed (Fabry disease) in recognition of the rarity and specialized nature of this condition.

The revised guideline begins to consider clinically silent brain infarction as an entry point for secondary prevention and an event to be prevented. Brain imaging may identify evidence for clinically silent cerebral infarction, as defined by brain parenchymal injury of presumed vascular origin without a history of acute neurological dysfunction attributable to the lesion. These seemingly silent infarctions are associated with typical risk factors for ischemic stroke, increased risk for future ischemic stroke, and unrecognized neurological signs in the absence of symptoms. Clinicians who diagnose silent infarction routinely ask whether this diagnosis warrants implementation of secondary prevention measures. The writing committee, therefore, identified silent infarction as an important and emerging issue in secondary stroke prevention. Although data to guide management of patients with silent infarction are limited, the writing committee agreed to summarize these data where they could be found and incorporate them into relevant sections of this guideline.

Methods

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 cardiology, epidemiology/biostatistics, internal medicine, neurology, nursing, radiology, and surgery. The writing committee 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 are available on request. Searches were limited to English language sources and to human subjects. Literature citations were generally restricted to published manuscripts that appeared in journals listed in Index Medicus and reflected literature published as of April 1, 2013. 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 almost exclusively for peer-reviewed articles 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 consensus with the final recommendations. Recommendations follow the AHA and the American College of Cardiology (ACC) methods of classifying the level of certainty of the treatment effect and the class of evidence (Tables 2 and 3).[24] The writing committee prepared recommendations to be consistent with other, current AHA statements, except where important new science warranted revision or differing interpretations of science could not be reconciled.

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. Recommendations in this statement are organized to aid the clinician who has arrived at a potential explanation of the cause of the ischemic stroke in an individual patient and is embarking on therapy to reduce the risk of a recurrent event and other vascular outcomes. Our intention is to have these statements updated every 3 years, with additional interval updates as needed, to reflect the changing state of knowledge on the approaches to prevent a recurrent stroke.

Definition of TIA and Ischemic Stroke Subtypes

The distinction between TIA and ischemic stroke has become less important in recent years because many of the preventative approaches are applicable to both.[25] They share pathophysiological mechanisms; prognosis may vary depending on their severity and cause; and definitions are dependent on the timing and extent of the diagnostic evaluation. By conventional clinical definitions, the occurrence of focal neurological

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Table 1. New or Substantially Revised Recommendations for 2014*

Section	2014 Recommendation	Description of Change From 2011
Hypertension	Initiation of BP therapy is indicated for previously untreated patients with ischemic stroke or TIA who, after the first several days, have an established BP ≥140 mm Hg systolic or ≥90 mm Hg diastolic (*Class I; Level of Evidence B*). Initiation of therapy for patients with BP <140 mm Hg systolic and <90 mm Hg diastolic is of uncertain benefit *(Class IIb; Level of Evidence C)*.	Clarification of parameters for initiating BP therapy
	Resumption of BP therapy is indicated for previously treated patients with known hypertension for both prevention of recurrent stroke and prevention of other vascular events in those who have had an ischemic stroke or TIA and are beyond the first several days *(Class I; Level of Evidence A)*.	Clarification of parameters for resuming BP therapy
	Goals for target BP level or reduction from pretreatment baseline are uncertain and should be individualized, but it is reasonable to achieve a systolic pressure <140 mm Hg and a diastolic pressure <90 mm Hg (*Class IIa; Level of Evidence B*). For patients with a recent lacunar stroke, it might be reasonable to target a systolic BP of <130 mm Hg *(Class IIb; Level of Evidence B)*.	Revised guidance for target values
Dyslipidemia	Statin therapy with intensive lipid-lowering effects is recommended to reduce risk of stroke and cardiovascular events among patients with ischemic stroke or TIA presumed to be of atherosclerotic origin and an LDL-C level ≥100 mg/dL with or without evidence for other ASCVD *(Class I; Level of Evidence B)*.	1. Revised to be consistent with wording in the 2013 ACC/AHA cholesterol guideline[16]
	Statin therapy with intensive lipid-lowering effects is recommended to reduce risk of stroke and cardiovascular events among patients with ischemic stroke or TIA presumed to be of atherosclerotic origin, an LDL-C level <100 mg/dL, and no evidence for other clinical ASCVD *(Class I; Level of Evidence C)*.	1. Added to be consistent with the 2013 ACC/AHA cholesterol guideline[16] but to indicate a lower level of evidence when LDL-C is <100 mg/dL
	Patients with ischemic stroke or TIA and other comorbid ASCVD should be otherwise managed according to the ACC/AHA 2013 guidelines, which include lifestyle modification, dietary recommendations, and medication recommendations *(Class I; Level of Evidence A)*.	1. Revised to be consistent with the 2013 ACC/AHA cholesterol guideline[16]
Glucose disorders	After a TIA or ischemic stroke, all patients should probably be screened for DM with testing of fasting plasma glucose, HbA_{1c}, or an oral glucose tolerance test. Choice of test and timing should be guided by clinical judgment and recognition that acute illness may temporarily perturb measures of plasma glucose. In general, HbA_{1c} may be more accurate than other screening tests in the immediate postevent period *(Class IIa; Level of Evidence C)*.	New recommendation
Obesity	All patients with TIA or stroke should be screened for obesity with measurement of BMI *(Class I; Level of Evidence C)*.	New recommendation
	Given the demonstrated beneficial effects of weight loss on cardiovascular risk factors, the usefulness of weight loss among patients with a recent TIA or ischemic stroke and obesity is uncertain *(Class IIb; Level of Evidence C)*.	New recommendation
Physical inactivity	For patients who are able and willing to initiate increased physical activity, referral to a comprehensive, behaviorally oriented program is probably recommended *(Class IIa; Level of Evidence C)*.	New recommendation
Nutrition	It is reasonable to conduct a nutritional assessment for patients with a history of ischemic stroke or TIA, looking for signs of overnutrition or undernutrition *(Class IIa; Level of Evidence C)*.	New recommendation
	Patients with a history of ischemic stroke or TIA and signs of undernutrition should be referred for individualized nutritional counseling *(Class I; Level of Evidence B)*.	New recommendation
	Routine supplementation with a single vitamin or combination of vitamins is not recommended *(Class III; Level of Evidence A)*.	New recommendation
	It is reasonable to recommend that patients with a history of stroke or TIA reduce their sodium intake to less than ≈2.4 g/d. Further reduction to <1.5 g/d is also reasonable and is associated with even greater BP reduction *(Class IIa; Level of Evidence C)*.	New recommendation
	It is reasonable to counsel patients with a history of stroke or TIA to follow a Mediterranean-type diet instead of a low-fat diet. The Mediterranean-type diet emphasizes vegetables, fruits, and whole grains and includes low-fat dairy products, poultry, fish, legumes, olive oil, and nuts. It limits intake of sweets and red meats *(Class IIa; Level of Evidence C)*.	New recommendation
Sleep apnea	A sleep study might be considered for patients with an ischemic stroke or TIA on the basis of the very high prevalence of sleep apnea in this population and the strength of the evidence that the treatment of sleep apnea improves outcomes in the general population *(Class IIb; Level of Evidence B)*.	New recommendation
	Treatment with continuous positive airway pressure might be considered for patients with ischemic stroke or TIA and sleep apnea given the emerging evidence in support of improved outcomes *(Class IIb; Level of Evidence B)*.	New recommendation

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Table 1. Continued

Section	2014 Recommendation	Description of Change From 2011
Carotid disease	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-based imaging or noninvasive imaging with corroboration and the anticipated rate of periprocedural stroke or death is <6% *(Class IIa; Level of Evidence B)*.	Class changed from I to IIa based on outcome findings reported in a meta-analysis of comparative trials
	It is reasonable to consider patient age in choosing between CAS and CEA. For older patients (ie, older than ≈70 years), CEA may be associated with improved outcome compared with CAS, particularly when arterial anatomy is unfavorable for endovascular intervention. For younger patients, CAS is equivalent to CEA in terms of risk for periprocedural complication (ie, stroke, MI, or death) and long-term risk for ipsilateral stroke *(Class IIa; Level of Evidence B)*.	New recommendation
	CAS and CEA in the above settings should be performed by operators with established periprocedural stroke and mortality rates of <6% for symptomatic patients, similar to that observed in trials comparing CEA to medical therapy and more recent observational studies *(Class I; Level of Evidence B)*.	Class changed from IIa to I
	Routine, long term follow-up imaging of the extracranial carotid circulation with carotid duplex ultrasonography is not recommended *(Class III; Level of Evidence B)*.	New recommendation
	For patients with recurrent or progressive ischemic symptoms ipsilateral to a stenosis or occlusion of a distal (surgically inaccessible) carotid artery, or occlusion of a midcervical carotid artery after institution of optimal medical therapy, the usefulness of EC/IC bypass is considered investigational *(Class IIb; Level of Evidence C)*.	New recommendation
Intracranial atherosclerosis	For patients with recent stroke or TIA (within 30 days) attributable to severe stenosis (70%–99%) of a major intracranial artery, the addition of clopidogrel 75 mg/d to aspirin for 90 days might be reasonable *(Class IIb; Level of Evidence B)*.	New recommendation
	For patients with stroke or TIA attributable to 50% to 99% stenosis of a major intracranial artery, the data are insufficient to make a recommendation regarding the usefulness of clopidogrel alone, the combination of aspirin and dipyridamole, or cilostazol alone *(Class IIb; Level of Evidence C)*.	New recommendation
	For patients with a stroke or TIA attributable to 50% to 99% stenosis of a major intracranial artery, maintenance of systolic BP below 140 mm Hg and high-intensity statin therapy are recommended *(Class I; Level of Evidence B)*.	1. New cholesterol recommendation is consistent with 2013 ACC/AHA cholesterol guideline[16] 2. Class changed from IIb to I
	For patients with a stroke or TIA attributable to moderate stenosis (50%–69%) of a major intracranial artery, angioplasty or stenting is not recommended given the low rate of stroke on medical management and the inherent periprocedural risk of endovascular treatment *(Class III; Level of Evidence B)*.	New recommendation
	For patients with stroke or TIA attributable to severe stenosis (70%–99%) of a major intracranial artery, stenting with the Wingspan stent system is not recommended as an initial treatment, even for patients who were taking an antithrombotic agent at the time of the stroke or TIA *(Class III; Level of Evidence B)*.	New recommendation
	For patients with stroke or TIA attributable to severe stenosis (70%–99%) of a major intracranial artery, the usefulness of angioplasty alone or placement of stents other than the Wingspan stent is unknown and is considered investigational *(Class IIb; Level of Evidence C)*.	1. Change from 50% to 99% stenosis to 70% to 99% stenosis 2. Rewording to mention Wingspan device used in SAMMPRIS
	For patients with severe stenosis (70%–99%) of a major intracranial artery and recurrent TIA or stroke after institution of aspirin and clopidogrel therapy, achievement of systolic BP <140 mm Hg, and high-intensity statin therapy, the usefulness of angioplasty alone or placement of a Wingspan stent or other stents is unknown and is considered investigational *(Class IIb; Level of Evidence C)*.	New recommendation
	For patients with severe stenosis (70%–99%) of a major intracranial artery and actively progressing symptoms after institution of aspirin and clopidogrel therapy, the usefulness of angioplasty alone or placement of a Wingspan stent or other stents is unknown and is considered investigational *(Class IIb; Level of Evidence C)*.	New recommendation
AF	For patients who have experienced an acute ischemic stroke or TIA with no other apparent cause, prolonged rhythm monitoring (≈30 days) for AF is reasonable within 6 months of the index event *(Class IIa; Level of Evidence C)*.	New recommendation
	VKA therapy *(Class I; Level of Evidence A)*, apixaban *(Class I; Level of Evidence A)*, and dabigatran *(Class I; Level of Evidence B)* are all indicated for the prevention of recurrent stroke in patients with nonvalvular AF, whether paroxysmal or permanent. The selection of an antithrombotic agent should be individualized on the basis of risk factors, cost, tolerability, patient preference, potential for drug interactions, and other clinical characteristics, including renal function and time in INR therapeutic range if the patient has been taking VKA therapy.	1. New recommendations regarding apixaban and dabigatran 2. New text regarding choice of agent

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Table 1. Continued

Section	2014 Recommendation	Description of Change From 2011
AF cont'd	Rivaroxaban is reasonable for the prevention of recurrent stroke in patients with nonvalvular AF *(Class IIa; Level of Evidence B)*.	New recommendation
	The combination of oral anticoagulation (ie, warfarin or one of the newer agents) with antiplatelet therapy is not recommended for all patients after ischemic stroke or TIA but is reasonable in patients with clinically apparent CAD, particularly an acute coronary syndrome or stent placement *(Class IIb; Level of Evidence C)*.	New recommendation
	For patients with ischemic stroke or TIA and AF who are unable to take oral anticoagulants, aspirin alone is recommended (*Class I; Level of Evidence A*). The addition of clopidogrel to aspirin therapy, compared with aspirin therapy alone, might be reasonable *(Class IIb; Level of Evidence B)*.	1. Reworded from the 2011 text 2. Class changed from III to IIb
	For most patients with a stroke or TIA in the setting of AF, it is reasonable to initiate oral anticoagulation within 14 days after the onset of neurological symptoms *(Class IIa; Level of Evidence B)*.	New recommendation
	In the presence of high risk for hemorrhagic conversion (ie, large infarct, hemorrhagic transformation on initial imaging, uncontrolled hypertension, or hemorrhage tendency), it is reasonable to delay initiation of oral anticoagulation beyond 14 days *(Class IIa; Level of Evidence B)*.	New recommendation
	The usefulness of closure of the left atrial appendage with the WATCHMAN device in patients with ischemic stroke or TIA and AF is uncertain *(Class IIb; Level of Evidence B)*.	New recommendation
MI and thrombus	Treatment with VKA therapy (target INR, 2.5; range, 2.0–3.0) for 3 months may be considered in patients with ischemic stroke or TIA in the setting of acute anterior STEMI without demonstrable left ventricular mural thrombus formation but with anterior apical akinesis or dyskinesis identified by echocardiography or other imaging modality *(Class IIb; Level of Evidence C)*.	New recommendation
	In patients with ischemic stroke or TIA in the setting of acute MI complicated by left ventricular mural thrombus formation or anterior or apical wall-motion abnormalities with a left ventricular ejection fraction <40% who are intolerant to VKA therapy because of nonhemorrhagic adverse events, treatment with an LMWH, dabigatran, rivaroxaban, or apixaban for 3 months may be considered as an alternative to VKA therapy for prevention of recurrent stroke or TIA *(Class IIb; Level of Evidence C)*.	New recommendation
Cardiomyopathy	In patients with ischemic stroke or TIA in sinus rhythm who have left atrial or left ventricular thrombus demonstrated by echocardiography or another imaging modality, anticoagulant therapy with a VKA is recommended for ≥3 months *(Class I; Level of Evidence C)*.	New recommendation
	In patients with ischemic stroke or TIA in the setting of a mechanical LVAD, treatment with VKA therapy (target INR, 2.5; range, 2.0–3.0) is reasonable in the absence of major contraindications (eg, active gastrointestinal bleeding) *(Class IIa; Level of Evidence C)*.	New recommendation
	In patients with ischemic stroke or TIA in sinus rhythm with dilated cardiomyopathy (LV ejection fraction ≤35%), restrictive cardiomyopathy, or a mechanical LVAD who are intolerant to VKA therapy because of nonhemorrhagic adverse events, the effectiveness of treatment with dabigatran, rivaroxaban, or apixaban is uncertain compared with VKA therapy for prevention of recurrent stroke *(Class IIb; Level of Evidence C)*.	New recommendation
Valvular heart disease	For patients with ischemic stroke or TIA who have rheumatic mitral valve disease and AF, long-term VKA therapy with an INR target of 2.5 (range, 2.0–3.0) is recommended *(Class I; Level of Evidence A)*.	1. Mention of patients without AF is removed 2. Class changed from IIa to I
	For patients with ischemic stroke or TIA who have rheumatic mitral valve disease without AF or another likely cause for their symptoms (eg, carotid stenosis), long-term VKA therapy with an INR target of 2.5 (range, 2.0–3.0) may be considered instead of antiplatelet therapy *(Class IIb; Level of Evidence C)*.	New recommendation focuses on patients without AF
	For patients with rheumatic mitral valve disease who have an ischemic stroke or TIA while being treated with adequate VKA therapy, the addition of aspirin might be considered *(Class IIb; Level of Evidence C)*.	New recommendation
	For patients with ischemic stroke or TIA and native aortic or nonrheumatic mitral valve disease who do not have AF or another indication for anticoagulation, antiplatelet therapy is recommended *(Class I; Level of Evidence C)*.	Class changed from IIb to I
	For patients with ischemic stroke or TIA and mitral annular calcification who do not have AF or another indication for anticoagulation, antiplatelet therapy is recommended as it would be without the mitral annular calcification *(Class I; Level of Evidence C)*.	Class changed from IIb to I

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Table 1. Continued

Section	2014 Recommendation	Description of Change From 2011
Valvular heart disease cont'd	For patients with mitral valve prolapse who have ischemic stroke or TIAs and who do not have AF or another indication for anticoagulation, antiplatelet therapy is recommended as it would be without mitral valve prolapse *(Class I; Level of Evidence C)*.	1. Change in wording 2. Class changed from IIb to I
Prosthetic HV	For patients with a mechanical aortic valve and a history of ischemic stroke or TIA before its insertion, VKA therapy is recommended with an INR target of 2.5 (range, 2.0–3.0) *(Class I; Level of Evidence B)*.	Modified to focus on aortic valve
	For patients with a mechanical mitral valve and a history of ischemic stroke or TIA before its insertion, VKA therapy is recommended with an INR target of 3.0 (range, 2.5–3.5) *(Class I; Level of Evidence C)*.	1. New recommendation focuses on mitral valve 2. INR target is revised for the mitral valve
	For patients with a mechanical mitral or aortic valve who have a history of ischemic stroke or TIA before its insertion and who are at low risk for bleeding, the addition of aspirin 75 to 100 mg/d to VKA therapy is recommended *(Class I; Level of Evidence B)*.	New recommendation
	For patients with a bioprosthetic aortic or mitral valve, a history of ischemic stroke or TIA before its insertion, and no other indication for anticoagulation therapy beyond 3 to 6 months from the valve placement, long-term therapy with aspirin 75 to 100 mg/d is recommended in preference to long-term anticoagulation *(Class I; Level of Evidence C)*.	New recommendation specifically addresses timing of TIA or stroke in relation to valve replacement and recommends aspirin in preference to anticoagulation
Antiplatelet therapy	The combination of aspirin and clopidogrel might be considered for initiation within 24 hours of a minor ischemic stroke or TIA and for continuation for 90 days *(Class IIb; Level of Evidence B)*.	New recommendation
	For patients with a history of ischemic stroke or TIA, AF, and CAD, the usefulness of adding antiplatelet therapy to VKA therapy is uncertain for purposes of reducing the risk of ischemic cardiovascular and cerebrovascular events *(Class IIb; Level of Evidence C)*. Unstable angina and coronary artery stenting represent special circumstances in which management may warrant DAPT/VKA therapy.	New recommendation
Aortic arch atheroma	For patients with an ischemic stroke or TIA and evidence of aortic arch atheroma, antiplatelet therapy is recommended *(Class I; Level of Evidence A)*.	New recommendation
	For patients with an ischemic stroke or TIA and evidence of aortic arch atheroma, statin therapy is recommended *(Class I; Level of Evidence B)*.	New recommendation
	For patients with ischemic stroke or TIA and evidence of aortic arch atheroma, the effectiveness of anticoagulation with warfarin, compared with antiplatelet therapy, is unknown *(Class IIb; Level of Evidence C)*.	New recommendation
	Surgical endarterectomy of aortic arch plaque for the purposes of secondary stroke prevention is not recommended *(Class III; Level of Evidence C)*.	New recommendation
PFO	For patients with an ischemic stroke or TIA and a PFO who are not undergoing anticoagulation therapy, antiplatelet therapy is recommended *(Class I; Level of Evidence B)*.	Class changed from IIa to I
	For patients with an ischemic stroke or TIA and both a PFO and a venous source of embolism, anticoagulation is indicated, depending on stroke characteristics *(Class I; Level of Evidence A)*. When anticoagulation is contraindicated, an inferior vena cava filter is reasonable *(Class IIa; Level of Evidence C)*.	New recommendations
	For patients with a cryptogenic ischemic stroke or TIA and a PFO without evidence for DVT, available data do not support a benefit for PFO closure *(Class III; Level of Evidence A)*.	Class changed from IIb to III
	In the setting of PFO and DVT, PFO closure by a transcatheter device might be considered, depending on the risk of recurrent DVT *(Class IIb; Level of Evidence C)*.	New recommendation
Homocysteinemia	Routine screening for hyperhomocysteinemia among patients with a recent ischemic stroke or TIA is not indicated *(Class III; Level of Evidence C)*.	New recommendation
	In adults with a recent ischemic stroke or TIA who are known to have mild to moderate hyperhomocysteinemia, supplementation with folate, vitamin B_6, and vitamin B_{12} safely reduces levels of homocysteine but has not been shown to prevent stroke (*Class III; Level of Evidence B*).	Class changed from IIb to III
Hypercoagulation	The usefulness of screening for thrombophilic states in patients with ischemic stroke or TIA is unknown *(Class IIb; Level of Evidence C)*.	New recommendation
	Anticoagulation might be considered in patients who are found to have abnormal findings on coagulation testing after an initial ischemic stroke or TIA, depending on the abnormality and the clinical circumstances *(Class IIb; Level of Evidence C)*.	Substantial rewording Class changed from IIa to IIb

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Table 1. Continued

Section	2014 Recommendation	Description of Change From 2011
Hypercoagulation cont'd	Antiplatelet therapy is recommended in patients who are found to have abnormal findings on coagulation testing after an initial ischemic stroke or TIA if anticoagulation therapy is not administered *(Class I; Level of Evidence A)*.	Represents a more firm recommendation for antiplatelet therapy in the circumstance described
Antiphospholipid antibodies	Routine testing for antiphospholipid antibodies is not recommended for patients with ischemic stroke or TIA who have no other manifestations of the antiphospholipid antibody syndrome and who have an alternative explanation for their ischemic event, such as atherosclerosis, carotid stenosis, or AF *(Class III; Level of Evidence C)*.	New recommendation
	For patients with ischemic stroke or TIA who have an antiphospholipid antibody but who do not fulfill the criteria for antiphospholipid antibody syndrome, antiplatelet therapy is recommended *(Class I; Level of Evidence B)*.	Clarifies circumstances in which antiplatelet therapy is recommended over anticoagulation
	For patients with ischemic stroke or TIA who meet the criteria for the antiphospholipid antibody syndrome but in whom anticoagulation is not begun, antiplatelet therapy is indicated *(Class I; Level of Evidence A)*.	New recommendation
Sickle cell disease	For patients with sickle cell disease and prior ischemic stroke or TIA, chronic blood transfusions to reduce hemoglobin S to <30% of total hemoglobin are recommended *(Class I; Level of Evidence B)*.	Class changed from IIa to I
Pregnancy	In the presence of a high-risk condition that would require anticoagulation outside of pregnancy, the following options are reasonable: a. LMWH twice daily throughout pregnancy, with dose adjusted to achieve the LMWH manufacturer's recommended peak anti-Xa level 4 hours after injection, or b. Adjusted-dose UFH throughout pregnancy, administered subcutaneously every 12 hours in doses adjusted to keep the midinterval aPTT at least twice control or to maintain an anti-Xa heparin level of 0.35 to 0.70 U/mL, or c. UFH or LMWH (as above) until the 13th week, followed by substitution of a VKA until close to delivery, when UFH or LMWH is resumed *(Class IIa; Level of Evidence C)*.	More detail is provided that is intended to be consistent with the recent statement by the American College of Chest Physicians[18]
	For pregnant women receiving adjusted-dose LMWH therapy for a high-risk condition that would require anticoagulation outside of pregnancy, and when delivery is planned, it is reasonable to discontinue LMWH ≥24 hours before induction of labor or cesarean section *(Class IIa; Level of Evidence C)*.	New recommendation
	In the presence of a low-risk situation in which antiplatelet therapy would be the treatment recommendation outside of pregnancy, UFH or LMWH, or no treatment may be considered during the first trimester of pregnancy depending on the clinical situation *(Class IIb; Level of Evidence C)*.	New recommendation
Breastfeeding	In the presence of a high-risk condition that would require anticoagulation outside of pregnancy, it is reasonable to use warfarin, UFH, or LMWH *(Class IIa; Level of Evidence C)*.	New recommendation
	In the presence of a low-risk situation in which antiplatelet therapy would be the treatment recommendation outside of pregnancy, low-dose aspirin use may be considered *(Class IIb; Level of Evidence C)*.	New recommendation
Implementation	Monitoring achievement of nationally accepted, evidence-based guidelines on a population-based level is recommended as a basis for improving health-promotion behaviors and reducing stroke healthcare disparities among high risk groups *(Class I; Level of Evidence C)*.	New recommendation
	Voluntary hospital-based programs for quality monitoring and improvement are recommended to improve adherence to nationally accepted, evidence-based guidelines for secondary stroke prevention *(Class I; Level of Evidence C)*.	New recommendation

ACC indicates American College of Cardiology; AF, atrial fibrillation; AHA, American Heart Association; aPTT, activated partial thromboplastin time; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CAS, carotid angioplasty and stenting; CEA, carotid endarterectomy; DAPT, dual-antiplatelet therapy; DM, diabetes mellitus; DVT, deep vein thrombosis; EC/IC, extracranial/intracranial; HbA_{1c}, hemoglobin A_{1c}; HV, heart valve; INR, international normalized ratio; LDL-C, low-density lipoprotein cholesterol; LMWH, low-molecular-weight heparin; LV, left ventricular; LVAD, left ventricular assist device; MI, myocardial infarction; PFO, patent foramen ovale; SAMMPRIS, Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis; STEMI, ST-elevation myocardial infarction; TIA, transient ischemic attack; UFH, unfractionated heparin; and VKA, vitamin K antagonist.

*Includes recommendations for which the class was changed from one whole number to another and recommendations for which a change in wording significantly changed meaning. This table does not list removed recommendations.

symptoms or signs that last <24 hours has been defined as a TIA. With the more widespread use of modern brain imaging, up to a third of patients with symptoms lasting <24 hours are found to have an infarction.[25,26] 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.[25] Notably, the majority of studies described in the present guideline used the older

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Table 2. 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 *No Benefit* or CLASS III *Harm* Procedure/Test / Treatment COR III: No benefit — Not Helpful / No Proven Benefit COR III: Harm — Excess Cost w/o Benefit or Harmful / Harmful to Patients
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	COR III: No Benefit: is not recommended; is not indicated; should not be performed/ administered/ other; is not useful/ beneficial/ effective COR III: Harm: potentially harmful; causes harm; associated with excess morbidity/mortality; should not be performed/ administered/ other
Comparative effectiveness phrases†	treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B		

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. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

†For comparative effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

definition. Recommendations provided by this guideline are believed to apply to both stroke and TIA regardless of which definition is applied.

In contrast to TIA, central nervous system infarction is defined as "brain, spinal cord, or retinal cell death attributable to ischemia, based on neuropathological, neuroimaging, and/or clinical evidence of permanent injury. … Ischemic stroke specifically refers to central nervous system infarction accompanied by overt symptoms, whereas silent infarction by definition causes no known symptoms."[27] When imaging or pathology is not available, clinical stroke is recognized by persistence of symptoms for 24 hours. Ischemic stroke is further classified on the basis of 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.[28] The certainty of the 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. Setting-specific recommendations for the timing and type of diagnostic workup for TIA and stroke patients are beyond the scope of this guideline statement; at a minimum, all stroke

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Table 3. Definition of Classes and Levels of Evidence Used in AHA/ASA 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

AHA/ASA indicates American Heart Association/American Stroke Association.

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 AF as the cause of ischemic symptoms.

Risk Factor Control for All Patients With TIA or Ischemic Stroke

Hypertension

Treatment of hypertension is possibly the most important intervention for secondary prevention of ischemic stroke. Defined as a systolic blood pressure (SBP) ≥140 mm Hg or a diastolic blood pressure (DBP) ≥90 mm Hg, an estimated 78 million Americans have hypertension.[1] The prevalence among patients with a recent ischemic stroke is ≈70%.[11,29,30] The risk for a first ischemic stroke is directly related to blood pressure (BP) starting with an SBP as low as 115 mm Hg.[31,32] The relationship with recurrent stroke has been less well studied but is presumably similar.

The first major trial to demonstrate the effectiveness of hypertension treatment for secondary prevention of stroke was the Post-Stroke Antihypertensive Treatment Study (PATS).[33] This Chinese study randomized 5665 patients with a recent TIA or minor stroke (hemorrhagic or ischemic) to indapamide or placebo. Patients were eligible regardless of baseline BP, and mean time from qualifying event to randomization was 30 months. At baseline, mean SBP was 153 mm Hg in the placebo group and 154 mm Hg in the indapamide group. During an average of 24 months of follow-up, mean SBP fell by 6.7 and 12.4 mm Hg in the placebo and indapamide groups, respectively. The main outcome of recurrent stroke was observed in 44.1% of patients assigned to placebo and 30.9% of those assigned to indapamide (relative risk reduction [RRR], 30%; 95% confidence interval [CI], 14%–43%).

The effectiveness of BP treatment for secondary prevention was subsequently confirmed in the Perindopril Protection Against Recurrent Stroke Study (PROGRESS), which randomized 6105 patients with a history of TIA or stroke (ischemic or hemorrhagic) to active treatment with a perindopril-based regimen or placebo.[6] Randomization was stratified according to the treating physician's judgment that there was a strong indication or contraindication to diuretic therapy. Thus, patients assigned to active treatment could receive perindopril alone or perindopril plus indapamide in a double-blind design. There was no specified BP eligibility criterion. Before the run-in period, however, 65% of patients were being treated for hypertension or had a measured BP >160/95 mm Hg. Thirty-five percent were on no BP therapy and had a BP <160/95 mm Hg. Thus, a definite but uncertain proportion of participants considered for the trial would meet the current definition for stage 1 hypertension (SBP ≥140–159 or DBP ≥90–99 mm Hg) or less than stage 1 hypertension. Baseline BP was measured on treatment in many trial participants, which complicates the interpretation of the results for untreated patients in clinical practice.[34] Mean time from qualifying event to randomization was 8 months. After 4 years, active treatment reduced SBP by 9 mm Hg and DBP by 4 mm Hg compared with placebo. BP was further reduced by combination therapy with indapamide, 12.3/5.0 mm Hg compared with placebo. Active therapy reduced the primary end point of fatal or nonfatal stroke by 28% (95% CI, 17%–38%). The treatment effect was similar in people with and without baseline hypertension as defined by SBP ≥160 mm Hg or DBP ≥90 mm Hg. Combination therapy was associated with greater risk reduction (RRR, 43%; 95% CI, 30%–54%).

The PROGRESS investigators published 2 post hoc analyses that examined (1) the effect of randomized treatment in 4 subgroups defined by baseline SBP (≥160, 140–159, 120–139, or <120 mm Hg) and (2) the association between achieved BP (same groupings) and risk for recurrent stroke.[35] The first analysis showed that the effectiveness of hypertension therapy for secondary stroke prevention diminished as baseline BP declined (RRRs were 39%, 31%, 14%, and 0%, respectively, in the groups defined above). This trend of diminishing effect was apparent despite successful reduction of mean SBP in each active-treatment group compared with placebo (11.1, 9.2, 7.6, and 7.4 mm Hg reductions, respectively, in the groups defined above). The findings were discordant for patients undergoing combination therapy and single-drug therapy; the hazard ratio (HR) favored treatment in all of the

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groups assigned to combination therapy but only in the groups with baseline SBP of 140 to 159 mm Hg and ≥160 mm Hg in the single-drug groups. Participants with lower baseline SBP did not appear to experience increased adverse event rates on active therapy. Of note, 40% of patients with a baseline BP <140 mm Hg were taking antihypertensive therapy at baseline. In the observational analysis of annual stroke rate according to achieved follow-up SBP, the investigators observed a direct relationship between lower achieved pressure and lower stroke rate, with no evidence of a J curve.

A meta-analysis of randomized trials confirmed that antihypertensive medications reduced the risk of recurrent stroke after stroke or TIA.[36] It included 10 randomized trials published through 2009 that compared hypertension therapy with placebo or no therapy. Together, these trials included participants with transient ischemic stroke, TIA, or intracerebral hemorrhage (ICH) randomized days to months after the index event and followed up for 2 to 5 years. No trials tested nonpharmacological interventions. Overall, treatment with antihypertensive drugs was associated with a significant reduction in recurrent strokes (RR, 0.78; 95% CI, 0.68–0.90).[36] Larger reductions in SBP tended to be associated with greater reduction in risk of recurrent stroke. A significant reduction in recurrent stroke was seen with diuretics (alone or in combination with angiotensin-converting enzyme inhibitors) but not with renin-angiotensin system inhibitors, β-blockers, or calcium-channel blockers used alone; nonetheless, statistical power was limited, particularly for the assessment of β-blockers and calcium channel blockers. The impact of antihypertensive agents after ischemic stroke appeared to be similar in a restricted group of subjects with hypertension and when all subjects, including those with and without hypertension, were included. Treatment also reduced the risk of MI and all vascular events.[37]

One additional large-scale, randomized trial of antihypertensive medications after stroke was not included in either meta-analysis because it included an active control or was published too late: Morbidity and Mortality after Stroke, Eprosartan Compared with Nitrendipine for Secondary Prevention (MOSES).[38] 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).[38] 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, 0.58–0.97), 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, 0.66–0.96). 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.

Research on treating hypertension for primary prevention of stroke provides strong indirect support for its effectiveness in secondary prevention. Meta-analyses of randomized controlled trials (RCTs) performed primarily among stroke-free individuals have shown that BP lowering is associated with a 30% to 40% stroke risk reduction.[32,39,40] Risk reduction is greater with larger reductions in BP.[40] Most placebo-controlled trials of primary prevention, however, defined hypertension as SBP ≥160 mm Hg or DBP ≥100 mm Hg (ie, grade 2 or 3 hypertension).[14,41–43] On the basis of consideration of trials and epidemiological data, older US and European guidelines recommend starting antihypertension therapy for grade 1 hypertension (>140/>90 mm Hg).[44] More recent European guidelines assign a class I recommendation to initiating therapy for grade 1 hypertension only in the presence of high-risk features (target-organ disease, cardiovascular disease (CVD), or chronic kidney disease). Therapy for low- or moderate-risk grade 1 hypertension is a class IIa recommendation in new European guidelines.[41] Most recent US guidelines have adopted conflicting positions on grade 1 hypertension. The 2013 science advisory from the AHA, ACC, and Centers for Disease Control and Prevention (CDC) stays with older recommendations (ie, initiate therapy in all adults with grade 1 hypertension).[45] The panel originally appointed by the National Heart, Lung, and Blood Institute to review the evidence on treatment of hypertension, in contrast, adopted more conservative recommendations for people aged ≥60 years (ie, initiate therapy at an SBP ≥150 mm Hg or DBP ≥90 mm Hg and treat to goals of SBP <150 mm Hg and DBP <90 mm Hg).[46]

The management of BP in the acute setting is discussed in the AHA's "Guidelines for the Early Management of Patients With Acute Ischemic Stroke."[47] This guideline examines evidence to guide initiation or resumption of antihypertension therapy after acute ischemic stroke and concludes that treatment within the first 24 hours is warranted only in specific situations (ie, therapy with tissue-type plasminogen activator, SBP >220 mm Hg, or DBP >120 mm Hg). The guideline states that otherwise, the benefit of treating arterial hypertension in the setting of acute stroke is uncertain, but restarting antihypertensive therapy is reasonable after the first 24 hours for patients who have preexisting hypertension and who are neurologically stable.

Limited data specifically assess the optimal BP target for secondary stroke prevention. Randomized clinical trial evidence among high-risk patients with DM indicates that there is no benefit in achieving an aggressive SBP of <120 versus <140 mm Hg.[48] Observational studies among hypertensive patients with DM and coronary artery disease (CAD),[49] as well as patients with a recent ischemic stroke,[50,51] suggest that there may even be harm associated with SBP levels <120 mm Hg. Very recently, the results of the Secondary Prevention of Small Subcortical Strokes (SPS3) trial were presented.[52] SPS3 enrolled 3020 patients with lacunar (small-vessel disease) strokes verified by MRI and randomized them (open label) to 2 different target levels of SBP control, <150 versus <130 mm Hg. Patients with cortical strokes, cardioembolic disease, or carotid stenosis were excluded. Mean time from qualifying event to randomization was 62 days. At baseline, mean SBP was 145 mm Hg in the higher-target group and 144 mm Hg in the lower-target group. At 12 months, achieved average SBP was 138 mm Hg in the higher-target group versus 127 mm Hg in the lower-target group, and at last observed visit, the average SBP difference between groups was 11 mm Hg. The primary outcome of recurrent stroke was observed in 152 patients assigned to higher-target

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group (2.8% per year) and 125 assigned to the lower-target group (2.3% per year; HR, 0.81; 95% CI, 0.64–1.03). The end point of ischemic stroke occurred in 131 patients assigned to the higher-target group (2.4% per year) and 112 assigned to the lower-target group (2.0% per year; HR, 0.84; 95% CI, 0.66–1.09), whereas the end point of hemorrhagic stroke occurred in 16 patients assigned to the higher-target group (0.29% per year) and 6 assigned to the lower-target group (0.11% per year; HR, 0.37; 95% CI, 0.15–0.95). There was no difference between target groups with regard to the composite outcome of stroke, MI, and vascular death (HR, 0.84; 95% CI, 0.68–1.04). Serious complications of hypotension were observed in 15 patients assigned to the higher-target group (0.26% per year) and 23 assigned to the lower-target group (0.40% per year; HR, 1.53; 95% CI, 0.80–2.93).

Evidence-based recommendations for BP treatment of people with hypertension are summarized in the AHA/American Stroke Association "Guidelines for the Primary Prevention of Stroke,"[53] the report from the panel originally appointed by the National Heart, Lung, and Blood Institute to review the evidence on treatment of hypertension,[46] the AHA,[45] and recent European guidelines.[41] Our recommendations listed below are generally consistent with these guidelines but adopt the AHA recommendation to start therapy at an SBP ≥140 mm Hg or DBP ≥90 mm Hg for all adults with a history of stroke or TIA. All guidelines stress the importance of lifestyle modifications. Lifestyle interventions associated with BP reduction include weight loss[54]; the consumption of a diet rich in fruits, vegetables, and low-fat dairy products; a Mediterranean-type diet[55]; reduced sodium intake[56]; regular aerobic physical activity; and limited alcohol consumption.[44]

Hypertension Recommendations

1. **Initiation of BP therapy is indicated for previously untreated patients with ischemic stroke or TIA who, after the first several days, have an established BP ≥140 mm Hg systolic or ≥90 mm Hg diastolic *(Class I; Level of Evidence B)*. Initiation of therapy for patients with BP <140 mm Hg systolic and <90 mm Hg diastolic is of uncertain benefit *(Class IIb; Level of Evidence C)*.** (Revised recommendation)
2. **Resumption of BP therapy is indicated for previously treated patients with known hypertension for both prevention of recurrent stroke and prevention of other vascular events in those who have had an ischemic stroke or TIA and are beyond the first several days *(Class I; Level of Evidence A)*.** (Revised recommendation)
3. **Goals for target BP level or reduction from pretreatment baseline are uncertain and should be individualized, but it is reasonable to achieve a systolic pressure <140 mm Hg and a diastolic pressure <90 mm Hg *(Class IIa; Level of Evidence B)*. For patients with a recent lacunar stroke, it might be reasonable to target an SBP of <130 mm Hg *(Class IIb; Level of Evidence B)*.** (Revised recommendation)
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; the 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 reductions 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 is useful *(Class I; Level of Evidence A)*.**
6. **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 DM) *(Class IIa; Level of Evidence B)*.**

Dyslipidemia

Modification of a primary serum lipid biomarker such as low-density lipoprotein cholesterol (LDL-C) is an important component in the secondary stroke risk reduction strategy for survivors of TIA or ischemic stroke. However, although epidemiological data point to a modest link between high serum LDL-C and greater risk of ischemic stroke, they have also suggested an association of low LDL-C with heightened risk of ICH.[57–59] In several clinical trials, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, or statins, which markedly reduce LDL-C levels, have proved efficacious in reducing primary stroke risk without any significant risk of ICH.[60] In the only trial to date dedicated to the evaluation of secondary stroke risk, the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study, 4731 people with stroke or TIA, LDL-C levels between 100 and 190 mg/dL, and no known history of coronary heart disease (CHD) were randomly assigned to 80 mg of atorvastatin daily versus placebo.[5] Over a median follow-up period of 4.9 years, 11.2% of those who received atorvastatin experienced a stroke compared with 13.1% who received placebo (absolute reduction in risk, 2.2%; HR, 0.84; 95% CI, 0.71–0.99; P=0.03). For the outcome of major cardiovascular events, the 5-year absolute reduction in risk was 3.5% in favor of the high-dose statin group (HR, 0.80; 95% CI, 0.69–0.92; P=0.002). There was a modestly higher rate of elevated liver enzymes and a rise in creatine kinase in the atorvastatin arm but no cases of hepatic failure or significant imbalance in cases of myopathy, myalgia, or rhabdomyolysis. Furthermore, the favorable benefit of atorvastatin was observed in the young and elderly, in men and women, and across ischemic stroke subtype at entry.[61–63]

A finding of note in SPARCL was the association of statin treatment with a higher incidence of hemorrhagic stroke (n=55 [2.3%] for statin treatment versus n=33 [1.4%] for placebo; HR, 1.66; 95% CI, 1.08–2.55).[64] A similar observation was seen in the subset of 3200 patients who had stroke before randomization in the Heart Protection Study (HPS), in which there was a 91% relative rise in risk of hemorrhagic stroke in patients assigned to statin treatment.[65] Further analyses of

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SPARCL showed that the risk of hemorrhagic stroke linked to the statin was independent of age, sex, and hypertension control, as well as degree of LDL-C lowering.[64] However, the results of SPARCL may understate the true treatment effect in fully compliant patients, because the net difference in actual statin use between the 2 SPARCL treatment groups (statin versus placebo) was only 78%.[5] Given the higher risk of hemorrhagic stroke with statin treatment observed among survivors of a stroke or TIA in SPARCL and the HPS, a history of ICH may identify a subset of stroke patients with greater hemorrhagic propensity in whom statins should be used very judiciously, if at all.

Because no major RCT has specifically tested the benefits of treating stroke or TIA patients according to LDL-C targets, the benefit of aiming for a given LDL-C target for the prevention of secondary stroke in these patients has not been established definitively. This notwithstanding, a post hoc analysis of the SPARCL trial revealed that achieving an LDL-C level of <70 mg/dL was related to a 28% reduction in risk of stroke (HR, 0.72; 95% CI, 0.59–0.89; *P*=0.0018) without a significant rise in the risk of hemorrhagic stroke (HR, 1.28; 95% CI, 0.78–2.09; *P*=0.3358).[66] In addition, stroke and TIA patients with ≥50% reduction in LDL-C had a 35% reduction in combined risk of nonfatal and fatal stroke.[66] Because the analyses were exploratory, these results should be seen only as suggesting that the achievement of nominal targets or a specific degree of LDL-C lowering may be beneficial. The ongoing Treat Stroke to Target (TST) trial (ClinicalTrials.gov, unique identifier: NCT01252875), which is evaluating the effects of targeted LDL-C levels on vascular events among recent ischemic stroke and TIA patients, should provide better clarity of this issue.

Data from observational studies indicate that serum lipid indices other than LDL-C are independently associated with risk of stroke. Furthermore, these lipid subfractions appear to predict future vascular risk despite the achievement of recommended target serum LDL-C levels.[67–69] In particular, elevated serum triglyceride levels have been associated with ischemic stroke and large-artery atherosclerotic stroke; low serum high-density lipoprotein cholesterol (HDL-C) levels have been linked to risk of ischemic stroke; and elevated lipoprotein (a) has been related to incident stroke.[70–77] Medications used to treat high serum triglyceride, low HDL-C levels, and lipoprotein(a) include fibrates, niacin, and cholesterol absorption inhibitors, but there is a paucity of data establishing the efficacy of these agents for the reduction of secondary stroke risk. Although systematic reviews and meta-analyses of clinical trials involving fibrates or niacin either show or suggest a beneficial effect on the risk of any stroke, many of the included studies were either conducted before statin therapy became standard of care, lumped together all stroke types, or largely examined primary stroke risk.[78–80]

Recently, the role of niacin among patients with established CVD and low HDL-C levels receiving intensive statin therapy was addressed in the Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial.[81] AIM-HIGH evaluated whether extended-release niacin added to intensive statin therapy versus statin therapy alone would reduce the risk of cardiovascular events in 3414 patients with known atherosclerotic disease and atherogenic dyslipidemia (low levels of HDL-C, elevated triglyceride levels, and small, dense particles of LDL-C). Patients in the niacin group received niacin at a dose of 1500 to 2000 mg/d. In both groups, the dose of the statin was adjusted to achieve and maintain the LDL-C level in the range of 40 to 80 mg/dL. The trial was stopped after an average follow-up period of 3 years because of a lack of efficacy. By 2 years of follow-up, add-on niacin therapy had boosted the median HDL-C level from 35 to 42 mg/dL, reduced the triglyceride level from 164 to 122 mg/dL, and lowered the LDL-C level from 74 to 62 mg/dL. The primary end point occurred in 282 patients (16.4%) in the niacin group versus 274 (16.2%) in the placebo group (HR, 1.02; 95% CI, 0.87–1.21; *P*=0.79). Of note, there was an unexpected imbalance in the rate of ischemic stroke as the first event between patients assigned to niacin versus placebo (27 [1.6%] versus 15 patients [0.9%]). Even when all the patients with ischemic strokes were considered (versus just those in whom stroke was the first study event), the pattern persisted (albeit nonsignificant: 29 [1.7%] versus 18 patients [1.1%]; HR, 1.61; 95% CI, 0.89–2.90; *P*=0.11). It is not clear whether this observation seen in AIM-HIGH reflects a causal relationship or the play of chance.

Initial reports from the HPS 2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS-2 THRIVE) study (ClinicalTrials.gov, unique identifier: NCT00461630), which evaluated a cohort of people with a history of symptomatic vascular disease (including ischemic stroke, TIA, or carotid revascularization), indicate that after almost 4 years of follow-up, the combination of extended-release niacin with the antiflushing agent laropiprant on top of background statin treatment did not significantly reduce the risk of the combination of coronary deaths, nonfatal MI, strokes, or coronary revascularizations versus statin therapy alone but boosted the risk of nonfatal but serious side effects.[82] Detailed results of HPS-2 THRIVE are expected to be available in 2014.

Inhibition of cholesteryl ester transfer protein increases HDL-C levels, and the hypothesis that cholesteryl ester transfer protein inhibitors will enhance cardiovascular outcomes has been tested in 2 clinical trials.[83,84] The Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE) trial evaluated whether torcetrapib lowered the risk of clinical cardiovascular events in 15 067 patients with a history of CVD.[83] Although there was a rise in HDL-C level of 72% and a drop of 25% in LDL-C level at 12 months among those who received torcetrapib, there was also an increase of 5.4 mm Hg in SBP, electrolyte derangements, and a higher rate of cardiovascular events. The HR estimate for stroke was 1.08 (95% CI, 0.70–1.66; *P*=0.74). The dal-OUTCOMES study randomly assigned 15 871 patients who had a recent acute coronary syndrome to receive dalcetrapib 600 mg daily versus placebo.[84] HDL-C levels rose from baseline by 31% to 40% in the dalcetrapib group. Dalcetrapib had a minimal effect on LDL-C levels. The trial was terminated for futility; compared with placebo, dalcetrapib did not significantly affect the risk of the primary end point nor any component of the primary end

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point, including stroke of presumed atherothrombotic cause (HR, 1.25; 95% CI, 0.92–1.70; *P*=0.16).

The "ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults" was released in 2013[16] and replaces prior guidance from the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Cholesterol in Adults (Adult Treatment Panel III).[85] The new guidelines move away from reliance on cholesterol measurement to select individuals for therapy and guide drug dosage. Instead, the ACC/AHA guidelines identify 4 "statin benefit groups" for drug treatment to reduce risk for atherosclerotic CVD (ASCVD): "Individuals with 1) *clinical* ASCVD, 2) primary elevations of LDL-C ≥190 mg/dL, 3) diabetes aged 40 to 75 years with LDL-C 70 to 189 mg/dL and without clinical ASCVD, or 4) without *clinical* ASCVD or diabetes and LDL-C 70 to 189 mg/dL and estimated 10-year ASCVD risk ≥7.5%." Risk is estimated by use of new pooled cohort equations.[86] Importantly, clinical ASCVD includes people with ischemic stroke or TIA presumed to be of atherosclerotic origin. Clinical ASCVD also includes people with a history of acute coronary syndromes, MI, stable or unstable angina, or coronary or other revascularization. High-dose statin therapy (ie, reduces LDL-C by ≥50%) is recommended for individuals with clinical ASCVD who are ≤75 years of age, have LDL-C ≥190 mg/dL, or have DM and a 10-year risk of ASCVD estimated at ≥7.5%. Moderate-dose therapy (ie, reduces LDL-C by ≈30% to <50%) is recommended for other groups. Our recommendations for secondary prevention, listed below, are consistent with the new ACC/AHA guidelines.[16]

Dyslipidemia 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 presumed to be of atherosclerotic origin and an LDL-C level ≥100 mg/dL with or without evidence for other clinical ASCVD *(Class I; Level of Evidence B)*.** (Revised recommendation)
2. **Statin therapy with intensive lipid-lowering effects is recommended to reduce risk of stroke and cardiovascular events among patients with ischemic stroke or TIA presumed to be of atherosclerotic origin, an LDL-C level <100 mg/dL, and no evidence for other clinical ASCVD *(Class I; Level of Evidence C)*.** (New recommendation)
3. **Patients with ischemic stroke or TIA and other comorbid ASCVD should be otherwise managed according to the 2013 ACC/AHA cholesterol guidelines,[16] which include lifestyle modification, dietary recommendations, and medication recommendations *(Class I; Level of Evidence A)*.** (Revised recommendation)

Disorders of Glucose Metabolism and DM

Definitions

The principal disorders of glucose metabolism are type 1 DM, pre-DM, and type 2 DM. Type 1 DM usually begins in childhood and accounts for 5% of DM among US adults.[87,88] It results from immune destruction of pancreatic β-cells with subsequent insulin deficiency. Pre-DM encompasses impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and intermediate elevations in hemoglobin A_{1c} (HbA_{1c}; 5.7%–6.4%). Pre-DM can begin in childhood but more commonly begins later in life. It invariably precedes the onset of type 2 DM, which accounts for 95% of DM among US adults.[87,89] Pre-DM and DM are the result of impairments in insulin action (ie, insulin resistance) with progressive β-cell dysfunction.

Each of the principal disorders of glucose metabolism is diagnosed from measures of plasma glucose, HbA_{1c}, and symptoms of hyperglycemia.[88] Normal fasting glucose is glucose <100 mg/dL (5.6 mmol/L). IFG is plasma glucose of 100 to 125 mg/dL (6.9 mmol/L). IGT is diagnosed when the 2-hour plasma glucose is ≥140 to 199 mg/dL (7.8–11.0 mmol/L) during a 75-g oral glucose tolerance test. Using HbA_{1c}, pre-DM is defined by values of 5.7% to 6.4%. DM is defined by an HbA_{1c} value ≥6.5%, a fasting plasma glucose level ≥126 mg/dL (7.0 mmol/L), a 2-hour plasma glucose ≥200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test, or a casual (random) plasma glucose ≥200 mg/dL (11.1 mmol/L) in the setting of symptoms attributable to hyperglycemia. Except for the latter, results of measured glucose and HbA_{1c} values should be confirmed by repeat testing before DM is diagnosed.

Epidemiology

The burden of DM is rising in both developed and developing countries.[89–91] In the United States, 11.3% of adults have diagnosed or occult DM.[90,92] The actual prevalence increases significantly with age so that prevalence rises from 3.7% among US adults aged 20 to 44 years to 26.9% among adults ≥65 years of age.[92] Other demographic risk factors include Hispanic ethnicity and black race.[87,92] The rate of diagnosed DM in the United States is 7.1% among non-Hispanic whites, 11.8% for Hispanics, and 12.6% for non-Hispanic blacks.[92]

DM is associated with a substantially increased risk for first ischemic stroke.[53] The adjusted RR is in the range of 1.5 to 3.7.[93–98] On a population level, DM may be responsible for >8% of first ischemic strokes.[53,94,99] IFG, IGT, and pre-DM diagnosed by HbA_{1c} also increase risk for first stroke.[100–102] The RR for IFG, however, is only apparent for values in the upper limit of that range (adjusted RR, 1.21; 95% CI, 1.02–1.44 for fasting glucose ≥110–125 mg/dL [6.1–6.9 mmol/L]).[101] The existence of IGT and HbA_{1c} in the range of 6.0% to ≤6.5% probably confers a greater risk for stroke than with IFG.[96,100–102] This is consistent with the generally held view that IGT represents a more severe metabolic derangement and that elevated HbA_{1c} is a more comprehensive marker of hyperglycemic burden than IFG.[89]

Disorders of glucose metabolism are also highly prevalent among patients with established cerebrovascular disease. Up to 28% of patients with ischemic stroke have pre-DM, and 25% to 45% have overt DM.[29,30,103–107] In total, 60% to 70% of patients may have 1 of these dysglycemic states.[106,108] The effect of pre-DM on prognosis has not been adequately studied, but DM itself is associated with increased risk for recurrent ischemic stroke.[30,109–111] In a substudy of the Cardiovascular Health Study that enrolled patients with a first ischemic stroke, DM

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was associated with a 60% increased risk for recurrence (RR, 1.59; 95% CI, 1.07–2.37).[30]

The impairments in insulin action (ie, insulin resistance) and β-cell function that cause type 2 DM are driven primarily by excess calorie intake in people who are susceptible by virtue of inherited traits, age, and acquired behaviors.[54,112] In these susceptible individuals, excess calorie intake (ie, overnutrition) results in central adipose deposition, dyslipidemia, deranged insulin signaling in target organs (eg, skeletal muscle and liver), and a proinflammatory state with altered secretion of a variant of cytokines. The net result is insulin resistance, dysfunctional insulin secretion, impaired glucose metabolism, and eventually, DM. In nonsusceptible individuals, overnutrition tends to result in preferential deposition of fat in peripheral sites, where it is metabolically quiescent and less likely to increase risk for DM or vascular disease. Approximately 25% of obese people have this so-called benign obesity.

Insulin resistance is the cardinal metabolic defect in almost all patients with IFG, IGT, and type 2 DM. It can be regarded as a third prediabetic condition when detected in isolation. The most accurate way to measure insulin resistance is with a hyperinsulinemic clamp, but more practical strategies involve measuring glucose and insulin concentrations while fasting or in response to a glucose load. In the absence of DM, insulin resistance is associated with a doubling of the risk for ischemic stroke.[96,113,114] Dysglycemia occurs when the normal β-cell response to insulin resistance decompensates.

Management

No major trials for secondary prevention of stroke have specifically examined interventions for pre-DM or DM. Management of stroke patients with these conditions, therefore, is based on trials in nonstroke or mixed populations.

Lifestyle interventions and pharmacotherapy can prevent progression from IGT to DM.[115,116] In the Diabetes Prevention Program trial, a lifestyle intervention among patients with IGT reduced the incidence of DM by 58% (95% CI, 48%–66%) compared with placebo.[116] Metformin reduced the incidence by 31% (95% CI, 17%–43%). The lifestyle intervention was significantly more effective than metformin. Acarbose is about as effective as metformin, but adherence is complicated by gastrointestinal side effects.[117] Rosiglitazone and pioglitazone are more effective than metformin[117–119] but are associated with weight gain and other potential side effects. Among available options, the American Diabetes Association (ADA) emphasizes lifestyle intervention over drugs.[88] Selected use of metformin is considered an option in the most at-risk patients.

Available evidence does not support the conclusion that treatment of IGT prevents macrovascular events. However, 1 of the DM prevention trials reported that acarbose, compared with placebo, was effective for prevention of cardiovascular events, including stroke (relative hazard, 0.75; 95% CI, 0.63–0.90).[120] These results are from a secondary analysis and have not been verified. A similar effect was not seen in the trial that involved rosiglitazone,[118] but pioglitazone was shown to slow the progression of intima-media thickness in the smaller Actos Now for Prevention of Diabetes (ACT NOW) trial.[121]

For patients who have already progressed to DM, preventive care emphasizes good nutrition, treatment of hyperlipidemia and hypertension, smoking cessation, and antiplatelet therapy.[88,122] All patients with DM at risk for vascular disease benefit from statin therapy regardless of pretreatment LDL-C.[123,124] In consideration of RCT data confirming this benefit, the ADA recommends stain therapy for all people with DM with existing CVD, including stroke,[88] and suggests a goal of LDL-C <100 mg/dL (<70 mg/dL optional). The appropriate goal for BP control in DM has been controversial, but results of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial indicate no advantage of setting the SBP goal lower than 140 mm Hg[48] for preventing major adverse cardiovascular events. The ADA recommends a goal of <140 mm Hg for SBP and <80 mm Hg for DBP but accepts that lower goals may be appropriate for selected individuals, such as young patients who tolerate the lower readings.

The optimal level of glucose control for prevention of macrovascular disease has been the subject of several major trials, which have converged on the conclusion that more intensive glycemic control (ie, HbA_{1c} <6% or <6.5%) may be modestly effective for preventing nonfatal CHD events, particularly MI, compared with current targets (ie, HbA_{1c} <7%–8%).[125–128] However, intensive treatment does not appear to reduce all-cause mortality or stroke risk (odds ratio [OR] for nonfatal stroke, 0.93; 95% CI, 0.81–1.06).[126] Intensive therapy, furthermore, is associated with doubling of the risk for severe hypoglycemia. The ADA and others have interpreted these data as indicating that a goal of <6.5% may be appropriate in selected, mainly younger individuals if it can be accomplished safely and without frequent hypoglycemia.[88,126] Patients with short-duration DM, long life expectancy, and minimal CVD may be most likely to benefit from intensive glycemic control.[88,129] The benefit will mainly be to decrease the long-term risk of microvascular complications.

Until the publication of the Look AHEAD (Action for Health in Diabetes) trial, it was assumed that weight loss among patients with DM and obesity would reduce risk for vascular events.[130,131] The Look AHEAD trial randomized 5145 overweight or obese patients with type 2 DM to an intensive behavioral intervention or usual care. The primary outcome was the composite of stroke, MI, or vascular death. After 9.6 years, the intervention group lost an average of 6% of initial body weight compared with the control group, which lost only 3.5%. Despite this achievement, there was no significant difference in cardiovascular outcomes, and the trial was stopped early for futility (HR, 0.95; 95% CI, 0.83–1.09).

Another key question in the care of patients with DM is whether one hypoglycemic drug may be more effective than others in preventing vascular events. Although no drug has been proven to reduce macrovascular events, preliminary evidence suggests some possible advantage for metformin,[132] pioglitazone,[133] and the dipeptidyl peptidase-4 inhibitor linagliptide.[134] Among patients with a history of stroke who entered the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) with a history of stroke, pioglitazone therapy was associated with a 47% RR reduction in recurrent stroke (HR, 0.53; 95% CI, 0.34–0.85) and a

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28% RR reduction in stroke, MI, or vascular death (HR, 0.72; 95% CI, 0.53–1.00).[135] The potential effectiveness of pioglitazone for secondary stroke prevention is being examined in the Insulin Resistance Intervention After Stroke (IRIS) trial (ClinicalTrials.gov, unique identifier: NCT00091949). It is too early to recommend any one diabetic drug over another for vascular prevention, but this is an area of intensive research. Consistent with this assessment, the ADA recently revised its treatment recommendations to encourage physicians to apply a patient-centered approach to selection of agents after metformin in patients with type 2 DM.[136] In this manner, the patient is matched to the most appropriate medication on the basis of a variety of factors, including desired HbA_{1c} reduction, side effect profiles and toxicities, potential nonglycemic benefits, and cost.

Disorders of Glucose Metabolism and DM Recommendations

1. **After a TIA or ischemic stroke, all patients should probably be screened for DM with testing of fasting plasma glucose, HbA_{1c}, or an oral glucose tolerance test. Choice of test and timing should be guided by clinical judgment and recognition that acute illness may temporarily perturb measures of plasma glucose. In general, HbA_{1c} may be more accurate than other screening tests in the immediate postevent period *(Class IIa; Level of Evidence C)*.** (New recommendation)
2. **Use of existing guidelines from the ADA for glycemic control and cardiovascular risk factor management is recommended for patients with an ischemic stroke or TIA who also have DM or pre-DM *(Class I; Level of Evidence B)*.**

Overweight and Obesity

Obesity, defined as a body mass index (BMI) of ≥30 kg/m^2, is an established risk factor for CHD and premature mortality.[137,138] The risk is thought to be mediated substantially by dyslipidemia, hypertension, insulin resistance, DM, and inflammatory pathways.[54]

Obesity is also associated with increased risk for incident stroke.[54,139–141] Recent epidemiological studies suggest that the risk increases in a near-linear fashion starting at a BMI of 20 kg/m^2 such that a 1-kg/m^2 increase in BMI is associated with a 5% increase in risk for stroke. The association between adiposity and risk for stroke is more evident for measures of central obesity (eg, waist circumference) than for general obesity (eg, BMI), for middle-aged adults than for older adults, and for ischemic stroke than for hemorrhagic stroke. As for CHD, however, the association between obesity and increased risk for stroke is largely explained by intermediate vascular risk factors.[54,142]

Among patients with established cerebrovascular disease, the consequences of obesity are more controversial and less well established. Obesity is diagnosed in 18% to 44% of patients with a recent TIA or ischemic stroke, although precise estimates are available from only a few studies, and estimates are likely to vary by region and country.[54] Increasing obesity among patients with TIA or stroke is associated an increasing prevalence of vascular risk factors.[142] Despite this relationship, however, obesity has not been established as a risk factor for recurrent stroke. In fact, the results of recent studies indicate that obese patients with stroke had somewhat lower risk for a major vascular event than did lean patients.[143,144] This unexpected relationship of obesity with improved prognosis after stroke has been termed the *obesity paradox* and has led some to question the appropriateness of recommending weight loss.[145] The obesity paradox is particularly perplexing because weight loss is associated with improvements in major cardiovascular risk factors, including dyslipidemia, DM, BP, and measures of inflammation.[54] Thus, it has been suggested that underestimation of the adverse effect of obesity may be explained by bias.[146]

Weight loss can be achieved with behavioral change, drugs, or bariatric surgery. Unfortunately, there are very few high-quality data on the effect of any of these interventions on risk vascular events. The Look AHEAD study is the only RCT that has been adequately designed to examine the effect of a behavioral intervention for weight loss on cardiovascular event risk. As described above, however, the modest weight loss achieved in that study (ie, 6% of initial body weight) did not reduce risk for cardiovascular outcomes.

A few trials of weight loss drugs have examined vascular end points, but none have identified safe and effective therapies for clinical use. Most notably, recent trials of the norepinephrine-serotonin reuptake inhibitor sibutramine and the endocannabinoid receptor blocker rimonabant raised safety concerns that prevented their use in the United States.[147–150]

No RCT of bariatric surgery has been adequately designed to examine an effect on stroke risk. However, results of a large, nonrandomized, controlled cohort study, the Swedish Obese Subjects (SOS) trial of bariatric surgery, reported a reduction in the incidence of MI (adjusted HR, 0.71; 95% CI, 0.54–0.94; P=0.02) and stroke (adjusted HR, 0.66; 95% CI, 0.49–0.90; P=0.008).[151] Secondary prevention through surgically induced weight loss has not been addressed.[152]

Weight loss is difficult to achieve and sustain. Simple advice by a healthcare provider is inadequate. Most patients will require intensive, ongoing, behaviorally based counseling. Drugs and bariatric surgery have only adjunctive roles if behavioral therapy fails.[54,153]

Obesity Recommendations

1. **All patients with TIA or stroke should be screened for obesity with measurement of BMI *(Class I; Level of Evidence C)*.** (New recommendation)
2. **Despite the demonstrated beneficial effects of weight loss on cardiovascular risk factors, the usefulness of weight loss among patients with a recent TIA or ischemic stroke and obesity is uncertain (*Class IIb; Level of Evidence C*).** (New recommendation)

Metabolic Syndrome

The metabolic syndrome refers to the confluence of several physiological abnormalities that increase risk for vascular disease.[154,159] Those abnormalities include overweight,

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hypertriglyceridemia, low HDL-C, high BP, and hyperglycemia.[156–158] Recent research 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.[155,159,160] Several diagnostic criteria for the metabolic syndrome have been advanced. In an effort to harmonize these, the AHA and several other organizations proposed a widely accepted definition that requires any 3 of the following features: elevated waist circumference (population and country-specific cutoffs), plasma triglyceride ≥150 mg/dL (1.7 mmol/L), HDL-C <40 mg/dL (1.0 mmol/L) for men or <50 mg/dL (1.3 mmol/L) for women, BP ≥130 mm Hg systolic or ≥85 mm Hg diastolic, or fasting glucose ≥100 mg/dL (5.6 mmol/L).[154] The metabolic syndrome affects ≈22% of US adults aged >20 years.[161,162] Among patients with ischemic stroke, the prevalence of the metabolic syndrome is 30% to 50%.[163–167]

Considerable controversy surrounds the definition of the metabolic syndrome, largely because of uncertainty regarding its pathogenesis and clinical usefulness. An early and still popular theory is that insulin resistance is the core defect in the syndrome, and that it leads to the cardinal manifestations, including hyperglycemia, dyslipidemia, inflammation, and hypertension. This theory came under scrutiny as scientists began to unravel the causes of insulin resistance, demonstrating that fat deposition in muscle, liver, and the abdomen can cause insulin resistance and the other abnormalities associated with the metabolic syndrome, particularly inflammation.[168–171] Under this emerging theory, therefore, the proximal cause of the metabolic syndrome is calorie excess that leads to ectopic fat accumulation. Even this theory, however, probably oversimplifies the genetic, cellular, and biochemical causes of this complex syndrome.

The metabolic syndrome is strongly related to an increased risk for DM (RR, 3–4) and is modestly associated with increased risk for CVD (RR, 2–3) and all-cause mortality (RR, 1.5–2.0).[172–175] However, it remains uncertain whether the metabolic syndrome has value in characterizing risk for individual patients; fasting glucose is a more accurate predictor of DM,[174] and simpler risk stratification instruments, such as the Framingham risk score, are at least as accurate for CVD.[175,176] Furthermore, the metabolic syndrome has not been associated with the risk of developing CVD in the elderly (70–82 years of age), which limits its generalizability in a typical stroke population.[167,174]

The metabolic syndrome is also associated with increased risk for ischemic stroke and silent brain infarction. More than 15 cohort studies have reported statistically significant adjusted RRs for ischemic stroke that range between 1.5 and 5.1, with most between 2.0 and 2.5.[162,175,177–183] A point estimate of 2.27 (95% CI, 1.80–2.85) was suggested by a meta-analysis that examined risk for any stroke (ie, ischemic or hemorrhagic). A few studies have reported no association.[110,167] Among components of the syndrome, hypertension and hyperglycemia may have the largest effect on ischemic stroke risk.[162,182] As is the case for CVD, classification of patients according to the metabolic syndrome does not significantly improve stroke risk estimation beyond what can be accomplished with traditional risk factors.[166,175,183,184] Information on silent brain infarction is from case-control studies that have reported ORs of 2.1 to 2.4 for any infarction[185,186] and 6.5 for lacunar infarction.[186]

Two secondary analyses from clinical trial cohorts have examined the association between the metabolic syndrome and risk for recurrence after ischemic stroke. One found an association,[166] and 1 did not.[110] Participants with the metabolic syndrome in the Warfarin Aspirin Symptomatic Intracranial Disease (WASID) trial 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, 1.1–2.4; P=0.0097). Patients with the metabolic syndrome were also at increased risk for ischemic stroke alone (HR, 1.7; 95% CI, 1.1–2.6; P=0.012). In contrast to WASID, no association was detected in the SPARCL trial of atorvastatin for patients with TIA or ischemic stroke.[110]

The cardinal features of the metabolic syndrome are all improved with weight loss. In particular, weight loss among adult 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.[187–189] Diet, exercise, and drugs that enhance insulin sensitivity have also been shown to produce many of these improvements among people with the metabolic syndrome.[188,190–194]

No adequately powered RCTs 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. No randomized trial of secondary preventive therapy has been conducted among patients who have had a stroke with the metabolic syndrome.

Metabolic Syndrome Recommendations

1. **At this time, the usefulness of screening patients for the metabolic syndrome after stroke is unknown *(Class IIb; Level of Evidence C)*.**
2. **For patients who are screened and classified as having the metabolic syndrome, management should focus on counseling for lifestyle modification (diet, exercise, and weight loss) for vascular risk reduction *(Class I; Level of Evidence C)*.**
3. **Preventive care for patient with the metabolic syndrome should include appropriate treatment for individual components of the syndrome, which are also stroke risk factors, particularly dyslipidemia and hypertension *(Class I; Level of Evidence A)*.**

Physical Inactivity

The AHA and ACC recommend that adults participate in 3 to 4 sessions of aerobic physical activity a week, lasting an average of 40 minutes and involving moderate (eg, brisk walking) or vigorous (eg, jogging) intensity.[17,54,195] Despite broad recognition of the benefits of exercise, fewer than 50% of US noninstitutionalized adults achieve this recommendation, and participation may be declining.[196]

Stroke survivors may encounter distinct barriers in achieving the recommendations for physical activity. Motor

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weakness, altered perception and balance, and impaired cognition may result in the inability to safely participate in conventional exercise programs.[197] It is not surprising, therefore, that recent surveys indicate low rates of exercise participation after stroke.[198]

Physical activity improves stroke risk factors and may reduce stroke risk itself.[139,195,199–202] High-quality data, including data from clinical trials, show clearly that exercise reduces BP,[195,203] improves endothelial function,[204] reduces insulin resistance,[205] improves lipid metabolism,[138,197,206] and may help reduce weight.[207] Epidemiological research strongly suggests that on average, high levels of leisure-time physical activity and moderate levels of occupational physical activity are associated with a 10% to 30% reduction in the incidence of stroke and CHD in both men and women.[195,199–201,208,209] These observations from epidemiological work, however, have not been tested in adequately designed clinical trials. In particular, no RCTs have examined the effectiveness of exercise for secondary prevention of stroke. Two trials using multimodal approaches that include physical activity are in progress and may help clarify the role of physical activity in secondary prevention.[210,211]

Several studies have shown that aerobic exercise and strength training will improve cardiovascular fitness after stroke.[197,210–215] Structured programs of therapeutic exercise have been shown to improve mobility, balance, and endurance,[213] and beneficial effects have been demonstrated in different ethnic groups and in both older and younger patients.[216] Together, these studies provide important information on the safety and selected clinical benefits of exercise after stroke.

Helping healthy people and patients with chronic disease become more physically active is a major goal of preventive medicine and US national health policy.[217] However, changing exercise behavior is not easy. Advice alone by healthcare providers is probably not effective.[218] Even more intensive face-to-face counseling and repeated verbal encouragement may not be effective for increasing physical activity, including among high-risk people with established vascular disease or DM.[54,219,220] Effective behavior change requires participation in a comprehensive, behaviorally oriented program, such as the Diabetes Prevention Program.[115]

Physical Inactivity Recommendations

1. **For patients with ischemic stroke or TIA who are capable of engaging in physical activity, at least 3 to 4 sessions per week of moderate- to vigorous-intensity aerobic physical exercise are reasonable to reduce stroke risk factors. Sessions should last an average of 40 minutes. Moderate-intensity exercise is typically defined as sufficient to break a sweat or noticeably raise heart rate (eg, walking briskly, using an exercise bicycle). Vigorous-intensity exercise includes activities such as jogging *(Class IIa; Level of Evidence C)*.** (Revised recommendation)
2. **For patients who are able and willing to initiate increased physical activity, referral to a comprehensive, behaviorally oriented program is reasonable *(Class IIa; Level of Evidence C)*.** (New recommendation)
3. **For individuals with 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)*.**

Nutrition

The epidemiology of diet and nutrition in patients with a recent ischemic stroke is coming under more intensive investigation. As a result, data are emerging to support preliminary recommendations for dietary management. Elsewhere in this guideline, we described the problem of overnutrition (ie, obesity) and offered recommendations for detection and treatment. In this section, therefore, we will focus on 3 different challenges: undernutrition, micronutrient deficiency or surfeit, and choice of optimal dietary pattern.

Undernutrition

Undernutrition, often termed protein-calorie malnutrition, refers to a global deficit in energy and all classes of nutrients (ie, micronutrients, carbohydrates, fats, and proteins). Undernutrition may affect stroke patients who have chronic illness, malabsorption, disordered metabolism, or limited access to food. There is no "gold standard" for the diagnosis of undernutrition, but potential indicators include BMI, serum albumin, triceps skinfold thickness, arm circumference, and delayed hypersensitivity. Using these and other measures, the prevalence of protein-calorie undernutrition among patients with acute stroke has been estimated as 8% to 13%,[221–223] although higher estimates have been reported.[224,225] Malnutrition may develop during the weeks after stroke and is associated with poor short-term outcome,[223,226,227] but routine food supplementation has not been shown to significantly improve outcome.[222,228,229] There is limited evidence that nutritional intervention that targets undernourished stroke patients may improve short-term outcomes, including response to rehabilitation.[230,231] A small RCT (n=124) suggested that individual counseling for acute stroke patients at nutritional risk (ie, BMI <20 kg/m^2, recent weight loss, or poor intake) or who are undernourished may prevent weight loss and improve quality of life and motor function at 3 months.[231] Long-term trials are not available.

Deficiency or Excess of Specific Micronutrients

Micronutrients refer to vitamins, essential fatty acids, and minerals required in small amounts to maintain normal physiological function. Among micronutrients, there is evidence that low serum levels of vitamin D and low dietary potassium may be associated with increased risk for stroke.[232–234] A recent meta-analysis that included 9 cohorts indicated that higher potassium intake was associated with a 24% lower risk of stroke.[235] Although stroke patients are commonly deficient in vitamin D,[236] and modern diets are often low in potassium, phase 3 trials have not yet explored whether supplementation with either of these micronutrients is effective for secondary prevention. To the best of our knowledge, there are only 2 large phase 2 trials of micronutrient supplementation after stroke or TIA. One examined B vitamin supplementation among patients with hyperhomocysteinemia and a recent ischemic stroke.[8] The other examined vitamin B supplementation among a broader range of patients with a

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recent stroke or TIA.[237] Neither showed efficacy for prevention of subsequent vascular events, but a follow-up analysis of the Vitamin Intervention for Stroke Prevention (VISP) study suggested there may be a subgroup of patients with hyperhomocysteinemia and intermediate vitamin B_{12} serum levels who may benefit from therapy.[238] Folate and vitamin B_{12} therapy was shown to prevent fractures among Japanese patients with a recent ischemic stroke.[239] Large RCTs in nonstroke patients have failed to show a benefit for routine supplementation with B vitamins, vitamin C, vitamin E, or beta carotene.[240] The exception may be folic acid, for which a recent meta-analysis of 8 RCTs reported a significant 18% reduced risk for stroke (RR, 0.82; 95% CI, 0.68–1.00).[241]

Some micronutrients appear to be harmful in excess. There is evidence that increased intake of sodium,[242] and possibly calcium supplementation,[243] may be associated with increased risk for stroke. Excess sodium is clearly associated with increased BP, which is, of course, a major modifiable stroke risk factor. Reducing sodium intake from 3.3 g/d to 2.5 and 1.5 g/d progressively reduces BP.[56]

Optimal Dietary Pattern

No data are yet available on dietary patterns among patients with a recent ischemic stroke or TIA, and no epidemiological data are yet available to link specific dietary patterns to prognosis for recurrence or other meaningful outcome events. No clinical trials have yet examined the effectiveness of specific diets for secondary prevention. Thus, recommendations on dietary behavior after stroke and TIA necessarily rely on research in populations that primarily comprise patients without symptomatic cerebrovascular disease.

Data from observational studies of mostly stroke-free people suggest that consumption of fish (1–4 servings/wk),[244–246] fruit and vegetables (≥3 servings/wk),[247] fiber,[248] olive oil,[249] and a Mediterranean diet[248] may be associated with reduced risk for stroke. Consumption of protein in Western diets does not appear to be associated with risk for stroke.[250]

Several large RCTs provide insight into the optimal diet for stroke prevention. Compared with a low-fat diet, Mediterranean-type diets (ie, rich in fish, fruit, vegetables, nuts, and olive oil) are associated with favorable effects on cardiovascular risk factors.[55,194] Trials of the Mediterranean diet among patients with CAD, although not definitive, provide strong evidence for protection against recurrent vascular events.[251,252] The only definitive trial of the Mediterranean diet among patients without CVD enrolled patients at high risk and demonstrated a significant effect on the prevention of MI, stroke or cardiovascular death compared with a low-fat diet.[20] Two permutations of the Mediterranean diet were examined in the study. The HR was 0.70 (95% CI, 0.54–0.92) for patients assigned to an olive oil–based permutation and 0.72 (95% CI, 0.54–0.96) for patients assigned to a nut-based permutation. The effect of the diet was even more striking for prevention of stroke among those assigned to the olive oil group (HR, 0.67; 95% CI, 0.46–0.98) or the nut-based group (HR, 0.54; 95% CI, 0.35–0.84). Fat restriction alone is not effective for stroke prevention.[253]

The recommendations below are consistent with those in the "2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk."[17] Our recommendation 5 is closely patterned on the AHA/ACC recommendation 1 from that guideline.[17]

Nutrition Recommendations

1. **It is reasonable to conduct a nutritional assessment for patients with a history of ischemic stroke or TIA, looking for signs of overnutrition or undernutrition *(Class IIa; Level of Evidence C)*.** (New recommendation)
2. **Patients with a history of ischemic stroke or TIA and signs of undernutrition should be referred for individualized nutritional counseling *(Class I; Level of Evidence B)*.** (New recommendation)
3. **Routine supplementation with a single vitamin or combination of vitamins is not recommended *(Class III; Level of Evidence A)*.** (New recommendation)
4. **It is reasonable to recommend that patients with a history of stroke or TIA reduce their sodium intake to less than ≈2.4 g/d. Further reduction to <1.5 g/d is also reasonable and is associated with even greater BP reduction *(Class IIa; Level of Evidence C)*.** (New recommendation)
5. **It is reasonable to counsel patients with a history of stroke or TIA to follow a Mediterranean-type diet instead of a low-fat diet. The Mediterranean-type diet emphasizes vegetables, fruits, and whole grains and includes low-fat dairy products, poultry, fish, legumes, olive oil, and nuts. It limits intake of sweets and red meats *(Class IIa; Level of Evidence C)*.** (New recommendation)

Obstructive Sleep Apnea

Sleep apnea is present in approximately half to three quarters of patients with stroke or TIA.[254–261,263–266] The diagnosis is made on the basis of the apnea-hypopnea index (AHI), which describes the number of respiratory events (cessations or reductions in air flow) that are observed during sleep. Sleep apnea is defined as being present if the AHI is ≥5 events per hour, and an increasing AHI indicates increasing sleep apnea severity.[267] The prevalence of sleep apnea among patients with stroke or TIA varies according to the AHI cutoff used. In a meta-analysis of 29 studies that included 2343 patients, 72% of patients with stroke or TIA were found to have sleep apnea on the basis of an AHI >5 events per hour, with 63% having an AHI >10 events per hour and 38% having an AHI >20 events per hour.[268] This meta-analysis also confirmed that central sleep apnea is much less common than obstructive sleep apnea, with 7% of patients having primarily central apneas.[268]

Despite being highly prevalent, as many as 70% to 80% of patients with sleep apnea are neither diagnosed nor treated.[269] The barriers to diagnosing and treating sleep apnea involve patient, provider, and system issues, including provider awareness and access to sleep laboratory–based testing.[269] The American Academy of Sleep Medicine's Adult Obstructive Sleep Apnea Task Force recommends that stroke or TIA patients with symptoms should receive polysomongraphy.[270] However, elements of the clinical history (eg, sleepiness)

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and physical examination (eg, BMI) that have been demonstrated to be reliable indicators of sleep apnea in community populations are inaccurate markers for sleep apnea among patients with cerebrovascular disease.[268,271–278] Specifically, stroke patients with sleep apnea do not experience the same degree of sleepiness as nonstroke patients with sleep apnea and have lower BMI values.[273] The Epworth Sleepiness Scale is often normal among stroke patients with sleep apnea.[272–276] The Berlin Questionnaire also has poor positive and negative predictive values among stroke patients.[277,278] Given that stroke and TIA patients are at high risk of having sleep apnea,[272] a sleep study should be considered to identify the presence of sleep apnea among patients with stroke or TIA even in the absence of sleep apnea signs or symptoms. The American Academy of Sleep Medicine recommends the use of polysomnography, either conducted in a sleep laboratory or unattended polysomnography conducted in patients' homes for the detection of sleep apnea[270]; however several studies have evaluated the use of autotitrating continuous positive airway pressure (CPAP) devices used diagnostically and found them to have acceptable validity among stroke and TIA populations.[264,265,268,271,279] This finding has particular relevance to the acute stroke population, in which the strongest evidence in favor of CPAP is among studies that provided immediate autotitrating CPAP without delaying to conduct polysomnography (see below).[264,280]

Sleep apnea has been associated with poor outcomes among patients with cerebrovascular disease, including higher mortality,[281–284] delirium,[261] depressed mood,[261] and worse functional status.[261,281,282,285,286] Sleep apnea can be treated with a variety of approaches, but the mainstay of therapy is CPAP.[267,271,287] Several RCTs and observational cohort studies have examined the effectiveness of CPAP in improving post-stroke or post-TIA outcomes. The 8 RCTs have all been relatively small, with sample sizes insufficient to identify changes in outcomes associated with treatment. The RCTs can be classified in terms of a focus on the acute stroke period versus the subacute or rehabilitation phase.

Four randomized trials evaluated the use of early CPAP in the acute stroke period.[263,264,287,288] One trial of 55 patients with acute stroke demonstrated a greater improvement in the National Institutes of Health Stroke Scale (NIHSS) with early CPAP (median time from symptom onset to CPAP initiation of 39 hours) than with usual care (improvement of 3.0 versus 1.0; *P*=0.03) over a 1-month period.[264] Similarly, a study of 50 stroke patients on the first night after symptom onset found that the NIHSS improvement was largest among patients with the greatest CPAP use over the first 8 days after stroke (improvement of 2.3 versus 1.4; *P*=0.022).[280] One feasibility trial randomized 32 patients with acute stroke to receive either CPAP or sham CPAP (median time from symptom onset to CPAP or sham of 4 days) and reported 3-month outcome data on 7 CPAP patients and 10 sham-CPAP patients without stochastic testing; the median NIHSS in the CPAP group was 1, and the median NIHSS in the sham-CPAP group was 2.[288] Parra et al[263] followed 126 patients with acute stroke with sleep apnea over a 2-year period. Patients were randomly assigned to either receive CPAP (with a mean time from symptom onset to CPAP initiation of 4.6 days) or usual care. At 1 month after stroke, no differences between the groups were observed in terms of the Barthel Index, but CPAP patients were more likely to have an improvement in the modified Rankin scale (91% versus 56%; *P*=0.002) and the Canadian Neurological Scale (88% versus 73%; *P*=0.038). By 2 years after stroke, the differences in these outcomes between the CPAP and control patients were no longer statistically significant. Over the 2-year study period, the stroke rate was similar in both groups (5.3% for CPAP versus 4.3% for control; *P*=1.0), and the cardiovascular mortality rate was also similar (0% for CPAP versus 4.4% for control; *P*=0.25). The mean time from stroke onset to the first cardiovascular event was longer in the CPAP group (15 versus 8 months; *P*=0.044).

One randomized trial evaluated the use of early CPAP among 70 patients with acute TIA (mean time from symptom onset to CPAP of 39.4 hours) and found no overall statistically significant differences in the combined vascular event (12% in the control group and 2% in the intervention group; *P*=0.13) but did find that the vascular event rate decreased as CPAP use increased (8% among patients with no CPAP use, 6% among patients with some CPAP use, and 0% among patients with good CPAP use).[265]

Three RCTs evaluated the use of CPAP in patients with subacute stroke and reported mixed results.[272,289,290] Hsu et al[290] randomized 30 patients 3 weeks after stroke who had sleep apnea to receive 2 months of CPAP or usual care and found no statistically significant differences in outcomes at 3 months after stroke. One study randomized 63 patients 2 to 4 weeks after stroke to receive either 1 month of CPAP or usual care and found improvements in depression in the CPAP group but no differences in delirium, cognition, or functional status.[289] Ryan et al[272] randomized 44 patients 3 weeks after stroke onset to 1 month of CPAP or usual care and found improvements in the Canadian Neurological Scale for the CPAP group and no statistically significant differences in several outcomes (eg, the 6-minute walk test).

The largest of the cohort studies (n=189) also had the longest follow-up period of any of the studies (7 years); Martínez-García et al[279] reported that patients ≥2 months after stroke with sleep apnea who did not use CPAP had much higher recurrent stroke rates than patients who used CPAP (32% versus 14%; *P*=0.021) and a higher adjusted incidence of nonfatal vascular events (HR, 2.87; 95% CI, 1.11–7.71). The number needed to treat to prevent 1 new vascular event was 4.9 patients (95% CI, 2–19).

The reported CPAP adherence has varied considerably across trials and cohort studies, from one third[279,291] to all[292] patients using CPAP. In general, most of the studies have reported that 40% to 65% of the population had some level of CPAP use.*

Given these generally promising albeit mixed results across the randomized trials and the observational cohort studies, what is clearly needed is a randomized trial with adequate sample size to examine whether and the extent to which treatment of sleep apnea with CPAP improves outcomes such as stroke severity, functional status, and recurrent vascular events.

* *References 264, 265, 287, 288, 290, 293–295.*

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Sleep Apnea Recommendations

1. **A sleep study might be considered for patients with an ischemic stroke or TIA on the basis of the very high prevalence of sleep apnea in this population and the strength of the evidence that the treatment of sleep apnea improves outcomes in the general population *(Class IIb; Level of Evidence B)*.** (New recommendation)
2. **Treatment with CPAP might be considered for patients with ischemic stroke or TIA and sleep apnea given the emerging evidence in support of improved outcomes *(Class IIb; Level of Evidence B)*.** (New recommendation)

Cigarette Smoking

Cigarette smoking is an important independent risk factor for first ischemic stroke[207–303] and contributes to an increased risk for silent brain infarction.[304] The evidence on smoking as a risk factor for first ischemic stroke is discussed extensively in the AHA/American Stroke Association's "Guidelines for the Primary Prevention of Stroke."[53] In contrast to the extensive data on the association between smoking and risk for first stroke, data on an association with recurrent stroke are sparse. In the Cardiovascular Health Study, however, smoking was associated with a substantially increased risk for stroke recurrence in the elderly (HR, 2.06; 95% CI, 1.39–3.56).[30]

Newer research has extended concerns about smoking by showing that exposure to environmental tobacco smoke or passive ("secondhand") smoke also increases the risk of stroke.[305–315] No clinical trials have examined the effectiveness of smoking cessation for secondary prevention of stroke or TIA. Given the overwhelming evidence on the harm of smoking and the result of observational studies on the benefits of cessation,[316] however, such trials are not likely to be initiated.

Tobacco dependence is a chronic condition for which there are effective behavioral and pharmacotherapy treatments.[317–322] Updated information on how to treat tobacco dependence is available in *Treating Tobacco Use and Dependence: 2008 Update*.[323]

Cigarette Smoking 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 advise patients after TIA or ischemic stroke to avoid environmental (passive) tobacco smoke *(Class IIa; Level of Evidence B)*.**
3. **Counseling, nicotine products, and oral smoking cessation medications are effective in helping smokers to quit *(Class I; Level of Evidence A)*.**

Alcohol Consumption

Most of the evidence describing the relationship between alcohol consumption and stroke risk relates to primary stroke prevention and is covered in detail by the AHA/American Stroke Association's "Guidelines for the Primary Prevention of Stroke."[53] Few studies have directly examined the association of alcohol with the risk of recurrent stroke. In patients with a stroke or TIA from intracranial stenosis, alcohol use was protective against future ischemic stroke[326] ; however, heavy alcohol use, binge drinking, and acute alcohol ingestion may increase stroke risk,[94,325–327] as well as risk of recurrent stroke.[328]

In general, light to moderate alcohol consumption has been associated with a reduced risk of first-ever stroke, although the effect of alcohol differs according to stroke subtype. For ischemic strokes, there appears to be a J-shaped association between alcohol intake and risk of ischemic stroke, with a protective effect seen in light to moderate drinkers (up to ≈1 drink/d for women and up to ≈2 drinks/d for men) but elevated stroke risk with heavier alcohol use.[94,329–331] However, the risk of hemorrhagic stroke increases with any alcohol consumption, with greater risk with heavy use.[329,330]

The protective effect of moderate alcohol consumption may be related to increased levels of HDL-C, apolipoprotein A1, and adiponectin, as well as lower levels of fibrinogen and decreased platelet aggregation.[332,333] Heavy alcohol use may elevate stroke risk through increasing risks of hypertension, AF, cardiomyopathy, and DM.[334–336]

It is well established that alcohol can cause dependence and that alcoholism is a major public health problem. The balance between appropriate alcohol consumption and the risk of excessive use and dependency needs to be weighed in each individual patient. A primary goal for secondary stroke prevention is to eliminate or reduce alcohol consumption in heavy drinkers through established screening and counseling methods, such as those outlined by the US Preventive Services Task Force update.[337,338]

Alcohol Consumption Recommendations

1. **Patients with ischemic stroke, TIA, or hemorrhagic stroke who are heavy drinkers should eliminate or reduce their consumption of alcohol *(Class I; Level of Evidence C)*.**
2. **Light to moderate amounts of alcohol consumption (up to 2 drinks per day for men and up to 1 drink per day for nonpregnant women) may be reasonable, although nondrinkers should not be counseled to start drinking *(Class IIb; Level of Evidence B)*.**

Interventional Approaches for the Patient With Large-Artery Atherosclerosis

Extracranial Carotid Disease

Symptomatic Extracranial Carotid Disease

Many clinical trials, randomized and nonrandomized, comparing surgical intervention (carotid endarterectomy, or CEA) plus medical therapy to 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 statins, alternative antiplatelet agents such as clopidogrel or combination sustained-release dipyridamole-aspirin, optimized BP control, and smoking cessation therapy. Surgical techniques have also evolved. Furthermore, carotid

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angioplasty and stenting (CAS) has emerged as an alternative treatment for stroke prevention in patients with carotid atherosclerosis. Within the past several years, a number of clinical trials comparing the safety and efficacy of CAS and CEA have been completed and have added significantly to the knowledge base regarding the management of extracranial carotid disease.

Carotid Endarterectomy

Three major randomized trials have demonstrated the superiority of CEA plus medical therapy over medical therapy alone for symptomatic patients with a high-grade (>70% angiographic stenosis) atherosclerotic carotid stenosis.[339–341] 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. 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.[342] Additionally, each of these major trials showed that for patients with stenoses <50%, surgical intervention did not offer benefit in terms of stroke risk reduction.

The role of CEA is less clear with symptomatic stenoses in the 50% to 69% range. Among 858 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).[343] Thus, to prevent 1 ipsilateral stroke during the 5-year follow up period, 15 patients would have to undergo CEA.[343] The conclusions justify CEA only given appropriate case selection and when the risk-benefit ratio is favorable for the patient. Patients with a moderate (50%–69%) stenosis who are at reasonable surgical and anesthetic risk may benefit from intervention when performed by a surgeon with excellent operative skills. In NASCET, the rate of perioperative stroke or death was 6.7%. More recent population-based studies report a rate of 6%.[344] Because medical management has improved since NASCET, current guidelines advise proceeding with CEA only if the surgeon's rate for perioperative stroke or death is <6%.[22]

Patient-Selection Criteria Influencing Surgical Risk

The effect of sex on CEA results has been controversial. Some studies have identified a clear sex effect on perioperative stroke and death rates, although many such series combined asymptomatic and symptomatic people. Subgroup analyses of the NASCET trial have questioned the benefit of CEA in symptomatic women, although women were not well represented, and the effect of sex was not overwhelming.[343,345] 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).[346] The Carotid Revascularization Endarterectomy versus Stent Trial (CREST) was an RCT designed with preplanned subgroup analysis intended to evaluate the effects of sex and age on the primary outcome end point. CREST included both symptomatic and asymptomatic patients, and although it will be discussed in greater detail in this section, it is notable that there was no significant interaction in the primary end point of CREST between sexes. Conversely, there was a significant interaction found in relation to age, with superior results for CEA in patients aged >70 years.[347,348] There are limited data on the safety and efficacy of carotid revascularization on patients with advanced age specific to symptomatic patients, because octogenarians were frequently excluded from trials, including NASCET. However, case series have documented the safety of CEA in those ≥80 years of age.[349]

With modern perioperative care and anesthetic techniques, the effects of controlled medical comorbidities on outcomes after carotid revascularization are also ambiguous. Some studies comparing CAS and CEA have focused specifically on patients considered at high risk for surgical intervention and will be discussed in greater detail in the subsequent section on CAS. These studies suffer from the lack of a medical control arm and high rates of adverse outcome.

Conflicting data from RCTs leave doubt as to the overall effect of patient-selection criteria. However, outcome differences in age and sex, along with medical comorbidities, should be considered when deciding whether or not to proceed with carotid revascularization.

Timing of Carotid Revascularization

After a completed nondisabling stroke, the optimal timing for CEA is suggested by examination of data from the 3 major RCTs.[339–341,345,350,351] In these trials, the median time from randomization to surgery was 2 to 14 days, and one third of the perioperative strokes attributed to surgery occurred in this time interval. In medically treated patients, the risk of stroke was greatest in the first 2 weeks and declined subsequently. By 2 to 3 years, the annual rate of stroke in medically treated patients was low and approached the rate observed for asymptomatic patients.[342,345,350,351] A detailed analysis of data from ECST and NASCET showed that for patients with ≥70% carotid stenosis, the attributable risk reduction for any ipsilateral stroke or any stroke or death within 30 days of trial surgery fell from 30% when surgery occurred within 2 weeks of the most recent cerebrovascular event to 18% at 2 to 4 weeks and 11% at 4 to 12 weeks.[352] These findings influenced the writing committee for the AHA statement on carotid revascularization to recommend that surgery be performed within 2 weeks if there was no contraindication (Class IIa; Level of Evidence B).[22]

These 3 trials included only patients with nondisabling stroke or TIA and reported low rates of ICH associated with surgery (0.2%).[351] The risk for perioperative ICH may be increased with early surgery in patients with major cerebral infarction or stroke in evolution.[352]

Carotid Angioplasty and Stenting

CAS has emerged as a therapeutic alternative to CEA for the treatment of extracranial carotid artery occlusive disease. Carotid artery angioplasty is a less invasive percutaneous procedure that has been under investigation in the United States since 1994.[353] The proposed advantages of CAS are its less invasive nature, decreased patient discomfort, and a shorter recuperation period, which was reflected within CREST in

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the improved health-related quality of life in the perioperative period, although notably, the difference was not sustained at 1 year.[354] Historically, CAS has been offered mainly to those patients considered high risk for open endarterectomy based on the available data from large, multicenter, randomized studies. High risk is defined as (1) patients with severe comorbidities (class III/IV congestive heart failure, class III/IV angina, left main CAD, ≥2-vessel CAD, left ventricular (LV) ejection fraction ≤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.[355]

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).[356] In that trial, published in 2001, symptomatic patients suitable for surgery were randomized 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 were adopted to reduce periprocedural stroke rates and are required in endovascular procedures reimbursed by the Centers for Medicare & Medicaid Services. 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 to CEA in 334 symptomatic and asymptomatic high-risk patients.[357] The perioperative 30-day combined rate of stroke, death, and MI was 9.9% for surgery versus 4.4% for stenting. The 1-year rates of the primary end point of death, stroke, or MI at 30 days plus ipsilateral stroke or death of neurological causes within 31 days to 1 year were 20.1% for surgery and 12.2% for stenting (P=0.05). Despite the fact that these differences primarily represented differences in periprocedural MI rates, the major conclusion from this trial was that CAS was noninferior to CEA in this specific high-risk patient cohort. However, postprocedure morbidity and mortality in both treatment arms were high enough to call into question the benefit of either procedure compared with medical management in asymptomatic patients.[358,359]

Other RCTs, the EVA-3S (Endarterectomy Versus Angioplasty in Patients With Symptomatic Severe Carotid Stenosis), SPACE (Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy), and ICSS (International Carotid Stenting Study) trials, have compared CEA and CAS for symptomatic patients.[360] A preplanned meta-analysis of these studies found that the rate of stroke and death at 120 day after randomization was 8.9% for CAS and 5.8% for CEA (HR, 1.53; 95% CI, 1.20–1.95; P=0.0006). Among numerous subgroup analyses, age was shown to modify the treatment effect. Among patients aged ≥70 years, the rate of stroke or death at 120 days was 12.0% with CAS compared with 5.9% with CEA (HR, 2.04; 95% CI, 1.48–2.82; P=0.0053). In patients younger than 70 years of age, there was no significant difference in outcome between CAS and CEA.[361]

CREST was an RCT that compared the efficacy of CAS with that of CEA. 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, and MI and 4-year ipsilateral stroke) in patients treated with CAS versus CEA (7.2% versus 6.8%; HR for stenting, 1.1; 95% CI, 0.81–1.51; P=0.51). No significant effect modification was observed for surgical indication. In asymptomatic patients, the 4-year rate of the primary end point was 5.6% with CAS versus 4.9% with CEA (HR, 1.17; 95% CI, 0.69–1.98; P=0.56). By comparison, in symptomatic patients, the rates were 8.6% with CAS versus 8.4% with CEA (HR, 1.08; 95% CI, 0.74–1.59; P=0.69).

When all patients were analyzed (symptomatic and asymptomatic), there was an interaction between age and treatment efficacy (P=0.02).[362] For the primary outcome, the HR for CAS compared with CEA rose from 0.6 (95% CI, 0.31–1.18) for patients <65 years of age to 1.08 (95% CI, 0.65–1.78) for patients 65 to 74 years old to 1.63 (95% CI, 0.99–2.69) for patients aged ≥75 years. The risk of MI did not increase with age in either treatment group. Instead, the effect of age was driven primarily by stroke risk, which increased with age more in the CAS group than in the CEA group. The age at which the HR was 1.0 was ≈70 years for the primary outcomes and 64 years for stroke. There was no difference between CAS and CEA in periprocedural events among men, but there was a nonstatistically significant trend toward fewer events with women and CEA.[347] One of the key differences between CREST and the 3 trials summarized above was the inclusion of MI in the primary composite end point. The trial did attempt to determine the differential effect of CEA and CAS on health-related quality of life as measured by the SF-36 (Short-Form 36) physical and mental health scales. Periprocedural major or minor stroke had a detrimental effect on health-related quality of life at 1 year, but MI did not.[354]

Periprocedural complications were low in CREST compared with older trials. In the first 30 days, the rate of any stroke, MI, or death was 5.2% with CAS versus 4.5% with CEA (HR, 1.18; 95% CI, 0.82–1.68). An analysis for type of periprocedural complication identified important distinctions. Patient who had CAS had lower rates of MI than patients who had CEA (1.1% versus 2.3%; HR, 0.50; 95% CI, 0.26–0.94) but higher rates of stroke (4.1% versus 2.3%; HR, 1.79; 95% CI, 1.14–2.82). Finally, complication rates differed according to surgical indication. For asymptomatic

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patients, the rates were 3.5% for CAS versus 3.6% with CEA. For symptomatic patients, the rates were 6.7% with CAS and 5.4% with CEA.

In 2012, the Cochrane Stroke Group updated a systematic review of the results of randomized trials comparing CAS and CEA.[363] Sixteen trials representing 7572 patients were included in the review. In symptomatic patients with standard surgical risk, CAS was associated with a higher risk than CEA for death or any stroke within 30 days of treatment (OR, 1.72; 95% CI, 1.29–2.31), but the subsequent risk of ipsilateral stroke during the follow-up period did not differ significantly (OR, 0.93; 95% CI, 0.60–1.45). When periprocedural complications and stroke during follow-up were considered together, CAS was associated with an increased risk for death, any periprocedural stroke, or ipsilateral stroke during follow-up compared with patients assigned to CEA (OR, 1.39; 95% CI, 1.10–1.75). Similar to CREST, this systematic review showed an interaction between age and treatment effect. Among people <70 years old, the risk for the primary outcome was similar (OR for CAS, 1.16; 95% CI, 0.80–1.67). Among people aged ≥70 years, the risk was elevated for CAS (OR, 2.20; 95% CI, 1.47–3.29).

Follow-Up Imaging and Restenosis After Extracranial Carotid Intervention

There is a paucity of data regarding follow-up imaging and restenosis after CAS or CEA. The Asymptomatic Carotid Atherosclerosis Study (ACAS) trial demonstrated that risk for restenosis after CEA, defined as ≥60% narrowing of the lumen, was highest in the first 18 months after surgery (7.6%), with an incidence of only 1.9% in the next 42 months. These 18-month estimates are comparable to findings from the CEA arm of the more recently completed CREST trial (6.3% risk of restenosis >70% at 24 months of observation). Other observational studies or smaller clinical trials have reported variable rates of restenosis after CEA.[364–369] Imaging technique, length of follow-up, stenosis criterion, loss rates, and case mix undoubtedly contribute to these disparate findings. According to a recent narrative review, however, the rate of hemodynamically significant restenosis after CEA is probably 5% to 7% during variable periods of follow-up.[22,347] The rate may be reduced to <5% by use of patch angioplasty.[366,370]

Rates of restenosis were reported in older trials to be higher after CAS than after CEA. In the SPACE trial, the rate of restenosis (≥70% luminal occlusion) was 10.7% for CAS compared with 4.6% for CEA after 2 years. In CAVATAS, the rates after 5 years were 30.7% compared with 10.5%, respectively.[368,369] Six trials reviewed in the Cochrane review of CAS[363] reported the numbers of patients with severe restenosis (equivalent to ≥70% according to the measurement of stenosis used in NASCET) detected on ultrasound during follow-up; however, 2 of these trials also included patients with asymptomatic stenosis. The overall comparison showed higher restenosis rates among patients randomized to endovascular treatment than among those assigned to surgery (OR, 2.41; 95% CI, 1.28–4.53; P=0.007).[363]

A more current comparison of CAS and CEA is available for CREST.[371] Among 2191 CREST patients with follow-up, investigators used ultrasonography to examine the incidence of restenosis. This represents the most reliable data on this topic because of the CREST accreditation of ultrasound facilities and standardization of the ultrasound protocol. At 2 years, there was no difference in the incidence of restenosis between the 2 groups (6% with CAS, 6.3% with CEA; P=0.58).[371] DM, hypertension, and female sex were independent predictors of restenosis. Smoking was an independent predictor for restenosis with CEA but not CAS.

In summary, restenosis is reported after both CAS and CEA, and the most current data suggest that rates are similar between the 2 procedures. Restenosis is not clearly associated with a significantly increased risk for stroke.[22,364] In the absence of recurrent symptoms, therefore, the indication for repeat or surveillance ultrasonography after carotid revascularization is not defined.

Extracranial-Intracranial Bypass

The first major trial of extracranial-intracranial (EC/IC) bypass surgery randomized 1377 patients within 3 months of a TIA or minor ischemic stroke to surgery or best medical care.[372] Eligible patients had narrowing or occlusion of the ipsilateral middle cerebral artery (MCA), stenosis of the (surgically inaccessible) ipsilateral distal internal carotid artery (ICA), or occlusion of the ipsilateral midcervical ICA. After almost 5 years of follow-up, the primary outcome of fatal or nonfatal stroke was more common among participants assigned to surgery.[372] A subsequent trial examined the effectiveness of EC/IC bypass for prevention of ipsilateral stroke among a more selective high-risk group of 195 patients with evidence on positron emission tomography scanning of hemodynamic cerebral ischemia distal to a symptomatic ipsilateral carotid occlusion.[372–375] Similar to the earlier study, eligible patients had a TIA or ischemic stroke within 4 months of randomization. The trial was terminated early for futility. The 30-day rate of ipsilateral stroke was 14.4% in the surgical group and 2.0% in the nonsurgical group. The 2-year rate for the primary outcome (30-day stroke or death or subsequent ipsilateral stroke) was 21.0% in the surgical group and 22.7% in the nonsurgical group (P=0.78).

Extracranial Carotid Disease Recommendations

1. **For patients with a TIA or ischemic stroke within the past 6 months and ipsilateral severe (70%–99%) carotid artery stenosis as documented by noninvasive imaging, 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%–69%) carotid stenosis as documented by catheter-based imaging or noninvasive imaging with corroboration (eg, magnetic resonance angiogram or computed tomography angiogram), 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%, CEA and CAS are not recommended *(Class III; Level of Evidence A)*.**

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4. **When revascularization is indicated for patients with TIA or minor, nondisabling stroke, it is reasonable to perform the procedure within 2 weeks of the index event rather than delay 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 ICA is reduced by >70% by noninvasive imaging or >50% by catheter-based imaging or noninvasive imaging with corroboration and the anticipated rate of periprocedural stroke or death is <6% *(Class IIa; Level of Evidence B)*.** (Revised recommendation)
6. **It is reasonable to consider patient age in choosing between CAS and CEA. For older patients (ie, older than ≈70 years), CEA may be associated with improved outcome compared with CAS, particularly when arterial anatomy is unfavorable for endovascular intervention. For younger patients, CAS is equivalent to CEA in terms of risk for periprocedural complications (ie, stroke, MI, or death) and long-term risk for ipsilateral stroke *(Class IIa; Level of Evidence B)*.** (New recommendation)
7. **Among patients with symptomatic severe stenosis (>70%) in whom anatomic or medical conditions are present that greatly increase the risk for surgery or when other specific circumstances exist such as radiation-induced stenosis or restenosis after CEA, CAS is reasonable *(Class IIa; Level of Evidence B)*.** (Revised recommendation)
8. **CAS and CEA in the above settings should be performed by operators with established periprocedural stroke and mortality rates of <6% for symptomatic patients, similar to that observed in trials comparing CEA to medical therapy and more recent observational studies *(Class I; Level of Evidence B)*.** (Revised recommendation)
9. **Routine, long-term follow-up imaging of the extracranial carotid circulation with carotid duplex ultrasonography is not recommended *(Class III; Level of Evidence B)*.** (New recommendation)
10. **For patients with a recent (within 6 months) TIA or ischemic stroke ipsilateral to a stenosis or occlusion of the middle cerebral or carotid artery, EC/IC bypass surgery is not recommended *(Class III; Level of Evidence A)*.**
11. **For patients with recurrent or progressive ischemic symptoms ipsilateral to a stenosis or occlusion of a distal (surgically inaccessible) carotid artery, or occlusion of a midcervical carotid artery after institution of optimal medical therapy, the usefulness of EC/IC bypass is considered investigational *(Class IIb; Level of Evidence C)*.** (New recommendation)
12. **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 A)*.**

Extracranial Vertebrobasilar Disease

Extracranial vertebral artery stenosis (ECVAS) is a recognized cause of posterior circulation stroke. Detailed analysis of one registry estimated ECVAS was responsible for up to 9% of posterior circulation strokes.[376] A recent single-center prospective registry found that 35% of patients with posterior circulation stroke and ECVAS had no valid explanation for their stroke other than a vertebral artery ostial lesion.[377] Possible mechanisms of stroke include plaque rupture with thromboembolism and hemodynamic insufficiency. Treatment options for symptomatic ECVAS include medical therapy, endovascular stenting, and open surgical revascularization procedures.

Treatment decisions are hampered by the absence of RCTs comparing available treatment options. The only RCT to compare outcomes after endovascular treatment versus optimal medical treatment alone among patients with ECVAS is CAVATAS.[378] In that trial, which enrolled patients with either carotid or vertebral artery stenosis, just 16 subjects with symptoms in the vascular territory supplied by a stenosed vertebral artery were randomized to receive either endovascular therapy (angioplasty or stenting) or medical management alone and followed up for a mean of 4.7 years. In the endovascular group, 6 patients underwent percutaneous transluminal angioplasty alone, and 2 had stenting. The primary end point of vertebrobasilar stroke was not met by any patient in either group. There were 2 periprocedural TIAs in the endovascular group. Of note, 3 patients in each arm of the study died of MI or carotid territory stroke during follow-up, which led the authors to conclude that medical treatment should focus on "global reduction in vascular risk." Larger randomized trials will be necessary to better define evidence-based recommendations for these patients and assess whether vertebral artery stenting is of relevance as a primary treatment strategy in patients with symptomatic ECVAS.

There have been medical advances since CAVATAS concluded enrollment in 1997. There are no studies examining what type of medical therapy is "optimal" specifically for recently symptomatic ECVAS, although the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial demonstrated that an aggressive medical therapy strategy of dual-antiplatelet therapy (DAPT) with aspirin plus clopidogrel, prasugrel, or ticagrelor for 3 months, BP control, lipid-lowering therapy with statin medication, glycemic control, and risk factor modification was highly effective for secondary prevention of stroke in a similar condition, recently symptomatic large-vessel intracranial stenosis.[379]

Aggressive medical therapy may or may not be as effective for patients with symptoms caused by hemodynamic compromise from ECVAS. Efforts are under way to define a population that may benefit from revascularization procedures because of the high risk of recurrent vertebrobasilar stroke from hemodynamic compromise caused by ECVAS,[380] but at present, there are no studies specifically addressing this situation.

There have been numerous retrospective, nonrandomized case series of stenting for symptomatic ECVAS. A review of 27 such studies with a total of 980 patients indicates a

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technical success rate of 99%, with a periprocedural risk of 1.2% for stroke and 0.9% for TIA.[381] Stroke or TIA in the vertebrobasilar territory after the perioperative period occurred in only 1.3% and 6.5%, respectively, with an average follow-up of 21 months.[381] In a prospectively maintained database of 114 patients undergoing stenting for 127 vertebral ostial lesions, 88% of which were considered to be either "highly likely" or "probably" the cause of the patient's posterior circulation symptoms, recurrence of symptoms at 1 year was just 2% after stenting.[377]

The largest review of extracranial vertebral artery stenting indicates that restenosis rates may be lower with drug-eluting stents than with bare-metal stents (11.2% versus 30%),[381] although not all case series have shown such a discrepancy.[377] Also, the clinical significance of restenosis remains unclear. Studies defining whether the need for long-term DAPT with drug-eluting stents is offset by improved clinical outcomes because of possible lower restenosis rates compared with bare-metal stents are lacking.

Open surgical procedures for revascularization of ECVAS include vertebral artery endarterectomy and vertebral artery transposition. In appropriately selected patients, these procedures can have low morbidity and relieve symptoms.[382,383] In 1 series of 27 patients, there was no perioperative stroke or death, and there were 2 permanent neurological complications (1 case of Horner syndrome and 1 case of hoarseness); in addition, 2 patients available for follow-up developed neurological symptoms referable to the posterior circulation after the perioperative period.[382]

Extracranial Vertebrobasilar Disease Recommendations

1. **Routine preventive therapy with emphasis on antithrombotic therapy, lipid lowering, BP control, and lifestyle optimization is recommended for all patients with recently symptomatic extracranial vertebral artery stenosis *(Class I; Level of Evidence C)*.**
2. **Endovascular stenting of patients with extracranial vertebral stenosis may be considered when patients are having symptoms despite optimal medical treatment *(Class IIb; Level of Evidence C)*.**
3. **Open surgical procedures, including vertebral endarterectomy and vertebral artery transposition, may be considered when patients are having symptoms despite optimal medical treatment *(Class IIb; Level of Evidence C)*.**

Intracranial Atherosclerosis

Intracranial atherosclerosis is one of the most common causes of stroke worldwide and is associated with a particularly high risk of recurrent stroke.[384] Despite this, there have only been a few large, multicenter randomized trials evaluating stroke preventive therapies for this disease.

WASID Trial

In the WASID study, 569 patients with stroke or TIA attributable to 50% to 99% intracranial stenoses of the MCA, intracranial ICA, intracranial vertebral artery, or basilar artery were randomized to aspirin 1300 mg or warfarin (target international normalized ratio [INR], 2–3).[385] This double-blind trial, which was stopped early because of higher rates of death and major hemorrhage in the warfarin arm, showed that the primary end point (ischemic stroke, brain hemorrhage, and nonstroke vascular death) occurred in 22% of patients in both treatment arms over a mean follow-up of 1.8 years. The 1- and 2-year rates of stroke in the territory of the stenotic artery were 12% and 15% in the aspirin arm and 11% and 13% in the warfarin arm, respectively.[385] In analyses of both arms combined, the rates of stroke in the territory of the stenotic artery at 1 year were 18% in patients with ≥70% stenosis and 7% to 8% in patients with 50% to 69% stenosis.[386] Multivariate analysis showed that the risk of stroke in the territory of the stenotic artery was highest for severe stenosis (≥70%) and for patients enrolled early (≤17 days, which was the median time to enrollment in the trial) after their qualifying event. Women also appeared to be at increased risk,[386] Post hoc analyses did not identify any subgroup that benefited from warfarin, including those patients who had their qualifying event while taking aspirin.[387,388]

The WASID trial also suggested that control of BP and LDL-C may reduce the risk of subsequent stroke. Although there had been concern that BP lowering might impair cerebral blood flow and thereby increase stroke risk in patients with large-vessel stenosis, post hoc analysis showed that patients with mean SBP ≥140 mm Hg had a significantly increased risk of recurrent stroke compared with patients with mean SBP <140 mm Hg (HR, 1.63; P=0.01).[324,389] Additionally, patients with a mean LDL-C ≥100 mg/dL had a significantly increased risk of recurrent stroke compared with patients with mean LDL-C <100 mg/dL (HR, 1.72; P=0.03). The small subset of patients with LDL-C <70 mg/dL had a low rate of vascular events.[324]

Antiplatelet Therapy Trials

Three trials have compared different antiplatelet therapies in patients with intracranial arterial stenosis, but the primary end points in all these trials were related to imaging or transcranial Doppler ultrasound findings.[390–392] Two of these trials were double-blind trials that focused on the possible role of the phosphodiesterase inhibitor cilostazol for limiting progression of intracranial arterial stenosis.[390,391] In the first trial, 135 patients with symptomatic stenosis of the MCA or the basilar artery were randomized to either cilostazol 200 mg/d plus aspirin 100 mg/d or aspirin 100 mg/d alone. Follow-up magnetic resonance angiography showed less progression and more regression of stenosis at 6 months in the cilostazol group, but there were no recurrent strokes in either group.[390] In a subsequent trial, 457 patients with symptomatic stenosis of the MCA or the basilar artery were randomized to either cilostazol (100 mg twice per day) plus aspirin (75–150 mg/d), or clopidogrel (75 mg/d) plus aspirin (75–150 mg/d) and followed up for progression of stenosis on magnetic resonance angiography at 7 months. The percentage of patients with progression of stenosis was not statistically lower in the cilostazol and aspirin group (9.9%) than in the clopidogrel and aspirin group (15.5%; P=0.092). There were also no significant differences between the cilostazol versus clopidogrel arms in the rates of cardiovascular

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events (6.4% versus 4.4%; *P*=0.312), new ischemic lesions on brain MRI (18.7% versus 12.0%; *P*=0.078), or major hemorrhages (0.9% versus 2.6%; *P*=0.163).[391]

The third antiplatelet therapy trial was an open-label, multicenter clinical trial in patients with ischemic stroke or TIA within the past 7 days related to extracranial carotid or intracranial stenosis who had microembolic signals detected by transcranial Doppler.[392] Patients were randomized to clopidogrel plus aspirin daily or aspirin alone. Transcranial Doppler recordings for microembolic signals were repeated on day 1, 2, and 7. In an analysis restricted to 70 patients with intracranial arterial stenosis (34 in the combination-therapy arm and 36 in the aspirin-alone arm), emboli at day 7 in the combination-therapy arm were significantly less frequent than in the aspirin-alone arm (RR, 56.5%; 95% CI, 2.5–80.6; *P*=0.029). The number of emboli in the combination-therapy arm was significantly lower at day 2 (*P*=0.043) and day 7 (*P*=0.018) than in the aspirin-alone arm.[392]

There have been no randomized trials to evaluate the effectiveness of clopidogrel alone or the combination of aspirin and dipyridamole for prevention of recurrent stroke in patients with intracranial arterial stenosis.

SAMMPRIS Trial

Although several studies have suggested that intracranial angioplasty alone or combined with stenting can be performed with a high degree of technical success in patients with symptomatic intracranial arterial stenosis,[393–400] there has been only 1 published randomized trial that compared endovascular therapy with medical therapy for the prevention of recurrent stroke in patients with symptomatic intracranial arterial stenosis: the SAMMPRIS trial. Although follow-up in SAMMPRIS is ongoing, enrollment in the trial was stopped in April 2011, and the early results have been published.[379] In SAMMPRIS, patients with TIA or stroke within the past 30 days related to 70% to 99% stenosis of a major intracranial artery were randomized to aggressive medical management alone or aggressive medical management plus angioplasty and stenting with the Wingspan stent system (Stryker Neurovascular, Fremont, CA, USA; formerly Boston Scientific Neurovascular). Aggressive medical therapy in both arms consisted of aspirin 325 mg/d, clopidogrel 75 mg/d for 90 days after enrollment, intensive risk factor management that primarily targeted SBP <140 mm Hg (<130 mm Hg in patients with DM) and LDL-C <70 mg/dL, and a lifestyle modification program. The Wingspan stent system is the only angioplasty or stent system with US Food and Drug Administration (FDA) approval for the treatment of atherosclerotic intracranial stenosis. This approval, which followed a single-arm trial of 45 patients treated with the device,[398] is under a humanitarian device exemption for patients with 50% to 99% intracranial stenosis who are refractory to medical therapy, which in practice has largely been interpreted to mean having a TIA or stroke while undergoing antithrombotic therapy.

Enrollment in SAMMPRIS was stopped after 451 patients had been randomized primarily because the 30-day rate of stroke and death was significantly higher in the stenting arm. Within 30 days of enrollment, stroke or death occurred in 33 patients (14.7%) in the stenting arm and in 13 (5.8%) in the medical arm (*P*=0.002). There were 5 stroke-related deaths in the stenting arm (2.2%) and 1 nonstroke death in the medical arm (0.4%) within 30 days of enrollment. Of the strokes that occurred within 30 days, 10 of 33 (30.3%) in the stenting arm and none of 12 (0%) in the medical arm were symptomatic brain hemorrhages (*P*=0.04). At the time that the analyses were performed for the initial publication, stroke in the same territory had occurred in 13 patients in each group beyond 30 days of enrollment, and the estimated 1-year rates of the primary end point were 20.0% in the stenting arm and 12.2% in the medical arm (*P*=0.009). Estimated 1-year rates of major hemorrhage (any brain hemorrhage or major non–stroke-related hemorrhage) were 9.0% in the stenting arm and 1.8% in the medical arm (*P*<0.001).[379]

Of the 451 patients enrolled in SAMMPRIS, 284 (63%) had their qualifying event while undergoing antithrombotic therapy. In this large subgroup of the SAMMPRIS cohort, the rates of the primary end point were 16.0% and 4.3% at 30 days and 20.9% and 12.9% at 1 year in the stenting and medical arms, respectively (*P*=0.028 for the log-rank test comparing the time-to-event curves between the treatment groups).[401,402] As such, stenting with the Wingspan system is not a safe or effective rescue treatment for patients who experience a TIA or stroke while already being treated with antithrombotic therapy.

The rate of the primary end point in the medical arm of SAMMPRIS was much lower than projected based on the WASID trial. The subgroup of patients in WASID with the same entrance criteria as SAMMPRIS who were treated with aspirin or warfarin and usual risk factor management had a 30-day rate of stroke and death of 10.7% and a 1-year rate of the primary end point of 25%.[400] In comparison, the equivalent rates in the medical arm of SAMMPRIS were 5.8% and 12.2%, respectively.[379] Although comparisons with historical controls have important limitations, the substantially lower than projected risk of the primary end point in the medical arm of SAMMPRIS suggests that the aggressive medical therapy used in SAMMPRIS (DAPT, intensive management of SBP and LDL-C, and a lifestyle program) may be more effective than aspirin alone and usual management of vascular risk factors. Results from extended follow-up of the SAMMPRIS cohort were published in 2014 and demonstrated persistence of the early benefit of medical management over stenting with the Wingspan devise.[402a]

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. Lower doses of aspirin were effective in other large trials of secondary prevention, most of which enrolled patients with more heterogenous types of stroke. In the SAMMPRIS trial, the medical arm used 325 mg of aspirin daily and achieved favorable rates of stroke outcome compared with the intervention arm. All things considered, these data suggest that doses lower than 1300 mg/d are probably effective in patients with intracranial stenosis.

Some[393–395] but not all[396] studies have suggested that angioplasty alone may be safer and potentially more effective than

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stenting for the treatment of symptomatic intracranial arterial stenosis; however, all of these studies were retrospective. There have been no multicenter, prospective studies of angioplasty for intracranial stenosis, and there are no randomized studies comparing angioplasty alone with medical therapy.

EC/IC Bypass Study

In the International Cooperative Study of Extracranial/Intracranial Arterial Bypass (EC/IC Bypass Study),[372] which focused on symptomatic patients with extracranial carotid occlusion but also included patients with MCA stenosis and patients with ICA stenosis above the second cervical vertebra (C2), 109 patients with ≥70% MCA stenosis and 149 patients with ≥70% ICA stenosis were randomly assigned to bypass surgery or medical treatment with aspirin 1300 mg/d. Patients in the trial were followed up for a mean of 55.8 months. The rates of stroke during follow-up in patients with ≥70% MCA stenosis were 23.7% (14 of 59) in the medical arm and 44% (22 of 50) in the bypass arm, a statistically significant difference. In patients with ≥70% ICA stenosis above C2, the rates of stroke during follow-up were 36.1% (26 of 72) in the medical arm and 37.7% (29 of 77) in the bypass arm.[372] Given these results, EC/IC bypass has largely been abandoned as a treatment for intracranial stenosis.

Intracranial Atherosclerosis Recommendations

1. **For patients with a stroke or TIA caused by 50% to 99% stenosis of a major intracranial artery, aspirin 325 mg/d is recommended in preference to warfarin *(Class I; Level of Evidence B)*.** (Revised recommendation)
2. **For patients with recent stroke or TIA (within 30 days) attributable to severe stenosis (70%–99%) of a major intracranial artery, the addition of clopidogrel 75 mg/d to aspirin for 90 days might be reasonable *(Class IIb; Level of Evidence B)*.** (New recommendation)
3. **For patients with stroke or TIA attributable to 50% to 99% stenosis of a major intracranial artery, the data are insufficient to make a recommendation regarding the usefulness of clopidogrel alone, the combination of aspirin and dipyridamole, or cilostazol alone *(Class IIb; Level of Evidence C)*.** (New recommendation)
4. **For patients with a stroke or TIA attributable to 50% to 99% stenosis of a major intracranial artery, maintenance of SBP below 140 mm Hg and high-intensity statin therapy are recommended *(Class I; Level of Evidence B)*.** (Revised recommendation)
5. **For patients with a stroke or TIA attributable to moderate stenosis (50%–69%) of a major intracranial artery, angioplasty or stenting is not recommended given the low rate of stroke with medical management and the inherent periprocedural risk of endovascular treatment *(Class III; Level of Evidence B)*.** (New recommendation)
6. **For patients with stroke or TIA attributable to severe stenosis (70%–99%) of a major intracranial artery, stenting with the Wingspan stent system is not recommended as an initial treatment, even for patients who were taking an antithrombotic agent at the time of the stroke or TIA *(Class III; Level of Evidence B)*.** (New recommendation)
7. **For patients with stroke or TIA attributable to severe stenosis (70%–99%) of a major intracranial artery, the usefulness of angioplasty alone or placement of stents other than the Wingspan stent is unknown and is considered investigational *(Class IIb; Level of Evidence C)*.** (Revised recommendation)
8. **For patients with severe stenosis (70%–99%) of a major intracranial artery and recurrent TIA or stroke after institution of aspirin and clopidogrel therapy, achievement of SBP <140 mm Hg, and high-intensity statin therapy, the usefulness of angioplasty alone or placement of a Wingspan stent or other stent is unknown and is considered investigational *(Class IIb; Level of Evidence C)*.** (New recommendation)
9. **For patients with severe stenosis (70%–99%) of a major intracranial artery and actively progressing symptoms after institution of aspirin and clopidogrel therapy, the usefulness of angioplasty alone or placement of a Wingspan stent or other stents is unknown and is considered investigational *(Class IIb; Level of Evidence C)*.** (New recommendation)
10. **For patients with stroke or TIA attributable to 50% to 99% stenosis of a major intracranial artery, EC/IC bypass surgery is not recommended *(Class III; Level of Evidence B)*.**

Medical Treatments for Patients With Cardiogenic Embolism

Atrial Fibrillation

AF affects >2.7 million Americans and becomes more prevalent with age, ranking as the leading cardiac arrhythmia in the elderly.[1] The principal adverse consequence of AF is ischemic stroke. In the United States, this arrhythmia may be responsible for >70 000 ischemic strokes each year (ie, 10%–12% of all ischemic strokes).[53,403]

The risk of stroke among people with AF can be estimated by use of validated prediction instruments such as $CHADS_2$[404] or CHA_2DS_2–VASc.[405] For $CHADS_2$, patients with AF are classified according to a scoring system that awards points for congestive heart failure (1 point), hypertension (1 point), age ≥75 years (1 point), DM (1 point), and prior stroke or TIA (2 points). The risk of stroke increases according to point score: 1.9% per year (0 points), 2.8% per year (1 point), 4.0% per year (2 points), 5.9% per year (3 points), 8.5% per year (4 points), 12.5% per year (5 points), and 18.2% (6 points).[404] The CHA_2DS_2-VASc adds to stroke risk by reliably identifying patients at very low risk. Additional points are assigned for an additional age category of 65 to 74 years (1 point), female sex (1 point), and vascular disease other than cerebrovascular disease (1 point). Two points are awarded for age ≥75 years. The risk of stroke increases according to point score: 0.5% per year (0 points), 1.5% per year (1 point), 2.5% per year (2 points), 5% per year (3 points), 6% per year (4 points), and 7% per year (5–6 points).[405]

Both $CHADS_2$ and CHA_2DS_2-VASc may underestimate stroke risk for patients with a recent TIA or ischemic stroke

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who have no other risk factors.[21,406] Their risk for stroke may be closer to 7% to 10% per year.[406,407] Thus, treatment of AF among patients with prior ischemic stroke is a major focus of preventive care in neurology. Fortunately, a large body of clinical trial research has demonstrated that anticoagulation therapy is very effective in prevention of first and recurrent stroke. Antiplatelet therapy has a more limited role.

Stroke risk and preventive care have been less thoroughly examined among patients with atrial flutter than among those with AF, but affected patients often have intervals of AF and are at increased risk for sustained AF.[408] For purposes of secondary stroke prevention, it is common to apply the same recommendations to both conditions.[408]

Detection of Occult AF

Approximately 10% of patients with acute ischemic stroke or TIA will have new AF detected during their hospital admission[409]; however, an additional 11% may be found to have AF if tested with 30 days of discharge by continuous electrocardiographic monitoring.[403] Longer monitoring protocols up to 6 months have yielded similar detection rates.[403,410] In stroke or TIA patients with an indication for a pacemaker, interrogation of the device identified a 28% incidence of occult AF during 1 year.[411] A similar rate of occult AF has been reported among high-risk nonstroke patients with implantable cardiac rhythm devices.[412,413] Occult AF detected during pacemaker interrogation in stroke-free patients or mixed populations is associated with increased risk for stroke.[413–415]

Warfarin Therapy

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.[416] An analysis of pooled data from 5 primary prevention trials demonstrated an RR reduction of 68% (95% CI, 50%–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.[417] This absolute risk reduction indicates that 32 ischemic strokes will be prevented each year for every 1000 patients treated [100/(4.5−1.4)].

In addition to primary prevention, the effectiveness of warfarin for secondary prevention was confirmed in the European Atrial Fibrillation Trial (EAFT). This trial randomized 669 patients with nonvalvular AF to adjusted-dose warfarin (target INR, 3.0), 300 mg of aspirin daily, or placebo.[407] Compared with placebo, warfarin substantially reduced the main outcome (vascular death, MI, stroke, or systemic embolism; HR, 0.53; 95% CI, 0.36–0.79). The annual risk of stroke was reduced from 12% to 4% (HR, 0.34; 95% CI, 0.20–0.57). Overall, warfarin use has been shown to be relatively safe, with an annual rate of major bleeding of 1.3% in patients given warfarin compared with 1% for patients given placebo or aspirin.[414,416,417]

The optimal intensity of oral anticoagulation for stroke prevention in patients with AF is an INR of 2.0 to 3.0.[418] Results from a large case-control study[419] and 1 RCT[420] 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.[421] For patients with AF who experience 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 bleeding risk.

Antiplatelet Therapy

Because some patients cannot tolerate warfarin, there has been considerable interest in aspirin as an alternative therapy. A pooled analysis of data from 3 trials resulted in an estimated RR reduction of 21% compared with placebo (95% CI, 0%–38%).[418] The largest aspirin effect was observed in the Stroke Prevention in Atrial Fibrillation (SPAF 1) Trial, which used aspirin 325 mg/d. However, based on the results of studies performed in multiple vascular indications, the best balance of the efficacy and safety of aspirin appears to be ≈75 to 100 mg/d.[418]

The Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE A) study compared aspirin with clopidogrel plus aspirin in 7550 AF patients "for whom vitamin K–antagonist therapy was unsuitable."[422] After a median of 3.6 years of follow-up, the investigators observed a reduction in the rate of stroke with combination therapy (3.3% per year compared with 2.4% per year; RR, 0.72; 95% CI, 0.62–0.83; $P<0.001$). 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, 1.29–1.92; $P<0.001$). An analysis of major vascular events combined with major hemorrhage showed no difference between the 2 treatment options (RR, 0.97; 95% CI, 0.89–1.06; $P=0.54$). Overall, the benefit of adding clopidogrel to aspirin was modest at best.[423]

Compared with warfarin, however, antiplatelet therapy is less effective for primary stroke prevention. 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.[424] This study was stopped prematurely by the safety monitoring committee after 3371 patients were enrolled because of clear superiority of warfarin (INR 2.0–3.0) over the antiplatelet combination (RR, 1.44; 95% CI, 1.18–1.76; $P=0.0003$).

The superior efficacy of anticoagulation over aspirin for stroke prevention in patients with AF and a recent TIA or minor stroke was demonstrated in EAFT.[407]

Other Oral Anticoagulants

The narrow therapeutic margin and drug or food interactions of warfarin require frequent INR testing and dose adjustments. In response to these challenges, several new oral anticoagulants have been developed, including direct thrombin inhibitors and factor Xa inhibitors.

Dabigatran is the first direct thrombin inhibitor to be approved for treatment of AF in the United States. In a pivotal open-label trial, >18 000 AF patients with at least 1 additional stroke risk factor were randomized to dabigatran 150 mg twice daily, dabigatran 110 mg twice daily, or open-label warfarin. Patients with a creatinine clearance of <30 mL/min, pregnancy, or active liver disease were excluded. In the intention-to-treat analysis, both doses of dabigatran were noninferior to warfarin. Dabigatran 150 mg twice per day was

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associated with less stroke or systemic embolism.[425,426] The annual rate was 1.71% in the warfarin group compared with 1.11% in the dabigatran 150 mg group (RR, 0.65; 95% CI, 0.52–0.81; *P*<0.001). Among trial participants assigned to warfarin, the mean percentage of the study period when the INR was in the therapeutic range was 64%, which is similar to other trials.[421] No significant safety concerns were noted with dabigatran other than a small, statistically insignificant increase in MI (0.81% per year versus 0.64% per year; RR, 1.27; 95% CI, 0.94–1.71). This safety finding has also been reported in a recent systematic review, which characterized the supporting evidence as "low."[427] Annual rates of major bleeding were similar in the 3 treatment groups. An increased risk for gastrointestinal bleeding with dabigatran 150 mg twice per day was reported in the trial but has not been confirmed in postmarket studies.[428] In a predefined subgroup of patients with prior stroke or TIA (n=3623), the RR for stroke or systemic embolism was nonsignificantly reduced for dabigatran 110 mg twice daily (RR, 0.84; 95% CI, 0.58–1.20) and dabigatran 150 mg twice daily (RR, 0.75; 95% CI, 0.52–1.08).[429] These findings were similar to findings in the full cohort, except that the 150-mg dose of dabigatran was noninferior, rather than superior, to warfarin.

Two factor Xa inhibitors have been reported to be effective in large clinical trials and are approved for use in the United States. In the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) trial, 14 265 patients with nonvalvular AF and increased risk for stroke were randomized to rivaroxaban 20 mg/d or adjusted-dose warfarin.[430] The dose of rivaroxaban was reduced to 15 mg if the creatinine clearance was 30 to 49 mL/min. Patients with a creatinine clearance <30 mL/min were excluded. In the intention-to-treat analysis, the primary end point of stroke or systemic embolism occurred in 269 patients assigned to rivaroxaban compared with 306 patients assigned to warfarin (HR with rivaroxaban, 0.88; 95% CI, 0.74–1.03; *P*<0.001 for noninferiority, *P*=0.12 for superiority). Rates of major bleeding were similar in the 2 treatment groups, but site-specific differences were observed. Specifically, the rate of ICH was lower for rivaroxaban (0.5% compared with 0.7%; *P*=0.02), as was the rate for fatal hemorrhage (0.2% compared with 0.5%; *P*=0.003). Major gastrointestinal bleeding was more common with rivaroxaban (3.2% versus 2.2%, *P*<0.001). Results of a subgroup analysis showed no evidence that the treatment effect of rivaroxaban was different among patients who entered the study with a prior stroke or TIA compared with patients who entered without this history (HR with rivaroxaban among patients with prior stroke or TIA, 0.77; 95% CI, 0.58–1.01).[431] Patients assigned to warfarin in ROCKET-AF were in the therapeutic range only 55% of the time,[21,430] which is low compared with other trials.[421] This raises some concern about interpretation of the ROCKET-AF results.

The efficacy of apixaban has been examined in 2 trials. In the Apixaban Versus Acetylsalicylic Acid to Prevent Strokes study (AVVEROES), 5599 participants with nonvalvular AF and 1 additional stroke risk factor who were deemed unsuitable for vitamin K antagonist (VKA) therapy were randomized to apixaban 5 mg twice daily or aspirin.[432] Patients with renal insufficiency (creatinine >2.5 mg/dL) were excluded. After 1.1 years' mean follow-up, the trial was stopped early based on a favorable effect of apixaban. The primary outcome of stroke or systemic embolism occurred in 51 patients assigned to apixaban compared with 113 assigned to aspirin (HR with apixaban, 0.45; 95% CI, 0.32–0.62). Rates of major bleeding were similar with apixaban (1.4%) and aspirin (1.2%; HR with apixaban,1.13; 95% CI, 0.74–1.75). Rates of gastrointestinal bleeding, in particular, were identical (0.4% per year). In the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, 18 201 patients with nonvalvular AF and at least 1 other stroke risk factor were randomized to apixaban 5 mg twice daily or adjusted-dose warfarin.[433] As in AVERROES, patients with renal insufficiency (serum creatinine level >2.5 mg/dL) were excluded. After a median follow-up of 1.8 years, the primary outcome of ischemic stroke, hemorrhagic stroke, or systemic embolism occurred in 212 patients assigned to apixaban compared with 265 assigned to warfarin (HR with apixaban, 0.79; 95% CI, 0.66–0.95; *P*<0.001 for noninferiority and *P*=0.01 for superiority). Rates of major ICH were significantly lower among patients assigned to apixaban. Rates of gastrointestinal bleeding were similar. Rates of the primary outcome were consistent among patients who entered with or without a prior history of stroke or TIA.[434] Patients assigned to warfarin were in the therapeutic range for a mean of 62% of the time.

Unlike warfarin, for which vitamin K and fresh-frozen plasma may be used to reverse anticoagulation during acute bleeding, no similar antidotes are available for the newer oral anticoagulants. The short half-life of these agents, however, provides some protection.

Combination Anticoagulation and Antiplatelet Therapy

There is no clear evidence that combining anticoagulation with antiplatelet therapy for AF patients reduces the risk of stroke or MI compared with anticoagulant therapy alone, but there is clear evidence of increased bleeding risk.[435–438] Therefore, the addition of aspirin to anticoagulation therapy should be avoided in most patients with stroke related to AF.

The exception to this may be patients with clinically apparent CAD, particularly an acute coronary syndrome or a drug-eluting stent. Approximately 20% of patients with ischemic stroke related to AF also have a history of clinically apparent CAD. Other patients with stroke related to AF will develop acute coronary syndromes in the future.[407,438,439] Because antiplatelet therapy is known to be effective for secondary prevention of CAD,[440] clinicians commonly add antiplatelet therapy to oral anticoagulation therapy for AF patients with comorbid CAD. For patients with acute coronary syndromes or coronary stent placement, in particular, there is broad agreement that DAPT is indicated.[441–443] The challenge is to balance the benefit of dual therapy (aspirin or an ADP receptor antagonist plus anticoagulation) or triple therapy (aspirin plus an ADP receptor antagonist plus anticoagulation) with the heightened risk of bleeding over anticoagulation alone.

The evidence to guide dual or triple therapy in patients with AF and clinically apparent CAD is sparse.[444] No trials

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have been designed to specifically test dual or triple therapy in patients with comorbid AF and clinically apparent CAD. The ACCP recently reviewed the data on this topic, however, and concluded that the benefits of dual therapy (oral anticoagulation plus aspirin or clopidogrel) outweighed the risks for patients at high risk for stroke (eg, $CHADS_2$ score ≥2) for the first 12 months after an acute coronary syndrome.[408] This group also concluded that the benefits of triple therapy (oral anticoagulation plus aspirin and clopidogrel) outweighed the risks in patients at high risk for stroke during a finite interval after placement of a coronary stent. The ACC Foundation/AHA guidelines for unstable angina/non–ST-segment–elevation MI include a recommendation to prescribe aspirin therapy indefinitely even if patients are also taking warfarin.[441] The ACC Foundation/AHA guidelines for ST-segment–elevation MI (STEMI) recommend indefinite aspirin therapy without specific mention of warfarin.[445] No trials have compared combination therapy antiplatelet/warfarin with warfarin alone in stroke populations specifically.

Of note, in trials of newer oral anticoagulants for treatment of AF (ie, ROCKET-AF, RE-LY [Randomized Evaluation of Long-Term Anticoagulation Therapy], ARISTOTLE), 30% to 40% of patients in compared treatment groups were taking aspirin, usually at a dose of <100 mg/d.

Nonpharmacological Approaches

An alternative strategy to prevent 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.[446] In this open-label trial, 707 warfarin-eligible AF patients were randomized to receive either the WATCHMAN (Boston Scientific, Natick, MA) 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 3.0 per 100 patient-years in the WATCHMAN group compared with 4.9 in the warfarin group (RR, 0.62; 95% CI, 0.35–1.25). The criterion for noninferiority was satisfied. 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 the greatest clinical utility for AF patients at high risk of stroke who are poor candidates for oral anticoagulation; however, more data are required in these patient populations before a recommendation can be made.

Timing of Therapeutic Initiation

The risk of early recurrence of ischemic stroke related to AF may be as high as 8% in 14 days.[3,447] In theory, early initiation of anticoagulation may be effective in preventing early recurrence. This potential benefit, however, must be balanced with the potential risk for ICH. The only randomized trial on this topic examined the effectiveness of dalteparin compared with aspirin for prevention of recurrence in 449 patients with acute ischemic stroke and AF.[447] Dalteparin was not effective, but the risk of ICH was low in both groups (2.7% with dalteparin, 1.8% with aspirin; OR, 1.52; 95% CI, 0.42–5.46). Observational data also suggest that the risk of initiating anticoagulation within 1 to 7 days is low in selected patients. Among 260 consecutive patients without high-risk features for bleeding (ie, large infarct, hemorrhagic transformation on initial imaging, uncontrolled hypertension, hemorrhage tendency), the risk for symptomatic ICH while undergoing anticoagulation therapy was 1.5% within 14 days.[448] Risk is higher among patients with larger infarcts or previous hemorrhagic stroke.

Other than the Heparin in Acute Embolic Stroke Trial (HAEST) trial described above,[447] prior trials have provided only rough guidance on timing. In EAFT,[407] which enrolled patients with TIA or minor stroke, oral anticoagulation was found to be effective in a protocol that initiated anticoagulation within 14 days of symptom onset in approximately half of the patients. In the trials of direct thrombin or factor Xa inhibitors, the study drug could not be started within 7 to 14 days of a stroke event.[426,430,433] The RE-LY trial delayed eligibility for 6 months after a severe stroke.[429]

After reviewing available evidence, the ACCP recently recommended initiation of anticoagulation within 2 weeks of a cardioembolic stroke, except for patients with large infarcts or other risk factors for hemorrhage.[449] Available data do not show greater efficacy of the acute administration of anticoagulants over antiplatelet agents in the setting of cardioembolic stroke.[47] 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 who are found on transesophageal echocardiogram to have a left atrial appendage thrombus).

Management of Therapeutic Failure

For patients with AF who have an ischemic stroke or TIA despite therapeutic anticoagulation, there are no data to indicate that either increasing the intensity of anticoagulation or adding an antiplatelet agent provides additional protection against future ischemic events. In addition, both of these strategies are associated with an increase in bleeding risk. For example, in the Stroke Prevention Using Oral Thrombin Inhibitor in Atrial Fibrillation (SPORTIF) study, AF patients with prior stroke or TIA who were treated with the combination of aspirin and warfarin had 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.[436] High INR values are clearly associated with increased hemorrhage risk; the risk of ICH increases dramatically at INR values >4.0.[418]

Bridge Therapy When Anticoagulation Must Be Interrupted

Patients with AF and prior stroke or TIA have increased stroke risk when oral anticoagulant therapy is temporarily interrupted (typically for surgical procedures).[450] The issue of whether to use bridging therapy with intravenous heparin or a low-molecular-heparin (LMWH) in these situations has been reviewed recently.[451] In general, bridging anticoagulation is recommended for AF patients taking warfarin who

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are assessed as being at particularly high risk for perioperative arterial or venous thromboembolism ($CHADS_2$ score of 5 or 6, stroke or TIA within 3 months, or rheumatic valvular heart disease). For AF patients at moderate risk ($CHADS_2$ score of 3–4), the decision for bridging or no bridging should take into consideration other factors related to the patient and the surgery. The preferred method for bridging is typically an LMWH administered in an outpatient setting in full treatment doses (as opposed to low prophylactic doses).[451] Optimal perioperative practices specifically for patients taking one of the new oral anticoagulant agents have not been developed.

Of note, however, abrupt discontinuation of newer oral anticoagulant agents may be associated with increased risk for stroke and other arterial occlusive events. When possible, patients should be transitioned to another anticoagulant agent without interruption of therapeutic effect.

Competing Causes of Stroke or TIA

Approximately one fourth of patients who present with AF and an ischemic stroke will be found to have other potential causes for the stroke, such as carotid stenosis.[452] For these patients, treatment decisions should focus on the presumed most likely stroke cause. In most cases, it will be appropriate to initiate anticoagulation because of the AF, as well as an additional therapy (such as CEA).

AF Recommendations

1. **For patients who have experienced an acute ischemic stroke or TIA with no other apparent cause, prolonged rhythm monitoring (≈30 days) for AF is reasonable within 6 months of the index event *(Class IIa; Level of Evidence C)*.** (New recommendation)
2. **VKA therapy *(Class I; Level of Evidence A)*, apixaban *(Class I; Level of Evidence A)*, and dabigatran *(Class I; Level of Evidence B)* are all indicated for the prevention of recurrent stroke in patients with nonvalvular AF, whether paroxysmal or permanent. The selection of an antithrombotic agent should be individualized on the basis of risk factors, cost, tolerability, patient preference, potential for drug interactions, and other clinical characteristics, including renal function and time in INR therapeutic range if the patient has been taking VKA therapy.** (Revised recommendation)
3. **Rivaroxaban is reasonable for the prevention of recurrent stroke in patients with nonvalvular AF *(Class IIa; Level of Evidence B)*.** (New recommendation)
4. **For patients with ischemic stroke or TIA with paroxysmal (intermittent), persistent, or permanent AF in whom VKA therapy is begun, a target INR of 2.5 is recommended (range, 2.0–3.0) *(Class I; Level of Evidence A)*.**
5. **The combination of oral anticoagulation (ie, warfarin or one of the newer agents) with antiplatelet therapy is not recommended for all patients after ischemic stroke or TIA but is reasonable in patients with clinically apparent CAD, particularly an acute coronary syndrome or stent placement (*Class IIb; Level of Evidence C*).** (New recommendation)
6. **For patients with ischemic stroke or TIA and AF who are unable to take oral anticoagulants, aspirin alone is recommended *(Class I; Level of Evidence A)*. The addition of clopidogrel to aspirin therapy, compared with aspirin therapy alone, might be reasonable *(Class IIb; Level of Evidence B)*.** (Revised recommendation)
7. **For most patients with a stroke or TIA in the setting of AF, it is reasonable to initiate oral anticoagulation within 14 days after the onset of neurological symptoms *(Class IIa; Level of Evidence B)*.** (New recommendation)
8. **In the presence of high risk for hemorrhagic conversion (ie, large infarct, hemorrhagic transformation on initial imaging, uncontrolled hypertension, or hemorrhage tendency), it is reasonable to delay initiation of oral anticoagulation beyond 14 days *(Class IIa; Level of Evidence B)*.** (New recommendation)
9. **For patients with AF and a history of stroke or TIA who require temporary interruption of oral anticoagulation, bridging therapy with an LMWH (or equivalent anticoagulant agent if intolerant to heparin) is reasonable, depending on perceived risk for thromboembolism and bleeding *(Class IIa; Level of Evidence C)*.**
10. **The usefulness of closure of the left atrial appendage with the WATCHMAN device in patients with ischemic stroke or TIA and AF is uncertain *(Class IIb; Level of Evidence B)*.** (New recommendation)

Acute MI and LV Thrombus

Patients with large anterior MI associated with an LV ejection fraction <40% and anteroapical wall-motion abnormalities are at increased risk for developing LV mural thrombus because of stasis of blood in the ventricular cavity and endocardial injury with associated inflammation. Before the advent of acute reperfusion interventions and aggressive antiplatelet and antithrombotic therapy in the peri-infarct period, LV mural thrombus was documented in 20% to 50% of patients with acute MI.[453–456] More recent studies indicate that the incidence of mural thrombus is ≈15% in patients with anterior MI and 27% in those with anterior STEMI and an LV ejection fraction <40%.[457–459] In the absence of systemic anticoagulation, the risk of embolization within 3 months among patients with MI complicated by mural thrombus is 10% to 20%.[456,460]

RCTs to assess the value of antithrombotic therapy for prevention of mural thrombus and stroke in patients with STEMI have not been conducted. However, in a randomized, open-label trial comparing warfarin, aspirin, or the combination in 3630 patients with acute MI followed up for a mean of 4 years, the primary composite outcome of death, nonfatal reinfarction, or thromboembolic stroke was observed in 241 of 1206 participants assigned to aspirin (20%), 203 of 1216 assigned to warfarin (16.7%), and 181 of 1208 assigned to combined therapy (15%).[461] The primary outcome was reduced by 19% in patients receiving warfarin (P=0.03) and by 29% in patients receiving combination therapy (P<0.001) compared with patients receiving aspirin alone. Moreover, there was a 48% reduction in the risk of thromboembolic stroke in both warfarin groups relative to aspirin. Major nonfatal bleeding

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was 4-fold more common in patients receiving warfarin (0.62% per year) than in those receiving aspirin (0.17% per year).[461] In addition, several observational studies have examined the association between anticoagulation and the risks of LV thrombus formation and systemic embolization in patients with anterior STEMI. In a meta-analysis of 11 such studies, Vaitkus and Barnathan[460] reported that treatment with VKAs decreased the risk of both LV thrombus formation (OR, 0.32; 95% CI, 0.20–0.52) and embolization (OR, 0.14; 95% CI, 0.04–0.52). The overall risk of embolization in patients with LV thrombus was 11% compared with 2% in patients without thrombus (OR, 5.45; 95% CI, 3.02–9.83).[460]

The potential benefits of systemic anticoagulation for prevention of LV mural thrombus formation and stroke/arterial embolization must be balanced against the risks of major bleeding complications, including intracranial hemorrhage. Current guidelines for the treatment of STEMI recommend percutaneous coronary intervention with placement of a bare-metal or drug-eluting stent at the site of acute coronary occlusion, if feasible (Class I; Level of Evidence A).[445] As a result, most patients with anterior STEMI will receive DAPT. Whether the addition of warfarin to DAPT provides incremental benefit in preventing stroke in high-risk patients is unknown. Although the risk of bleeding associated with triple-antithrombotic therapy varies considerably as a function of age, sex, and prevalent comorbidities, an analysis conducted by the ACCP estimated that in patients with large anterior STEMI without LV mural thrombus, the addition of warfarin to DAPT would prevent 7 nonfatal strokes at a cost of 15 nonfatal extracranial hemorrhages per 1000 treated patients.[462] Among patients with documented LV thrombus, warfarin added to DAPT would prevent 44 nonfatal strokes at the same cost of 15 nonfatal extracranial bleeds.[462] In addition, it was estimated that compared with DAPT, triple therapy would be associated with 11 fewer MIs per 1000 treated patients.[462]

The duration of risk of thrombus formation and embolization after a large MI is uncertain, but the risk appears to be highest during the first 1 to 2 weeks, with a subsequent decline over a period of up to 3 months.[462] After 3 months, the risk of embolization diminishes as residual thrombus becomes organized, fibrotic, and adherent to the LV wall. However, patients with persistent mobile or protruding thrombus visualized by echocardiography or another imaging modality may remain at increased risk for stroke and other embolic events beyond 3 months.[445]

To date, no studies have examined the efficacy and safety of newer antithrombotic agents, including dabigatran, rivaroxaban, apixaban, or fondaparinux, for prevention of LV thrombus or stroke in patients with acute MI. Therefore, if long-term anticoagulation is planned, VKA therapy remains the agent of choice for this indication.[445]

Current ACC Foundation/AHA guidelines for the treatment of acute STEMI provide a Class IIa recommendation (Level of Evidence C) for VKA therapy in patients with STEMI and asymptomatic LV thrombus.[445] This recommendation does not consider the specific circumstances of patients with ischemic stroke or TIA before or in the setting of MI with documented LV thrombus, who may be at increased risk for recurrent ischemic cerebrovascular events.

Acute MI and LV Thrombus Recommendations

1. **Treatment with VKA therapy (target INR, 2.5; range, 2.0–3.0) for 3 months is recommended in most patients with ischemic stroke or TIA in the setting of acute MI complicated by LV mural thrombus formation identified by echocardiography or another imaging modality *(Class I; Level of Evidence C)*. Additional antiplatelet therapy for cardiac protection may be guided by recommendations such as those from the ACCP.** (Revised recommendation)
2. **Treatment with VKA therapy (target INR, 2.5; range, 2.0–3.0) for 3 months may be considered in patients with ischemic stroke or TIA in the setting of acute anterior STEMI without demonstrable LV mural thrombus formation but with anterior apical akinesis or dyskinesis identified by echocardiography or other imaging modality *(Class IIb; Level of Evidence C)*.** (New recommendation)
3. **In patients with ischemic stroke or TIA in the setting of acute MI complicated by LV mural thrombus formation or anterior or apical wall-motion abnormalities with an LV ejection fraction <40% who are intolerant to VKA therapy because of nonhemorrhagic adverse events, treatment with an LMWH, dabigatran, rivaroxaban, or apixaban for 3 months may be considered as an alternative to VKA therapy for prevention of recurrent stroke or TIA *(Class IIb; Level of Evidence C)*.** (New recommendation)

Cardiomyopathy

Patients with ischemic or nonischemic dilated cardiomyopathy are at increased risk for stroke. In 1 study of 1886 patients with LV ejection fraction ≤35% and sinus rhythm, the incidence of stroke was 3.9% over a 35-month follow-up period.[463] In another study of 2114 patients with sinus rhythm and LV ejection fraction ≤35%, the annual rate of thromboembolic events without antithrombotic therapy was 1.7%.[464] Stroke rates may be higher in certain subgroups, including patients with prior stroke or TIA, lower ejection fraction, LV noncompaction, peripartum cardiomyopathy, and Chagas heart disease.[464–469] Conversely, ≈10% of patients with ischemic stroke have an LV ejection fraction ≤30%.[470]

There have been at least 4 published randomized trials that evaluated the effects of antithrombotic therapy on clinical outcomes, including strokes, in patients with heart failure and reduced LV ejection fraction.[471–474] In the largest and most recent of these studies (Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction [WARCEF]), 2305 patients with sinus rhythm, heart failure, and an LV ejection fraction ≤35% were randomized to aspirin 325 mg/d or warfarin with a target INR of 2.0 to 3.5.[474] The primary outcome was time to first event, with a composite outcome of death of any cause, ischemic stroke, or intracranial hemorrhage. After a mean follow-up of 3.5 years, there was no difference in primary outcome event rates between aspirin and warfarin (7.93 versus 7.47 per 100 patient-years; HR with warfarin, 0.93; 95% CI, 0.79–1.10; P=0.40). Warfarin was associated with a reduced risk of ischemic stroke (0.72 versus 1.36 per 100 patient-years; HR, 0.52; 95% CI, 0.33–0.82; P=0.005). The

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rates of intracranial hemorrhage did not differ between groups, but the risk of major bleeding was higher with warfarin (1.78 versus 0.87 per 100 patient-years; $P<0.001$). A total of 294 patients (12.8%) with prior stroke or TIA were included in WARCEF, but subgroup analysis of outcomes in these patients has not been reported.

The main findings of WARCEF were recently confirmed in a meta-analysis of data on all 3681 patients enrolled in the 4 randomized trials.[475] In that analysis, warfarin was associated with a 41% reduction in the risk of stroke (pooled relative risk, 0.59; 95% CI, 0.41–0.85; $P=0.004$; number needed to treat to prevent 1 event=61) and a nearly 2-fold increase in the risk of major hemorrhage (pooled relative risk, 1.95; 95% CI, 1.37–2.76; $P=0.0001$; number needed to harm=34). There were more than twice as many intracranial hemorrhages among warfarin-treated patients (pooled risk ratio, 2.17), but the difference was not statistically significant. There were no differences between warfarin and aspirin with respect to mortality, MI, or heart failure exacerbation. These findings have been confirmed in a second meta-analysis that adopted death or stroke as its primary end point.[476] Among patients with heart failure and sinus rhythm enrolled in 4 trials of warfarin compared with aspirin, there was no significant difference for the primary end point (RR, 0.94; 95% CI, 0.84–1.06). Warfarin was associated with a reduced risk for any stroke (RR, 0.56; 95% CI, 0.38–0.82) and ischemic stroke (RR, 0.45; 95% CI, 0.24–0.86). Warfarin had no effect on death, but its use did result in higher risk for major bleeding.

Although less common than dilated cardiomyopathies, restrictive cardiomyopathies, such as amyloid heart disease and hypereosinophilic syndrome with endocardial fibrosis (Loeffler syndrome), are also associated with increased risk of stroke and arterial embolization attributable to left atrial appendage thrombus or LV mural thrombus.[477–479] In the absence of contraindications, systemic anticoagulation is recommended in patients with restrictive cardiomyopathy and evidence of thrombus in the left atrium or ventricle or history of arterial embolization.[477–479]

Recently, mechanical LV assist devices (LVADs) have been implanted with increasing frequency in patients with advanced heart failure caused by severe LV systolic dysfunction as a bridge to transplantation, bridge to recovery, or destination therapy. Current-generation LVADs are associated with nonhemorrhagic cerebrovascular infarction rates of 4% to 9% per year,[480] and the risk is 2- to 3-fold higher in patients with prior stroke or postoperative infections.[481] Routine anticoagulation with VKA therapy and antiplatelet agents is recommended after LVAD implantation.[480] However, because patients with LVADs are also at increased risk for major hemorrhage, the dose of antithrombotic therapy must be individualized.

As with acute MI, no data are available on the use of newer anticoagulant agents for prevention of stroke in patients with cardiomyopathy or mechanical assist devices. Thus, VKA therapy is recommended for use in patients for whom systemic anticoagulation is indicated.

Cardiomyopathy Recommendations

1. **In patients with ischemic stroke or TIA in sinus rhythm who have left atrial or LV thrombus demonstrated by echocardiography or another imaging modality, anticoagulant therapy with a VKA is recommended for ≥3 months *(Class I; Level of Evidence C)*.** (New recommendation)
2. **In patients with ischemic stroke or TIA in the setting of a mechanical LVAD, treatment with VKA therapy (target INR, 2.5; range, 2.0–3.0) is reasonable in the absence of major contraindications (eg, active gastrointestinal bleeding) *(Class IIa; Level of Evidence C)*.** (New recommendation)
3. **In patients with ischemic stroke or TIA in sinus rhythm with either dilated cardiomyopathy (LV ejection fraction ≤35%) or restrictive cardiomyopathy without evidence of left atrial or LV thrombus, the effectiveness of anticoagulation compared with antiplatelet therapy is uncertain, and the choice should be individualized *(Class IIb; Level of Evidence B)*.** (Revised recommendation)
4. **In patients with ischemic stroke or TIA in sinus rhythm with dilated cardiomyopathy (LV ejection fraction ≤35%), restrictive cardiomyopathy, or a mechanical LVAD who are intolerant to VKA therapy because of nonhemorrhagic adverse events, the effectiveness of treatment with dabigatran, rivaroxaban, or apixaban is uncertain compared with VKA therapy for prevention of recurrent stroke *(Class IIb; Level of Evidence C)*.** (New recommendation)

Valvular Heart Disease

The magnitude of risk for brain embolism from a diseased heart valve depends on the nature and severity of the disease. Patients at high risk may be suitable candidates for anticoagulation. Others may be treated with antiplatelet therapy or no therapy. In all cases, careful therapeutics requires weighing the risks for thromboembolism and bleeding.

Mitral Stenosis

The principal mitral valve diseases include stenosis, regurgitation, prolapse, and mitral annular calcification. Mitral stenosis most commonly results from rheumatic fever.[482–484] After the initial streptococcal infection, the mitral valve leaflets undergo progressive fibrotic change that narrows the orifice. Symptoms usually do not appear for several years.[485] The main proximate cause for embolic stroke in mitral stenosis of any cause is AF,[486,487] although embolism sometimes can occur before AF develops. Other factors associated with increased stroke risk in mitral stenosis include older age, left atrial enlargement, reduced cardiac output, and prior embolic event.[483] In older studies from before the era of chronic anticoagulation, recurrent cerebral embolism was reported in 30% to 65% of patients within 6 to 12 years.[488,489] The majority of patients in these studies had AF, and more than half of recurrences developed within the first year.[488,489] The effectiveness of antithrombotic therapy in mitral stenosis has not been examined in clinical trials[484]; however, there is broad agreement that anticoagulation is indicated in mitral stenosis complicated by AF, prior embolism, or left atrial thrombus.[23,483490,491] Anticoagulation may be considered when the left atrium is

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enlarged ≥55 mm according to echocardiography.[23,490] The safety and efficacy of combining antiplatelet and anticoagulant therapy have not been evaluated in patients with rheumatic valve disease, but it is well known that combination therapy increases bleeding risk.[492]

Mitral Valve Regurgitation and Mitral Valve Prolapse

Chronic mitral regurgitation is the most common valvular heart disease in the United States.[493] Two classes of mechanisms are recognized, organic and functional.[494] Organic mechanisms are mediated by damaged valve leaflets, most commonly myxomatous degeneration, endocarditis, and rheumatic fever. Functional mechanisms are mediated by ventricular remodeling (valves are normal), most commonly cardiomyopathy. In the absence of AF, mitral regurgitation is probably not associated with a significant increase in risk for first or recurrent stroke.

An early case-control study reported that mitral valve prolapse, the most common cause of organic mitral regurgitation, was associated with an increased risk for ischemic stroke in people <45 years of age (OR, 7.00; 95% CI, 3.81–10.19).[495] However, possible bias was introduced in the selection of subjects, and the diagnosis was based on echocardiographic criteria that are no longer used. More recent observational cohort and case-control studies have not confirmed an association.[496–498] In the midst of some lingering uncertainty in this area, observational studies provide reassuring information that the risk for stroke in people with mitral valve prolapse is low (<1% annually).[499–502]

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

Mitral Annular Calcification

Idiopathic calcification of the mitral valve is common in the general population[503–508] and is detected on ultrasonography in ≥10% of patients with TIA or ischemic stroke.[509,510] The condition affects women more than men and is strongly associated with age.[508] The association between mitral annular calcification and risk for stroke has been examined in at least 4 population-based cohort studies.[503,506,508,511] All 4 excluded patients with a prior stroke. In the Framingham Heart Study, mitral annular calcification was associated with increased risk for all types of stroke during 8 years of observation (adjusted RR, 2.10; 95% CI, 1.24–3.57); however, only 14 of 22 outcome strokes were embolic, and some were associated with development of AF during follow-up. In an analysis confined to the outcome of ischemic stroke, the association remained only marginally significant (adjusted RR, 1.78; 95% CI, 1.00–3.16). Two of the other 3 population-based studies did not reveal a significant association between mitral annular calcification and risk for ischemic stroke in adjusted analyses.[503,506] No association was observed among 568 patients assigned to placebo in an AF trial.[512] Mitral annular calcification is associated with cardiovascular risk factors and atherosclerosis in other vascular distributions.[504,513,514] Therefore, the association between mitral annular calcification and increased risk for stroke observed in some studies may be the result of shared risk factors rather than direct causation.[511] No research has adequately examined the association between mitral annular calcification and risk for recurrent ischemic stroke.

No RCTs have examined the safety and efficacy of antithrombotic therapy specifically in patients with TIA or stroke who also have mitral annular calcification.

Aortic Valve Disease

Aortic valvular disease includes aortic regurgitation and aortic stenosis. Chronic aortic regurgitation is most commonly caused by age-related calcification, infective endocarditis, aortic disease, or rheumatic disease.[483] The most common causes of aortic stenosis are a bicuspid valve, age-related calcification, and rheumatic disease.[483] Neither aortic regurgitation nor aortic stenosis is known to be associated with increased risk for first or recurrent stroke in patients who are free of AF or associated mitral valve disease.

Studies of lesser degrees of aortic disease, including aortic valve sclerosis and aortic annular calcification, have also not confirmed an association with increased risk for stroke.[503,511] The evidence for an association between native aortic valve disease and increased risk for stroke is from case reports and case series of patients with specific cardiac lesions such as such as Libman-Sacks endocarditis,[515] age-related calcification,[516] or bicuspid valves.[517] Pathological studies have demonstrated microthrombi on damaged aortic valves, which suggests a possible source for emboli,[518] but the clinical significance is uncertain.

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.

Mitral Stenosis, Mitral Regurgitation, Mitral Prolapse, Mitral Annular Calcification, and Aortic Valve Disease Recommendations

1. **For patients with ischemic stroke or TIA who have rheumatic mitral valve disease and AF, long-term VKA therapy with an INR target of 2.5 (range, 2.0–3.0) is recommended *(Class I; Level of Evidence A)*.** (Revised recommendation)
2. **For patients with ischemic stroke or TIA who have rheumatic mitral valve disease without AF or another likely cause for their symptoms (eg, carotid stenosis), long-term VKA therapy with an INR target of 2.5 (range, 2.0–3.0) may be considered instead of antiplatelet therapy *(Class IIb; Level of Evidence C)*.** (New recommendation)
3. **For patients with rheumatic mitral valve disease who are prescribed VKA therapy after an ischemic stroke or TIA, antiplatelet therapy should not be routinely added *(Class III; Level of Evidence C)*.**
4. **For patients with rheumatic mitral valve disease who have an ischemic stroke or TIA while being treated with adequate VKA therapy, the addition of aspirin might be considered *(Class IIb; Level of Evidence C)*.** (New recommendation)
5. **For patients with ischemic stroke or TIA and native aortic or nonrheumatic mitral valve disease**

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who do not have AF or another indication for anticoagulation, antiplatelet therapy is recommended *(Class I; Level of Evidence C)*. (Revised recommendation)

6. **For patients with ischemic stroke or TIA and mitral annular calcification who do not have AF or another indication for anticoagulation, antiplatelet therapy is recommended as it would be without the mitral annular calcification *(Class I; Level of Evidence C)*.** (Revised recommendation)
7. **For patients with mitral valve prolapse who have ischemic stroke or TIAs and who do not have AF or another indication for anticoagulation, antiplatelet therapy is recommended as it would be without mitral valve prolapse *(Class I; Level of Evidence C)*.** (Revised recommendation)

Prosthetic Heart Valves

Mechanical Valves

All patients with mechanical heart valves are at increased risk for thromboembolic events, but the risk can be reduced with use of oral VKAs.[519,520] The recommended INR intensity varies depending on the type of mechanical valve, the location of the valve, and other factors that may influence risk for embolism, including embolic events preceding or during therapy.[23,490,521]

Current recommendations from the ACC/AHA and from the ACCP are divergent with respect to the intensity of anticoagulation therapy for patients with mechanical valves in the aortic position who have a prior thromboembolic event, including ischemic stroke or TIA.[23,490,522] The former recommends an INR of 2.5 to 3.5, whereas the latter recommends an INR of 2.0 to 3.0. The more conservative recommendation of the ACCP is based on the absence of compelling evidence that prior embolism increases risk for future stroke and the absence of any clinical trial evidence to guide the choice of therapy in patients with embolic stroke before or after aortic valve replacement surgery. Both organizations suggest more intensive therapy (ie, INR 2.5–3.5) for patients with mechanical valves in the mitral position compared with the aortic position, regardless of prior embolism, and both organizations recommend addition of aspirin therapy to all patients with mechanical valves who are at low risk for bleeding.[523,524]

Effective intervention for secondary prevention may be different for patients who have a first stroke before versus after mechanical valve replacement. Unfortunately, the evidence to refine decision making on the basis of this distinction has not yet been developed.

Of note, recent trials of novel oral anticoagulant agents in AF excluded patients with mechanical and bioprosthetic heart valves.[426,430,432,433] A recent trial of dabigatran compared with warfarin in patients with mechanical heart valves, the RE-ALIGN Trial (Randomized Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients After Heart Valve Replacement; ClinicalTrials.gov, unique identifier: NCT01505881), was stopped early without demonstrating a benefit for dabigatran.

Bioprosthetic Valves

Bioprosthetic valves are associated with a lower rate of thromboembolism than mechanical valves[23,483,490]; however, risk for thromboembolism is not uniform and is affected by specific patient features, such as AF. Guidelines from the ACCP recommend antiplatelet therapy alone for long-term protection in patients in sinus rhythm.[23] The ACC/AHA guidelines are similar but recommend VKA therapy in the presence of other thromboembolism risk factors besides AF (ie, previous thromboembolism, severe LV dysfunction, or hypercoagulable condition).[522]

Patients who have a thromboembolic stroke after placement of a bioprosthetic valve may be at increased risk for recurrence.[23] Limited data suggest the annual risk for a second event is ≈5%.[525] No clinical trial data are available to guide therapy in people who develop a stroke after implantation of a prosthetic valve, but the ACC/AHA recommends intensification of therapy once adequate adherence to the initial regimen is assured.[490]

The recommendations below are closely based on those of the ACCP.[23]

Prosthetic Heart Valve Recommendations

1. **For patients with a mechanical aortic valve and a history of ischemic stroke or TIA before its insertion, VKA therapy is recommended with an INR target of 2.5 (range, 2.0–3.0) *(Class I; Level of Evidence B)*.** (Revised recommendation)
2. **For patients with a mechanical mitral valve and a history of ischemic stroke or TIA before its insertion, VKA therapy is recommended with an INR target of 3.0 (range, 2.5–3.5) *(Class I; Level of Evidence C)*.** (New recommendation)
3. **For patients with a mechanical mitral or aortic valve who have a history of ischemic stroke or TIA before its insertion and who are at low risk for bleeding, the addition of aspirin 75 to 100 mg/d to VKA therapy is recommended *(Class I; Level of Evidence B)*.** (New recommendation)
4. **For patients with a mechanical heart valve who have an ischemic stroke or systemic embolism despite adequate antithrombotic therapy, it is reasonable to intensify therapy by increasing the dose of aspirin to 325 mg/d or increasing the target INR, depending on bleeding risk *(Class IIa; Level of Evidence C)*.** (Revised recommendation)
5. **For patients with a bioprosthetic aortic or mitral valve, a history of ischemic stroke or TIA before its insertion, and no other indication for anticoagulation therapy beyond 3 to 6 months from the valve placement, long-term therapy with aspirin 75 to 100 mg/d is recommended in preference to long-term anticoagulation *(Class I; Level of Evidence C)*.** (New recommendation)
6. **For patients with a bioprosthetic aortic or mitral valve who have a TIA, ischemic stroke, or systemic embolism despite adequate antiplatelet therapy, the addition of VKA therapy with an INR target of 2.5 (range, 2.0–3.0) may be considered *(Class IIb; Level of Evidence C)*.** (Revised recommendation)

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Antithrombotic Therapy for Noncardioembolic Stroke or TIA

Antiplatelet Agents

Four antiplatelet drugs have been approved by the FDA for prevention of vascular events among patients with a stroke or TIA (ie, aspirin, combination aspirin/dipyridamole, clopidogrel, and ticlopidine). On average, these agents reduce the RR of stroke, MI, or death by ≈22%,[440] 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.[526–529] In a meta-regression analysis of placebo-controlled trials of aspirin therapy for secondary stroke prevention, the RR reduction for any type of stroke (ie, hemorrhagic or ischemic) was estimated at 15% (95% CI, 6%–23%).[530] The magnitude of the benefit is similar for doses ranging from 50 to 1500 mg,[440,526–528,530,531] although the data for doses <75 mg are limited.[440] 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.[526,527] For patients who use lower doses of aspirin (≤325 mg) for prolonged intervals, the annual risk of serious gastrointestinal hemorrhage is ≈0.4%, which is 2.5 times the risk for nonusers.[526,527,532,533] Aspirin therapy is associated with an increased risk of hemorrhagic stroke that is smaller than the risk for ischemic stroke, which results in a net benefit.[534]

Ticlopidine

Ticlopidine is a platelet ADP receptor antagonist that has been evaluated in 3 randomized trials of patients with cerebrovascular disease.[535–537] Ticlopidine was superior to placebo in 1 trial[537] and to aspirin in another,[536] and a third trial found no benefit compared with aspirin.[535] Because of the side effect profile and availability of newer agents, ticlopidine is rarely used in current clinical practice

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, it has been tested for secondary stroke prevention in 2 trials, 1 comparing it with aspirin[533] alone and 1 comparing it with combination aspirin/dipyridamole.[538] In each trial, rates of primary outcomes were similar between the treatment groups. Clopidogrel has not been compared with placebo for secondary stroke prevention.[539]

Clopidogrel was compared with aspirin alone in the Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial.[533] More than 19 000 patients with stroke, MI, or peripheral vascular disease were randomized to aspirin 325 mg/d or clopidogrel 75 mg/d. The 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%–16.5%; P=0.043). Notably, in a subgroup analysis of patients who entered CAPRIE after having 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, −5.7% to 18.7%; P=0.26). CAPRIE was not designed to determine whether clopidogrel was superior or equivalent to aspirin among stroke patients.

Clopidogrel was compared with combination aspirin and extended-release dipyridamole in the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial. PRoFESS was designed as a noninferiority study. Among 20 332 patients with noncardioembolic ischemic stroke who were followed up for a mean of 2.5 years, recurrent stroke occurred in 9.0% of participants assigned to aspirin/dipyridamole compared with 8.8% assigned to clopidogrel (HR, 1.01; 95% CI, 0.92–1.11). Because the upper bound of the CI crossed the noninferiority margin (HR, 1.075), the investigators concluded that the results failed to show that aspirin/dipyridamole was not inferior to clopidogrel. Although the risk of intracranial hemorrhage was not significantly different with the 2 treatments, the risk of gastrointestinal hemorrhage was increased significantly with aspirin plus extended-release dipyridamole compared with clopidogrel.

Overall, the safety of clopidogrel is comparable to that of aspirin, with only minor differences.[533] 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 than among those given aspirin or placebo in published trials,[443,533] but a few cases of thrombotic thrombocytopenic purpura have been described.[540] Recently, evidence has emerged that proton pump inhibitors (PPIs), such as esomeprazole, may reduce the effectiveness of clopidogrel.[541] However, a large population study from Denmark suggested that PPIs themselves may increase the risk of cardiovascular events, so that when they are used with clopidogrel, the PPI may be the culprit.[542] When antacid therapy is required in a patient taking clopidogrel, an H2 blocker should be considered, and if a PPI is used, pantoprazole may be preferable to omeprazole because of reduced effects at the CYP2C19 P-450 cytochrome site.[543] In addition to PPI effects on the CYP2C19 system, 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).[544]

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 RCTs. 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),[545] which randomized 2500

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patients to placebo or the combination of 325 mg of aspirin plus 75 mg of immediate-release dipyridamole 3 times per 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 per day plus extended-release dipyridamole 200 mg twice per day; (2) aspirin 25 mg twice daily; (3) extended-release dipyridamole alone; and (4) placebo.[546] Compared with placebo, the risk of stroke was reduced by 18% with aspirin monotherapy ($P=0.013$), 16% with dipyridamole monotherapy ($P=0.039$), and 37% ($P<0.001$) with the combination. Compared with aspirin alone, combination therapy reduced the risk of stroke by 23% ($P=0.006$) and of 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, the European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT), was investigator driven and 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.[547] Although the dose of aspirin could vary at the discretion of the treating physician from 30 to 325 mg/d, 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, 0.66–0.98; absolute risk reduction, 1.0% per year; 95% CI, 0.1–1.8). 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 explain in part the differing outcome rates.

The fourth trial was the PRoFESS study described above,[538] which showed no difference in stroke rates between patients assigned to clopidogrel and those assigned to combination dipyridamole and aspirin. Major hemorrhagic events were more common among patients assigned to aspirin plus extended-release dipyridamole (4.1% compared with 3.6%), but this did not meet statistical significance. Adverse events that led to drug discontinuation (16.4% compared with 10.6%) were more common among patients assigned to aspirin plus extended-release dipyridamole. The combination therapy was shown to be less well tolerated than single-antiplatelet therapy, with a higher rate of side effects and more early discontinuations.

A recent study compared extended-release dipyridamole (200 mg) plus aspirin (25 mg) twice daily with aspirin 100 mg once daily for preservation of neurological function at 90 days after an ischemic stroke. Therapy was initiated within 24 hours of symptom onset. Patients assigned to aspirin alone were converted to the combination therapy after day 7. At day 90, there was no significant difference in functional ability as measured by the modified Rankin scale.[548]

Combination 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.[549] A total of 7599 patients were followed up for 3.5 years for the occurrence of the primary composite outcome of ischemic stroke, MI, vascular death, or rehospitalization for any central or peripheral ischemic event. There was no significant benefit of combination therapy compared with clopidogrel alone in reducing the primary outcome or any of the secondary outcomes. The risk of major hemorrhage was significantly increased in the combination group compared with clopidogrel alone, with a 1.3% absolute increase in life-threatening bleeding. Although clopidogrel plus aspirin is recommended over aspirin for acute coronary syndromes, the results of MATCH do not suggest a similar risk-benefit ratio for patients with stroke and TIA who initiate therapy beyond the acute period.

Combination clopidogrel and aspirin has been compared with aspirin alone in 4 secondary prevention trials, 3 large[7,550,551] and 1 small.[552] The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial[550] enrolled 15 603 patients with clinically evident CVD (including stroke or TIA within 5 years) or multiple risk factors. After a median of 28 months, the primary outcome (MI, stroke, or death of 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, 0.83–1.05; $P=0.22$). An analysis among the subgroup of patients who entered the study after having had a stroke showed increased bleeding risk but no statistically significant benefit of combination therapy compared with aspirin alone. In the recently published SPS3 trial, 3026 patients with MRI-confirmed lacunar stroke within 180 days were randomized to clopidogrel 75 mg plus aspirin 325 mg daily versus aspirin 325 mg daily.[7] The primary outcome measure was recurrent ischemic or hemorrhagic stroke, and a rate of 2.7% per year was seen in the aspirin-monotherapy group and 2.5% in the combination-therapy group. The ischemic stroke rate was slightly lower in the combination group, but the intracranial hemorrhage rate was slightly higher. All-cause mortality was significantly higher in the combination-therapy group, as was the risk for major hemorrhagic side effects, primarily driven by an increased risk for gastrointestinal hemorrhage.

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Two trials have examined the effectiveness of the combination of aspirin and clopidogrel for prevention of stroke in the months immediately after a TIA. The Fast Assessment of Stroke and Transient Ischemic Attack to Prevent Early Recurrence (FASTER) trial[552] was designed to test the effectiveness of combination therapy (aspirin 81 mg daily plus clopidogrel 300-mg loading dose followed by 75 mg daily) 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 and demonstrated a trend toward a reduced rate of ischemic outcome events with combination therapy, with only a small 1% increased risk for symptomatic ICH. More recently, a large RCT in China demonstrated a benefit of combination therapy for patients with an acute minor ischemic stroke or TIA.[551] The Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events (CHANCE) trial enrolled patients aged ≥40 years within 24 hours of their event. The study was double-blind and placebo controlled. Participants in both treatment groups received aspirin 75 to 300 mg on day 1 (dose selected at the discretion of the treating physician). Participants assigned to combination therapy received aspirin 75 mg daily on days 2 to 21, clopidogrel 300 mg on day 1, and clopidogrel 75 mg on days 2 to 90. Participants assigned to aspirin received 75 mg on days 2 to 90. The primary outcome of ischemic or hemorrhagic stroke was observed in 8.6% of participants assigned to combination therapy compared with 11.7% assigned to aspirin monotherapy (HR, 0.68; 95% CI, 0.57–0.81). Rates of moderate or severe bleeding were similar in the 2 groups. Because the epidemiology of stroke and secondary prevention practices are different in China compared with the United States and Europe, the authors of the CHANCE study allude to the importance of ongoing similar trials in these populations for confirmation of the international applicability of their findings.

Selection of Oral Antiplatelet Therapy

With publication of the CHANCE study, timing may need to be considered in the selection of an antiplatelet agent. The combination of aspirin and clopidogrel, initiated within 24 hours after a minor ischemic stroke or TIA, may be effective in preventing recurrent stroke within the first 90 days. Results of the ongoing Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) trial (ClinicalTrials.gov, unique identifier: NCT00991029) will provide further guidance in this area of therapeutics.

When therapy is initiated after the acute period or continued beyond 90 days, 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 to placebo, and studies comparing it to other antiplatelet agents have not clearly established that it is superior to any one of them. Observation of the survival curves from CAPRIE and PRoFESS indicate that clopidogrel is probably as effective as the combination of aspirin/dipyridamole and, by inference, aspirin. Clopidogrel appears to be safer than the aspirin/dipyridamole combination.

Selection among agents for long-term secondary prevention 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[546] and the combination of stroke, MI, death, or major bleeding.[547] On average, compared with aspirin alone, the combination may prevent 1 event among 100 patients treated for 1 year.[547] Ticlopidine may be more effective than aspirin for secondary prevention,[536] but safety concerns and side effects limit its clinical value. Ticlopidine is associated with thrombotic thrombocytopenic purpura and should be used only cautiously in patients who cannot tolerate other agents.

Risk for gastrointestinal hemorrhage or other major hemorrhage may be greater with aspirin or combination aspirin/dipyridamole than with clopidogrel.[533,538] The difference is small, however, amounting to 1 major hemorrhage event per 500 patient-years.[538] The risk appears to be similar for aspirin at doses of 50 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.

In terms of cost, aspirin is by far the least expensive agent. The cost of aspirin, at acquisition, is less than 1/20th the cost of other agents.

Patient characteristics that may affect choice of agent include tolerance of specific agents and comorbid illness. For patients intolerant to 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[443] or recent vascular stenting.[442,443]

Resistance or Nonresponsiveness of Antiplatelet Agents

A substantial minority of patients taking aspirin or clopidogrel are resistant to the effects of these drugs as measured by platelet function testing. The cause of the differential patient response to these antiplatelet drug assays is multifactorial and may be related to comorbid conditions such as DM, genetic factors, and concomitant drug use.[553] Patients with coronary ischemia who are nonresponders to aspirin and clopidogrel are at greater risk of subsequent ischemic vascular events and death.[554] Although it might seem intuitive to switch patients who are resistant to the effects of aspirin or clopidogrel to an alternative therapy or add a second drug, the risks and benefits of such an approach have not been well studied. In a trial of patients receiving coronary stents, patients assigned to platelet function monitoring and drug adjustment based on these results tended to have more outcome events than patients who were not monitored and did not have their medication adjusted.[555] In another recent report, 250 ischemic stroke patients and 74 TIA patients underwent platelet function testing by optical platelet aggregation responses to arachidonic acid or ADP. Of those taking aspirin, 43% were deemed to be nonresponders, as were 35% of those taking clopidogrel.[556] Of the 324 total patients in the study, 73 had their antiplatelet regimen modified and 251 did not. The rate of subsequent death, bleeding, or ischemic events with or without propensity score adjustment was significantly higher when modification

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of antiplatelet therapy was performed than for patients in whom no modification was performed (40% versus 21%). Modifications of antiplatelet therapy occurred significantly more frequently in patients who were nonresponsive to aspirin or clopidogrel. Although this study was modest in size, it has substantial clinical implications and should be replicated by other groups with a larger sample of stroke/TIA patients. The clinical significance of abnormal results on currently available platelet function tests remains unclear with respect to risk of future stroke or TIA. At this time, routine platelet function testing in this population cannot be recommended, and the results should not be used to modify current antiplatelet therapy treatment.

Selection of Antiplatelet Agents for Patients Who Have a Stroke While Undergoing Therapy

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

Combination of Oral Anticoagulants and Antiplatelet Agents

Although the combination of oral anticoagulants and antiplatelet agents is seldom used in stroke/TIA patients without cardiovascular comorbidity, this combination is frequently used in patients with AF and CAD.[557] As discussed, oral anticoagulation is highly effective in reducing stroke risk in AF patients, and it is well established that antiplatelet agents reduce the primary and secondary risk for MI in CAD patients.[558] The risk for major bleeding side effects is increased substantially with combination therapy, and such therapy may not be needed in most patients with combined AF and CAD, because prior studies demonstrated that oral anticoagulation with VKA therapy is at least as effective as antiplatelet therapy for prevention of MI.[438,559] Therefore, in most patients with AF with or without a history of stroke and concomitant CAD, the use of VKA therapy alone should be sufficient to reduce the risk of both cardiovascular and cerebrovascular events. The exception is patients with a recent stent placement, for whom there is no evidence that VKA therapy alone is sufficient.

Newer Agents

At least 3 additional antiplatelet agents have been investigated for their potential effectiveness in secondary stroke prevention: triflusal, cilostazol, and sarpogrelate.[560–562] A recent noninferiority trial failed to show that sarpogrelate was not inferior to aspirin.[560] Triflusal has been examined in several trials and has not been found to be superior to asprin.[562] Cilostazol has FDA approval for treatment of intermittent claudication and is further along in its development as a stroke treatment. The effectiveness of cilostazol compared with aspirin (doses not specified) was examined initially in a randomized, double-blind pilot study that enrolled 720 patients with a recent ischemic stroke.[561] During 12 to 18 months of follow-up, cilostazol was associated with a nonsignificant reduction in the primary end point of any stroke (HR, 0.62; 95% CI, 0.30–1.26). In a larger phase 3 noninferiority trial, 2757 Asian patients with noncardioembolic stroke were randomized to cilostazol 100 mg twice daily or aspirin 81 mg once daily.[563] Rates of drug discontinuation were high (34% in the cilostazol group and 25% in the aspirin group). After a mean follow-up of 29 months, the annual rates for the primary end point of any stroke were 2.76% in the cilostazol group and 3.71% in the aspirin group (HR, 0.74; 95% CI, 0.64–0.98). The criterion for noninferiority was met. Cerebral infarction, a secondary end point, was not reduced significantly by cilostazol (2.43% per year versus 2.75% per year; HR, 0.89; 95% CI, 0.65–1.20). The benefit of cilostazol compared with aspirin appears to be related to fewer intracranial and systemic hemorrhages (0.77% versus 1.78% per year; HR, 0.46; 95% CI, 0.30–0.71). In particular, intracranial hemorrhage was less frequent in the cilostazol group than in the aspirin group (8 versus 27 events, respectively). Cilostazol has not been studied in non-Asian populations, so it is uncertain whether this effect is translatable to other groups. The novel antiplatelet agent terutroban was compared with aspirin in a large trial that enrolled >19 000 patients with ischemic stroke and TIA.[564] Terutroban did not demonstrate noninferiority when compared with aspirin, and development was stopped. Thus far, none of these newer agents have been approved by the FDA for prevention of recurrent stroke.

Antiplatelet Agent 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 (50–325 mg/d) monotherapy (*Class I; Level of Evidence A*) or the combination of aspirin 25 mg and extended-release dipyridamole 200 mg twice daily *(Class I; Level of Evidence B)* is indicated as initial therapy after TIA or ischemic stroke for prevention of future stroke.** (Revised recommendation)
3. **Clopidogrel (75 mg) monotherapy is a reasonable option for secondary prevention of stroke in place of aspirin or combination aspirin/dipyridamole *(Class IIa; Level of Evidence B)*. This recommendation also applies to patients who are allergic to aspirin**.
4. **The selection of an antiplatelet agent should be individualized on the basis of patient risk factor profiles, cost, tolerance, relative known efficacy of the agents, and other clinical characteristics *(Class I; Level of Evidence C)*.**
5. **The combination of aspirin and clopidogrel might be considered for initiation within 24 hours of a minor ischemic stroke or TIA and for continuation for 90 days *(Class IIb; Level of Evidence B)*.** (New recommendation)
6. **The combination of aspirin and clopidogrel, when initiated days to years after a minor stroke or TIA and continued for 2 to 3 years, increases the risk of hemorrhage relative to either agent alone and is not recommended for routine long-term secondary prevention after ischemic stroke or TIA *(Class III; Level of Evidence A)*.**
7. **For patients who have an ischemic stroke or TIA while taking aspirin, there is no evidence that**

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increasing the dose of aspirin provides additional benefit. Although alternative antiplatelet agents are often considered, no single agent or combination has been adequately studied in patients who have had an event while receiving aspirin *(Class IIb; Level of Evidence C)*.

8. **For patients with a history of ischemic stroke or TIA, AF, and CAD, the usefulness of adding antiplatelet therapy to VKA therapy is uncertain for purposes of reducing the risk of ischemic cardiovascular and cerebrovascular events *(Class IIb; Level of Evidence C)*. Unstable angina and coronary artery stenting represent special circumstances in which management may warrant DAPT/VKA therapy.** (New recommendation)

Oral Anticoagulants

Several randomized trials have compared VKAs with antiplatelet therapy to prevent recurrent stroke among patients presenting with noncardioembolic stroke or TIA.[385,565–570] Most of these trials enrolled patients with heterogeneous causes of stroke such as large-artery extracranial or intracranial atherosclerosis, small-vessel disease, or cryptogenic stroke, but 2 of these studies[385,568] restricted enrollment to patients presenting with TIA or stroke related to atherosclerotic intracranial arterial stenosis. None of these randomized trials have shown a benefit of VKAs over antiplatelet therapy for preventing recurrent stroke, whereas some of these trials have shown an increased risk of major hemorrhage in the VKA arm.[385,565,567]

The largest of these trials were the Stroke Prevention in Reversible Ischemia Trial (SPIRIT),[565] the Warfarin-Aspirin Recurrent Stroke Study (WARSS),[566] and ESPRIT.[567] SPIRIT enrolled 1316 patients and was stopped early because of increased bleeding among those treated with high-intensity oral anticoagulation (INR 3.0–4.5) compared with aspirin (30 mg/d).[565] In WARSS, warfarin (INR 1.4–2.8) was compared with aspirin (325 mg/d) in a double-blinded manner in 2206 patients with a noncardioembolic stroke.[566] There was no significant difference between warfarin and aspirin for the prevention of recurrent stroke or death within 2 years (warfarin 17.8% versus aspirin 16.0%, P=0.25; HR, 1.13; 95% CI, 0.92–1.38). The rates of major bleeding were not significantly different (2.2 per 100 patient-years in the warfarin group versus 1.49 per 100 patient-years in the aspirin group). Subgroup analyses showed no benefit of warfarin over aspirin among different baseline stroke subtypes, including large-artery stenosis or occlusion, small-vessel disease, or cryptogenic stroke. In ESPRIT, oral anticoagulation (INR 2.0–3.0) was compared with aspirin (30–325 mg/d) in 1068 patients.[567] The trial was stopped early because of the superiority of the combination of aspirin and dipyridamole over aspirin alone in a companion trial. The mean follow-up in ESPRIT was 4.6 years, and the mean INR achieved was 2.57. The primary outcome (death of all vascular causes, nonfatal stroke, nonfatal MI, or major bleeding) occurred in 19% of patients in the anticoagulation arm and 18% of patients in the aspirin arm (HR, 1.02; 95% CI, 0.77–1.35). Patients treated with anticoagulation experienced a significantly higher rate of major bleeding (HR, 2.56; 95% CI, 1.48–4.43) and a nonstatistically significant lower rate of ischemic events (HR, 0.73; 95% CI, 0.52–1.01) compared with aspirin alone.[567]

A recent meta-analysis of 8 randomized trials[571] (including SPIRIT, WARSS, and ESPRIT) involving a total of 5762 patients who were treated with either a VKA or antiplatelet therapy showed that VKAs were not associated with a significantly lower rate of vascular events than antiplatelet therapy (medium-intensity anticoagulation: RR, 0.80; 95% CI, 0.56–1.14; high-intensity anticoagulation: RR, 1.02; 95% CI, 0.49–2.13). Additionally, VKAs were associated with a higher risk of major bleeding at medium- and high-intensity levels of anticoagulation (INR 2–4.5; medium intensity: RR, 1.93; 95% CI, 1.27–2.94; high intensity: RR, 9.0; 95% CI, 3.9–21) but not at low-intensity levels of anticoagulation (RR, 1.27; 95% CI, 0.79–2.03).[571] There have been no randomized trials comparing newer anticoagulants (direct thrombin or factor Xa inhibitors) with antiplatelet therapy to prevent recurrent stroke among patients presenting with noncardioembolic stroke or TIA.

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

Oral Anticoagulant Recommendation

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)*.**

Treatments for Stroke Patients With Other Specific Conditions

Aortic Arch Atheroma

Association With Cerebrovascular Disease

There are numerous compelling retrospective studies that suggest an association between atherosclerotic disease of the aortic arch or thoracic aorta (aortic atheroma or plaque) and increased risk for cerebral ischemic events[572–577]; however, it remains to be established whether the association is causal. The risk of atheroembolism from aortic plaque during cardiac or aortic surgery has been well recognized for many decades, and various surgical strategies or alternatives to surgery have been developed for mitigating this risk.[578,579] In an early autopsy series, Amarenco et al[573] determined that among 500 consecutive patients with cerebrovascular and other neurological diseases, ulcerated plaques in the aortic arch were more common in those with versus without evidence of cerebrovascular disease (26% versus 5%; P<0.001). After controlling for age and heart weight, the adjusted OR was 4.0 (P<0.001). After adjustment for covariates, the prevalence of plaque was higher among patients with cryptogenic cerebral infarction than among those with a known cause (57.8% versus 20.2%; P<0.001; adjusted OR, 5.7). These aortic plaques were associated with stroke independent of the presence of cervical carotid or vertebral artery disease, and this study established aortic arch disease as a new, potentially modifiable stroke risk factor.

This work was followed by several retrospective[576] and prospective cohort studies that showed that atherosclerotic

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plaque ≥4 mm was an independent risk factor for recurrent stroke. The French Study of Aortic Plaques in Stroke[572] conducted follow-up of 331 patients aged ≥60 years admitted for ischemic stroke who had transesophageal echocardiography (TEE) evidence of aortic arch atheroma proximal to the ostium of the left subclavian artery for recurrent stroke or a consolidated vascular end point of brain infarction, MI, peripheral embolism, and death. The incidence of recurrent brain infarction was significantly higher (P<0.001) in patients with aortic wall thickness (including plaque) ≥4 mm (11.9 per 100 person-years) than in those with wall thickness of 1 to 3.9 mm (3.5 per 100 person-years) and <1 mm (2.8 per 100 person-years). After adjustment for the presence of carotid stenosis, AF, peripheral arterial disease, and other risk factors, wall thickness ≥4 mm was an independent predictor of recurrent brain infarction (RR, 3.8; 95% CI, 1.8–7.8; P=0.0012) and of a consolidated vascular end point (RR, 3.5; 95% CI, 2.1–5.9; P<0.001).

This association between aortic plaque and recurrent events has also been replicated in ethnically diverse populations[575] using TEE to characterize plaque morphology and size. In patients with patent carotid arteries (normal or mild stenosis), 36% of patients had large or complex aortic atheromas; therefore, the absence of arch disease cannot be inferred by the absence of cervical artery disease. This underscores the fact that although atherosclerosis is often a systemic disease, the relationship between sites of predilection remains obscure. Importantly, no significant differences were found in the frequency of atheromas by ethnic group. Aortic arch plaque progression was independently associated with an increased risk of stroke and a composite vascular event after adjustment for a propensity score based on confounders (HR, 5.8; 95% CI, 2.3–14.5; P=0.0002).[577] It also appears that some aspects of plaque morphology, particularly lack of calcification, may increase the risk of subsequent vascular events. Further analysis of the French Study of Aortic Plaques in Stroke found the highest RR of events among patients with noncalcified, lipid-rich plaques (RR, 10.3; 95% CI, 4.2–25.2; P<0.001).[574] The role of aortic arch atheroma among nonselected patients in the primary prevention of cerebrovascular ischemic events is more controversial[580,581] and is beyond the scope of this guideline.

Treatment Studies

No clinical trials have been designed to specifically examine the effectiveness of therapy for reducing the risk of first or recurrent stroke among patients with complex aortic plaque. However, observational studies among patients with a recent embolic event, including stroke or TIA, suggest that statins may be effective in preventing recurrent events.[582]

Data on the utility of antiplatelet versus anticoagulant therapy for secondary prevention of atheroembolism are mixed; no randomized studies exist, and the remaining studies are small and confounded and do not reflect current medical management paradigms.[583–586] The SPAF III trial[583] evaluated the rate of ischemic stroke or systemic embolism in patients with nonvalvular AF randomly assigned to adjusted-dose warfarin therapy versus low-dose warfarin plus 325 mg of aspirin. Among a subgroup of 382 participants with aortic plaque documented on TEE, adjusted-dose warfarin was associated with a lower annual rate of embolic events than low-dose warfarin plus aspirin (5.9% versus 17.3%; log-rank test, P=0.01). However, because this was primarily an AF trial, it is not clear whether prevention of recurrent events was attributable to reduced plaque-related versus AF-related emboli. The benefits of adjusted-dose warfarin were not confirmed in a subgroup of patients with aortic plaque enrolled in WARSS.[584]

The Aortic Arch Related Cerebral Hazard (ARCH) trial recently completed enrollment but has not yet reported results. It is a prospective, randomized, open-label, blinded end-point trial to compare the efficacy and tolerance (net benefit) of warfarin (INR 2–3) versus clopidogrel 75 mg/d plus aspirin 75 mg/d for prevention of brain infarction, brain hemorrhage, MI, peripheral embolism, and vascular death in patients with atherothrombosis of the aortic arch and a recent cerebral or peripheral embolic event. The study includes patients with atherosclerotic plaque by TEE in the thoracic aorta ≥4 mm or a plaque <4 mm but with a mobile component (ClinicalTrials.gov, unique identifier: NCT00235248).

Surgical resection of aortic arch plaque was explored as an option for reduction of the risk of recurrent atheroembolism during cardiac surgery with unpromising outcomes, and as a result, it is rarely performed.[578] Stern et al[578] analyzed stroke risk during heart surgery in 268 patients who had arch atheromas ≥5 mm or with mobile components on intraoperative TEE. Arch endarterectomy was performed in 43 of these patients to prevent intraoperative stroke. The overall mortality (14.9%) and intraoperative stroke (15.3%) rates were high. On multivariate analysis, age (OR, 3.9 per year; P=0.01) and arch endarterectomy (OR, 3.6; P=0.001) were independent predictors of intraoperative stroke. On the basis of these limited data, current surgical guidelines for the management of thoracic aortic disease do not recommend prophylactic endarterectomy or aortic arch stenting for purposes of stroke prevention.[587]

The current "ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults" recommends statin therapy to reduce the risk of stroke and cardiovascular events among patients with ischemic stroke or TIA who have evidence of atherosclerosis[16] (Class I; Level of Evidence A). This recommendation has been adopted for the present guideline with slight modification regarding level of evidence ("Dyslipidemia"). Because all patients with aortic arch atheroma by definition have evidence of atherosclerosis, statin therapy is indicated in these patients for secondary prevention.

Aortic Arch Atheroma Recommendations

1. **For patients with an ischemic stroke or TIA and evidence of aortic arch atheroma, antiplatelet therapy is recommended *(Class I; Level of Evidence A)*.** (New recommendation)
2. **For patients with an ischemic stroke or TIA and evidence of aortic arch atheroma, statin therapy is recommended *(Class I; Level of Evidence B)*.** (New recommendation)
3. **For patients with ischemic stroke or TIA and evidence of aortic arch atheroma, the effectiveness of**

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anticoagulation with warfarin, compared with antiplatelet therapy, is unknown *(Class IIb; Level of Evidence C)*. (New recommendation)

4. **Surgical endarterectomy of aortic arch plaque for the purposes of secondary stroke prevention is not recommended *(Class III; Level of Evidence C)*.** (New recommendation)

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 approximately half occur spontaneously or after a trivial injury.[588] 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. At present, none of these underlying conditions are amenable to disease-specific modifying treatment. Ischemic stroke related to dissection may be a result of thromboembolism or hemodynamic compromise, although the former appears to be the dominant mechanism.[589–591] 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, particularly if treated with acute anticoagulation, as well as cerebral infarction.[592]

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 had been classically advocated at the time of diagnosis,[593–595] particularly because the risk of stroke is greatest in the first few days after the initial vascular injury.[593,595–598] However, there have been no controlled trials supporting the use of any particular antithrombotic regimen, and observational data are conflicting. A Cochrane systematic review of 1262 patients with carotid dissection in 36 observational studies found no statistically significant difference in subsequent ischemic stroke when antiplatelet agents were compared with anticoagulants (OR, 0.63; 95% CI, 0.21–1.86).[599] Recurrent stroke was seen in 1.9% of cases with anticoagulation and 2.0% with antiplatelet therapy. Another systematic review that included 762 patients with carotid or vertebral artery dissection from 34 case series similarly showed no significant difference in risk of stroke, which occurred in 1.9% of patients given antiplatelet agents and 2.0% given anticoagulants.[600] These studies pooled data from many smaller studies and likely suffer from substantial heterogeneity, as well as publication bias. Two large cohorts, including a retrospective cohort of 432 patients with carotid or vertebral artery dissection[601] and a prospective cohort of 298 subjects with only carotid dissection,[602] reported a much lower risk of subsequent stroke, 0.3% over the 3- to 12-month period after dissection. In contrast, a cohort study of 250 patients with acute stroke or TIA caused by cervical dissection found a cumulative risk of subsequent stroke of 10.7% at 1 year, with significantly fewer strokes among those treated with anticoagulants than among those given antiplatelet agents (2.0% versus 16.7%; HR, 0.11; 95% CI, 0.02–0.69).[603] Some of the inconsistencies among studies may be related to the study populations. Specifically, a clinical presentation of ischemic symptoms (ie, TIA or stroke) may be associated with an increased risk of subsequent stroke compared with a presentation with only local symptoms (eg, Horner syndrome, head or neck pain, or cranial nerve palsy) or no symptoms. In addition, the timing and acuity of symptoms may be important, because most subsequent strokes occur early after presentation. Overall, existing observational data suggest that antiplatelet therapy and anticoagulation are associated with a similar risk of subsequent stroke but that the former is likely safer. A randomized trial comparing these strategies is under way.[604]

Dissections usually heal over time, and an antithrombotic therapeutic regimen is commonly maintained in such patients 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.[597,605,606] Anatomic healing of the dissection with recanalization occurs in the majority of patients.[607] Those dissections that do not fully heal do not appear to be associated with an increased risk of recurrent strokes.[601,608] 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.[608]

Although most ischemic strokes caused by dissection are a result of early thromboembolism, a minority are attributed to hemodynamic compromise.[609,610] The prognosis may be worse in these cases, and revascularization procedures such as stenting or bypass surgery have been proposed in this setting,[609,611–614] although prospective studies do not currently exist.

Stroke
American Heart Association

Arterial Dissection Recommendations

1. **For patients with ischemic stroke or TIA and extracranial carotid or vertebral arterial dissection, antithrombotic treatment with either antiplatelet or anticoagulant therapy 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)*.**
3. **For patients with stroke or TIA and extracranial carotid or vertebral arterial dissection who have definite recurrent cerebral ischemic events despite 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 have definite recurrent cerebral ischemic events despite medical therapy and also fail or are not candidates for endovascular therapy may be considered for surgical treatment *(Class IIb; Level of Evidence C)*.**

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Patent Foramen Ovale

Patent foramen ovale (PFO) is an embryonic defect (hole) in the interatrial septum that can be the conduit for an embolism traveling from the deep veins of the legs or pelvis to the brain.[615,616] It can be detected in 15% to 25% of the adult population[617–619] and has been associated with increased risk for ischemic stroke.

Evidence for the association between PFO and increased risk for stroke comes from prevalence studies in groups defined by the presence or absence of alternative causes of ischemic stroke and from case-control studies. The prevalence of PFO is higher among young adults with cryptogenic stroke than among control subjects without stroke or patients with stroke of known cause.[620] Young adults with cryptogenic ischemic stroke, furthermore, are more likely to have both PFO and pelvic deep vein thrombosis (DVT) than young adults with ischemic stroke of known cause.[621] More than 23 case-control studies have examined the association between PFO and risk for cryptogenic stroke.[622] Meta-analyses of these studies have demonstrated that the association between PFO and increased risk for cryptogenic ischemic stroke is stronger in younger patients than in older patients.[622,623] In the most recent of these analyses, the OR was 5.1 (95% CI, 3.3–7.8) for patients aged <55 years and 2.0 (95% CI, 1.0–3.7) for patients aged ≥55 years.[622] The observed association between PFO and increased risk for stroke, furthermore, may be stronger when there is a coexistent atrial septal aneurysm, although evidence is limited.[622,624]

Patients with PFO and cryptogenic ischemic stroke are at risk for recurrence of cerebrovascular events, although estimates are variable. A recent meta-analysis of observational studies reported an annual incidence rate of 2.53 events (95% CI, 1.91–3.35) per 100 person-years among patients receiving medical therapy.[625] This overall rate was similar to the rate from the subset of studies examining outcomes in people aged <60 years (incidence rate, 2.30; 95% CI, 1.43–3.68). In recently completed clinical trials of PFO closure compared with medical therapy, the rate of recurrent ischemic stroke among medically treated participants has ranged from 0.6% to 1.5% per year.[626–628] Predictors of high risk for recurrence among patients with PFO and cryptogenic stroke are uncertain. Evidence is conflicting regarding the role of atrial septal aneurysm, and there is little evidence that the size of the PFO defect affects stroke risk.[625,629–633]

Only 1 study[631] compared outcomes in patients with PFO and stroke randomized to either aspirin or warfarin. Among 630 patients in the Patent Foramen Ovale in Cryptogenic Stroke (PICSS) substudy of WARSS, the 2-year event rate of recurrent stroke or death was 16.5% in the warfarin-treated group and 13.2% in the aspirin-treated group (HR, 1.3; 95% CI, 0.6–2.6). For the subgroup with cryptogenic stroke, the 2-year event rates were 9.5% in the warfarin-treated group and 17.9% in the aspirin-treated group (HR, 0.5; 95% CI, 0.2–1.7). Although these data are from an RCT, this substudy did not have adequate statistical power to test the superiority of warfarin over aspirin. An addition limitation is that it included mainly older patients, rather than those with early-onset stroke.

To date, 3 RCTs of transcatheter device closure versus medical management have been published.[626–628,634] All 3 included patients up to age 60 years who had no other identified cause for the index event other than paradoxical embolism. Patients with atherosclerotic vascular risk factors were eligible. Lacunar strokes were included in the Evaluation of STARFlex Septal Closure System in Patients With a Stroke and/or Transient Ischemic Attack due to Presumed Paradoxical Embolism Through a Patent Foramen Ovale (CLOSURE 1) trial and the Percutaneous Closure of Patent Foramen Ovale Using the Amplatzer PFO Occluder With Medical Treatment in Patients With Cryptogenic Embolism (PC) trial but not in the Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (RESPECT) trial. TIAs were included in CLOSURE 1 and the PC Trial but not in RESPECT. Patients with an indication for anticoagulation other than the index event, such as concurrent DVT, were excluded from the CLOSURE 1 trial. The decision to prescribe antiplatelet therapy or anticoagulation for patients in the medical arm was at the discretion of the treating physician. Although the point estimates favored device closure to various degrees in each trial, none of the studies demonstrated a statistically significant finding for their primary end point in an intention-to-treat analysis. Serious procedural complications occurred in 0% to 4.2% of patients who underwent PFO closure in the 3 trials. As stated above, the rate of stroke in the medical arms ranged from 0.6% to 1.5% per year. Subgroup analysis of the RESPECT trial showed a significant benefit for device closure among patients with atrial septal aneurysms or substantial shunts, but these findings were not supported by the CLOSURE 1 trial. The PC Trial also showed no trend for an advantage of device closure among those with atrial septal aneurysms and did not report the subgroup with substantial shunts. AF occurred in 5.7% of CLOSURE 1 patients treated in the device arm and 0.7% of medically treated patients. Continuing follow-up of the patients in the RESPECT trial[635] and other randomized trials may shed further light on the effectiveness of PFO closure devices.

Young patients with cryptogenic TIA or stroke and PFO should be evaluated for lower-extremity or pelvic venous thrombosis, which would be an indication for anticoagulation. In the setting of a large acute stroke, however, full-dose anticoagulation is not recommended, and an inferior vena cava filter may be the safest alternative. In patients with cryptogenic TIA or stroke, a PFO, and DVT, guidelines from the ACCP currently recommend VKA therapy for 3 months and consideration of PFO closure rather than no VKA therapy or aspirin therapy.[23]

PFO Recommendations

1. **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)*.**
2. **For patients with an ischemic stroke or TIA and a PFO who are not undergoing anticoagulation therapy, antiplatelet therapy is recommended *(Class I; Level of Evidence B)*.** (Revised recommendation)

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3. **For patients with an ischemic stroke or TIA and both a PFO and a venous source of embolism, anticoagulation is indicated, depending on stroke characteristics *(Class I; Level of Evidence A)*. When anticoagulation is contraindicated, an inferior vena cava filter is reasonable *(Class IIa; Level of Evidence C)*.** (New recommendation)
4. **For patients with a cryptogenic ischemic stroke or TIA and a PFO without evidence for DVT, available data do not support a benefit for PFO closure *(Class III; Level of Evidence A)*.** (Revised recommendation)
5. **In the setting of PFO and DVT, PFO closure by a transcatheter device might be considered, depending on the risk of recurrent DVT *(Class IIb; Level of Evidence C)*.** (New recommendation)

Hyperhomocysteinemia

Homocysteine may increase risk for stroke through multiple mechanisms: thrombosis, impaired thrombolysis, increased production of hydrogen peroxide, endothelial dysfunction, and increased oxidation of LDL-C.[636,637] Cohort and case-control studies have consistently demonstrated a roughly 2-fold greater risk of stroke associated with hyperhomocysteinemia.[638–643]

Elevated levels of homocysteine are common in healthy men (43%) and women (47%) aged ≥60 years.[644] On the basis of screening performed in the VISP study, roughly 70% of patients with a noncardioembolic stroke population have mild to moderate hyperhomocysteinemia, although this may be an overestimate in populations with a folate-enriched grain supply.[8] In patients <45 years of age with venous or arterial occlusive disease, moderate hyperhomocysteinemia was detected in 13.1% (95% CI, 7.6%–21.3%) and 19.2% (95% CI, 9.0%–31.9%), respectively.[645] Approximately 75% of the cases of high homocysteine concentrations are associated with low folate or vitamin B_{12} concentrations.[644]

In 2 large meta-analyses of population-based cohort studies, a 25% (3 μmol/L) reduction in total homocysteine was associated with an 11% to 16% decrease in the risk of stroke.[646,647] In a more recent meta-analysis of clinical trials evaluating the efficacy of folate supplementation for stroke prevention, folate therapy was associated with an 18% (RR, 0.82; 95% CI, 0.68–1.00; *P*=0.045) reduction in primary stroke risk.[241] Supplementation also appeared to be beneficial for stroke prevention in patients receiving folate for >36 months, in cases of patients with ≥20% reduction in homocysteine, and in populations without folate grain supplementation. Despite this, clinical trials focusing on secondary prevention in patients with CVD or stroke in regions with folate supplementation have failed to demonstrate a benefit to the use of homocysteine-reducing vitamins. Large-scale stroke prevention studies identifying high-risk patients through genetic testing (eg, *MTHFR* 677C→T) that target populations with low folate intake have not been performed.[648]

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, and 2 mg of vitamin B_{12}) or placebo in 5522 patients >55 years old with vascular disease or DM, irrespective of baseline homocysteine.[649] 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 attributable 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, 0.59–0.97; *P*=0.03) in the active-therapy group. The VISP study randomized 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.[8] The risk of stroke was related to level of homocysteine; the mean reduction in homocysteine was greater in the high-dose group, but there was no reduction in stroke rates in the high-dose vitamin–treated patients. The 2-year stroke rates were 9.2% in the high-dose and 8.8% in the low-dose arms. In a post hoc "efficacy analysis" of 2155 VISP patients that excluded those deemed unlikely to benefit from vitamin supplementation (B_{12} levels <250 and >637 pmol/L, or with renal failure), there was a 21% reduction of stroke/death/coronary events (unadjusted *P*=0.049; adjusted for age, sex, BP, smoking, and B_{12} level, *P*=0.056).[238]

The Vitamins to Prevent Stroke (VITATOPS) trial was a randomized, double-blind, parallel, placebo-controlled trial in patients within 7 months of a stroke or TIA. Participants were eligible regardless of blood homocysteine level. The primary end point was the composite of stroke, MI, or vascular death. Between November 19, 1998, and December 31, 2008, 8164 subjects were randomized to B vitamins (2 mg of folic acid, 25 mg of vitamin B_6, and 0.5 mg of vitamin B_{12}) or placebo and followed up for a median of 3.4 years. A total of 616 patients (15%) assigned to B vitamins and 678 (17%) assigned to placebo reached the primary end point (RR, 0.91 [95% CI, 0.82–1.00], *P*=0.05; absolute risk reduction, 1.56% [95% CI, −0.01 to 3.16]). A post hoc analysis of VITATOPS assessed for potential interaction between B vitamin supplementation and antiplatelet use. In subjects taking antiplatelet drugs at baseline, B vitamins had no significant effect on the primary outcome, which occurred in 488 patients in the B vitamins group (15%) versus 519 in the placebo group (16%; HR, 0.94; 95% CI, 0.83–1.07). However, in subjects not taking antiplatelet drugs at baseline, B vitamins did have a significant effect on the primary outcome, which occurred in 123 patients in the B vitamins group (17%) versus 153 in the placebo group (21%); HR, 0.76; 95% CI, 0.60–0.96). The interaction between antiplatelet therapy and the effect of B vitamins on the primary outcome was significant (adjusted *P* for interaction=0.0204).[237,650]

Hyperhomocysteinemia Recommendations

1. **Routine screening for hyperhomocysteinemia among patients with a recent ischemic stroke or TIA is not indicated *(Class III; Level of Evidence C)*.** (New recommendation)
2. **In adults with a recent ischemic stroke or TIA who are known to have mild to moderate hyperhomocysteinemia, supplementation with folate, vitamin B_6, and vitamin B_{12} safely reduces levels of homocysteine but has not been shown to prevent stroke *(Class III; Level of Evidence B)*.** (Revised Recommendation)

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Hypercoagulable States

Inherited Thrombophilias

Inherited thrombophilias (eg, protein C deficiency, protein S deficiency, antithrombin III deficiency, factor V Leiden, the prothrombin G20210A mutation, and the methylenetetrahydrofolate reductase [MTHFR] C677T mutation) are rarely the primary mechanism for adult stroke but do play a role in pediatric stroke.[651–653] The most prevalent inherited coagulation disorder is factor V Leiden, which is resistant to neutralization by activated protein C.[654] In a meta-analysis of 18 case-control studies of ischemic stroke in adults ≤50 years of age, factor V Leiden was found in 7.5% of those with stroke and 4.1% of nonstroke control subjects (OR, 2.0; 95% CI, 1.59–2.51).[655] The association was even more pronounced when the meta-analysis was stratified by method of case selection. Among 9 studies that selected stroke cases with an enriched likelihood of thrombophilia (ie, cases with cryptogenic stroke or cases referred for coagulopathy evaluation), the OR for the association between factor V Leiden and risk for stroke was 2.73 (95% CI, 1.98–3.75). For 8 "unselected" studies, the OR was 1.40 (95% CI, 1.0–1.9). The results of this meta-analysis are consistent with a previous meta-analysis[656] that reported an OR of 1.33 (95% CI, 1.12–1.58), but both must be interpreted with caution because of potential selection bias in some of the case-control studies that were included.[657] Most studies on factor V Leiden and stroke, particularly among older patients, have not confirmed an association.[654,655,658–667]

Research on the prothrombin gene mutation G20210A is mixed. A nested case-control study among 14 916 men in the Physicians Health Study with a mean age of 59 years showed no association with any-type stroke (adjusted RR, 1.1; 95% CI, 0.5–2.4).[661] Two smaller case-control studies among younger patients have reported positive findings. One reported an association between the prothrombin gene mutation and increased risk for stroke among 72 stroke patients <50 years of age (OR, 5.1; 95% CI, 1.6–16.3).[662] Another small study of 49 patients with cryptogenic stroke who were <50 years of age reported similar findings (OR 3.75; 95% CI, 1.05–13.34).[668] Among 2 meta-analyses, 1 from 2003 reported that the prothrombin gene mutation was not associated with increased risk for ischemic stroke (OR, 1.30; 95% CI, 0.91–1.87)[669] and the other from 2004 reported that it was (OR, 1.44; 95% CI, 1.11–1.86).[656] A more recent systematic analysis concluded that available evidence did not support an association between the prothrombin gene mutation and risk for ischemic stroke.[657]

Research on the MTHFR mutation and risk for stroke has been summarized in 5 meta-analyses.[648,656,669–671] The first, from 2002, reported an association between the TT genotype and increased risk for ischemic stroke that did not reach statistical significance (OR, 1.23; 95% CI, 0.96–1.58). All 4 subsequent meta-analyses reported significant associations, including the 2 meta-analyses from 2003 and 2004 cited in the paragraph immediately above.[656,669] Both reported significant associations, with ORs of 1.46 (95% CI, 1.19–1.79)[669] and 1.24 (95% CI, 1.08–1.42).[656] The most recent meta-analysis reported that the MTHFR 677 C→T variant was more associated with risk for stroke in geographic regions of low folate availability (OR, 1.68; 95% CI, 1.44–1.97) than in regions with high folate availability (OR, 1.03; 95% CI, 0.84–1.25).[648]

Deficiencies of protein C, protein S, or antithrombin III in adults are rare (<1% population) but are associated with increased risk for venous thrombosis.[672] Although case reports[657] and 1 observational cohort study[673] have suggested an association between inherited protein C deficiency and increased risk for ischemic stroke,[674,675] this finding has not been confirmed in case-control studies and meta-analyses.[657] Thus, these rare conditions are of uncertain significance in adults with ischemic stroke.

Little is known specifically about the effect of inherited thrombophilias on the risk of recurrent stroke after ischemic stroke or TIA; however, a recent observational cohort study of 511 patients aged 18 to 45 years with ischemic stroke examined the association of 3 genetic factors (thrombin gene mutation 20210A, factor V Leiden, and the MTHFR C677T mutation) with risk for the composite end point of MI, ischemic stroke, and TIA.[676] For patients with 1 mutation, the OR was 2.01 (95% CI, 1.38–2.93), and for patients with 2 mutations, the OR was 4.05 (95% CI, 1.91–8.57). No clinical stroke trial has compared the efficacy of different antithrombotic approaches based on genotype.

The presence of venous thrombosis is an indication for short- or long-term anticoagulant therapy depending on the clinical and hematologic circumstances.[672,677–682] An AHA statement on the diagnosis and management of cerebral venous thrombosis, in particular, recommends consideration of indefinite anticoagulation for patients with severe thrombophilia[683] (Class IIb; Level of Evidence C). No clinical trials are available to guide therapy in patients with ischemic stroke who are found to have an inherited thrombophilia.

Overall, research indicates that acquired thrombophilia may be associated with a modest increase in risk for ischemic stroke, particularly in young adults with cryptogenic events. The evidence is most developed for factor V Leiden and the MTHFR mutation. The evidence is very weak or nonexistent for the prothrombin gene mutation and deficiencies of protein C, protein S, and antithrombin. Even for factor V Leiden and the MTHFR mutation, however, the evidence is not strong; many positive studies have not adequately protected against selection and other biases. Questions remain as to the mechanism of stroke risk among patients with coagulation defects (eg, paradoxical venous thromboembolism), the effect of gene-environment interaction, and the optimal strategies for stroke prevention in affected patients.

Hypercoagulable States Recommendations

1. **The usefulness of screening for thrombophilic states in patients with ischemic stroke or TIA is unknown *(Class IIb; Level of Evidence C)*.** (New recommendation)
2. **Anticoagulation might be considered in patients who are found to have abnormal findings on coagulation testing after an initial ischemic stroke or TIA, depending on the abnormality and the clinical circumstances *(Class IIb; Level of Evidence C)*.** (Revised recommendation)

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3. **Antiplatelet therapy is recommended for patients who are found to have abnormal findings on coagulation testing after an initial ischemic stroke or TIA if anticoagulation therapy is not administered *(Class I; Level of Evidence A)*.** (Revised recommendation)
4. **Long-term anticoagulation might be reasonable for patients with spontaneous cerebral venous sinus thrombosis or a recurrent ischemic stroke of undefined origin and an inherited thrombophilia *(Class IIb; Level of Evidence C)*.**

Antiphospholipid Antibodies

The antiphospholipid antibody syndrome (APS) consists of venous and arterial thrombosis or 1 of several specific pregnancy complications in the presence of persistent antiphospholipid antibodies.[684,685] Antiphospholipid antibodies are directed against phospholipid-binding plasma proteins and include anticardiolipin antibody and antibodies directed against β_2-glycoprotein I. The presence of antiphospholipid antibodies can also be inferred from the presence of lupus anticoagulant activity. The APS should be suspected in a patient with TIA or ischemic stroke who has other features of the syndrome, such as livedo reticularis, obstetric complications, unexplained thrombocytopenia, or prolongation of a coagulation test.[686]

An association between antiphospholipid antibodies and stroke has been described for young adults (<50 years of age).[687] A case-control study from the Netherlands examined the association between the lupus anticoagulant and risk for stroke among women <50 years of age.[688] The lupus anticoagulant was detected in 30 of 175 patients (17%) with ischemic stroke. The OR for the association was 43.1 (95% CI, 12.2–152.0) in the overall cohort, 201.0 (95% CI, 22.1–1828.0) in women taking oral contraceptives, and 87.0 (95% CI, 14.5–523.0) in smokers. The presence of anti-β_2-glycoprotein I antibodies was also associated with an increased risk for ischemic stroke (OR, 2.3; 95% CI, 1.4–3.7). Neither anticardiolipin nor anti-prothrombin antibodies were associated with risk for ischemic stroke.

The findings in older patients are more mixed.[689–694] In a case-control study of 255 patients with a mean age of 66 years, the presence of an anticardiolipin antibody was associated with a significantly increased risk for ischemic stroke (adjusted OR, 2.31; 95% CI, 1.09–4.90).[695] These findings were not replicated in a subsequent prospective cohort study that was part of WARSS.[691] A total of 1770 WARSS participants agreed to be tested for antiphospholipid antibodies. A patient was classified as antiphospholipid positive if he or she had an anticardiolipin antibody, the lupus anticoagulant, or both. The testing was performed once, and persistence of an abnormality was not required for classification. Among the 1770 participants tested, 741 (42%) were antiphospholipid positive. Over an average of 24 months, there was no increased risk for thrombo-occlusive events associated with antiphospholipid-positive status in either the warfarin- or aspirin-treatment groups. Antibody status was not associated with a differential response to warfarin or aspirin. A high-quality nested, case-control study from the Physicians Health Study demonstrated no association between the elevated levels of anticardiolipin antibodies and risk for ischemic stroke.[696]

A limited number of studies have examined the effect of antiphospholipid antibodies specifically on the risk for recurrent thromboembolic events after an initial TIA or stroke.[697–699] In the only study to exclusively enroll young adults <50 years of age, antiphospholipid antibodies were associated with increased risk for recurrent stroke or venous thromboembolism.[700] Other studies that enrolled older patients or a mixture of young and old patients with ischemic stroke indicated wide variability in the prevalence of antiphospholipid antibodies, from 6% to 46%, and inconsistent findings for an association.[690–694,696–699,701] The wide variability reflects differences in diagnostic criteria, including persistence.

There remains a lack of consensus regarding optimal antithrombotic management of patients with ischemic stroke/TIA and antiphospholipid antibodies.[702] Patients with ischemic stroke or TIA with antiphospholipid antibodies that persist at moderate to high titers for >12 weeks meet the diagnostic criteria for the antiphospholipid syndrome. Some groups recommend treatment with high-intensity warfarin or the combination of moderate-intensity warfarin and an antiplatelet agent.[702] However, there are no large, placebo-controlled clinical trials to support this recommendation, and many patients with ischemic stroke or TIA have alternative explanations for their ischemia other than the antiphospholipid antibody. In 1 study of patients with antiphospholipid antibodies and arterial or venous thrombotic events, high-intensity warfarin therapy (INR 3.1–4.0) was not more effective than moderate-intensity warfarin (INR 2–3) for the prevention of recurrent thrombosis.[703] A small clinical trial of 30 patients with ischemic stroke and antiphospholipid antibodies suggested that the combination of aspirin and anticoagulation may be more effective than aspirin alone in preventing recurrent stroke.[704] In summary, therefore, the evidence to guide therapy in stroke patients who meet the case definition for the APS is incomplete.

AMERICAN HEART ASSOCIATION

Antiphospholipid Antibodies Recommendations

1. **Routine testing for antiphospholipid antibodies is not recommended for patients with ischemic stroke or TIA who have no other manifestations of the APS and who have an alternative explanation for their ischemic event, such as atherosclerosis, carotid stenosis, or AF *(Class III; Level of Evidence C)*.** (New recommendation)
2. **For patients with ischemic stroke or TIA who have an antiphospholipid antibody but do not fulfill the criteria for APS, antiplatelet therapy is recommended *(Class I; Level of Evidence B)*.** (Revised recommendation)
3. **For patients with ischemic stroke or TIA who meet the criteria for the APS, anticoagulant therapy might be considered depending on the perception of risk for recurrent thrombotic events and bleeding *(Class IIb; Level of Evidence C)*.** (Revised recommendation)
4. **For patients with ischemic stroke or TIA who meet the criteria for the APS but in whom anticoagulation is not begun, antiplatelet therapy is indicated *(Class I; Level of Evidence A)*.** (New recommendation)

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Sickle Cell Disease

Stroke is a common complication of sickle cell disease, and stroke is a major cause of death in both children and adults with sickle cell disease.[705] The highest risk of stroke is in patients with the SS genotype, but stroke can occur in patients with other genotypes.[706] For adults with sickle cell disease, 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 years.[706] In sickle cell disease patients with their first stroke as an adult (age ≥20 years), the recurrent stroke rate has been reported at 1.6 events per 100 patient-years,[706] and most recurrent events in adults occur within the first few years.[706,707] TIA is also strongly associated with the risk of subsequent ischemic stroke.[706]

The most common mechanism of ischemic stroke in sickle cell disease patients appears to be large-artery arteriopathy,[708,709] which is believed to be caused by intimal hyperplasia related to repeated endothelial injury,[710] but other mechanisms of stroke can occur. Low levels of protein C and S have been associated with ischemic stroke,[711] and other markers of hypercoagulability have been reported in sickle cell disease patients, albeit not directly linked to stroke.[712,713] Cerebral venous sinus thrombosis (CVST) is another mechanism of brain ischemia reported in sickle cell disease patients.[714] Cardiogenic embolism appears either rare or underreported. Traditional risk factors may also be present, but their interactions with sickle cell disease are uncertain.

Recommendations for treatment of sickle cell disease patients with large-artery arteriopathy are largely based on stroke primary prevention studies performed in a pediatric population. The Stroke Prevention Trial in Sickle Cell Anemia (STOP) was a randomized, placebo-controlled trial that showed that a chronic prophylactic transfusion strategy was effective for primary prevention of stroke in children with sickle cell disease and high transcranial Doppler velocities.[715] The STOP results are not directly applicable to the present guideline and are summarized in the AHA's "Guidelines for the Primary Prevention of Stroke"[53] and statement on "Management of Stroke in Infants and Children."[716] For secondary stroke prevention, there are no RCTs to support transfusion in adults or children. A retrospective multicenter review of sickle cell disease patients with stroke, either observed or transfused, suggested that regular blood transfusion sufficient to suppress native hemoglobin S formation reduced recurrent stroke risk.[495] 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 initiation of 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 control subjects.[717] Most of the patients in the 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 was associated with less progression of large-vessel stenoses on angiography[718] and fewer silent infarcts in sickle cell disease patients with elevated transcranial Doppler velocities than in patients who did not receive transfusions.[719] Regular transfusions are associated with long-term complications, especially iron overload, typically requiring iron chelation therapy.

Early studies suggested that hydroxyurea might replace regular blood transfusion therapy[720–723]; however, an RCT called Stroke With Transfusions Changing to Hydroxyurea (SWiTCH) found no strokes with chronic transfusion but 10% with hydroxyurea, which resulted in termination of the trial.[724] In situations in which transfusion is not available, a nonrandomized group comparison study of patients with an initial stroke suggested that patients who do not receive hydroxyurea at the maximum tolerated dose are at increased risk for recurrent stroke (HR, 9.4; 95% CI, 1.5–70.6).[723]

Other therapies for secondary stroke prevention in adult sickle cell disease patients also have limited evidence to support their efficacy. Hematopoietic cell transplantation can be curative from a hematologic perspective for a small number of sickle cell disease patients with a suitable donor and access to expert care[725] but is usually undertaken in young children, not adults. This option is generally reserved for patients who appear to be refractory to other treatments and who have a matched donor, and it results in survival without sickle cell disease in 80% to 90% of patients. Both clinical and subclinical infarctions have been reported to be arrested by this procedure.[726] Surgical bypass operations have also been reported to have improved outcomes in a few small series of sickle cell disease patients with moyamoya vasculopathy, but no randomized or controlled data are available.[727,728] Given the lack of systematic experience with antiplatelet agents, anticoagulants, and anti-inflammatory agents for secondary stroke prevention in sickle cell disease patients, specific stroke prevention medications cannot be recommended outside of general treatment recommendations. Risk factor reduction with statins and antihypertensive agents can also only be recommended on the basis of their importance in the general population.

Sickle Cell Disease Recommendations

1. **For patients with sickle cell disease and prior ischemic stroke or TIA, chronic blood transfusions to reduce hemoglobin S to <30% of total hemoglobin are recommended *(Class I; Level of Evidence B)*.** (Revised recommendation)
2. **For patients with sickle cell disease and prior ischemic stroke or TIA for whom transfusion therapy is not available or practical, treatment with hydroxyurea may be considered *(Class IIb; Level of Evidence B)*.** (Revised recommendation)
3. **For adults with sickle cell disease and ischemic stroke or TIA, general treatment recommendations cited elsewhere in this guideline are reasonable with regard to the control of risk factors and the use of antiplatelet agents *(Class IIa; Level of Evidence B)*.**

Cerebral Venous Sinus Thrombosis

CVST diagnosis and treatment guidelines have been published elsewhere.[683]

The estimated annual incidence of CVST is 3 to 4 cases per 1 million population.[729] Although cerebral venous thrombosis accounts for <1% of all strokes, it is an important diagnostic consideration because of the differences in management from arterial strokes.[729] Early anticoagulation is often considered as

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both treatment and early secondary prophylaxis for patients with CVST, although controlled trial data remain limited to 2 studies.[730,731]

One trial compared dose-adjusted unfractionated heparin (UFH; partial thromboplastin time ≥2 times control) to placebo. The study was terminated early, after only 20 patents had been enrolled, because of the superiority of heparin therapy ($P<0.01$). Eight of the 10 patients randomized to heparin recovered completely, and the other 2 had only mild neurological deficits. In the placebo group, only 1 patient had a complete recovery, and 3 died.[730] The same research group also reported a retrospective study of 43 patients with CVST 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 group not receiving anticoagulation.[730]

In another small randomized study of CVST (n=59), nadroparin (90 anti-factor Xa units per kilogram twice daily) was compared with placebo.[731] After 3 months of follow-up, 13% of the 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 versus 4 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 pooled RRs of 0.33 (95% CI, 0.08–1.21) for death and 0.46 (95% CI, 0.16–1.31) for death or dependency. No new symptomatic ICHs were observed in either study. One major gastrointestinal hemorrhage occurred after anticoagulant treatment. Two control patients (placebo) had a diagnosis of probable pulmonary embolism (1 fatal).[732] On the basis of these 2 trials, the use of anticoagulation with heparin or LMWH acutely in the setting of CVST is recommended, regardless of the presence of hemorrhagic conversion.

Although most patients with CVST will recover with anticoagulation therapy, 9% to 13% of patients may have poor outcomes that could be related to incomplete recanalization or persistent thrombosis. A number of invasive endovascular therapeutic procedures have been described for the treatment of CVST, including direct transcatheter chemical thrombolysis and direct mechanical thrombectomy with or without thrombolysis. The efficacies of these procedures are not supported by any RCTs or large case series. The evidence supporting their use comes from anecdotal reports and small case series. The use of these procedures can be considered in refractory cases in which clinical deterioration progresses despite anticoagulation or intracranial hypertension develops or persists despite other standard therapeutic approaches.[683]

No RCT data exist to guide duration of anticoagulation therapy, and treatment periods between 3 and 12 months after an initial event have been reported. Patients with inherited thrombophilia are often treated with anticoagulation for longer periods than those with a transient (reversible) risk factor such as oral contraceptive use. In 1 large cohort study, the risk of CVST recurrence was 1.5% per year; although most patients in the study received anticoagulation therapy for >3 months, no impact of anticoagulation was discernible in this observational study.[733] Given the absence of data on duration of anticoagulation in patients with CVST, it is reasonable to follow the externally established guidelines set for patients with extracerebral DVTs, which include anticoagulation treatment for 3 months for first-time DVTs in patients with transient risk factor, ≥3 months for an unprovoked first-time DVT, and anticoagulation for an indefinite period in patients with a second unprovoked DVT.[734] Antiplatelet therapy is often given indefinitely after discontinuation of warfarin, although there are no data to support this.

CVST Recommendations

1. **Anticoagulation is reasonable for patients with acute CVST, even in selected patients with intracranial hemorrhage *(Class IIa; Level of Evidence B)*.** (Revised recommendation)
2. **In CVST patients without a recognized thrombophilia, it is reasonable to administer anticoagulation for ≥3 months, followed by antiplatelet therapy *(Class IIa; Level of Evidence C)*. Recommendations for patients with a recognized thrombophilia are discussed elsewhere in this document.**

Risk of Stroke During Pregnancy

Stroke can occur during pregnancy, the puerperium, or postpartum. The incidence of pregnancy-related arterial ischemic stroke varies between 4 and 26 per 100 000 deliveries, with the greatest risk in the 3 days surrounding birth and the postpartum period.[735,736] For women with a prior ischemic stroke, data addressing the risk of recurrent stroke during a future pregnancy are much more limited. The risk of recurrent stroke is increased in the postpartum period but not during the 9 months of pregnancy,[737] consistent with the risk period for first stroke. The absolute risk of stroke recurrence during pregnancy in patients with prior arterial ischemic stroke depends on the clinical circumstances, but case series suggest an overall rate of 1 in 143, or 0.7% (95% CI, 0.04%–4.4%).[737–739] Approximately 40% of women in these series[737,738] did not receive prophylactic treatment during the first trimester. These data suggest that the risk of stroke recurrence during pregnancy is generally low, similar to the <1% yearly risk of recurrent stroke among young adults who have no vascular risk factors.[740] Women with vascular risk factors or with a definite cause of stroke,[737,741] including thrombophilic disorders,[742] have an increased risk of recurrent stroke.

Antithrombotic Therapy During Pregnancy

Pregnancy complicates the selection of antithrombotic treatments among women who have had a prior TIA or stroke because the clinician must balance the risk of stroke recurrence in the mother against the risk of adverse effects on the fetus and mother. For stroke prevention treatment during pregnancy, recommendations are based on 2 scenarios: (1) There is a high-risk condition that would require anticoagulation outside of pregnancy, or (2) there is a lower-risk situation in which antiplatelet therapy would be the treatment recommendation outside of pregnancy. A full review of the first scenario is beyond the scope of these guidelines; however, a recent detailed discussion is available from a writing group of the ACCP.[18] The strongest indication and the most

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well-characterized options for anticoagulation in pregnancy are for mechanical heart valves. Secondary prevention in the setting of mechanical heart valves is complex given that there is no completely safe option for both mother and fetus; therefore, individualized recommendations and full discussion of the risks and benefits with the patient are particularly important. Prevention of recurrent stroke related to other high-risk conditions that would require anticoagulation outside of pregnancy, such as AF, is managed by analogy with treatment for mechanical heart valves. Recommendations for anticoagulation during pregnancy are based on ACCP guidelines.[18]

Treatment for High-Risk Conditions That Would Require Anticoagulation Outside of Pregnancy

Considerations underlying anticoagulation treatment during pregnancy relate to risk of fetal malformations, effectiveness in preventing thrombosis, maternal side effects, and pharmacodynamic changes during pregnancy. VKAs cross the placenta, with the period of highest risk of embryopathy occurring between week 6 of gestation and the end of the first trimester.[18] Among women with mechanical heart valves, the use of UFH or LMWH is associated with a higher rate of valve thrombosis or maternal thromboembolism than the use of VKAs[18]; the addition of aspirin 75 to 100 mg/d to anticoagulation therapy can be considered for women with mechanical valves at high risk for thrombosis. Compared with UFH, LMWH has the advantages of a lower risk of heparin-induced thrombocytopenia and of osteoporosis. Pharmacokinetic changes have been observed among pregnant women taking LMWH, so doses must be normalized for body weight changes, and anti-Xa activity need to be monitored closely over time.[743]

Treatment for Low-Risk Conditions That Would Require Antiplatelet Therapy Outside of Pregnancy

For scenario 2, a lower-risk situation in which antiplatelet therapy would be recommended outside of pregnancy, a distinction must be made between treatment before versus after the first trimester. After the first trimester, there is substantial evidence that low-dose aspirin, 50 to 150 mg/d, is safe. A large RCT of 60 mg of aspirin after the first trimester for preeclampsia prevention found a slight increase in use of blood transfusion after delivery (4% versus 3.2%), but this difference was not associated with differences in the occurrence or degree of postpartum hemorrhage or risk of epidural anesthesia. Low-dose aspirin was safe for the fetus and newborn infant, with no evidence of an increased likelihood of bleeding, no increased risk of congenital malformations, and no adverse effects on early childhood development.[744,745] A recent meta-analysis of antiplatelet agents for the prevention of preeclampsia and its complications found a reduction of adverse pregnancy outcomes, including premature births, small-for-gestational-age births, and fetal or neonatal deaths.[746]

Data on the safety of aspirin during the first trimester are more limited. Because aspirin crosses the placenta, its use during first-trimester organogenesis could increase the risk of birth defects. Case-control studies have been inconsistent; some, but not all, studies have found an association between first-trimester aspirin use and both gastrochisis[747–750] and anophthalmia/microphthalmia.[750] Aspirin currently carries an FDA category "D" rating, which indicates that "there is positive evidence of human fetal risk…but potential benefits may warrant use of the drug in pregnant women despite potential risks."[751] Alternative antiplatelet agents have not been studied during pregnancy.

Although heparin does not cross the placenta and thus cannot be teratogenic or cause fetal bleeding, its risk-benefit ratio in scenarios in which antiplatelet therapy would be indicated is not clear. Except in cardioembolic stroke, the effectiveness of heparin for prevention of recurrent stroke has not been studied.

Given the extreme paucity of evidence regarding the risk-benefit ratio of secondary prevention of noncardioembolic stroke during the first trimester, it is not surprising that a survey of members of the American Academy of Neurology's Stroke and Vascular Neurology section[752] showed no consensus on this issue. Approximate percent recommendations were 40% for aspirin 81 mg, 25% for no treatment, and 10% for UFH or LMWH, with the remainder being other choices. Among the limitations of this survey, respondents were unable to take into consideration the specifics of the clinical situation, including the presence of risk factors, the mechanism of prior strokes, or maternal attitudes toward risk.

For these reasons, it is suggested that low-dose aspirin, UFH or LMWH, or no treatment could be acceptable during the first trimester depending on the clinical context and the maternal attitude toward risk.

Antithrombotic Therapy Postpartum for Nursing Mothers

Available evidence suggests that antithrombotic therapy can be safely given to nursing mothers without risk to the breastfed infant.[18] Warfarin, the oral anticoagulant prescribed for most patients in North America, is polar, nonlipophilic, and highly protein bound. Breast milk from mothers taking warfarin does not contain detectable levels of warfarin and does not induce an anticoagulant effect in the breastfed infant.[753,754] The safety of other VKAs in nursing infants is less clear.[18] UFH also does not pass into breast milk and can be safely given to nursing mothers.[18] Although LMWH is detectable in breast milk, given the very small amount that passes into breast milk and the very low bioavailability of oral heparin, it is unlikely to have a clinically relevant effect on the nursing infant.[755] Breast milk from mothers taking aspirin contains salicylate and salicylate metabolites.[18] High doses of maternal aspirin ingestion have been associated with metabolic acidosis in the infant,[756] and there are theoretical risks of platelet dysfunction, gastrointestinal bleeding, or Reye's syndrome. However, the use of low-dose aspirin during breastfeeding has not been reported to result in adverse infant outcomes.[757–759]

Recommendations During Pregnancy

1. **In the presence of a high-risk condition that would require anticoagulation outside of pregnancy, the following options are reasonable[18]:**
   a. **LMWH twice daily throughout pregnancy, with dose adjusted to achieve the LMWH manufacturer's recommended peak anti-Xa activity 4 hours after injection, or**
   b. **Adjusted-dose UFH throughout pregnancy, administered subcutaneously every 12 hours in**

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doses adjusted to keep the midinterval activated partial thromboplastin time at least twice control or to maintain an anti-Xa heparin level of 0.35 to 0.70 U/mL, or

c. UFH or LMWH (as above) until the 13th week, followed by substitution of a VKA until close to delivery, when UFH or LMWH is resumed. *(Class IIa; Level of Evidence C)* (Revised recommendation)

2. **For pregnant women receiving adjusted-dose LMWH therapy for a high-risk condition that would require anticoagulation outside of pregnancy, and when delivery is planned, it is reasonable to discontinue LMWH ≥24 hours before induction of labor or cesarean section**[18] ***(Class IIa; Level of Evidence C).*** (New recommendation)
3. **In the presence of a low-risk situation in which antiplatelet therapy would be the treatment recommendation outside of pregnancy, UFH or LMWH, or no treatment may be considered during the first trimester of pregnancy depending on the clinical situation *(Class IIb; Level of Evidence C).*** (New recommendation)
4. **In the presence of a low-risk situation in which antiplatelet therapy would be the treatment recommendation outside of pregnancy, low-dose aspirin (50–150 mg/d) is reasonable after the first trimester of pregnancy *(Class IIa; Level of Evidence B).*** (Revised recommendation)

Recommendations for Breastfeeding Women

1. **In the presence of a high-risk condition that would require anticoagulation outside of pregnancy, it is reasonable to use warfarin, UFH, or LMWH *(Class IIa; Level of Evidence C).*** (New recommendation)
2. **In the presence of a low-risk situation in which antiplatelet therapy would be the treatment recommendation outside of pregnancy, low-dose aspirin use may be considered *(Class IIb; Level of Evidence C).*** (New recommendation)

Use of Anticoagulation After Intracranial Hemorrhage

One of the most difficult problems that clinicians face is the management of antithrombotic therapy in patients who have an intracranial hemorrhage. Management during the acute period is discussed in the AHA "Guidelines for the Management of Spontaneous Intracerebral Hemorrhage."[760] Management after the acute period will be discussed here.

There are several key variables to consider, including the location of the 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. There are very few case series addressing subarachnoid hemorrhage. 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 the important management questions of whether to resume antithrombotic therapy, and if so, when.

Warfarin-related ICH typically occurs in patients who are undergoing this therapy for treatment of venous thromboembolism or prevention of stroke and systemic arterial embolism from a mechanical heart valve or AF. When warfarin therapy is interrupted after an ICH, these patients are at risk for venous or arterial thromboembolism related to their underlying condition. If it is resumed, they may be at increased risk for ICH. The decision of whether and when to reinstitute anticoagulation must consider these RRs of recurrent ICH and arterial thromboembolism. Unfortunately, there are no randomized clinical trials to settle the matter.

The available data are primarily from observational cohort studies that have compared outcome rates among patients in whom warfarin was reinstituted or withheld. A consistent finding among these studies is that clinicians are more likely to reinstitute anticoagulation among younger patients and patients with mechanical heart valves than patients who were undergoing anticoagulation for AF.[761–763] Reported rates of outcomes of ischemic and hemorrhagic stroke, therefore, may be influenced by these selection decisions. Among 284 consecutive patients with warfarin-related ICH or subarachnoid hemorrhage from 13 centers in the Canadian Stroke Network, warfarin was reinstituted in 91 patients while they were in the hospital. The rate of recurrent bleeding at 1 year after discharge was 2.5% among those treated with warfarin and 0% among those who were not treated with warfarin (*P* value not stated). Mortality at 1 year was nonsignificantly lower among those treated with warfarin (OR, 0.79; 95% CI, 0.43–1.43).[763] A single-center cohort study evaluated 52 patients with warfarin-associated ICH, 23 of whom restarted warfarin treatment, most within 2 weeks of their hemorrhage.[761] Among the 23 who restarted warfarin, 3 experienced a recurrent ICH (1 warfarin related and 2 trauma related) over a mean follow-up of 43 months (4 per 100 person-years). Among the 29 patients who did not restart warfarin, 4 experienced an arterial thromboembolic event (3 ischemic strokes and 1 systemic embolism).

Because the data comparing outcomes in those who resume or refrain from warfarin are from small, observational studies, they do not provide information of sufficient reliability to determine clinical policy for when and whether to resume anticoagulation. However, it is reassuring that the reported rates of bleeding among patients taking warfarin after an ICH, as described above, are not substantially higher than rates observed in patients treated primarily without warfarin. Population-based cohort studies of ICH patients treated primarily without warfarin estimate the risk for recurrent ICH at 2.1% to 3.7% per year.[760] A recent report from 1 hospital in New Zealand reported that among all patients who survive the acute hospitalization, the recurrence rate declines from 2.1% in the first year to 1.2% per year thereafter.[764] These uncontrolled data can help inform clinical decision making while more reliable evidence is gathered.

Observational research is also helpful in estimating individual risk for recurrent ICH. Clinical features associated with increased risk for new or recurrent ICH may include

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lobar location, advanced age, hypertension, anticoagulation, dialysis, leukoaraiosis, and the presence of microbleeds on MRI.[764–769] The presence of microbleeds on MRI (often seen on gradient echo images) may signify an underlying microangiopathy or the presence of cerebral amyloid angiopathy. One study found the risk of ICH in patients receiving anticoagulation to be 9.3% in patients with microbleeds compared with 1.3% in those without MRI evidence of prior hemorrhage.[766] A decision analysis study recommended against restarting anticoagulation in patients with lobar ICH and AF.[770]

When a decision is made to reinstitute anticoagulation, timing is a key consideration. Clinicians are often concerned that early reinstitution may result in avoidable recurrent ICH, but also that delay will place patients at high risk for recurrent arterial thromboembolism. There are no unbiased data to guide this decision, only noncontrolled observational studies.[771] Several case series and small cohort studies have followed up patients no longer taking anticoagulants after an intracranial bleed for several days and weeks, with few reported instances of ischemic stroke.[771] Rates of ischemic stroke within 30 days range from 0% to 2.1%.[771–773]

In an effort to account for the dual risk of ischemic stroke and recurrent ICH, timing was specifically examined in a recent observational cohort study of 234 patients with warfarin-associated ICH from 3 hospitals in Sweden and Canada.[762] Among 132 patients with a cardiac indication for anticoagulation who survived 1 week, the combined risk for ischemic stroke and recurrent intracranial hemorrhage reached a nadir if warfarin was initiated at 10 to 30 weeks after the initial bleed. This finding was at odds with recent suggestions that anticoagulation be restarted within 2 weeks.[774] Some of the discrepancy might be explained by the distinct patient population in this new study and uncertain effects of patient selection.[762,774] Not surprisingly, in the absence of more reliable data, updated guidelines for the management of patients with ICH are silent on the question of timing for resumption of anticoagulation.[760]

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.[775] Failure to reverse the warfarin and achieve a normal INR has been associated with an increased risk of rebleeding, and failure to achieve a therapeutic partial thromboplastin time with intravenous heparin has been associated with increased risk of ischemic stroke.[775] 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.[776] There are few data from RCTs 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 than an ICH. In general, these hemorrhages are often asymptomatic or cause minimal symptoms, rarely progress in size or extent, and are relatively common occurrences.[777,778] 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.[779] Each case must be assessed individually on the basis of variables such as size of the hemorrhagic transformation, patient status, and indication for anticoagulation.[769]

Anticoagulation After Intracranial Hemorrhage Recommendations

1. **The decision to restart antithrombotic therapy after ICH related to antithrombotic therapy depends on the risk of subsequent arterial or venous thromboembolism, the risk of recurrent ICH, and the overall status of the patient and must therefore be individualized to each patient. For patients with a comparatively lower risk of cerebral infarction (eg, AF without prior ischemic stroke) and a higher risk of recurrent ICH (eg, elderly patients with lobar ICH or presumed amyloid angiopathy) or with very poor overall neurological function, an antiplatelet agent may be considered for prevention of ischemic stroke (*Class IIb; Level of Evidence B*).**
2. **For patients who require resumption or initiation of anticoagulation after an acute ICH, subarachnoid hemorrhage, or subdural hematoma, the optimal timing is uncertain. For most patients, however, it might be reasonable to wait ≥1 week *(Class IIb; Level of Evidence B)*.**
3. **For patients with hemorrhagic cerebral infarction, continuation of anticoagulation may be considered, 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

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 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 CAD prevention strategies based on guideline dissemination did not produce dramatic improvements in the 1990s to 2000s.[780–785] Specific examples include population control of BP and hypercholesterolemia, which remained poor even after publication of major national guidelines.[786] Guideline dissemination, therefore, must be coupled with effective implementation strategies to change healthcare provider practice.

Proposed implementation strategies have included enabling strategies (eg, office reminders), reinforcing strategies (eg, feedback), and predisposing strategies (eg, practice guidelines) to improve the quality of practice.[787] One example of a novel reinforcing strategy is the AHA voluntary quality

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improvement program, Get With The Guidelines (GWTG), which has hospital-based modules to support implementation of guideline-based secondary prevention of CHD, heart failure, and stroke. Hospitals participating in the stroke module are encouraged to identify and abstract data on consecutive patients who are admitted with an acute stroke or TIA. Trained personnel abstract data on demographics, medical history, brain imaging, in-hospital treatment, in-hospital events, discharge treatment, counseling, mortality, and discharge destination. Hospital personnel achieve quality improvement by monitoring reports on compliance with guidelines and using this information to redesign care. Hospitals share best practices across the collaboration. High-performing sites are eligible for awards from the AHA. All states and regions of the United States are represented, and a variety of centers participate, from community hospitals to large tertiary centers.

The GWTG-Stroke program was implemented nationally in 2003. As of March 2013, 2000 hospitals have participated in the program, and >2.4 million patient records have been entered. In the first million patients with stroke or TIA, participation in GWTG-Stroke has been associated with improvements in multiple measures related to secondary stroke prevention. Significant improvements over time from 2003 to 2009 in quality of care delivery were observed for 7 independent, evidence-based measures, ranging in absolute percentage points from 4.3% for discharge antithrombotic drug use to 51.0% for smoking cessation ($P<0.0001$ for all comparisons), with a 40.3% increase for an all-or-none measure that captures the percentage of patients who received all the 7 interventions for which they were eligible (44.0% versus 84.3%; $P<0.0001$). After adjustment for patient and hospital variables, the cumulative adjusted OR for the all-or-none measure over the 6 years was 9.4 (95% CI, 8.3–10.6; $P<0.0001$). Temporal improvements in length of stay and risk-adjusted in-hospital mortality rate (for ischemic stroke and TIA) were also observed.[788]

An observational cohort study nested within 106 GWTG-Stroke hospitals followed 2888 adults admitted with ischemic stroke or TIA and measured regimen persistence, including use of antiplatelet therapies, warfarin, antihypertensive therapies, lipid-lowering therapies, or DM medications, from discharge to 3 months.[789] At 3 months, 25% of subjects were no longer taking all the secondary prevention medications prescribed at discharge. Persistence at 3 months was associated with several vulnerability factors, including age, health insurance, financial hardship, geographic region, and hospital size.

Another example of a reinforcing strategy is the CDC's Paul Coverdell National Acute Stroke Registry. The CDC was directed by the US Congress in 2001 to implement statement-based registries to measure, track, and improve the quality of acute stroke care. After an initial 3-year pilot phase in 8 states, the CDC provided funding and technical assistance to state health departments to develop, implement, and enhance systems for collecting data on patients experiencing an acute stroke and to use those results to guide quality improvement interventions in hospitals for acute stroke care. From 2005 through mid 2012, >250 000 patients benefitted from hospital participation in the Paul Coverdell National Acute Stroke Registry. Currently, 11 state health departments are funded by the CDC's Paul Coverdell National Acute Stroke Registry. Average annual improvements in adherence to stroke care measures were seen across a broad array of 10 evidence-based measures.[790]

Stepping into the challenge of implementation, the Institute of Medicine of the National Academy of Sciences recommended coordinated systems of care that integrate preventive and treatment services and promote patient access to evidence-based care.[791] One example of integrated care for stroke is the PROTECT (Preventing Recurrence Of Thromboembolic Events Through Coordinated Treatment) program, which systematically implements, at the time of acute TIA or ischemic stroke admission, 8 medication/behavioral secondary prevention measures known to improve outcome in patients with cerebrovascular disease. PROTECT investigators examined these 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.[317] More work is needed to develop interventions to improve adherence with secondary stroke prevention guidelines so that the field can catch up with the more developed research in acute stroke.[792,793]

Identifying and Responding to Populations at Highest Risk

Special approaches may be required to reduce the burden of recurrent stroke in high-risk populations defined by older age, socioeconomic position, and ethnicity.[781,794,795] The elderly are at increased risk for recurrence and complications from treatments such as oral anticoagulants and carotid endarterectomy.[417,796] Many clinical trials, however, 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.[797] By contrast, trials of medical therapies such as statins have included relatively large numbers of elderly patients with CAD or recent stroke and support safety and event reduction in these groups, although further study in the elderly may still be needed.[62,798–800] Recent data from GWTG-Stroke show substantial temporal improvements in measures of stroke care performance from 2003 to 2009 in each 10-year age group >50 years, and many age-related treatment gaps were narrowed or eliminated over time. These and data from other systems suggest that age-related disparities in hospital-based care for stroke may be decreasing over time.[801,802]

The socioeconomically disadvantaged constitute a population at high risk for stroke primarily because of limited access to care.[803] 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 caused by 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

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arrival at a hospital after hours.[804–807] Many rural institutions lack the resources for adequate emergency stroke treatment and the extensive community and professional educational services needed to improve stroke awareness and prevention. Telemedicine has become a tool to support improved rural health care and the acute treatment and primary and secondary prevention of stroke.[808,809] In GWTG-Stroke, geographic regional variation (south, northeast, midwest, and west) in stroke prevention has been documented.[810] Care varied regionally for use of lipid-lowering medications (72.5%–75.7%), antihypertensive agents (80.1%–83.6%), antithrombotic drugs (95.6%–96.8%), DVT prophylaxis (88.0%–91.4%), and weight loss education (49.3%–54.7%).

Stroke prevention efforts are of particular concern in ethnic groups identified as being at the highest risk. Although death rates attributed to stroke have declined by 11% in the United States from 1990 through 1998, not all groups have benefited equally, and substantial differences among ethnic groups persist.[818] In the Michigan Coverdell prototype registry from 2001 to 2004,[812] blacks were less likely to receive smoking cessation counseling (OR, 0.27). In GWTG-Stroke, an analysis of patients with ischemic stroke from 2003 through 2008 examined the effect of race and ethnicity on the delivery of guideline-based care.[813] After adjustment for both patient- and hospital-level variables, quality of care improved in all 3 racial/ethnic groups but not equally. Black patients had lower odds relative to white patients of receiving intravenous thrombolysis (OR, 0.84), DVT prophylaxis (OR, 0.88), smoking cessation (OR, 0.85), discharge antithrombotic drugs (OR, 0.88), anticoagulants for AF (OR, 0.84), and lipid therapy (OR, 0.91). Hispanic patients received similar care as their white counterparts on all 7 measures. The Brain Attack Surveillance in Corpus Christi (BASIC) project noted the similarities in stroke risk factor profiles in Mexican Americans and non-Hispanic whites.[814] A study from the US Department of Veterans Affairs demonstrated that racial disparities in carotid imaging were evident at minority-serving hospitals (where 40% of black patients received their inpatient stroke care) but that racial disparities were not observed at non–minority-serving hospitals.[815] The role of hypertension in blacks and its disproportionate impact on stroke risk has been clearly identified,[816–818] yet studies indicate that risk factors differ between different ethnic groups within the worldwide black population.[819]

Studies have also suggested worse poststroke outcomes in women. A GWTG-Stroke study of the relationship between sex and quality of care, as well as outcomes (in-hospital mortality and discharge home), showed that although sex differences in individual performance measures were relatively modest, they consistently identified women as being less likely to receive care than men.[820] Overall, women received less "all or none" care than men (66.3% versus 71.1%; adjusted OR, 0.86; 95% CI, 0.85–0.87) and were less likely to be discharged home (41.0% versus 49.5%; adjusted OR, 0.84; 95% CI, 0.83–0.85). Further studies are needed to address the causes and consequences of sex-based differences in health promotion behavior and stroke care.

For the aged, socioeconomically disadvantaged, women, and specific ethnic groups, inadequate implementation of guidelines and noncompliance with prevention recommendations are critical problems. Postdischarge adherence to care is also impacted by these vulnerabilities.

Expert panels have indicated the need for a multilevel approach to include the patient, provider, and organization delivering health care. The National Institute of Neurological Disorders and Stroke (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.[821] The panel encouraged projects aimed at stroke surveillance in multiethnic communities such as those in southern Texas,[814] northern Manhattan (New York),[818] Illinois,[822] and suburban Washington, DC,[823] as well as stroke awareness programs targeted directly at minority communities. Alliances with the federal government through the NINDS, CDC, nonprofit organizations such as the AHA/American Stroke Association, and medical specialty groups such as the American Academy of Neurology and the Brain Attack Coalition are needed to coordinate, develop, and optimize implementation of evidence-based stroke prevention recommendations. With increased attention to new models of care delivery designed to address the needs and costs of the highest-risk medically ill populations, Accountable Care Organizations may find new solutions to improve secondary prevention of CVD and stroke. Expanding the medical home to include a neighborhood of specialists may help foster greater collaboration between primary and specialty care and make progress toward the goal of eliminating existing disparities. In addition, linking financial reimbursement to compliance might improve the quality of care for stroke survivors. Leveraging data from quality improvement registries to identify gaps in guideline-based treatment and to design targeted interventions to address those gaps reflects a likely future evolution in the use of continuous quality improvement strategies for secondary prevention.

Special Approaches in High-Risk Populations Recommendations

1. **Monitoring achievement of nationally accepted, evidence-based guidelines on a population-based level is recommended as a basis for improving health-promotion behaviors and reducing stroke healthcare disparities among high-risk groups *(Class I; Level of Evidence C)*.** (New recommendation)
2. **Voluntary hospital-based programs for quality monitoring and improvement are recommended to improve adherence to nationally accepted, evidence-based guidelines for secondary stroke prevention *(Class I; Level of Evidence C)*.** (New recommendation)

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Writing Group Disclosures

Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/ Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
Walter N. Kernan	Yale University	NIH†	None	None	None	None	None	None
Bruce Ovbiagele	Medical University of South Carolina	NIH/NINDS†	None	None	None	None	None	None
Henry R. Black	New York University School of Medicine	Medtronic*	None	Harvard Medical School*; Ipca Laboratories†; MSD†; Novartis†; Ohio State University*	None	None	Bayer*; FDS*; Johnson & Johnson*; Mitsubishi*; MSD*; National Football League*; Nicox*; Pfizer*; Servier†; Xoma*	WebMD†
Dawn M. Bravata	Department of Veterans Affairs	NIH/NHLBI†; VA†	None	None	None	None	None	None
Marc I. Chimowitz	Medical University of South Carolina	NIH/NINDS†	None	None	Witness for plaintiff and defense in cases of medical malpractice (nonindustry)*	None	None	None
Michael D. Ezekowitz	Lankenau Medical Center	None	None	Boehringer Ingelheim†	None	None	ARYx Therapeutics†; AstraZeneca*; Boehringer Ingelheim†; Bristol-Myers Squibb†; Daiichi Sankyo†; Eisai*; Gilead†; Janssen Scientific Affairs†; Johnson & Johnson†; Medtronic†; Merck†; Pfizer†; PORTOLA†; Pozen Inc*; Sanofi†	None
Margaret C. Fang	University of California, San Francisco	NIH†	None	None	None	None	None	None
Marc Fisher	University of Massachusetts Memorial Health Care	NINDS†	None	None	None	None	None	Editor for journal *Stroke*†
Karen L. Furie	Massachusetts General Hospital	AHA†; NINDS†	None	None	None	None	UpToDate*	Deputy Editor for *Journal of Neurology, Neurosurgery, and Psychiatry*†; Vice Editor for journal *Stroke*†
Donald V. Heck	Triad Radiology Associates/Forsyth Medical Center	Abbott*; Cordis*; W.L. Gore*	None	None	None	None	W.L. Gore*	None
S. Claiborne (Clay) Johnston	UCSF	AstraZeneca*; NCATS†; NINDS†	None	Longwood Medical*; University of Texas*	Phillips Lytle, LLP (Avandia and Glaxo SmithKline)*	Co-holder of patent on the RNA panel to identify TIA and risk strategy*	Biogen Idec*; Sanofi-Aventis*	None
Scott E. Kasner	University of Pennsylvania	AstraZeneca*; NIH†; W.L. Gore*	None	None	None	None	Boehringer Ingelheim*; Daiichi Sankyo*; Medtronic*; Pfizer*	None

(*Continued*)

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Writing Group Disclosures, *Continued*

Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/ Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
Steven J. Kittner	Baltimore Veterans Administration Medical Center and University of Maryland School of Medicine	NIH/NINDS†	None	None	None	None	None	None
Pamela H. Mitchell	University of Washington	NIH†	None	None	None	None	None	None
Michael W. Rich	Washington University School of Medicine	None	None	None	None	None	None	None
DeJuran Richardson	Lake Forest College/ Rush University Medical Center	None	None	None	None	None	None	None
Lee H. Schwamm	Massachusetts General Hospital	None	None	None	None	None	Massachusetts Department of Public Health†; Medtronic*	Chair, AHA GWTG steering committee (unpaid volunteer)*
John A. Wilson	Wake Forest School of Medicine	None	None	None	None	None	None	None

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

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Reviewer Disclosures

Reviewer	Employment	Research Grant	Other Research Support	Speakers' Bureau/ Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
Mark Gorman	University of Vermont	NINDS (coinvestigator of the IRIS trial [Insulin Resistance Intervention After Stroke Trial])†	None	None	None	None	Symetis Corporation*	None
Millie Hepburn-Smith	New York University	None	None	None	None	None	None	None
William Mack	University of Southern California	None	None	None	None	None	Penumbra, Inc*	None
Peter Panagos	Washington University	None	None	None	None	None	None	None
Alejandro Rabinstein	Mayo Clinic	None	None	None	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 (a) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

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

Walter N. Kernan, Bruce Ovbiagele, Henry R. Black, Dawn M. Bravata, Marc I. Chimowitz, Michael D. Ezekowitz, Margaret C. Fang, Marc Fisher, Karen L. Furie, Donald V. Heck, S. Claiborne (Clay) Johnston, Scott E. Kasner, Steven J. Kittner, Pamela H. Mitchell, Michael W. Rich, DeJuran Richardson, Lee H. Schwamm and John A. Wilson

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Executive Summary: Guidelines for the Prevention of Stroke in Patients With Stroke and 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.

Endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons

Walter N. Kernan, MD, Chair; Bruce Ovbiagele, MD, MSc, MAS, Vice Chair; Henry R. Black, MD; Dawn M. Bravata, MD; Marc I. Chimowitz, MBChB, FAHA; Michael D. Ezekowitz, MBChB, PhD; Margaret C. Fang, MD, MPH; Marc Fisher, MD, FAHA; Karen L. Furie, MD, MPH, FAHA; Donald V. Heck, MD; S. Claiborne (Clay) Johnston, MD, PhD; Scott E. Kasner, MD, FAHA; Steven J. Kittner, MD, MPH, FAHA; Pamela H. Mitchell, PhD, RN, FAHA; Michael W. Rich, MD; DeJuran Richardson, PhD; Lee H. Schwamm, MD, FAHA; John A. Wilson, MD; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease

In recognition of the morbidity of recurrent brain ischemia, the aim of the present American Heart Association/American Stroke Association (AHA/ASA) document, "Guidelines for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack," is to provide clinicians with evidence-based recommendations for the prevention of future stroke among survivors of ischemic stroke or transient ischemic attack. The current average annual rate of future stroke (≈3%–4%) represents a historical low that is the result of important discoveries in prevention science. These include antiplatelet therapy and effective strategies for treatment of hypertension, atrial fibrillation (AF), arterial obstruction, and hyperlipidemia. New approaches and improvements in existing approaches are constantly emerging. To help clinicians safeguard past success and drive the rate of secondary stroke even lower, this guideline is updated every 2 to 3 years. Additional interval updates may be published, as needed, to reflect the changing state of knowledge on the approaches to prevent a recurrent stroke.

Important revisions since the last guideline are displayed in Table 1. New sections were added for sleep apnea and aortic arch atherosclerosis, in recognition of maturing literature to confirm these as prevalent risk factors for recurrent stroke. The section on diabetes mellitus (DM) has been expanded to include pre-DM. The revised guideline gives somewhat greater emphasis to lifestyle and obesity as potential targets for risk reduction. A section on nutrition was added. The sections on carotid stenosis, AF, and prosthetic heart valves have been revised substantially in a manner that is consistent with recently published AHA and American College of Chest Physicians guidelines. Sections on pregnancy and intracranial atherosclerosis have also been rewritten substantially. One section was removed (Fabry disease) in recognition of the rarity and specialized nature of this condition.

The revised guideline begins to consider clinically silent brain infarction as an entry point for secondary prevention and an event to be prevented. Brain imaging may identify evidence for clinically silent cerebral infarction, as defined by brain parenchymal injury of presumed vascular origin without a history of acute neurological dysfunction attributable to the lesion. These seemingly silent infarctions are associated with typical risk factors for ischemic stroke, increased risk for future ischemic stroke, and unrecognized neurological signs in the absence of symptoms. Clinicians who diagnose silent infarction routinely ask whether this diagnosis warrants implementation of secondary prevention measures. The writing committee, therefore, identified silent infarction as an important and emerging issue in secondary stroke prevention. Although data to guide management of patients with silent infarction are limited, the writing committee agreed to summarize these data where they could be found and incorporate them into relevant sections of this guideline.

Recommendations follow the AHA and the American College of Cardiology methods of classifying the level of certainty of the treatment effect and the class of evidence (Tables 2 and 3). The writing group prepared recommendations to be consistent with other, current AHA statements/guidelines, except where

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important new science warranted revision or differing interpretations of science could not be reconciled. 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 transient ischemic attack (TIA), including subsequent stroke, myocardial infarction (MI), and vascular death. Recommendations in this guideline are organized to aid the clinician who has arrived at a potential explanation of the cause of the ischemic stroke in an individual patient and is embarking on therapy to reduce the risk of a recurrent event and other vascular outcomes.

Recommendations

Hypertension

1. Initiation of blood pressure (BP) therapy is indicated for previously untreated patients with ischemic stroke or TIA who, after the first several days, have an established BP ≥140 mm Hg systolic or ≥90 mm Hg diastolic *(Class I; Level of Evidence B)*. Initiation of therapy for patients with BP <140 mm Hg systolic and <90 mm Hg diastolic is of uncertain benefit *(Class IIb; Level of Evidence C)*. (Revised recommendation)
2. Resumption of BP therapy is indicated for previously treated patients with known hypertension for both prevention of recurrent stroke and prevention of other vascular events in those who have had an ischemic stroke or TIA and are beyond the first several days *(Class I; Level of Evidence A)*. (Revised recommendation)
3. Goals for target BP level or reduction from pretreatment baseline are uncertain and should be individualized, but it is reasonable to achieve a systolic pressure <140 mm Hg and a diastolic pressure <90 mm Hg *(Class IIa; Level of Evidence B)*. For patients with a recent lacunar stroke, it might be reasonable to target a systolic blood pressure (SBP) of <130 mm Hg *(Class IIb; Level of Evidence B)*. (Revised recommendation)
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; the 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 reductions 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 is useful *(Class I; Level of Evidence A)*.
6. 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 mellitus [DM]) *(Class IIa; Level of Evidence B)*.

Dyslipidemia

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 presumed to be of atherosclerotic origin and an low-density lipoprotein cholesterol (LDL-C) level ≥100 mg/dL with or without evidence for other clinical atherosclerotic cardiovascular disease (ASCVD) *(Class I; Level of Evidence B)*. (Revised recommendation)
2. Statin therapy with intensive lipid-lowering effects is recommended to reduce risk of stroke and cardiovascular events among patients with ischemic stroke or TIA presumed to be of atherosclerotic origin, an LDL-C level <100 mg/dL, and no evidence for other clinical ASCVD *(Class I; Level of Evidence C)*. (New recommendation)
3. Patients with ischemic stroke or TIA and other comorbid ASCVD should be otherwise managed according to the 2013 ACC/AHA cholesterol guidelines,[16] which include lifestyle modification, dietary recommendations, and medication recommendations *(Class I; Level of Evidence A)*. (Revised recommendation)

Disorders of Glucose Metabolism and DM

1. After a TIA or ischemic stroke, all patients should probably be screened for DM with testing of fasting plasma glucose, HbA_{1c}, or an oral glucose tolerance test. Choice of test and timing should be guided by clinical judgment and recognition that acute illness may temporarily perturb measures of plasma glucose. In general, HbA_{1c} may be more accurate than other screening tests in the immediate postevent period *(Class IIa; Level of Evidence C)*. (New recommendation)
2. Use of existing guidelines from the American Diabetes Association for glycemic control and cardiovascular risk factor management is recommended for patients with an ischemic stroke or TIA who also have DM or pre-DM *(Class I; Level of Evidence B)*.

Obesity

1. All patients with TIA or stroke should be screened for obesity with measurement of body mass index *(Class I; Level of Evidence C)*. (New recommendation)
2. Despite the demonstrated beneficial effects of weight loss on cardiovascular risk factors, the usefulness of weight loss among patients with a recent TIA or ischemic stroke and obesity is uncertain *(Class IIb; Level of Evidence C)*. (New recommendation)

Metabolic Syndrome

1. At this time, the usefulness of screening patients for the metabolic syndrome after stroke is unknown *(Class IIb; Level of Evidence C)*.
2. For patients who are screened and classified as having the metabolic syndrome, management should focus on counseling for lifestyle modification (diet, exercise, and weight loss) for vascular risk reduction *(Class I; Level of Evidence C)*.

Table 1. New or Substantially Revised Recommendations for 2014*

Section	2014 Recommendation	Description of Change From 2011
Hypertension	Initiation of BP therapy is indicated for previously untreated patients with ischemic stroke or TIA who, after the first several days, have an established BP ≥140 mm Hg systolic or ≥90 mm Hg diastolic (*Class I; Level of Evidence B)*. Initiation of therapy for patients with BP <140 mm Hg systolic and <90 mm Hg diastolic is of uncertain benefit *(Class IIb; Level of Evidence C)*.	Clarification of parameters for initiating BP therapy
	Resumption of BP therapy is indicated for previously treated patients with known hypertension for both prevention of recurrent stroke and prevention of other vascular events in those who have had an ischemic stroke or TIA and are beyond the first several days *(Class I; Level of Evidence A)*.	Clarification of parameters for resuming BP therapy
	Goals for target BP level or reduction from pretreatment baseline are uncertain and should be individualized, but it is reasonable to achieve a systolic pressure <140 mm Hg and a diastolic pressure <90 mm Hg (*Class IIa; Level of Evidence B)*. For patients with a recent lacunar stroke, it might be reasonable to target a systolic BP of <130 mm Hg *(Class IIb; Level of Evidence B)*.	Revised guidance for target values
Dyslipidemia	Statin therapy with intensive lipid-lowering effects is recommended to reduce risk of stroke and cardiovascular events among patients with ischemic stroke or TIA presumed to be of atherosclerotic origin and an LDL-C level ≥100 mg/dL with or without evidence for other ASCVD *(Class I; Level of Evidence B)*.	1. Revised to be consistent with wording in the 2013 ACC/AHA cholesterol guideline[16]
	Statin therapy with intensive lipid-lowering effects is recommended to reduce risk of stroke and cardiovascular events among patients with ischemic stroke or TIA presumed to be of atherosclerotic origin, an LDL-C level <100 mg/dL, and no evidence for other clinical ASCVD *(Class I; Level of Evidence C)*.	1. Added to be consistent with the 2013 ACC/AHA cholesterol guideline[16] but to indicate a lower level of evidence when LDL-C is <100 mg/dL
	Patients with ischemic stroke or TIA and other comorbid ASCVD should be otherwise managed according to the ACC/AHA 2013 guidelines, which include lifestyle modification, dietary recommendations, and medication recommendations *(Class I; Level of Evidence A)*.	1. Revised to be consistent with the 2013 ACC/AHA cholesterol guideline[16]
Glucose disorders	After a TIA or ischemic stroke, all patients should probably be screened for DM with testing of fasting plasma glucose, HbA_{1c}, or an oral glucose tolerance test. Choice of test and timing should be guided by clinical judgment and recognition that acute illness may temporarily perturb measures of plasma glucose. In general, HbA_{1c} may be more accurate than other screening tests in the immediate postevent period *(Class IIa; Level of Evidence C)*.	New recommendation
Obesity	All patients with TIA or stroke should be screened for obesity with measurement of BMI *(Class I; Level of Evidence C)*.	New recommendation
	Given the demonstrated beneficial effects of weight loss on cardiovascular risk factors, the usefulness of weight loss among patients with a recent TIA or ischemic stroke and obesity is uncertain *(Class IIb; Level of Evidence C)*.	New recommendation
Physical inactivity	For patients who are able and willing to initiate increased physical activity, referral to a comprehensive, behaviorally oriented program is probably recommended *(Class IIa; Level of Evidence C)*.	New recommendation
Nutrition	It is reasonable to conduct a nutritional assessment for patients with a history of ischemic stroke or TIA, looking for signs of overnutrition or undernutrition *(Class IIa; Level of Evidence C)*.	New recommendation
	Patients with a history of ischemic stroke or TIA and signs of undernutrition should be referred for individualized nutritional counseling *(Class I; Level of Evidence B)*.	New recommendation
	Routine supplementation with a single vitamin or combination of vitamins is not recommended *(Class III; Level of Evidence A)*.	New recommendation
	It is reasonable to recommend that patients with a history of stroke or TIA reduce their sodium intake to less than ≈2.4 g/d. Further reduction to <1.5 g/d is also reasonable and is associated with even greater BP reduction *(Class IIa; Level of Evidence C)*.	New recommendation
	It is reasonable to counsel patients with a history of stroke or TIA to follow a Mediterranean-type diet instead of a low-fat diet. The Mediterranean-type diet emphasizes vegetables, fruits, and whole grains and includes low-fat dairy products, poultry, fish, legumes, olive oil, and nuts. It limits intake of sweets and red meats *(Class IIa; Level of Evidence C)*.	New recommendation
Sleep apnea	A sleep study might be considered for patients with an ischemic stroke or TIA on the basis of the very high prevalence of sleep apnea in this population and the strength of the evidence that the treatment of sleep apnea improves outcomes in the general population *(Class IIb; Level of Evidence B)*.	New recommendation
	Treatment with continuous positive airway pressure might be considered for patients with ischemic stroke or TIA and sleep apnea given the emerging evidence in support of improved outcomes *(Class IIb; Level of Evidence B)*.	New recommendation

(*Continued*)

Table 1. Continued

Section	2014 Recommendation	Description of Change From 2011
Carotid disease	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-based imaging or noninvasive imaging with corroboration and the anticipated rate of periprocedural stroke or death is <6% *(Class IIa; Level of Evidence B)*.	Class changed from I to IIa based on outcome findings reported in a meta-analysis of comparative trials
	It is reasonable to consider patient age in choosing between CAS and CEA. For older patients (ie, older than ≈70 years), CEA may be associated with improved outcome compared with CAS, particularly when arterial anatomy is unfavorable for endovascular intervention. For younger patients, CAS is equivalent to CEA in terms of risk for periprocedural complication (ie, stroke, MI, or death) and long-term risk for ipsilateral stroke *(Class IIa; Level of Evidence B)*.	New recommendation
	CAS and CEA in the above settings should be performed by operators with established periprocedural stroke and mortality rates of <6% for symptomatic patients, similar to that observed in trials comparing CEA to medical therapy and more recent observational studies *(Class I; Level of Evidence B)*.	Class changed from IIa to I
	Routine, long term follow-up imaging of the extracranial carotid circulation with carotid duplex ultrasonography is not recommended *(Class III; Level of Evidence B)*.	New recommendation
	For patients with recurrent or progressive ischemic symptoms ipsilateral to a stenosis or occlusion of a distal (surgically inaccessible) carotid artery, or occlusion of a midcervical carotid artery after institution of optimal medical therapy, the usefulness of EC/IC bypass is considered investigational *(Class IIb; Level of Evidence C)*.	New recommendation
Intracranial atherosclerosis	For patients with recent stroke or TIA (within 30 days) attributable to severe stenosis (70%–99%) of a major intracranial artery, the addition of clopidogrel 75 mg/d to aspirin for 90 days might be reasonable *(Class IIb; Level of Evidence B)*.	New recommendation
	For patients with stroke or TIA attributable to 50% to 99% stenosis of a major intracranial artery, the data are insufficient to make a recommendation regarding the usefulness of clopidogrel alone, the combination of aspirin and dipyridamole, or cilostazol alone *(Class IIb; Level of Evidence C)*.	New recommendation
	For patients with a stroke or TIA attributable to 50% to 99% stenosis of a major intracranial artery, maintenance of systolic BP below 140 mm Hg and high-intensity statin therapy are recommended *(Class I; Level of Evidence B)*.	1. New cholesterol recommendation is consistent with 2013 ACC/AHA cholesterol guideline[16] 2. Class changed from IIb to I
	For patients with a stroke or TIA attributable to moderate stenosis (50%–69%) of a major intracranial artery, angioplasty or stenting is not recommended given the low rate of stroke on medical management and the inherent periprocedural risk of endovascular treatment *(Class III; Level of Evidence B)*.	New recommendation
	For patients with stroke or TIA attributable to severe stenosis (70%–99%) of a major intracranial artery, stenting with the Wingspan stent system is not recommended as an initial treatment, even for patients who were taking an antithrombotic agent at the time of the stroke or TIA *(Class III; Level of Evidence B)*.	New recommendation
	For patients with stroke or TIA attributable to severe stenosis (70%–99%) of a major intracranial artery, the usefulness of angioplasty alone or placement of stents other than the Wingspan stent is unknown and is considered investigational *(Class IIb; Level of Evidence C)*.	1. Change from 50% to 99% stenosis to 70% to 99% stenosis 2. Rewording to mention Wingspan device used in SAMMPRIS
	For patients with severe stenosis (70%–99%) of a major intracranial artery and recurrent TIA or stroke after institution of aspirin and clopidogrel therapy, achievement of systolic BP <140 mm Hg, and high-intensity statin therapy, the usefulness of angioplasty alone or placement of a Wingspan stent or other stents is unknown and is considered investigational *(Class IIb; Level of Evidence C)*.	New recommendation
	For patients with severe stenosis (70%–99%) of a major intracranial artery and actively progressing symptoms after institution of aspirin and clopidogrel therapy, the usefulness of angioplasty alone or placement of a Wingspan stent or other stents is unknown and is considered investigational *(Class IIb; Level of Evidence C)*.	New recommendation
AF	For patients who have experienced an acute ischemic stroke or TIA with no other apparent cause, prolonged rhythm monitoring (≈30 days) for AF is reasonable within 6 months of the index event *(Class IIa; Level of Evidence C)*.	New recommendation
	VKA therapy *(Class I; Level of Evidence A)*, apixaban *(Class I; Level of Evidence A)*, and dabigatran *(Class I; Level of Evidence B)* are all indicated for the prevention of recurrent stroke in patients with nonvalvular AF, whether paroxysmal or permanent. The selection of an antithrombotic agent should be individualized on the basis of risk factors, cost, tolerability, patient preference, potential for drug interactions, and other clinical characteristics, including renal function and time in INR therapeutic range if the patient has been taking VKA therapy.	1. New recommendations regarding apixaban and dabigatran 2. New text regarding choice of agent

(*Continued*)

Table 1. Continued

Section	2014 Recommendation	Description of Change From 2011
AF cont'd	Rivaroxaban is reasonable for the prevention of recurrent stroke in patients with nonvalvular AF *(Class IIa; Level of Evidence B)*.	New recommendation
	The combination of oral anticoagulation (ie, warfarin or one of the newer agents) with antiplatelet therapy is not recommended for all patients after ischemic stroke or TIA but is reasonable in patients with clinically apparent CAD, particularly an acute coronary syndrome or stent placement *(Class IIb; Level of Evidence C)*.	New recommendation
	For patients with ischemic stroke or TIA and AF who are unable to take oral anticoagulants, aspirin alone is recommended (*Class I; Level of Evidence A*). The addition of clopidogrel to aspirin therapy, compared with aspirin therapy alone, might be reasonable *(Class IIb; Level of Evidence B)*.	1. Reworded from the 2011 text 2. Class changed from III to IIb
	For most patients with a stroke or TIA in the setting of AF, it is reasonable to initiate oral anticoagulation within 14 days after the onset of neurological symptoms *(Class IIa; Level of Evidence B)*.	New recommendation
	In the presence of high risk for hemorrhagic conversion (ie, large infarct, hemorrhagic transformation on initial imaging, uncontrolled hypertension, or hemorrhage tendency), it is reasonable to delay initiation of oral anticoagulation beyond 14 days *(Class IIa; Level of Evidence B)*.	New recommendation
	The usefulness of closure of the left atrial appendage with the WATCHMAN device in patients with ischemic stroke or TIA and AF is uncertain *(Class IIb; Level of Evidence B)*.	New recommendation
MI and thrombus	Treatment with VKA therapy (target INR, 2.5; range, 2.0–3.0) for 3 months may be considered in patients with ischemic stroke or TIA in the setting of acute anterior STEMI without demonstrable left ventricular mural thrombus formation but with anterior apical akinesis or dyskinesis identified by echocardiography or other imaging modality *(Class IIb; Level of Evidence C)*.	New recommendation
	In patients with ischemic stroke or TIA in the setting of acute MI complicated by left ventricular mural thrombus formation or anterior or apical wall-motion abnormalities with a left ventricular ejection fraction <40% who are intolerant to VKA therapy because of nonhemorrhagic adverse events, treatment with an LMWH, dabigatran, rivaroxaban, or apixaban for 3 months may be considered as an alternative to VKA therapy for prevention of recurrent stroke or TIA *(Class IIb; Level of Evidence C)*.	New recommendation
Cardiomyopathy	In patients with ischemic stroke or TIA in sinus rhythm who have left atrial or left ventricular thrombus demonstrated by echocardiography or another imaging modality, anticoagulant therapy with a VKA is recommended for ≥3 months *(Class I; Level of Evidence C)*.	New recommendation
	In patients with ischemic stroke or TIA in the setting of a mechanical LVAD, treatment with VKA therapy (target INR, 2.5; range, 2.0–3.0) is reasonable in the absence of major contraindications (eg, active gastrointestinal bleeding) *(Class IIa; Level of Evidence C)*.	New recommendation
	In patients with ischemic stroke or TIA in sinus rhythm with dilated cardiomyopathy (LV ejection fraction ≤35%), restrictive cardiomyopathy, or a mechanical LVAD who are intolerant to VKA therapy because of nonhemorrhagic adverse events, the effectiveness of treatment with dabigatran, rivaroxaban, or apixaban is uncertain compared with VKA therapy for prevention of recurrent stroke *(Class IIb; Level of Evidence C)*.	New recommendation
Valvular heart disease	For patients with ischemic stroke or TIA who have rheumatic mitral valve disease and AF, long-term VKA therapy with an INR target of 2.5 (range, 2.0–3.0) is recommended *(Class I; Level of Evidence A)*.	1. Mention of patients without AF is removed 2. Class changed from IIa to I
	For patients with ischemic stroke or TIA who have rheumatic mitral valve disease without AF or another likely cause for their symptoms (eg, carotid stenosis), long-term VKA therapy with an INR target of 2.5 (range, 2.0–3.0) may be considered instead of antiplatelet therapy *(Class IIb; Level of Evidence C)*.	New recommendation focuses on patients without AF
	For patients with rheumatic mitral valve disease who have an ischemic stroke or TIA while being treated with adequate VKA therapy, the addition of aspirin might be considered *(Class IIb; Level of Evidence C)*.	New recommendation
	For patients with ischemic stroke or TIA and native aortic or nonrheumatic mitral valve disease who do not have AF or another indication for anticoagulation, antiplatelet therapy is recommended *(Class I; Level of Evidence C)*.	Class changed from IIb to I
	For patients with ischemic stroke or TIA and mitral annular calcification who do not have AF or another indication for anticoagulation, antiplatelet therapy is recommended as it would be without the mitral annular calcification *(Class I; Level of Evidence C)*.	Class changed from IIb to I

(*Continued*)

Table 1. Continued

Section	2014 Recommendation	Description of Change From 2011
Valvular heart disease cont'd	For patients with mitral valve prolapse who have ischemic stroke or TIAs and who do not have AF or another indication for anticoagulation, antiplatelet therapy is recommended as it would be without mitral valve prolapse *(Class I; Level of Evidence C)*.	1. Change in wording 2. Class changed from IIb to I
Prosthetic HV	For patients with a mechanical aortic valve and a history of ischemic stroke or TIA before its insertion, VKA therapy is recommended with an INR target of 2.5 (range, 2.0–3.0) *(Class I; Level of Evidence B)*.	Modified to focus on aortic valve
	For patients with a mechanical mitral valve and a history of ischemic stroke or TIA before its insertion, VKA therapy is recommended with an INR target of 3.0 (range, 2.5–3.5) *(Class I; Level of Evidence C)*.	1. New recommendation focuses on mitral valve 2. INR target is revised for the mitral valve
	For patients with a mechanical mitral or aortic valve who have a history of ischemic stroke or TIA before its insertion and who are at low risk for bleeding, the addition of aspirin 75 to 100 mg/d to VKA therapy is recommended *(Class I; Level of Evidence B)*.	New recommendation
	For patients with a bioprosthetic aortic or mitral valve, a history of ischemic stroke or TIA before its insertion, and no other indication for anticoagulation therapy beyond 3 to 6 months from the valve placement, long-term therapy with aspirin 75 to 100 mg/d is recommended in preference to long-term anticoagulation *(Class I; Level of Evidence C)*.	New recommendation specifically addresses timing of TIA or stroke in relation to valve replacement and recommends aspirin in preference to anticoagulation
Antiplatelet therapy	The combination of aspirin and clopidogrel might be considered for initiation within 24 hours of a minor ischemic stroke or TIA and for continuation for 21 days *(Class IIb; Level of Evidence B)*.	New recommendation
	For patients with a history of ischemic stroke or TIA, AF, and CAD, the usefulness of adding antiplatelet therapy to VKA therapy is uncertain for purposes of reducing the risk of ischemic cardiovascular and cerebrovascular events *(Class IIb; Level of Evidence C)*. Unstable angina and coronary artery stenting represent special circumstances in which management may warrant DAPT/VKA therapy.	New recommendation
Aortic arch atheroma	For patients with an ischemic stroke or TIA and evidence of aortic arch atheroma, antiplatelet therapy is recommended *(Class I; Level of Evidence A)*.	New recommendation
	For patients with an ischemic stroke or TIA and evidence of aortic arch atheroma, statin therapy is recommended *(Class I; Level of Evidence B)*.	New recommendation
	For patients with ischemic stroke or TIA and evidence of aortic arch atheroma, the effectiveness of anticoagulation with warfarin, compared with antiplatelet therapy, is unknown *(Class IIb; Level of Evidence C)*.	New recommendation
	Surgical endarterectomy of aortic arch plaque for the purposes of secondary stroke prevention is not recommended *(Class III; Level of Evidence C)*.	New recommendation
PFO	For patients with an ischemic stroke or TIA and a PFO who are not undergoing anticoagulation therapy, antiplatelet therapy is recommended *(Class I; Level of Evidence B)*.	Class changed from IIa to I
	For patients with an ischemic stroke or TIA and both a PFO and a venous source of embolism, anticoagulation is indicated, depending on stroke characteristics *(Class I; Level of Evidence A)*. When anticoagulation is contraindicated, an inferior vena cava filter is reasonable *(Class IIa; Level of Evidence C)*.	New recommendations
	For patients with a cryptogenic ischemic stroke or TIA and a PFO without evidence for DVT, available data do not support a benefit for PFO closure *(Class III; Level of Evidence A)*.	Class changed from IIb to III
	In the setting of PFO and DVT, PFO closure by a transcatheter device might be considered, depending on the risk of recurrent DVT *(Class IIb; Level of Evidence C)*.	New recommendation
Homocysteinemia	Routine screening for hyperhomocysteinemia among patients with a recent ischemic stroke or TIA is not indicated *(Class III; Level of Evidence C)*.	New recommendation
	In adults with a recent ischemic stroke or TIA who are known to have mild to moderate hyperhomocysteinemia, supplementation with folate, vitamin B_6, and vitamin B_{12} safely reduces levels of homocysteine but has not been shown to prevent stroke (*Class III; Level of Evidence B*).	Class changed from IIb to III
Hypercoagulation	The usefulness of screening for thrombophilic states in patients with ischemic stroke or TIA is unknown *(Class IIb; Level of Evidence C)*.	New recommendation
	Anticoagulation might be considered in patients who are found to have abnormal findings on coagulation testing after an initial ischemic stroke or TIA, depending on the abnormality and the clinical circumstances *(Class IIb; Level of Evidence C)*.	Substantial rewording Class changed from IIa to IIb

(*Continued*)

Table 1. Continued

Section	2014 Recommendation	Description of Change From 2011
Hypercoagulation cont'd	Antiplatelet therapy is recommended in patients who are found to have abnormal findings on coagulation testing after an initial ischemic stroke or TIA if anticoagulation therapy is not administered *(Class I; Level of Evidence A)*.	Represents a more firm recommendation for antiplatelet therapy in the circumstance described
Antiphospholipid antibodies	Routine testing for antiphospholipid antibodies is not recommended for patients with ischemic stroke or TIA who have no other manifestations of the antiphospholipid antibody syndrome and who have an alternative explanation for their ischemic event, such as atherosclerosis, carotid stenosis, or AF *(Class III; Level of Evidence C)*.	New recommendation
	For patients with ischemic stroke or TIA who have an antiphospholipid antibody but who do not fulfill the criteria for antiphospholipid antibody syndrome, antiplatelet therapy is recommended *(Class I; Level of Evidence B)*.	Clarifies circumstances in which antiplatelet therapy is recommended over anticoagulation
	For patients with ischemic stroke or TIA who meet the criteria for the antiphospholipid antibody syndrome but in whom anticoagulation is not begun, antiplatelet therapy is indicated *(Class I; Level of Evidence A)*.	New recommendation
Sickle cell disease	For patients with sickle cell disease and prior ischemic stroke or TIA, chronic blood transfusions to reduce hemoglobin S to <30% of total hemoglobin are recommended *(Class I; Level of Evidence B)*.	Class changed from IIa to I
Pregnancy	In the presence of a high-risk condition that would require anticoagulation outside of pregnancy, the following options are reasonable: a. LMWH twice daily throughout pregnancy, with dose adjusted to achieve the LMWH manufacturer's recommended peak anti-Xa level 4 hours after injection, or b. Adjusted-dose UFH throughout pregnancy, administered subcutaneously every 12 hours in doses adjusted to keep the midinterval aPTT at least twice control or to maintain an anti-Xa heparin level of 0.35 to 0.70 U/mL, or c. UFH or LMWH (as above) until the 13th week, followed by substitution of a VKA until close to delivery, when UFH or LMWH is resumed *(Class IIa; Level of Evidence C)*.	More detail is provided that is intended to be consistent with the recent statement by the American College of Chest Physicians[18]
	For pregnant women receiving adjusted-dose LMWH therapy for a high-risk condition that would require anticoagulation outside of pregnancy, and when delivery is planned, it is reasonable to discontinue LMWH ≥24 hours before induction of labor or cesarean section *(Class IIa; Level of Evidence C)*.	New recommendation
	In the presence of a low-risk situation in which antiplatelet therapy would be the treatment recommendation outside of pregnancy, UFH or LMWH, or no treatment may be considered during the first trimester of pregnancy depending on the clinical situation *(Class IIb; Level of Evidence C)*.	New recommendation
Breastfeeding	In the presence of a high-risk condition that would require anticoagulation outside of pregnancy, it is reasonable to use warfarin, UFH, or LMWH *(Class IIa; Level of Evidence C)*.	New recommendation
	In the presence of a low-risk situation in which antiplatelet therapy would be the treatment recommendation outside of pregnancy, low-dose aspirin use may be considered *(Class IIb; Level of Evidence C)*.	New recommendation
Implementation	Monitoring achievement of nationally accepted, evidence-based guidelines on a population-based level is recommended as a basis for improving health-promotion behaviors and reducing stroke healthcare disparities among high risk groups *(Class I; Level of Evidence C)*.	New recommendation
	Voluntary hospital-based programs for quality monitoring and improvement are recommended to improve adherence to nationally accepted, evidence-based guidelines for secondary stroke prevention *(Class I; Level of Evidence C)*.	New recommendation

ACC indicates American College of Cardiology; AF, atrial fibrillation; AHA, American Heart Association; aPTT, activated partial thromboplastin time; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CAS, carotid angioplasty and stenting; CEA, carotid endarterectomy; DAPT, dual-antiplatelet therapy; DM, diabetes mellitus; DVT, deep vein thrombosis; EC/IC, extracranial/intracranial; HbA_{1c}, hemoglobin A_{1c}; HV, heart valve; INR, international normalized ratio; LDL-C, low-density lipoprotein cholesterol; LMWH, low-molecular-weight heparin; LV, left ventricular; LVAD, left ventricular assist device; MI, myocardial infarction; PFO, patent foramen ovale; SAMMPRIS, Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis; STEMI, ST-elevation myocardial infarction; TIA, transient ischemic attack; UFH, unfractionated heparin; and VKA, vitamin K antagonist.

*Includes recommendations for which the class was changed from one whole number to another and recommendations for which a change in wording significantly changed meaning. This table does not list removed recommendations.

3. Preventive care for patient with the metabolic syndrome should include appropriate treatment for individual components of the syndrome, which are also stroke risk factors, particularly dyslipidemia and hypertension *(Class I; Level of Evidence A)*.

Physical Inactivity

1. For patients with ischemic stroke or TIA who are capable of engaging in physical activity, at least 3 to 4 sessions per week of moderate- to vigorous-intensity aerobic physical

Table 2. 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** *No Benefit* or **CLASS III** *Harm* Procedure/Test / Treatment COR III: No benefit — Not Helpful / No Proven Benefit COR III: Harm — Excess Cost w/o Benefit or Harmful / Harmful to Patients
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	COR III: No Benefit: is not recommended; is not indicated; should not be performed/ administered/ other; is not useful/ beneficial/ effective COR III: Harm: potentially harmful; causes harm; associated with excess morbidity/mortality; should not be performed/ administered/ other
Comparative effectiveness phrases†	treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B		

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. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

†For comparative effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

exercise are reasonable to reduce stroke risk factors. Sessions should last an average of 40 minutes. Moderate-intensity exercise is typically defined as sufficient to break a sweat or noticeably raise heart rate (eg, walking briskly, using an exercise bicycle). Vigorous-intensity exercise includes activities such as jogging *(Class IIa; Level of Evidence C)*. (Revised recommendation)

2. For patients who are able and willing to initiate increased physical activity, referral to a comprehensive, behaviorally oriented program is reasonable *(Class IIa; Level of Evidence C)*. (New recommendation)
3. For individuals with 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)*.

Nutrition

1. It is reasonable to conduct a nutritional assessment for patients with a history of ischemic stroke or TIA, looking for signs of overnutrition or undernutrition *(Class IIa; Level of Evidence C)*. (New recommendation)
2. Patients with a history of ischemic stroke or TIA and signs of undernutrition should be referred for

Table 3. Definition of Classes and Levels of Evidence Used in AHA/ASA 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

AHA/ASA indicates American Heart Association/American Stroke Association.

individualized nutritional counseling *(Class I; Level of Evidence B)*. (New recommendation)

3. Routine supplementation with a single vitamin or combination of vitamins is not recommended *(Class III; Level of Evidence A)*. (New recommendation)
4. It is reasonable to recommend that patients with a history of stroke or TIA reduce their sodium intake to less than ≈2.4 g/d. Further reduction to <1.5 g/d is also reasonable and is associated with even greater BP reduction *(Class IIa; Level of Evidence C)*. (New recommendation)
5. It is reasonable to counsel patients with a history of stroke or TIA to follow a Mediterranean-type diet instead of a low-fat diet. The Mediterranean-type diet emphasizes vegetables, fruits, and whole grains and includes low-fat dairy products, poultry, fish, legumes, olive oil, and nuts. It limits intake of sweets and red meats *(Class IIa; Level of Evidence C)*. (New recommendation)

Sleep Apnea

1. A sleep study might be considered for patients with an ischemic stroke or TIA on the basis of the very high prevalence of sleep apnea in this population and the strength of the evidence that the treatment of sleep apnea improves outcomes in the general population *(Class IIb; Level of Evidence B)*. (New recommendation)
2. Treatment with continuous positive airway pressure might be considered for patients with ischemic stroke or TIA and sleep apnea given the emerging evidence in support of improved outcomes *(Class IIb; Level of Evidence B)*. (New recommendation)

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 advise patients after TIA or ischemic stroke to avoid environmental (passive) tobacco smoke *(Class IIa; Level of Evidence B)*.
3. Counseling, nicotine products, and oral smoking cessation medications are effective in helping smokers to quit *(Class I; Level of Evidence A)*.

Alcohol Consumption

1. Patients with ischemic stroke, TIA, or hemorrhagic stroke who are heavy drinkers should eliminate or reduce their consumption of alcohol *(Class I; Level of Evidence C)*.
2. Light to moderate amounts of alcohol consumption (up to 2 drinks per day for men and up to 1 drink per day for nonpregnant women) may be reasonable, although nondrinkers should not be counseled to start drinking *(Class IIb; Level of Evidence B)*.

Extracranial Carotid Disease

1. For patients with a TIA or ischemic stroke within the past 6 months and ipsilateral severe (70%–99%) carotid artery stenosis as documented by noninvasive imaging, 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%–69%) carotid stenosis as documented by catheter-based imaging or noninvasive imaging with corroboration (eg, magnetic resonance angiogram or computed tomography angiogram), 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%, CEA and carotid angioplasty and stenting (CAS) are not recommended *(Class III; Level of Evidence A)*.
4. When revascularization is indicated for patients with TIA or minor, nondisabling stroke, it is reasonable to perform the procedure within 2 weeks of the index event rather than delay 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-based imaging or noninvasive imaging with corroboration and the anticipated rate of periprocedural stroke or death is <6% *(Class IIa; Level of Evidence B)*. (Revised recommendation)

6. It is reasonable to consider patient age in choosing between CAS and CEA. For older patients (ie, older than ≈70 years), CEA may be associated with improved outcome compared with CAS, particularly when arterial anatomy is unfavorable for endovascular intervention. For younger patients, CAS is equivalent to CEA in terms of risk for periprocedural complications (ie, stroke, MI, or death) and long-term risk for ipsilateral stroke *(Class IIa; Level of Evidence B)*. (New recommendation)
7. Among patients with symptomatic severe stenosis (>70%) in whom anatomic or medical conditions are present that greatly increase the risk for surgery or when other specific circumstances exist such as radiation-induced stenosis or restenosis after CEA, CAS is reasonable *(Class IIa; Level of Evidence B)*. (Revised recommendation)
8. CAS and CEA in the above settings should be performed by operators with established periprocedural stroke and mortality rates of <6% for symptomatic patients, similar to that observed in trials comparing CEA to medical therapy and more recent observational studies *(Class I; Level of Evidence B)*. (Revised recommendation)
9. Routine, long-term follow-up imaging of the extracranial carotid circulation with carotid duplex ultrasonography is not recommended *(Class III; Level of Evidence B)*. (New recommendation)
10. For patients with a recent (within 6 months) TIA or ischemic stroke ipsilateral to a stenosis or occlusion of the middle cerebral or carotid artery, extracranial/intracranial (EC/IC) bypass surgery is not recommended *(Class III; Level of Evidence A)*.
11. For patients with recurrent or progressive ischemic symptoms ipsilateral to a stenosis or occlusion of a distal (surgically inaccessible) carotid artery, or occlusion of a midcervical carotid artery after institution of optimal medical therapy, the usefulness of EC/IC bypass is considered investigational *(Class IIb; Level of Evidence C)*. (New recommendation)
12. 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 A)*.

Extracranial Vertebrobasilar Disease

1. Routine preventive therapy with emphasis on antithrombotic therapy, lipid lowering, BP control, and lifestyle optimization is recommended for all patients with recently symptomatic extracranial vertebral artery stenosis *(Class I; Level of Evidence C)*.
2. Endovascular stenting of patients with extracranial vertebral stenosis may be considered when patients are having symptoms despite optimal medical treatment *(Class IIb; Level of Evidence C)*.
3. Open surgical procedures, including vertebral endarterectomy and vertebral artery transposition, may be considered when patients are having symptoms despite optimal medical treatment *(Class IIb; Level of Evidence C)*.

Intracranial Atherosclerosis

1. For patients with a stroke or TIA caused by 50% to 99% stenosis of a major intracranial artery, aspirin 325 mg/d is recommended in preference to warfarin *(Class I; Level of Evidence B)*. (Revised recommendation)
2. For patients with recent stroke or TIA (within 30 days) attributable to severe stenosis (70%–99%) of a major intracranial artery, the addition of clopidogrel 75 mg/d to aspirin for 90 days might be reasonable *(Class IIb; Level of Evidence B)*. (New recommendation)
3. For patients with stroke or TIA attributable to 50% to 99% stenosis of a major intracranial artery, the data are insufficient to make a recommendation regarding the usefulness of clopidogrel alone, the combination of aspirin and dipyridamole, or cilostazol alone *(Class IIb; Level of Evidence C)*. (New recommendation)
4. For patients with a stroke or TIA attributable to 50% to 99% stenosis of a major intracranial artery, maintenance of SBP below 140 mm Hg and high-intensity statin therapy are recommended *(Class I; Level of Evidence B)*. (Revised recommendation)
5. For patients with a stroke or TIA attributable to moderate stenosis (50%–69%) of a major intracranial artery, angioplasty or stenting is not recommended given the low rate of stroke with medical management and the inherent periprocedural risk of endovascular treatment *(Class III; Level of Evidence B)*. (New recommendation)
6. For patients with stroke or TIA attributable to severe stenosis (70%–99%) of a major intracranial artery, stenting with the Wingspan stent system is not recommended as an initial treatment, even for patients who were taking an antithrombotic agent at the time of the stroke or TIA *(Class III; Level of Evidence B)*. (New recommendation)
7. For patients with stroke or TIA attributable to severe stenosis (70%–99%) of a major intracranial artery, the usefulness of angioplasty alone or placement of stents other than the Wingspan stent is unknown and is considered investigational *(Class IIb; Level of Evidence C)*. (Revised recommendation)
8. For patients with severe stenosis (70%–99%) of a major intracranial artery and recurrent TIA or stroke after institution of aspirin and clopidogrel therapy, achievement of SBP <140 mm Hg, and high-intensity statin therapy, the usefulness of angioplasty alone or placement of a Wingspan stent or other stent is unknown and is considered investigational *(Class IIb; Level of Evidence C)*. (New recommendation)
9. For patients with severe stenosis (70%–99%) of a major intracranial artery and actively progressing symptoms after institution of aspirin and clopidogrel therapy, the usefulness of angioplasty alone or placement of a Wingspan stent or other stents is unknown and is considered investigational *(Class IIb; Level of Evidence C)*. (New recommendation)

10. For patients with stroke or TIA attributable to 50% to 99% stenosis of a major intracranial artery, EC/IC bypass surgery is not recommended *(Class III; Level of Evidence B)*.

Atrial Fibrillation

1. For patients who have experienced an acute ischemic stroke or TIA with no other apparent cause, prolonged rhythm monitoring (≈30 days) for atrial fibrillation (AF) is reasonable within 6 months of the index event *(Class IIa; Level of Evidence C)*. (New recommendation)
2. Vitamin K antagonist (VKA) therapy *(Class I; Level of Evidence A)*, apixaban *(Class I; Level of Evidence A)*, and dabigatran *(Class I; Level of Evidence B)* are all indicated for the prevention of recurrent stroke in patients with nonvalvular AF, whether paroxysmal or permanent. The selection of an antithrombotic agent should be individualized on the basis of risk factors, cost, tolerability, patient preference, potential for drug interactions, and other clinical characteristics, including renal function and time in international normalized ratio (INR) therapeutic range if the patient has been taking VKA therapy. (Revised recommendation)
3. Rivaroxaban is reasonable for the prevention of recurrent stroke in patients with nonvalvular AF *(Class IIa; Level of Evidence B)*. (New recommendation)
4. For patients with ischemic stroke or TIA with paroxysmal (intermittent), persistent, or permanent AF in whom VKA therapy is begun, a target INR of 2.5 is recommended (range, 2.0–3.0) *(Class I; Level of Evidence A)*.
5. The combination of oral anticoagulation (ie, warfarin or one of the newer agents) with antiplatelet therapy is not recommended for all patients after ischemic stroke or TIA but is reasonable in patients with clinically apparent coronary artery disease, particularly an acute coronary syndrome or stent placement *(Class IIb; Level of Evidence C)*. (New recommendation)
6. For patients with ischemic stroke or TIA and AF who are unable to take oral anticoagulants, aspirin alone is recommended *(Class I; Level of Evidence A)*. The addition of clopidogrel to aspirin therapy, compared with aspirin therapy alone, might be reasonable *(Class IIb; Level of Evidence B)*. (Revised recommendation)
7. For most patients with a stroke or TIA in the setting of AF, it is reasonable to initiate oral anticoagulation within 14 days after the onset of neurological symptoms *(Class IIa; Level of Evidence B)*. (New recommendation)
8. In the presence of high risk for hemorrhagic conversion (ie, large infarct, hemorrhagic transformation on initial imaging, uncontrolled hypertension, or hemorrhage tendency), it is reasonable to delay initiation of oral anticoagulation beyond 14 days *(Class IIa; Level of Evidence B)*. (New recommendation)
9. For patients with AF and a history of stroke or TIA who require temporary interruption of oral anticoagulation, bridging therapy with an low-molecular-weight heparin (LMWH) (or equivalent anticoagulant agent if intolerant to heparin) is reasonable, depending on perceived risk for thromboembolism and bleeding *(Class IIa; Level of Evidence C)*.
10. The usefulness of closure of the left atrial appendage with the WATCHMAN device in patients with ischemic stroke or TIA and AF is uncertain *(Class IIb; Level of Evidence B)*. (New recommendation)

Acute MI and Left Ventricular Thrombus

1. Treatment with VKA therapy (target INR, 2.5; range, 2.0–3.0) for 3 months is recommended in most 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 imaging modality *(Class I; Level of Evidence C)*. Additional antiplatelet therapy for cardiac protection may be guided by recommendations such as those from the American College of Chest Physicians. (Revised recommendation)
2. Treatment with VKA therapy (target INR, 2.5; range, 2.0–3.0) for 3 months may be considered in patients with ischemic stroke or TIA in the setting of acute anterior ST-segment MI without demonstrable LV mural thrombus formation but with anterior apical akinesis or dyskinesis identified by echocardiography or other imaging modality *(Class IIb; Level of Evidence C)*. (New recommendation)
3. In patients with ischemic stroke or TIA in the setting of acute MI complicated by LV mural thrombus formation or anterior or apical wall-motion abnormalities with an LV ejection fraction <40% who are intolerant to VKA therapy because of nonhemorrhagic adverse events, treatment with an LMWH, dabigatran, rivaroxaban, or apixaban for 3 months may be considered as an alternative to VKA therapy for prevention of recurrent stroke or TIA *(Class IIb; Level of Evidence C)*. (New recommendation)

Cardiomyopathy

1. In patients with ischemic stroke or TIA in sinus rhythm who have left atrial or LV thrombus demonstrated by echocardiography or another imaging modality, anticoagulant therapy with a VKA is recommended for ≥3 months *(Class I; Level of Evidence C)*. (New recommendation)
2. In patients with ischemic stroke or TIA in the setting of a mechanical LV assist device, treatment with VKA therapy (target INR, 2.5; range, 2.0–3.0) is reasonable in the absence of major contraindications (eg, active gastrointestinal bleeding) *(Class IIa; Level of Evidence C)*. (New recommendation)
3. In patients with ischemic stroke or TIA in sinus rhythm with either dilated cardiomyopathy (LV ejection fraction ≤35%) or restrictive cardiomyopathy without evidence of left atrial or LV thrombus, the effectiveness of anticoagulation compared with antiplatelet therapy is uncertain, and the choice should be individualized *(Class IIb; Level of Evidence B)*. (Revised recommendation)

4. In patients with ischemic stroke or TIA in sinus rhythm with dilated cardiomyopathy (LV ejection fraction ≤35%), restrictive cardiomyopathy, or a mechanical LV assist device who are intolerant to VKA therapy because of nonhemorrhagic adverse events, the effectiveness of treatment with dabigatran, rivaroxaban, or apixaban is uncertain compared with VKA therapy for prevention of recurrent stroke *(Class IIb; Level of Evidence C)*. (New recommendation)

Mitral Stenosis, Mitral Regurgitation, Mitral Prolapse, Mitral Annular Calcification, and Aortic Valve Disease

1. For patients with ischemic stroke or TIA who have rheumatic mitral valve disease and AF, long-term VKA therapy with an INR target of 2.5 (range, 2.0–3.0) is recommended *(Class I; Level of Evidence A)*. (Revised recommendation)
2. For patients with ischemic stroke or TIA who have rheumatic mitral valve disease without AF or another likely cause for their symptoms (eg, carotid stenosis), long-term VKA therapy with an INR target of 2.5 (range, 2.0–3.0) may be considered instead of antiplatelet therapy *(Class IIb; Level of Evidence C)*. (New recommendation)
3. For patients with rheumatic mitral valve disease who are prescribed VKA therapy after an ischemic stroke or TIA, antiplatelet therapy should not be routinely added *(Class III; Level of Evidence C)*.
4. For patients with rheumatic mitral valve disease who have an ischemic stroke or TIA while being treated with adequate VKA therapy, the addition of aspirin might be considered *(Class IIb; Level of Evidence C)*. (New recommendation)
5. For patients with ischemic stroke or TIA and native aortic or nonrheumatic mitral valve disease who do not have AF or another indication for anticoagulation, antiplatelet therapy is recommended *(Class I; Level of Evidence C)*. (Revised recommendation)
6. For patients with ischemic stroke or TIA and mitral annular calcification who do not have AF or another indication for anticoagulation, antiplatelet therapy is recommended as it would be without the mitral annular calcification *(Class I; Level of Evidence C)*. (Revised recommendation)
7. For patients with mitral valve prolapse who have ischemic stroke or TIAs and who do not have AF or another indication for anticoagulation, antiplatelet therapy is recommended as it would be without mitral valve prolapse *(Class I; Level of Evidence C)*. (Revised recommendation)

Prosthetic Heart Valve

1. For patients with a mechanical aortic valve and a history of ischemic stroke or TIA before its insertion, VKA therapy is recommended with an INR target of 2.5 (range, 2.0–3.0) *(Class I; Level of Evidence B)*. (Revised recommendation)
2. For patients with a mechanical mitral valve and a history of ischemic stroke or TIA before its insertion, VKA therapy is recommended with an INR target of 3.0 (range, 2.5–3.5) *(Class I; Level of Evidence C)*. (New recommendation)
3. For patients with a mechanical mitral or aortic valve who have a history of ischemic stroke or TIA before its insertion and who are at low risk for bleeding, the addition of aspirin 75 to 100 mg/d to VKA therapy is recommended *(Class I; Level of Evidence B)*. (New recommendation)
4. For patients with a mechanical heart valve who have an ischemic stroke or systemic embolism despite adequate antithrombotic therapy, it is reasonable to intensify therapy by increasing the dose of aspirin to 325 mg/d or increasing the target INR, depending on bleeding risk *(Class IIa; Level of Evidence C)*. (Revised recommendation)
5. For patients with a bioprosthetic aortic or mitral valve, a history of ischemic stroke or TIA before its insertion, and no other indication for anticoagulation therapy beyond 3 to 6 months from the valve placement, long-term therapy with aspirin 75 to 100 mg/d is recommended in preference to long-term anticoagulation *(Class I; Level of Evidence C)*. (New recommendation)
6. For patients with a bioprosthetic aortic or mitral valve who have a TIA, ischemic stroke, or systemic embolism despite adequate antiplatelet therapy, the addition of VKA therapy with an INR target of 2.5 (range, 2.0–3.0) may be considered *(Class IIb; Level of Evidence C)*. (Revised recommendation)

Antiplatelet Agent

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 (50–325 mg/d) monotherapy (*Class I; Level of Evidence A*) or the combination of aspirin 25 mg and extended-release dipyridamole 200 mg twice daily *(Class I; Level of Evidence B)* is indicated as initial therapy after TIA or ischemic stroke for prevention of future stroke. (Revised recommendation)
3. Clopidogrel (75 mg) monotherapy is a reasonable option for secondary prevention of stroke in place of aspirin or combination aspirin/dipyridamole *(Class IIa; Level of Evidence B)*. This recommendation also applies to patients who are allergic to aspirin.
4. The selection of an antiplatelet agent should be individualized on the basis of patient risk factor profiles, cost, tolerance, relative known efficacy of the agents, and other clinical characteristics *(Class I; Level of Evidence C)*.
5. The combination of aspirin and clopidogrel might be considered for initiation within 24 hours of a minor ischemic stroke or TIA and for continuation for 21 days *(Class IIb; Level of Evidence B)*. (New recommendation)
6. The combination of aspirin and clopidogrel, when initiated days to years after a minor stroke or TIA and continued for 2 to 3 years, increases the risk of hemorrhage relative to either agent alone and is not recommended for routine long-term secondary prevention after ischemic stroke or TIA *(Class III; Level of Evidence A)*.

7. For patients who have an ischemic stroke or TIA 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 adequately studied in patients who have had an event while receiving aspirin *(Class IIb; Level of Evidence C)*.
8. For patients with a history of ischemic stroke or TIA, AF, and coronary artery disease, the usefulness of adding antiplatelet therapy to VKA therapy is uncertain for purposes of reducing the risk of ischemic cardiovascular and cerebrovascular events *(Class IIb; Level of Evidence C)*. Unstable angina and coronary artery stenting represent special circumstances in which management may warrant dual antiplatelet therapy/VKA therapy. (New recommendation)

Oral Anticoagulant

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)*.

Aortic Arch Atheroma

1. For patients with an ischemic stroke or TIA and evidence of aortic arch atheroma, antiplatelet therapy is recommended *(Class I; Level of Evidence A)*. (New recommendation)
2. For patients with an ischemic stroke or TIA and evidence of aortic arch atheroma, statin therapy is recommended *(Class I; Level of Evidence B)*. (New recommendation)
3. For patients with ischemic stroke or TIA and evidence of aortic arch atheroma, the effectiveness of anticoagulation with warfarin, compared with antiplatelet therapy, is unknown *(Class IIb; Level of Evidence C)*. (New recommendation)
4. Surgical endarterectomy of aortic arch plaque for the purposes of secondary stroke prevention is not recommended *(Class III; Level of Evidence C)*. (New recommendation)

Arterial Dissection

1. For patients with ischemic stroke or TIA and extracranial carotid or vertebral arterial dissection, antithrombotic treatment with either antiplatelet or anticoagulant therapy 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)*.
3. For patients with stroke or TIA and extracranial carotid or vertebral arterial dissection who have definite recurrent cerebral ischemic events despite 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 have definite recurrent cerebral ischemic events despite medical therapy and also fail or are not candidates for endovascular therapy may be considered for surgical treatment *(Class IIb; Level of Evidence C)*.

Patent Foramen Ovale

1. There are insufficient data to establish whether anticoagulation is equivalent or superior to aspirin for secondary stroke prevention in patients with patent foramen ovale (PFO) *(Class IIb; Level of Evidence B)*.
2. For patients with an ischemic stroke or TIA and a PFO who are not undergoing anticoagulation therapy, antiplatelet therapy is recommended *(Class I; Level of Evidence B)*. (Revised recommendation)
3. For patients with an ischemic stroke or TIA and both a PFO and a venous source of embolism, anticoagulation is indicated, depending on stroke characteristics *(Class I; Level of Evidence A)*. When anticoagulation is contraindicated, an inferior vena cava filter is reasonable *(Class IIa; Level of Evidence C)*. (New recommendation)
4. For patients with a cryptogenic ischemic stroke or TIA and a PFO without evidence for deep vein thrombosis (DVT) available data do not support a benefit for PFO closure *(Class III; Level of Evidence A)*. (Revised recommendation)
5. In the setting of PFO and DVT, PFO closure by a transcatheter device might be considered, depending on the risk of recurrent DVT *(Class IIb; Level of Evidence C)*. (New recommendation)

Hyperhomocysteinemia

1. Routine screening for hyperhomocysteinemia among patients with a recent ischemic stroke or TIA is not indicated *(Class III; Level of Evidence C)*. (New recommendation)
2. In adults with a recent ischemic stroke or TIA who are known to have mild to moderate hyperhomocysteinemia, supplementation with folate, vitamin B_6, and vitamin B_{12} safely reduces levels of homocysteine but has not been shown to prevent stroke *(Class III; Level of Evidence B)*. (Revised Recommendation)

Hypercoagulable States

1. The usefulness of screening for thrombophilic states in patients with ischemic stroke or TIA is unknown *(Class IIb; Level of Evidence C)*. (New recommendation)
2. Anticoagulation might be considered in patients who are found to have abnormal findings on coagulation testing after an initial ischemic stroke or TIA, depending on the abnormality and the clinical circumstances *(Class IIb; Level of Evidence C)*. (Revised recommendation)
3. Antiplatelet therapy is recommended for patients who are found to have abnormal findings on coagulation testing after an initial ischemic stroke or TIA if anticoagulation therapy is not administered *(Class I; Level of Evidence A)*. (Revised recommendation)
4. Long-term anticoagulation might be reasonable for patients with spontaneous cerebral venous sinus thrombosis or a recurrent ischemic stroke of undefined origin

and an inherited thrombophilia *(Class IIb; Level of Evidence C)*.

Antiphospholipid Antibodies

1. Routine testing for antiphospholipid antibodies is not recommended for patients with ischemic stroke or TIA who have no other manifestations of the antiphospholipid antibody syndrome (APS) and who have an alternative explanation for their ischemic event, such as atherosclerosis, carotid stenosis, or AF *(Class III; Level of Evidence C)*. (New recommendation)
2. For patients with ischemic stroke or TIA who have an antiphospholipid antibody but do not fulfill the criteria for APS, antiplatelet therapy is recommended *(Class I; Level of Evidence B)*. (Revised recommendation)
3. For patients with ischemic stroke or TIA who meet the criteria for the APS, anticoagulant therapy might be considered depending on the perception of risk for recurrent thrombotic events and bleeding *(Class IIb; Level of Evidence C)*. (Revised recommendation)
4. For patients with ischemic stroke or TIA who meet the criteria for the APS but in whom anticoagulation is not begun, antiplatelet therapy is indicated *(Class I; Level of Evidence A)*. (New recommendation)

Sickle Cell Disease

1. For patients with sickle cell disease and prior ischemic stroke or TIA, chronic blood transfusions to reduce hemoglobin S to <30% of total hemoglobin are recommended *(Class I; Level of Evidence B)*. (Revised recommendation)
2. For patients with sickle cell disease and prior ischemic stroke or TIA for whom transfusion therapy is not available or practical, treatment with hydroxyurea may be considered *(Class IIb; Level of Evidence B)*. (Revised recommendation)
3. For adults with sickle cell disease and ischemic stroke or TIA, general treatment recommendations cited elsewhere in this guideline are reasonable with regard to the control of risk factors and the use of antiplatelet agents *(Class IIa; Level of Evidence B)*.

Cerebral Venous Sinus Thrombosis

1. Anticoagulation is reasonable for patients with acute cerebral venous sinus thrombosis, even in selected patients with intracranial hemorrhage *(Class IIa; Level of Evidence B)*. (Revised recommendation)
2. In cerebral venous sinus thrombosis patients without a recognized thrombophilia, it is reasonable to administer anticoagulation for ≥3 months, followed by antiplatelet therapy *(Class IIa; Level of Evidence C)*. Recommendations for patients with a recognized thrombophilia are discussed elsewhere in this document.

Pregnancy

1. In the presence of a high-risk condition that would require anticoagulation outside of pregnancy, the following options are reasonable[18]:
   a. LMWH twice daily throughout pregnancy, with dose adjusted to achieve the LMWH manufacturer's recommended peak anti-Xa activity 4 hours after injection, or
   b. Adjusted-dose unfractionated heparin (UFH) throughout pregnancy, administered subcutaneously every 12 hours in doses adjusted to keep the midinterval activated partial thromboplastin time at least twice control or to maintain an anti-Xa heparin level of 0.35 to 0.70 U/mL, or
   c. UFH or LMWH (as above) until the 13th week, followed by substitution of a VKA until close to delivery, when UFH or LMWH is resumed. *(Class IIa; Level of Evidence C)* (Revised recommendation)
2. For pregnant women receiving adjusted-dose LMWH therapy for a high-risk condition that would require anticoagulation outside of pregnancy, and when delivery is planned, it is reasonable to discontinue LMWH ≥24 hours before induction of labor or cesarean section[18] *(Class IIa; Level of Evidence C)*. (New recommendation)
3. In the presence of a low-risk situation in which antiplatelet therapy would be the treatment recommendation outside of pregnancy, UFH or LMWH, or no treatment may be considered during the first trimester of pregnancy depending on the clinical situation *(Class IIb; Level of Evidence C)*. (New recommendation)
4. In the presence of a low-risk situation in which antiplatelet therapy would be the treatment recommendation outside of pregnancy, low-dose aspirin (50–150 mg/d) is reasonable after the first trimester of pregnancy *(Class IIa; Level of Evidence B)*. (Revised recommendation)

Breastfeeding Women

1. In the presence of a high-risk condition that would require anticoagulation outside of pregnancy, it is reasonable to use warfarin, UFH, or LMWH *(Class IIa; Level of Evidence C)*. (New recommendation)
2. In the presence of a low-risk situation in which antiplatelet therapy would be the treatment recommendation outside of pregnancy, low-dose aspirin use may be considered *(Class IIb; Level of Evidence C)*. (New recommendation)

Anticoagulation After Intracranial Hemorrhage

1. The decision to restart antithrombotic therapy after intracranial hemorrhage (ICH) related to antithrombotic therapy depends on the risk of subsequent arterial or venous thromboembolism, the risk of recurrent ICH, and the overall status of the patient and must therefore be individualized to each patient. For patients with a comparatively lower risk of cerebral infarction (eg, AF without prior ischemic stroke) and a higher risk of recurrent ICH (eg, elderly patients with lobar ICH or presumed amyloid angiopathy) or with very poor overall neurological function, an antiplatelet agent may be considered for prevention of ischemic stroke *(Class IIb; Level of Evidence B)*.

2. For patients who require resumption or initiation of anticoagulation after an acute ICH, subarachnoid hemorrhage, or subdural hematoma, the optimal timing is uncertain. For most patients, however, it might be reasonable to wait ≥1 week *(Class IIb; Level of Evidence B)*.
3. For patients with hemorrhagic cerebral infarction, continuation of anticoagulation may be considered, depending on the specific clinical scenario and underlying indication for anticoagulant therapy *(Class IIb; Level of Evidence C)*.

Special Approaches in High-Risk Populations

1. Monitoring achievement of nationally accepted, evidence-based guidelines on a population-based level is recommended as a basis for improving health-promotion behaviors and reducing stroke healthcare disparities among high-risk groups *(Class I; Level of Evidence C)*. (New recommendation)
2. Voluntary hospital-based programs for quality monitoring and improvement are recommended to improve adherence to nationally accepted, evidence-based guidelines for secondary stroke prevention *(Class I; Level of Evidence C)*. (New recommendation)

References

References are available in the full text of this guideline: http://stroke.ahajournals.org/cgi/reprint/STR.0000000000000024.