

PRACTICE GUIDELINES

2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/ SAIP/SCAI/SIR/SNIS/SVM/SVS Guideline on the Management of Patients With Extracranial Carotid and Vertebral Artery Disease: Executive Summary

A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of NeuroInterventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery

Developed in Collaboration With the American Academy of Neurology and Society of Cardiovascular Computed Tomography

Writing Committee Members

Thomas G. Brott, MD, *Co-Chair**
Jonathan L. Halperin, MD, *Co-Chair†*

Suhny Abbara, MD‡
J. Michael Bacharach, MD§
John D. Barr, MD||
Ruth L. Bush, MD, MPH
Christopher U. Cates, MD¶
Mark A. Creager, MD#
Susan B. Fowler, PhD**
Gary Friday, MD††
Vicki S. Hertzberg, PhD

E. Bruce McIff, MD‡‡
Wesley S. Moore, MD
Peter D. Panagos, MD§§
Thomas S. Riles, MD|||
Robert H. Rosenwasser, MD¶¶
Allen J. Taylor, MD##

*ASA Representative; †ACCF/AHA Representative and ACCF/AHA Task Force on Performance Measures Liaison; ‡SCCT Representative; §SVM Representative; ||ACR, ASNR, and SNIS Representative; ¶SCAI Representative; #ACCF/AHA Task Force on Practice Guidelines Liaison; **AANN Representative; ††AAN Representative; ‡‡SIR Representative; §§ACEP Representative; |||SVS Representative; ¶¶AANS and CNS Representative; ##SAIP Representative. Authors with no symbol by their name were included to provide additional content expertise apart from organizational representation.

The writing committee gratefully acknowledges the memory of Robert W. Hobson II, MD, who died during the development of this document but contributed immensely to our understanding of extracranial carotid and vertebral artery disease.

This document was approved by the American College of Cardiology Foundation Board of Trustees in August 2010, the American Heart Association Science Advisory and Coordinating Committee in August 2010, the Society for Vascular Surgery in December 2010, and the American Association of Neuroscience Nurses in January 2011. All other partner organizations approved the document in November 2010. The American Academy of Neurology affirms the value of this guideline.

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**ACCF/AHA
Task Force
Members**

Alice K. Jacobs, MD, FACC, FAHA, *Chair*
2009–2011
Sidney C. Smith, JR, MD, FACC, FAHA,
*Immediate Past Chair 2006–2008****
Jeffery L. Anderson, MD, FACC, FAHA,
Chair-Elect

Cynthia D. Adams, MSN, APRN-BC,
FAHA***
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Christopher E. Buller, MD, FACC**
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Robert A. Guyton, MD, FACC
Jonathan L. Halperin, MD, FACC, FAHA

Judith S. Hochman, MD, FACC, FAHA
Sharon Ann Hunt, MD, FACC, FAHA***
Harlan M. Krumholz, MD, FACC, FAHA***
Frederick G. Kushner, MD, FACC, FAHA
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Rick A. Nishimura, MD, FACC, FAHA***
E. Magnus Ohman, MD, FACC
Richard L. Page, MD, FACC, FAHA***
Barbara Riegel, DNSc, RN, FAHA***
William G. Stevenson, MD, FACC, FAHA
Lynn G. Tarkington, RN***
Clyde W. Yancy, MD, FACC, FAHA

***Former Task Force member during this writing effort.

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Preamble

It is essential that the medical profession play a central role in critically evaluating the evidence related to drugs, devices, and procedures for the detection, management, or prevention of disease. Properly applied, rigorous, expert analysis of the available data documenting absolute and relative benefits and risks of these therapies and procedures can improve the effectiveness of care, optimize patient outcomes, and favorably affect the cost of care by focusing resources on the most effective strategies. One important use of such data is the production of clinical practice guidelines that, in turn, can provide a foundation for a variety of other applications such as performance measures, appropriate use criteria, clinical decision support tools, and quality improvement tools.

The American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) have jointly engaged in the production of guidelines in the area of cardiovascular disease since 1980. The ACCF/AHA Task Force on Practice Guidelines (Task Force) is charged with developing, updating, and revising practice guidelines for cardiovascular diseases and procedures, and the Task Force directs and oversees this effort. Writing committees are charged with assessing the evidence as an independent group of authors to develop, update, or revise recommendations for clinical practice.

Experts in the subject under consideration have been selected from both organizations to examine subject-specific data and write guidelines in partnership with representatives from other medical practitioner and specialty groups. Writing committees are specifically charged to perform a formal literature review; weigh the strength of evidence for or against particular tests, treatments, or procedures; and include estimates of expected health outcomes where data exist. Patient-specific modifiers, comorbidities, and issues of patient preference that may influence the choice of tests or therapies are considered. When available, information from studies on cost is considered, but data on efficacy and clinical

Table 1. Applying Classification of Recommendations and Level of Evidence

		SIZE OF TREATMENT EFFECT ➔			
		CLASS I <i>Benefit >>> Risk</i> Procedure/Treatment SHOULD be performed/administered	CLASS IIa <i>Benefit >> Risk</i> Additional studies with <i>focused objectives needed</i> IT IS REASONABLE to perform procedure/administer treatment	CLASS IIb <i>Benefit ≥ Risk</i> Additional studies with <i>broad objectives needed; additional registry data would be helpful</i> Procedure/Treatment MAY BE CONSIDERED	CLASS III <i>No Benefit</i> or CLASS III <i>Harm</i>
ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	<ul style="list-style-type: none"> Recommendation that procedure or treatment is useful/effective Sufficient evidence from multiple randomized trials or meta-analyses 	<ul style="list-style-type: none"> Recommendation in favor of treatment or procedure being useful/effective Some conflicting evidence from multiple randomized trials or meta-analyses 	<ul style="list-style-type: none"> Recommendation's usefulness/efficacy less well established Greater conflicting evidence from multiple randomized trials or meta-analyses 	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Recommendation that procedure or treatment is useful/effective Evidence from single randomized trial or nonrandomized studies 	<ul style="list-style-type: none"> Recommendation in favor of treatment or procedure being useful/effective Some conflicting evidence from single randomized trial or nonrandomized studies 	<ul style="list-style-type: none"> Recommendation's usefulness/efficacy less well established Greater conflicting evidence from single randomized trial or nonrandomized studies 	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Recommendation that procedure or treatment is useful/effective Only expert opinion, case studies, or standard of care 	<ul style="list-style-type: none"> Recommendation in favor of treatment or procedure being useful/effective Only diverging expert opinion, case studies, or standard of care 	<ul style="list-style-type: none"> Recommendation's usefulness/efficacy less well established Only diverging expert opinion, case studies, or standard of care 	<ul style="list-style-type: none"> 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 COR III: Harm
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		is not recommended is not indicated should not be done is not useful/beneficial/effective	potentially harmful causes harm associated with excess morbidity/mortality should not be done

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

†For 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.

outcomes constitute the primary basis for recommendations in these guidelines.

In analyzing the data and developing the recommendations and supporting text, the writing committee used evidence-based methodologies developed by the Task Force that are described elsewhere (1). The committee reviewed and ranked evidence supporting current recommendations with the weight of evidence ranked as Level A if the data were derived from multiple randomized clinical trials or meta-analyses. The committee ranked available evidence as Level B when data were derived from a single randomized trial or nonrandomized studies. Evidence was ranked as Level C when the primary source of the recommendation was consensus opinion, case studies, or standard of care. In the narrative portions of these guidelines, evidence is generally presented in chronological order of development. Studies are identified as observational, retrospective, pro-

spective, or randomized when appropriate. For certain conditions for which inadequate data are available, recommendations are based on expert consensus and clinical experience and ranked as Level C. An example is the use of penicillin for pneumococcal pneumonia, for which there are no randomized trials and treatment is based on clinical experience. When recommendations at Level C are supported by historical clinical data, appropriate references (including clinical reviews) are cited if available. For issues for which sparse data are available, a survey of current practice among the clinicians on the writing committee was the basis for Level C recommendations, and no references are cited. The schema for Classification of Recommendations and Level of Evidence is summarized in Table 1, which also illustrates how the grading system provides an estimate of the size and the certainty of the treatment effect. A new addition to the ACCF/AHA methodology is a

separation of the Class III recommendations to delineate whether the recommendation is determined to be of “no benefit” or associated with “harm” to the patient. In addition, in view of the increasing number of comparative effectiveness studies, comparator verbs and suggested phrases for writing recommendations for the comparative effectiveness of one treatment/strategy with respect to another for Class of Recommendation I and IIa, Level of Evidence A or B only have been added.

The Task Force makes every effort to avoid actual, potential, or perceived conflicts of interest that may arise as a result of relationships with industry and other entities (RWI) among the writing committee. Specifically, all members of the writing committee, as well as peer reviewers of the document, are asked to disclose all current relationships and those 24 months before initiation of the writing effort that may be perceived as relevant. All guideline recommendations require a confidential vote by the writing committee and must be approved by a consensus of the members voting. Any writing committee member who develops a new relationship with industry during his or her tenure is required to notify guideline staff in writing. These statements are reviewed by the Task Force and all members during each conference call and/or meeting of the writing committee and are updated as changes occur. For detailed information about guideline policies and procedures, please refer to the ACCF/AHA methodology and policies manual (1). Authors’ and peer reviewers’ relationships with industry and other entities pertinent to this guideline are disclosed in [Appendixes 1 and 2](#), respectively. Disclosure information for the Task Force is available online at www.cardiosource.org/ACC/About-ACC/Leadership/Guidelines-and-Documents-Task-Forces.aspx. The work of the writing committee was supported exclusively by the ACCF and AHA (and other partnering organizations) without commercial support. Writing committee members volunteered their time for this effort.

The ACCF/AHA practice guidelines address patient populations (and healthcare providers) residing in North America. As such, drugs that are currently unavailable in North America are discussed in the text without a specific class of recommendation. For studies performed in large numbers of subjects outside of North America, each writing committee reviews the potential impact of different practice patterns and patient populations on the treatment effect and the relevance to the ACCF/AHA target population to determine whether the findings should inform a specific recommendation.

The ACCF/AHA practice guidelines are intended to assist healthcare providers in clinical decision making by describing a range of generally acceptable approaches for the diagnosis, management, and prevention of specific diseases or conditions. These practice guidelines represent a consensus of expert opinion after a thorough review of the available

current scientific evidence and are intended to improve patient care. The guidelines attempt to define practices that meet the needs of most patients in most circumstances. The ultimate judgment regarding care of a particular patient must be made by the healthcare provider and patient in light of all the circumstances presented by that patient. Thus, there are situations in which deviations from these guidelines may be appropriate. Clinical decision making should consider the quality and availability of expertise in the area where care is provided. When these guidelines are used as the basis for regulatory or payer decisions, the goal should be improvement in quality of care. The Task Force recognizes that situations arise for which additional data are needed to better inform patient care; these areas will be identified within each respective guideline when appropriate.

Prescribed courses of treatment in accordance with these recommendations are effective only if they are followed. Because lack of patient understanding and adherence may adversely affect outcomes, physicians and other healthcare providers should make every effort to engage the patient’s active participation in prescribed medical regimens and lifestyles.

The guidelines will be reviewed annually by the Task Force and considered current unless they are updated, revised, or withdrawn from distribution. The full-text guideline is e-published in the *Journal of the American College of Cardiology*, *Circulation*, and *Stroke* and is posted on the American College of Cardiology (www.cardiosource.org) and AHA (my.americanheart.org) World Wide Web sites.

Alice K. Jacobs, MD, FACC, FAHA
Chair, ACCF/AHA Task Force on Practice Guidelines

Sidney C. Smith, Jr, MD, FACC, FAHA
Immediate Past Chair, ACCF/AHA Task Force
on Practice Guidelines

1. Introduction

1.1. Methodology and Evidence Review

The ACCF/AHA writing committee to create the 2011 Guideline on the Management of Patients With Extracranial Carotid and Vertebral Artery Disease (ECVD) conducted a comprehensive review of the literature relevant to carotid and vertebral artery interventions through May 2010.

The recommendations listed in this document are, whenever possible, evidence-based. Searches were limited to studies, reviews, and other evidence conducted in human subjects and published in English. Key search words included but were not limited to *angioplasty*, *atherosclerosis*, *carotid artery disease*, *carotid endarterectomy (CEA)*, *carotid revascularization*, *carotid stenosis*, *carotid stenting*, *carotid artery stenting (CAS)*, *extracranial carotid artery stenosis*, *stroke*, *transient ischemic attack (TIA)*, and *vertebral artery disease*. Additional searches cross-referenced these topics

with the following subtopics: *acetylsalicylic acid, antiplatelet therapy, carotid artery dissection, cerebral embolism, cerebral protection, cerebrovascular disorders, complications, comorbidities, extracranial atherosclerosis, intima-media thickness, medical therapy, neurological examination, noninvasive testing, pharmacological therapy, preoperative risk, primary closure, risk factors, and vertebral artery dissection*. Additionally, the committee reviewed documents related to the subject matter previously published by the ACCF and AHA (and other partnering organizations). References selected and published in this document are representative and not all-inclusive.

To provide clinicians with a comprehensive set of data, whenever deemed appropriate or when published in the article, data from the clinical trial were used to calculate the absolute risk difference and number needed to treat or harm; data related to the relative treatment effects are also provided, such as odds ratio (OR), relative risk, hazard ratio (HR), or incidence rate ratio, along with confidence intervals (CIs) when available.

The committee used the evidence-based methodologies developed by the Task Force and acknowledges that adjudication of the evidence was complicated by the timing of the evidence when 2 different interventions were contrasted. Despite similar study designs (e.g., randomized controlled trials), research on CEA was conducted in a different era (and thus, evidence existed in the peer-reviewed literature for more time) than the more contemporary CAS trials. Because evidence is lacking in the literature to guide many aspects of the care of patients with nonatherosclerotic carotid disease and most forms of vertebral artery disease, a relatively large number of the recommendations in this document are based on consensus.

The writing committee chose to limit the scope of this document to the vascular diseases themselves and not to the management of patients with acute stroke or to the detection or prevention of disease in individuals or populations at risk, which are covered in another guideline (2). The full-text guideline is based on the presumption that readers will search the document for specific advice on the management of patients with ECVD at different phases of illness. Following the typical chronology of the clinical care of patients with ECVD, the guideline is organized in sections that address the pathogenesis, epidemiology, diagnostic evaluation, and management of patients with ECVD, including prevention of recurrent ischemic events. The text, recommendations, and supporting evidence are intended to assist the diverse array of clinicians who provide care for patients with ECVD. In particular, they are designed to aid primary care clinicians, medical and surgical cardiovascular specialists, and trainees in the primary care and vascular specialties, as well as nurses and other healthcare personnel who seek clinical tools to promote the proper evaluation and management of patients with ECVD in both inpatient and outpatient settings. Application of the recommended diagnostic and therapeutic strategies, combined with careful

clinical judgment, should improve diagnosis of each syndrome, enhance prevention, and decrease rates of stroke and related long-term disability and death. The ultimate goal of the guideline statement is to improve the duration and quality of life for people with ECVD.

1.2. Organization of the Writing Committee

The writing committee to develop the 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS Guideline on the Management of Patients With Extracranial Carotid and Vertebral Artery Disease was composed of experts in the areas of medicine, surgery, neurology, cardiology, radiology, vascular surgery, neurosurgery, neuroradiology, interventional radiology, noninvasive imaging, emergency medicine, vascular medicine, nursing, epidemiology, and biostatistics. The committee included representatives of the American Stroke Association (ASA), ACCF, AHA, American Academy of Neurology (AAN), American Association of Neuroscience Nurses (AANN), American Association of Neurological Surgeons (AANS), American College of Emergency Physicians (ACEP), American College of Radiology (ACR), American Society of Neuroradiology (ASNR), Congress of Neurological Surgeons (CNS), Society of Atherosclerosis Imaging and Prevention (SAIP), Society for Cardiovascular Angiography and Interventions (SCAI), Society of Cardiovascular Computed Tomography (SCCT), Society of Interventional Radiology (SIR), Society of NeuroInterventional Surgery (SNIS), Society for Vascular Medicine (SVM), and Society for Vascular Surgery (SVS).

1.3. Document Review and Approval

The document was reviewed by 55 external reviewers, including individuals nominated by each of the ASA, ACCF, AHA, AANN, AANS, ACEP, American College of Physicians, ACR, ASNR, CNS, SAIP, SCAI, SCCT, SIR, SNIS, SVM, and SVS, and by individual content reviewers, including members from the ACCF Catheterization Committee, ACCF Interventional Scientific Council, ACCF Peripheral Vascular Disease Committee, ACCF Surgeons' Scientific Council, ACCF/SCAI/SVMB/SIR/ASITN Expert Consensus Document on Carotid Stenting, ACCF/AHA Peripheral Arterial Disease Guideline Writing Committee, AHA Peripheral Vascular Disease Steering Committee, AHA Stroke Leadership Committee, and individual nominees. All information on reviewers' relationships with industry and other entities was distributed to the writing committee and is published in this document (Appendix 2).

This document was reviewed and approved for publication by the governing bodies of the ASA, ACCF and AHA and endorsed by the AANN, AANS, ACR, ASNR, CNS, SAIP, SCAI, SCCT, SIR, SNIS, SVM, and SVS. The AAN affirms the value of this guideline.

2. Recommendations for Duplex Ultrasonography to Evaluate Asymptomatic Patients With Known or Suspected Carotid Stenosis

CLASS I

1. In asymptomatic patients with known or suspected carotid stenosis, duplex ultrasonography, performed by a qualified technologist in a certified laboratory, is recommended as the initial diagnostic test to detect hemodynamically significant carotid stenosis. (*Level of Evidence: C*)

CLASS IIa

1. It is reasonable to perform duplex ultrasonography to detect hemodynamically significant carotid stenosis in asymptomatic patients with carotid bruit. (*Level of Evidence: C*)
2. It is reasonable to repeat duplex ultrasonography annually by a qualified technologist in a certified laboratory to assess the progression or regression of disease and response to therapeutic interventions in patients with atherosclerosis who have had stenosis greater than 50% detected previously. Once stability has been established over an extended period or the patient's candidacy for further intervention has changed, longer intervals or termination of surveillance may be appropriate. (*Level of Evidence: C*)

CLASS IIb

1. Duplex ultrasonography to detect hemodynamically significant carotid stenosis may be considered in asymptomatic patients with symptomatic peripheral arterial disease (PAD), coronary artery disease, or atherosclerotic aortic aneurysm, but because such patients already have an indication for medical therapy to prevent ischemic symptoms, it is unclear whether establishing the additional diagnosis of ECVD in those without carotid bruit would justify actions that affect clinical outcomes. (*Level of Evidence: C*)
2. Duplex ultrasonography might be considered to detect carotid stenosis in asymptomatic patients without clinical evidence of atherosclerosis who have 2 or more of the following risk factors: hypertension, hyperlipidemia, tobacco smoking, a family history in a first-degree relative of atherosclerosis manifested before age 60 years, or a family history of ischemic stroke. However, it is unclear whether establishing a diagnosis of ECVD would justify actions that affect clinical outcomes. (*Level of Evidence: C*)

CLASS III: NO BENEFIT

1. Carotid duplex ultrasonography is not recommended for routine screening of asymptomatic patients who have no clinical manifestations of or risk factors for atherosclerosis. (*Level of Evidence: C*)
2. Carotid duplex ultrasonography is not recommended for routine evaluation of patients with neurological or psychiatric disorders unrelated to focal cerebral ischemia, such as brain tumors, familial or degenerative cerebral or motor neuron disorders, infectious and inflammatory conditions affecting the brain, psychiatric disorders, or epilepsy. (*Level of Evidence: C*)
3. Routine serial imaging of the extracranial carotid arteries is not recommended for patients who have no risk factors for development of atherosclerotic carotid disease and no disease evident on initial vascular testing. (*Level of Evidence: C*)

3. Recommendations for Diagnostic Testing in Patients With Symptoms or Signs of Extracranial Carotid Artery Disease

CLASS I

1. The initial evaluation of patients with transient retinal or hemispheric neurological symptoms of possible ischemic origin should include noninvasive imaging for the detection of ECVD. (*Level of Evidence: C*)
2. Duplex ultrasonography is recommended to detect carotid stenosis in patients who develop focal neurological symptoms corresponding to the territory supplied by the left or right internal carotid artery. (*Level of Evidence: C*)
3. In patients with acute, focal ischemic neurological symptoms corresponding to the territory supplied by the left or right internal carotid artery, magnetic resonance angiography (MRA) or computed tomography angiography (CTA) is indicated to detect carotid stenosis when sonography either cannot be obtained or yields equivocal or otherwise nondiagnostic results. (*Level of Evidence: C*)
4. When extracranial or intracranial cerebrovascular disease is not severe enough to account for neurological symptoms of suspected ischemic origin, echocardiography should be performed to search for a source of cardiogenic embolism. (*Level of Evidence: C*)
5. Correlation of findings obtained by several carotid imaging modalities should be part of a program of quality assurance in each laboratory that performs such diagnostic testing. (*Level of Evidence: C*)

CLASS IIa

1. When an extracranial source of ischemia is not identified in patients with transient retinal or hemispheric neurological symptoms of suspected ischemic origin, CTA, MRA, or selective cerebral angiography can be useful to search for intracranial vascular disease. (*Level of Evidence: C*)
2. When the results of initial noninvasive imaging are inconclusive, additional examination by use of another imaging method is reasonable. In candidates for revascularization, MRA or CTA can be useful when results of carotid duplex ultrasonography are equivocal or indeterminate. (*Level of Evidence: C*)
3. When intervention for significant carotid stenosis detected by carotid duplex ultrasonography is planned, MRA, CTA, or catheter-based contrast angiography can be useful to evaluate the severity of stenosis and to identify intrathoracic or intracranial vascular lesions that are not adequately assessed by duplex ultrasonography. (*Level of Evidence: C*)
4. When noninvasive imaging is inconclusive or not feasible because of technical limitations or contraindications in patients with transient retinal or hemispheric neurological symptoms of suspected ischemic origin, or when noninvasive imaging studies yield discordant results, it is reasonable to perform catheter-based contrast angiography to detect and characterize extracranial and/or intracranial cerebrovascular disease. (*Level of Evidence: C*)
5. MRA without contrast is reasonable to assess the extent of disease in patients with symptomatic carotid atherosclerosis and renal insufficiency or extensive vascular calcification. (*Level of Evidence: C*)
6. It is reasonable to use magnetic resonance imaging (MRI) systems capable of consistently generating high-quality images while avoiding low-field systems that do not yield diagnostically accurate results. (*Level of Evidence: C*)
7. CTA is reasonable for evaluation of patients with clinically suspected significant carotid atherosclerosis who are not suitable candidates

for MRA because of claustrophobia, implanted pacemakers, or other incompatible devices. (Level of Evidence: C)

CLASS IIb

1. Duplex carotid ultrasonography might be considered for patients with nonspecific neurological symptoms when cerebral ischemia is a plausible cause. (Level of Evidence: C)
2. When complete carotid arterial occlusion is suggested by duplex ultrasonography, MRA, or CTA in patients with retinal or hemispheric neurological symptoms of suspected ischemic origin, catheter-based contrast angiography may be considered to determine whether the arterial lumen is sufficiently patent to permit carotid revascularization. (Level of Evidence: C)
3. Catheter-based angiography may be reasonable in patients with renal dysfunction to limit the amount of radiographic contrast material required for definitive imaging for evaluation of a single vascular territory. (Level of Evidence: C)

4. Recommendations for the Treatment of Hypertension

CLASS I

1. Antihypertensive treatment is recommended for patients with hypertension and asymptomatic extracranial carotid or vertebral atherosclerosis to maintain blood pressure below 140/90 mm Hg (3–7). (Level of Evidence: A)

CLASS IIa

1. Except during the hyperacute period, antihypertensive treatment is probably indicated in patients with hypertension and symptomatic extracranial carotid or vertebral atherosclerosis, but the benefit of treatment to a specific target blood pressure (e.g., below 140/90 mm Hg) has not been established in relation to the risk of exacerbating cerebral ischemia. (Level of Evidence: C)

5. Recommendation for Cessation of Tobacco Smoking

CLASS I

1. Patients with extracranial carotid or vertebral atherosclerosis who smoke cigarettes should be advised to quit smoking and offered smoking cessation interventions to reduce the risks of atherosclerosis progression and stroke (8–12). (Level of Evidence: B)

6. Recommendations for Control of Hyperlipidemia

CLASS I

1. Treatment with a statin medication is recommended for all patients with extracranial carotid or vertebral atherosclerosis to reduce low-density lipoprotein (LDL) cholesterol below 100 mg/dL (4,13,14). (Level of Evidence: B)

CLASS IIa

1. Treatment with a statin medication is reasonable for all patients with extracranial carotid or vertebral atherosclerosis who sustain ischemic stroke to reduce LDL-cholesterol to a level near or below 70 mg/dL (13). (Level of Evidence: B)
2. If treatment with a statin (including trials of higher-dose statins and higher-potency statins) does not achieve the goal selected for a patient,

- intensifying LDL-lowering drug therapy with an additional drug from among those with evidence of improving outcomes (i.e., bile acid sequestrants or niacin) can be effective (15–18). (Level of Evidence: B)
3. For patients who do not tolerate statins, LDL-lowering therapy with bile acid sequestrants and/or niacin is reasonable (15,17,19). (Level of Evidence: B)

7. Recommendations for Management of Diabetes Mellitus in Patients With Atherosclerosis of the Extracranial Carotid or Vertebral Arteries

CLASS IIa

1. Diet, exercise, and glucose-lowering drugs can be useful for patients with diabetes mellitus and extracranial carotid or vertebral artery atherosclerosis. The stroke prevention benefit, however, of intensive glucose-lowering therapy to a glycosylated hemoglobin A1c level less than 7.0% has not been established (20,21). (Level of Evidence: A)
2. Administration of statin-type lipid-lowering medication at a dosage sufficient to reduce LDL-cholesterol to a level near or below 70 mg/dL is reasonable in patients with diabetes mellitus and extracranial carotid or vertebral artery atherosclerosis for prevention of ischemic stroke and other ischemic cardiovascular events (22). (Level of Evidence: B)

8. Recommendations for Antithrombotic Therapy in Patients With Extracranial Carotid Atherosclerotic Disease Not Undergoing Revascularization

CLASS I

1. Antiplatelet therapy with aspirin, 75 to 325 mg daily, is recommended for patients with obstructive or nonobstructive atherosclerosis that involves the extracranial carotid and/or vertebral arteries for prevention of myocardial infarction (MI) and other ischemic cardiovascular events, although the benefit has not been established for prevention of stroke in asymptomatic patients (14,23–25). (Level of Evidence: A)
2. In patients with obstructive or nonobstructive extracranial carotid or vertebral atherosclerosis who have sustained ischemic stroke or TIA, antiplatelet therapy with aspirin alone (75 to 325 mg daily), clopidogrel alone (75 mg daily), or the combination of aspirin plus extended-release dipyridamole (25 and 200 mg twice daily, respectively) is recommended (Level of Evidence: B) and preferred over the combination of aspirin with clopidogrel (14,25–29) (Level of Evidence: B). Selection of an antiplatelet regimen should be individualized on the basis of patient risk factor profiles, cost, tolerance, and other clinical characteristics, as well as guidance from regulatory agencies.
3. Antiplatelet agents are recommended rather than oral anticoagulation for patients with atherosclerosis of the extracranial carotid or vertebral arteries with (30,31) (Level of Evidence: B) or without (Level of Evidence: C) ischemic symptoms. (For patients with allergy or other contraindications to aspirin, see Class IIa recommendation #2, this section)

CLASS IIa

1. In patients with extracranial cerebrovascular atherosclerosis who have an indication for anticoagulation, such as atrial fibrillation or a mechanical prosthetic heart valve, it can be beneficial to administer

- a vitamin K antagonist (such as warfarin, dose-adjusted to achieve a target international normalized ratio [INR] of 2.5 [range 2.0 to 3.0]) for prevention of thromboembolic ischemic events (32). (Level of Evidence: C)
2. For patients with atherosclerosis of the extracranial carotid or vertebral arteries in whom aspirin is contraindicated by factors other than active bleeding, including allergy, either clopidogrel (75 mg daily) or ticlopidine (250 mg twice daily) is a reasonable alternative. (Level of Evidence: C)

CLASS III: NO BENEFIT

1. Full-intensity parenteral anticoagulation with unfractionated heparin or low-molecular-weight heparinoids is not recommended for patients with extracranial cerebrovascular atherosclerosis who develop transient cerebral ischemia or acute ischemic stroke (2,33,34). (Level of Evidence: B)
2. Administration of clopidogrel in combination with aspirin is not recommended within 3 months after stroke or TIA (27). (Level of Evidence: B)

9. Recommendations for Selection of Patients for Carotid Revascularization*

CLASS I

1. Patients at average or low surgical risk who experience nondisabling ischemic stroke[†] or transient cerebral ischemic symptoms, including hemispheric events or amaurosis fugax, within 6 months (symptomatic patients) should undergo CEA if the diameter of the lumen of the ipsilateral internal carotid artery is reduced more than 70%[‡] as documented by noninvasive imaging (35,36) (Level of Evidence: A) or more than 50% as documented by catheter angiography (35-38) (Level of Evidence: B) and the anticipated rate of perioperative stroke or mortality is less than 6%.
2. 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 more than 70% as documented by noninvasive imaging or more than 50% as documented by catheter angiography and the anticipated rate of periprocedural stroke or mortality is less than 6% (39). (Level of Evidence: B)
3. Selection of asymptomatic patients for carotid revascularization should be guided by an assessment of comorbid conditions, life expectancy, and other individual factors and should include a thorough discussion of the risks and benefits of the procedure with an understanding of patient preferences. (Level of Evidence: C)

CLASS IIa

1. It is reasonable to perform CEA in asymptomatic patients who have more than 70% stenosis of the internal carotid artery if the risk of perioperative stroke, MI, and death is low (38,40-44). (Level of Evidence: A)
2. It is reasonable to choose CEA over CAS when revascularization is indicated in older patients, particularly when arterial pathoanatomy

*Recommendations for revascularization in this section assume that operators are experienced, having successfully performed the procedures in >20 cases with proper technique and a low complication rate based on independent neurological evaluation before and after each procedure.

[†]Nondisabling stroke is defined by a residual deficit associated with a score ≤2 according to the Modified Rankin Scale.

[‡]The degree of stenosis is based on catheter-based or noninvasive vascular imaging compared with the distal arterial lumen or velocity measurements by duplex ultrasonography. See Section 7 text in the full-text version of the guideline for details.

is unfavorable for endovascular intervention (39,45-49). (Level of Evidence: B)

3. It is reasonable to choose CAS over CEA when revascularization is indicated in patients with neck anatomy unfavorable for arterial surgery (50-54).[§] (Level of Evidence: B)
4. When revascularization is indicated for patients with TIA or stroke and there are no contraindications to early revascularization, intervention within 2 weeks of the index event is reasonable rather than delaying surgery (55). (Level of Evidence: B)

CLASS IIb

1. Prophylactic CAS might be considered in highly selected patients with asymptomatic carotid stenosis (minimum 60% by angiography, 70% by validated Doppler ultrasound), but its effectiveness compared with medical therapy alone in this situation is not well established (39). (Level of Evidence: B)
2. In symptomatic or asymptomatic patients at high risk of complications for carotid revascularization by either CEA or CAS because of comorbidities,^{||} the effectiveness of revascularization versus medical therapy alone is not well established (42,43,47,50-53,56-58). (Level of Evidence: B)

CLASS III: NO BENEFIT

1. Except in extraordinary circumstances, carotid revascularization by either CEA or CAS is not recommended when atherosclerosis narrows the lumen by less than 50% (37,41,50,56,59). (Level of Evidence: A)
2. Carotid revascularization is not recommended for patients with chronic total occlusion of the targeted carotid artery. (Level of Evidence: C)
3. Carotid revascularization is not recommended for patients with severe disability[¶] caused by cerebral infarction that precludes preservation of useful function. (Level of Evidence: C)

10. Recommendations for Periprocedural Management of Patients Undergoing Carotid Endarterectomy

CLASS I

1. Aspirin (81 to 325 mg daily) is recommended before CEA and may be continued indefinitely postoperatively (24,60). (Level of Evidence: A)
2. Beyond the first month after CEA, aspirin (75 to 325 mg daily), clopidogrel (75 mg daily), or the combination of low-dose aspirin plus extended-release dipyridamole (25 and 200 mg twice daily, respectively) should be administered for long-term prophylaxis against ischemic cardiovascular events (26,30,61). (Level of Evidence: B)

[§]Conditions that produce unfavorable neck anatomy include but are not limited to arterial stenosis distal to the second cervical vertebra or proximal (intrathoracic) arterial stenosis, previous ipsilateral CEA, contralateral vocal cord paralysis, open tracheostomy, radical surgery, and irradiation.

^{||}Comorbidities that increase the risk of revascularization include but are not limited to age >80 years, New York Heart Association class III or IV heart failure, left ventricular ejection fraction <30%, class III or IV angina pectoris, left main or multivessel coronary artery disease, need for cardiac surgery within 30 days, MI within 4 weeks, and severe chronic lung disease.

[¶]In this context, severe disability refers generally to a Modified Rankin Scale of ≥3, but individual assessment is required, and intervention may be appropriate in selected patients with considerable disability when a worse outcome is projected with continued medical therapy alone.

3. Administration of antihypertensive medication is recommended as needed to control blood pressure before and after CEA. (Level of Evidence: C)
4. The findings on clinical neurological examination should be documented within 24 hours before and after CEA. (Level of Evidence: C)

CLASS IIa

1. Patch angioplasty can be beneficial for closure of the arteriotomy after CEA (62,63). (Level of Evidence: B)
2. Administration of statin lipid-lowering medication for prevention of ischemic events is reasonable for patients who have undergone CEA irrespective of serum lipid levels, although the optimum agent and dose and the efficacy for prevention of restenosis have not been established (64). (Level of Evidence: B)
3. Noninvasive imaging of the extracranial carotid arteries is reasonable 1 month, 6 months, and annually after CEA to assess patency and exclude the development of new or contralateral lesions (45,65). Once stability has been established over an extended period, surveillance at longer intervals may be appropriate. Termination of surveillance is reasonable when the patient is no longer a candidate for intervention. (Level of Evidence: C)

11. Recommendations for Management of Patients Undergoing Carotid Artery Stenting

CLASS I

1. Before and for a minimum of 30 days after CAS, dual-antiplatelet therapy with aspirin (81 to 325 mg daily) plus clopidogrel (75 mg daily) is recommended. For patients intolerant of clopidogrel, ticlopidine (250 mg twice daily) may be substituted. (Level of Evidence: C)
2. Administration of antihypertensive medication is recommended to control blood pressure before and after CAS. (Level of Evidence: C)
3. The findings on clinical neurological examination should be documented within 24 hours before and after CAS. (Level of Evidence: C)

CLASS IIa

1. Embolic protection device (EPD) deployment during CAS can be beneficial to reduce the risk of stroke when the risk of vascular injury is low (66,67). (Level of Evidence: C)
2. Noninvasive imaging of the extracranial carotid arteries is reasonable 1 month, 6 months, and annually after revascularization to assess patency and exclude the development of new or contralateral lesions (45). Once stability has been established over an extended period, surveillance at extended intervals may be appropriate. Termination of surveillance is reasonable when the patient is no longer a candidate for intervention. (Level of Evidence: C)

12. Recommendations for Management of Patients Experiencing Restenosis After Carotid Endarterectomy or Stenting

CLASS IIa

1. In patients with symptomatic cerebral ischemia and recurrent carotid stenosis due to intimal hyperplasia or atherosclerosis, it is reasonable to repeat CEA or perform CAS using the same criteria as recommended for initial revascularization. (Level of Evidence: C)
2. Reoperative CEA or CAS after initial revascularization is reasonable when duplex ultrasound and another confirmatory imaging method identify rapidly progressive restenosis that indicates a threat of complete occlusion. (Level of Evidence: C)

CLASS IIb

1. In asymptomatic patients who develop recurrent carotid stenosis due to intimal hyperplasia or atherosclerosis, reoperative CEA or CAS may be considered using the same criteria as recommended for initial revascularization. (Level of Evidence: C)

CLASS III: HARM

1. Reoperative CEA or CAS should not be performed in asymptomatic patients with less than 70% carotid stenosis that has remained stable over time. (Level of Evidence: C)

13. Recommendations for Vascular Imaging in Patients With Vertebral Artery Disease

CLASS I

1. Noninvasive imaging by CTA or MRA for detection of vertebral artery disease should be part of the initial evaluation of patients with neurological symptoms referable to the posterior circulation and those with subclavian steal syndrome. (Level of Evidence: C)
2. Patients with asymptomatic bilateral carotid occlusions or unilateral carotid artery occlusion and incomplete circle of Willis should undergo noninvasive imaging for detection of vertebral artery obstructive disease. (Level of Evidence: C)
3. In patients whose symptoms suggest posterior cerebral or cerebellar ischemia, MRA or CTA is recommended rather than ultrasound imaging for evaluation of the vertebral arteries. (Level of Evidence: C)

CLASS IIa

1. In patients with symptoms of posterior cerebral or cerebellar ischemia, serial noninvasive imaging of the extracranial vertebral arteries is reasonable to assess the progression of atherosclerotic disease and exclude the development of new lesions. (Level of Evidence: C)
2. In patients with posterior cerebral or cerebellar ischemic symptoms who may be candidates for revascularization, catheter-based contrast angiography can be useful to define vertebral artery pathoanatomy when noninvasive imaging fails to define the location or severity of stenosis. (Level of Evidence: C)
3. In patients who have undergone vertebral artery revascularization, serial noninvasive imaging of the extracranial vertebral arteries is reasonable at intervals similar to those for carotid revascularization. (Level of Evidence: C)

14. Recommendations for Management of Atherosclerotic Risk Factors in Patients With Vertebral Artery Disease

CLASS I

1. Medical therapy and lifestyle modification to reduce atherosclerotic risk are recommended in patients with vertebral atherosclerosis according to the standards recommended for those with extracranial carotid atherosclerosis (15,68). (Level of Evidence: B)
2. In the absence of contraindications, patients with atherosclerosis involving the vertebral arteries should receive antiplatelet therapy with aspirin (75 to 325 mg daily) to prevent MI and other ischemic events (25,69). (Level of Evidence: B)
3. Antiplatelet drug therapy is recommended as part of the initial management for patients who sustain ischemic stroke or TIA associated with extracranial vertebral atherosclerosis. Aspirin (81 to 325 mg daily), the combination of aspirin plus extended-release dipyrid-

amole (25 and 200 mg twice daily, respectively), and clopidogrel (75 mg daily) are acceptable options. Selection of an antiplatelet regimen should be individualized on the basis of patient risk factor profiles, cost, tolerance, and other clinical characteristics, as well as guidance from regulatory agencies (14,25-29). (Level of Evidence: B)

CLASS IIa

1. For patients with atherosclerosis of the extracranial vertebral arteries in whom aspirin is contraindicated by factors other than active bleeding, including those with allergy to aspirin, either clopidogrel (75 mg daily) or ticlopidine (250 mg twice daily) is a reasonable alternative. (Level of Evidence: C)

15. Recommendations for the Management of Patients With Occlusive Disease of the Subclavian and Brachiocephalic Arteries

CLASS IIa

1. Extra-anatomic carotid-subclavian bypass is reasonable for patients with symptomatic posterior cerebral or cerebellar ischemia caused by subclavian artery stenosis or occlusion (subclavian steal syndrome) in the absence of clinical factors predisposing to surgical morbidity or mortality (70-72). (Level of Evidence: B)
2. Percutaneous endovascular angioplasty and stenting is reasonable for patients with symptomatic posterior cerebral or cerebellar ischemia caused by subclavian artery stenosis (subclavian steal syndrome) who are at high risk of surgical complications. (Level of Evidence: C)
3. Revascularization by percutaneous angioplasty and stenting, direct arterial reconstruction, or extra-anatomic bypass surgery is reasonable for patients with symptomatic ischemia involving the anterior cerebral circulation caused by common carotid or brachiocephalic artery occlusive disease. (Level of Evidence: C)
4. Revascularization by percutaneous angioplasty and stenting, direct arterial reconstruction, or extra-anatomic bypass surgery is reasonable for patients with symptomatic ischemia involving upper-extremity claudication caused by subclavian or brachiocephalic arterial occlusive disease. (Level of Evidence: C)
5. Revascularization by either extra-anatomic bypass surgery or subclavian angioplasty and stenting is reasonable for asymptomatic patients with subclavian artery stenosis when the ipsilateral internal mammary artery is required as a conduit for myocardial revascularization. (Level of Evidence: C)

CLASS III: NO BENEFIT

1. Asymptomatic patients with asymmetrical upper-limb blood pressure, periclavicular bruit, or flow reversal in a vertebral artery caused by subclavian artery stenosis should not undergo revascularization unless the internal mammary artery is required for myocardial revascularization. (Level of Evidence: C)

16. Recommendations for Carotid Artery Evaluation and Revascularization Before Cardiac Surgery

CLASS IIa

1. Carotid duplex ultrasound screening is reasonable before elective coronary artery bypass graft (CABG) surgery in patients older than 65 years of age and in those with left main coronary stenosis, PAD,

a history of cigarette smoking, a history of stroke or TIA, or carotid bruit. (Level of Evidence: C)

2. Carotid revascularization by CEA or CAS with embolic protection before or concurrent with myocardial revascularization surgery is reasonable in patients with greater than 80% carotid stenosis who have experienced ipsilateral retinal or hemispheric cerebral ischemic symptoms within 6 months. (Level of Evidence: C)

CLASS IIIb

1. In patients with asymptomatic carotid stenosis, even if severe, the safety and efficacy of carotid revascularization before or concurrent with myocardial revascularization are not well established. (Level of Evidence: C)

17. Recommendations for Management of Patients With Fibromuscular Dysplasia of the Extracranial Carotid Arteries

CLASS IIa

1. Annual noninvasive imaging of the carotid arteries is reasonable initially for patients with fibromuscular dysplasia (FMD) to detect changes in the extent or severity of disease, although the effect on outcomes is unclear. Studies may be repeated less frequently once stability has been confirmed. (Level of Evidence: C)
2. Administration of platelet-inhibitor medication can be beneficial in patients with FMD of the carotid arteries to prevent thromboembolism, but the optimum drug and dosing regimen have not been established. (Level of Evidence: C)
3. Carotid angioplasty with or without stenting is reasonable for patients with retinal or hemispheric cerebral ischemic symptoms related to FMD of the ipsilateral carotid artery, but comparative data addressing these methods of revascularization are not available. (Level of Evidence: C)

CLASS III: NO BENEFIT

1. Revascularization is not recommended for patients with asymptomatic FMD of a carotid artery, regardless of the severity of stenosis. (Level of Evidence: C)

18. Recommendations for Management of Patients With Cervical Artery Dissection

CLASS I

1. Contrast-enhanced CTA, MRA, and catheter-based contrast angiography are useful for diagnosis of cervical artery dissection. (Level of Evidence: C)

CLASS IIa

1. For patients with symptomatic cervical artery dissection, anticoagulation with intravenous heparin (dose-adjusted to prolong the partial thromboplastin time to 1.5 to 2.0 times the control value) followed by warfarin (dose-adjusted to achieve a target INR of 2.5 [range 2.0 to 3.0]), low-molecular-weight heparin (in the dose recommended for treatment of venous thromboembolism with the selected agent) followed by warfarin (dose-adjusted to achieve a target INR of 2.5 [range 2.0 to 3.0]), or oral anticoagulation without antecedent heparin can be beneficial for 3 to 6 months, followed by antiplatelet therapy with aspirin (81 to 325 mg daily) or clopidogrel (75 mg daily). (Level of Evidence: C)

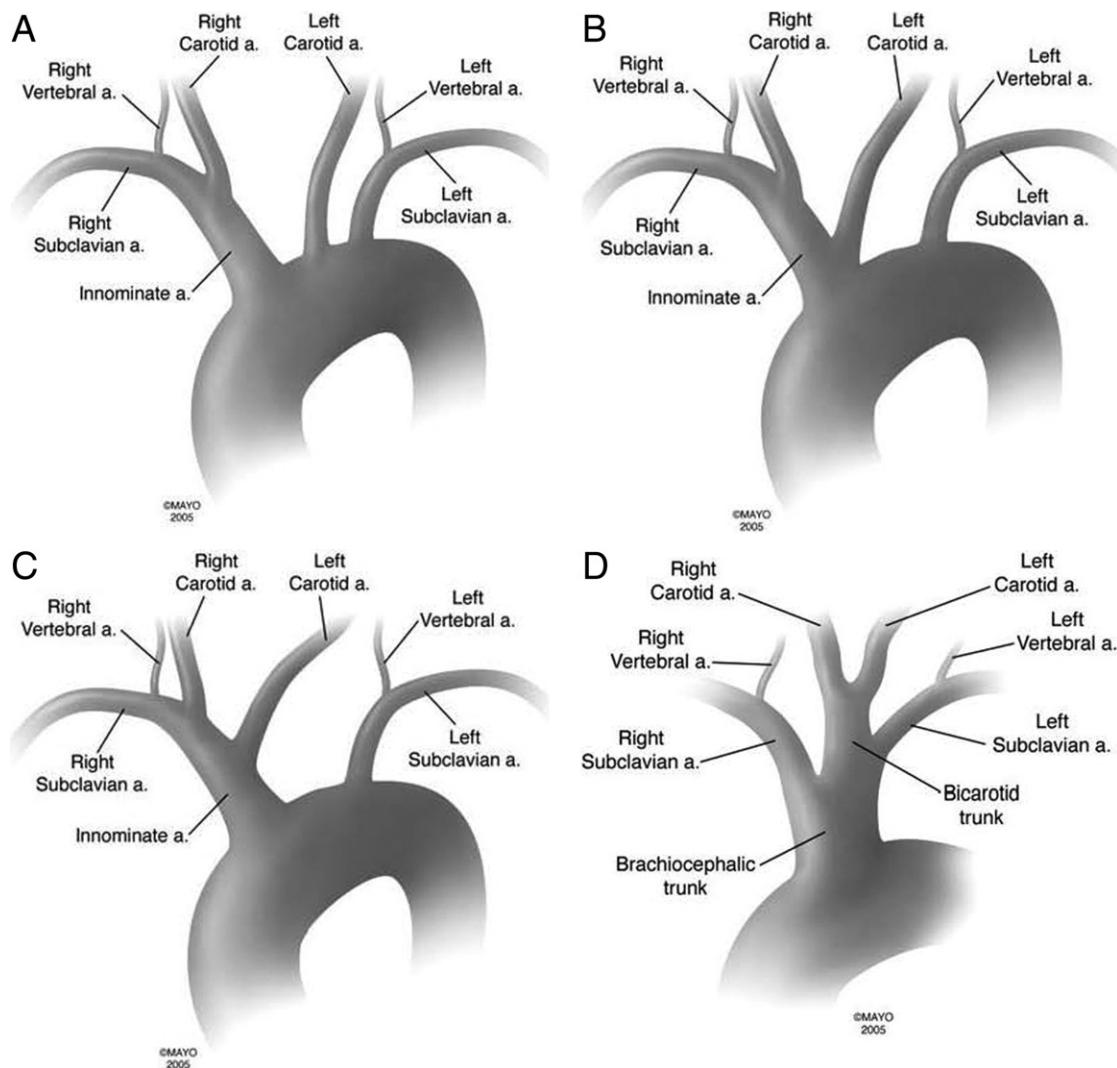


Figure 1. Aortic Arch Types

Panel A. The most common aortic arch branching pattern found in humans has separate origins for the innominate, left common carotid, and left subclavian arteries. Panel B. The second most common pattern of human aortic arch branching has a common origin for the innominate and left common carotid arteries. This pattern has erroneously been referred to as a "bovine arch." Panel C. In this variant of aortic arch branching, the left common carotid artery originates separately from the innominate artery. This pattern has also been erroneously referred to as a "bovine arch." Panel D. The aortic arch branching pattern found in cattle has a single brachiocephalic trunk originating from the aortic arch that eventually splits into the bilateral subclavian arteries and a bicarotid trunk. A indicates artery. Reprinted with permission from Layton et al. (74).

CLASS IIb

1. Carotid angioplasty and stenting might be considered when ischemic neurological symptoms have not responded to antithrombotic therapy after acute carotid dissection. (Level of Evidence: C)
2. The safety and effectiveness of pharmacological therapy with a beta-adrenergic antagonist, angiotensin inhibitor, or nondihydropyridine calcium channel antagonist (verapamil or diltiazem) to lower blood pressure to the normal range and reduce arterial wall stress are not well established. (Level of Evidence: C)

19. Cerebrovascular Arterial Anatomy

The anatomy of the aortic arch and cervical arteries that supply the brain is subject to considerable variation (73).

Three aortic arch morphologies are distinguished on the basis of the relationship of the brachiocephalic (innominate) arterial trunk to the aortic arch (Figure 1).

Extracranial cerebrovascular disease encompasses several disorders that affect the arteries that supply the brain and is an important cause of stroke and transient cerebral ischemic attack. The most frequent cause is atherosclerosis, but other causes include FMD, cystic medial necrosis, arteritis, and dissection. Atherosclerosis is a systemic disease, and patients with ECVD typically face an escalated risk of other adverse cardiovascular events, including MI, PAD, and death. To improve survival, neurological and functional outcomes, and quality of life, preventive and therapeutic strategies must address both cerebral and systemic risk.

19.1. Epidemiology of Extracranial Cerebrovascular Disease and Stroke

Stroke is the third-leading cause of death in industrialized nations, the most frequent neurological diagnosis requiring hospitalization (75), and a leading cause of long-term disability (76). Extracranial cerebrovascular disease is an important cause of stroke and transient cerebral ischemic attack. The most frequent cause is atherosclerosis; others include FMD, cystic medial necrosis, arteritis, and dissection. Patients with atherosclerotic ECVD face an escalated risk of MI, PAD, and death. Clinical strategies must therefore address both cerebral and systemic risk.

20. Atherosclerotic Disease of the Extracranial Carotid and Vertebral Arteries

Stroke and transient cerebrovascular ischemia may arise as a consequence of several mechanisms that originate in atherosclerotic extracranial cerebral arteries, including 1) embolism of thrombus formed on an atherosclerotic plaque, 2) atheroembolism, 3) thrombotic occlusion resulting from plaque rupture, 4) dissection or subintimal hematoma, and 5) reduced perfusion resulting from stenotic or occlusive plaque.

Screening to identify people with asymptomatic carotid stenosis has not been shown to reduce the risk of stroke, so there is no consensus on which patients should undergo tests for detection of carotid disease. Auscultation for cervical bruits is part of the physical examination of adults, but a bruit correlates better with systemic atherosclerosis than with significant carotid stenosis (77). Because carotid ultrasonography is widely available and is associated with negligible risk and discomfort, the issue is appropriate resource utilization. Recommendations favor the targeted screening of patients at greatest risk.

Many patients with carotid stenosis face a greater risk of death due to MI than to stroke (78,79). The IMT of the carotid artery wall measured by carotid ultrasound is a marker of systemic atherosclerosis and risk for coronary events and stroke (80,81). Measurement of carotid IMT may enhance cardiovascular risk assessment but has not become a routine element of carotid ultrasound examinations in the United States (82,83).

21. Clinical Presentation

There is a correlation between the degree of stenosis in both symptomatic (37) and asymptomatic (84,85) patients, although absolute rates depend on the aggressiveness of medical and interventional therapy. In NASCET (North American Symptomatic Carotid Endarterectomy Trial), patients with >70% stenosis had a stroke rate of 24% after 18 months, and those with 50% to 69% stenosis had a stroke

rate of 22% over 5 years (86). The incidence of stroke in asymptomatic patients with carotid stenosis in various studies is summarized in Table 2.

Because the correlation between severity of stenosis and ischemic events is imperfect, other characteristics have been explored as potential markers of plaque vulnerability and stroke risk. Molecular and cellular processes responsible for plaque composition (94–96) may be more important than the degree of stenosis in determining the risk of stroke, but the severity of stenosis forms the basis for most clinical decision making.

22. Clinical Assessment of Patients With Focal Cerebral Ischemic Symptoms

Acute management of patients with focal ischemic neurological symptoms should follow guidelines for stroke care (2). After diagnosis, stabilization of the patient, and initial therapy, evaluation is directed toward establishing the cause and pathophysiology of the event (2,4,97,98) and toward risk stratification.

The risk of stroke in patients with TIA is as high as 13% in the first 90 days and up to 30% within 5 years (99–106). In patients with ischemia in the territory of a stenotic carotid artery, CEA within the first 2 weeks reduces the risk of stroke (35,93), but the benefit of surgery diminishes with time after the initial event (107).

Transient monocular blindness (amaurosis fugax) is caused by temporary reduction of blood flow to an eye (108). The most common cause is atherosclerosis of the ipsilateral internal carotid artery, but other causes include carotid artery stenosis, occlusion, dissection, arteritis, radiation-induced arteriopathy, embolism, hypotension, intracranial hypertension, glaucoma, migraine, and vasospastic or occlusive disease of the ophthalmic artery. The risk of subsequent stroke is related to the presence of other risk factors such as hypertension, hypercholesterolemia, diabetes, and cigarette smoking (109–111).

Intracranial arterial stenosis may be caused by atherosclerosis, intimal fibroplasia, vasculitis, adventitial cysts, or vascular tumors; intracranial arterial occlusion may develop on the basis of thrombosis or embolism arising from the cardiac chambers, heart valves, aorta, proximal atheromatous disease of the carotid or vertebral arteries, or paradoxical embolism involving a defect in cardiac septation or other right-to-left circulatory shunt. Evaluation of the intracranial vasculature may be important in patients with ECVD to exclude tandem lesions. Brief, stereotyped, repetitive symptoms suggestive of transient cerebral dysfunction raise the possibility of partial seizure, whereas nonfocal neurological events, including transient global amnesia, acute confusion, syncope, isolated vertigo, nonrotational dizziness, bilateral weakness, and paresthesia, are not clearly attributable to ECVD. A small proportion of patients with

Table 2. Event Rates in Patients With Carotid Artery Stenosis Managed Without Revascularization

Study (Reference)	No. of Patients	Symptom Status	Stenosis, %	Follow-Up	Medication Therapy	Endpoint	Event Rate Over Study Period (%)
Observational studies							
Hertzner et al. (87)	290	Asymptomatic	≥50	33–38 mo	Aspirin or dipyridamole (n=104); or anticoagulation with warfarin (n=9); or no medical treatment (n=82)	Death TIA Stroke	22.0, or 7.33 annualized 8.21, or 2.74 annualized 9.23, or 3.1 annualized
Spence et al. (88)	168	Asymptomatic	≥60	≥12 mo	Multiple, including antiplatelet, statins, exercise, Mediterranean diet, ACE inhibitors	Stroke	3.8, or 1.3 annualized
Marquardt et al. (89)	1,153	Asymptomatic	≥50	Mean 3 y	Multiple, including antiplatelet, anticoagulation, statin, antihypertensive drugs	Ipsilateral stroke	0.34 (95% CI 0.01 to 1.87) average annual event rate
Abbott et al. (90)	202	Asymptomatic	60–90	Mean 34 mo	Multiple, including antiplatelet, warfarin, antihypertensive drugs, cholesterol-lowering therapy	Ipsilateral stroke or TIA; ipsilateral carotid hemispheric stroke	Ipsilateral stroke or TIA or retinal event: 3.1 (95% CI 0.7 to 5.5) average annual rate; Ipsilateral carotid hemispheric stroke: 1.0 (95% CI 0.4 to 2.4) average annual rate
Goessens et al. (91)	2,684	Asymptomatic	≥50	Mean 3.6 y (SD 2.3)	Multiple, including antiplatelet, antihypertensive drugs, lipid-lowering agents, ACE inhibitors, and/or AIIA	Ischemic stroke; death	Death: 9.0 or 2.5 annualized; ischemic stroke: 2.0 or 0.54 annualized
Randomized trial cohorts							
ECST (36)	3,024	Symptomatic	≥80	3 y	No surgery within 1 y or delay of surgery	Major stroke or death	26.5 over 3 y or annualized 8.83% for 1 y*
NASCET (86)	659	Symptomatic	≥70	2 y	Aspirin	Ipsilateral stroke	26.0 over 2 y or annualized 13.0 for 1 y†
VA 309 (92)	189	Symptomatic	>50	1 y	Aspirin	Ipsilateral stroke or TIA or surgical death	19.4 over 11.9–12 mo
NASCET (35)	858	Symptomatic	50–69	5 y	Antiplatelet (usually aspirin)	Ipsilateral stroke	22.2 over 5 y or annualized 4.44 for 1 y‡
NASCET (35)	1,368	Symptomatic	≤50	5 y	Antiplatelet (usually aspirin)	Ipsilateral stroke	18.7 over 5 y or annualized 3.74 for 1 y‡
ACAS (41)	1,662	Asymptomatic	>60	5 y	Aspirin	Ipsilateral stroke, surgical death	11.0 over 5 y or annualized 2.2 for 1 y§
ACST (93)	3,120	Asymptomatic	≥60	5 y	Indefinite deferral of any CEA	Any stroke	11.8 over 5 y or annualized 2.36 for 1 y§
VA (40)	444	Asymptomatic	≥50	4 y	Aspirin	Ipsilateral stroke	9.4 over 4 y or annualized 2.35 over 1 y

*Frequency based on Kaplan-Meier. †Risk event rate based on Kaplan-Meier. ‡Failure rate based on Kaplan-Meier. §Risk rate based on Kaplan-Meier.

AIIA indicates angiotensin II antagonist; ACAS, Asymptomatic Carotid Atherosclerosis Study; ACE, angiotensin-converting enzyme; ACST, Asymptomatic Carotid Surgery Trial; CEA, carotid endarterectomy; CI, confidence interval; ECST, European Carotid Surgery Trial; n, number; N/A, not applicable; NASCET, North American Symptomatic Carotid Endarterectomy Trial; SD, standard deviation; TIA, transient ischemic attack; VA 309, Veterans Affairs Cooperative Studies Program 309; and VA, Veterans Affairs Cooperative Study Group.

Modified from Bates et al. (56).

severe carotid stenosis present with memory, speech, or hearing difficulty. When symptoms are purely sensory, radiculopathy, neuropathy, microvascular cerebral or spinal pathology, and lacunar stroke should be considered.

23. Diagnosis and Testing

The severity of stenosis defined according to angiographic criteria by the method used in NASCET (37) corresponds

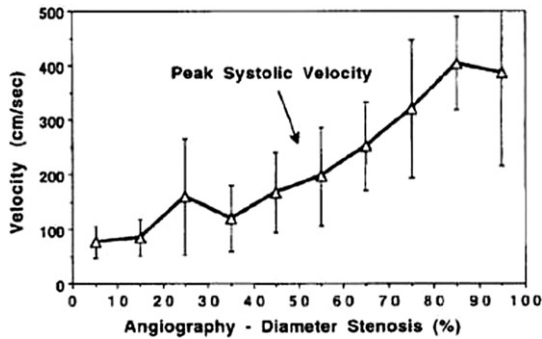


Figure 2. Peak Systolic Flow Velocity as a Measure of Internal Carotid Stenosis

The relationship between peak systolic flow velocity in the internal carotid artery and the severity of stenosis as measured by contrast angiography is illustrated. Note the considerable overlap between adjacent categories of stenosis. Error bars indicate ± 1 standard deviation about the mean values. Reprinted with permission from Grant et al. (113).

to assessment by sonography (112), CTA, and MRA, although some methods may overestimate stenosis severity. Catheter-based angiography may be necessary to resolve discordance between noninvasive imaging findings. Indications for carotid sonography include cervical bruit in asymptomatic patients, follow-up of known stenosis ($>20\%$) in asymptomatic individuals, vascular assessment in patients with multiple risk factors for atherosclerosis, stroke risk assessment in patients with coronary or PAD, amaurosis fugax, hemispheric TIA, stroke in candidates for carotid revascularization, follow-up after carotid revascularization, and intraoperative assessment during CEA or CAS. Because quality differs from one institution to another, no single modality can be recommended as uniformly superior.

Duplex ultrasound does not directly measure the diameter of the stenotic lesion; instead, blood flow velocity is an indicator of severity (Figure 2). The peak systolic velocity in the internal carotid artery and the ratio of the peak systolic velocity in the internal carotid artery to that in the ipsilateral common carotid artery correlate with angiographically determined stenosis.

Typically, 2 categories of internal CAS severity are defined by ultrasound, one (50% to 69% stenosis) that represents the inflection point at which flow velocity accelerates above normal because of atherosclerotic plaque and the other (70% to 99% stenosis) representing more severe nonocclusive disease. Subtotal arterial occlusion may sometimes be mistaken for total occlusion, and it is sometimes difficult to distinguish 70% stenosis from less severe stenosis, which supports the use of corroborating vascular imaging methods in equivocal cases.

MRA can provide accurate anatomic imaging of the aortic arch and the cervical and cerebral arteries (114) and may be used to plan revascularization without exposure to ionizing radiation. Among the strengths of MRA relative to carotid ultrasound and CTA is its relative insensitivity to arterial calcification. Pitfalls include overestimation of ste-

nosis, inability to discriminate between subtotal and complete arterial occlusion, and inability to examine patients who have claustrophobia, extreme obesity, or incompatible implanted devices. Gadolinium-based compounds used as magnetic resonance contrast agents are associated with a lower incidence of nephrotoxicity and allergic reactions than the iodinated radiographic contrast materials used for CTA and conventional angiography, but exposure of patients with preexisting renal dysfunction to high doses of gadolinium-based contrast agents in conjunction with MRA has been associated with nephrogenic systemic fibrosis (115).

CTA provides direct imaging of the arterial lumen suitable for evaluation of stenosis and compares favorably with catheter angiography for evaluation of patients with ECVD. The need for iodinated contrast media restricts application of CTA to patients with adequate renal function. As with sonography, heavily calcified lesions are difficult to assess for severity of stenosis, and the differentiation of subtotal from complete arterial occlusion can be problematic (116). Metallic implants or surgical clips in the neck may obscure the cervical arteries. Obese or moving patients are difficult to scan accurately, but pacemakers and defibrillators are not impediments to CTA.

Conventional digital angiography is the standard against which other methods of vascular imaging are compared in patients with ECVD. There are several methods for measuring stenosis in the internal carotid arteries that yield markedly different measurements in vessels with the same degree of anatomic narrowing (Figure 3), but the method used in NASCET has been used in most clinical trials. It is essential to specify the methodology used both in the evaluation of individual patients with ECVD and in assessment of the accuracy of noninvasive imaging techniques.

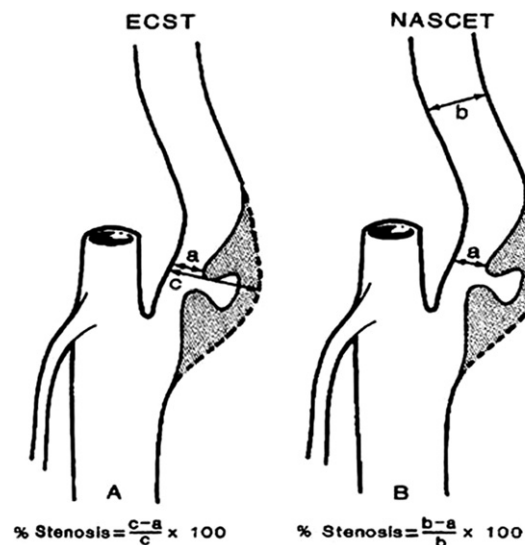


Figure 3. Angiographic Methods for Determining Carotid Stenosis Severity

ECST indicates European Carotid Surgery Trial; and NASCET, North American Symptomatic Carotid Endarterectomy Trial. Reprinted with permission from Osborn (117).

Among the impediments to angiography as a screening modality are its costs and associated risks. The most feared complication is stroke, the incidence of which is <1% when the procedure is performed by experienced physicians (118–125). Angiography may be the preferred method for evaluation when obesity, renal dysfunction, or in-dwelling ferromagnetic material renders CTA or MRA technically inadequate or impossible and is appropriate when noninvasive imaging produces conflicting results. In practice, however, catheter-based angiography is unnecessary for diagnostic evaluation of most patients with ECVD and is used increasingly as a therapeutic revascularization maneuver in conjunction with CAS.

24. Medical Therapy for Patients With Atherosclerotic Disease of the Extracranial Carotid or Vertebral Arteries

24.1. Risk Factor Management

Risk factors associated with ECVD, such as cigarette smoking, hypercholesterolemia, diabetes, and hypertension, are the same as for atherosclerosis elsewhere, although differences exist in their relative contribution to risk in the various vascular beds. There is a clear relationship between blood pressure and stroke risk (126–128), and antihypertensive therapy reduces this risk (6). The type of therapy appears less important than the response (6). Epidemiological studies, including ARIC (Atherosclerosis Risk in Communities) (129), the Cardiovascular Health Study (130), the Framingham Heart Study (131), and MESA (Multi-Ethnic Study of Atherosclerosis) (132), among others, found an association between hypertension and carotid atherosclerosis (129,130,132–134). In patients who had experienced ischemic stroke, a combination of the angiotensin-converting enzyme inhibitor perindopril and a diuretic (indapamide) reduced the risk of recurrent ischemic events among 6,105 participants randomized in the PROGRESS (Preventing Strokes by Lowering Blood Pressure in Patients With Cerebral Ischemia) trial (relative risk reduction 28%, 95% confidence interval 17% to 38%; $p < 0.0001$) (5). The protective value of blood pressure lowering extends even to patients without hypertension, as demonstrated in the HOPE (Heart Outcomes Protection Evaluation) trial (135). In symptomatic patients with severe carotid artery stenosis, however, it is not known whether antihypertensive therapy is beneficial or confers harm by reducing cerebral perfusion.

Smoking increases the relative risk of ischemic stroke by 25% to 50% (9–12,136–138). Stroke risk decreases substantially within 5 years in those who quit smoking compared with continuing smokers (10,12).

In the Framingham Heart Study, the relative risk of carotid artery stenosis >25% was approximately 1.1 for every 10-mg/dL increase in total cholesterol (131). In the MESA study, carotid plaque lipid core detected by MRI

was strongly associated with total cholesterol (139). Lipid-lowering therapy with statins reduces the risk of stroke in patients with atherosclerosis (140). In the randomized SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) trial, atorvastatin (80 mg daily) reduced the absolute risk of stroke at 5 years by 2.2%, the RR of all stroke by 16%, and the RR of ischemic stroke by 22% among patients with recent stroke or TIA (13). In the Heart Protection Study, there was a 50% reduction in CEA in patients randomized to statin therapy (141). It is less clear whether lipid-modifying therapies other than high-dose statins reduce the risk of ischemic stroke or the severity of carotid artery disease.

The risk of ischemic stroke in patients with diabetes mellitus is increased 2- to 5-fold (142–144). In the United Kingdom Prospective Diabetes Study, intensive treatment of blood glucose compared with conventional management did not affect the risk of stroke in patients with type 2 diabetes mellitus (145). In the ACCORD (Action to Control Cardiovascular Risk in Diabetes) (20) and ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation) (21) trials, intensive treatment to achieve glycosylated hemoglobin levels <6.0% and <6.5%, respectively, did not reduce the risk of stroke in patients with type 2 diabetes mellitus compared with conventional treatment. In patients with type 1 diabetes mellitus, intensive insulin treatment reduced rates of nonfatal MI, stroke, and death caused by cardiovascular disease by 57% during the long-term follow-up phase of DCCT (Diabetes Control and Complications Trial/EDIC) study, but the absolute risk reduction was less than 1% during 17 years of follow-up (146). These observations suggest that it would be necessary to treat 700 patients for 17 years to prevent cardiovascular events in 19 patients; the number needed to treat per year to prevent a single event equals 626, a relatively low return on effort for prevention of stroke (146).

At least as important as treatment of hyperglycemia in patients with diabetes is aggressive control of other modifiable risk factors. In the UK-TIA (United Kingdom Transient Ischemic Attack) trial, treatment of hypertension was more useful than glucose control in reducing the rate of recurrent stroke (147). In patients with type 2 diabetes mellitus who had normal serum levels of LDL-cholesterol, administration of 10 mg of atorvastatin daily was safe and effective in reducing the risk of cardiovascular events by 37% and of stroke by 48% (22). Administration of a statin in diabetic patients may be beneficial even when serum lipid levels are not elevated. Other agents, such as those of the fibrate class, do not appear to offer similar benefit (148,149).

Hyperhomocysteinemia increases the risk of stroke. Meta-analysis of 30 studies comprising more than 16,000 patients found a 25% difference in plasma homocysteine concentration, which corresponded to approximately 3 micromoles per liter, to be associated with a 19% difference in stroke risk (25). Studies of patients with established vascular

disease, however, have not confirmed a benefit of homocysteine lowering by B-complex vitamin therapy on cardiovascular outcomes, including stroke. The writing committee considers the evidence insufficient to justify a recommendation for or against routine therapeutic use of vitamin supplements in patients with ECVD.

The metabolic syndrome (defined by the World Health Organization and the National Cholesterol Education Program on the basis of blood glucose, hypertension, dyslipidemia, body mass index, waist/hip ratio, and urinary albumin excretion) is associated with carotid atherosclerosis after adjustment for other risk factors (150–159). This relationship to carotid atherosclerosis is strengthened in proportion to the number of components of metabolic syndrome ($p < 0.001$) (160–162) but appears strongest for hypertension (152,155,156,161,163,164). Abdominal adiposity bears a graded association with the risk of stroke and TIA independent of other vascular disease risk factors (165).

Physical inactivity is a well-documented, modifiable risk factor for stroke, but the risk reduction associated with treatment is unknown. It is unclear whether exercise alone is beneficial with respect to stroke risk in the absence of effects on other risk factors, such as reduction of obesity and improvements in serum lipid values and glycemic control.

24.2. Antithrombotic Therapy

Antiplatelet drugs reduce the risk of stroke in patients with TIA or previous stroke (25) (Table 3). In the Veterans Affairs Cooperative Study (40) and ACAS (Asymptomatic Carotid Atherosclerosis Study) (41), stroke rates were approximately 2% per year in groups treated with aspirin alone (40,41,166). No controlled studies of stroke have shown superior results with antiplatelet agents other than aspirin in patients with asymptomatic ECVD.

WARSS (Warfarin-Aspirin Recurrent Stroke Study) compared aspirin and warfarin for stroke prevention in patients with recent stroke (30). In the subgroup with severe large-artery stenosis or occlusion (259 patients), including ECVD, there was no benefit of warfarin over aspirin after 2 years, but patients with carotid stenosis sufficiently severe to warrant surgical intervention were excluded.

The combination of clopidogrel and aspirin did not reduce stroke risk compared with either treatment alone in the MATCH (Management of Atherothrombosis with Clopidogrel in High-Risk Patients) and CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trials (27,61); however, in ESPS-2 (Second European Stroke Prevention Study), the combination of aspirin plus dipyridamole was superior to aspirin alone in patients with prior TIA or stroke (28). Outcomes in a subgroup defined on the basis of ECVD were not reported. The PROFESS (Prevention Regimen for Effectively Avoiding Second Strokes) trial directly compared the combination of dipyridamole plus aspirin versus clopidogrel (29) in 20,332 patients with prior stroke. Over a mean of 2.5 years, recurrent stroke occurred in

Table 3. American Heart Association/American Stroke Association Guidelines for Antithrombotic Therapy in Patients With Ischemic Stroke of Noncardioembolic Origin (Secondary Prevention)

Guideline	Classification of Recommendation, Level of Evidence*
Antiplatelet agents recommended over oral anticoagulants	I, A
For initial treatment, aspirin (50–325 mg/d),† the combination of aspirin and extended-release dipyridamole, or clopidogrel	I, A
Combination of aspirin and extended-release dipyridamole recommended over aspirin alone	I, B
Clopidogrel may be considered instead of aspirin alone	IIb, B
For patients hypersensitive to aspirin, clopidogrel is a reasonable choice	IIa, B
Addition of aspirin to clopidogrel increases risk of hemorrhage	III, A

*Recommendation: I indicates treatment is useful and effective; IIa, conflicting evidence or divergence of opinion regarding treatment usefulness and effectiveness; IIb, usefulness/efficacy of treatment is less well established; and III, treatment is not useful or effective. Level of Evidence: A indicates data from randomized clinical trials; and B, data from a single randomized clinical trial or nonrandomized studies. †Insufficient data are available to make evidence-based recommendations about antiplatelet agents other than aspirin.

Modified with permission from Sacco et al. (4).

9% of patients in the aspirin-plus-dipyridamole group and in 8.8% of those assigned to clopidogrel (HR 1.01, 95% CI 0.92 to 1.11). Neither treatment was superior for prevention of recurrent stroke, and the risk of the composite outcome of stroke, MI, or vascular death was identical in the 2 treatment groups (13.1%). Major hemorrhagic events, including intracranial hemorrhage, were more common in patients assigned to dipyridamole plus aspirin (4.1% versus 3.6%). Variations in response to clopidogrel based on genetic factors and drug interactions make individualized treatment selection appropriate for optimum stroke prophylaxis.

24.3. Carotid Endarterectomy

24.3.1. Symptomatic Patients

The NASCET (1991) tested the hypothesis that symptomatic patients with either TIA or mild stroke and 30% to 99% ipsilateral carotid stenosis would have fewer strokes after CEA and medical management than those given medical therapy (including aspirin) alone (37). Randomization was stratified according to stenosis severity (Figure 3). The trial was stopped after 18 months of follow-up for patients with 70% to 99% stenosis because of a significant benefit with CEA (cumulative ipsilateral stroke risk, including perioperative stroke, was 9% at 2 years for the CEA group versus 26% with medical therapy alone) (37). Over 5 years, the rate of ipsilateral stroke, including perioperative events, was 15.7% with CEA compared with 22% for medically managed patients (35,37,86,167).

The ECST (European Carotid Surgery Trial), which was nearly concurrent with NASCET, randomized 2518 pa-

tients with stenosis using a different method of measurement whereby the minimal residual lumen through the zone of stenosis was compared with the estimated diameter of the carotid bulb rather than the distal internal carotid artery (Figure 3). The study found a benefit of CEA for patients with 70% to 99% stenosis but no benefit in those with milder stenosis. When the angiograms of ECST participants were analyzed according to the method used in NASCET, no benefit for surgical treatment over medical treatment was found for those with 50% to 69% stenosis, but for those with higher degrees of stenosis, CEA had a similar benefit for symptomatic patients across both trials and for both men and women (168). With the exception of patients with chronic carotid occlusion, surgery was beneficial when the degree of stenosis was >50% as measured by the technique used in NASCET (37) and most effective in patients with >70% carotid stenosis (169). When fatal or disabling ipsilateral ischemic stroke, perioperative stroke, and death were considered together, the benefit of surgery was evident only in patients with 80% to 99% stenosis.

24.3.2. Asymptomatic Patients

A U.S. Veterans Affairs trial of CEA in asymptomatic patients found 30-day mortality of 1.9% in those assigned to CEA; the incidence of stroke was 2.4%, for a combined rate of 4.3%. By 5 years, differences in outcomes reached statistical significance, with a 10% rate of adverse events in the surgical group versus 20% in the group given medical therapy alone. ACAS tested the hypothesis that CEA plus aspirin and risk factor control (albeit limited by modern standards) would reduce the rate of stroke and death compared with aspirin and risk factor control without surgery. The trial was stopped after randomization of 1,662 patients when an advantage to CEA became apparent among patients with >60% stenosis as measured by the method used in NASCET. (Projected 5-year rates of ipsilateral stroke, perioperative stroke, and death were 5.1% for surgical patients and 11% for patients treated medically.) ACST randomized 3,120 asymptomatic patients with carotid stenosis to immediate versus delayed CEA (85) and found a 3.1% 30-day risk of stroke or death in either group, including perioperative events. Five-year rates were 6.4% for the early-surgery group versus 11.7% for the group initially managed medically. A summary of outcomes of randomized trials of CEA in asymptomatic patients is given in Table 4. The benefit of surgery today may be less than in the early trials, and the 3% complication rate should be interpreted in the context of advances in medical therapy.

The risks associated with CEA involve neurological complications, hypertension, hypotension, hemorrhage, acute arterial occlusion, stroke, MI, venous thromboembolism, cranial nerve palsy, infection, arterial restenosis, and death (173). Risk is related mainly to the patient's preoperative clinical status. Symptomatic patients have a higher risk than asymptomatic patients (OR 1.62; $p < 0.0001$), as do those with hemispheric versus retinal symptoms (OR

2.31; $p < 0.001$), urgent versus nonurgent operation (OR 4.9; $p < 0.001$), and reoperation versus primary surgery (OR 1.95; $p < 0.018$) (174-176). Other rate and relative risk data for perioperative stroke or death after CEA are listed in Table 5.

Results of a meta-analysis of nearly 16,000 symptomatic patients undergoing CEA (38) suggest a 3-fold increase in reported events when independent adjudication is used and support a policy of evaluation by a neurologist for patients undergoing CEA. Other than stroke, neurological complications include intracerebral hemorrhage, which may occur as a consequence of the hyperperfusion syndrome despite control of blood pressure. Cardiovascular instability has been reported in 20% of patients undergoing CEA, with hypertension reported in 20%, hypotension in 5%, and perioperative MI in 1%. The risk of cardiopulmonary complications is related to advanced age, New York Heart Association Class II or IV heart failure, active angina pectoris, left main or multivessel coronary disease, urgent cardiac surgery in the preceding 30 days, left ventricular ejection fraction 30% or less, MI within 30 days, severe chronic lung disease, and severe renal insufficiency (184-186).

24.4. Carotid Artery Stenting

CAS may be superior to CEA in certain patient groups, such as those exposed to previous neck surgery or radiation injury, and in patients at high risk of complications with surgical therapy. A summary of stroke and mortality outcomes among symptomatic and asymptomatic patients enrolled in major randomized trials and registries is provided in Tables 5 and 6.

Although 30-day morbidity and mortality rates are important benchmarks for determining the benefit of a procedure in a population, the confidence bounds that surround estimates of event rates with CEA and CAS often overlap. When performed in conjunction with an EPD, the risks associated with CAS may be lower than those associated with CEA in patients at elevated risk of surgical complications.

Several nonrandomized multicenter registries encompassing experience in more than 17,000 patients and large, industry-sponsored postmarket surveillance registries have described outcomes among a broad cohort of carotid stent operators and institutions. The results emphasized the importance of adequate training for optimal operator performance (43,56).

The risks and potential complications of CAS involve neurological deficits; injury of the vessels accessed to approach the lesion, the artery in the region of stenosis, and the distal vessels; device malfunction; general medical and access-site complications; restenosis; and mortality. The risk of MI is generally reported as approximately 1% but reached 2.4% in the ARCHeR (ACCULINK for Revascularization of Carotids in High-Risk Patients) trial and was as low as 0.9% in the CAPTURE (Carotid ACCULINK/ACCUNET Post-Approval Trial to Uncover Unanticipated or Rare Events) registry of 3,500 patients (42,181,187-196). The risk of arterial

Table 4. Comparative Utility of Various Management Strategies for Patients With Carotid Stenosis in Clinical Trials

Trial, Year (Reference)	Patient Population	Intervention	Comparator	No. of Patients		Events, %		Event Used to Calculate NNT	ARR, %	NNT*
				Treatment Group	Comparator Group	Treatment Group	Comparator Group			
Symptomatic CEA										
NASCET (1991) (86)	Symptomatic, 70% to 99% stenosis	CEA	Medical therapy	328	321	9	26	Ipsilateral stroke	17.00	12
ECST (2003) (170)	Symptomatic, 70% to 99% stenosis	CEA	Medical therapy	Not reported	Not reported	Not reported	Not reported	Ipsilateral ischemic stroke and surgical stroke or death; ARR provided in study	18.70	27
ECST (2003) (170)	Symptomatic, 70% to 99% stenosis	CEA	Medical therapy	429	850	6.80	N/A	Stroke or surgical death; ARR provided in study	21.20	24
NASCET (1998) (35)	Symptomatic, 50% to 69% stenosis	CEA	Medical therapy	430	428	15.70	22.20	Ipsilateral stroke	6.50	77
ECST (2003) (170)	Symptomatic, 50% to 69% stenosis	CEA	Medical therapy	Not reported	Not reported	Not reported	Not reported	Ipsilateral ischemic stroke and surgical stroke or death; ARR provided in study	2.90	173
ECST (2003) (170)	Symptomatic, 50% to 69% stenosis	CEA	Medical therapy	646	850	10.00	N/A	All stroke or surgical death; ARR provided in study	5.70	88
Asymptomatic CEA										
ACAS (1995) (41)	Asymptomatic	CEA	Medical therapy	825	834	5.10	11	Ipsilateral stroke and periprocedural stroke or death	6	84
ACAS (1995) (41)	Asymptomatic	CEA	Medical therapy	825	834	13.40	13.60	Stroke or death	0.20	1,351
ACST (2004) (93)	Asymptomatic	Immediate CEA	Deferred CEA	1560	1560	3.80	3.97	Ipsilateral stroke in carotid artery territory	0.17	2,000
ACST (2004) (93)	Asymptomatic	Immediate CEA	Deferred CEA	1560	1560	3.80	11.00	Stroke risks	7.20	70
Symptomatic										
SPACE 2-y data (2008) (45)	Symptomatic	CEA	CAS	589	607	8.80	9.50	All periprocedural strokes or deaths and ipsilateral ischemic strokes up to 2 y after the procedure	0.70	286
SPACE 2-y data (2008) (45)	Symptomatic	CEA	CAS	589	607	1.90	2.20	Ipsilateral ischemic stroke within 31 d and 2 y	0.30	667
SPACE 2-y data (2008) (45)	Symptomatic	CEA	CAS	589	607	10.10	10.90	All stroke	0.80	250
EVA-3S 4-y data (2008) (171)	Symptomatic	CEA	CAS	262	265	1.50	1.50	Ipsilateral stroke	0	~
EVA-3S 4-y data (2008) (171)	Symptomatic	CEA	CAS	262	265	6.20	11.10	Composite of periprocedural stroke, death, and nonprocedural ipsilateral stroke during 4 y of follow-up	4.90	82
EVA-3S 4-y data (2008) (171)	Symptomatic	CEA	CAS	262	265	3.40	9.10	All strokes	5.70	71

dissection or thrombosis in all published series was <1%. Target-vessel perforation occurred in <1% of cases, and external carotid artery stenosis or occlusion occurred in 5% to 10% (42,53,181,187–214), but this event is typically benign, requiring no further intervention. The incidence of restenosis after CAS has been in the range of 3% to 5% (215–233).

The incidence of TIA has been reported as 1% to 2% in patients undergoing CAS. Intracranial hemorrhage and the hyperperfusion syndrome related to hypertension and anti-coagulation have been reported as complications in <1% of CAS procedures. Seizures are related predominantly to hypoperfusion and also occur in <1% of cases (234–242). Subclinical ischemic injury has also been detected by MRI (172,243,244). In the recent randomized trial ICSS (International Carotid Stenting Study), comparisons were possible between patients with CAS and CEA. These injuries, which presumably resulted from microembolism, were more frequent after CAS, as will be discussed further below (49).

Device malfunction that results in deployment failure, stent malformation, and migration after deployment is rare, occurring in <1% of procedures (245–251). If properly

deployed, an EPD can reduce the neurological risks associated with CAS, but these devices may also be associated with failures (53,196,198,247,252–258).

Among the general risks is access-site injury, which complicates 5% of cases, but most such injuries involve pain and hematoma formation and are self-limited (259–262). Contrast-induced nephropathy has been reported in <1% of cases, because CAS is generally avoided in patients with severe renal dysfunction (263).

The results of observational studies suggest that EPDs reduce rates of adverse events during CAS (264–266) when operators are experienced with the apparatus (56); in unfamiliar hands, the devices are associated with worse clinical outcomes (67,178,180) and a higher rate of stroke (267).

24.5. Comparative Assessment of Carotid Endarterectomy and Stenting

Several meta-analyses of randomized trials comparing CAS with CEA disclosed no difference in stroke or death rates at 30 days; in MI, stroke, or death rates at 30 days; or in stroke or death rates at 1 year (181,268). The studies included both symptomatic and asymptomatic patients across a range of

Table 4. Continued

Trial, Year (Reference)	Patient Population	Intervention	Comparator	No. of Patients		Events, %		Event Used to Calculate NNT	ARR, %	NNT*
				Treatment Group	Comparator Group	Treatment Group	Comparator Group			
Mixed patient populations										
SAPPHIRE 1-y data (2004) (51)	Mixed population: Symptomatic, ≥50% stenosis; Asymptomatic, ≥80% stenosis	CEA	CAS	167	167	7.90	6.20	Stroke	1.70	58
SAPPHIRE 1-y data (2004) (51)	Mixed population: Symptomatic, ≥50% stenosis; Asymptomatic, ≥80% stenosis	CEA	CAS	167	167	4.80	4.20	Ipsilateral stroke	0.60	167
SAPPHIRE 1-y data (2004)† (51)	Mixed population: Symptomatic, ≥50% stenosis; Asymptomatic, ≥80% stenosis	CEA	CAS	167	167	20.10	12.20	Cumulative incidence of death, stroke, or MI within 30 d after the procedure or death or ipsilateral stroke between 31 d and 1 y	7.90	13
SAPPHIRE 3-y data (2008) (50)	Mixed population: Symptomatic, ≥50% stenosis; Asymptomatic, ≥80% stenosis	CEA	CAS	167	167	26.90	24.60	Composite of death, stroke, or MI within 30 d after the procedure; death or ipsilateral stroke between 31 d and 1,080 d; 1,080 d was converted to 3 y for normalization and NNT calculation	2.30	130
SAPPHIRE 3-y data (2008) (50)	Mixed population: Symptomatic, ≥50% stenosis; Asymptomatic, ≥80% stenosis	CEA	CAS	167	167	9.00	9.00	Stroke	0	~
SAPPHIRE 3-y data (2008) (50)	Mixed population: Symptomatic, ≥50% stenosis; Asymptomatic, ≥80% stenosis	CEA	CAS	167	167	5.40	6.60	Ipsilateral stroke	1.20	250
Symptomatic										
ICSS (2010) (172)	Symptomatic	CEA	CAS	858	855	4.10	7.70	All strokes within 120 d after randomization‡	3.60	7
ICSS (2010) (172)	Symptomatic	CEA	CAS	858	855	3.30	7.00	All strokes within 30 d after randomization‡	3.70	2
CREST symptomatic										
CREST 4-y data (2010) (39)	Symptomatic	CEA	CAS	653	668	8.40	8.60	All strokes, MIs, or deaths within periprocedural period and postprocedural ipsilateral strokes	0.20	2,000
CREST 4-y data (2010) (39)	Symptomatic	CEA	CAS	653	668	6.40	8.00	All periprocedural strokes or deaths or postprocedural ipsilateral strokes	1.60	250
CREST 4-y data (2010) (39)	Symptomatic	CEA	CAS	653	668	6.40	7.60	All periprocedural strokes or postprocedural ipsilateral strokes	1.20	333
CREST asymptomatic										
CREST 4-y data (2010) (39)	Asymptomatic	CEA	CAS	587	594	4.90	5.60	All strokes, MIs, or deaths within periprocedural period and postprocedural ipsilateral strokes	0.70	571
CREST 4-y data (2010) (39)	Asymptomatic	CEA	CAS	587	594	2.70	4.50	All periprocedural strokes or postprocedural ipsilateral strokes	1.80	223
CREST 4-y data (2010) (39)	Asymptomatic	CEA	CAS	587	594	2.70	4.50	All periprocedural strokes or deaths or postprocedural ipsilateral strokes	1.80	223
CREST mixed population										
CREST 4-y data (2010) (39)	Patient population not separated in table; mixed patient population	CEA	CAS	1,240	1,262	7.90	10.20	All stroke	2.30	174

*NNT indicates number of patients needed to treat over the course of 1 year with the indicated therapy as opposed to the comparator to prevent the specified event(s). All NNT calculations have been annualized. For details of methodology, please see Suissa (172a). †The 1-year data from the SAPPHIRE trial included the primary endpoint; long-term data were used to calculate rates of the major secondary endpoint. ‡Annualized data. ~Cannot be calculated because ARR is 0.

ACAS indicates Asymptomatic Carotid Arteriosclerosis Study; ACST, Asymptomatic Carotid Surgery Trial; ARR, absolute risk reduction; CAS, carotid artery stenting; CEA, carotid endarterectomy; CREST, Carotid Revascularization Endarterectomy versus Stenting Trial; ECST, European Carotid Surgery Trial; EVA-3S, Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis; ICSS, International Carotid Stenting Study; NASCET, North American Symptomatic Carotid Endarterectomy Trial; NNT, number needed to treat; N/A, not applicable; SAPPHIRE, Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy; and SPACE, Stent-Protected Angioplasty versus Carotid Endarterectomy.

Table 5. Randomized Trials Comparing Endarterectomy With Stenting in Symptomatic Patients With Carotid Stenosis

Trial, Year (Reference)	No. of Patients	Key Features	Death or Any Stroke	OR (95% CI)	Comments
Leicester, 1998 (177)	Seventeen had received their allocated treatment before trial suspension	Single center; patients with symptomatic carotid stenosis >70%.	CEA: 0/10 (0%)* CAS: 5/7 (71.4%)*	p=0.0034; OR not reported	Terminated prematurely because of safety concerns.
CAVATAS-CEA, 2001 (178)	504	Multicenter; patients of any age with symptomatic or asymptomatic carotid stenosis suitable for CEA or CAS.	CEA: 25/253 (9.9%) CAS: 25/251 (10.0%)	p=NS in original article; OR not reported	Follow-up to 3 y; relatively low stent use (26%) in CAS group.
Kentucky, 2001 (179)	104	Single center; patients with symptomatic carotid stenosis >70% (events within 3 mo of evaluation).	CEA: 1/51 (2.0%) CAS: 0/53 (0%)	0.31 (0.01 to 7.90)	
SAPPHIRE, 2004 (51)	334	Multicenter randomized trial of patients with ≥80% asymptomatic carotid stenosis (70%) and ≥50% symptomatic carotid stenosis (30%).	CEA: 9.3% symptomatic patients† CAS: 2.1% symptomatic patients†	p=0.18‡	Terminated prematurely because of a drop in randomization.
EVA-3S, 2006 (67)	527	Multicenter; patients with symptomatic carotid stenosis >60% within 120 d before enrollment suitable for CEA or CAS.	CEA: 10/259 (3.9%) CAS: 25/261 (9.6%)	RR 2.5 (1.2 to 5.1), p=0.01	Study terminated prematurely because of safety and fertility issues; concerns about operator inexperience in the CAS arm and nonuniform use of embolism protection devices.
SPACE, 2006 (180)	1,183	Multicenter; patients >50 y old with symptomatic carotid stenosis >70% in the 180 d before enrollment.	Primary endpoint of ipsilateral ischemic stroke or death from time of randomization to 300 d after the procedure: CEA: 37/584 (6.3%) CAS: 41/599 (6.8%)	1.19 (0.75 to 1.92)	Study terminated prematurely after fertility analysis; concerns about operator inexperience in the CAS arm and nonuniform use of embolism protection devices.
EVA-3S 4-y follow-up, 2008 (171)	527	Multicenter, randomized, open, assessor-blinded, noninferiority trial. Compared outcome after CAS with outcome after CEA in 527 patients who had carotid stenosis of at least 60% that had recently become symptomatic.	Major outcome events up to 4 y for any periprocedural stroke or death: CEA: 6.2% CAS: 11.1%	HR for any stroke or periprocedural death 1.77 (1.03 to 3.02); p=0.04 HR for any stroke or death 1.39 (0.96 to 2.00); p=0.08 HR for CAS versus CEA 1.97 (1.06 to 3.67); p=0.03	A hazard function analysis showed 4-y differences in cumulative probabilities of outcomes between CAS and CEA were largely accounted for by the higher periprocedural (within 30 d of the procedure) risk of stenting compared with endarterectomy. After the periprocedural period, the risk of ipsilateral stroke was low and similar in the 2 treatment groups.

Table 5. Continued

Trial, Year (Reference)	No. of Patients	Key Features	Death or Any Stroke	OR (95% CI)	Comments
SPACE 2-y follow-up, 2008 (45)	1,214	Patients with symptomatic, severe ($\geq 70\%$) carotid artery stenosis were recruited to this noninferiority trial and randomly assigned with a block randomization design to undergo CAS or CEA.	<p>Intention-to-treat population: Ipsilateral ischemic strokes within 2 y, including any periprocedural strokes or deaths: CAS: 56 (9.5%) CEA: 50 (8.8%)</p> <p>Any deaths between randomization and 2 y: CAS: 32 (6.3%) CEA: 28 (5.0%)</p> <p>Any strokes between randomization and 2 y: CAS: 64 (10.9%) CEA: 57 (10.1%)</p> <p>Ipsilateral ischemic stroke within 31 d and 2 y: CAS: 12 (2.2%) CEA: 10 (1.9%)</p> <p>Per-protocol population: Ipsilateral ischemic strokes within 2 y, including any periprocedural strokes or deaths: CAS: 53 (9.4%) CEA: 43 (7.8%)</p> <p>Any deaths between randomization and 2 y: CAS: 29 (6.2%) CEA: 25 (4.9%)</p> <p>Any strokes between randomization and 2 y: CAS: 61 (11.5%) CEA: 51 (9.8%)</p> <p>Ipsilateral ischemic stroke within 31 d and 2 y: CAS: 12 (2.3%) CEA: 10 (2.0%)</p>	<p>Intention-to-treat population: Ipsilateral ischemic strokes within 2 y, including any periprocedural strokes or deaths: HR 1.10 (0.75 to 1.61)</p> <p>Any deaths between randomization and 2 y: HR 1.11 (0.67 to 1.85)</p> <p>Any strokes between randomization and 2 y: HR 1.10 (0.77 to 1.57)</p> <p>Ipsilateral ischemic stroke within 31 d and 2 y: HR 1.17 (0.51 to 2.70)</p> <p>Per-protocol population: Ipsilateral ischemic strokes within 2 y, including any periprocedural strokes or deaths: HR 1.23 (0.82 to 1.83)</p> <p>Any deaths between randomization and 2 y: HR 1.14 (0.67 to 1.94)</p> <p>Any strokes between randomization and 2 y: HR 1.19 (0.83 to 1.73)</p> <p>Ipsilateral ischemic stroke within 31 d and 2 y: HR 1.18 (0.51 to 2.73)</p>	In both the intention-to-treat and per-protocol populations, recurrent stenosis of $\geq 70\%$ was significantly more frequent in the CAS group than the CEA group, with a life-table estimate of 10.7% versus 4.6% ($p=0.0009$) and 11.1% versus 4.6% ($p=0.0007$), respectively.
SAPPHIRE 3-y follow-up, 2008 (50)	260	Long-term data were collected for 260 individuals; included symptomatic carotid artery stenosis of at least 50% of the luminal diameter or an asymptomatic stenosis of at least 80%.	<p>Stroke: CAS: 15 (9.0%) CEA: 15 (9.0%)</p> <p>Ipsilateral stroke: CAS: 11 (7.0%) CEA: 9 (5.4%)</p> <p>Death: CAS: 31 (18.6%) CEA: 35 (21%)</p> <p>Note: data were calculated using $n=167$ for both groups because breakdowns of CAS and CEA for $n=260$ were not given.</p>	<p>Stroke: $p=0.99$ (-6.1 to 6.1)</p> <p>Death: $p=0.68$ (-10.9 to 6.1)</p>	
Wallstent, 2005 (181)	219	Included symptomatic angiographic carotid stenosis $>70\%$.	<p>CAS: 13 (12.2%) CEA: 5 (4.5%)</p>	N/A	Premature termination based on futility analysis.

Table 5. Continued

Trial, Year (Reference)	No. of Patients	Key Features	Death or Any Stroke	OR (95% CI)	Comments
SAPPHIRE (symptomatic data), 2008 (182)	96	Included patients with $\geq 50\%$ carotid stenosis.	CEA: 3 (6.5%) CAS: 0	N/A	Premature termination secondary to declining enrollment.
ICSS, 2010 (49)	1,713	Multicenter study. In the study, the degree of carotid stenosis was 70% to 99% in 89% of stent patients and in 91% of endarterectomy patients. Study patients had $>50\%$ carotid artery stenosis measured by the NASCET criteria.	120-d follow-up data available only: CAS: 72/853 (8.5%) CEA: 40/857 (4.7%)	OR not available; HR=1.86 (1.26 to 2.74) $p=0.001$	Primary outcome was 3-y rate of fatal or disabling stroke in any territory; interim results have been provided for 120-d rate of stroke, death, or procedural MI.
CREST, 2010 (39)	2,502	The study included 1,321 symptomatic patients and 1,181 asymptomatic patients. Symptomatic patients in the study had $\geq 50\%$ carotid stenosis by angiography, $\geq 70\%$ by ultrasound or $\geq 70\%$ by CTA or MRA. Asymptomatic patients had carotid stenosis (patients with symptoms beyond 180 d were considered asymptomatic) $\geq 60\%$ by angiography, $\geq 70\%$ by ultrasound, or $\geq 80\%$ by CTA or MRA.	Any periprocedural stroke or postprocedural ipsilateral stroke: Symptomatic: CAS: 37 (5.5 \pm 0.9 SE) CEA: 21 (3.2 \pm 0.7 SE) Any periprocedural stroke or death or postprocedural ipsilateral stroke: Symptomatic: CAS: 40 (6.0 \pm 0.9 SE) CEA: 21 (3.2 \pm 0.7 SE)	Any periprocedural stroke or postprocedural ipsilateral stroke: Symptomatic: $p=0.04$ Any periprocedural stroke or death or postprocedural ipsilateral stroke: Symptomatic: $p=0.02$	The risk of composite primary outcome of stroke, MI, or death did not differ significantly among symptomatic and asymptomatic patients between CAS and CEA.

*Death and ipsilateral stroke. †Death, stroke, and MI. ‡Combined asymptomatic and symptomatic patients for death, any stroke.

CAS indicates carotid artery stent; CAVATAS, Carotid And Vertebral Artery Transluminal Angioplasty Study; CEA, carotid endarterectomy; CI, confidence interval; CREST, Carotid Revascularization Endarterectomy versus Stenting Trial; CTA, computed tomography angiography; EVA-3S, Endarterectomy Versus Angioplasty in patients with Symptomatic Severe carotid Stenosis; HR, hazard ratio; ICSS, International Carotid Stenting Study; MI, myocardial infarction; MRA, magnetic resonance angiography; N/A, not available; NASCET, North American Symptomatic Carotid Endarterectomy Trial; NS, not significant; OR, odds ratio; RR, risk reduction; SAPPHIRE, Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy; SE, standard error; and SPACE, Stent-Protected Angioplasty versus Carotid Endarterectomy.

Modified from Ederle et al. (183).

surgical risk, as well as stenting with and without EPDs. In some studies, CAS was associated with a lower rate of MI and procedural morbidity such as cranial nerve injury (181), but others found CAS to be inferior to CEA or associated with higher rates of periprocedural stroke (269–272).

The SAPPHIRE (Stenting and Angioplasty with Protection in Patients of High Risk Endarterectomy) study (51,52) is the only randomized trial that specifically enrolled high-risk patients to compare CEA to CAS with EPD. The inclusion criteria included symptomatic stenosis $>50\%$ or asymptomatic stenosis $>80\%$, plus at least 1 high-risk criterion. The trial was stopped prematurely because of slow enrollment, and many potential participants were excluded because they were considered to be at exceedingly high risk for complications if randomized to undergo CEA (50). The primary endpoint (the composite of MI, stroke, or death within 30 days plus death because of neurological causes or ipsilateral stroke between 31 days and 1 year) occurred in 12.2% of patients assigned to CAS and 20.1% of those assigned to CEA ($p=0.004$ for noninferiority and $p=0.053$ for superiority). In patients with symptomatic stenosis, the

occurrence of the primary endpoint was similar after CAS and CEA (16.8% versus 16.5%, respectively). In asymptomatic patients, fewer primary endpoints occurred after CAS (9.9% versus 21.5%). The 3-year incidence of stroke (7.1% versus 6.7%; $p=0.945$) and target-vessel revascularization (3% versus 7.1%; $p=0.084$) was similar for CAS and CEA (51,52,56).

In the CAVATAS (Carotid and Vertebral Artery Transluminal Angioplasty Study) randomized trial of endovascular versus medical therapy ($n=504$) (178), the combined stroke or death rate at 30 days was 10% in both groups. The angioplasty and CAS group experienced less cranial neuropathy, major hematoma, MI, and pulmonary embolism and more restenosis at 1 year (14% versus 4%; $p<0.001$), which reflects a relatively low rate of stent use (22%) in the endovascular arm. Stroke or death at 3 years was similar in the 2 groups (14.2%) (178). The SPACE (Stent-Protected Angioplasty versus Carotid Endarterectomy) trial (180) included patients with $>70\%$ carotid stenosis determined by ultrasound, TIA or stroke within 180 days, and a Modified Rankin Scale score <4 . Subjects were randomized between

Table 6. Trials Comparing Endarterectomy With Stenting in Asymptomatic Patients With Carotid Stenosis

Trial, Year (Reference)	No. of Patients	Key Features	Death or Any Stroke	p	Comments
SAPPHIRE, 2004 (51)	334	Multicenter randomized trial of patients with >50% symptomatic carotid stenosis (58%) or >80% asymptomatic carotid stenosis (42%) with 1 or more comorbidity criteria* (high-surgical-risk group).	Asymptomatic: CEA: 10.2%† CAS: 5.4%† Combined: CEA: 9.8%† CAS: 4.8%†	0.20 0.09	Terminated prematurely because of a drop in randomization.
SAPPHIRE, 2008 (50)	334	Multicenter randomized trial of patients with >80% asymptomatic carotid stenosis (70%) and ≥50% symptomatic carotid stenosis (30%).	SAPPHIRE 3-y data, Stroke: CEA: 15/167 CAS: 15/197 Death: CEA: 35/167 CAS: 31/167	Stroke: 0.99 Death: 0.68 (OR not reported)	No significant difference could be shown in long-term outcomes between patients who underwent CAS with an EPD and those who underwent CEA.
CREST, 2010 (39)	2,502	The study included 1,321 symptomatic patients and 1,181 asymptomatic patients. Symptomatic patients in the study had ≥50% carotid stenosis by angiography, ≥70% by ultrasound, or ≥70% by CTA or MRA. Asymptomatic patients in the study had carotid stenosis (patients with symptoms beyond 180 d were considered asymptomatic) ≥60% by angiography, ≥70% by ultrasound, or ≥80% by CTA or MRA.	Any periprocedural stroke or postprocedural ipsilateral stroke: Asymptomatic: CAS: 15 (2.5±0.6 SE) CEA: 8 (1.4±0.5 SE) Any periprocedural stroke or death or postprocedural ipsilateral stroke: Asymptomatic: CAS: 15 (2.5±0.6 SE) CEA: 8 (1.4±0.5 SE)	Any periprocedural stroke or postprocedural ipsilateral stroke: Asymptomatic: 0.15 Any periprocedural stroke or death or postprocedural ipsilateral stroke: Asymptomatic: 0.15	The risk of the composite primary outcome of stroke, MI, or death did not differ significantly among symptomatic and asymptomatic patients between CAS and CEA.

*Criteria for high risk (at least 1 factor required): clinically significant cardiac disease (congestive heart failure, abnormal stress test, or need for open heart surgery); severe pulmonary disease; contralateral carotid occlusion; contralateral laryngeal nerve palsy; previous radical neck surgery or radiation therapy to the neck; recurrent stenosis after endarterectomy; and age >80 years. High risk is defined by age ≥80 years, New York Heart Association class III/IV heart failure, chronic obstructive pulmonary disease, contralateral carotid stenosis 50% or more, prior CEA or CAS, or prior coronary artery bypass graft surgery. †Death, stroke, and MI.

CAS indicates carotid artery stent; CEA, carotid endarterectomy; CREST, Carotid Revascularization Endarterectomy versus Stent Trial; CTA, computed tomography angiography; EPD, embolic protection device; MI, myocardial infarction; MRA, magnetic resonance angiography; OR, odds ratio; SAPPHIRE, Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy; and SE, standard error.

2001 and 2006 to CEA (n=595) or CAS (n=605). Surgeons included in the study had performed at least 25 CEA procedures with acceptable mortality and morbidity in the prior year, and CAS operators had performed at least 25 successful angioplasty or stent procedures, not necessarily involving carotid arteries. The study was terminated because of insufficient enrollment, and there was no significant difference in outcomes between CAS and CEA at 30 days. The EVA-3S (Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis) trial randomized patients within 120 days of TIA or stroke who had >60% ipsilateral carotid stenosis determined by duplex ultrasound and angiography (67). The primary outcome was the composite of stroke or death within 30 days of the procedure. Surgeons included in the study had performed at least 25 CEA procedures during the previous year, and operators performing CAS were required to have performed at least 12 CAS procedures or 35 stenting procedures in other vessels or were proctored. Enrollment stopped in 2005, with 520 patients enrolled, because of higher 30-day rates of stroke and adverse events in the CAS arm.

At least 4 additional randomized clinical trials have been reported, are in progress, or are under consideration to compare CEA to CAS with EPD in conventional-risk

patients. ICSS is an ongoing randomized trial designed to compare the safety and effectiveness of CEA versus CAS in symptomatic patients with >50% carotid stenosis (49). Eighty-eight percent of patients were treated at experienced centers. An interim safety analysis involving 1,713 randomized patients found a 120-day composite rate of stroke, death, or procedural MI of 8.5% in the CAS group versus 5.2% in the CEA group (HR 1.69; 95% CI 1.16 to 2.45), but conclusions await completion of longer-term follow-up of the cohort.

CREST (Carotid Revascularization Endarterectomy versus Stent Trial), a randomized multicenter trial, compared CAS with CEA in symptomatic and asymptomatic patients (273,274). During the lead-in phase (274), the 30-day stroke and death rate was 3.9% among 1,246 nonrandomized patients, and the mortality and stroke morbidity rate was 5.6% for symptomatic patients and 3.4% for asymptomatic patients undergoing CEA (275). The primary endpoint is the combination of stroke, death, or MI during the periprocedural period and ipsilateral stroke thereafter up to 4 years. Among 2502 patients followed up for a mean of 2.5 years, there was no significant difference in primary events between the 2 arms (7.2% with CAS versus 6.8% with CEA; HR 1.11, 95% CI 0.81 to 1.51). There were

Table 7. Summary of Recommendations Regarding the Selection of Revascularization Techniques for Patients With Carotid Artery Stenosis

	Symptomatic Patients		Asymptomatic Patients
	50% to 69% Stenosis	70% to 99% Stenosis*	70% to 99% Stenosis*
Endarterectomy	Class I LOE: B	Class I LOE: A	Class IIa LOE: A
Stenting	Class I LOE: B	Class I LOE: B	Class IIb LOE: B

The severity of stenosis is defined according to angiographic criteria by the method used in NASCET (37) but generally corresponds as well to assessment by sonography (112) and other accepted methods of measurement. See Sections 7.2 to 7.4.4 for details.

LOE indicates level of evidence.

differences, however, in rates of the component periprocedural events. Although the absolute rates were low, stroke was more frequent with CAS, and MI was more likely after CEA. The primary results did not vary between treatment groups by sex or symptom status, although event rates were higher among symptomatic patients (periprocedural stroke and death $\leq 6\%$ for CAS and CEA; $p=NS$) than among asymptomatic patients (periprocedural stroke and death $\leq 3\%$ for CAS and CEA; $p=NS$). There was a differential outcome based on patient age that favored CAS for patients younger than 70 years of age and CEA for those older than 70 years of age (39).

24.5.1. Selection of Carotid Endarterectomy or Carotid Artery Stenting for Individual Patients With Carotid Stenosis

Table 7 summarizes recommendations for the selection of revascularization techniques for patients with carotid artery stenosis. Although no adequate studies have validated the specific high-risk criteria that might warrant preferential selection of CAS rather than CEA for individual patients, generally accepted anatomic features are listed in Table 6.

24.6. Durability of Carotid Revascularization

Clinical durability refers to the sustained efficacy of CEA and CAS in preventing stroke. In the large randomized clinical trials, the ipsilateral stroke rates after the first 30 days were approximately 1% to 2% per year for symptomatic patients (ECST, NASCET) and approximately 0.5% to 0.8% per year for asymptomatic patients (ACAS, ACST). The clinical durability of CEA and CAS beyond 5 years cannot be clearly determined from available studies (45,171).

Restenosis after CEA has been reported in 5% to 10% of cases when assessed by postoperative ultrasonography but consistently in fewer than 5% of cases when patching was used in recent series (63,176,276-281). Hemodynamically significant recurrent stenosis rates of 5% to 7% have been reported in multicenter trials (62,176,276,282-299). Data comparing restenosis after CEA and CAS must be interpreted cautiously because of selection bias and stent-

generated artifacts in ultrasound velocity measurements. After 1 year of follow-up in the SPACE trial, 4.6% of patients who underwent CEA and 10.7% of those undergoing CAS had developed $\geq 70\%$ recurrent stenosis as assessed by ultrasound ($p=0.0009$) (45).

Although limited data suggest that CAS is noninferior to CEA in patients with various comorbidities, available data are insufficient to justify a recommendation favoring one procedure over the other in patients with carotid stenosis and occlusion of the contralateral carotid artery. Restenosis is generally benign and does not require revascularization except when it leads to recurrent ischemic symptoms or progresses to preocclusive severity. Under these circumstances, it may be justifiable to repeat revascularization, either by CEA in the hands of an experienced surgeon or by CAS.

25. Vertebral Artery Disease

Symptomatic obstructive disease of the vertebral arteries is less common than carotid stenosis, and the prevalence, pathophysiology, and natural history of vertebral artery disease are not as well understood. Like patients with carotid atherosclerosis, however, those with vertebral artery disease face an increased risk of other cardiovascular ischemic events.

25.1. Anatomy of the Vertebrobasilar Arterial Circulation

The vertebral arteries usually arise from the subclavian arteries, but in approximately 5% of individuals the left vertebral artery arises from the aortic arch. The left and right vertebral arteries are typically described as having 4 segments each (V_1 through V_4), the first 3 of which are extracranial, but anatomic variants are more common than in the carotid circulation. Important anatomic variations must be considered in clinical assessment and treatment.

25.2. Epidemiology of Vertebral Artery Disease

The incidence of posterior circulation strokes may be underestimated (300), but vertebral artery atherosclerosis may be the causative basis for approximately 20% of posterior circulation strokes (300-303). A study using contrast-enhanced MRA in consecutive patients with posterior circulation TIA or minor stroke found a prevalence of $>50\%$ vertebral and basilar arterial stenosis, and vertebrobasilar arterial stenosis was more often associated with multiple ischemic episodes and a higher risk of early recurrent stroke (304).

25.3. Clinical Presentation of Patients With Vertebrobasilar Arterial Insufficiency

Atherosclerotic stenosis most commonly affects the first portion of the vertebral arteries or extends from plaques that compromise the origin of the vertebral arteries. In patients with lesions at the midportion of the vertebral arteries, the

transverse process of a vertebra may impinge on the artery, causing symptoms upon head turning. Compromised vertebrobasilar perfusion is not the only mechanism of symptoms, because atheroembolism may be the cause of brainstem or cerebellar infarction. Symptoms associated with vertebral artery disease include dizziness, vertigo, diplopia, perioral numbness, blurred vision, tinnitus, ataxia, bilateral sensory deficits, and syncope, all of which can be caused by other disease entities, including cardiac arrhythmias, orthostatic hypotension, and vestibular disorders.

25.4. Evaluation of Patients With Vertebral Artery Disease

Evaluation of a patient with presumed vertebrobasilar insufficiency should begin with a thorough clinical history and examination followed by noninvasive imaging as for patients with carotid artery disease (305). In 11 studies that compared noninvasive imaging with catheter-based angiography for detection of vertebral artery stenosis, CTA and contrast-enhanced MRA were associated with higher sensitivity (94%) and specificity (95%) than ultrasonography (sensitivity 70%) (114). Neither MRA nor CTA reliably delineates the origins of the vertebral arteries, and hence, catheter-based angiography is typically required before revascularization for patients with symptomatic posterior cerebral ischemia.

25.5. Medical Therapy of Patients With Vertebral Artery Disease

Although various medical, interventional, and surgical approaches have been developed for treatment of patients with vertebral artery disease, none have been evaluated in randomized trials. Despite the paucity of evidence applicable to patients with vertebral artery disease, we recommend that medical management follow the guidelines for those with disease of the carotid arteries.

For patients with acute ischemic syndromes that involve the vertebral artery territory and angiographic evidence of thrombus in the extracranial portion of the vertebral artery, anticoagulation is generally recommended for at least 3 months, whether or not thrombolytic therapy is used initially (306–309). The WASID (Warfarin versus Aspirin for Symptomatic Intracranial Disease) trial found aspirin and warfarin to be equally efficacious after initial noncardioembolic ischemic stroke (310,311). Ticlopidine was superior to aspirin for secondary prevention of ischemic events in patients with symptomatic posterior circulation disease (312). In ESPS-2, vertebrobasilar territory stroke or TIA occurred in 5.7% of 255 patients treated with a combination of aspirin plus dipyridamole compared with 10.8% of those given a placebo (313).

25.6. Vertebral Artery Revascularization

Operations are rarely performed to treat vertebral artery occlusive disease, and no randomized trials have addressed operative procedures for posterior cerebral circulation dis-

ease, but studies of surgical treatment have demonstrated the feasibility of endarterectomy and vessel reconstruction (314–321). For proximal vertebral artery reconstruction, early complication rates of 2.5% to 25% and perioperative mortality rates of 0% to 4% have been reported (315,316). For distal vertebral artery reconstruction, mortality rates have ranged from 2% to 8% (314,317,318,320,321). Intracranial bypass surgery is associated with mortality rates of 3% to 12% and neurological and systemic complication rates of 22% to 55% (317–321).

The surgical approach to atherosclerotic lesions at the origin of the vertebral artery includes trans-subclavian vertebral endarterectomy, transposition of the vertebral artery to the ipsilateral common carotid artery, and reimplantation of the vertebral artery with vein graft extension to the subclavian artery. Distal reconstruction of the vertebral artery may be accomplished by anastomosis of the principal trunk of the external carotid artery to the vertebral artery (322). In appropriately selected patients, these operations can relieve symptoms, with low morbidity and mortality (314,323–330).

There is little evidence from randomized trials that endovascular management is superior to best medical management. In a review of 300 interventions for proximal vertebral artery stenosis, the risk was 0.3% for death, 5.5% for periprocedural neurological complications, and 0.7% for posterior stroke at a mean follow-up of 14.2 months. Restenosis occurred in 26% of cases after a mean of 12 months but was not consistently correlated with recurrent symptoms (331). Among 170 angioplasty procedures in patients with distal vertebrobasilar disease, neurological complications developed in 24%, but the rate approached 80% in cases of urgent revascularization. Restenosis developed in 10% after a mean follow-up interval of 12.6 months (331). The annual stroke risk after angioplasty for distal vertebrobasilar disease is approximately 3% (331), and rates of stroke and restenosis appear to be related to more distal and anatomically complex lesions.

26. Diseases of the Subclavian and Brachiocephalic Arteries

Occlusive disease involving the subclavian and brachiocephalic arteries may be caused by atherosclerosis, Takayasu arteritis, giant cell arteritis, FMD, and radiation-induced arteriopathy; of these, atherosclerosis is the most frequent cause. The clinical presentation depends on the vessel involved and the severity of disease. Symptoms may reflect upper-extremity ischemia, such as arm or hand claudication, paresthesia, or rest pain. Some patients become asymptomatic as collaterals develop. In asymptomatic patients who require myocardial revascularization, subclavian intervention may be performed to preserve blood flow to the internal mammary artery. To our knowledge, no randomized trials

of subclavian artery or brachiocephalic revascularization have been published.

When the dominant vertebral artery is subtended by subclavian obstruction, reversal of flow may reduce basilar artery perfusion and cause posterior cerebrovascular insufficiency. Symptoms are typically aggravated by exercising the ipsilateral arm, which amplifies the flow reversal. A periclavicular or infraclavicular bruit suggests subclavian stenosis, and subclavian arterial occlusive disease may cause asymmetry of left and right arm blood pressure, but blood pressure may be symmetrical when bilateral subclavian disease or aortic arch syndrome compromises perfusion of both upper limbs equally.

The diagnosis of subclavian steal syndrome should be considered in patients with posterior cerebral circulatory insufficiency aggravated by upper-limb exercise. In the vertebral ischemic form of subclavian steal syndrome, upper-extremity exertion may cause lightheadedness, syncope, vertigo, ataxia, diplopia, motor deficits; or upper-limb claudication. Duplex ultrasonography may identify reversal of flow in a vertebral artery.

26.1. Revascularization of the Brachiocephalic and Subclavian Arteries

Symptomatic patients should be considered for subclavian revascularization by use of endovascular or surgical techniques. The surgical approach involves prosthetic extra-anatomic bypass grafting from the ipsilateral carotid artery to the subclavian artery. Other methods of extra-anatomic revascularization include carotid-axillary or axilloaxillary bypass and subclavian-carotid arterial transposition. Surgical repair is associated with low morbidity and mortality and excellent long-term patency (70,332).

Subclavian artery stenosis is also amenable to balloon angioplasty, atherectomy, and stenting, but no randomized trials have compared these methods with surgical revascularization. A report comparing 121 patients undergoing stenting and 51 undergoing carotid-subclavian bypass described initial success rates of 98% and 100% for the endovascular and surgical approaches, respectively, with periprocedural complication rates of 15.1% and 5.9%, lower in the surgical group (333). Primary patency after surgical bypass was 100% at 1 year and 96% at 5 years. Among patients managed by endovascular therapy, patency was 93% at 1 year and 70% at 5 years. Freedom from recurrent symptoms was greater in the surgical bypass group ($p < 0.0001$) (333). Balloon angioplasty and stenting are associated with high rates of success and better outcomes than angioplasty alone (334–339), which makes endovascular stenting an alternative to open surgery in patients with obstructive disease of the subclavian or brachiocephalic arteries. Numerous reports suggest that angioplasty and stenting of the subclavian and brachiocephalic arteries can be performed with a high degree of technical success and safety, but long-term follow-up data are scant (333,340–343).

27. Special Populations

27.1. Neurological Risk Reduction in Patients With Carotid Artery Disease Undergoing Cardiac Surgery

Patients with high-grade carotid artery stenosis undergoing CABG surgery face a higher risk of stroke than patients without carotid disease, but most strokes are mechanistically unrelated to carotid disease. There is no convincing evidence that carotid revascularization in patients with asymptomatic stenosis undergoing CABG surgery produces benefit in the majority of cases (344). Published reports involving patients with symptomatic carotid disease indicate that CEA before CABG surgery is associated with a lower stroke rate but a higher rate of fatal and nonfatal MI. The strategy of combined CEA and CABG surgery has not been tested in prospective trials. Proof is lacking that carotid revascularization reduces adverse events in patients with asymptomatic carotid stenosis who are undergoing myocardial revascularization surgery (345), and therefore, a patient-specific approach is warranted. Periprocedural treatment with potent platelet-inhibitor drugs such as clopidogrel increases the risk of bleeding associated with CABG surgery, but delaying antiplatelet therapy raises the risk of stent thrombosis and stroke. Carotid intervention immediately before coronary surgery followed by administration of intravenous heparin between the procedures has not been well evaluated (344,346–351). In the nonrandomized Nationwide Inpatient Sample of 27,084 patients discharged from 2000 to 2004 (352), fewer major adverse events, postoperative strokes (2.4% versus 3.9%), and combined strokes and deaths (6.9% versus 8.6%; $p < 0.001$) were reported among patients undergoing CAS plus CABG surgery than in those undergoing CEA plus CABG surgery, although rates of in-hospital mortality were similar (5.2% versus 5.4%). Whether the lower rate of complications with CAS than CEA in this population undergoing CABG surgery reflects case selection bias or an intrinsic safety advantage remains uncertain, and properly designed prospective studies are needed.

28. Nonatherosclerotic Carotid and Vertebral Artery Diseases

Compared with atherosclerosis, nonatherosclerotic diseases of the extracranial carotid arteries are relatively uncommon. Among these, FMD and cervical artery dissection are the most common.

28.1. Fibromuscular Dysplasia

FMD is a nonatherosclerotic, noninflammatory vascular disease characterized by stenosis due to thickening of the arterial wall (353). Carotid FMD is most commonly encountered in middle-aged women, who may be symptomatic or asymptomatic. Clinical manifestations may include stroke, TIA, carotid dissection, Horner syndrome, cranial

nerve palsies, or subarachnoid hemorrhage (353–356). The pathophysiology and natural history are unknown. Gross pathological manifestations include elongation, kinking and coiling of the carotid artery (357), spontaneous dissection, and aneurysmal degeneration.

Antiplatelet therapy and sequential imaging are generally recommended even for asymptomatic patients. Both surgical revascularization (358) and endovascular approaches have been successful in alleviating ischemic symptoms in patients with FMD of the carotid arteries, and percutaneous angioplasty with or without stenting has been advocated on the basis of case reports and small series (359,360).

28.2. Cervical Artery Dissection

Dissection results from an intimal tear that initiates an intramural hematoma. Subintimal dissection tends to cause stenosis, whereas subadventitial dissection can result in aneurysmal degeneration. A number of pathological associations have been described, most of which involve connective tissue disorders. Carotid dissection is observed in 1% to 5% of patients with a bicuspid aortic valve. The association of carotid dissection with FMD is approximately 15%, but the mechanism of this relationship is unknown. Other suspected risk factors include penetrating trauma (361) and amphetamine abuse (362).

Carotid dissection accounts for approximately 2% of all ischemic strokes and up to 15% of ischemic strokes among younger patients (363). The incidence of vertebral artery dissection has not been well defined. Sudden or excessive neck movement might increase the risk of vertebral artery dissection (364).

Some patients develop sudden catastrophic neurological events, but the typical presentation involves pain on one side of the head or neck, accompanied by Horner syndrome. After these warning symptoms occur, cerebral or retinal ischemia develops in 50% to 95% of cases of carotid dissection. Patients with vertebral artery dissection may present with headache, neck pain, vertigo, nausea, visual disturbances, or syncope.

Diagnosis begins with clinical examination and brain imaging, followed by vascular imaging when an ischemic cause is suspected. Carotid duplex ultrasonography may identify a dissection flap and differential flow in the true and false lumens, but CTA or MRA is increasingly used to establish the diagnosis, largely supplanting catheter-based and digital subtraction angiography.

Treatment is usually conservative, involving anticoagulation, and the prognosis is usually favorable (365–367). There have been no randomized trials comparing anticoagulant and antiplatelet therapy with one another or with placebo (368). Once symptoms resolve, antiplatelet therapy may replace anticoagulation, but no approach has gained uniform support. Surgical or endovascular revascularization is reserved for patients with persistent or recurrent symptoms that fail to respond to anticoagulation.

29. Future Research

As evident from the number of recommendations in this document that are based on consensus in a void of definitive evidence, there are vast opportunities for future research. These begin with the need to define more precisely the scope of clinical carotid artery disease as a cause of stroke in major segments of the population through well-designed population studies of ischemic stroke in which ECVD and intracranial vascular disease are separately and objectively classified to provide accurate estimates of disease prevalence.

Given the imperfect correlation between the severity of carotid stenosis and ischemic brain events, the search for other indexes of plaque vulnerability linked to stroke risk must advance. Enhanced noninvasive imaging technology has improved diagnostic accuracy, but limitations lead to overestimation of stenosis severity and failure to reliably distinguish subtotal from complete arterial occlusion.

The value of specific therapies to prevent stroke, even in symptomatic patients with severe carotid artery stenosis, largely lacks validation. Although antiplatelet drugs reduce the risk of stroke compared with placebo in patients with TIA or previous stroke, no adequately powered studies have demonstrated their efficacy for stroke prevention in asymptomatic patients with ECVD. Few studies have investigated the role of anticoagulant drugs in the management of patients with ECVD who develop acute ischemic stroke, especially after administration of thrombolytic therapy.

Beyond the acute phase of ischemic stroke, it remains unclear whether women benefit as much as men from CEA, and further studies must recruit sufficient numbers of women and older patients to address these important subsets of patients with symptomatic ECVD. The reasons for differences in outcomes based on these demographic variables, as well as race and ethnicity, have not been investigated.

CREST answered some questions about the relative value of CAS and CEA but raised others. The reported event rates were generally low with either method of revascularization among symptomatic patients, but there was an important difference related to patient age that requires explanation. The most pressing question is how either technique of revascularization compares with intensive contemporary medical therapy, particularly among asymptomatic patients, and a direct comparative trial should include a sufficiently broad range of patients to permit meaningful analysis of subgroups based on age, sex, ethnicity, and risk status.

Huge gaps in knowledge of vertebral arterial disease will be more difficult to address because of its relative infrequency compared with carotid stenosis. This requires well-designed registries that capture data about prevalence, pathophysiology, natural history, and prognosis.

Staff

American College of Cardiology Foundation

John C. Lewin, MD, Chief Executive Officer
Charlene May, Senior Director, Science and Clinical Policy
Lisa Bradfield, CAE, Director, Science and Clinical Policy
Allison McDougall, Senior Specialist, Science and Clinical Policy
Debjani Mukherjee, MPH, Associate Director, Evidence-Based Medicine
Erin A. Barrett, MPS, Senior Specialist, Science and Clinical Policy
Jesse M. Welsh, Specialist, Science and Clinical Policy

American Heart Association

Nancy Brown, Chief Executive Officer
Rose Marie Robertson, MD, FACC, FAHA, Chief Science Officer
Anne Leonard, MPH, RN, CCRC, FAHA, Science and Medicine Advisor

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Key Words: ACCF/AHA Practice Guidelines ■ carotid endarterectomy ■ carotid stenosis ■ carotid stenting ■ extracranial carotid artery ■ revascularization ■ stroke ■ vertebral artery disease.

APPENDIX 1. AUTHOR RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES—2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS GUIDELINE ON THE MANAGEMENT OF PATIENTS WITH EXTRACRANIAL CAROTID AND VERTEBRAL ARTERY DISEASE

Committee Member	Employment	Consultant	Speaker	Ownership/ Partnership/ Principal	Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Thomas G. Brott, Co-Chair	Mayo Clinic—Director for Research	None	None	None	<ul style="list-style-type: none"> Abbott NIH* (CREST-PI) 	None	None
Jonathan L. Halperin, Co-Chair	Mount Sinai Medical Center—Professor of Medicine	<ul style="list-style-type: none"> Astellas Pharma Bayer HealthCare Biotronik* Boehringer Ingelheim Daiichi Sankyo U.S. Food and Drug Administration Cardiovascular and Renal Drugs Advisory Committee GlaxoSmithKline Johnson & Johnson Portola Sanofi-aventis 	None	None	<ul style="list-style-type: none"> NIH (National Heart, Lung, and Blood Institute) 	None	None
Suhny Abbara	Harvard Medical School—Director, Noninvasive Cardiac and Vascular Imaging	<ul style="list-style-type: none"> E-Z-EM Magellan Healthcare Partners Imaging Perceptive Informatics Siemens Medical 	None	None	<ul style="list-style-type: none"> Bracco NIH 	None	None
J. Michael Bacharach	North Central Heart Institute	None	<ul style="list-style-type: none"> ABComm Bristol-Myers Squibb/Sanofi Otsuka 	None	None	None	None
John D. Barr	Scripps Memorial Hospitals—Director, Neurointerventional Surgery	<ul style="list-style-type: none"> Boston Scientific* Cordis Neurovascular 	<ul style="list-style-type: none"> Cordis Neurovascular 	<ul style="list-style-type: none"> Boston Scientific* 	<ul style="list-style-type: none"> Abbott Guidant 	None	None

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Robert H. Rosenwasser	Thomas Jefferson University Jefferson Hospital for Neuroscience— Professor and Chairman, Department of Neurological Surgery	None	None	• Boston Scientific*	• Micrus/Boston Scientific • NIH	None	None
Allen J. Taylor	Washington Hospital Center— Co-Director, Noninvasive Imaging	• Kos • Pfizer*	None	None	• Kos	None	None

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*Significant relationship.

CREST indicates Carotid Revascularization Endarterectomy versus Stenting Trial; NIH, National Institutes of Health; and PI, principal investigator.

APPENDIX 2. REVIEWER RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES—2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS GUIDELINE ON THE MANAGEMENT OF PATIENTS WITH EXTRACRANIAL CAROTID AND VERTEBRAL ARTERY DISEASE

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Tracey Anderson	Official Reviewer—American Association of Neuroscience Nurses	None	None	None	None	None	None
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Carl Black	Official Reviewer—Society of Interventional Radiology	None	None	None	None	None	None
Jeffery Cavendish	Official Reviewer—ACCF Board of Governors	None	None	None	None	None	None
Seemant Chaturvedi	Official Reviewer—ASA	None	None	None	None	None	None
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John Connors	Official Reviewer— American College of Radiology	None	None	None	None	None	None
Daniel Edmundowicz	Official Reviewer—Society of Atherosclerosis Imaging and Prevention	<ul style="list-style-type: none"> • Abbott • GNC Corporation* • Merck Schering- Plough 	None	None	None	None	None
Steven M. Ettinger	Official Reviewer—ACCF/ AHA Task Force on Practice Guidelines	None	None	None	None	None	None
Larry B. Goldstein	Official Reviewer—ASA	<ul style="list-style-type: none"> • Abbott • Pfizer 	None	None	<ul style="list-style-type: none"> • AHA/Bugher* • NIH/CREST* 	None	None
William Gray	Official Reviewer—Society for Cardiovascular Angiography and Interventions	<ul style="list-style-type: none"> • Abbott Vascular • Aramanth Medical • BioCardia • Coherex Medical • Contego Medical • FiatLux 3D • Lutonix • Mercator • QuantumCor • Silk Road • Spirx Closure • Stereotaxis • W.L. Gore 	None	<ul style="list-style-type: none"> • CoAptus* • Ovalis • Paragon • Pathway Medical 	<ul style="list-style-type: none"> • Atritech • Cordis • NIH/CREST 	None	None
Catherine Harris	Official Reviewer— American Association of Neuroscience Nurses	None	None	None	None	None	None
Donald Heck	Official Reviewer—Society of NeuroInterventional Surgery	<ul style="list-style-type: none"> • Codman Neurovascular 	None	None	<ul style="list-style-type: none"> • Abbott Vascular • Boston Scientific • Cordis Endovascular 	None	None
David Holmes	Official Reviewer—ACCF Board of Trustees	None	None	None	None	None	None
Elad Levy	Official Reviewer— Congress of Neurological Surgeons	<ul style="list-style-type: none"> • Boston Scientific* • Cordis Neurovascular* • ev3* • Micrus Endovascular* 	None	<ul style="list-style-type: none"> • Intratech Medical* • Micrus Endovascular* 	<ul style="list-style-type: none"> • Boston Scientific* 	<ul style="list-style-type: none"> • Abbott Vascular* • ev3* 	None
William Mackey	Official Reviewer—Society for Vascular Surgery	None	None	None	None	None	None
Jon Matsumura	Official Reviewer—AHA	<ul style="list-style-type: none"> • Abbott* 	None	None	<ul style="list-style-type: none"> • Bard* • Cook* • Cordis* • ev3* • Lumen* • Medtronic* • W.L. Gore* 	None	<ul style="list-style-type: none"> • W.L. Gore

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Timothy Sullivan	Content Reviewer	None	None	None	None	None	None
Christopher White	Content Reviewer—ACCF/AHA Peripheral Arterial Disease Guideline Writing Committee; ACC Interventional Scientific Council; AHA Peripheral Vascular Disease Steering Committee	<ul style="list-style-type: none"> • Boston Scientific 	None	None	<ul style="list-style-type: none"> • Boston Scientific 	None	None

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*Significant relationship.

ACCF indicated American College of Cardiology Foundation; AHA, American Heart Association; ASA, American Stroke Association; CREST, Carotid Revascularization Endarterectomy versus Stenting Trial; NIH, National Institutes of Health; and NINDS, National Institute of Neurological Disorders and Stroke.