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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

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

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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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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 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, prospective, 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 where 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,

Table 1. Applying Classification of Recommendations and Level of Evidence

SIZE OF TREATMENT EFFECT →

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT

	CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/ administered	**CLASS IIa** *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	**CLASS IIb** *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	**CLASS III** *No Benefit* or **CLASS III** *Harm* Procedure/ Test / Treatment COR III: No benefit — Not Helpful — No Proven Benefit COR III: Harm — Excess Cost w/o Benefit or Harmful — Harmful to Patients
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations†	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit is not recommended is not indicated should not be done is not useful/ beneficial/ effective COR III: Harm potentially harmful causes harm associated with excess morbidity/mortality should not be done
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		

*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.

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 or 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 RWI 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' RWI 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 the 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 recommen-

dation. 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 executive summary and recommendations are published in the *Journal of the American College of Cardiology, Circulation, Catheterization and Cardiovascular Interventions,* the *Journal of Cardiovascular Computed Tomography,* the *Journal of NeuroInterventional Surgery, Stroke,* and *Vascular Medicine.*

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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 (IMT), 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 trials were used to calculate the absolute risk difference and number needed to treat (NNT) or harm; data related to the relative treatment effects are also provided, such as odds ratio (OR), relative risk (RR), hazard ratio (HR), or incidence rate ratio, along with confidence interval (CI) 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' RWI 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.

1.4. Anatomy and Definitions

The normal anatomy of the aortic arch and cervical arteries that supply the brain is subject to considerable variation (3). Three aortic arch morphologies are distinguished on the basis of the relationship of the brachiocephalic (innominate) arterial trunk to the aortic arch (Figure 1). The Type I aortic arch is characterized by the origin of all 3 major vessels in the horizontal plane defined by the outer curvature of the arch. In Type II, the brachiocephalic artery originates between the horizontal planes of the outer and inner curvatures of the arch. In Type III, it originates below the horizontal plane of the inner curvature of the arch. In addition to aortic arch anatomy, the configuration of the great vessels varies. Most commonly, the brachiocephalic artery, left common carotid artery, and left subclavian artery originate separately from the aortic arch (4). The term *bovine aortic arch* refers to a frequent variant of human aortic arch branching in which the brachiocephalic and left common carotid arteries share a common origin. This anatomy is not generally found in cattle, so the term *bovine arch* is a misnomer (5,6).

The distal common carotid artery typically bifurcates into the internal and external carotid arteries at the level of the thyroid cartilage, but anomalous bifurcations may occur up to 5 cm higher or lower. The carotid bulb, a dilated portion at the origin of the internal carotid artery, usually extends superiorly for a distance of approximately 2 cm, where the diameter of the internal carotid artery becomes more uniform. The length and tortuosity of the internal carotid artery are additional sources of variation, with undulation, coiling, or kinking in up to 35% of cases, most extensively in elderly patients.

The intracranial portion of each carotid artery begins at the base of the skull, traverses the petrous bone, and enters the subarachnoid space near the level of the ophthalmic artery. There, the artery turns posteriorly and superiorly, giving rise to the posterior communicating artery, which connects through the circle of Willis with the posterior cerebral artery that arises from the vertebrobasilar circulation. The internal carotid artery then bifurcates into the anterior cerebral and middle cerebral arteries. The anterior cerebral arteries connect with the circle of Willis through the anterior communicating artery. Among the most important collateral pathways are those from the external carotid artery to the internal carotid artery (via the internal maxillary branch of the external carotid artery and the superficial temporal artery to the ophthalmic branches of the

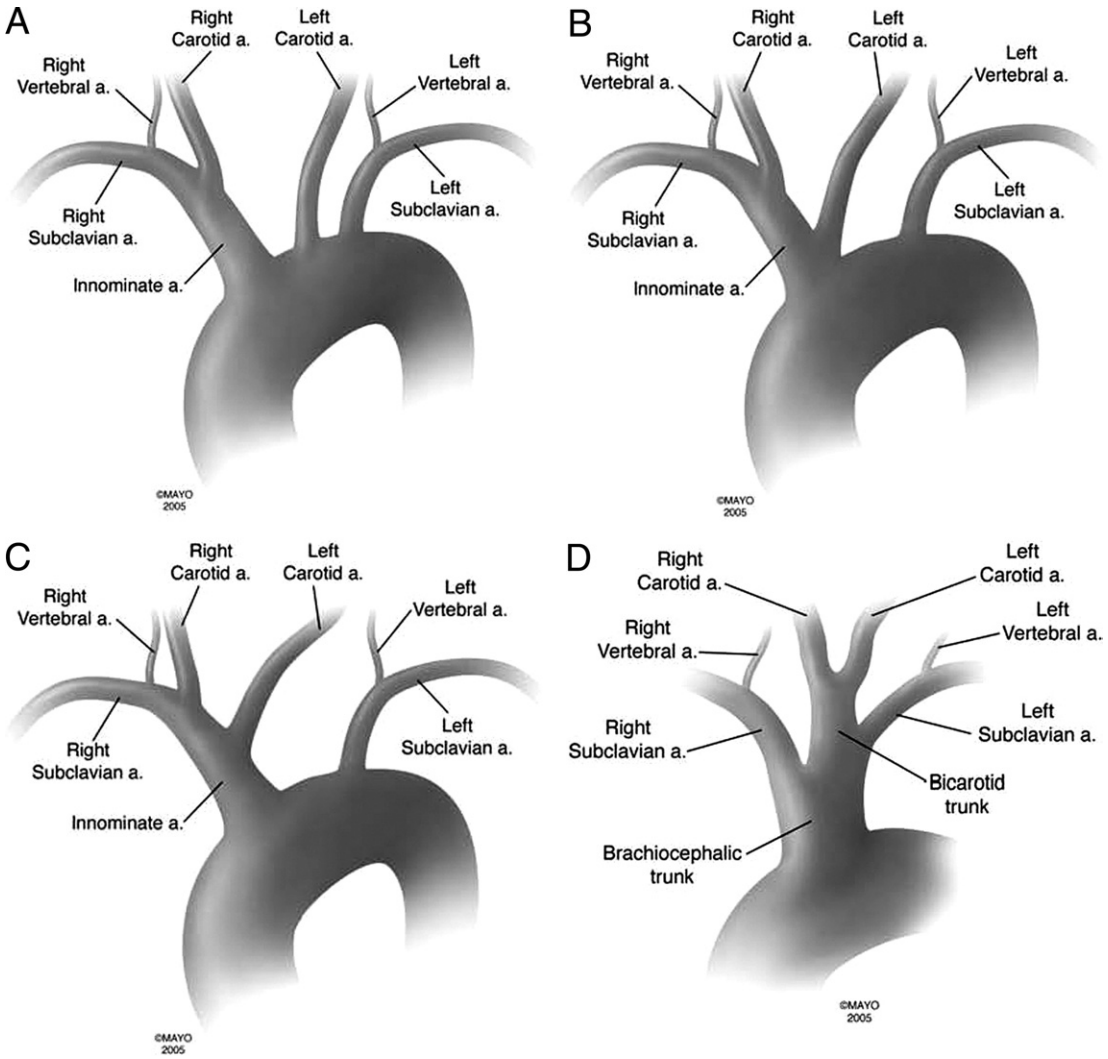

Figure 1. Aortic Arch Types

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. (6).

internal carotid artery), from the external carotid artery to the vertebral artery (via the occipital branch of the external carotid artery), from the vertebrobasilar arterial system to the internal carotid artery (via the posterior communicating artery), and between the left and right internal carotid arteries (via the interhemispheric circulation through the anterior communicating artery). The configuration of the circle of Willis is also highly variable, with a complete circle in fewer than 50% of individuals. Variations due to tortuosity, calcification, intracranial arterial stenosis, collateral circulation, aneurysms, and arteriovenous malformation have important implications that must be considered in applying treatment recommendations to individual patients.

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 fibromuscular dysplasia (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 myocardial infarction (MI), peripheral arterial disease (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.

1.5. Epidemiology of Extracranial Cerebrovascular Disease and Stroke

When considered separately from other cardiovascular diseases, stroke is the third-leading cause of death in industrialized nations, behind heart disease and cancer, and a

leading cause of long-term disability (7). Population studies of stroke involve mainly regional populations, and the results may not be generalizable across the nation because of geographic variations. Data from the Greater Cincinnati/Northern Kentucky Stroke Study suggest an annual incidence of approximately 700,000 stroke events, of which approximately 500,000 are new and 200,000 are recurrent strokes (8). In 2003, the Centers for Disease Control and Prevention reported a higher prevalence in the "stroke belt" of 10 southeastern states (9). Among persons younger than 65 years of age, excess deaths caused by stroke occur in most racial/ethnic minority groups compared with whites (10). In NOMASS (Northern Manhattan Stroke Study), the age-adjusted incidence of first ischemic stroke per 100,000 population was 191 among blacks (95% CI 160 to 221), 149 among Hispanics (95% CI 132 to 165), and 88 (95% CI 75 to 101) among whites (11). The average annual age-adjusted overall (initial and recurrent) stroke incidence per 100,000 for those ≥20 years old was 223 for blacks, 196 for Hispanics, and 93 for whites, which represents a 2.4-fold RR for blacks and a 2-fold increase for Hispanics compared with whites (12). On a national level, however, a large number of strokes apparently go unreported. The prevalence of silent cerebral infarction between ages 55 and 64 years is approximately 11%, increasing to 22% between ages 65 and 69, 28% between ages 70 and 74, 32% between ages 75 and 79, 40% between ages 80 and 85, and 43% beyond age 85. The application of these rates to 1998 US population estimates yielded an estimated 13 million people with silent stroke (13).

Most (54%) of the 167,366 deaths attributed to stroke in 1999 were not specified by *International Classification of Disease, 9th Revision* codes for hemorrhage or infarction (14). On the basis of data from the Framingham Heart Study (15), the ARIC (Atherosclerosis Risk in Communities) study (16,17), and the Greater Cincinnati/Northern Kentucky Stroke Study (8), approximately 88% of all strokes are ischemic, 9% are intracerebral hemorrhages, and 3% are subarachnoid hemorrhages (18–22).

In the Framingham Heart Study population, the prevalence of >50% carotid stenosis was 7% in women and 9% in men ranging in age from 66 to 93 years (23). In the Cardiovascular Health Study of subjects older than 65 years of age, 7% of men and 5% of women had moderate (50% to 74%) carotid stenosis; severe (75% to 100%) stenosis was detected in 2.3% of men and 1.1% of women (24). In NOMASS, a population-based study of people older than 40 years of age who lived in northern Manhattan, New York, 62% had carotid plaque thickness of 0.9 mm by sonography, and 39% had minimal or no (0.0 to 0.9 mm) carotid plaque (25). In those with subclinical disease, mean plaque thickness was 1.0 mm for whites, 1.7 mm for blacks, and 1.2 mm for Hispanics (25). In a population-based study of patients in Texas with TIA, 10% of those undergoing carotid ultrasonography had >70% stenosis of at least 1 internal carotid artery (26). Even subclinical carotid disease is associated with future stroke, as in the ARIC study, in which the IMT of the carotid artery walls of people 45 to 64 years old without ulcerated or hemodynamically significant plaque at baseline predicted stroke (16).

Carotid stenosis or occlusion as a cause of stroke has been more difficult to determine from population studies. For the NOMASS population, cerebral infarction attributed to ECVD was defined as clinical stroke with evidence of infarction on brain imaging associated with >60% stenosis or occlusion of an extracranial carotid or vertebral artery documented by noninvasive imaging or angiography. Between 1993 and 1997, the incidence of cerebral infarction attributable to ECVD was 17 per 100,000 (95% CI 8 to 26) for blacks, 9 per 100,000 (95% CI 5 to 13) for Hispanics, and 5 per 100,000 (95% CI 2 to 8) for whites (11). Approximately 7% of all first ischemic strokes were associated with extracranial carotid stenosis of 60% or more (11). From a Mayo Clinic study of the population of Rochester, Minn, for the period 1985 to 1989, 18% of all first ischemic strokes were attributed to extracranial or intracranial large-vessel disease (27), but the report did not separately classify those with extracranial or intracranial vascular disease.

Beyond the impact on individual patients, ECVD and its consequences create a substantial social and economic burden in the United States and are increasingly recognized as a major drain on health resources worldwide. Stroke is the most frequent neurological diagnosis that requires hospitalization (21), amounting to more than half a million hospitalizations annually (18). From the 1970s to the latest figures available, the number of noninstitutionalized stroke survivors in the United States increased from an estimated 1.5 million to 6 million (19). Survivors face risks of recurrent stroke as high as 4% to 15% within a year after incident stroke and 25% by 5 years (20,28). The direct and indirect cost for acute and convalescent care for stroke victims in the United States was estimated at $68.9 billion in 2009. The economic burden and lifetime cost vary considerably by type of stroke, averaging $103,576 across all stroke types, with costs associated with first strokes estimated as $228,030 for subarachnoid hemorrhage, $123,565 for intracerebral hemorrhage, and $90,981 for ischemic stroke (22).

2. Atherosclerotic Disease of the Extracranial Carotid and Vertebral Arteries

The pathobiology of carotid and vertebral artery atherosclerosis is similar in most respects to atherosclerosis that affects other arteries. Early lesion development is initiated by intimal accumulation of lipoprotein particles. These particles undergo oxidative modification and elaborate cytokines that cause expression of adhesion molecules and chemoattractants that facilitate uptake and migration of monocytes

into the artery wall. These monocytes become lipid-laden macrophages, or foam cells, as a consequence of accumulation of modified lipoproteins and subsequently release additional cytokines, oxidants, and matrix metalloproteinases. Smooth muscle cells migrate from the media to the intima, proliferate, and elaborate extracellular matrix as extracellular lipid accumulates in a central core surrounded by a layer of connective tissue, the fibrous cap, which in many advanced plaques becomes calcified. Initially, the atherosclerotic lesion grows in an outward direction, a process designated "arterial remodeling." As the plaque continues to grow, however, it encroaches on the lumen and causes stenosis. Plaque disruption and thrombus formation contribute to progressive narrowing of the lumen and to clinical events. The mechanisms that account for plaque disruption in the extracranial carotid and vertebral arteries are similar to those proposed for the coronary arteries (29). These include rupture of the fibrous cap, superficial erosion, and erosion of a calcium nodule. Contact of blood elements, including platelets and coagulation proteins, with constituents of the atherosclerotic plaque, such as collagen and tissue factor, promotes thrombosis. In addition, intraplaque hemorrhage caused by friable microvessels at the base of the plaque may contribute to plaque expansion.

Atherosclerotic plaques often develop at flow dividers and branch points, where there is both turbulence and shifts in shear stress. As such, there is a predilection for plaque formation at the bifurcation of the common carotid artery into the internal and external carotid arteries. Stroke and transient cerebrovascular ischemia may arise as a consequence of several mechanisms that originate in the extracranial cerebral arteries, including 1) artery-to-artery embolism of thrombus formed on an atherosclerotic plaque, 2) atheroembolism of cholesterol crystals or other atheromatous debris (e.g., Hollenhorst plaque), 3) acute thrombotic occlusion of an extracranial artery resulting from plaque rupture, 4) structural disintegration of the arterial wall resulting from dissection or subintimal hematoma, and 5) reduced cerebral perfusion resulting from critical stenosis or occlusion caused by progressive plaque growth. For neurological symptoms to result from arterial stenosis or occlusion, the intracranial collateral circulation must also be deficient, and this represents the cause of a relatively small proportion of clinical ischemic events.

2.1. Evaluation of Asymptomatic Patients at Risk of Extracranial Carotid Artery Disease

2.1.1. 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 PAD, coronary artery disease (CAD), 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*)

Although there is evidence from randomized trials that referred patients with asymptomatic hemodynamically significant carotid stenosis benefit from therapeutic intervention, no screening program aimed at identifying people with asymptomatic carotid stenosis has been shown to reduce their risk of stroke. Hence, there is no consensus on which patients should undergo screening tests for detection of carotid disease. Auscultation of the cervical arteries for bruits is a standard part of the physical examination of adults, but detection of a bruit correlates more closely with systemic atherosclerosis than with significant carotid stenosis (30). In the largest reported study of screening in asymptomatic patients, the prevalence of carotid stenosis >35% in those without a bruit was 6.6%, and the prevalence of >75% carotid stenosis was 1.2% (31). Because the

sensitivity of detection of a carotid bruit and the positive predictive value for hemodynamically significant carotid stenosis are relatively low, however, ultrasonography may be appropriate in some high-risk asymptomatic patients irrespective of findings on auscultation (32).

Because carotid ultrasonography is a widely available technology associated with negligible risk and discomfort, the issue becomes one of appropriate resource utilization. Lacking data from health economic studies to support mass screening of the general adult population, our recommendations are based on consensus and driven by awareness that resources are limited and as a result favor targeted screening of patients at greatest risk of developing carotid stenosis. Additional pertinent considerations are that the stroke reduction that accrues from screening asymptomatic patients and treating them with specific interventions is unknown, that the benefit is limited by the low overall prevalence of disease amenable to specific therapy in asymptomatic patients, and that revascularization procedures are associated with tangible risks.

2.1.2. Recommendations From Other Panels

The AHA/ASA guideline for primary prevention of ischemic stroke recommended against screening the general population for asymptomatic carotid stenosis on the basis of concerns about lack of cost-effectiveness, the potential adverse impact of false-positive and false-negative results in the general population, and the small absolute benefit of intervention (33). In addition, the American Society of Neuroimaging recommended against the screening of unselected populations but advised the screening of adults older than 65 years of age who have 3 or more cardiovascular risk factors (34). The ACCF/SCAI/SVMB/SIR/ASITN Clinical Expert Consensus Panel on Carotid Stenting recommended the screening of asymptomatic patients with carotid bruits who are potential candidates for carotid revascularization and the screening of those in whom coronary artery bypass graft (CABG) surgery is planned (35). The US Preventive Services Task Force recommended against screening for asymptomatic carotid artery stenosis in the general adult population (36).

2.2. Extracranial Cerebrovascular Disease as a Marker of Systemic Atherosclerosis

Because atherosclerosis is a systemic disease, patients with extracranial carotid or vertebral atherosclerosis frequently have atherosclerosis elsewhere, notably in the aorta, coronary arteries, and peripheral arteries (37–40). Patients with ECVD are at increased risk of MI and death attributable to cardiac disease (41–46), such that many patients with carotid stenosis face a greater risk of death caused by MI than of stroke (47,48). Coronary atherosclerosis is prevalent in patients with fatal stroke of many origins and occurs more frequently in those with carotid or vertebral artery atherosclerosis. In 803 autopsies of consecutive patients with neurological disease (49), the prevalences of atherosclerotic coronary plaque, >50% coronary artery stenosis, and pathological evidence of MI were 72%, 38%, and 41%, respectively, among the 341 patients with a history of stroke compared with 27%, 10%, and 13%, respectively, of the 462 patients with neurological diseases other than stroke (all $p<0.001$). Two thirds of the cases of MI found at autopsy had been clinically silent. The frequency of coronary atherosclerosis and MI was similar in patients with various stroke subtypes, but the severity of coronary atherosclerosis was related to the severity of ECVD (adjusted linear p for trend <0.005). 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. A more detailed description of risk factors and their management appears in Section 6.

The IMT of the carotid artery wall, a measurement obtained by carotid ultrasound, is also a marker of systemic atherosclerosis. Carotid IMT is a marker of risk for coronary events and stroke in patients without clinical cardiovascular disease (50,51), although in the Framingham Heart Study coefficients of correlation between carotid IMT and coronary calcification were typically <0.3 (52–55). Data from the ARIC study suggest that carotid IMT data may enhance cardiovascular risk assessment, particularly among individuals classified as being at intermediate risk by use of conventional risk factors (56,57). In epidemiological studies (58–62), IMT progresses at an average rate of ≤0.03 mm per year. Progression can be retarded by 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor drugs (statins), the combination of colestipol and niacin, and risk factor modifications (58–62). The use of IMT measurements to guide treatment based on outcomes of specific interventions for patients has not been documented.

Measurement of IMT has not yet become a routine or certified element of carotid ultrasound examinations in the United States and is not currently recognized as a screening method for atherosclerotic risk (63,64). There is no indication for measurement of IMT in patients with carotid plaque or stenosis. For specific recommendations for screening for atherosclerosis by measurement of carotid IMT in asymptomatic patients, the reader is referred to the 2010 ACCF/AHA Guidelines for Assessment of Cardiovascular Risk in Asymptomatic Adults (65).

2.2.1. Screening for Coronary or Lower-Extremity Peripheral Arterial Disease in Patients With Atherosclerosis of the Carotid or Vertebral Arteries

Whether symptomatic or asymptomatic, individuals with carotid atherosclerosis are more likely to have atherosclerosis that involves other vascular beds, although the associations are quantitatively modest. Specific recommendations for screening for CAD and PAD in patients with ECVD are beyond the scope of this document, and the reader is referred to the ACC/AHA 2005 Guidelines for the Man-

agement of Patients with Peripheral Arterial Disease (66) and the AHA/ASA scientific statement on coronary risk evaluation in patients with TIA and ischemic stroke (67).

3. Clinical Presentation

3.1. Natural History of Atherosclerotic Carotid Artery Disease

Extracranial atherosclerotic disease accounts for up to 15% to 20% of all ischemic strokes (68,69). The progression of carotid atherosclerosis may be similar to that in other arterial beds, but the relationship between plaque growth, increasing stenosis, and TIA or stroke is complex. There was a clear correlation between the degree of stenosis and the risk of stroke in the NASCET (North American Symptomatic Carotid Endarterectomy Trial) (70), but the relationship between stroke risk and severity of stenosis in asymptomatic patients was less clear in other studies. After 18 months of medical therapy without revascularization, stroke rates were 19% in those with 70% to 79% initial stenosis, 28% in those with 80% to 89% stenosis, and 33% in the 90% to 99% stenosis group, and the risk diminished with near-occlusion (70). In ACAS (Asymptomatic Carotid Atherosclerosis Study) and ACST (Asymptomatic Carotid Surgery Trial), asymptomatic patients with 60% to 80% stenosis had higher stroke rates than those with more severe stenosis (71,72). However, medical therapy in the era during which these trials were conducted was considerably limited compared with today's standards.

The natural history of asymptomatic carotid disease in patients with cervical bruits or other risk factors for stroke has been reported in case series, population-based studies, and observational arms of randomized clinical trials. In the Framingham Heart Study, the calculated age-adjusted incidence of stroke in patients with cervical bruits was 2.6 times that of those without bruits (15). A number of early natural history studies showing the incidence of stroke in asymptomatic patients with >75% stenosis are summarized in Table 2 (section on observational studies); the aggregate annual stroke rate exceeded 5% (73).

Table 2 (section on randomized trial cohorts) also summarizes event rates in randomized trial cohorts. ACAS demonstrated a rate of 11% during a 5-year period for ipsilateral stroke or death in the group managed with medical therapy, which consisted essentially of aspirin alone (neither the statin class of lipid-lowering drugs nor inhibitors of the renin-angiotensin system were conventionally used) (74). In ACST, the risk of ipsilateral stroke or death during a 5-year period in patients with ≥70% stenosis randomized to initial medical therapy was 4.7% (75). The difference in rates suggests that medical therapy has been associated with diminishing event rates over time and that asymptomatic disease may follow a relatively benign course in many individuals. Several other randomized trials have also documented a low rate of neurological events in asymptomatic patients with moderate to severe internal carotid artery stenosis (76,77).

3.2. Characterization of Atherosclerotic Lesions in the Extracranial Carotid Arteries

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. Among asymptomatic patients with carotid bruit in the Framingham Heart Study cohort, fewer than half of the stroke events affected the cerebral hemisphere ipsilateral to the bruit and carotid stenosis (15).

Investigations of the relationship between cerebral symptoms and morphological characteristics of plaque defined by ultrasound found an association of clinical cerebral ischemic events with ulceration, echolucency, intraplaque hemorrhage, and high lipid content (86,87). Molecular and cellular processes responsible for plaque composition (86–88) may be more important than the degree of stenosis in determining the risk of subsequent TIA and stroke, but the degree of carotid stenosis estimated by ultrasonography remains the main determinant of disease severity and forms the basis for most clinical decision making. Quantitative analysis of duplex ultrasound images correlates with histological findings of intraplaque hemorrhage, fibromuscular hyperplasia, calcium, and lipid composition, and the feasibility of identifying symptomatic and unstable plaques on the basis of these features has been described (87). Computer-generated measurements of carotid plaque echogenicity and surface characteristics (smooth, irregular, or ulcerated) have been performed on images obtained from patients with symptomatic or asymptomatic ipsilateral cerebral infarction, but the prognostic value of these features has not been established (89–92). Hypoechoic plaques are associated with subcortical and cortical cerebral infarcts of suspected embolic origin, and hyperechoic plaques are associated with diffuse white matter infarcts of presumed hemodynamic origin (including lacunar and basal ganglia infarctions due to proximal arterial and distal intracranial vascular disease) (93).

Contrast-enhanced magnetic resonance imaging (MRI) at 1.5- and 3.0-Tesla field strengths, intravascular MRI, and computed tomography (CT) have also been used to characterize carotid atherosclerotic plaques. Thin or ruptured fibrous caps, intraplaque hemorrhage, relatively large lipid-rich or necrotic plaque cores, and overall plaque thickness have been associated with subsequent ischemic brain events in preliminary studies of asymptomatic patients with 50% to 79% carotid stenosis (94).

Metabolic activity in the vessel wall surrounding carotid plaques can be detected by positron emission tomography (PET) (95). Carotid plaques of symptomatic patients with stroke demonstrate infiltration of the fibrous cap by inflammatory cells including monocytes, macrophages, and lymphocytes (96,97). Increased uptake of ^{18}F-fluorodeoxyglucose measured by PET imaging is believed to reflect inflammation (98,99).

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							
Hertzer et al. (78)	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. (79)	168	Asymptomatic	≥60	≥12 mo	Multiple, including antiplatelet, statins, exercise, Mediterranean diet, ACE inhibitors	Stroke	3.8, or 1.3 annualized
Marquardt et al. (80)	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. (81)	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. (82)	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 (83)	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 (84)	659	Symptomatic	≥70	2 y	Aspirin	Ipsilateral stroke	26.0 over 2 y or annualized 13.0 for 1 y†
VA 309 (85)	189	Symptomatic	>50	1 y	Aspirin	Ipsilateral stroke or TIA or surgical death	19.4 over 11.9~12 mo
NASCET (20)	858	Symptomatic	50–69	5 y	Antiplatelet (usually aspirin)	Ipsilateral stroke	22.2 over 5 y or annualized 4.44 for 1 y‡
NASCET (20)	1,368	Symptomatic	≤50	5 y	Antiplatelet (usually aspirin)	Ipsilateral stroke	18.7 over 5 y or annualized 3.74 for 1 y‡
ACAS (74)	1,662	Asymptomatic	>60	5 y	Aspirin	Ipsilateral stroke, surgical death	11.0 over 5 y or annualized 2.2 for 1 y§
ACST (75)	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 (76)	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. (35).

Macrophage activity quantified by PET (100) and neovascular angiogenesis assessed by MRI have been observed in experimental models (101). Biomarkers such as C-reactive protein and certain matrix metalloproteinases with the potential to identify carotid plaque instability have also been investigated (102–104), but the reliability of biomarkers in predicting clinical events has not been established. Several studies have shown that plaque composition is modified by treatment with statins (105–109). Despite these advances in understanding the pathophysiology of atherosclerotic plaque, the utility of mor-

phological, pathological, and biochemical features in predicting the occurrence of TIA, stroke, or other symptomatic manifestations of ECVD has not been established clearly by prospective studies.

3.3. Symptoms and Signs of Transient Ischemic Attack and Ischemic Stroke

TIA is conventionally defined as a syndrome of acute neurological dysfunction referable to the distribution of a single brain artery and characterized by symptoms that last <24 hours. With advances in brain imaging, many patients with symptoms briefer than 24 hours are found to have cerebral infarction. A revised definition has been developed specifying symptoms that last <1 hour, and the typical duration of symptoms is <15 minutes (110), but this change has not been accepted universally, and the 24-hour threshold is still the standard definition (111). In patients with acute ischemic stroke, symptoms and signs of neurological deficit persist longer than 24 hours.

Symptoms and signs that result from ischemia or infarction in the distribution of the right internal carotid artery or middle cerebral artery include but are not limited to left-sided weakness, left-sided paresthesia or sensory loss, left-sided neglect, abnormal visual-spatial ability, monocular blindness that affects the right eye, and right homonymous hemianopsia (visual loss that involves the right visual field). Ischemia or infarction in the distribution of the left internal carotid artery or middle cerebral artery may cause right-sided weakness, right-sided paresthesia or sensory loss, aphasia, and monocular blindness that affects the left eye or left visual field. Aphasia may be a sign of ischemia or infarction in the distribution of the right internal carotid artery in ambidextrous or left-handed individuals. Symptoms and signs that result from ischemia or infarction in the vertebrobasilar system include but are not limited to ataxia, cranial nerve deficits, visual field loss, dizziness, imbalance, and incoordination.

3.3.1. Public Awareness of Stroke Risk Factors and Warning Indicators

The AHA and ASA have developed educational materials for patients that emphasize recognition of the symptoms and signs that warn of TIA and stroke and that encourage those who observe these symptoms to seek immediate medical attention, pointing out that rapid action could limit disability and prevent death.

The joint Stroke Collaborative campaign of the AAN, the ACEP, and the AHA/ASA seeks to increase stroke symptom awareness among Americans (see http://www.giveme5forstroke.org). A report from the region of Cincinnati, Ohio (112), found significant improvement in public knowledge of stroke warning signs as promulgated by the ASA, National Stroke Association, and the National Institute of Neurological Disorders and Stroke between 1995 and 2000 but less improvement in knowledge of stroke risk factors during the same period.

Patients with acute stroke face disease-specific causes of delay in seeking medical treatment. In 1 study, 23% had dysphasia, 77% had an upper-limb motor deficit, and 19% had an altered level of consciousness (113). In addition to clinical characteristics, demographic, cognitive, perceptual, social, emotional, and behavioral factors affect the prehospital delay in patients with ischemic stroke symptoms (114). A gender analysis of the interval from symptom onset to hospital arrival (115) found that nearly 4 times as many men and 5 times as many women exceeded the goal of <3 hours than those who did not.

4. Clinical Assessment of Patients With Focal Cerebral Ischemic Symptoms

4.1. Acute Ischemic Stroke

The immediate management of a patient presenting with a suspected acute focal neurological syndrome should follow published guidelines for emergency stroke care (2). Once the diagnosis of acute ischemic stroke is established, the patient has been stabilized, thrombolytic therapy has been administered to an eligible patient, and initial preventive therapy has been implemented, further evaluation is directed toward establishing the vascular territory involved and the cause and pathophysiology of the event (2,111,116,117). Risk stratification and secondary prevention are important for all patients.

4.2. Transient Ischemic Attack

TIA is an important predictor of stroke; the risk is highest in the first week, as high as 13% in the first 90 days after the initial event, and up to 30% within 5 years (26,118–124). On the basis of the conventional definition, an estimated 240,000 TIAs are diagnosed annually in the United States, and the number of undiagnosed cases is likely considerably greater (118). Early recognition of TIA, identification of patients at risk, and risk factor modification (125) are important stroke prevention measures.

In patients who display ischemic symptoms in the territory of a carotid artery that has high-grade stenosis, surgical intervention reduces the risk of major neurological events (20,75). The benefit of CEA in preventing stroke is greatly diminished beyond 2 weeks after the onset of symptoms, in large part because the risk of recurrent ischemic events is highest in this early period. After 4 weeks in women and 12 weeks in men, the benefit of surgery in these symptomatic patients is no more than that observed with surgery for asymptomatic patients, and in some cases, surgery may be harmful (126). Interventional decisions for a particular patient should be based on balancing the risks of revascularization against the risk of worsening symptoms and disability with medical therapy alone.

4.3. Amaurosis Fugax

Transient monocular blindness (amaurosis fugax) is caused by temporary reduction of blood flow to an eye with sudden

loss of vision, often described as a shade drawn upward or downward over the field of view (127). The most common cause is atherosclerosis of the ipsilateral internal carotid artery, but other causes have been associated with this syndrome as well. The mechanism may involve ophthalmic artery embolism, observed as fibrin, cholesterol crystals (Hollenhorst plaques), fat, or material arising from fibrocalcific degeneration of the aortic or mitral valves. Causes of transient monocular blindness follow:

- Carotid artery stenosis or occlusion
- Atherosclerosis
- Dissection
- Arteritis
- Radiation-induced arteriopathy
- Arterial embolism
- Cardiogenic embolism
- Atheroembolism
- Hypotension
- Intracranial hypertension
- Glaucoma
- Migraine
- Vasospastic or occlusive disease of the ophthalmic artery

The risk of stroke was lower among patients with transient monocular blindness than among those with hemispheric TIA in the NASCET cohort (128). The 3-year risk of stroke with medical treatment alone in patients with transient monocular blindness was related to the number of stroke risk factors (hypertension, hypercholesterolemia, diabetes, and cigarette smoking) and was specifically 1.8% in those with 0 or 1 risk factor, 12.3% in those with 2 risk factors, and 24.2% in those with 3 or 4 risk factors. In addition to the risk of stroke, permanent blindness may occur in the affected eye as a result of the initial or subsequent episodes (128–130).

4.4. Cerebral Ischemia Due to Intracranial Arterial Stenosis and Occlusion

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. The diagnosis and management of these disorders are outside the scope of this guideline, but evaluation of the intracranial vasculature may be important in some patients with ECVD to exclude high-grade tandem lesions that have implications for clinical management.

4.5. Atherosclerotic Disease of the Aortic Arch as a Cause of Cerebral Ischemia

Atheromatous disease of the aortic arch is an independent risk factor for ischemic stroke (131), but the diagnosis and management of this disorder are outside the scope of this guideline. See the 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM Guidelines for the Diagnosis and Management of Patients With Thoracic Aortic Disease (132).

4.6. Atypical Clinical Presentations and Neurological Symptoms Bearing an Uncertain Relationship to Extracranial Carotid and Vertebral Artery Disease

Most studies of the natural history and treatment of TIA have included patients who experienced focal transient ischemic events. The significance of nonfocal neurological events, including transient global amnesia, acute confusion, syncope, isolated vertigo, nonrotational dizziness, bilateral weakness, or paresthesias, is less well studied. Brief, stereotyped, repetitive symptoms suggestive of transient cerebral dysfunction raise the possibility of partial seizure, and electroencephalography may be useful in such cases. When symptoms are purely sensory (numbness, pain, or paresthesia), then radiculopathy, neuropathy, microvascular cerebral or spinal pathology, or lacunar stroke should be considered. A small proportion of patients with critical (>70% and usually >90%) carotid stenosis present with memory, speech, and hearing difficulty related to hypoperfusion of the dominant cerebral hemisphere.

In a study from the Netherlands, patients with transient neurological attacks of either focal or nonfocal neurological symptoms faced an increased risk of stroke compared with those without symptoms (HR 2.14 and 1.56, respectively) (133). The pathophysiological mechanism responsible for transient global amnesia has not been elucidated, and it is not clear whether, in fact, this syndrome is related to ECVD at all (134). Vertigo (in contrast to nonrotational dizziness) was associated with a risk of subsequent stroke in a population-based study of patients 65 years of age or older, but a direct causative relationship to ECVD has not been established (135).

5. Diagnosis and Testing

5.1. 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 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*)

Carotid ultrasonography, CTA, and MRA can provide the information needed to guide the choice of medical, endovascular, or surgical treatment in most cases. The severity of stenosis is defined according to angiographic criteria by the method used in NASCET (70), but it corresponds as well to assessment by sonography (136) and other accepted methods of measurement such as CTA and MRA, although the latter may overestimate the severity of stenosis. It is important to bear in mind that 75% diameter stenosis of a vessel corresponds to >90% reduction in the cross-sectional area of the lumen.

Catheter-based angiography may be necessary in some cases for definitive diagnosis or to resolve discordance between noninvasive imaging findings. These advanced imaging techniques generally do not replace carotid duplex ultrasonography for initial evaluation of suspected carotid stenosis in those with symptomatic manifestations of ischemia (or in asymptomatic individuals at risk), either as a solitary diagnostic method or as a confirmatory test to assess the severity of known stenosis. Indications for carotid duplex sonography follow (137,138):

- Cervical bruit in an asymptomatic patient
- Follow-up of known stenosis (>20%) in asymptomatic individuals
- Vascular assessment in a patient with multiple risk factors for atherosclerosis
- Stroke risk assessment in a patient with CAD or PAD
- Amaurosis fugax
- Hemispheric TIA
- Stroke in a candidate for carotid revascularization
- Follow-up after a carotid revascularization procedure
- Intraoperative assessment during CEA or stenting

Each imaging modality has strengths and weaknesses, and because the quality of images produced by each noninvasive modality differs from one institution to another, no single modality can be recommended as uniformly superior. In general, correlation of findings obtained by multiple modalities should be part of a program of quality assurance in every laboratory and institution. It is most important that data obtained in patients undergoing catheter-based angiography for evaluation of ECVD be compared with noninvasive imaging findings to assess and improve the accuracy of noninvasive vascular testing. The following discussion pertains mainly to evaluation of the cervical carotid arteries for atherosclerotic disease. There is a paucity of literature addressing evaluation of the vertebral arteries and of both the carotid and vertebral arteries for nonatherosclerotic disorders such as traumatic injury (139–141). The relative roles of noninvasive imaging and conventional angiography for these indications have not been defined.

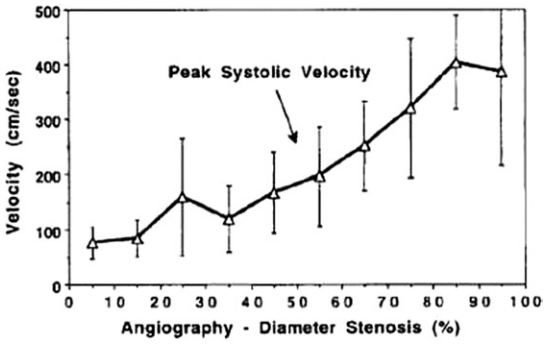

Figure 2. Peak Systolic Flow Velocity as a Measure of Internal Carotid Stenosis

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. (142).

Accurate assessment of the severity of arterial stenosis is essential to the selection of appropriate patients for surgical or endovascular intervention, and imaging of the extracranial carotid arteries should be performed whenever cerebral ischemia is a suspected mechanism of neurological symptoms in a viable patient. Choosing among the available vascular imaging modalities, deciding when to combine multiple modalities, and judicious application of angiography are challenging aspects of evaluation in patients with ECVD. Imaging of the aortic arch, proximal cervical arteries, and the artery distal to the site of stenosis is required before endovascular therapy to ascertain the feasibility of intervention. Less anatomic information is necessary before surgical intervention at the carotid bifurcation because the procedure entails direct exposure of the target artery.

5.2. Carotid Duplex Ultrasonography

Duplex ultrasound modalities combine 2-dimensional real-time imaging with Doppler flow analysis to evaluate vessels of interest (typically the cervical portions of the common, internal, and external carotid arteries) and measure blood flow velocity. The method does not directly measure the diameter of the artery or stenotic lesion. Instead, blood flow velocity is used as an indicator of the severity of stenosis (Figure 2). Several schemes have been developed for assessment of carotid stenosis by duplex ultrasound (136,143,144). 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 appear to correlate best with angiographically determined arterial stenosis.

Ultrasonography is an accurate method for measuring the severity of stenosis, with the caveat that subtotal arterial occlusion may sometimes be mistaken for total occlusion. 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, although the correlation with angiographic stenosis is approximate and varies among laboratories. According to a consensus document (136), when ultrasound is used, 50% to 69% stenosis of the internal carotid artery is associated with sonographically visible plaque and a peak systolic velocity of 125 to 230 cm/s in this vessel. Additional criteria include a ratio of internal to common carotid artery peak systolic velocities between 2 and 4 and an end-diastolic velocity of 40 to 100 cm/s in the internal carotid artery. Nonocclusive stenosis >70% in the internal carotid artery is associated with a peak systolic velocity >230 cm/s in this vessel and plaque and luminal narrowing visualized by gray-scale and color Doppler sonography. Additional criteria include a ratio of internal to common carotid artery peak systolic velocity >4 and end-diastolic velocity >100 cm/s in the internal carotid artery. The considerable overlap of velocities associated with stenosis of varying severities may make it difficult to distinguish 70% stenosis from less severe stenosis and supports the use of corroborating vascular imaging methods for more accurate assessment in equivocal or uncertain cases. The ratio of flow velocities in the internal and common carotid arteries may help distinguish between increased compensatory flow through collaterals and true contralateral internal carotid stenosis or occlusion.

Among the pitfalls in velocity-based estimation of internal carotid artery stenosis are higher velocities in women than in men and elevated velocities in the presence of contralateral carotid artery occlusion (145,146). Severe arterial tortuosity, high carotid bifurcation, obesity, and extensive vascular calcification reduce the accuracy of ultrasonography. Furthermore, in situ carotid stents decrease compliance of the vessel wall and can accelerate flow velocity (147). Ultrasonography may fail to differentiate between subtotal and complete arterial occlusion, although the distinction is of critical clinical importance. In such cases, intravenous administration of sonographic contrast agents may improve diagnostic accuracy (148,149), but the safety of these agents has been questioned (150). In addition to these technical factors, variability in operator expertise greatly affects the quality of examinations and reliability of results (Table 3) (151–153). Despite these limitations, ultrasonography performed by well-trained, experienced technologists provides accurate and relatively inexpensive assessment of the cervical carotid arteries (151–153,162–164). The technique is truly noninvasive and does not involve venipuncture or exposure to ionizing radiation or potentially nephrotoxic contrast material. Although results vary greatly between laboratories and operators, the sensitivity and specificity for detection or exclusion of ≥70% stenosis of the internal carotid artery are 85% to 90% compared with conventional angiography (Table 4) (141,165,166).

Every vascular laboratory should have a quality assurance program that compares estimates of stenosis by color Doppler ultrasound imaging with angiographic measurements.

Table 3. Variability of Doppler Ultrasonography

Author/Type of Study (Reference)	Study Parameters	Conclusions
Variability between different centers		
Perkins et al./survey (154)	Questionnaire on carotid duplex practice; 73 vascular laboratories	Diversity in diagnostic criteria; diversity in method of stenosis grading
Robless et al./survey (155)	Questionnaire on carotid duplex practice; 71 vascular laboratories	Diversity in method of stenosis grading; diversity concerning the Doppler angle used
Alexandrov et al./prospective (156)	2 Vascular laboratories in 2 hospitals; same equipment	A definite velocity criterion does not have the same validity and predictive value to grade carotid stenosis at different laboratories
Schwartz et al./prospective (157)	10 Systems, 9 hospitals	Predictive ability of different parameters to quantify stenosis was different from 1 device to another
Fillinger et al./consecutive (158)	2 Vascular laboratories, 4 systems, 360 bifurcations	Most accurate duplex criteria for a ≥60% ICA stenosis were machine specific
Howard (151)	37 Centers, 63 Doppler devices	Performance of Doppler ultrasound was heterogeneous between devices
Howard/prospective (100)	19 Centers, 30 Doppler devices	Performance relates to the device-sonographer-reader system. Cut point for the peak systolic flow to ensure a positive predictive value of 90% in predicting a ≥60% stenosis ranged from 151 to 390 cm/s or from 5,400 to 11,250 Hz
Interequipment variability		
Ranke/prospective (159)	20 ICA, 10 patients, 2 different systems, same observer	Intrastenotic peak flow velocity values were significantly higher with 1 system
Wolstenhulme/prospective (160)	2 Systems, 43 patients, same observer	Limits of agreements (within 95% of different lie) between systems: −0.47 to 0.45 m/s
Daigle/in vitro (161)	6 Systems, velocity-calibrated string flow phantom	Five of 6 systems: overestimation of all peak velocities compared with the calibrated string flow phantom
Interobserver and intraobserver variability		
Ranke/prospective (159)	20 ICA, 11 patients, same system, 2 observers	Interobserver variation expressed as 95% CI for predicted stenosis between 2 observers was 13.6% with peak systolic velocity and 15.4% with mean velocity ratio
Wolstenhulme/prospective (160)	20 Patients, 2 systems, 1 observer	Intraobserver reproducibility coefficient for both machines was 0.48 cm/s

CI indicates confidence interval; and ICA, internal carotid artery.
Reprinted with permission from Long et al. (167).

The use of appropriately credentialed sonographers and adherence to stringent quality assurance programs, as required for accreditation by the Intersocietal Commission for the Accreditation of Vascular Laboratories, have been associated with superior results (Standards for Accreditation in Noninvasive Vascular Testing, Part II, Vascular Laboratory Operations: Extracranial Cerebrovascular Testing; available at http://www.icavl.org). Characterization of plaque morphology is possible in some cases and may have therapeutic implications (181), but this is not yet widely used in practice. Future technological advances may bring about less operator-dependent 3-dimensional, high-resolution arterial imaging.

5.3. Magnetic Resonance Angiography

MRA can generate high-resolution noninvasive images of the cervical arteries. The radiofrequency signal characteristics of flowing blood are sufficiently distinct from surrounding soft tissue to allow imaging of the arterial lumen (182). However, there is an increasing shift to contrast-enhanced MRA to amplify the relative signal intensity of flowing blood compared with surrounding tissues and allow more detailed evaluation of the cervical arteries (183–188). Slowly flowing blood is also better imaged with contrast-enhanced MRA, which is sensitive to both the velocity and direction of blood flow. Despite artifacts and other limitations, high-quality MRA can provide accurate anatomic imaging of the aortic arch and the cervical and cerebral arteries (167) and may be used to plan revascularization without exposure to ionizing radiation.

Technological advancements have reduced image acquisition time, decreased respiratory and other motion-based artifacts, and greatly improved the quality of MRA to rival that of conventional angiography for many applications, including evaluation of patients with ECVD. Higher-field-strength systems, such as the 3-Tesla apparatus, more powerful gradients, and sophisticated software are associated with better MRA image quality than systems with lower field strengths. Although popular with patients, low-field-strength, open MRI systems are rarely capable of producing high-quality MRA. Correlations with angiogra-

Table 4. Sensitivity and Specificity of Duplex Ultrasonography as a Function of Degree of Carotid Stenosis

Study, Year (Reference)	Degree of Stenosis	Carotids, n	Sensitivity, %	Specificity, %
Serfaty et al., 2000 (168)	Occlusion	46	100	90
Hood et al., 1996 (169)	Occlusion	457	100	99
White et al., 1994 (170)	Occlusion	120	80	100
Turnipseed et al., 1993 (171)	Occlusion	34	100	100
Riles et al., 1992 (172)	Occlusion	75	100	100
Riles et al., 1992 (172)	Stenosis ≥80%	75	85	80
Johnson et al., 2000 (173)	Stenosis ≥70%	76	65	95
Serfaty et al., 2000 (168)	Stenosis ≥70%	46	64	97
Huston et al., 1998 (174)	Stenosis ≥70%	100	97	75
Link et al., 1997 (175)	Stenosis ≥70%	56	87	98
Hood et al., 1996 (169)	Stenosis ≥70%	457	86	97
Bray et al., 1995 (176)	Stenosis ≥70%	128	85	96–97
Patel et al., 1995 (177)	Stenosis ≥70%	171	94	83
Turnipseed et al., 1993 (171)	Stenosis ≥70%	34	94	89
Bluth et al., 2000 (178)	Stenosis ≥60%	40	62	100
Jackson et al., 1998 (179)	Stenosis ≥60%	99	89	92
White et al., 1994 (170)	Stenosis ≥60%	120	73	88
Walters et al., 1993 (180)	Stenosis ≥60%	102	88	88
Serfaty et al., 2000 (168)	Stenosis ≥50%	46	94	83
Hood et al., 1996 (169)	Stenosis ≥50%	457	99.5	89
Bray et al., 1995 (176)	Stenosis ≥50%	128	87–95	96
Riles et al., 1992 (172)	Stenosis ≥50%	75	98	69

Modified from Long et al. (167).

phy suggest that high-quality MRA is associated with a sensitivity that ranges from 97% to 100% and a specificity that ranges from 82% to 96% (183–186,189), although these estimates may be subject to reporting bias.

Pitfalls in MRA evaluation of ECVD include overestimation of stenosis (more so with noncontrast examinations) and inability to discriminate between subtotal and complete arterial occlusion. More problematic is the inability to examine the substantial fraction of patients who have claustrophobia, extreme obesity, or incompatible implanted devices such as pacemakers or defibrillators, many of whom are at high risk for atherosclerotic ECVD. On the other hand, among the notable strengths of MRA relative to carotid ultrasound and CTA is its relative insensitivity to arterial calcification. Like sonography, MRI may be used to assess atheromatous plaque morphology (190,191), but the utility of this application in clinical practice requires further validation.

Gadolinium-based compounds used as magnetic resonance contrast agents are associated with a much lower incidence of nephrotoxicity and allergic reactions than the iodinated radiographic contrast materials used for CTA and conventional angiography. However, 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. This poorly understood disorder causes cutaneous sclerosis, subcutaneous edema, disabling joint contractures, and injury to internal organs (192).

5.4. Computed Tomographic Angiography

Multiplanar reconstructed CTA may be obtained from thin, contiguous axial images acquired after intravenous administration of radiographic contrast material. Rapid image acquisition and processing, continuous image acquisition ("spiral CT"), and multiple-detector systems have made high-resolution CTA clinically practical (193–199). Like MRA, CTA provides anatomic imaging from the aortic arch through the circle of Willis. Multiplanar reconstruction and analysis allows evaluation of even very tortuous vessels. Unlike ultrasonography or MRA, CTA provides direct imaging of the arterial lumen suitable for evaluation of stenosis. With severe stenosis, volume averaging affects the accuracy of measurement as the diameter of the residual vessel lumen approaches the resolution limit of the CT system.

Like MRA, CTA is undergoing rapid technological evolution. Increasing the number of detector rows facilitates faster, higher-resolution imaging and larger fields of view, and 16-, 32-, 64-, 256-, and 320-row detector and dual-source systems are in clinical use (200,201). Slower image acquisition by equipment with fewer detector rows allows the intravenous contrast bolus to traverse the arteries and enter the capillaries and veins before imaging is complete, degrading images by competing enhancement of these structures. Conversely, scanners with a greater number of detector rows offer faster acquisition during the arterial phase, reduce motion and respiratory artifacts, and lessen the volume of contrast required. Equipment, imaging protocols, and interpreter experience factor heavily into the

Table 5. Sensitivity and Specificity of Computed Tomographic Angiography as a Function of Degree of Carotid Stenosis

Study, Year (Reference)	Degree of Stenosis	Carotids, n	Sensitivity, %	Specificity, %
Anderson et al., 2000 (207)	Occlusion	80	69–100	98
Leclerc et al., 1999 (208)	Occlusion	44	100	100
Marcus et al., 1999 (209)	Occlusion	46	100	100
Verhoek et al., 1999 (210)	Occlusion	38	66–75	87–100
Magarelli et al., 1998 (211)	Occlusion	40	100	100
Link et al., 1997 (175)	Occlusion	56	100	100
Leclerc et al., 1995 (212)	Occlusion	39	100	100
Dillon et al., 1993 (213)	Occlusion	50	81–87.5	97–100
Schwartz et al., 1992 (214)	Occlusion	40	100	100
	Stenosis ≥80%	NA	NA	NA
Anderson et al., 2000 (207)	Stenosis ≥70%	80	67–77	84–92
Leclerc et al., 1999 (208)	Stenosis ≥70%	44	67–100	94–97
Marcus et al., 1999 (209)	Stenosis ≥70%	46	85–93	93–97
Verhoek et al., 1999 (210)	Stenosis ≥70%	38	80–100	95–100
Magarelli et al., 1998 (211)	Stenosis ≥70%	40	92	98.5
Link et al., 1997 (175)	Stenosis ≥70%	56	100	100
Leclerc et al., 1995 (212)	Stenosis ≥70%	39	87.5–100	96–100
Dillon et al., 1993 (213)	Stenosis ≥70%	50	81–82	94–95
Schwartz et al., 1992 (214)	Stenosis ≥70%	40	100	100
	Stenosis ≥60%	NA	NA	NA
Anderson et al., 2000 (207)	Stenosis ≥50%	80	85–90	82–91

NA indicates not available.
Modified from Long et al. (167).

accuracy of CTA (202–205), but in contemporary studies CTA has compared favorably with catheter angiography for evaluation of patients with ECVD, with 100% sensitivity and 63% specificity (95% CI 25% to 88%); the negative predictive value of CTA demonstrating <70% carotid artery stenosis was 100% (206) (Table 5). However, on the basis of a study that compared sonography, CTA, and MRA performed with and without administration of intravenous contrast material, the accuracy of noninvasive imaging for evaluation of cervical carotid artery stenosis may be generally overestimated in the literature (215).

The need for relatively high volumes of iodinated contrast media restricts the application of CTA to patients with adequate renal function. Although several strategies have been evaluated, discussion of medical therapies designed to reduce the risk of contrast-induced nephropathy is beyond the scope of this document. Faster imaging acquisition and a greater number of detector rows ameliorate this problem. 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 (216). Metallic dental implants or surgical clips in the neck generate artifacts that may obscure the cervical arteries. Obese or uncooperative (moving) patients are difficult to scan accurately, but pacemakers and defibrillators implanted in the chest are not impediments to CTA of the cervical arteries.

Other perfusion-based CT imaging techniques can provide additional information about cerebral blood flow and help determine the hemodynamic significance of stenotic lesions in the extracranial and intracranial arteries that supply the brain. As is the case with carotid duplex sonography, transcranial Doppler sonography, MRI, and radionuclide imaging to assess cerebral perfusion, there is no convincing evidence that available imaging methods reliably predict the risk of subsequent stroke, and there is no adequate foundation on which to recommend the broad application of these techniques for evaluation of patients with cervical arterial disease.

5.5. Catheter-Based Contrast Angiography

Conventional digital angiography remains 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 is dominant and has been used in most modern clinical trials. It is essential to specify the methodology used both in the evaluation of individual patients with ECVD and in the assessment of the accuracy of noninvasive imaging techniques. 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 (218–225). Substantially higher rates of stroke have been reported with diagnostic angiography in some series, most notably in ACAS (71), in which the incidence was 1.2% because of unusually frequent complications at a few centers. Complication rates in other studies have been substantially lower (226), and most authorities regard a stroke rate >1% with diagnostic angiography as unacceptable (227). Angiogra-

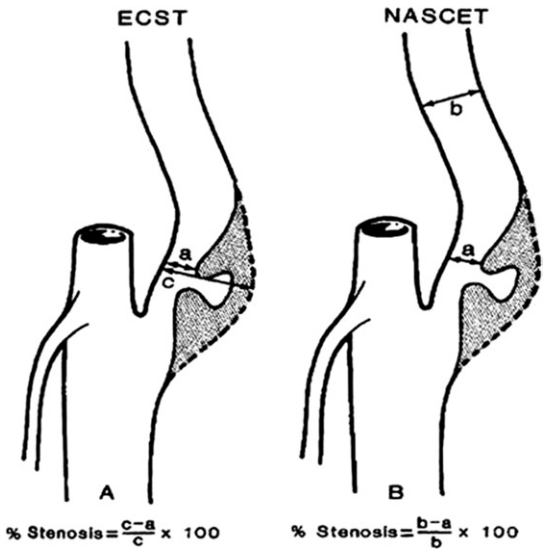

Figure 3. Angiographic Methods for Determining Carotid Stenosis Severity

ECST indicates European Carotid Surgery Trial; and NASCET, North American Symptomatic Carotid Endarterectomy Trial. Reprinted with permission from Osborn (217).

phy may be the preferred method for evaluation of ECVD when obesity, renal dysfunction, or indwelling ferromagnetic material renders CTA or MRA technically inadequate or impossible, and angiography is appropriate when noninvasive imaging studies produce 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 stent deployment.

5.6. Selection of Vascular Imaging Modalities for Individual Patients

Because of its widespread availability and relatively low cost, carotid duplex ultrasonography is favored for screening patients at moderate risk of disease. When this method does not suggest significant stenosis in a symptomatic patient, further anatomic assessment should be considered by use of other modalities capable of detecting more proximal or distal disease. If ultrasound imaging results are equivocal or indeterminate, MRA or CTA may be performed to confirm the extent of atherosclerotic disease and provide additional anatomic information. Conversely, patients with a high pretest probability of disease may be studied initially by MRA or CTA to more completely evaluate the cerebral vessels distal to the aortic arch, because sonographic imaging alone does not provide assessment of intrathoracic or intracranial lesions beyond the limited range of the ultrasound probe. Moreover, duplex ultrasonography may overestimate the severity of stenosis contralateral to internal carotid occlusion. This is an important consideration during the selection of asymptomatic patients for carotid revascularization, and in such cases, confirmation of the sonographic findings by another modality is recommended. Patients poorly suited to MRA because of claustrophobia, implanted pacemakers, or other factors may be evaluated by CTA, whereas those with extensive calcification should undergo MRA. In patients with renal insufficiency, for whom exposure to iodinated radiographic contrast stands as a relative contraindication to CTA, the relatively rare occurrence of nephrogenic systemic fibrosis has reduced the use of gadolinium contrast-enhanced MRA as well.

Because high-quality imaging potentially can be obtained by any of the recommended modalities, these are simply general suggestions. Given the variation in image quality and resource availability at one facility compared with another, other factors may govern the selection of the optimum testing modality for a particular patient. In general, though, conventional angiography is usually reserved for patients in whom adequate delineation of disease cannot be obtained by other methods, when noninvasive imaging studies have yielded discordant results, or for those with renal dysfunction in whom evaluation of a single vascular territory would limit exposure to contrast material. A patient presenting with a left hemispheric stroke or TIA, for instance, might best be evaluated by selective angiography of the left common carotid artery, which entails a small volume of contrast that is unlikely to exacerbate renal insufficiency while providing definitive images of the culprit vessel and its branches.

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

6.1. 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 (111,228–231). (*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*)

Hypertension increases the risk of stroke, and the relationship between blood pressure and stroke is continuous (232–234). For each 10-mm Hg increase in blood pressure, the risk of stroke increases by 30% to 45% (235). Conversely, antihypertensive therapy reduces the risk of stroke (230); meta-analysis of more than 40 trials and >188,000 patients found a 33% decreased risk of stroke for each 10-mm Hg reduction in systolic blood pressure to 115/75 mm Hg (230,231). A systematic review of 7 randomized trials found that antihypertensive therapy reduced the risk of recurrent stroke by 24% (228). The type of therapy appears less important than the response (230). For these reasons,

the AHA/ASA Guidelines for the Prevention of Stroke in Patients With Ischemic Stroke or Transient Ischemic Attack recommend antihypertensive treatment beyond the hyperacute period for patients who have experienced ischemic stroke or TIA (111).

Epidemiological studies, including the ARIC study (17), Cardiovascular Health Study (236), Framingham Heart Study (237), and MESA (Multi-Ethnic Study of Atherosclerosis) (238), among others, found an association between hypertension and the risk of developing carotid atherosclerosis (17,236,238–240). In the Framingham Heart Study, for example, there was a 2-fold greater risk of carotid stenosis >25% for each 20-mm Hg increase in systolic blood pressure (237). In SHEP (Systolic Hypertension in the Elderly Program), systolic blood pressure ≥160 mm Hg was the strongest independent predictor of carotid stenosis (241). Meta-analysis of 17 hypertension treatment trials involving approximately 50,000 patients found a 38% reduction in risk of stroke and 40% reduction in fatal stroke with antihypertensive therapy (242). These beneficial effects were shared among whites and blacks across a wide age range (242). In patients who had experienced ischemic stroke, administration of a combination of the angiotensin-converting enzyme inhibitor perindopril and a diuretic (indapamide) significantly reduced the risk of recurrent ischemic events compared with placebo among 6105 participants randomized in the PROGRESS (Preventing Strokes by Lowering Blood Pressure in Patients With Cerebral Ischemia) trial (RR reduction 28%, 95% CI 17% to 38%; $p<0.0001$) (229). The protective value of blood pressure lowering extends even to patients without hypertension, as demonstrated in the HOPE (Heart Outcomes Protection Evaluation) trial, in which patients with systemic atherosclerosis randomized to treatment with ramipril displayed a significantly lower risk of stroke than those given a placebo (RR 0.68; $p<0.001$) (243).

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. In some patients with severe carotid artery stenosis, impaired cerebrovascular reactivity may be associated with an increased risk of ipsilateral ischemic events (244). The Seventh Report of the Joint National Committee for the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) recommends blood pressure lowering for patients with ischemic heart disease or PAD but offers no specific recommendation for treatment of hypertension in patients with ECVD (245).

6.2. Cessation of Tobacco Smoking

6.2.1. 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 (246–250). (*Level of Evidence: B*)

Smoking increases the RR of ischemic stroke by 25% to 50% (247–253). Stroke risk decreases substantially within 5 years in those who quit smoking compared with continuing smokers (248,250). In large epidemiological studies, cigarette smoking has been associated with extracranial carotid artery IMT and the severity of carotid artery stenosis (23,254–257). In the ARIC study, current and past cigarette smoking, respectively, were associated with 50% and 25% increases in the progression of carotid IMT over 3 years compared with nonsmokers (252). In the Framingham Heart Study, extracranial carotid artery stenosis correlated with the quantity of cigarettes smoked over time (237). In the Cardiovascular Health Study, the severity of carotid artery stenosis was greater in current smokers than in former smokers, and there was a significant relationship between the severity of carotid stenosis and pack-years of exposure to tobacco (239). The RRs of finding >60% carotid stenosis were 1.5 and 3.9 among cigarette smokers with cerebral ischemia in the NOMASS and the BCID (Berlin Cerebral Ischemia Databank) studies, respectively (258).

6.3. Control of Hyperlipidemia

6.3.1. 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 (111,259,260). (*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 (259). (*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 (261–264). (*Level of Evidence: B*)
3. For patients who do not tolerate statins, LDL-lowering therapy with bile acid sequestrants and/or niacin is reasonable (261,263,265). (*Level of Evidence: B*)

The relationship between cholesterol and ischemic stroke is not as evident as that between cholesterol and MI, and findings from population-based studies are inconsistent. In the MR FIT (Multiple Risk Factor Intervention Trial), comprising more than 350,000 men, the RR of death increased progressively with serum cholesterol, exceeding 2.5 in those with the highest levels (266). An analysis of 45 prospective observational cohorts involving approximately 450,000 individuals, however, found no association of hypercholesterolemia with stroke (267). In the ARIC study, the relationships between lipid values and incident ischemic

stroke were weak (268). Yet in the Women's Health Study, a prospective cohort study among 27,937 U.S. women 45 years of age and older, total and LDL cholesterol levels were strongly associated with increased risk of ischemic stroke (269). The RR of a future ischemic stroke in the highest quintile of non–high-density lipoprotein (HDL) cholesterol levels compared with the lowest quintile was 2.25. In a meta-analysis of 61 prospective observational studies, most conducted in western Europe or North America, consisting of almost 900,000 adults between the ages of 40 and 89 years without previous disease and nearly 12 million person-years at risk, total cholesterol was only weakly related to ischemic stroke mortality in the general population between ages 40 and 59 years, and this was largely accounted for by the association of cholesterol with hypertension (270). Moreover, in those with below-average blood pressures, a positive relation was seen only in middle age. At older ages (70 to 89 years) and for those with systolic blood pressure >145 mm Hg, total serum cholesterol was inversely related to hemorrhagic and total stroke mortality (270). Epidemiological studies, however, have consistently found an association between cholesterol and carotid artery atherosclerosis as determined by measurement of IMT (25,255,271). In the Framingham Heart Study, the RR of carotid artery stenosis >25% was approximately 1.1 for every 10-mg/dL increase in total cholesterol (237). In the MESA study, carotid plaque lipid core detected by MRI was strongly associated with total cholesterol (272).

Lipid-lowering therapy with statins reduces the risk of stroke in patients with atherosclerosis (273). Two large meta-analyses examined the effect of statins on the risk of stroke among patients with CAD or other manifestations of atherosclerosis or at high risk for atherosclerosis (274,275). One such analysis of 26 trials comprising >90,000 patients found that statins reduced the risk of all strokes by approximately 21% (274), with stroke risk decreasing 15.6% for each 10% reduction in serum LDL cholesterol (274). Another meta-analysis of 9 trials comprising more than 65,000 patients found a 22% reduction in ischemic stroke per 1-mmol/L (~40 mg/dL) reduction in serum LDL cholesterol (275). There was no effect in either meta-analysis of lowering LDL cholesterol on the risk of hemorrhagic stroke.

A randomized trial, SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels), prospectively compared the effect of atorvastatin (80 mg daily) against placebo on the risk of stroke among patients with recent stroke or TIA (259). Statin therapy 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% (206).

There are multiple causes of ischemic stroke, and only a limited number of studies have specifically examined the effect of statins on stroke in patients with ECVD; the available data suggest that statins are beneficial. In a secondary subgroup analysis of the trial data, there was no heterogeneity in the treatment effect for the primary endpoint (fatal and nonfatal stroke) or for secondary endpoints between patients with and without carotid stenosis (276). In those with carotid stenosis, greater benefit occurred in terms of reduction of all cerebrovascular and cardiovascular events combined, and treatment with atorvastatin was associated with a 33% reduction in the risk of any stroke (HR 0.67, 95% CI 0.47 to 0.94; p=0.02) and a 43% reduction in risk of major coronary events (HR 0.57, 95% CI 0.32 to 1.00; p=0.05). Subsequent carotid revascularization was reduced by 56% (HR 0.44, 95% CI 0.24 to 0.79; p=0.006) in the group randomized to atorvastatin (276). Hence, consistent with the overall results of the trial, lipid lowering with high-dose atorvastatin reduced the risk of cerebrovascular events in particular and cardiovascular events in general in patients with and without carotid stenosis, yet those with carotid stenosis derived greater benefit (276).

Statins reduce the risk of MI by 23% and cardiovascular death by 19% in patients with CAD (275). Moreover, statin therapy reduces progression or induces regression of carotid atherosclerosis. In the Heart Protection Study, there was a 50% reduction in CEA in patients randomized to statin therapy (277). A meta-analysis of 9 trials of patients randomized to statin treatment or control found the statin effect to be closely associated with LDL cholesterol reduction. Each 10% reduction in LDL cholesterol reduced the risk of all strokes by 15.6% (95% CI 6.7 to 23.6) and of carotid IMT by 0.73% per year (95% CI 0.27 to 1.19) (274). METEOR (Measuring Effects on Intima-Media Thickness: An Evaluation of Rosuvastatin) found that compared with placebo, rosuvastatin reduced progression of carotid IMT over 2 years in patients with low Framingham risk scores and elevated serum LDL cholesterol levels (278). Two of the trials included in the meta-analysis compared greater- to lesser-intensity statin therapy. In the ARBITER (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol) trial, carotid IMT regressed after 12 months of treatment with atorvastatin (80 mg daily) but remained unchanged after treatment with pravastatin (40 mg daily) (279). The LDL cholesterol levels in the atorvastatin and pravastatin treatment groups were 76±23 and 110±30 mg/dL, respectively. In the ASAP (Atorvastatin versus Simvastatin on Atherosclerosis Progression) trial of patients with familial hypercholesterolemia, carotid IMT decreased after 2 years of treatment with 80 mg of atorvastatin daily but increased in patients randomized to 40 mg of simvastatin daily (280).

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. Among patients participating in the Coronary Drug Project, niacin reduced the 15-year mortality rate (9 years after study completion), primarily by decreasing the incidence of death caused by coronary disease, with a relatively small beneficial trend in the risk of death caused by cerebrovascular disease (281). In the Veterans Affairs HDL Intervention trial of men with CAD and low serum HDL cholesterol levels, gemfibrozil

reduced the risk of total strokes, which consisted mainly of ischemic strokes (282). Fenofibrate did not reduce the stroke rate in the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) study of patients with diabetes mellitus (283). In the CLAS (Cholesterol Lowering Atherosclerosis) trial, the combination of colestipol and niacin reduced progression of carotid IMT (58). In the ARBITER-2 study of patients with CAD and low levels of HDL cholesterol, carotid IMT progression did not differ significantly after the addition of extended-release niacin to statin therapy compared with statin therapy alone, although there was a trend favoring the dual therapy (284). In the ENHANCE (Effect of Combination Ezetimibe and High-Dose Simvastatin vs. Simvastatin Alone on the Atherosclerotic Process in Patients with Heterozygous Familial Hypercholesterolemia) study, in patients with familial hypercholesterolemia, the addition of ezetimibe to simvastatin did not affect progression of carotid IMT more than the use of simvastatin alone (285).

6.4. Management of Diabetes Mellitus

6.4.1. 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 (286,287). (*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 (288). (*Level of Evidence: B*)

The risk of ischemic stroke in patients with diabetes mellitus is increased 2- to 5-fold (289–291) compared with patients without diabetes. The Cardiovascular Health Study investigators reported that elevated fasting and postchallenge glucose levels were associated with an increased risk of stroke (292), and diabetes was associated with carotid IMT and the severity of carotid artery stenosis (24). In the Insulin Resistance Atherosclerosis Study, diabetes and fasting glucose levels were associated with carotid IMT, and carotid IMT progressed twice as rapidly in patients with diabetes as in those without diabetes (293–295). Similarly, in the ARIC study, diabetes was associated with progression of carotid IMT (254,291,296), and in the Rotterdam study, diabetes predicted progression to severe carotid obstruction (297). In the EDIC (Epidemiology of Diabetes Interventions and Complications) study, the progression of carotid IMT was greater in patients with diabetes than in those without diabetes (298) and less in patients with diabetes treated with intensive insulin therapy than in those managed more conventionally. In several randomized studies, pioglitazone caused less progression or induced regression of carotid IMT compared with glimepiride (299,300).

Several trials examined the effect of intensive glucose control on vascular events, with stroke included as a secondary outcome. 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 (301). In the ACCORD (Action to Control Cardiovascular Risk in Diabetes) (286) and ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) (287) 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, or death due to cardiovascular disease by 57% during the long-term follow-up phase of the DDCT (Diabetes Control and Complications Trial)/EDIC study, but the absolute risk reduction was $<1\%$ during 17 years of follow-up. These observations suggest that it would be necessary to treat 700 patients for 17 years to prevent cardiovascular events in 19 patients; the NNT per year to prevent a single event equals 626, a relatively low return on effort for prevention of stroke (302). Effects on fatal and nonfatal strokes were not reported separately (302).

At least as important as treatment of hyperglycemia is aggressive control of other modifiable risk factors in patients with diabetes. In the UK-TIA (United Kingdom Transient Ischemic Attack) trial, treatment of hypertension was more useful than blood glucose control in reducing the rate of recurrent stroke (303). 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% (288). Although the severity of carotid atherosclerosis was not established in the trial cohort, the findings suggest that administration of a statin may be beneficial in patients with diabetes even when serum lipid levels are not elevated. Other agents, such as those of the fibrate class, do not appear to offer similar benefit in this situation (283,304).

6.5. Hyperhomocysteinemia

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 (305). The risk of developing $>25\%$ extracranial carotid stenosis is increased 2-fold among elderly patients with elevated homocysteine levels (306), and plasma concentrations of folate and pyridoxal 5′ phosphate are inversely associated with carotid stenosis (306). In the ARIC study,

increased carotid IMT was approximately 3-fold more likely among participants with the highest than the lowest quintile of homocysteine (307), and findings were similar in the Perth Carotid Ultrasound Disease Assessment study (308), but adjustment for renal function eliminated or attenuated the relationship between homocysteine levels and carotid IMT (309).

Stroke rates decreased and average plasma homocysteine concentrations fell after folic acid fortification of enriched grain products in the United States and Canada, but not in England and Wales, where fortification did not occur (310). Meta-analysis of 8 randomized primary prevention trials found that folic acid supplementation reduced the risk of stroke by 18% (311). Despite these observations, studies of patients with established vascular disease have not confirmed a benefit of homocysteine lowering by B-complex vitamin therapy on cardiovascular outcomes, including stroke. In the VISP (Vitamin Intervention for Stroke Prevention) study, a high-dose formulation of pyridoxine (B_6), cobalamin (B_{12}), and folic acid lowered the plasma homocysteine level 2 micromoles per liter more than a low-dose formulation of these vitamins but did not reduce the risk of recurrent ischemic stroke (312). Among patients with established vascular disease or diabetes, a combination of vitamins B_6, B_{12}, and folic acid lowered plasma homocysteine by 2.4 micromoles per liter without effects on the composite endpoint of cardiovascular death, MI, or stroke or its individual components (313). Similarly, this combination of B-complex vitamins lowered plasma homocysteine concentration by more than 2 micromoles per liter (18.5%) in women with established cardiovascular disease or 3 or more risk factors but did not alter rates of the primary composite endpoint of MI, stroke, coronary revascularization, or cardiovascular death or the secondary endpoint of stroke (314).

Given that in patients with CAD, hyperhomocysteinemia is a marker of risk but not a target for treatment and that vitamin supplementation does not appear to affect clinical outcomes, the writing committee considers the evidence insufficient to justify a recommendation for or against routine therapeutic use of vitamin supplements in patients with ECVD.

6.6. Obesity and the Metabolic Syndrome

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 in men and women across several age strata and ethnic groups (315–324). This relationship to carotid atherosclerosis is strengthened in proportion to the number of components of metabolic syndrome present ($p<0.001$) (325–327). With regard to the individual components, the relationship appears strongest for hypertension (317,320,321,326,328,329), with hypercholesterolemia and obesity also related to carotid atherosclerosis in several reports (317,330). Abdominal adiposity bears a graded association with the risk of stroke and TIA independent of other vascular disease risk factors (331).

6.7. Physical Inactivity

Physical inactivity is a well-documented, modifiable risk factor for stroke, with a prevalence of 25%, an attributable risk of 30%, and an RR of 2.7, but the risk reduction associated with treatment is unknown (33,332). Nevertheless, several meta-analyses and observational studies suggest a lower risk of stroke among individuals engaging in moderate to high levels of physical activity (333). The relationship between physical activity and carotid IMT as a marker of subclinical atherosclerosis has been inconsistent (334–337). Furthermore, it is not clear 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.

6.8. Antithrombotic Therapy

6.8.1. 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 MI and other ischemic cardiovascular events, although the benefit has not been established for prevention of stroke in asymptomatic patients (33,260,305,338). (*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 (260,305,339–342) (*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 (343,344) (*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

Table 6. 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. (111).

3.0]) for prevention of thromboembolic ischemic events (345). (*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 (2,346,347). (*Level of Evidence: B*)
2. Administration of clopidogrel in combination with aspirin is not recommended within 3 months after stroke or TIA (340). (*Level of Evidence: B*)

Although antiplatelet drugs reduce the risk of stroke compared with placebo in patients with TIA or previous stroke (305) (Table 6), no adequately powered controlled studies have demonstrated the efficacy of platelet-inhibitor drugs for prevention of stroke in asymptomatic patients with ECVD. The Asymptomatic Cervical Bruit Study compared enteric-coated aspirin, 325 mg daily, against placebo in neurologically asymptomatic patients with carotid stenosis of >50% as determined by duplex ultrasonography. On the basis of just under 2 years of follow-up, the annual rate of ischemic events and death due to any cause was 12.3% in the placebo group and 11.0% in the aspirin group (p=0.61), but the sample size of 372 patients may have been insufficient to detect a clinically meaningful difference (348). In the Veterans Affairs Cooperative Study Group (76) and ACAS (74), the stroke rates were approximately 2% per year in groups treated with aspirin alone (74,76,349). No controlled studies of stroke have shown superior results with antiplatelet agents other than aspirin in patients with asymptomatic ECVD.

Randomized studies have compared aspirin with CEA in symptomatic patients (111). In NASCET, 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 with antiplatelet therapy (predominantly aspirin) and without revascularization (84). WARSS (Warfarin-Aspirin Recurrent Stroke Study) compared aspirin and warfarin for stroke prevention in patients with recent stroke (343). 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. Patients with carotid stenosis sufficiently severe to warrant surgical intervention were excluded, which limits application of the results.

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 (340,350). However, in ESPS-2 (Second European Stroke Prevention Study), the combination of 25 mg of aspirin twice daily plus 200 mg of extended-release dipyridamole twice daily was superior to the use of only 50 mg of aspirin daily in patients with prior TIA or stroke (341). Outcomes in a subgroup defined on the basis of ECVD have not been reported.

The PROFESS (Prevention Regimen for Effectively Avoiding Second Strokes) trial directly compared the combination of extended-release dipyridamole and aspirin versus clopidogrel (342) in 20,332 patients with prior stroke. Over a mean follow-up of 2.5 years, recurrent stroke occurred in 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 were more common in patients assigned to extended-release dipyridamole plus aspirin (4.1%) than in those assigned to clopidogrel (3.6%; HR 1.15, 95% CI 1.00 to 1.32), including intracranial hemorrhage (HR 1.42, 95% CI 1.11 to 1.83). The net risk of recurrent stroke or major hemorrhage was similar in the 2 groups (11.7% with aspirin plus dipyridamole versus 11.4% with clopidogrel; HR 1.03, 95% CI 0.95 to 1.11) (342). Accordingly, although clopidogrel monotherapy was associated with equal efficacy and lower risk of hemorrhage than the combination of dipyridamole plus aspirin and no less efficacy than the combination of clopidogrel plus aspirin, variations in the response to clopidogrel based on genetic factors and drug interactions make individualized treatment selection appropriate for optimum stroke prophylaxis.

Optimum therapy for patients experiencing recurrent cerebral ischemia during antiplatelet therapy has not been addressed in adequately powered randomized trials. Lacking firm evidence, physicians choose an alternative antiplatelet regimen in such cases. Aspirin or clopidogrel resistance, defined as the inability of these agents to inhibit platelet function, is one potential cause of failure in stroke prevention. There is no agreement on which platelet function test should be used to determine aspirin or clopidogrel resistance. In a study of 129 patients admitted with a diagnosis of stroke, TIA, or ECVD, no antiplatelet effect of aspirin or clopidogrel was demonstrated in 37% of cases. Aspirin resistance was more frequent in those taking 81 mg daily than in those taking 325 mg daily and was higher in those taking enteric-coated preparations of aspirin than in those taking uncoated aspirin (351). Clopidogrel resistance has also been described (352). Its effectiveness is diminished when conversion into its active form by the cytochrome P450 system, which depends primarily on the function of CYP2C19, is inhibited either because of genetic variations or owing to drugs that impede CYP2C19 activity, which adversely affects clopidogrel metabolism. Whether variation in the response to aspirin or clopidogrel is associated with a greater risk of stroke has not been established, and it is not known whether testing for or treatment of drug resistance improves outcomes.

In 2010, the U.S. Food and Drug Administration issued a boxed warning to clinicians that addressed the use of pharmacogenomic testing to identify patients with altered clopidogrel metabolism who were thus at risk of a suboptimal clinical response to clopidogrel (353,354). Variability in response to clopidogrel results from both clinical and genetic factors; genotyping and measurement of platelet inhibition may be appropriate in patients with cerebrovascular disease who have experienced ischemic events despite compliance with clopidogrel therapy or in those at high risk for such events. Genetic variability in CYP enzymes that affect platelet function has been associated with adverse outcomes. Although CYP2C19*2 is the most common genetic variant associated with impaired response to clopidogrel, other genetic polymorphisms may also contribute to the variable responsiveness of individual patients to clopidogrel, and the specific role of individual genetic polymorphisms remains uncertain.

Information about the predictive value of pharmacogenomic testing is the focus of ongoing studies, but data on the role of genotyping in the selection of antiplatelet therapy for patients with symptomatic or asymptomatic ECVD are presently insufficient to justify specific or general recommendations. New agents such as prasugrel and ticagrelor, which are not affected by CYP2C19 genetic variants, may prove to be more effective than clopidogrel in conventional doses but have not been evaluated adequately in patients with carotid or vertebral artery disease.

Early administration of unfractionated heparin or low-molecular-weight heparin/danaparoid did not improve the outcome of patients with acute ischemic stroke (355).

6.8.2. Nonsteroidal Anti-Inflammatory Drugs

In a population-based stroke registry, nonsteroidal anti-inflammatory drugs (NSAIDs) were not associated with either an increased risk of hemorrhagic stroke or protection against initial ischemic stroke (357). A systematic review and meta-analysis of randomized trials involving cyclo-oxygenase type 2 inhibitors found no significant incremental risk of events compared with placebo or nonselective NSAIDs (OR 1.03, 95% CI 0.71 to 1.50 and OR 0.86, 95% CI 0.64 to 1.16, respectively) (358). Hence, in available data sets, the vascular risk associated with NSAIDs in general and cyclo-oxygenase type 2 inhibitors in particular is more apparent for MI than for stroke. The writing committee makes no recommendation for or against the use of NSAIDs because of a lack of evidence specifically pertinent to patients with ECVD, except to note the association of the use of these drugs with increased risks of both MI and gastrointestinal bleeding.

7. Revascularization

7.1. 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 (20,83) (*Level of Evidence: A*) or more than 50% as documented by catheter angiography (20,70,83,359) (*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% (360). (*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 (74,76,359,361–363). (*Level of Evidence: A*)

*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 for details.

2. It is reasonable to choose CEA over CAS when revascularization is indicated in older patients, particularly when arterial pathoanatomy is unfavorable for endovascular intervention (360,364–368). (*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 (369–373).§ (*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 (374). (*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 (360). (*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 (35,361,362,366,369–372,375,376). (*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% (35,70,74,369,377). (*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*)

7.2. Carotid Endarterectomy

CEA dramatically reduces the incidence of ipsilateral stroke beyond the 30-day perioperative period, but the risk of periprocedural stroke must be considered in the assessment of overall safety and efficacy. For symptomatic patients undergoing surgical revascularization, the incidence of subsequent stroke is approximately 1.1% per year, which corresponds to stroke-free survival of approximately 93% at 5 years (Table 7). The actuarial 5-year survival in patients with carotid stenosis is approximately 75%, with CAD being the major cause of death. For asymptomatic patients, the risk of ipsilateral stroke after CEA is <0.5% per year, but this rate may not be significantly lower than that currently associated with medical therapy alone.

7.2.1. Randomized Trials of Carotid Endarterectomy

7.2.1.1. CAROTID ENDARTERECTOMY IN SYMPTOMATIC PATIENTS

The NASCET (reported in 1991) was designed to test 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 (70). Randomization was stratified according to the severity of stenosis. The high-grade stenosis category was 70% to 99% diameter reduction measured by contrast angiography by a method originally defined for an ECVD disease study in the 1960s, in which the luminal diameter at the point of greatest stenosis severity was compared with the diameter of the distal internal carotid artery (Figure 3). The lower-grade stenosis category included patients with 30% to 69% stenosis.

NASCET was stopped for the 70% to 99% stenosis group after 18 months of follow-up because a significant benefit for CEA was evident (70). In the 328 patients assigned to surgical management, the cumulative risk of ipsilateral stroke at 2 years, including perioperative events, was 9%. For the 331 patients in the high-grade stenosis category assigned to medical therapy alone, the cumulative risk of ipsilateral stroke at 2 years was 26% (absolute risk reduction 17% in favor of surgical management) (70).

Subsequently, the NASCET investigators also demonstrated a benefit of CEA for patients with 50% to 69% carotid stenosis but not for those with <50% stenosis. Among patients in the surgical group with 50% to 69% stenosis, the rate of operative mortality or stroke was 6.7% at 30 days. Over longer-term follow-up, the rate of ipsilateral stroke, including perioperative events, was 15.7% at 5 years compared with 22% for medically managed patients. In other words, approximately 15 patients would have had to undergo CEA to prevent 1 stroke over 5 years (NNT=77 patients per year) (20,70,84,381).

The ECST (European Carotid Surgery Trial), performed at about the same time as NASCET, randomized 2,518 patients over a 10-year period, yielding a mean follow-up of 3 years. Patients were stratified into 3 categories that corresponded to mild (10% to 29%), moderate (30% to 69%), and severe (70% to 99%) carotid stenosis by a different method of measurement. According to the method used in ECST, 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, which was the method used in NASCET (Figure 3, Table 8). The European study found a highly significant 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

§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 CAD, 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 score 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.

Table 7. 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) (84)	Symptomatic, 70% to 99% stenosis	CEA	Medical therapy	328	321	9	26	Ipsilateral stroke	17.00	12
ECST (2003) (378)	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) (378)	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) (20)	Symptomatic, 50% to 69% stenosis	CEA	Medical therapy	430	428	15.70	22.20	Ipsilateral stroke	6.50	77
ECST (2003) (378)	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) (378)	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) (74)	Asymptomatic	CEA	Medical therapy	825	834	5.10	11	Ipsilateral stroke and periprocedural stroke or death	6	84
ACAS (1995) (74)	Asymptomatic	CEA	Medical therapy	825	834	13.40	13.60	Stroke or death	0.20	1,351
ACST (2004) (75)	Asymptomatic	Immediate CEA	Deferred CEA	1,560	1,560	3.80	3.97	Ipsilateral stroke in carotid artery territory	0.17	2,000
ACST (2004) (75)	Asymptomatic	Immediate CEA	Deferred CEA	1,560	1,560	3.80	11.00	Stroke risks	7.20	70
Symptomatic										
SPACE 2-y data (2008) (364)	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) (364)	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) (364)	Symptomatic	CEA	CAS	589	607	10.10	10.90	All stroke	0.80	250
EVA-3S 4-y data (2008) (379)	Symptomatic	CEA	CAS	262	265	1.50	1.50	Ipsilateral stroke	0	~
EVA-3S 4-y data (2008) (379)	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) (379)	Symptomatic	CEA	CAS	262	265	3.40	9.10	All strokes	5.70	71
Mixed patient populations										
SAPPHIRE 1-y data (2004) (370)	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) (370)	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)† (370)	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) (369)	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

Table 7. 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			
SAPPHIRE 3-y data (2008) (369)	Mixed population: Symptomatic, ≥50% stenosis; Asymptomatic, ≥80% stenosis	CEA	CAS	167	167	9.00	9.00	Stroke	0	~
SAPPHIRE 3-y data (2008) (369)	Mixed population: Symptomatic, ≥50% stenosis; Asymptomatic, ≥80% stenosis	CEA	CAS	167	167	5.40	6.60	Ipsilateral stroke	1.20	250
Symptomatic										
ICSS (2010) (380)	Symptomatic	CEA	CAS	858	855	4.10	7.70	All strokes within 120 d after randomization‡	3.60	7
ICSS (2010) (380)	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) (360)	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) (360)	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) (360)	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) (360)	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) (360)	Asymptomatic	CEA	CAS	587	594	2.70	4.50	All periprocedural strokes or postprocedural ipsilateral strokes	1.80	223
CREST 4-y data (2010) (360)	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) (360)	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 (381a). †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 Atherosclerosis 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.

69% stenosis (382). For higher degrees of stenosis severity, adjusted for primary endpoints and duration of follow-up, CEA had a similar benefit for symptomatic patients across the NASCET and ESCT trials for both men and women (383).

A U.S. Veterans Affairs trial of CEA, the VACS (Veterans Affairs Cooperative Study), was stopped after 189 patients with symptomatic stenosis had been randomly allocated to surgery plus medication therapy versus medical management alone (85). At that point, with mean follow-up of 11.9 months, 7.7% of patients assigned to surgical treatment had experienced death, stroke, or TIA compared with 19.4% of those managed without surgery. Despite the small number of patients and abbreviated follow-up, this difference reached statistical significance (85), and the implications of the interim analysis were strengthened by the results of NASCET, which had become available concurrently.

Table 8. Comparison of the Methods of Stenosis Measurement Used in ECST and NASCET

European Stenosis Scale*	North American Stenosis Scale*
65% Stenosis	30% Stenosis
70% Stenosis	40% Stenosis
90% Stenosis	80% Stenosis

*All values are approximations.

ECST indicates European Carotid Surgery Trial; and NASCET, North American Symptomatic Carotid Endarterectomy Trial.

Pooled analysis of the 3 largest randomized trials (VACS, NASCET, and ECST) involving more than 3,000 symptomatic patients found a 30-day stroke and death rate of 7.1% after CEA (382) (Table 7). Differences between trials in the method of measurement of carotid stenosis and definitions of outcome events confound interpretation of the meta-analysis. Analysis of individual patient-level data partially overcomes these limitations, and such an analysis

incorporating reassessment of carotid angiograms found the results of ECST and NASCET to be more consistent than the originally reported results suggested. The lack of benefit of CEA in patients with moderate stenosis reported by the ECST investigators (83) can be explained by differences in the method of measuring stenosis severity and definition of outcome events. With the exception of patients with chronic carotid occlusion or near-occlusion, surgery was beneficial when the degree of stenosis was >50% as measured by the technique used in NASCET (70) and VACS (85) (approximately equivalent to 65% stenosis by the method used in ECST). In patients with 50% to 69% stenosis by the method used in NASCET, the benefit was modest but increased over time. Surgery was most effective in patients with >70% carotid stenosis without occlusion or near-occlusion (382). When the combined outcome of fatal or disabling ipsilateral ischemic stroke, perioperative stroke, or death was considered, the benefit of surgery was evident only in patients with 80% to 99% stenosis. Surgery offered little or no long-term benefit to patients with near-occlusion of a carotid artery, in whom the risk of stroke was lower among medically treated patients than in those with lesser degrees of severe stenosis, perhaps as a result of collateral blood flow (384,385).

7.2.1.2. CAROTID ENDARTERECTOMY IN ASYMPTOMATIC PATIENTS

The first major trial of CEA in asymptomatic patients was conducted in 10 U.S. Veterans Affairs medical centers to test the hypothesis that surgery in combination with aspirin and risk factor modification would result in fewer TIAs, strokes, and deaths than medical management alone (76). Among 444 patients randomized over a 54-month period, 211 CEA procedures were performed and 233 patients were treated medically. The 30-day mortality rate was 1.9% in patients assigned to undergo surgery, and the incidence of stroke was 2.4%, for a combined rate of 4.3%. By 5 years, the differences in outcomes reached statistical significance, with a 10% overall rate of adverse events in the surgical group compared with 20% in the group given medical therapy alone. Inclusion of TIA in the primary composite endpoint was a source of controversy, because the study was not powered to detect a difference in the composite endpoint of death and stroke without TIA (76,386,387).

The hypothesis that CEA plus aspirin and risk factor control (albeit limited by modern standards) would reduce the rate of TIA, stroke, and death compared with aspirin and risk factor control without surgery was evaluated in ACAS (74). In response to criticism of the VACS design, the primary endpoint did not include TIA, which raised the requisite recruitment. The trial was stopped before completion after randomization of 1,662 patients when an advantage to CEA became apparent among patients with lesions producing >60% stenosis as measured by the method used in NASCET. After a mean follow-up of 2.7 years, the projected 5-year rates of ipsilateral stroke, perioperative stroke, and death were 5.1% for surgical patients and 11% for patients treated medically. The 30-day perioperative death and stroke rate for patients undergoing CEA was 2.3%, but some patients assigned to the surgical group experienced stroke during contrast angiography and did not undergo surgery (74,388–391).

The ACST, sponsored by the Medical Research Council of Great Britain, randomized 3,120 asymptomatic patients with hemodynamically significant carotid artery stenosis to immediate CEA versus delayed surgery on the basis of the onset of symptoms (72). The 30-day risk of stroke or death in either group, including the perioperative period, was 3.1%. Five-year rates, including perioperative events, were 6.4% for the early-surgery group versus 11.7% for the group initially managed medically. The primary endpoint in ACST differed from that in ACAS by inclusion of strokes contralateral to the index carotid lesion. As with ACAS, during the conduct of ACST (1993 to 2003), medical therapy was scant by modern standards (see Section 7.2.6).

A summary of outcomes of randomized trials of CEA in asymptomatic patients is given in Table 7, as well as an analysis of the benefit of revascularization in terms of the NNT to prevent stroke over a period of 1 year. It is important to emphasize that selection of asymptomatic patients for carotid revascularization should include careful consideration of life expectancy, age, sex, and comorbidities. The benefit of surgery may now be less than anticipated on the basis of earlier randomized trials, and the cited 3% complication rate should be interpreted in the context of interim advances in medical therapy. Even when the data from ACAS and ACST are combined to increase the statistical power of the estimate of benefit, it remains unclear whether women benefit as much as men from CEA (363).

7.2.2. Factors Affecting the Outcome of Carotid Endarterectomy

A wide range of patient- and operator-related factors, some more tangible than others, can substantially influence both the immediate- and long-term outcomes of CEA.

7.2.2.1. TECHNICAL CONSIDERATIONS

In the more than 50 years that CEA has been performed, there has been considerable variation in surgical technique. Initially, local anesthesia was advocated instead of general anesthesia to permit observation of the patient's level of consciousness and motor function during temporary clamping of the carotid artery. Because only 10% of patients undergoing CEA develop cerebral dysfunction during arterial clamping, other techniques have been developed, including electroencephalographic or other types of monitoring, to assess cerebral function under anesthesia (392,393). Advocates of local anesthesia maintain that adverse cardiac events occur less frequently than during CEA under general anesthesia, but retrospective analyses and data from surgical trials have failed to demonstrate a significant difference in outcomes based on the type of anesthesia used.

A key reason to monitor cerebral function dynamically during surgery, including measurement of residual collateral perfusion pressure (394) or internal carotid artery back pressure, is to select patients who may benefit from shunting during the period of arterial clamping. Arguments for selective as opposed to routine shunting are related to the complications that occasionally occur during shunting, including embolism of atheromatous debris or air through the shunt, mechanical injury to the distal internal carotid artery during shunt placement, and obscuring of the arterial anatomy at the distal zone of CEA. To date, however, no study has shown a difference in 30-day morbidity and mortality with routine versus selective shunting during CEA.

Variations in the technique of arterial repair after CEA depend mainly on the length of the arteriotomy. The advantage of primary closure is speed, but disadvantages include higher incidences of residual and recurrent stenosis. The advantage of patch closure is visual confirmation of complete plaque removal, but the disadvantage is the greater length of time required for closure. Multiple comparative reviews have failed to demonstrate a consistent difference in outcomes with either technique compared with the other (395–405). One report involved a single experienced surgeon and a series of patients who required staged bilateral CEA in whom 1 side was randomly allocated to primary closure and the other side to patch angioplasty (406). Patch angioplasty was associated with lower 30-day surgical morbidity and mortality and fewer cases of residual or recurrent stenosis as assessed by periodic duplex scanning for up to 1 year postoperatively. On the basis of these observations and a Cochrane meta-analysis of case series (407), patch angioplasty after open CEA is now favored by most surgeons.

Eversion CEA is a major variation in operative technique designed in part to avoid patch angioplasty closure and to relocate the proximal internal carotid artery when the artery becomes redundant after CEA. The avoidance of a longitudinal arteriotomy reduces the likelihood of stricture and the need for patching, but the technique is difficult in patients with high carotid bifurcations or long lesions. Furthermore, the eversion technique makes internal shunting more difficult. Randomized trials comparing the eversion and direct arteriotomy techniques have found no difference in morbidity, mortality, or rates of restenosis (408,409).

7.2.2.2. CASE SELECTION AND OPERATOR EXPERIENCE

The relationships of perioperative mortality, neurological morbidity, and other adverse events after CEA to surgeon and hospital volume are complex. Hospitals in which fewer than 100 CEA operations are performed annually typically have poorer results than those in which larger numbers are performed (410–421). However, the threshold criteria for patient selection for CEA can also influence outcomes. Perioperative results are best for asymptomatic patients, who are more numerous than symptomatic patients. Surgeons with higher volumes are likely to operate on more asymptomatic cases and have better results. Surgeons who favor selection of symptomatic patients typically have higher 30-day rates of stroke and death. In ACAS, surgeons were selected for participation on the basis of individual experience, morbidity and mortality, and a minimum annual caseload of 12, with the expectation that the average would be closer to 20 operations per year. With this process, the 30-day surgical morbidity and mortality rate for CEA in ACAS was 1.5% (389,391,415,416,422,423), but case volume did not influence results. Extrapolation of the results of this and other carotid revascularization trials to clinical decision making requires consideration of patient selection and procedural results.

7.2.2.3. DEMOGRAPHIC AND CLINICAL FACTORS

The influence of patient age on surgical risk is unclear, but advanced age does not preclude elective CEA in appropriately selected patients, and several case series report neurological morbidity and mortality rates in octogenarians comparable to those in younger patients (424,425). Patients older than 80 years of age were excluded from participation in both NASCET (prior to 1991) (70) and ACAS (74), although in NASCET, the greatest benefit of surgery compared with medical management was observed in older patients (up to the age of 80 years) (70). In the randomized ACST study, no benefit accrued from CEA in patients 80 years of age or older (72). More recent results from the SPACE (Stent-Protected Angioplasty versus Carotid Endarterectomy) trial showed a 5.9% combined rate of stroke and death after CEA for symptomatic patients younger than 75 years of age with carotid stenosis. The rate among those older than 75 years of age was lower than reported for symptomatic patients in NASCET and ECST, which indicates either that surgical therapy has become safer with time or that the inherent risks of these cohorts differed in important ways. Several reports point to higher risks of complications among older patients undergoing CEA (426,427), but others suggest that patients 75 years of age or older with few cardiovascular risk factors face risks of perioperative stroke and death comparable to younger patients (428).

Women undergoing CEA face higher operative risk than men (10.4% versus 5.8% for men in ECST) (83,429–431). In the ACAS and NASCET studies, women had less favorable outcomes than men in terms of surgical mortality, neurological morbidity, and recurrent carotid stenosis and gained little or no benefit from surgery (70,74). The reasons for these sex-based differences are complex, and several studies have found that patch angioplasty closure in women materially improves results (432,433). Because the number of minorities enrolled in randomized trials has been insufficient to permit meaningful statistical analysis, it is difficult to evaluate differences in the results of CEA on the basis of race beyond general observations. For example, although Chinese populations appear to develop atherosclerosis at the

carotid bifurcations at different frequencies than white populations (434), the immediate and long-term results of CEA appear comparable. Black patients develop intracranial disease more frequently than ECVD and may undergo CEA less often than members of other racial groups. Among the uncertainties is how much the perceived differences reflect biological factors as opposed to inequities in access to diagnosis and treatment (435,436).

7.2.3. Risks Associated With Carotid Endarterectomy

The risks associated with CEA involve neurological and nonneurological complications, including hypertension or hypotension, hemorrhage, acute arterial occlusion, stroke, MI, venous thromboembolism, cranial nerve palsy, infection, arterial restenosis, and death (437). The risk of stroke or death 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; $p<0.018$) (438–440). A report of external case-by-case reviews by nonsurgeons of a total of 1972 CEA procedures in asymptomatic patients performed by 64 surgeons at 6 hospitals in 1997 and 1998 reported rates of 7.11% for stroke or death, 2.28% for stroke, and 2.93% for TIA (441). Patients with high-risk anatomic criteria, such as restenosis after CEA and contralateral carotid arterial occlusion, face much higher perioperative stroke/death rates than observed in the NASCET or ACAS patient cohorts (74,437). Reports of perioperative stroke and death rates of 19.9% have been documented in patients undergoing reoperative CEA procedures (442). In NASCET, the stroke and death rate at 30 days was 14.3% among patients with contralateral carotid occlusion (443). The more recent literature documents considerably lower complication rates (444–451), although outcomes of CEA in patients at high surgical risk are still relatively unfavorable, with the combined rate of stroke, death, or MI at 7.4% for high-risk patients compared with 2.9% among low-risk patients in 1 series (452) that did not separately report rates of stroke and death without MI. Other rate and relative risk data for perioperative stroke or death after CEA are listed in Table 9.

In a meta-analysis of nearly 16,000 symptomatic patients undergoing CEA, the 30-day risk of stroke or death was 7.7% when a neurologist evaluated the patient and 2.3% when a vascular surgeon performed the evaluation (359). These data 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. Clinical neurological assessment is crucial to the application of recommendations for selection of patients for CEA, which includes estimation of perioperative stroke risk. Recent trials of CEA that included rigorous independent neurological examination before and after CEA confirmed low rates of perioperative stroke (1.4% in previously asymptomatic patients and 3.2% in symptomatic patients in CREST [Carotid Revascularization Endarterectomy versus Stenting Trial] [360] and 3.3% among symptomatic patients in ICSS [International Carotid Stenting Study] [368] based on 30-day per-protocol analysis).

Other than stroke, neurological complications include intracerebral hemorrhage, which may occur as a consequence of the hyperperfusion syndrome despite control of blood pressure. This syndrome occurs in fewer than 1% of patients when blood pressure has been stable preoperatively and well managed perioperatively (461–464). Cranial nerve injury has been reported in as many as 7% of patients undergoing CEA but was not disabling in most studies, resulting in permanent injury in fewer than 1% of cases (382,465,466). In ECST, in which patients underwent extensive preoperative and postoperative neurological assessments, the incidence of cranial neuropathy was 5.1% (465). The neuropathy that appeared early in the postoperative period resolved in one fourth of the cases by the time of discharge, leaving 3.7% of patients with residual cranial nerve deficits. In decreasing order of frequency, these deficits involved palsies of the hypoglossal, marginal mandibular, recurrent laryngeal, and spinal accessory nerves and Horner syndrome (437,451,465,467,468). The only clinical factor linked to cranial nerve dysfunction was duration of the surgical procedure longer than 2 hours.

Cardiovascular instability has been reported in 20% of patients undergoing CEA, with hypertension in 20%, hypotension in 5%, and perioperative MI in 1%. The use of local anesthesia or cervical block in selected patients may lessen the likelihood of these complications (469). Because atherosclerosis of the carotid bifurcation is commonly associated with coronary atherosclerosis, myocardial ischemia is a major cause of perioperative complications, including nonfatal MI, and late mortality in patients undergoing CEA. The risk of cardiopulmonary complications is related to advanced age, New York Heart Association class III 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%, MI within 30 days, severe chronic lung disease, and severe renal insufficiency (470–472). In NASCET, 10% of patients experienced a complication in the perioperative period. The majority of these were cardiovascular (8.1%) or pulmonary (0.8%). In NASCET (70) and ECST (83), the incidence of perioperative MI was 0.3% and 0.2%, respectively. Venous thromboembolism is rare among patients undergoing CEA (473–475); in ECST, the rate was 0.1%, and no cases were reported in NASCET (377,382,437,473–478).

Wound complications are related primarily to infection (incidence ≤1%) (479,480) and hematoma (≤5%), depending in part on perioperative antiplatelet therapy (481), duration of surgery, perioperative use of heparin and protamine, and other factors. Prior ipsilateral CEA, contralateral laryngeal nerve palsy, and permanent tracheostomy may complicate wound management (465).

Table 9. 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 (453)	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 (454)	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 (455)	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 (370)	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 (456)	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 futility issues; concerns about operator inexperience in the CAS arm and nonuniform use of embolism protection devices.
SPACE, 2006 (457)	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 futility analysis; concerns about operator inexperience in the CAS arm and nonuniform use of embolism protection devices.
EVA-3S 4-y follow-up, 2008 (379)	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 9. Continued

Trial, Year (Reference)	No. of Patients	Key Features	Death or Any Stroke	OR (95% CI)	Comments
SPACE 2-y follow-up, 2008 (364)	1,214	Patients with symptomatic, severe (≥70%) carotid artery stenosis were recruited to this noninferiority trial and randomly assigned with a block randomization design to undergo CAS or CEA.	Intention-to-treat population: Ipsilateral ischemic strokes within 2 y, including any periprocedural strokes or deaths: CAS: 56 (9.5%) CEA: 50 (8.8%) Any deaths between randomization and 2 y: CAS: 32 (6.3%) CEA: 28 (5.0%) Any strokes between randomization and 2 y: CAS: 64 (10.9%) CEA: 57 (10.1%) Ipsilateral ischemic stroke within 31 d and 2 y: CAS: 12 (2.2%) CEA: 10 (1.9%) Per-protocol population: Ipsilateral ischemic strokes within 2 y, including any periprocedural strokes or deaths: CAS: 53 (9.4%) CEA: 43 (7.8%) Any deaths between randomization and 2 y: CAS: 29 (6.2%) CEA: 25 (4.9%) Any strokes between randomization and 2 y: CAS: 61 (11.5%) CEA: 51 (9.8%) Ipsilateral ischemic stroke within 31 d and 2 y: CAS: 12 (2.3%) CEA: 10 (2.0%)	Intention-to-treat population: Ipsilateral ischemic strokes within 2 y, including any periprocedural strokes or deaths: HR 1.10 (0.75 to 1.61) Any deaths between randomization and 2 y: HR 1.11 (0.67 to 1.85) Any strokes between randomization and 2 y: HR 1.10 (0.77 to 1.57) Ipsilateral ischemic stroke within 31 d and 2 y: HR 1.17 (0.51 to 2.70) Per-protocol population: Ipsilateral ischemic strokes within 2 y, including any periprocedural strokes or deaths: HR 1.23 (0.82 to 1.83) Any deaths between randomization and 2 y: HR 1.14 (0.67 to 1.94) Any strokes between randomization and 2 y: HR 1.19 (0.83 to 1.73) Ipsilateral ischemic stroke within 31 d and 2 y: HR 1.18 (0.51 to 2.73)	In both the intention-to-treat and per-protocol populations, recurrent stenosis of ≥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 (369)	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%.	Stroke: CAS: 15 (9.0%) CEA: 15 (9.0%) Ipsilateral stroke: CAS: 11 (7.0%) CEA: 9 (5.4%) Death: CAS: 31 (18.6%) CEA: 35 (21%) Note: data were calculated using n=167 for both groups because breakdowns of CAS and CEA for N=260 were not given.	Stroke: $p=0.99$ (−6.1 to 6.1) Death: $p=0.68$ (−10.9 to 6.1)	
Wallstent, 2005 (458)	219	Included symptomatic angiographic carotid stenosis >70%.	CAS: 13 (12.2%) CEA: 5 (4.5%)	N/A	Premature termination based on futility analysis.

Table 9. Continued

Trial, Year (Reference)	No. of Patients	Key Features	Death or Any Stroke	OR (95% CI)	Comments
SAPPHIRE (symptomatic data), 2008 (459)	96	Included patients with ≥50% carotid stenosis.	CEA: 3 (6.5%) CAS: 0	N/A	Premature termination secondary to declining enrollment.
ICSS, 2010 (368)	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 (360)	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 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: Symptomatic: CAS: 37 (5.5±0.9 SE) CEA: 21 (3.2±0.7 SE) Any periprocedural stroke or death or postprocedural ipsilateral stroke: Symptomatic: CAS: 40 (6.0±0.9 SE) CEA: 21 (3.2±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. †Combined asymptomatic and symptomatic patients for death, any stroke. ‡Death, stroke, and MI.

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. (460).

Other medical comorbidities contribute to the risk associated with CEA (444,452,482). Patients with pulmonary disease, particularly those requiring supplemental oxygen, are at risk of complications including ventilator dependence and pneumonia (483). Renal insufficiency is an independent risk factor for adverse outcomes of pulmonary complications and cardiac events after CEA (484). Additionally, in a retrospective analysis of data collected at 123 Veterans Affairs Medical Centers as part of the National Surgical Quality Improvement Program (n=20,899), patients with severe chronic renal insufficiency (glomerular filtration rate <30 mL/min) had significantly higher mortality rates by both univariate and multivariate analyses. Patients with impaired renal function, including those who required dialysis, faced higher risks of mortality and stroke-related morbidity in some reports, whereas in others the results appeared to be independent of renal function (485). A study of more than 1,000 CEA operations in nearly 900 patients found a higher perioperative mortality rate among those with chronic renal insufficiency and a significant association between chronic renal insufficiency and 30-day mortality (486). In a series of 184 patients, the mortality rate was 3% among patients with chronic renal insufficiency compared with no deaths in a control group without renal insufficiency. Among the 23 patients with serum creatinine levels 3 mg/dL or higher, the mortality rate was 17% (p<0.001) (487).

7.2.4. Carotid Endarterectomy in Patients With Unfavorable Anatomy

A high carotid bifurcation or an atheromatous lesion that extends into the internal carotid artery beyond the exposed surgical field represents a technical challenge during CEA, and carotid lesions located at or above the level of the second cervical vertebra are particularly problematic. High cervical exposure increases the risk of cranial nerve injury. Similarly, lesions below the clavicle, prior radical neck surgery or radiation, and contralateral carotid occlusion are each associated with higher risk (488,489). Several maneuvers are available to improve arterial exposure under these

circumstances, and in the hands of experienced surgeons, these maneuvers yield satisfactory outcomes.

Among the challenges of reoperative CEA for recurrent stenosis is the accumulation of scar tissue after ipsilateral CEA. Contralateral laryngeal nerve palsy is a relative contraindication to CEA, because bilateral nerve palsies could compromise the airway (465). Patients who have undergone radical neck surgery or tracheostomy pose surgical challenges because of the difficulty of exposing the artery and the relatively high risk of perioperative infection. The risk of cranial nerve injury is higher in these situations, but the overall risks of mortality and stroke are comparable.

Patients who have undergone cervical radiation therapy face an increased incidence of disease at the carotid bifurcation. Modern radiation therapy has been designed specifically to avoid severe fibrotic tissue reactions. Several series indicate that CEA can be performed successfully after neck radiation (490), although the procedure is technically challenging. In this situation, CAS may be safer to perform, but the rate of restenosis after CAS is high, ranging from 18% to 80% over 3 years (373,491,492).

7.2.5. Evolution in the Safety of Carotid Surgery

Complication rates associated with CEA have improved steadily over 2 generations. The 30-day stroke and mortality rates of 2.3% among asymptomatic patients in ACAS (1994) and 5.0% for symptomatic patients in the first part of the NASCET (1999) are often cited as benchmarks against which other forms of interventional therapy are compared. More recent reports, however, suggest considerably lower risks than reported in those early trials. Surgical training and case volume are important determinants of clinical outcomes with CEA. The experiences of individual surgeons include a series of 442 consecutive CEAs in 391 patients with a 0.45% cumulative 30-day rate of stroke and death (493). A population-based study of 14,095 CEA procedures in the state of Virginia between 1997 and 2001 reported cumulative stroke and mortality rates of 1.0% and 0.5%, respectively, and a progressive decline in these rates each year (494). For 23,237 CEA procedures performed in Maryland between 1994 and 2003, the cumulative stroke rate was 0.73%. The stroke rate was 2.12% in 1994, 1.47% in 1995, and from 0.29% to 0.65% between 1996 and 2003, with a more pronounced reduction in perioperative stroke among symptomatic patients than among asymptomatic patients (412). Similar findings were noted in California, where 51,231 CEA procedures performed between 1999 and 2003 were associated with a cumulative in-hospital stroke rate of 0.54%. Methodologies varied with rates of perioperative stroke and were generally higher when documented by a neurologist. Mortality rates in both states remained relatively stable over the reported periods, 0.33% to 0.58% in Maryland and 0.78% to 0.91% in California (412), and trends were similar in other states (495) and countries including, Australia (496), Italy (497), and Sweden (498).

7.2.6. Evolution of Medical Therapy

Trials of carotid revascularization must be interpreted in the context of the evolution of medical therapy for patients with atherosclerotic disease. Although pharmacotherapy aimed at risk reduction was incorporated in most trials, guidelines and strategies have changed, and more effective measures have enhanced the therapeutic armamentarium. The outcomes of trials that use modern atherosclerotic risk factor treatment may differ from those reported, which reduces the generalizability of the results to contemporary practice.

Concurrently, surgical outcomes have improved with advances in training, increased hospital and operator volumes, and better perioperative medical management, including control of blood pressure with beta blockers and angiotensin inhibitors and the widespread use of statins (415,422,423,499). A 1991 report indicated that 55% of participants in NASCET were treated with antihypertensive drugs. Treatment with lipid-lowering agents was used infrequently in NASCET (20), and medical therapy was not described in the primary report of ACAS. The evolution of medical therapy, with which patients typically gain benefit whether or not surgery is performed, is pertinent to the interpretation of the results of randomized trials, most of which were performed more than a decade ago. The ACST investigators reported changes in medical therapies over time for the 10-year period that began in 1993. By the last follow-up in 2002 to 2003, 81% of patients were taking antihypertensive medication and 70% were undergoing lipid-lowering treatment, but the outcomes of CEA were reported for only the first 5 years (ending in 1998), during which concurrent use of such medical therapy was considerably less frequent (60% of participants had systolic blood pressure >160 mm Hg; 33% had total serum cholesterol >250 mg/dL; management of diabetes [20% prevalence] was not detailed; and the proportion of participants who were active tobacco smokers was not reported). As typically occurs in patient care, advances that result in a decline in adverse event rates over time must be considered in interpreting the safety and efficacy of interventions, and caution is necessary with regard to assumptions about the constancy of the response to medical therapy alone over time.

7.2.7. 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 (338,500). (*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 (339,343,350). (*Level of Evidence: B*)

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 (406,407). (*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 (501). (*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 (364,502). 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*)

In the ACE (Acetylsalicylic Acid and Carotid Endarterectomy) study, a randomized trial involving 2849 patients and 4 different daily aspirin-dose regimens, the risk of stroke, MI, and death within 30 days and 3 months of CEA was lower for patients assigned to the lower-dose aspirin groups (81 mg or 325 mg daily) than for those taking 650 mg or 1300 mg of aspirin (RR 1.31 [95% CI 0.98 to 1.75], 5.4% versus 7.0% at 30 days [p=0.07] and RR 1.34 [95% CI 1.03 to 1.75], 6.2% versus 8.4% at 3 months [p=0.03], respectively) (500). The optimum duration of antithrombotic therapy after CEA has not been established, but beyond the first month postoperatively, it appears reasonable to use antithrombotic therapy as recommended for long-term prevention of ischemic events in patients with atherosclerosis.

A retrospective review of 1,566 patients undergoing CEA by 13 surgeons at a single center between 1994 and 2004 (42% symptomatic; 8% in combination with myocardial revascularization surgery) found lower rates of perioperative stroke (1.2% versus 4.5%; p<0.01), TIA (1.5% versus 3.6%; p<0.01), all-cause mortality (0.3% versus 2.1%; p<0.01), and length of hospital stay (2 [interquartile range 2 to 5] versus 3 [2 to 7] days; p<0.05) among the 42% of patients who received statin medication for at least 1 week before surgery than among those who did not (503). By multivariate analysis adjusted for demographics and comorbidities, statin use was associated with a 3-fold reduction in the risk of stroke (OR 0.35, 95% CI 0.15 to 0.85; p<0.05) and a 5-fold reduction in the risk of death (OR 0.20, 95% CI 0.04 to 0.99; p<0.05).

7.3. Carotid Artery Stenting

The results of randomized trials have not shown consistent outcome differences between CAS and CEA. CAS may be superior to CEA in certain patient groups, such as those exposed to previous neck surgery or radiation injury. A summary of stroke and mortality outcomes among symptomatic and asymptomatic patients enrolled in major randomized trials and registries is provided in Tables 9 and 10.

Although 30-day morbidity and mortality rates are important benchmarks for determining the benefit of a procedure in a population with a known event rate, the confidence bounds that surround estimates of event rates with CEA and CAS often overlap. When performed in conjunction with an embolic protection device (EPD), the risks associated with CAS may be lower than those associated with CEA in patients at elevated risk of surgical complications. On the other hand, in a nationwide U.S. sample of 226,111 CEA procedures during 2003 and 2004, the mortality rate was 0.44% and the rate of stroke was 0.95%, whereas the in-hospital stroke rate for asymptomatic patients undergoing CAS was 2-fold higher than that after CEA (504). The risks of stroke among octogenarians were 1% for CEA and 3% for CAS, whereas the mortality rates were similar and low for both procedures. These data have been criticized, however, because severity of illness may not have been comparable in the 2 cohorts and because the primary outcome measures were self-reported and not audited (505).

7.3.1. Multicenter Registry Studies

Several voluntary, 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 (35,362). The CASES-PMS (Carotid Artery Stenting with Embolic Protection Surveillance) study (362) enrolled 1493 patients at 73 sites and compared results with the pooled results of the pivotal SAPPHIRE (Stenting and Angioplasty with Protection in Patients at HIgh Risk for Endarterectomy) (370) stent arms. The rate of occurrence of the primary 30-day endpoint of major adverse events (stroke, MI, or death) was 5.0% for the CASES-PMS group and 6.2% in the pooled SAPPHIRE trial arms (362). In the CAPTURE (Carotid ACCULINK/ACCUNET Post-Approval Trial to Uncover Unanticipated or Rare Events) registry, 2,500 high-risk patients underwent CAS performed by more than 300 different specialty operators with a broad range of experience. The 30-day endpoint of MI, stroke, and death occurred in 6.3%, and the 30-day rate of major stroke or death was 2.9% (372).

7.3.2. Risks Associated With Carotid Artery Stenting

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.

7.3.2.1. CARDIOVASCULAR COMPLICATIONS

Baroreflex responses such as bradycardia, hypotension, and vasovagal reactions occur in 5% to 10% of cases but have

Table 10. 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 (370)	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 (369)	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 (360)	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.

been reported in as many as 33% of patients undergoing CAS (506–508); most are transient and do not require ongoing treatment after the procedure. With appropriate preprocedural management, rates can be kept in the lower range (375,507,509–513). 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 registry of 3500 patients (361,446,458,508,514–521).

The risk of arterial dissection or thrombosis in all published series, including the ARCHeR and CAPTURE cohorts, was <1%. Target-vessel perforation occurred in <1% of cases, and external carotid artery stenosis or occlusion occurred in 5% to 10% of cases (361,372,446,458,508,514–539), but this event is typically benign and requires no further intervention. Transient vasospasm occurs in 10% to 15% of procedures related to manipulation of the vessel with guidewires, catheters, or protection devices and is more common in smokers and in those with hypertension (540–543).

The incidence of restenosis after CAS has been reported to be in the range of 3% to 5%. This problem can be minimized by avoiding multiple or high-pressure balloon inflations, particularly in heavily calcified arteries (425,491,544–560).

7.3.2.2. NEUROLOGICAL COMPLICATIONS

The incidence of TIA has been reported as 1% to 2% in patients undergoing CAS. In the ARCHeR trial, the overall incidence of stroke was 5.5%, with disabling stroke occurring in 1.5% and relatively minor events occurring in 4.0% of cases (361,458,514,515,517,518,520,521). In the CAPTURE registry, the rate of disabling stroke was 2% and that of nondisabling stroke was 2.9% (372,524–529,531,533,534). Intracranial hemorrhage and the hyperperfusion syndrome related to hypertension and anticoagulation have been reported as complications in <1% of CAS procedures. Seizures are related predominantly to hypoperfusion and also occur in <1% of cases (561–569). Subclinical ischemic injury has also been detected by MRI (380,570,571). In a recent randomized trial (ICSS), comparisons were possible between patients with CAS and CEA; these injuries, which presumably resulted from microembolism, were more frequent after CAS (368).

Device malfunction that results in deployment failure, stent malformation, and migration after deployment is rare, occurring in <1% of procedures (540,541,572–576). If properly deployed, EPDs can reduce the neurological risks associated with CAS, but these devices may also be associated with failures (372,521,523,572,577–583), including

inability to deliver the device to the target zone because of a large profile and reduced steerability and ischemia if the device becomes overloaded with embolic material during deployment. Sizing of the EPD is important, because undersizing allows passage of debris into the distal circulation and oversizing can cause endothelial damage or provoke vasospasm.

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 (584–587). The risk of groin infection is <1% and that of pseudoaneurysm is 1% to 2%. Blood transfusion is required in 2% to 3% of cases because of bleeding from the catheter insertion site or retroperitoneal hematoma (588–591). Contrast-induced nephropathy has been reported in <1% of cases, because CAS is generally avoided in patients with severe renal dysfunction (592).

7.3.3. Prevention of Cerebral Embolism in Patients Undergoing Catheter-Based Carotid Intervention

Designed to prevent cerebral atheroembolism during catheter-based interventions, EPDs are effective in aorto-coronary saphenous vein graft angioplasty, in which there is typically a relatively large burden of thrombus (593,594), but no randomized studies have compared rates of ischemic stroke in patients undergoing CAS with and without these devices. The results of several observational studies suggest that EPDs reduce rates of adverse events during CAS (595–597) when operators are experienced with the apparatus (35); in unfamiliar hands, the devices are associated with worse clinical outcomes (454,456,457) and a higher rate of ischemic abnormalities on postprocedural brain imaging (598). Two postmarketing studies (362,372,375) found similar outcomes when physicians trained in different specialties with various levels of initial experience received training in CAS with EPD techniques. In an international survey of 12,392 CAS procedures performed by experienced operators in 11,243 patients at 53 sites, technical success was achieved in 98.9%, with rates of stroke and death of 2.8% when the devices were used and 6.2% when they were not (595). Although there was no difference in outcomes when experienced operators used the devices with a single CAS system in the ARCHeR trial (361), other studies have found that EPDs improved outcomes (366,369,370,376,580).

7.3.4. Intravascular Ultrasound Imaging in Conjunction With Catheter-Based Carotid Intervention

Intravascular ultrasound (IVUS) is an adjunctive imaging technique that can provide detailed information about the diameter of the vascular lumen, extent of atherosclerosis, and degree of calcification. IVUS has been used in coronary and peripheral arteries to verify complete deployment of intravascular stents, to measure plaque protrusion, and to detect arterial dissection after angioplasty. Identification of these complications during the procedure may permit modification of technique or suggest supplementary interventions to improve outcomes (599,600). Additionally, limited studies suggest that IVUS may be useful to assess plaque burden and composition.

Studies of IVUS in patients with ECVD have focused mainly on the safety of the technique and its potential contribution to the success of carotid revascularization (601,602). Experience to date suggests that IVUS can safely yield imaging information complementary to contrast angiography (603,604), and although incomplete stent expansion or small postprocedural stent diameter may be associated with a greater risk of restenosis (605), the use of IVUS has not been proven to improve outcomes, reduce periprocedural stroke rates, or prevent restenosis. Although the technique has been used safely in a small series of patients undergoing carotid intervention, the additional catheter manipulation required to traverse stenotic lesions carries risk, and more evidence demonstrating benefit is needed before the incremental risk associated with IVUS can be justified as the basis for recommendations regarding routine use of this technology in patients undergoing endovascular evaluation and treatment of ECVD.

7.3.5. Management of Patients Undergoing Endovascular Carotid Artery Stenting

7.3.5.1. 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. EPD deployment during CAS can be beneficial to reduce the risk of stroke when the risk of vascular injury is low (456,606). (*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 (364). 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*)

The periprocedural management of patients undergoing CAS can be organized according to distinct time frames. First is the preprocedural evaluation, which includes careful documentation of neurological status and identification of comorbidities that impact the patient's candidacy for endovascular intervention, such as peripheral arterial obstructive disease that limits catheter access, renal insufficiency, and contraindications to intensive platelet-inhibitor therapy. Second is the intraprocedural component, which involves

conscious sedation and analgesia along with monitoring and supportive care. Third is the immediate postprocedure period, when continued in-hospital support and monitoring are required with control of blood pressure, prevention of bleeding and access-site complications, and neurological reassessment. The fourth and final stage involves long-term postprocedural care, which is generally accomplished in the outpatient setting, aimed at preservation of neurological health and secondary prevention of complications of systemic atherosclerosis.

Intraprocedural management includes adequate anticoagulation, continuous assessment of neurological and hemodynamic parameters, and successful technical handling of the CAS procedure. Adequate anticoagulation can be achieved with unfractionated heparin given in sufficient dosage to maintain the activated clotting time between 250 and 300 seconds. Bivalirudin may have advantages over heparin, including obviating the need for monitoring of activated clotting time (607,608).

CAS is associated with a number of periprocedural events, including hypotension and vasovagal and vasodepressor reactions. For this reason, continuous electrocardiogram and blood pressure monitoring has become routine. Several pharmacological agents have been used to correct hemodynamic derangements during CAS. Atropine, 0.5 to 1 mg given intravenously, may be administered prophylactically before the angioplasty or stent portion of the procedure to avoid or attenuate bradycardia. Infrequently, persistent bradycardia may require insertion of a temporary transvenous pacemaker. Sustained hypotension is not rare, and it may be helpful to ensure adequate hydration and careful adjustment of antihypertensive medication immediately before the procedure. In the event of persistent hypotension, intravenous phenylephrine (1 to 10 mcg/kg/min) or dopamine (5 to 15 mcg/kg/min) should be available. Hypertension occasionally develops immediately before, during, or after the procedure, and maintenance of systolic blood pressure below 180 mm Hg is advised to minimize the risk of intracranial hemorrhage or the hyperperfusion syndrome.

The patient's neurological status, particularly level of consciousness, speech, and motor function, should be monitored throughout the stent procedure by the physician or circulating nurse. It is important to avoid excessive sedation to facilitate this ongoing assessment. When neurological dysfunction develops, management is complex and governed by the likely cause and the stage of the procedure at which it becomes manifest. If a neurological event occurs early in the procedure, such as during placement of the guidewire, it may be prudent to abort the procedure and reassess the patient for later intervention, if appropriate. If the event occurs near the completion of the procedure, it may be best to finish as quickly as possible and immediately assess the patient clinically and angiographically for correctable causes. A determination must then be made regarding neurological rescue or alternative management techniques (609).

Immediate postprocedural management includes care of the access site and monitoring of neurological and hemodynamic function. Formal neurological assessment should be documented within 24 hours after intervention. Patients who are stable and neurologically intact may be discharged on the first postprocedural day. In addition to aspirin (81 to 325 mg daily), it is conventional to administer clopidogrel (75 mg daily) for at least 4 weeks, mainly on the basis of experience gained in patients undergoing CAS. Smoking cessation and medications for control of hypertension, hyperlipidemia, and diabetes should be resumed or initiated. For neurologically intact patients with persistent hypotension, an additional period of in-hospital observation may be required. The use of the oral adrenergic agent ephedrine (25 to 50 mg orally, 3 or 4 times daily) may be useful in managing persistent hypotension.

Longer-term postprocedural management includes pharmacotherapy with antiplatelet medication and serial noninvasive imaging to assess stent patency and exclude the development of new areas of stenosis. Atherosclerotic risk factor modification is an ongoing task. The role of risk factor–modifying therapies, including smoking cessation and lipid-lowering and antihypertensive agents, was discussed in Sections 6.1 and 6.3.

Serial follow-up assessment most commonly involves duplex ultrasound imaging. By recent trial convention, surveillance should be performed at 1 month, 6 months, and annually to assess for restenosis. Imaging by CTA or MRA may also be helpful for surveillance after CAS, particularly when Doppler interrogation is difficult because of a superior anatomic location of the region of interest.

7.4. Comparative Assessment of Carotid Endarterectomy and Stenting

7.4.1. Nonrandomized Comparison of Carotid Endarterectomy With Carotid Artery Stenting

The CaRESS (Carotid Revascularization Using Endarterectomy or Stenting Systems) feasibility trial compared CAS and CEA in a broad population of patients with symptomatic carotid stenosis (>50%) or asymptomatic carotid stenosis (>75%) (610,611). To reflect the spectrum of patient characteristics encountered in clinical practice, enrollment was not limited to high-risk surgical candidates. The primary endpoint was the combined incidence of death and stroke within 30 days after the procedure. Treatment was not randomized but was determined on the basis of the recommendation of the treating physicians. A total of 397 patients underwent either CEA or CAS in a ratio of 2:1. Despite the lack of randomization, patient characteristics were reasonably balanced across treatment arms; 87% of patients undergoing CEA and 84% of those treated by CAS were considered high-risk surgical cases, as defined by age >80 years, New York Heart Association class III or IV heart failure, chronic obstructive pulmonary disease, >50%

Table 11. Kaplan-Meier Estimates of Event Rates in the CaRESS Trial

	≤30 Days (%)		≤365 Days (%)	
Event	CEA	CAS	CEA	CAS
Death	0.40	0.00	6.60	6.30
Stroke	3.60	2.10	9.80	5.50
MI	0.80	0.00	2.40	1.70
Death/stroke	3.60	2.10	13.60	10.00
Death/stroke/MI	4.40	2.10	14.30	10.90
Restenosis	N/A	N/A	3.60	6.30
Carotid revascularization	N/A	N/A	1.00	1.80

CaRESS indicates Carotid Revascularization Using Endarterectomy or Stenting Systems; CAS, carotid artery stenting; CEA, carotid endarterectomy; MI, myocardial infarction; and N/A, not available.

Modified from CaRESS Steering Committee (611).

contralateral carotid stenosis, prior CEA or CAS, or prior CABG surgery (610,611).

Kaplan-Meier estimates of event rates at 30 and 365 days after the procedure are provided in Table 11, along with observed rates of restenosis and carotid revascularization. There were no significant differences between the CEA and CAS groups for any outcome. Although these results may suggest similar outcomes with CEA and CAS in the first year, the nonrandomized design is an important limitation.

7.4.2. Meta-Analyses Comparing Carotid Endarterectomy and Stenting

A meta-analysis of 5 randomized trials comparing CAS with CEA disclosed no difference in stroke or death rates at 30 days (8.1% versus 6.3%); in MI, stroke, or death rates at 30 days (8.1% versus 7.8%); or in stroke or death rates at 1 year (13.5% versus 13.3%) (458). Another analysis of 6 trials involving 1,177 patients found no difference between CAS and CEA in 30-day or 1-year rates of stroke and death (612). The studies included both symptomatic and asymptomatic patients across a range of surgical risk, as well as stenting with and without EPDs. The authors noted that CAS was associated with a lower rate of MI (RR 0.3, 95% CI 0.1 to 0.8; p=0.02) and procedural morbidity such as cranial nerve injury (RR 0.05, 95% CI 0.01 to 0.3; p<0.001) (458). Other meta-analyses found CAS to be inferior to CEA or associated with higher rates of periprocedural stroke (613–615). In another meta-analysis of 11 trials that included 4,796 patients (10 of which reported on short-term outcomes [n=4,709] and 9 of which reported on intermediate-term outcomes, or 1 to 4 years), the risk of periprocedural mortality or stroke was lower with CEA than with CAS (OR 0.67, 95% CI 0.47 to 0.95; p=0.025). This was based mainly on a lower risk of stroke (OR 0.65, 95% CI 0.43 to 1.00; p=0.049), because the risk of death (OR 1.14, 95% CI 0.56 to 2.31; p=0.727) and the composite endpoint of mortality or disabling stroke (OR 0.74, 95% CI 0.53 to 1.05; p=0.088) did not differ significantly. The odds of periprocedural MI (2.69, 95% CI 1.06 to 6.79; p=0.036) or cranial nerve injury (10.2, 95% CI 4.0 to 26.1; p<0.001) were higher with CEA than with CAS. In the intermediate term, the treatments did not differ significantly for stroke or death (HR 0.90, 95% CI 0.74 to 1.1; p=0.314) (616).

7.4.3. Randomized Trials Comparing Carotid Endarterectomy and Carotid Artery Stenting

7.4.3.1. HIGH-RISK PATIENTS

The SAPPHIRE study (370,371) is the only randomized trial that specifically enrolled high-risk patients to compare CEA to CAS with an 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 after 334 patients were randomized, and many potential participants were excluded because they were considered to be at exceedingly high risk for complications if randomized to undergo CEA. Enrollment in the randomized portion of the trial diminished sharply 12 months after the study was initiated in 2000 (369). Technical success was achieved in 95.6% of patients who underwent CAS. The 30-day incidence of MI, stroke, or death was 4.8% after CAS and 9.8% after CEA (p=0.09). 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). The protocol required the collection of cardiac serum biomarker data as the basis for diagnosis of periprocedural MI, the majority of which were asymptomatic events. This was not the approach taken in earlier studies of revascularization, and the higher reported incidence of MI should be interpreted accordingly.

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%). At 1 year, CEA was associated with more cranial nerve palsy (4.9% versus none; p=0.004) and target-vessel revascularization (4.3% versus 0.6%; p=0.04). 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 (35,370,371).

7.4.3.2. CONVENTIONAL-RISK PATIENTS

The CAVATAS (Carotid And Vertebral Artery Transluminal Angioplasty Study) international randomized trial of endovascular versus medical therapy involved 504 patients (454). Although 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 intervention arm. Stroke or death at 3 years was similar in the 2 groups (14.2%) (454).

Table 12. SPACE Trial Results at 30 Days After the Procedure

Study Arm	CEA (N=584), n (%)	CAS (N=599), n (%)	Absolute Difference (CAS−CEA)
Primary response events	37 (6.3)	41 (6.8)	0.51% (−1.89% to 2.91%)*
Death	5 (0.9)	4 (0.7)	
All stroke	36 (6.2)	45 (7.5)	
Ischemic stroke	30 (5.1)	39 (6.5)	
Ipsilateral			
Hemorrhagic stroke	5 (0.9)	1 (0.2)	
Stroke			
Disabling stroke†	17 (2.9)	24 (4.0)	

*90% confidence interval. †Stroke resulting in a Modified Rankin Scale score of ≥3.
CAS indicates carotid artery stenting; CEA, carotid endarterectomy; and SPACE, Stent-Protected Angioplasty versus Carotid Endarterectomy.

The SPACE trial was designed to test the hypothesis that CAS would be noninferior to CEA in symptomatic patients with high-grade carotid artery stenosis (Table 12) (457). Patients were required to have >70% carotid stenosis determined by duplex ultrasound, TIA or stroke within the previous 180 days, and a Modified Rankin Scale score <4. Surgical risk status was not a determinant of eligibility. The primary outcome was a composite of ipsilateral stroke or death within 30 days of the procedure. Subjects were randomized between 2001 and 2006 to CEA (n=595) or CAS (n=605). The surgeons were required to have performed at least 25 CEA procedures with acceptable rates of mortality and morbidity in the prior year, and CAS operators were required to have performed at least 25 successful angioplasty or stent procedures, not necessarily involving carotid arteries. The use of shunting during CEA and the use of an EPD during CAS were optional. The 1,200-patient enrollment fell short of the planned sample size of 1,900 when the study was terminated because of inability to enroll the intended number of patients. Patient demographics and lesion characteristics were similar in the 2 groups, and there was no significant difference in outcomes between CAS and CEA at 30 days. Among the limitations of the SPACE trial were the unequal training and experience of surgeons performing CEA (617) and nonuniform use of EPDs during CAS procedures (618).

The EVA-3S (Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis) trial randomized patients within 120 days of TIA or completed stroke who had >60% ipsilateral carotid stenosis determined by duplex ultrasound and angiography (456). Patients were excluded if they had experienced a disabling stroke (Modified Rankin Scale score >3), but surgical risk status was not a specified exclusion criterion. The primary outcome was the composite of stroke or death within 30 days of the procedure. Surgeons were required to have 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. Trainees with little stenting experience were eligible to perform CAS if proctored by qualified operators. The use of EPDs was limited. After 520 patients were randomized, enrollment was stopped in 2005 because of higher 30-day rates of stroke and other adverse events in the CAS arm (Table 13). More patients assigned to CAS had occlusions of the contralateral carotid artery (5% versus 1.2%), a high-risk anatomic feature.

As with the SPACE trial (457), an important criticism of the EVA-3S trial (619) centers on inadequate training requirements for operators performing CAS and the nonuniform requirement to use an EPD, which may have compromised the results of CAS. The single-antiplatelet medication regimen used in some subjects has also been questioned. Although dual-antiplatelet therapy has been the standard in North American carotid stent trials, comparative outcome data from randomized clinical trials are available only for stents deployed in other (mainly coronary) vascular beds. Hence, the optimum dosing, timing, and duration of dual-antiplatelet therapy for patients undergoing CAS have not been established.

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. The ICSS is an ongoing randomized trial designed to compare the safety and effectiveness of CEA versus CAS in symptomatic patients with >50% carotid stenosis (368). Participating centers were classified as either experienced or supervised. Experience required that at least 1 surgeon at the center had performed at least 50 CEA procedures (mini-

Table 13. Result of the EVA-3S Trial at 30 Days After the Procedure

	CEA (N=259), n (%)	CAS (N=261), n (%)	OR (95% CI)	p
Primary response events	10 (3.9)	25 (9.6)	0.38 (0.16 to 0.84)	0.0133
Death	3 (1.2)	2 (0.8)	0.66 (0.17 to 18.30)	0.6851
All stroke	9 (3.5)	24 (9.2)	0.36 (0.14 to 0.81)	0.0108
Fatal stroke	2 (0.8)	1 (0.4)	2.02 (0.10 to 119.82)	0.6228
Nonfatal stroke	7 (2.7)	23 (8.8)	0.29 (0.10 to 0.71)	0.0041
Disabling stroke*	1 (0.4)	7 (2.7)	0.14 (0.0031 to 1.11)	0.0682

*Stroke resulting in a Modified Rankin Scale score of >3 with an increase of >2 over the score before the stroke.
CAS indicates carotid artery stenting; CEA, carotid endarterectomy; CI, confidence interval; EVA-3S, Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis. Adapted from Ringleb et al. (457) and Mas et al. (456).

mum of 10 per year) and at least 1 interventionist had performed at least 50 stenting procedures and a minimum of 10 carotid stents. Supervised centers were designated as experienced after randomization and treatment of 20 cases by CEA or CAS if the results were acceptable to a proctor and credentialing committee. Under this classification, 88% of patients were treated at experienced centers. The primary endpoint is the 3-year rate of fatal or disabling stroke, but only an interim safety analysis has been reported. Among 1713 randomized patients, the 120-day composite rate of stroke, death, or procedural MI was 8.5% in the CAS group versus 5.2% in the CEA group (HR 1.69, 95% CI 1.16 to 2.45). Although the investigators suggested at that point that CEA should be preferred over CAS in similar patients, firm conclusions await completion of longer-term follow-up of the cohort.

CREST is a randomized multicenter trial comparing CAS to CEA in both symptomatic and asymptomatic patients (620–622). The primary endpoint is the occurrence of stroke, death, or MI during the periprocedural period and ipsilateral stroke thereafter up to 4 years. CREST is unique among the reported randomized trials comparing CAS and CEA in conventional-risk patients because it included both symptomatic patients with >50% carotid stenosis and asymptomatic patients with >60% stenosis. Among 2502 patients followed up for a mean of 2.5 years, there was no significant difference in primary events between the 2 methods of revascularization (7.2% with CAS versus 6.8% with CEA; HR 1.11, 95% CI 0.81 to 1.51). Despite the similarity in primary outcome, there were differences in rates of the component periprocedural events. Stroke was significantly more frequent with CAS (4.1% versus 2.3%; p=0.01), and MI was more likely after CEA (2.3% versus 1.1%; p=0.03), although the absolute rates of either were low. Questions have arisen regarding the comparative impact of periprocedural stroke and MI on the patient. In CREST at 1 year, quality of life was impacted significantly by major and minor stroke but not by MI. The lack of a detectable impact of MI on quality of life may relate to sensitive ascertainment techniques, including biomarker assessments, such that the rate of MI in CREST was higher than that reported in other randomized trials. The comparative primary results between treatment groups did not vary by sex or symptom status, although event rates were higher among symptomatic patients in both groups than among asymptomatic patients. For both symptomatic and asymptomatic patients, the periprocedural stroke and death rates at the 117 centers in CREST were at or below the recommended safety requirements in current guideline statements (111). Consistent with reports from the SPACE trial, there was a differential outcome based on patient age: For patients younger than 70 years of age, the primary results favored CAS, whereas in those older than 70 years of age, results favored CEA (360). Also, as in previous randomized trials, cranial nerve palsy was more common after CEA (360).

Table 14. 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 (70) but generally corresponds as well to assessment by sonography (136) and other accepted methods of measurement. See Sections 7.2 to 7.4.4 for details.
LOE indicates level of evidence.

ACST-2 and ACT-1 (Asymptomatic Carotid Trial) compare CEA with CAS in patients with asymptomatic carotid stenosis (http://www.ClinicalTrials.gov and http://www.controlled-trials.com), but no outcome data have yet been reported.

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

Table 14 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 10. In addition to these are comorbid medical conditions associated with increased surgical risk, such as advanced cardiopulmonary disease that might complicate surgical anesthesia.

Recent large trials like CREST make it clear that with adequate training, physicians can perform CAS and CEA with low complication rates. Taken together with the results of previous trials, it appears that CAS is associated with a higher periprocedural risk of stroke or death. Although this difference remained significant in CREST for up to 4 years, a meta-analysis of studies that preceded CREST found CEA to be superior to CAS with regard to short-term but not longer-term outcomes (616). Hence, additional long-term data are needed before clear conclusions can be drawn regarding the relative risks and benefits of the 2 procedures (623). Although the increased risk of nonfatal stroke with CAS is statistically offset by an increased risk of nonfatal MI with CEA, stroke appears to have more detrimental health consequences. Similarly, local complications, particularly cranial nerve palsies, are more frequently associated with CEA, whereas microembolic cerebral injury after CAS may have implications for cognitive function. Although the reasons remain speculative, the interaction of patient age with the outcomes of CAS and CEA must also be considered carefully by clinicians, with CEA favored for elderly patients. Finally, the benefit of revascularization by either method versus modern aggressive medical therapy has not

been established for patients with asymptomatic carotid stenosis.

7.5. Durability of Carotid Revascularization

7.5.1. 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 (see Sections 7.5.2 and 7.5.3). (*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*)

7.5.2. Clinical Durability of Carotid Surgery and Carotid Stenting

Clinical durability refers to the sustained efficacy of CEA and CAS in preventing stroke, as discussed for CEA in Section 7.2. 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). For clinical durability of CEA compared with CAS, longer-term results from EVA-3S and SPACE are now available and show promising results for both procedures. EVA-3S outcomes projected to 4 years showed ipsilateral stroke rates beyond 30 days of <1% per year for both CEA and CAS. In SPACE, at 2 years, the ipsilateral stroke rate was approximately 1% per year for CEA and CAS when periprocedural events were excluded. The clinical durability of CEA and CAS beyond 5 years cannot be clearly determined from available studies (364,379).

The mechanism responsible for arterial restenosis after CEA is related to the postoperative interval. Early restenosis (within 2 years) typically involves intimal hyperplasia, whereas later restenosis usually reflects progression of atherosclerotic disease. Outcomes are similar regardless of whether the patch material is vein, polyethylene terephthalate, polytetrafluoroethylene, or bovine pericardium (624–627). The role of CAS as an alternative to reoperative CEA in patients who experience restenosis after initial CEA is discussed in Section 7.3.

7.5.3. Anatomic Durability of Carotid Surgery and Carotid Stenting

The incidence of recurrent carotid stenosis depends on the method used for detection. Restenosis after CEA has been reported in 5% to 10% of cases when assessed by postoperative ultrasonography, but the rate has been consistently below 5% when patching was used in more recent series (407,440,468,624,625,628–630). When periodic duplex scanning is used, hemodynamically significant recurrent stenosis rates of 5% to 7% have been reported in multicenter trials in which the quality of surgery is monitored carefully (396,403,404,406,440,628,631–645).

Recurrent carotid stenosis after CEA is a trimodal phenomenon. The first event is not really recurrence but instead represents an unsatisfactory or incomplete CEA. This is usually detected when the first postoperative duplex ultrasound scan identifies residual stenosis, and its occurrence can be minimized by intraoperative completion angiography or duplex ultrasound imaging. Because the quality of CEA has improved, this phenomenon occurs in <1% of cases. The second peak of recurrent carotid stenosis, occurring within 18 months and usually within 6 months after operation, is due to intimal hyperplasia. This is usually benign, seldom requires reoperation, and has been reduced through the routine incorporation of patch angioplasty closure into the operative procedure. The third form of recurrent stenosis usually develops 5 years or longer after operation and reflects progressive atherosclerotic disease either at the site of CEA or in proximal or distal arterial segments.

For both CEA and CAS, comparative data on restenosis are becoming available but should be interpreted with caution. A minority of patients in contemporary studies have undergone follow-up ultrasound scanning, which introduces potential important selection bias. For CAS, the role of stent-generated artifacts in ultrasound velocity measurements has yet to be resolved with angiographic comparisons. In the CAVATAS study, a stent was used in only 22% of the angioplasty patients, and carotid ultrasound at 1 year detected 70% to 99% stenosis in 4% of the CEA patients and in 14% of the patients managed by CAS ($p<0.001$). In SAPPHIRE, all CAS patients received a stent; 96 of the CEA patients and 122 of the CAS patients underwent carotid ultrasound at 1 year. Four CEA patients (4.2%) and 1 CAS patient (0.8%) had >70% recurrent stenosis ($p=0.17$). After 1 year of follow-up in the SPACE trial, 4.6% of patients who underwent CEA and 10.7% of those who underwent CAS had developed ≥70% recurrent stenosis as assessed by ultrasound ($p=0.0009$). Comparative restenosis rates for CEA and CAS are also available from case series (646–649), but inference is limited by potential selection bias.

In patients who develop restenosis after CEA, CAS is an alternative to reoperative CEA (see Section 7.2.4) and may be appropriate in asymptomatic patients with restenosis that

produces >80% luminal narrowing or in symptomatic patients with >50% recurrent stenosis. Contralateral occlusion arguably increases the risk associated with CAS, because the procedure does not provide an option to use a shunt, and little collateral circulation is available in the event of thrombosis or occlusion of an EPD. On the other hand, 3 studies (ARCHeR, a nonrandomized prospective study [361]; SAPPHIRE, a randomized comparison [370]; and CAPTURE, a multicenter registry [372]) specifically addressed the use of CAS in patients with carotid stenosis and contralateral carotid occlusion. The prevalence of contralateral carotid occlusion was 16.5% in ARCHeR, 24.5% in SAPPHIRE, and 8.2% in CAPTURE. Although the overall results of these limited studies suggested that CAS was noninferior to CEA in patients with various comorbidities (including but not limited to contralateral occlusion), the 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 a benign condition that does not require revascularization except in selected circumstances, such as when restenosis 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 as in the general approach to patients with unsuitable neck anatomy.

8. Vertebral Artery Disease

Symptomatic obstructive disease of the vertebral arteries is encountered less commonly in clinical practice than carotid stenosis, and the volume of evidence available to guide its evaluation and management is less substantial. The prevalence, pathophysiology, and natural history of vertebral artery disease are not as well understood as disease of the extracranial carotid circulation. Like patients with carotid atherosclerosis, however, those with vertebral artery disease face an increased risk of other cardiovascular ischemic events, including MI, PAD, and vascular death.

8.1. Anatomy of the Vertebrobasilar Arterial Circulation

The left and right vertebral arteries are typically described as having 4 segments each (V1 through V4), the first 3 of which are extracranial. The first segments (V1) extend cephalad and posteriorly from the origin of the vertebral arteries between the longus colli and scalenus anterior muscles to the level of the transverse foramina, typically adjacent to the sixth cervical vertebra. The second segments (V2) extend cephalad from the point at which the arteries enter the most inferior transverse portion of the foramina to their exits from the transverse foramina at the level of the second cervical vertebra. These segments of the left and right vertebral arteries therefore have an alternating intraosseous and interosseous course, a unique anatomic environment that exposes the V2 segments to the possibility of extrinsic compression from spondylotic exostosis of the spine. Small branches from the V2 segments supply the vertebrae and adjacent musculature and, most importantly, may anastomose with the spinal arteries. The third segments (V3) extend laterally from the points at which the arteries exit the C2 transverse foramina, cephalad and posterior to the superior articular process of C2, cephalad and medially across the posterior arch of C1, and then continue into the foramen magnum. Branches of the V3 segments typically anastomose with branches of the occipital artery at the levels of the first and second cervical vertebrae. The fourth segments (V4) of each vertebral artery extend from the point at which the arteries enter the dura to the termination of these arteries at the vertebrobasilar junction. Important branches of the V4 segments include the anterior and posterior spinal arteries, the posterior meningeal artery, small medullary branches, and the posterior inferior cerebellar artery.

Anatomic variants of vertebral artery anatomy are much more common than variants of the carotid circulation. The vertebral arteries typically arise from the subclavian arteries; in approximately 5% of individuals, however, the left vertebral artery arises directly from the aortic arch. The diameter of the left vertebral artery diameter is larger than (in 50% of individuals) or equal to (in 25% of individuals) that of the right vertebral artery. In approximately 10% of people, 1 vertebral artery is markedly smaller than the other. When this is the case, the smaller vertebral artery may terminate in the posterior inferior cerebellar artery or have a hypoplastic segment that extends beyond the posterior inferior cerebellar artery to the basilar artery, contributing little to basilar artery blood flow. These important anatomic variations must be considered in clinical assessment and treatment.

8.2. Epidemiology of Vertebral Artery Disease

Because it may be difficult to visualize the origins of the vertebral arteries by ultrasound imaging, the incidence of posterior circulation strokes may be underestimated (650), but vertebral artery atherosclerosis may be the causative basis for approximately 20% of posterior circulation strokes (650–653). In the New England Medical Center Posterior Circulation Registry, 82 of 407 patients with ischemia affecting the posterior circulation had >50% stenosis of the extracranial vertebral artery (654). Annual stroke rates for patients with symptomatic intracranial vertebral and basilar artery stenosis are 8% and 11%, respectively (655–657). A study using contrast-enhanced MRA in consecutive patients with posterior circulation TIA or minor stroke found a greater prevalence of >50% vertebral and basilar arterial stenosis than of >50% carotid stenosis in patients with carotid territory events, and vertebrobasilar arterial stenosis was more often associated with multiple ischemic episodes and a higher risk of early recurrent stroke (658).

8.3. 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 as they arise from the brachiocephalic and subclavian arteries. Lesions at the midportion of the vertebral arteries can occur when overgrowth of the transverse process of a vertebra impinges on the artery as it passes through the bony canal. In such cases, symptoms are commonly provoked by head turning, during which an osteophyte obstructs the vertebral artery.

Symptoms associated with vertebral artery occlusive 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.

8.4. 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 (659).

8.5. Vertebral Artery Imaging

8.5.1. 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*)

In contrast to the wealth of literature on carotid arterial imaging, published data on noninvasive imaging of the vertebrobasilar arterial system are relatively sparse. A systematic review found 11 studies that evaluated noninvasive imaging methods compared 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 duplex ultrasonography (sensitivity 70%), and CTA had slightly superior accuracy (167). The relative insensitivity of ultrasound reflects the technical difficulty involved in sonographic interrogation and makes this method less suitable for detection of disease in this anatomic region. Local expertise and availability of imaging techniques must also be considered in the selection of noninvasive modalities in a given clinical situation. Because neither MRA nor CTA reliably delineates the origins of the vertebral arteries, catheter-based contrast angiography is typically required before revascularization for patients with symptomatic posterior cerebral ischemia. Digital subtraction arteriography with intravenous contrast administration is sometimes used when selective catheterization of the vertebral arteries cannot be achieved, but the accuracy of this method compared with CTA has not been established.

8.6. Medical Therapy of Patients With Vertebral Artery Disease

8.6.1. 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 (261,660). (*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 (305,661). (*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 dipyridamole (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 (260,305,339–342). (*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*)

Optimum management of patients with symptomatic vertebral artery stenosis is not as well established as that for patients with carotid stenosis. 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. In fact, few trials involving ischemic stroke have distinguished between anterior or posterior circulatory disease. In general, despite the relative paucity of evidence specifically applicable to patients with vertebral artery disease, we recommend that medical management follow the guidelines set forth for those with disease of the carotid arteries. This is particularly true of measures directed at reduction of systemic atherosclerotic risk and the prevention of ischemic complications in other vascular beds.

For patients with acute ischemic syndromes that involve the vertebral artery territory, studies of intravenous thrombolytic therapy have reported variable outcomes (650,662,663). When there is angiographic evidence of thrombus at the origin or extracranial portion of the vertebral artery, anticoagulation is generally recommended for at least 3 months, whether or not thrombolytic therapy is used initially (662,664–666). The WASID (Warfarin versus Aspirin for Symptomatic Intracranial Disease) trial found aspirin and warfarin to be equally efficacious after initial noncardioembolic ischemic stroke (656,667). Ticlopidine was superior to aspirin for secondary prevention of ischemic events in patients with symptomatic posterior circulation disease (668). In ESPS-2, vertebrobasilar territory stroke or TIA occurred in 5.7% of 255 patients treated with a combination of low-dose aspirin and sustained-release dipyridamole twice daily compared with 10.8% of those given a placebo (669).

8.7. Vertebral Artery Revascularization

8.7.1. Surgical Management of Vertebral Artery Disease

Compared with CEA, operations are rarely performed to treat vertebral artery occlusive disease. Although no randomized trials have addressed operative procedures for posterior cerebral circulation disease, reports of surgical treatment of patients with extracranial vertebral artery stenosis have demonstrated the feasibility of endarterectomy and vessel reconstruction with favorable outcomes (670–677). For proximal vertebral artery reconstruction, early complication rates of 2.5% to 25% and perioperative mortality rates of 0% to 4% have been reported (671,672). For distal vertebral artery reconstruction, mortality rates have ranged from 2% to 8% (670,673,674,676,677). Intracranial bypass surgery is associated with mortality rates of 3% to 12% and neurological and systemic complication rates of 22% to 55% (673–677).

When symptoms can be clearly attributed to occlusive disease of the vertebral arteries, corrective surgery may be effective. Indications for surgery on the first portion of the vertebral artery are relatively rare. When both vertebral arteries are patent and 1 has a significant stenotic lesion, the contralateral vertebral artery usually supplies sufficient blood flow to the basilar artery, provided there is anatomic continuity. This is particularly true if the uninvolved vertebral artery is the larger (dominant) vessel. Compromised vertebrobasilar perfusion is not the only mechanism of symptoms, however, because atheroembolism from lesions at the origin of the vertebral artery may be the source of brainstem or cerebellar infarction.

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, necessitated by total occlusion of the midportion, may be accomplished by anastomosis of the principal trunk of the external carotid artery to the vertebral artery at the level of the second cervical vertebra (678). Such operations, although rare, can relieve symptoms, with low rates of morbidity and mortality in appropriately selected patients (670,679–686).

8.7.2. Catheter-Based Endovascular Interventions for Vertebral Artery Disease

Although angioplasty and stenting of the vertebral vessels are technically feasible, as for high-risk patients with carotid disease, there is insufficient evidence from randomized trials to demonstrate that endovascular management is superior to best medical management. In a review of 300 interventions for proximal vertebral artery stenosis, the risk of death was 0.3%, the risk of periprocedural neurological complications was 5.5%, and risk of posterior stroke was 0.7% at a mean follow-up of 14.2 months. Restenosis occurred in 26% of cases (range 0% to 43%) after a mean of 12 months (range 3 to 25 months), although restenosis was not consistently correlated with recurrent symptoms (687). Among 170 angioplasty procedures in patients with distal vertebrobasilar disease, neurological complications developed in 24%, but the rate approached 80% in cases of urgent vertebrobasilar revascularization. Restenosis developed in 10% after a mean follow-up interval of 12.6 months (687). When data from 14 case series were combined, the annual stroke risk after angioplasty for distal vertebrobasilar disease was approximately 3% (687), and rates of stroke and restenosis appeared to be related to ascending (more distal) location and the anatomic complexity of the offending lesion.

CAVATAS (688), the only randomized study to date to compare outcomes after endovascular and medical treatment for patients with vertebral artery stenosis, included only 16 such patients (454,688,689), in contrast to 504 patients with carotid stenosis, and because no patient in either arm had recurrent vertebral basilar territory stroke by 8 years after randomization, there was no difference in outcomes among those treated by stenting or medical therapy. The lower rate of diagnosis of symptomatic verte-

bral artery stenosis versus carotid artery disease illustrates the inherent difficulty in demonstrating a benefit of vertebral artery revascularization.

9. Diseases of the Subclavian and Brachiocephalic Arteries

9.1. 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 (690–692). (*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*)

9.2. Occlusive Disease of the Subclavian and Brachiocephalic Arteries

Occlusive disease that involves the subclavian and brachiocephalic arteries is relatively uncommon. Causes include 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 severity of disease. Symptoms may reflect upper-extremity ischemia, such as arm or hand claudication, paresthesia, or rest pain.

Subclavian artery stenosis is generally associated with a favorable prognosis. Some patients with high-grade stenosis and mild upper-extremity claudication become asymptomatic as collateral blood supply develops. In asymptomatic patients, subclavian intervention may be performed in preparation for coronary revascularization surgery that requires use of the ipsilateral internal mammary artery as a bypass conduit or to preserve blood flow to the internal mammary artery in patients who require myocardial revascularization. To our knowledge, no randomized trials of subclavian artery or brachiocephalic revascularization have been published.

9.3. Subclavian Steal Syndrome

When the proximal subclavian artery becomes stenotic or occluded, branches distal to the obstruction become sources of collateral circulation to the arm by flow reversal in the vertebral artery and internal mammary arteries. Usually, this does not cause symptoms except for muscular fatigue in the affected arm, akin to claudication. Because 2 vertebral arteries normally supply blood to the basilar artery, antegrade flow through 1 is usually sufficient to maintain posterior cerebral circulation. When the dominant vertebral artery is subtended by subclavian obstruction, reversal of flow in the vertebral artery may reduce basilar artery perfusion and cause posterior cerebrovascular insufficiency. Symptoms are typically aggravated by exercising the ipsilateral arm, which amplifies the flow reversal as a source of collateral circulation to the subclavian artery and its branches. The same phenomenon affects the internal mammary artery, compromising its utility as a conduit for CABG surgery.

Detection of a periclavicular or infraclavicular bruit suggests the possibility of subclavian stenosis, but subclavian arterial occlusive disease is most readily recognized on the basis of asymmetry between left and right arm blood pressure measurements. The side with the lower pressure is suspect for subclavian artery stenosis or occlusion, and blood pressure tends to fall further in the affected limb after arm exercise. Blood pressure measurements may not be asymmetrical 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 symptoms of posterior cerebral circulatory insufficiency aggravated by upper-limb exercise. In the vertebral ischemic form of subclavian steal syndrome, upper-extremity exertion leads to retrograde flow in the ipsilateral vertebral artery, and symptoms of posterior cerebral or cerebellar hypoperfusion, including lightheadedness, syncope, vertigo, ataxia, diplopia, and motor deficits may occur; the patient may also develop upper-limb claudication. In the less common coronary ischemic form of subclavian steal syndrome, blood is diverted from the coronary arteries to the upper limb through an internal mammary artery graft during arm exercise, producing angina pectoris. Involvement of the brachiocephalic or common carotid artery can lead to symptomatic cerebral hypoperfusion. Duplex ultrasonography may identify reversal of flow in a vertebral

artery, and CTA or MRA of the aortic arch may identify stenosis of the subclavian artery.

Asymptomatic patients with asymmetrical upper-limb blood pressure, reversal of flow in a vertebral artery, or other manifestations of subclavian steal syndrome need no specific intervention other than strategies directed at the secondary prevention of ischemic events related to systemic atherosclerosis, unless the ipsilateral internal mammary artery is required for myocardial revascularization. Symptomatic patients should be considered for subclavian revascularization with endovascular or surgical techniques.

9.4. Revascularization of the Brachiocephalic and Subclavian Arteries

The main surgical approach to revascularization involves prosthetic extra-anatomic bypass grafting from the ipsilateral carotid artery to the subclavian artery, which is highly effective in delivering blood to the subclavian artery and restoring antegrade vertebral artery flow to the basilar artery. In addition to carotid-subclavian bypass, commonly used extra-anatomic methods of subclavian artery revascularization include carotid-axillary or axilloaxillary bypass with polytetrafluoroethylene or Dacron grafts and subclavian-carotid arterial transposition. Surgical repair is associated with low morbidity and mortality and excellent long-term patency (690,693).

Subclavian artery stenosis is also amenable to balloon angioplasty, atherectomy, and stenting. No randomized trials have compared these methods with surgical revascularization, but numerous reports from single institutions have provided data about early and long-term results, and 2 reports compared results of catheter-based and surgical revascularization in patients with symptomatic obstructive subclavian artery disease (692,694,695). In a series of 110 patients reported in 2005, the procedure was considered initially successful in 93% of cases (694). In 6% of cases, total occlusion of the subclavian artery precluded cannulation. Of the cases in which the artery was initially opened, the median obstruction-free interval was 23 months, and 89% maintained patency at 5 years. Four recurrent stenoses were treated successfully by percutaneous angioplasty, and 4 required surgical revascularization. In a nonrandomized comparison of endovascular revascularization with extra-anatomic bypass surgery for subclavian stenosis, all bypass grafts remained patent except 1 that occluded 19 years after operation (692). In contrast, 6 of 46 attempted subclavian artery angioplasties could not be completed because of occlusive lesions. Among the arteries successfully opened, the 4-year patency rate was 82%.

In a report that compared 121 patients undergoing stenting and 51 undergoing carotid-subclavian bypass, initial success rates were 98% and 100% for the endovascular and surgical approaches, respectively, whereas periprocedural complication rates were 15.1% and 5.9%, being lower in the surgical group (695). There were no cases of perioperative stroke or mortality in those selected for bypass surgery, whereas complications in the stent group included thromboembolism, heart failure, arm edema after reperfusion, arterial pseudoaneurysm, and 1 death. 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 ($p<0.0001$) (695). Whether the use of drug-eluting stents for this application will reduce the need for subsequent revascularization has not been determined.

Balloon angioplasty and stenting are associated with high rates of success and better outcomes than balloon angioplasty alone (694,696–700), which makes endovascular stenting an alternative to open surgery in patients with obstructive disease of the subclavian or brachiocephalic arteries. Few studies have compared these approaches, but 1 demonstrated equal effectiveness and fewer complications with stenting (697). Numerous reports have suggested 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 (695,701–704). A retrospective comparison of percutaneous revascularization with carotid-subclavian bypass surgery in patients with isolated subclavian artery disease described excellent technical success with both methods, but the primary patency rates at 1, 3, and 5 years were higher with bypass surgery. Although the currently prevailing view favors bypass surgery for good surgical candidates and percutaneous stenting of the subclavian artery for patients at high risk of surgical complications, physicians experienced with both techniques may prefer to take a percutaneous catheter-based approach initially when the anatomy is suitable and reserve surgery for patients with total arterial occlusion or stenotic lesions that are anatomically unsuited to catheter intervention.

Brachiocephalic artery occlusive disease is often accompanied by carotid or subclavian artery stenosis (705), but the natural history is less well understood. Patients may present with an asymptomatic blood pressure disparity between arms or with upper-extremity claudication, subclavian steal, TIA, or stroke. Transthoracic surgical revascularization involves aorta-innominate or aorta-carotid bypass with subclavian artery reimplantation; brachiocephalic endarterectomy is less commonly used. Transthoracic revascularization is preferred in patients with embolism when the source can be excluded concurrent with distal brachiocephalic artery revascularization. Graft patency is excellent, but the combined rate of perioperative stroke and death is as high as 16% (705,706). Survival after transthoracic arterial reconstruction has been reported as 73% and 52% at 5 and 10 years, respectively (705).

10. Special Populations

10.1. Neurological Risk Reduction in Patients With Carotid Artery Disease Undergoing Cardiac or Noncardiac Surgery

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

CLASS IIa

1. Carotid duplex ultrasound screening is reasonable before elective 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 IIb

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*)

10.1.2. Neurological Risk Reduction in Patients With Carotid Artery Disease Undergoing Coronary Bypass Surgery

Whether or not symptomatic of carotid atherosclerosis, 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. Considerable evidence suggests that patients undergoing combined CABG surgery plus CEA are at high risk of stroke, but there is no convincing evidence that such intervention in a patient with asymptomatic stenosis undergoing CABG surgery produces benefit in the majority of cases (707). In patients with symptomatic carotid stenosis, published reports indicate that the performance of CEA before CABG surgery is associated with a lower stroke rate but a higher rate of fatal and nonfatal MI. Combined CEA and CABG surgery has been associated with a lower rate of MI, stroke, and death than staged surgery in some reports, but this strategy has not been tested in prospective trials. Other studies suggest that the combination of CEA with CABG surgery is associated with a higher risk of stroke and death than CABG surgery alone (495,708). Proof is lacking that carotid revascularization reduces adverse events in patients with asymptomatic carotid stenosis who are undergoing myocardial revascularization surgery (709), so clinical practice must follow a patient-specific approach.

Although carotid angioplasty and stenting would appear to be a logical alternative to CEA in this situation, catheter-based carotid interventions require periprocedural treatment with potent platelet-inhibitor drugs such as clopidogrel, which greatly increases the risk of major bleeding associated with CABG surgery, and delaying antiplatelet therapy raises the risk of stent thrombosis and stroke. Another strategy is to perform carotid intervention immediately before coronary surgery and administer intravenous heparin between the procedures, but this approach and the optimum revascularization strategy in general for patients with combined carotid artery disease and CAD that requires intervention have not been evaluated properly (707,708,710–714). The Nationwide Inpatient Sample included 27,084 patients discharged after undergoing CAS before CABG surgery or combined CEA and CABG surgery during the 5 years from 2000 to 2004 (715). Of these, 96.7% underwent CEA plus CABG surgery versus 3.3% (887 patients) who had CAS plus CABG surgery. Fewer major adverse events were reported among patients undergoing CAS plus CABG surgery than among those undergoing CEA plus CABG surgery. Patients who had CAS plus CABG surgery also had a lower incidence of postoperative stroke (2.4% versus 3.9%) and of combined stroke and death (6.9% versus 8.6%) than those managed by the combination of CEA with CABG surgery ($p<0.001$), although rates of in-hospital mortality were similar with the 2 approaches (5.2% versus 5.4%). In this nonrandomized cohort, patients undergoing CEA plus CABG surgery faced a 62% greater risk of postoperative stroke than patients undergoing CAS before CABG surgery (OR 1.62, 95% CI 1.1 to 2.5; $p=0.02$). There was no difference in the combined risk of stroke and death according to treatment strategy (OR 1.26, 95% CI 0.9 to 1.6; p=NS) (715). Whether the lower rate of complications with CAS than with CEA in this population undergoing CABG surgery reflects case-selection bias or an intrinsic safety advantage remains uncertain, and the findings justify the conduct of properly designed prospective studies to compare these approaches.

10.1.3. Neurological Risk Reduction in Patients Undergoing Noncoronary Cardiac or Noncardiac Surgery

For guidance about the management of patients undergoing other types of cardiac and noncardiac surgery, the reader is referred to the 2009 ACCF/AHA Focused Update on Perioperative Beta Blockade Incorporated Into the ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery (716).

11. 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.

11.1. Fibromuscular Dysplasia

11.1.1. 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 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*)

FMD is a nonatherosclerotic, noninflammatory vascular disease characterized by either focal stenosis or multiple constrictions due to thickening of a layer of the arterial wall. Multiple histological subtypes have been defined (717), most commonly medial fibroplasia, which imparts a beaded appearance to the carotid artery. Intimal fibroplasia, which causes a focal, concentric, or tubular stenosis similar to atherosclerotic narrowing, is much less common. The disease can affect any portion of the cervical or intracranial arteries but most frequently involves the internal carotid arteries bilaterally. The incidence of carotid FMD is low; it is most commonly encountered in middle-aged women, who may be symptomatic or asymptomatic. When symptomatic, clinical manifestations of FMD depend on the location and the extent of arterial obstruction. Stroke, TIA, carotid dissection, Horner syndrome, cranial nerve palsies, and subarachnoid hemorrhage have been described (717–720).

The pathophysiology and natural history of FMD are unknown. Gross pathological manifestations include elongation, kinking, and coiling of the carotid artery. Web-like lesions may obstruct flow, and aneurysmal dilation of the carotid artery has been described (721). Symptoms are thought to result from reduced blood flow or thromboembolism. The relationship of FMD to carotid arterial dissection is poorly understood, but spontaneous dissection and aneurysmal degeneration are additional causes of symptomatic events in patients with carotid FMD.

Treatment of carotid FMD depends on whether the patient is symptomatic. Antiplatelet therapy and sequential imaging to monitor changes in the extent of disease over time are generally recommended even for asymptomatic patients. Both surgical revascularization (722) 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 increasingly has been advocated on the basis of case reports and series of limited scope (723,724).

11.2. Cervical Artery Dissection

11.2.1. 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. Antithrombotic treatment with either an anticoagulant (heparin, low molecular weight heparin, or warfarin*) or a platelet inhibitor (aspirin, clopidogrel, or the combination of extended-release dipyridamole plus aspirin*) for at least 3 to 6 months is reasonable for patients with extracranial carotid or vertebral arterial dissection associated with ischemic stroke or TIA (724a–724d). (*Level of Evidence: B*)

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*)

Carotid or vertebral artery dissection is an uncommon but sometimes dramatic cause of acute or progressive neurological ischemic symptoms. Carotid artery dissection may occur spontaneously, unheralded by symptoms. Minor trauma such as hyperflexion or hyperextension of the neck (the so-called beauty parlor stroke), chiropractic manipulation, coughing, and nose blowing have been associated with carotid dissection (725).

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. The underlying structural defect of the arterial wall remains unknown, but a number of pathological associations have been described. Specific connective tissue disorders thought to form an etiologic basis for carotid dissection include the Ehlers-Danlos syndrome type IV, Marfan syndrome, autosomal dominant polycystic kidney disease, hyperhomocysteinemia, and osteogenesis imperfecta. There may also be an association with bicuspid aortic valve, but carotid dissection is observed in only 1% to

*Drugs are not listed in order of preference.

5% of patients with this disorder. The association of carotid dissection with FMD is greater, at approximately 15%, but the mechanistic relation between these disorders is not well understood.

Community-based studies suggest that the annual incidence of spontaneous carotid artery dissection is approximately 2.5 to 3 per 100,000 population and that carotid artery dissection accounts for approximately 2% of ischemic strokes. The proportion is greater among younger patients, in whom carotid dissection may account for 10% to 15% of ischemic strokes (726). The incidence of vertebral artery dissection has not been well defined. One of the 4 segments of the vertebral artery (V3) is connected to highly mobile cervical vertebrae, and this mechanical vulnerability underlies the presumption that sudden or excessive neck movement might increase the risk of vertebral artery dissection (727). Other suspected risk factors for cervical arterial dissection include penetrating trauma (728) and amphetamine abuse (729). A structured review found that the incidence of vertebral artery dissection or occlusion attributable to cervical manipulation in patients <45 years of age was approximately 1.3 per 100,000 within 1 week of manipulative therapy (730).

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

The diagnostic algorithm 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 of carotid artery dissection, largely supplanting catheter-based and digital subtraction angiography. Selective catheterization of the arteries that supply the posterior cerebral circulation is sometimes the only way to delineate collateral filling via the circle of Willis, which may be important in guiding management. Dissection that begins cephalad of the angle of the mandible may not be detected by ultrasound, and in these cases contrast-enhanced CTA and MRA are superior modalities.

Treatment is usually conservative, involving anticoagulation with heparin followed by warfarin; with this approach, the prognosis is usually favorable (731–733). There have been no placebo-controlled trials of anticoagulant or antiplatelet agents or randomized trials comparing anticoagulant and antiplatelet therapy (734). In a small observational study of patients with cervical artery dissection conducted by the Canadian Stroke Consortium, the annual rate of recurrent stroke, TIA, or death was 12.4% among patients treated with aspirin versus 8.3% in those given anticoagulants (735). Anticoagulation may adversely influence the outcome of subarachnoid hemorrhage in the event of intracranial extension of cervical artery dissection. Regardless of initial antithrombotic therapy during the acute phase, antiplatelet therapy may replace anticoagulation once symptoms resolve, but no uniform approach has been developed regarding the timing of this transition, and no antithrombotic regimen has been established as superior to another.

Surgical or endovascular revascularization is reserved for patients with persistent or recurrent symptoms that fail to respond to anticoagulation. Surgical revascularization techniques include direct carotid repair and resection with vein graft replacement (736,737). Endovascular stent angioplasty has been successful in a small number of patients but has been associated with complications in others (738–748).

12. 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.

A major hurdle to overcome is the lack of sound evidence with which to target asymptomatic patients above specific risk thresholds for detection of hemodynamically significant carotid stenosis and, more pertinent, to identify those who may benefit from therapeutic intervention. To date, no screening program for detection of carotid stenosis has demonstrated the capacity to reduce stroke risk for any defined cohort, and as a result, no solid consensus can be developed concerning which patients should undergo diagnostic screening. More work is also needed to gauge the value of measuring the IMT of the carotid artery wall as a way of directing preventive therapies to those at risk of progressive carotid atherosclerosis. Outcome-based validation of the value of IMT measurements to guide treatment interventions for individual patients would help overcome an important impediment to proper application of this imaging technology and improve understanding of the pathogenesis of the most common cause of ECVD.

Despite considerable progress in understanding the pathophysiology of atherosclerosis, the practical utility of these morphological and biochemical assessments in predicting stroke due to ECVD requires validation by prospective studies. 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. The most promising currently

available technology involves detection of metabolic activity in the vessel wall in the region of carotid plaques by PET imaging. Whether the tracers should optimally target the intensity of local inflammation, macrophage activity, angiogenesis, or some combination of these variables has not been clarified. Opportunities exist for combined assessment by PET/CT or PET/MRI to identify carotid plaque instability and enhance the value of biomarkers of inflammation, cytokine activation, and matrix metalloproteinase accumulation as predictors of clinical events.

Advancements in noninvasive imaging technology have accelerated the acquisition of data, overcome motion-based artifacts, and greatly improved diagnostic accuracy to rival that of conventional angiography for evaluation of patients with ECVD. Ever-higher field-strength systems, more powerful magnetic gradients, and simplification of sophisticated software promise to expand the availability of CT and MRA to broader segments of the patient population, but there is an urgent need to overcome limitations that lead to overestimation of stenosis severity and reliably distinguish subtotal from complete arterial occlusion. We must develop intravascular contrast materials free of the nephrotoxicity, osmotic effects, allergic reactions, and other toxicity of agents currently used for catheter angiography, CTA, and MRA to allow application of these technologies across a wider range of patient comorbidities. As these challenges are met, however, it will become more essential to clarify which imaging methods can reliably identify patients at significantly increased risk of stroke, because data of this type ultimately represent the only foundation on which to recommend broad application of techniques for evaluation of patients with cervical arterial disease.

The value of specific therapies to prevent stroke, even in symptomatic patients with severe carotid artery stenosis, largely lacks validation. An example involves antihypertensive therapy in those with impaired cerebral perfusion due to arterial obstructive disease. Clinical trials evaluating treatment of hypertension in patients with ECVD could substantiate specific approaches and better inform future clinical practice guidelines. Similarly, the relationship between cholesterol and ischemic stroke should be buttressed by stronger evidence than currently exists, because findings from population-based studies have been inconsistent. There are multiple causes of ischemic stroke, and available studies have not specifically established a benefit of statins (or other lipid-lowering strategies) to reduce the frequency or severity of stroke in patients with ECVD, so our recommendations are based on inference. Statins not only decrease cholesterol but also stabilize the endothelial cell layer, increase the bioavailability of nitric oxide, reduce oxidative stress, and decrease inflammation in the vascular wall and in the atheromatous plaque itself, and studies focused on these specific mechanisms in patients with ECVD would not only shed light on the optimum timing and intensity of drug therapy but would also provide important clues to other methods of stroke prevention. The same can be said of interventions to manage blood glucose homeostasis in patients with diabetes, even though the risk of ischemic stroke in patients with diabetes mellitus is manifold higher than in those without this prevalent condition. Finally, among the roster of risk factors, it is not even clear whether regular exercise reduces the risk of first or recurrent stroke independent of beneficial effects on other risk factors, and this plays out daily as an unanswered question faced by thousands of patients with ECVD.

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. Further studies are needed to evaluate the safety and efficacy of newer antiplatelet agents, particularly those in the thienopyridine class, relative to aspirin in patients with asymptomatic ECVD. It is critical to define optimum antithrombotic therapy for patients who experience recurrent cerebral ischemia during antiplatelet therapy, which requires not only studies of comparative effectiveness but careful genetic profiling with respect to the factors that contribute to drug resistance. Parallel work is needed to establish the optimum method to assess platelet function as a guide to assessment of drug resistance, to establish whether resistance to platelet inhibitors is associated with a greater risk of stroke, and to clarify whether testing for or treatment of drug resistance leads to improved clinical outcomes.

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. If parallels to the management of patients with acute MI continue to expand in the care of acute stroke victims, then earlier catheter-based revascularization will be tested, but such studies must be advanced carefully because of the high risk of exacerbating irreversible ischemic injury and functional deficit. The judicious use of thrombin inhibitors, factor Xa inhibitors, and other antithrombotic agents in conjunction with antiplatelet agents is fertile ground for future investigation but one equally fraught with risk.

In the days and weeks after the acute phase of ischemic stroke, it remains unclear whether women benefit as much as men from CEA, and further studies must aim to recruit sufficient numbers of women and older patients to address these important demographic subsets of patients with symptomatic ECVD. This begs the question of how to address differences in the results of CEA based on race, ethnicity, and other clinical features. Such studies must consider not only the differential rates at which patients develop ECVD but also address uncertainties about how these differences reflect biological factors as opposed to inequities in access to diagnosis and treatment. The outcomes of trials that evaluate revascularization in these subjects must incorporate comprehensive atherosclerotic risk factor management to ensure accurate assessment of treatment effects and their

generalizability to contemporary practice. In addition, careful attention should be paid to determining the optimum duration and intensity of antithrombotic therapy after revascularization, because women, older patients, and members of other ethnic groups may not respond the same way as middle-aged white males. This applies during the periprocedural period as well as over the longer term, and it is important to define when in the course of longitudinal care it becomes reasonable for such therapy to merge into the regimen recommended for long-term prevention of ischemic events in patients with atherosclerosis. The reasons for differences in outcomes based on these demographic variables have not been investigated, and there may be a need for both extravascular and intravascular imaging to provide more detailed information about the vascular lumen, pathobiology of atherosclerosis, plaque composition, and calcification, any or all of which could provide useful clues to the myriad clinical manifestations of ECVD.

CREST has answered important questions about the value of CAS relative to CEA but raised several others. Rigorous training and credentialing of the operators contributed to the low absolute rates of stroke, MI, and death during the CREST study, but delivering this level of success in clinical practice outside the rubric of a controlled clinical trial will both raise practical challenges and hopefully stimulate objective studies of which physicians to train, how to train them, and for what period of time. The event rates reported by the CREST investigators were generally low with either method of revascularization among symptomatic patients of either sex, but there was an important difference related to patient age, the explanation for which is unknown. More research is needed to validate this observation and uncover the conditions responsible for the differential advantage of CEA over CAS among older patients. The most pressing question, however, is how either technique of revascularization compares with intensive contemporary medical therapy, particularly among asymptomatic patients, and a direct comparative trial of both methods of revascularization versus modern medical management should be initiated as quickly as feasible and include a sufficiently broad range of patients to permit meaningful analysis of subgroups based on age, gender, ethnicity, and risk status.

Beyond these many issues involving carotid atherosclerosis lie still deeper challenges involving less common forms of ECVD. In this uncharted territory of future research are questions about the pathophysiology and clinical outcomes of patients with FMD of the cervical arteries, including its relationship to carotid arterial dissection and ischemic brain events. The management of dissection itself is fodder for fresh investigation, beginning with placebo-controlled trials of anticoagulant or antiplatelet drug regimens, with or without CAS. Huge gaps in knowledge of vertebral arterial disease will be more difficult to address because of its relative infrequency compared with carotid stenosis. This circumstance requires well-designed collaborative registries that capture in a structured format data about prevalence, pathophysiology, natural history, and prognosis. Before conclusions can be drawn about which findings on noninvasive imaging are relevant to clinical decision making, the accuracy of each method compared with catheter-based angiography must be established more clearly. Given the plethora of medical, interventional, and surgical approaches available for treatment of patients with vertebral artery disease, clarity about comparative effectiveness can come only from well-designed randomized trials that involve a large number of practitioners and that are conducted across a broad range of clinical sites. Our recommendations that medical management follow guidelines set forth for patients with disease of the carotid arteries are largely extrapolative, awaiting confirmation or refutation through soundly designed prospective studies, but the lower rate of diagnosis of vertebral artery stenosis than carotid artery disease is a root cause of the inherent difficulty in demonstrating therapeutic benefit.

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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	• Abbott • NIH* (CREST-PI)	None	None
Jonathan L. Halperin, Co-Chair	Mount Sinai Medical Center—Professor of Medicine	• 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	• NIH (National Heart, Lung, and Blood Institute)	None	None
Suhny Abbara	Harvard Medical School—Director, Noninvasive Cardiac and Vascular Imaging	• E-Z-EM • Magellan Healthcare • Partners Imaging • Perceptive Informatics • Siemens Medical	None	None	• Bracco • NIH	None	None
J. Michael Bacharach	North Central Heart Institute	None	• ABComm • Bristol-Myers Squibb/Sanofi • Otsuka	None	None	None	None

Committee Member	Employment	Consultant	Speaker	Ownership/ Partnership/ Principal	Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
John D. Barr	Scripps Memorial Hospitals—Director, NeuroInterventional Surgery	• Boston Scientific* • Cordis Neurovascular	• Cordis Neurovascular	• Boston Scientific*	• Abbott • Guidant	None	None
Ruth L. Bush	Scott & White Hospital Texas A&M University Health Science Center—Associate Professor, Division of Vascular Surgery	• Abbott • Endologix • Guidant • InaVein • VNUS	None	None	None	None	None
Christopher U. Cates	Emory University Hospital—Associate Professor of Medicine	• Boston Scientific • Cordis Endovascular • Medtronic	None	None	None	None	None
Mark A. Creager	Brigham & Women's Hospital—Professor of Medicine	• Sanofi-aventis	• Bristol-Myers Squibb/Sanofi Partnership*	None	• Merck • Sanofi-aventis	None	None
Susan B. Fowler	Morristown Memorial Hospital—Clinical Nurse Researcher	None	• Genentech	None	None	None	None
Gary Friday	Bryn Mawr Hospital Lankenau Institute for Medical Research—Neurologist	None	None	None	• NIH* • Pfizer	None	• Bayer,* phenylpropanolamine (2007) and Aprotinin (2010) • Johnson & Johnson, defendant, Evra (2007) • Pfizer,* defendant, Neurontin (2008), Bextra (2007)
Vicki S. Hertzberg	Emory University School of Public Health—Associate Professor, Biostatistics and Bioinformatics	None	None	None	None	None	None
E. Bruce McIff	University of Utah College of Medicine	• Cordis • Medtronic	None	None	None	None	None
Wesley S. Moore	David Geffen School of Medicine at UCLA Division of Vascular Surgery—Professor of Surgery	None	None	None	• Abbott Vascular • Medtronic	None	None
Peter D. Panagos	Washington University—Assistant Professor, Emergency Medicine	None	• Genentech • PDL Biopharma	None	• NIH (National Institute of Neurological Disorders and Stroke)*	None	None
Thomas S. Riles	New York University School of Medicine Division of Surgery—Frank C. Spencer Professor of Cardiac Surgery	None	None	None	None	None	None

Committee Member	Employment	Consultant	Speaker	Ownership/ Partnership/ Principal	Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
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

This table represents the relationships of committee members with industry and other entities that were reported by authors to be relevant to this document. These relationships were reviewed and updated in conjunction with all meetings and/or conference calls of the writing committee during the document development process. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of 5% or more of the voting stock or share of the business entity or ownership of $10,000 or more of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. A relationship is considered to be modest if it is less than significant under the preceding definition. Relationships in this table are modest unless otherwise noted.

*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

Peer Reviewer	Representation	Consultant	Speaker	Ownership/ Partnership/ Principal	Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Amjad Almahameed	Official Reviewer—Society for Vascular Medicine	None	None	None	None	None	None
Sepideh Amin-Hanjani	Official Reviewer—Congress of Neurological Surgeons	None	None	None	None	None	None
Tracey Anderson	Official Reviewer—American Association of Neuroscience Nurses	None	None	None	None	None	None
Joshua Beckman	Official Reviewer—AHA	• Bristol-Myers Squibb* • GlaxoSmithKline • Sanofi*	• Merck	None	None	None	None
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

Peer Reviewer	Representation	Consultant	Speaker	Ownership/ Partnership/ Principal	Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Yung-Wei Chi	Official Reviewer—Society for Vascular Medicine	None	None	None	None	None	None
Kevin Cockroft	Official Reviewer—American Association of Neurological Surgeons	None	• Bayer • EKR Therapeutics • PBC Biopharma	None	• CoAxia • MRC • NIH	None	None
John Connors	Official Reviewer—American College of Radiology	None	None	None	None	None	None
Daniel Edmundowicz	Official Reviewer—Society of Atherosclerosis Imaging and Prevention	• 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	• Abbott • Pfizer	None	None	• AHA/Bugher* • NIH/CREST*	None	None
William Gray	Official Reviewer—Society for Cardiovascular Angiography and Interventions	• Abbott Vascular • Aramanth Medical • BioCardia • Coherex Medical • Contego Medical • FiatLux 3D • Lutonix • Mercator • QuantumCor • Silk Road • Spirx Closure • Stereotaxis • W.L. Gore	None	• CoAptus* • Ovalis • Paragon • Pathway Medical	• 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	• Codman Neurovascular	None	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	• Boston Scientific* • Cordis Neurovascular* • ev3* • Micrus Endovascular*	None	• Intratech Medical* • Micrus Endovascular*	• Boston Scientific*	• Abbott Vascular* • ev3*	None

Peer Reviewer	Representation	Consultant	Speaker	Ownership/ Partnership/ Principal	Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
William Mackey	Official Reviewer—Society for Vascular Surgery	None	None	None	None	None	None
Jon Matsumura	Official Reviewer—AHA	• Abbott*	None	None	• Bard* • Cook* • Cordis* • ev3* • Lumen* • Medtronic* • W.L. Gore*	None	• W.L. Gore
J. Mocco	Official Reviewer—American Association of Neurological Surgeons	• Cordis	None	None	None	None	None
Christopher Moran	Official Reviewer—Society of NeuroInterventional Surgery	• Boston Scientific • Cordis Neurovascular • ev3	• Boston Scientific • Cordis Neurovascular • ev3	None	None	None	None
Issam Moussa	Official Reviewer—Society for Cardiovascular Angiography and Interventions	None	None	None	None	None	None
Paolo Raggi	Official Reviewer—Society of Atherosclerosis Imaging and Prevention	None	None	None	None	None	None
Caron Rockman	Official Reviewer—Society for Vascular Surgery	None	None	None	None	None	None
Robert Tarr	Official Reviewer—American Society of Neuroradiology	• Boston Scientific • Cordis Neurovascular	None	None	None	None	None
Susan Tocco	Official Reviewer—American Association of Neuroscience Nurses	None	None	None	None	None	None
Pat Zrelak	Official Reviewer—American Association of Neuroscience Nurses	None	None	None	None	None	None
Christopher Zylak	Official Reviewer—Society of Interventional Radiology	None	• Abbott • Concentric Medical	None	None	None	None
Don Casey	Organizational Reviewer—American College of Physicians	None	None	None	None	None	None

Peer Reviewer	Representation	Consultant	Speaker	Ownership/ Partnership/ Principal	Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Jonathan A. Edlow	Organizational Reviewer—American College of Emergency Physicians	None	None	None	None	None	None
J. Stephen Huff	Organizational Reviewer—American College of Emergency Physicians	None	None	None	None	None	None
Eric Bates	Content Reviewer—Expert Consensus Document on Carotid Stenting	• Bristol-Myers Squibb • Daiichi Sankyo • Lilly • Momenta • Novartis • Sanofi-aventis • Takeda	None	None	None	None	None
Jorge Belardi	Content Reviewer—ACCF Interventional Scientific Committee	• Boston Scientific • Medtronic	None	None	None	None	None
Sharon Christman	Content Reviewer—AHA Peripheral Vascular Disease Steering Committee	None	None	None	None	None	None
Michael Cowley	Content Reviewer	None	None	None	None	None	None
Colin Derdeyn	Content Reviewer—AHA	• W.L. Gore*	None	• nFocus	• Genentech*	None	None
Jose Diez	Content Reviewer—ACCF Catheterization Committee	None	None	None	None	None	None
Bruce Ferguson	Content Reviewer—ACCF Surgeons' Scientific Council	None	None	None	None	None	None
Karen Furie	Content Reviewer—AHA	None	None	None	• ASA-Bugher* • NINDS*	None	None
Hitinder Gurm	Content Reviewer—ACCF Peripheral Vascular Disease Committee	None	None	None	None	None	None
Norman Hertzer	Content Reviewer—ACCF/AHA Peripheral Arterial Disease Guideline Writing Committee	None	None	None	None	None	None
Loren Hiratzka	Content Reviewer—ACCF/AHA Peripheral Arterial Disease Guideline Writing Committee	None	• AHA	None	None	None	• 2007; defendant; misdiagnosis of thoracic aortic disease

Peer Reviewer	Representation	Consultant	Speaker	Ownership/ Partnership/ Principal	Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Scott E. Kasner	Content Reviewer—AHA	• AstraZeneca • Cardionet	None	None	• W.L. Gore* • NIH*	None	None
Debabrata Mukherjee	Content Reviewer—ACCF Catheterization Committee	None	None	None	None	• Cleveland Clinic Foundation	None
Srihari Naidu	Content Reviewer—ACCF Catheterization Committee	None	• Abbott Vascular • Cordis • Medtronic	None	None	None	None
Rick Nishimura	Content Reviewer—ACCF/AHA Task Force on Practice Guidelines	None	None	None	None	None	None
Constantino Peña	Content Reviewer—Society of Cardiovascular Computed Tomography	None	• General Electric Healthcare • W.L. Gore	None	None	None	None
C. Steven Powell	Content Reviewer	None	None	None	None	None	None
Kenneth Rosenfield	Content Reviewer—ACCF/AHA Peripheral Arterial Disease Guideline Writing Committee	• Abbott* • Bard* • Boston Scientific • Complete Conference Management • Cordis • ev3 • Lutonix	None	• Angioguard • CardioMind • Lumen • Medical Simulation • XTENT	• Abbott* • Accumetrix* • Boston Scientific* • Cordis* • IDEV	• Cordis*	None
David Sacks	Content Reviewer—ACCF/AHA Peripheral Arterial Disease Guideline Writing Committee	None	None	None	None	None	None
Michael Sloan	Content Reviewer—AHA Stroke Leadership	• Bayer Healthcare • Genentech • National Association for Continuing Education • Network for Continuing Medical Education* • NovoNordisk	• National Association for Continuing Education • Network for Continuing Medical Education*	None	• NovoNordisk	None	• Acute stroke intervention • Carotid endarterectomy
Timothy Sullivan	Content Reviewer	None	None	None	None	None	None

Peer Reviewer	Representation	Consultant	Speaker	Ownership/ Partnership/ Principal	Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Christopher White	Content Reviewer—ACCF/AHA Peripheral Arterial Disease Guideline Writing Committee; ACC Interventional Scientific Council; AHA Peripheral Vascular Disease Steering Committee	• Boston Scientific	None	None	• Boston Scientific	None	None

This table represents the relationships of peer reviewers with industry and other entities that were reported by reviewers via the ACCF disclosure system and filtered to list those relevant to this document. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of 5% or more of the voting stock or share of the business entity or ownership of $10,000 or more of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. A relationship is considered to be modest if it is less than significant under the preceding definition. Relationships in this table are modest unless otherwise noted.

*Significant relationship.

ACCF indicates 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.

APPENDIX 3. ABBREVIATION LIST

CABG = coronary artery bypass graft
CAD = coronary artery disease
CAS = carotid artery stenting
CEA = carotid endarterectomy
CT = computed tomography
CTA = computed tomography angiography
ECVD = extracranial carotid and vertebral artery disease
EPD = embolic protection device
FMD = fibromuscular dysplasia
IMT = intima-media thickness
IVUS = intravascular ultrasound
LDL = low-density lipoprotein
MI = myocardial infarction
MRA = magnetic resonance angiography
MRI = magnetic resonance imaging
NSAID = nonsteroidal anti-inflammatory drugs
PAD = peripheral arterial disease
PET = positron emission tomography
TIA = transient ischemic attack