

Updated Society for Vascular Surgery guidelines for management of extracranial carotid disease

John J. Ricotta, MD,^a Ali AbuRahma, MD, FACS,^b Enrico Ascher, MD,^c Mark Eskandari, MD,^d Peter Faries, MD,^e and Brajesh K. Lal MD,^f *Washington, DC; Charleston, WV; Brooklyn, NY; Chicago, Ill; New York, NY; and Baltimore, Md*

Management of carotid bifurcation stenosis is a cornerstone of stroke prevention and has been the subject of extensive clinical investigation, including multiple controlled randomized trials. The appropriate treatment of patients with carotid bifurcation disease is of major interest to the community of vascular surgeons. In 2008, the Society for Vascular Surgery published guidelines for treatment of carotid artery disease. At the time, only one randomized trial, comparing carotid endarterectomy (CEA) and carotid stenting (CAS), had been published. Since that publication, four major randomized trials comparing CEA and CAS have been published, and the role of medical management has been re-emphasized. The current publication updates and expands the 2008 guidelines with specific emphasis on six areas: imaging in identification and characterization of carotid stenosis, medical therapy (as stand-alone management and also in conjunction with intervention in patients with carotid bifurcation stenosis), risk stratification to select patients for appropriate interventional management (CEA or CAS), technical standards for performing CEA and CAS, the relative roles of CEA and CAS, and management of unusual conditions associated with extracranial carotid pathology. Recommendations are made using the GRADE (Grades of Recommendation Assessment, Development and Evaluation) system, as has been done with other Society for Vascular Surgery guideline documents. In contrast to the multispecialty guidelines recently published, the committee recommends CEA as the first-line treatment for most symptomatic patients with stenosis of 50% to 99% and asymptomatic patients with stenosis of 60% to 99%. The perioperative risk of stroke and death in asymptomatic patients must be <3% to ensure benefit for the patient. CAS should be reserved for symptomatic patients with stenosis of 50% to 99% at high risk for CEA for anatomic or medical reasons. CAS is not recommended for asymptomatic patients at this time. Asymptomatic patients at high risk for intervention or with <3 years life expectancy should be considered for medical management as the first-line therapy. (*J Vasc Surg* 2011;54:e1-e31.)

TABLE OF CONTENTS

I. Indications for carotid bifurcation imaging

- A. Indications for imaging the neurologically symptomatic patient
- B. Indications for imaging the neurologically asymptomatic patient
 1. Screening for asymptomatic carotid stenosis
 - a. Screening patients with asymptomatic bruit
 - b. Potential “high-risk groups” who might benefit from screening for asymptomatic stenosis

- Recommendations for the use of carotid bifurcation imaging

II. Selecting imaging modalities for carotid evaluation

From the Washington Hospital Center, Georgetown University School of Medicine, Washington, DC^a; University of West Virginia, Charleston^b; Maimonides Medical Center, Brooklyn^c; Northwestern University, Chicago^d; Mount Sinai University School of Medicine, New York^e; and University Maryland, Baltimore.^f

Competition of interest: none.

Reprint requests: John J. Ricotta, MD, Chairman Department of Surgery, Washington Hospital Center, 110 Irving St NW, Ste G253, Washington, DC 20010 (e-mail: john.j.ricotta@medstar.net).

The editors and reviewers of this article have no relevant financial relationships to disclose per the JVS policy that requires reviewers to decline review of any manuscript for which they may have a competition of interest.

0741-5214/\$36.00

Copyright © 2011 by the Society for Vascular Surgery.

doi:10.1016/j.jvs.2011.07.031

A. Carotid duplex ultrasound imaging

B. Magnetic resonance imaging and angiography

C. Computed tomography angiography

D. Catheter-based digital subtraction arteriography

E. Comparison of CDUS, MRA, CTA, and DSA

- Recommendations for selection of carotid imaging modalities

III. Medical management of patients with carotid stenosis

A. Treatment of hypertension

B. Treatment of diabetes mellitus

C. Treatment of lipid abnormalities

D. Smoking cessation

E. Antithrombotic treatment

F. Anticoagulant therapy

G. Medical management for the perioperative period of CEA

H. Medical management for the perioperative period of CAS

- Recommendations for medical management of patients with carotid atherosclerosis

IV. Technical recommendations for carotid interventions

A. Carotid endarterectomy

B. Carotid artery stenting

- Recommendations regarding CEA and CAS technique

V. Selecting the appropriate therapy: medical management, CAS, or CEA

- A. Assessing the risk associated with intervention
 1. Anatomic and lesion characteristics
 - a. Lesion location
 - b. Lesion characteristics
 - c. Other anatomic considerations
 2. Patient characteristics
 - B. Neurologically asymptomatic patients with $\geq 60\%$ carotid artery stenosis
 1. CEA for asymptomatic lesions
 2. CAS in asymptomatic lesions
 3. Medical management of asymptomatic carotid stenosis
 - C. Neurologically symptomatic patients with $\geq 50\%$ carotid artery disease
 1. CEA in symptomatic stenosis
 2. CAS in symptomatic stenosis
 - D. Meta-analysis: CEA vs CAS
 - Recommendations for selecting therapy
- VI. Unusual conditions associated with carotid stenosis**
- A. Acute neurologic syndromes
 1. Management of acute stroke
 - a. Presentation within 0-6 hours
 - b. Presentation later than 6 hours
 2. Stroke in evolution (fluctuating neurologic deficits)
 3. Crescendo TIA
 4. Acute postintervention stroke/occlusion
 - Recommendations for management of acute neurologic syndromes
 - B. ICA occlusion with persistent symptoms/external carotid stenosis
 - Recommendations for management of symptomatic ICA occlusion
 - C. Carotid dissection
 - Recommendations for management of carotid dissection
 - D. Combined carotid and coronary disease
 - Recommendations for management of combined carotid and coronary disease

Management of extracranial carotid disease has been the focus of intense investigation and debate by multiple medical specialists since the introduction of carotid endarterectomy (CEA) as a therapeutic option for the treatment and prevention of stroke more than half a century ago. Initial hopes that CEA could reverse the clinical course of stroke were proven false, and the role of surgical management of extracranial carotid and vertebral obstructions was defined by one of the earliest efforts at a multicentered randomized clinical trial, The Joint Study on The Extracranial Circulation.¹ The results of this decade-long study, involving 5000 patients, established the role of CEA in the treatment of minor stroke, transient ischemic attack (TIA), and amaurosis fugax, confirmed that surgery had a limited

role in the treatment of established stroke, and established the limited role of vertebral reconstruction in the treatment of cerebral insufficiency. Over the ensuing decades, surgical results of CEA improved, asymptomatic carotid stenosis was increasingly identified by noninvasive studies, and CEA assumed a primarily prophylactic role as prevention of major stroke in asymptomatic patients or those with evidence of transient cerebral or ocular ischemia. Large randomized trials²⁻⁶ have established the role and efficacy of carotid endarterectomy (CEA) in stroke prevention.

In the last decade, carotid artery stenting (CAS) has emerged as a catheter-based alternative to CEA, and medical therapy for stroke treatment and prevention has evolved. Currently, approximately 135,000 interventions on lesions in the carotid bifurcation are being performed annually in the United States, by a variety of specialists, including vascular surgeons, general surgeons, thoracic surgeons, neurosurgeons, cardiologists, interventional radiologists, and interventional neurologists.^{7,8} Approximately 11% of these interventions are catheter-based, and 90% of interventions are in patients without neurologic symptoms.⁷

As in any situation where there are multiple options for the treatment of a single condition, defining optimal treatment can be difficult. This is further compounded when multiple specialists, often with nonoverlapping expertise, are involved in the treatment of the patient. As a result, a voluminous and often conflicting literature has developed around the current standards of diagnosis and management of extracranial carotid stenosis. Recently two large, prospective, randomized trials have been published comparing the efficacy of CEA and CAS in the management of extracranial carotid stenosis.^{9,10} A meta-analysis comparing CAS and CEA, including these trials has recently been published in the *Journal of Vascular Surgery*.¹¹

In 2008, the Society for Vascular Surgery published clinical practice guidelines for the management of extracranial carotid artery disease in the *Journal of Vascular Surgery*.¹² More recently, a multispecialty document has been published on the "Management of Patients with Extracranial Carotid and Vertebral Artery Disease."¹³ This extensive document represents an effort to evaluate the existing literature on extracranial carotid and vertebral disease and is an important reference.

As with most multispecialty documents, however, the conclusions drawn do not necessarily represent the unanimous opinion of the participating organizations. Although the Society for Vascular Surgery supported this multispecialty effort, there were significant concerns about how some of the presented data were analyzed and the recommendations that followed from this analysis. In particular, there was concern about how the results of the two recent randomized trials^{9,10} were interpreted and the relative weight given to these results in developing final guidelines regarding carotid interventions. The data contained in the recently published randomized trials has prompted the Society for Vascular Surgery to publish an update of its 2008 guidelines, confined to management of extracranial

carotid artery disease. This is particularly appropriate because vascular surgeons play a major if not predominant role in the management of patients with carotid bifurcation disease.

In developing these recommendations, the committee placed more weight on the reduction of stroke and death and less on the importance of nonfatal myocardial infarction (MI). Because the latter end point often represents the main benefit of CAS, the recommendations in this document are more circumspect with regard to the role of CAS and more supportive of the role of CEA than the recommendations of the American Heart Association (AHA) guidelines committee. This document is divided into six major sections:

- I. Indications for imaging of the extracranial circulation
- II. Selection of imaging modality
- III. The importance of medical therapy in the overall management of patients with carotid stenosis, including medical management in the peri-intervention period.
- IV. Technical considerations for performing CEA and CAS
- V. The relative roles of medical management, CEA and CAS for stroke risk reduction in patients with carotid stenosis based on review of the literature, with particular reference to risk factor stratification and the most recent completed trials
- VI. The management of unusual conditions associated with extracranial carotid pathology, including acute neurologic conditions, symptomatic carotid occlusion, carotid dissection, and patients with carotid stenosis in need of coronary artery revascularization

The committee reviewed the literature pertinent to each of the six areas and provided recommendations for treatment using the GRADE (Grades of Recommendation Assessment, Development and Evaluation) system.¹⁴ This system, adopted by more than 40 other organizations, incorporates an evaluation of the strength of the evidence and the risks/benefits of implementing the recommendation. For the purposes of this review, we placed the highest priorities on reducing overall stroke risk, periprocedural stroke risk, and periprocedural mortality. Lesser importance was given to reducing nonfatal MI, cost, and the ability to perform a percutaneous procedure. Recommendations are characterized as *strong* GRADE 1 or *weak* GRADE 2, based on the quality of evidence, the balance between desirable effects and undesirable ones, the values and preferences, and the resources and costs.

GRADE 1 recommendations are meant to identify practices where benefit clearly outweighs risk. These recommendations can be made by clinicians and accepted by patients with a high degree of confidence. GRADE 2 recommendations are made when the benefits and risks are more closely matched and are more dependent on specific clinical scenarios. In general, physician and patient preference plays a more important role in the decision-making process in these circumstances.

In addition to the GRADE of recommendation, the level of evidence to support the recommendation is noted. Evidence is divided into 3 categories: A (high quality), B (moderate quality), and C (low quality). Conclusions based on high-quality evidence are unlikely to change with further study, those based on moderate-quality evidence are more likely to be affected by further investigation, and those based on low-quality evidence are the least supported by current data and the most likely to be subject to change in the future.

It is important to note that a GRADE 1 recommendation can be made based on low-quality (C) evidence by the effect on patient outcome. For example, although there are little data on the efficacy of CEA in asymptomatic patients with <60% stenosis, one can recommend with confidence that CEA not be performed in these patients. A full explanation of the GRADE system is presented in the recent article by Murad et al¹⁴ referenced earlier. It is important to note that this grading system differs somewhat from the one used in the recent American College of Cardiology (ACC)/AHA Task force report.¹³

Each member of the committee was assigned responsibility for compiling information pertinent to a specific area of the document. These data were distributed to all members for review, and each area was subsequently discussed in conference calls. A consensus of the recommendation and level of evidence to support it was reached. Each recommendation in this document represents the unanimous opinion of the task force. Although some recommendations are GRADE 2 with Level 3 data, the task force felt it appropriate to present these as the unanimous opinion of its members regarding optimal current management. This was done with the recognition that such recommendations could change in the future but that it was unlikely that new data would emerge soon. These guidelines are likely to be a "living document" that will change as techniques are further refined, technology develops, medical therapy improves, and new data emerge.

I. INDICATIONS FOR CAROTID BIFURCATION IMAGING

Stroke is the third leading cause of death, behind coronary artery disease (CAD) and cancer, and is the leading cause of disability in the United States and Western Europe. Approximately 80% of strokes are ischemic and 20% are hemorrhagic.¹⁵ Significant carotid stenosis (>50%) is seen in 12% to 20% of all anterior circulation ischemic strokes, which is two to three times higher than the risk for less severe asymptomatic stenosis.^{16,17} Unfortunately, only 15% of stroke victims have a warning TIA before stroke, and waiting until symptoms occur is not ideal.¹⁸ The purpose of carotid bifurcation imaging is to detect "stroke-prone" carotid bifurcation plaque and identify a high-risk patient likely to benefit from therapy designed to reduce stroke risk.

Stroke risk is dependent on many factors, but for patients with carotid bifurcation disease, the most important are a history of neurologic symptoms, the degree of stenosis

of the carotid bifurcation plaque, and to a lesser extent, plaque characteristics such as ulcerations, intraplaque hemorrhage, and lipid content.

The North American Symptomatic Carotid Endarterectomy Trial (NASCET) and European Carotid Surgery Trial (ECST) clearly demonstrated the efficacy of CEA in reducing stroke in patients with symptoms of carotid territory cerebral ischemia and carotid bifurcation stenosis that reduced luminal diameter by >50%.²⁻⁴ In these studies, the risk of stroke was higher in patients with a clear history of carotid territory ischemic events (as opposed to amaurosis fugax), and stroke risk increased with the severity of stenosis. Asymptomatic Carotid Atherosclerosis Study (ACAS) and Asymptomatic Carotid Surgery Trial (ACST)^{5,6} found that CEA was also effective in reducing stroke risk in patients with asymptomatic carotid stenosis >60%, although the stroke risk inherent in an asymptomatic stenosis was much less than that in a symptomatic lesion. It follows then that neurologically symptomatic patients and neurologically asymptomatic patients at high risk for harboring a carotid stenosis of $\geq 60\%$ would be candidates for carotid bifurcation imaging.

A. Indications for imaging the neurologically symptomatic patient

Typical carotid territory ischemic symptoms include contralateral weakness of the face, arm, or leg, or both; contralateral sensory deficit or paresthesia of the face, arm, or leg, or both; or transient ipsilateral blindness (amaurosis fugax). If the right cerebral hemisphere is involved, other manifestations may be noted, including anosognosia, asomatognosia, neglect, visual, or sensory extinction. If the left hemisphere is involved, patients may show manifestation of aphasia, alexia, anomia, and agraphesthesia. Symptoms not typically associated with carotid territory events include vertigo, ataxia, diplopia, visual disturbances, dysarthria, nausea, vomiting, decreased consciousness, and weakness, which may include quadriplegia.

The physical examination may show signs of stroke: facial/eyelid drooping, motor or sensory deficits, and speech disturbances. Ocular examinations can occasionally identify Hollenhorst plaques. Neck auscultation may elicit carotid bruit; however, the absence of a neck bruit does not exclude the possibility of a significant carotid bifurcation lesion. Given the incidence of significant carotid stenosis in patients who present with stroke^{15,19} and the effectiveness of CEA in reducing stroke in symptomatic patients with >50% carotid stenosis,²⁻⁴ it is important to evaluate the carotid bifurcation in every patient with symptoms of carotid territory ischemia.

Amaurosis fugax or the finding of a Hollenhorst plaque on funduscopic examination, or both, is also correlated with the presence of significant carotid bifurcation stenosis. However, neither amaurosis fugax nor identification of a Hollenhorst plaque are associated with the same stroke risk as transient cerebral ischemia.²⁰ Identification of carotid stenosis in that clinical scenario implies a stroke risk some-

where between a neurologically symptomatic patient and one who is asymptomatic.

B. Indications for imaging the neurologically asymptomatic patient

Evaluation and treatment of patients who are neurologically asymptomatic is much more controversial. The benefit of carotid endarterectomy for stenosis >60%, although statistically significant in large trials, is much less than for neurologically symptomatic individuals and rests on the premise that intervention can be performed with minimal morbidity.^{5,6} Identification of these asymptomatic patients may occur by routine screening using duplex ultrasound (DUS) imaging or selective application of DUS imaging to high-risk individuals.

1. Screening for asymptomatic carotid stenosis. To date, there is no consensus on which patients should undergo carotid screening for the detection of carotid stenosis. The American Society of Neuroimaging²¹ concluded that the efficacy of screening would be related to the prevalence of the disease in the screened populations. When the prevalence of stenosis is $\geq 20\%$, screening reduced risk of stroke in a cost-effective manner, with intermediate prevalence of between 5% and 20%: screening reduced the risk of stroke in a cost-effective manner in some studies; however, the benefit was usually marginal and was lost if complications of the intervention >5%. With a prevalence of <5%, screening has not been shown to reduce the risk of stroke in a cost-effective manner and may be harmful.

Given these assumptions, screening of the general population is not indicated. This position is supported by multiple professional organizations, including the National Stroke Association,²² the Canadian Stroke Consortium²³ and the U.S. Preventive Services Task Force.²⁴ The American Stroke Association/AHA Stroke Council²⁵ concluded that highly selected patient populations may benefit, but screening of the general population for asymptomatic carotid stenosis was unlikely to be cost-effective and might have the potential adverse effect of false-negative or false-positive results. Finally, the American College of Cardiology Foundation, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and American Society of Interventional & Therapeutic Neuroradiology Clinical Expert Consensus Panel on Carotid Stenting recommended screening for asymptomatic patients with carotid bruit who are potential candidates for carotid intervention and for those in whom coronary artery bypass grafting (CABG) is planned.²⁶

a. Screening patients with asymptomatic bruit. Zhu and Norris,²⁷ in the largest reported study of carotid screening in asymptomatic patients, reported the prevalence of carotid stenosis >75% for those with a carotid bruit was 1.2%. Although the presence of a neck bruit has not been found to predict carotid stenosis >60% in a neurologically asymptomatic population,²⁷ focal ipsilateral carotid bruits in neurologically symptomatic patients had a sensitivity of 63% and a specificity of 61% for high-grade carotid

stenosis (range, 70%-99%).²⁸ The absence of a bruit did not significantly change the probability of significant stenosis in this group of patients (pretest, 52%; post-test, 40%). Ratchford et al²⁹ found in a selected high-risk subgroup of asymptomatic patients that if a bruit was heard, 25% had a >60% stenosis. The presence of carotid bruit has been shown to increase the absolute risk of stroke,³⁰⁻³² MI, and death.³³ In general population-based studies, the prevalence of severe bifurcation stenosis is not high enough to make bruit alone an indication for carotid screening. With these facts in mind, screening should be pursued only if a bruit is associated with other risk factors for stenosis and stroke in patients who have a low operative risk^{5,6,12,34} and are willing to undergo carotid intervention, whether CEA or CAS.

b. Potential "high-risk groups" who might benefit from screening for asymptomatic stenosis. Two studies have identified specific groups among the general population with a higher prevalence of significant carotid stenosis that may >30%. Jacobowitz et al³⁵ developed a model identifying patients at high risk for >50% asymptomatic carotid stenosis. The screened patients were aged >60 years and had one or more of the following risk factors: history of hypertension, CAD, current smoking, and a first-degree family relative with a history of stroke. The prevalence of carotid artery stenosis was only 2% if no risk factor was present, 6% with one risk factor, which increased to 14% for two risk factors, to 16% for three risk factors, and to 67% for four risk factors.

Qureshi et al³⁶ identified the following variables associated with $\geq 60\%$ asymptomatic carotid stenosis: age >65 years (odds ratio, 4.1), current smoking (odds ratio, 2), CAD (odds ratio, 2.4), and hypercholesterolemia (odds ratio, 1.9). Patients undergoing coronary revascularization are another group with an increased prevalence of carotid stenosis of 2% to 27%.^{37,38} Overall, the prevalence of carotid artery stenosis among patients undergoing CABG is higher than the general population. In patients with symptomatic CAD and other risk factors, such as age >65 years, history of stroke or TIA, left main coronary stenosis, diabetes mellitus, carotid bruit, peripheral arterial disease (PAD), and previous carotid operation, it is feasible that a subset of patients with a prevalence >20% can be identified who might benefit from carotid screening.^{37,39-45} The ACC/AHA guidelines⁴⁶ note that carotid screening before CABG is probably indicated in the following subset of patients: age >65 years, left main coronary stenosis, history of smoking, history of TIA/stroke or carotid bruit, and PAD.

Several studies⁴⁷⁻⁵¹ have suggested that the prevalence of $\geq 60\%$ carotid artery stenosis among patients with symptomatic PAD is >20%, regardless of the patient's age. However, the prevalence of $\geq 60\%$ carotid artery stenosis among patients with abdominal aortic aneurysms (AAA) is <20%.⁵²⁻⁵⁴ This suggests that screening patients with AAA would have only a modest benefit and only if intervention could be performed with low morbidity and mortality.²³ Because there is no evidence that stroke risk after AAA

repair is increased by the presence of carotid stenosis, routine carotid screening of AAA patients is not indicated.

In patients with prior head and neck radiotherapy, the prevalence of significant carotid artery stenosis may be high enough, depending on the time between radiotherapy exposure and screening, to justify routine carotid screening.⁵⁵⁻⁵⁹ The highest incidence is generally observed 15 years after radiotherapy exposure, with 21.3% and 5.3% rates of ipsilateral and contralateral stenosis, respectively. The data also suggest that the ipsilateral common carotid (CCA) and internal carotid arteries (ICA) are both involved. The rate of contralateral carotid artery stenosis may also be higher than that observed in the general population.

Unfortunately, limited data are available regarding carotid screening after radiotherapy among patients with head and neck cancer. However, the distribution of disease and clinical course in patients after radiation for head and neck malignancy is different from that of the typical atherosclerotic population. There is a higher incidence of diffuse disease, often involving the CCA, and many of these patients remain neurologically asymptomatic. Further, CEA in this group is considered relatively "high risk," and prior radiotherapy is a relative indication for CAS rather than CEA. There are no robust data on the long-term results of CAS in asymptomatic stenosis associated with prior radiotherapy. Therefore, issues other than the increased prevalence of disease must be considered in formulating recommendations concerning screening in this group of patients.

Brain imaging will occasionally identify patients who have evidence of focal cerebral infarction despite the absence of any history of neurologic symptoms and a normal result on the neurologic examination. These infarcts can vary in size and are often found in the frontal lobes or the nondominant temporal lobe. They may occur as small symmetric lacunar infarcts, implying small-vessel disease, or they may also be asymmetric, which tends to implicate ipsilateral carotid stenosis. These can be secondary to blood flow changes distal to carotid occlusion, which may increase the risk of lacunar infarcts in those with small vessel disease. However, Kakkos et al⁶⁰ reported a higher stroke rate of 4.4% vs 1.3% in patients with 60% to 79% clinically asymptomatic stenosis if a silent infarct was present. Carotid screening is recommended in patients with asymptomatic infarctions.

• Recommendations for the use of carotid bifurcation imaging

1. Imaging of the cervical carotid artery is recommended in all patients with symptoms of carotid territory ischemia. This recommendation is based on the significant incidence of clinically relevant carotid stenosis in this patient group and the efficacy of CEA for clinically significant lesions in reducing overall stroke (GRADE 1, Level of Evidence A).
2. Imaging should be strongly considered for patients who present with amaurosis fugax, evidence of retinal artery embolization on funduscopy examination, or asymptomatic cerebral infarction, and are candidates for CEA.

This recommendation is based on the intermediate stroke risk in this group of patients and the efficacy of CEA in reducing risk of subsequent stroke (GRADE 1, Level of Evidence A).

3. Routine screening is *not recommended* to detect clinically asymptomatic carotid stenosis in the general population. Screening is *not recommended* for presence of a neck bruit alone without other risk factors. This recommendation is based on the low prevalence of disease in the population at large, including those with neck bruits, as well as the potential harm of indiscriminate application of carotid bifurcation intervention to a large number of asymptomatic individuals (GRADE 1, Level of Evidence A).
4. Screening for asymptomatic clinically significant carotid bifurcation stenosis should be considered in certain groups of patients with multiple risk factors that increase the incidence of disease as long as the patients are fit for and willing to consider carotid intervention if a significant stenosis is discovered. The presence of a carotid bruit in these patients increases the likelihood of a significant stenosis (GRADE 1, Level of Evidence B). Such groups of patients include:
 - a. Patients with evidence of clinically significant peripheral vascular disease regardless of age.
 - b. Patients aged ≥ 65 years with a history of one or more of the following atherosclerotic risk factors: CAD, smoking, or hypercholesterolemia. In general, the more risk factors present, the higher the yield of screening should be expected.
5. Carotid screening may be considered in patients before CABG. This is most likely to be fruitful if the patients are aged >65 years and have left main disease or a history of peripheral vascular disease. The strongest indication for screening these patients from the data available is to identify patients at high risk for perioperative stroke (GRADE 2, Level of Evidence B).
6. Carotid screening is *not recommended* for patients with AAA who do not fit into one of the above categories (GRADE 2, Level of Evidence B).
7. Carotid screening is *not recommended* for asymptomatic patients who have undergone prior head and neck radiotherapy. Although the incidence of disease is increased in this group of patients, the utility of intervention in the absence of neurologic symptoms has not been clearly established (GRADE 2, Level of Evidence B).

II. SELECTING IMAGING MODALITIES FOR CAROTID EVALUATION

The two most important features of carotid bifurcation atheroma are the degree of diameter stenosis and the character of the bifurcation plaque. In addition to information about the carotid bifurcation, there are clinical scenarios where the clinician requires information on the status of the vessels proximal or distal to the cervical carotid artery. These factors need to be considered when choosing between imaging studies. It is common—but not universal—

to use multiple modalities when evaluating a patient with suspected cervical carotid stenosis.

In NASCET^{2,3} and ECST,⁴ a higher degree of stenosis in symptomatic patients was associated with a higher stroke risk. The ACAS⁵ found no correlation between the severity of carotid stenosis and the incidence of stroke; however, there were too few strokes in this study to permit a subgroup analysis of the effect of degree of stenosis on the ability to benefit from CEA. Angiographic data from the ECST study⁶¹ on contralateral asymptomatic carotid arteries from 2295 patients demonstrated a $<2\%$ annual stroke risk in patients with $<70\%$ neurologically asymptomatic stenosis. Asymptomatic lesions with greater degrees of stenosis had a greater risk of stroke: 9.8% for patients with 70% to 79% stenosis and 14.4% for those with 80% to 99% stenosis. These data suggest that the degree of stenosis is a marker of stroke risk in symptomatic and asymptomatic lesions. Pathologic studies have demonstrated that more stenotic carotid plaques are more likely to have ulceration, intraplaque hemorrhage, and intraluminal thrombus formation, all of which are clearly related to cerebral embolization and stroke.⁶²

Plaque morphology is an important feature in assessing future risk of neurologic events. Heterogeneous plaques have been shown to increase the risk of neurologic symptoms (TIA/stroke)^{63,64} and were also associated with an incidence of TIA/stroke that was higher than that in homogenous plaques for all grades of stenosis.⁶⁴ Using DUS imaging and computerized image analysis⁶⁵ quantifying the gray scale median of the plaque, Biasi et al⁶⁶ demonstrated that gray scale median values of ≤ 25 were associated with an increased stroke risk of carotid stenting procedures.

Nicolaidis et al⁶⁷ recently concluded that morphologic assessment of plaque structure may allow the identification of a subgroup of asymptomatic carotid stenoses with a 4.5-fold increase in the risk of developing ipsilateral neurologic symptoms compared with those with a similar degree of stenosis, which will reduce the number of patients requiring intervention to prevent one stroke. At present, however, this type of plaque analysis^{66,67} is not widely available and requires further prospective evaluation to determine its ultimate clinical utility.

The imaging modalities most often used to evaluate patients for cervical carotid stenosis are carotid DUS (CDUS), magnetic resonance imaging (MRI) and angiography (MRA), computed tomography angiography (CTA), and digital subtraction angiography (DSA). Each of these will be discussed in turn.

A. Carotid duplex ultrasound imaging

DUS imaging provides an accurate and reliable noninvasive tool to determine the degree of cervical carotid stenosis and plaque morphology in most patients. It is usually the initial study in patients who present with symptoms or a carotid bruit. Because the study is highly dependent on technique, testing should be done in an accredited vascular laboratory (eg, Intersocietal Commission for the Accreditation of Vascular Laboratories), and the images

should be reviewed by physicians experienced in vascular ultrasound interpretation.

Determining the degree of carotid artery stenosis is largely based on an analysis of the peak systolic velocity (PSV) or the end-diastolic velocity (EDV), or both, of the carotid artery. A panel of experts from several medical specialties convened in October 2002 in San Francisco, California, under the auspices of the Society of Radiologists in Ultrasound, to arrive at a consensus regarding the performance of Doppler US imaging to aid in the diagnosis of ICA stenosis.⁶⁸ This panel of experts recommended a cut-off PSV of the ICA of ≥ 125 cm/s for predicting angiographic $>50\%$ stenosis and ≥ 230 cm/s for predicting $>70\%$ ICA stenosis. These recommended criteria are based on an analysis of several published studies and the experience of the panelists rather than values validated against other imaging modalities.

AbuRahma et al⁶⁹ recently analyzed the CDUS and angiography results of 376 carotid arteries in their institution. Using the consensus criteria, they demonstrated a sensitivity of 93%, specificity of 68%, and overall accuracy of 85% for stenosis between 50% and 69%. A PSV of ≥ 230 cm/s for $\geq 70\%$ stenosis had a sensitivity of 99%, specificity of 86%, and overall accuracy of 95%. Receiver operator curves showed that the ICA PSV was significantly better than EDV or ICA/CCA ratio ($P = .036$) in detecting $\geq 70\%$ stenosis and $\geq 50\%$ stenosis. There was no improvement in accuracy by adding the EDV values or the ratios, or both, to the PSV values.

Velocity-based estimation of carotid artery stenosis may need to be adjusted in certain circumstances, for example, higher velocities in women than in men and higher velocities in the presence of contralateral carotid artery occlusion.^{70,71} High carotid bifurcation, severe arterial tortuosity, extensive vascular calcification, and obesity may also reduce the accuracy of DUS imaging. Carotid stents will decrease compliance of the vessel wall and flow velocity.⁷² DUS imaging may also fail to differentiate between subtotal and total carotid occlusion. Intravenous administration of contrast agents may improve diagnostic accuracy,^{73,74} but the safety of these agents has been questioned.

Power Doppler and contrast DUS imaging can be used to differentiate between preocclusive stenosis and complete occlusion.⁷⁵ Overall, each vascular laboratory should have in place an internal validation process of their own criteria for their internal use.

DUS imaging of the carotid artery has two major limitations: quality dependence on the technician's examination and limitations of visualization of the proximal carotid artery and intracranial portions. Although the intracranial cerebral arteries can be assessed with transcranial Doppler imaging, this technique is not as widely available at most institutions as other imaging modalities.

In addition to determining percent stenosis, DUS, as noted above, has been used to determine plaque characteristics (echogenicity) using gray scale median values, which predict the stroke risk of a particular plaque. Plaque characterization is not routine in every vascular laboratory and

requires specific protocols to assure standardization of results.

B. Magnetic resonance imaging and angiography

MRA has the advantage of being noninvasive, does not require iodinated contrast or ionizing radiation, and provides an unlimited number of projections of the carotid lumen from a single acquisition. MRA can also assess intrathoracic and intracranial lesions that are not amenable to DUS interrogation. MRA does not visualize the surrounding soft tissue structures, unless additional MRI is performed, and calcium within the plaque is not defined. It cannot be used in patients with implanted ferromagnetic devices, such as implantable defibrillators and pacemakers, and is of limited use in uncooperative patients and those with claustrophobia. The gadolinium-based compounds used as a contrast agent for MRA have been associated with nephrogenic systemic fibrosis in patients with pre-existing renal disorders.⁷⁶

MRA has a tendency to overestimate the degree of carotid stenosis. The sensitivity and specificity for diagnosing 70% to 99% stenosis with time-of-flight MRA are identical to DUS imaging (88% and 84%, respectively); however, MRA has a tendency to "over-read" stenosis, making it difficult to differentiate more moderate (50% to 69%) from severe stenosis. Similarly, high-grade stenosis will result in a loss of signal on MRA. This does not represent a carotid occlusion when the more distal cervical carotid is visualized. However, when there is no reconstitution of the cervical carotid artery on MRA, the diagnosis of carotid occlusion can be made with a high degree of certainty.^{76,77}

MRI can be used to analyze plaque morphology, specifically the structure of the atherosclerotic plaque. It can identify the lipid-rich necrotic core and the fibrous capsule with high sensitivity and specificity⁷⁸ and can distinguish between an intact thick, thin, or ruptured fibrous cap.⁷⁹ When dedicated protocols are used, MR also can demonstrate specific plaque components, including calcium, lipid, fibrocellular element, or thrombus within the plaques.

C. Computed tomography angiography

CTA is less susceptible than MRA to overestimating the severity of carotid stenosis. The rapid acquisition of spiral CT images allows excellent timing with contrast administration and provides quality images that can be viewed in multiple planes. CTA is extremely fast and offers submillimeter spatial resolution (0.3 vs 0.8 mm for contrast-enhanced MRA), is less expensive than contrast-enhanced MRA, provides a faster processing time, and can visualize soft tissue, bone, and blood vessels at the same time. CTA can also demonstrate vascular anomalies, has the ability to quantify the extent of calcification, and can interrogate the arterial tree from the aortic arch to the circle of Willis. Stenoses can be measured with electronic microcalipers based on NASCET or ECST methods.⁸⁰

A meta-analysis of 28 studies analyzing the diagnostic accuracy of CTA compared with DSA showed a pooled

sensitivity of 85% and specificity of 93% for CTA in detecting 70% to 99% carotid stenosis and a sensitivity and specificity for occlusions of 97% and 99%.⁸¹ CTA was also highly accurate in identifying calcification but less reliable in describing carotid plaque morphology, specifically the lipid component, or ulceration. CTA appears less reliable than DUS imaging or MRA for assessing plaque morphology.⁸² Other limitations of this technique include cost (compared with DUS), contrast exposure, and the added concern of radiation exposure. In addition, a large calcium burden can limit the ability to distinguish contrast from calcium during postprocessing imaging.

D. Catheter-based DSA

Many authorities still consider carotid conventional digital angiography to be the gold standard against all other imaging modalities in patients with extracranial cerebrovascular disease. Measurement of carotid stenosis using DSA is generally done using the NASCET method.² Conventional angiography is generally reserved for patients with conflicting imaging studies before CEA or in patients considered for CAS. DSA provides high-quality imaging that is accurate, objective, and easy to interpret. It can identify lesions from the aortic arch to the intracranial vessels. Major limitations of angiography that make it inappropriate as a screening modality include its cost and associated risks, specifically of stroke.⁸³⁻⁸⁵ Overall, DSA is most useful in patients when less invasive imaging studies produce conflicting results. When DUS imaging is equivocal, DSA is preferred over CT and MR in evaluating patients with renal dysfunction (by minimizing contrast load), obesity, or indwelling ferromagnetic material, which render CTA or MRA technically inadequate or difficult.

E. Comparison of CDUS, MRA, CTA, and DSA

The U.K. Health Technology Assessment concluded that although contrast-enhanced MRA was the most accurate imaging modality overall, it was limited by unavailability, inaccessibility, and delays. Therefore, they concluded that color DUS imaging remained the preferred imaging modality for identifying patients with 70% to 99% stenosis.⁸⁶ As such, CDUS is the preferred imaging modality for the identification of asymptomatic stenosis.

This recommendation was based on several factors, including low cost, a much higher number of strokes likely to be prevented in the long-term by the rapid availability of CDUS imaging in contrast with other imaging, and the good sensitivity of imaging in detecting significant stenosis. However, the Health Technology Assessment highlighted the concern of the accuracy of DUS in diagnosing 50% to 69% stenosis, which carries a sensitivity of only 36% and a specificity of 91%.⁸⁶

The utility of CDUS will depend on the clinical presentation of the patient. In neurologically symptomatic patients, a diagnosis by CDUS of stenosis between 50% and 69% is sufficient to proceed with surgery based on its specificity. However, a negative CDUS result would mandate another imaging study because of the low sensitivity of

CDUS in this setting. In neurologically asymptomatic patients, a moderate stenosis (50% to 69%) diagnosed by CDUS should be confirmed by another imaging study before intervention is undertaken.

F. Imaging after carotid intervention

The prevalence of carotid artery restenosis after CEA varies between 1% and 37%,⁸⁷⁻⁹⁰ although symptomatic recurrent stenoses is infrequent (0% to 8%).⁸⁷ Factors associated with restenosis include continued smoking, small ICA diameter, operative defect detected at intraoperative assessment, and primary closure after CEA. The aggregate incidence of residual and recurrent carotid stenosis after CEA in ACAS was 13%.⁸⁸ Of 136 patients who had restenosis, 8 (5.9%) underwent reoperation, only 1 of whom was symptomatic. There was no correlation between late stroke and recurrent stenosis. Similarly, Cao et al⁸⁹ randomized 1353 patients who underwent CEA. Of these, the eversion technique was used in 678, and standard CEA with primary closure was done in 419 and patch closure in 256. The life-table estimate of the cumulative risk of restenosis at 4 years was 4% in the eversion CEA group and 9% in the standard CEA group, and 98% of these patients were asymptomatic.

Several studies have reported the progression of contralateral stenosis after CEA.⁹¹⁻⁹³ Contralateral carotid stenosis progression was more frequent than ipsilateral recurrent stenosis during the long-term follow-up in these studies. These studies also identified that the risk of contralateral carotid artery stenosis progression depends on the existing disease at the time of the initial CEA.⁹¹⁻⁹³ The risk of progression for moderate stenosis at the initial surveillance to severe stenosis can be as high as five times.⁹²

Several large prospective studies⁹⁴⁻⁹⁹ have analyzed the rate of carotid in-stent restenosis after CAS. More patients had >70% stenosis of the ipsilateral carotid artery 1 year after CAS than after CEA (19% vs 5%). Use of CDUS to diagnose post-CAS restenosis is confounded by changes in the velocity criterion caused by the stent itself, and standard diagnostic criteria do not apply. Artifacts associated with both CTA and MRA similarly limit the utility of these techniques in the post-CAS patient. DSA is required to confirm restenosis after CAS identified by CDUS when reintervention is contemplated. In contrast, CDUS is sufficient to diagnose and plan therapy for restenosis after CEA.

• Recommendations for selection of carotid imaging modalities

1. CDUS in an accredited vascular laboratory is the initial diagnostic imaging of choice for evaluating the severity of stenosis in symptomatic and asymptomatic patients. Unequivocal identification of stenosis of 50% to 99% in neurologically symptomatic patients or 70% to 99% in asymptomatic patients is sufficient to make a decision regarding intervention (GRADE 1, Level of Evidence A).

2. CDUS in an accredited vascular laboratory is the imaging modality of choice to screen asymptomatic populations at high risk (GRADE 1, Level of Evidence B).
3. When CDUS is nondiagnostic or suggests stenosis of intermediate severity (50% to 69%) in an asymptomatic patient, additional imaging with MRA, CTA or DSA is required before embarking on any intervention (GRADE 1, Level of Evidence B).
4. When evaluation of the vessels proximal or distal to the cervical carotid arteries is needed for diagnosis or to plan therapy, imaging with CTA, MRA, or catheter angiography in addition to CDUS is indicated. CTA is preferable to MRI or MRA for delineating calcium. When there is discordance between two minimally invasive imaging studies (CDUS, MRA, CTA), DSA is indicated to resolve conflicting results. DSA is generally reserved for situations where there is inconclusive evidence of stenosis on less invasive studies or when CAS is planned (GRADE 1, Level of Evidence B).
5. A postoperative DUS study ≤ 30 days is recommended to assess the status of the endarterectomized vessel. In patients with $\geq 50\%$ stenosis on this study, further follow-up imaging to assess progression or resolution is indicated. In patients with a normal DUS study result and primary closure of the endarterectomy site, ongoing imaging is recommended to identify recurrent stenosis. In patients with a normal DUS after patch or eversion endarterectomy, further imaging of the endarterectomized vessel may be indicated if the patient has multiple risk factors for progression of atherosclerosis. There are insufficient data to make recommendations on imaging after CAS (GRADE 2, Level of Evidence C). Although the data in this area are not robust concerning intervals for follow-up imaging, the committee was unanimous in this recommendation, recognizing that follow-up DUS carries little risk.
6. Imaging after CAS or CEA is indicated to monitor contralateral disease progression in patients with contralateral stenosis $\geq 50\%$. In patients with multiple risk factors for vascular disease, follow-up DUS may be indicated with lesser degrees of stenosis. The likelihood of disease progression is related to the initial severity of stenosis (GRADE 2, Level of Evidence C). Although the data in this area are not robust concerning intervals for follow-up imaging, the committee was unanimous in this recommendation, recognizing that follow-up DUS carries little risk.

III. MEDICAL MANAGEMENT OF PATIENTS WITH CAROTID STENOSIS

Optimal medical management is an important part of overall treatment of all patients with carotid bifurcation disease, regardless of the degree of stenosis or the plan for intervention. This therapy is directed both at the reduction of stroke and overall cardiovascular events, including cardiovascular-related mortality. The best medical management for stroke prevention was highlighted in clinical practice guidelines issued jointly in 2006 by the AHA and the

American Stroke Association, and cosponsored by the Council on Cardiovascular Radiology and Intervention and the American Academy of Neurology.¹⁰⁰

A. Treatment of hypertension

Elevated blood pressure increases the risk for stroke,¹⁰¹ and reducing blood pressure decreases the risk for stroke.¹⁰² The relationship between blood pressure and stroke risk is “continuous, consistent, and independent of other risk factors.”¹⁰³ The Framingham Heart study,¹⁰⁴ the Atherosclerosis Risk in Communities (ARIC) study,¹⁰⁵ and the Cardiovascular Health Study¹⁰⁶ each found that hypertension was independently associated with an elevated risk for carotid artery atherosclerosis. Each 10-mm Hg increase in blood pressure results in an increase in risk for stroke of 30% to 45%. Each 10-mm Hg reduction in blood pressure amongst hypertensive patients decreases the risk for stroke by 33%.¹⁰²

Lowering blood pressure to a target $< 140/90$ mm Hg by lifestyle interventions and antihypertensive treatment is recommended in individuals who have hypertension with asymptomatic carotid atherosclerosis.¹⁰⁰ Aggressive lowering of blood pressure may harm patients who have had a recent stroke by reducing cerebral perfusion. In fact, the Joint National Committee for the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure-VII has remained ambiguous regarding recommendations for antihypertensive management in patients with a recent stroke.¹⁰³ However, antihypertensive therapy aimed at reducing blood pressures to $< 140/90$ is recommended for patients who have had an ischemic stroke or TIA and are beyond the hyperacute period.¹⁰⁰

B. Treatment of diabetes mellitus

In the Cardiovascular Health Study, an elevated fasting glucose level was associated with an increased risk for stroke in patients with carotid atherosclerosis.¹⁰⁷ The Insulin Resistance Atherosclerosis Study¹⁰⁸ and the Atherosclerosis Risk in the Community study¹⁰⁹ showed that diabetes was associated with intima-media thickness of the carotid artery and with progression in intima-media thickness. The United Kingdom Prospective Diabetes Study (UKPDS),¹¹⁰ the Action to Control Cardiovascular Risk in Diabetes (ACCORD)¹¹¹ study, and the Action in Diabetes and Vascular Disease: Preterax and Diamcron MR Controlled Evaluation (ADVANCE)¹¹² trial all tested whether tight control of serum glucose levels in diabetic patients would reduce the risk for stroke. Despite achieving hemoglobin A_{1C} levels $< 6.5\%$, no reduction in stroke risk was identified in these trials. Glucose control to nearly normoglycemic levels (target hemoglobin A_{1C} $< 7\%$) is recommended among diabetic patients to reduce microvascular complications and, with lesser certainty, macrovascular complications other than stroke.

C. Treatment of lipid abnormalities

The relationship between elevated cholesterol and incident MI in patients with coronary artery atherosclerosis is

well established; however, the relationship between hypercholesterolemia and incident stroke is less clear. A meta-analysis of 45 studies of strokes in patients with hypercholesterolemia did not suggest an increased risk for stroke in patients with elevated serum cholesterol.¹¹³ However, several other prospective studies in men and women have subsequently identified an increase in incident stroke associated with elevated cholesterol levels.¹¹⁴⁻¹¹⁶

Patients with known atherosclerosis have demonstrated reduced stroke rates when treated with lipid-lowering therapy. The Multiple Risk Factor Intervention Trial of statin therapy in hypercholesterolemic patients observed that greater reductions in levels of low-density lipoprotein (LDL) were associated with a reduction in stroke risk. A meta-analysis of 26 trials observed that the risk of stroke decreased by >15% for every 10% reduction in serum LDL¹¹⁷ in patients with known coronary or other atherosclerosis.

Further meta-analyses of statin trials that also reported on stroke as an outcome have shown that statin therapy reduces the risk of stroke by 15% to 30%.¹¹⁸ The Stroke Prevention by Aggressive Reduction in Cholesterol trial found that atorvastatin treatment of patients with a recent stroke or TIA resulted in a reduction in stroke rate by 16% over 5 years.¹¹⁹

It is less clear if aggressive lipid-lowering therapy results in regression of carotid artery atherosclerosis. Aggressive statin therapy in the Measuring Effects on Intima-Media Thickness: an Evaluation of Rosuvastatin study,¹²⁰ the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol¹²¹ study, and the Atorvastatin vs Simvastatin on Atherosclerosis Progression¹²² study all showed increased regression of the carotid artery intima-media thickness compared with controls.

Although LDL is the primary determinant of cardiovascular and stroke risk, low levels of high-density lipoprotein (HDL) cholesterol also influence stroke risk, and elevation of HDL has been shown to reduce the risk of stroke.¹²³ In an analysis of a large (>9200) series of patients, treated by dual therapy aimed at decreasing LDL and raising HDL, elevation of HDL level was independently associated with a reduction of stroke risk by a factor of 0.86. Conversely, an elevated total cholesterol/HDL ratio increased stroke risk by a factor of 1.22. Reducing cholesterol absorption has also been shown to reduce stroke risk in patients with familial hypercholesterolemia.¹²⁴ Overall, however, the HDL level had much less effect on stroke risk than did the level of LDL.

Elevated cholesterol, comorbid CAD, or evidence of an atherosclerotic etiology of carotid stenosis should be managed according to National Cholesterol Education Program-Adult Treatment Panel III guidelines,¹²⁵ which include lifestyle modification or medications, or both. Statin agents are recommended targeting LDL of 100 mg/dL, for those with coronary heart disease or symptomatic atherosclerotic disease, and LDL of 70 mg/dL for very high-risk persons with multiple risk factors.

D. Smoking cessation

Smoking nearly doubles the risk of stroke.^{126,127} Smoking also acts synergistically on other risk factors that are known to increase the risk of stroke, such as CAD and PAD. Conversely, smoking cessation results in a reduction in risk for CAD and for coronary mortality.¹²⁸ Cessation also reduces the risk of stroke in men and women.¹²⁸⁻¹³⁰ Counseling and smoking cessation medications are effective in helping smokers to quit. Physician counseling is an important and effective intervention that reduces smoking in patients by 10% to 20%¹³¹ but continues to be underused.¹³² Nicotine replacement therapy, in the form of patches and gums, is effective in reducing smoking.¹³³ Patients with extracranial carotid stenosis who are smoking cigarettes should be counseled to quit.

E. Antithrombotic treatment

No adequately powered studies have been performed in asymptomatic patients with carotid atherosclerosis to confirm a benefit with antithrombotic treatment in reducing incident stroke. The US Preventative Services Task Force has recommended daily aspirin as cardiovascular prophylaxis in patients with anticipated cardiac morbidity of >3% for men aged >45 years and in women aged >55 years.¹³⁴ These recommendations are based primarily on an observed reduction in overall cardiovascular morbidity and death with aspirin therapy. The AHA Primary Prevention of Cardiovascular Disease and Stroke agrees with this recommendation.¹³⁵ There is no evidence to suggest that antiplatelet agents other than aspirin have improved benefit in asymptomatic patients with carotid atherosclerosis.

Evidence for antithrombotic treatment for secondary prevention of recurrent stroke in symptomatic patients with carotid atherosclerosis is more robust.^{100,136-139} The choice of antiplatelet therapy among aspirin, clopidogrel, and dipyridamole plus aspirin is not clearly defined because the data are uncertain.

The Clopidogrel in Unstable Angina to Prevent Recurrent Events¹⁴⁰ and Clopidogrel for the Reduction of Events During Observation¹⁴¹ trials each showed a benefit of clopidogrel plus aspirin compared with aspirin alone in reducing vascular events in patients with prior acute coronary syndromes. The Management of Atherothrombosis with Clopidogrel in High-risk Patients¹⁴² subsequently demonstrated no significant difference in vascular events between symptomatic patients with carotid stenosis treated with clopidogrel plus aspirin compared with clopidogrel alone.

Clopidogrel alone was initially shown to have a small advantage over aspirin in this subset of patients in the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events¹⁴³ trial. However, it costs more than aspirin, and the subsequent Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance¹⁴⁴ trial showed that clopidogrel plus aspirin was equivalent to aspirin alone in preventing vascular events in

patients with a prior stroke, TIA, or other cardiovascular disease or in patients with high risk for cardiovascular disease.

Antiplatelet agents are therefore recommended for patients with non-cardioembolic ischemic stroke or TIA associated with carotid atherosclerosis. Aspirin (50-325 mg/d), the combination of aspirin and extended-release dipyridamole, and clopidogrel, are all acceptable options for initial therapy; a combination of aspirin and clopidogrel is not recommended.

Aspirin is currently the most commonly used antiplatelet agent and one of the most frequently prescribed drugs, with as many as 30 million Americans on long-term aspirin regimens. A growing body of evidence suggests that some patients compliant with aspirin therapy may still develop atherothrombotic complications, such as stroke. Reduced antiaggregant effect is more common in patients taking lower-dose aspirin (81 mg) or 325 mg aspirin with an enteric coating than it is in patients taking 325 mg of noncoated aspirin daily.¹⁴⁵ The lack of consensus for the definition of aspirin resistance and for the specific laboratory test to identify it has led to large variability in its reported prevalence.¹⁴⁶ The routine laboratory evaluation of platelet reactivity is not justifiable. The pharmacologic response to clopidogrel also demonstrates significant inter-individual variability.

Patients with reduced platelet inhibition in response to clopidogrel appear to be at increased risk for cardiovascular events. This resistance may result from reduced bioavailability, polymorphisms of cytochrome P450, additional genetic variants, or increased platelet turnover.¹⁴⁷ Prasugrel is an alternate platelet-inhibiting pharmacologic agent of the same class as clopidogrel that does not have these limitations. It has been approved for use in acute coronary syndromes,¹⁴⁸ but no data are available on its use for stroke prevention.

As in the case of aspirin resistance, current evidence does not suggest the routine use of platelet function or genetic testing for clopidogrel resistance. In the absence of randomized trial data, the general approach to patients developing clinical events while taking aspirin or clopidogrel has been to confirm compliance and increase the dosage, followed by the addition or substitution of another antiplatelet agent.¹⁴⁹ However, data in this area are insufficient to allow clear recommendations.

F. Anticoagulant therapy

Parenteral and oral anticoagulants are effective in the prevention of embolic stroke in patients with atrial fibrillation or prosthetic heart valves. However, warfarin anticoagulation has been shown to be less effective than antiplatelet therapy for secondary prevention of neurologic events in patients with carotid atherosclerosis who do not have a history of atrial fibrillation and is not indicated in patients with symptoms of cerebral ischemia.^{150,151} The Warfarin-Aspirin Reduced Cardiac Ejection Fraction Study trial is currently investigating the potential advantage in prevent-

ing cardioembolic stroke of anticoagulation vs aspirin in patients with chronic congestive heart failure.¹⁵²

G. Medical management for the perioperative period of CEA

Hypertension is a common comorbidity in patients undergoing CEA. Blood pressure fluctuations, both above and below normal, are a significant source of morbidity and may contribute to MI and postoperative reperfusion syndrome. Careful perioperative blood pressure management is critical to obtaining optimal results from the operation. Although the most recent AHA guidelines do not classify CEA as a high-risk surgical procedure mandating β -blockade, they do indicate that all patients with known CAD should receive β -blockade therapy before CEA to achieve a stable blood pressure and heart rate of 60 to 80 beats/min.^{153,154} Given the near ubiquity of this condition in patients with carotid stenosis, β -blockade is nearly universally required in this patient group.

Patients taking combined aspirin and clopidogrel therapy in the perioperative period have a 0.4% to 1.0% higher risk of major bleeding compared with aspirin alone.¹⁵⁵ Aspirin therapy alone does not have to be discontinued before CEA.¹⁵⁶ The risks of perioperative MI from aspirin withdrawal outweigh the risk of fatal or severe bleeding from aspirin use. The ACC Perioperative Guidelines endorses the continued use of aspirin before and after CEA.¹⁵³ A low dose (81 to 325 mg) appears at least as effective as higher doses, and higher doses may in fact be less effective.¹⁵⁷ Patients should continue aspirin therapy after CEA indefinitely, according to recommendations for high-risk patients with atherosclerosis.^{100,136-139}

There has been a consensus that preoperative clopidogrel should be stopped approximately 5 days before elective CABG.⁴⁶ Recent data from a large, retrospective, multicentered clinical experience¹⁵⁸ suggest that clopidogrel may be safely continued through the perioperative period without increased bleeding risk. It is therefore reasonable to individualize the management of perioperative clopidogrel therapy. There is no clear information regarding the risks or benefits of continued clopidogrel monotherapy in the perioperative period for CEA.

One meta-analysis showed preoperative statin therapy resulted in a significant reduction in perioperative mortality in patients undergoing vascular surgery.¹⁵⁹ One small randomized trial found that perioperative death, MI, and stroke in patients undergoing vascular surgery was reduced in the group treated with atorvastatin.¹⁶⁰ In one large observational study of hospital records of 780,591 patients undergoing noncardiac surgery, the risk-adjusted mortality rate was significantly lower in those who received perioperative statins than in those who were not taking statins (odds ratio, 0.62; 95% confidence interval [CI], 0.58-0.67).¹⁶¹ The evidence for continued use of statin therapy currently remains largely observational. Furthermore, the optimal time for starting therapy, the duration of therapy, dose, or

target LDL levels to be achieved still remain to be determined.

H. Medical management for the perioperative period of CAS

Antihypertensive, β -blocker, and lipid-lowering therapy should be initiated in patients undergoing CAS according to the same recommendations for CEA. Patients should be started on dual antiplatelet therapy with aspirin (325 mg) and clopidogrel (75 mg) or ticlopidine (250 mg). No randomized trial has yet compared CAS performed with dual-antiplatelet therapy vs aspirin alone. However, the published periprocedural stroke, MI, and death rates in all recent clinical trials have been achieved with this combination therapy.^{9,10,162,163} Dual-antiplatelet therapy should be continued for 1 month after the procedure, and aspirin should be continued indefinitely.

• Recommendations for medical management of patients with carotid atherosclerosis

1. In patients with carotid artery stenosis, treatment of hypertension, hypercholesterolemia, and efforts at smoking cessation are recommended to reduce overall cardiovascular risk and risk of stroke regardless of whether intervention is planned. Targets are those defined by the National Cholesterol Education Program guidelines (GRADE 1, Level of Evidence A).
2. Aggressive treatment of hypertension in the setting of acute stroke is *not recommended*; however, treatment of hypertension after this period has passed is associated with reduced risk of subsequent stroke. The target parameters are not well defined (GRADE 1, Level of Evidence C).
3. Treatment of diabetes with the goal of tight glucose control has not been shown to reduce stroke risk or decrease complication rates after CEA and is *not recommended* for these purposes (GRADE 2, Level of Evidence A).
4. Anticoagulation is *not recommended* for the treatment of TIA or acute stroke, unless there is evidence of a cardioembolic source (GRADE 1, Level of Evidence B).
5. Antiplatelet therapy in asymptomatic patients with carotid atherosclerosis is recommended to reduce overall cardiovascular morbidity, although it has not been shown to be effective in the primary prevention of stroke (GRADE 1, Level of Evidence A).
6. Antiplatelet therapy is recommended for secondary stroke prevention: aspirin, aspirin combined with dipyridamole, and clopidogrel are all effective. Clopidogrel combined with aspirin is not more effective than either drug alone (GRADE 1, Level of Evidence B).
7. Perioperative medical management of patients undergoing carotid revascularization should include blood pressure control (<140/80 mm Hg), β -blockade (heart rate, 60-80 beats/min), and statin therapy (LDL <100 mg/dL) (GRADE 1, Level of Evidence B).
8. Perioperative antithrombotic therapy for CEA should include aspirin (81-325 mg) (GRADE 1, Level of Evi-

dence A). The use of clopidogrel in the perioperative period should be decided case-by-case (GRADE 2 Level of Evidence B).

9. Perioperative antithrombotic management of CAS patients should include dual-antiplatelet therapy with aspirin and ticlopidine or clopidogrel. Dual-antiplatelet therapy should be initiated at least 3 days before CAS and continued for 1 month, and aspirin therapy should be continued indefinitely (GRADE 1, Level of Evidence C).

IV. TECHNICAL RECOMMENDATIONS FOR CAROTID INTERVENTIONS

The efficacy of carotid interventions depends on minimizing perioperative complication rates. This involves appropriate risk factor assessment and patient selection, perioperative therapy, and performance of a technically excellent operation. Perioperative therapy and medical management have been discussed in the previous sections. Specific recommendations on techniques to reduce complications of CEA and CAS are beyond the scope of this report and can be found elsewhere.^{164,165} However, some general recommendations can be made regarding the conduct of CEA and CAS.

A. Carotid endarterectomy

Among the variables that have been studied to determine their effect on the outcome of CEA are local vs regional anesthesia, routine vs selective use of shunts, monitoring of brain function during the procedure, routine patch closure after endarterectomy, and completion imaging. Although several authors have suggested that use of regional or local anesthesia is associated with a reduced incidence of perioperative hemodynamic changes and cardiac events, a prospective randomized trial¹⁶⁶ and systematic review of the literature¹⁶⁷ failed to show any difference between the two anesthetic approaches.

An abundant literature exists on the indications identifying patients at risk of flow-related ischemia during CEA and the role of shunting in reducing this complication. Factors associated with increased risk of cerebral ischemia during carotid cross-clamping, and therefore the increased likelihood that a shunt will be needed, during CEA, include recent stroke, contralateral carotid occlusion, and symptoms suggestive of hemodynamic cerebral insufficiency.^{168,169} Despite extensive study on the routine or selective use of shunts and cerebral monitoring during CEA, no clear benefit of one approach over the other has emerged.¹⁷⁰

The routine use of completion imaging after CEA also remains an area of controversy. Although a number of authors have reported detecting abnormalities in 5% to 10% of patients using completion DUS imaging,^{171,172} and a cost-benefit analysis suggests completion DUS imaging increases quality-adjusted life-years by 2%,¹⁷³ the clinical significance of many of these abnormalities is uncertain, and several series have reported excellent results without use of completion imaging.¹⁷⁴⁻¹⁷⁶ Like the choice of anes-

thetia and shunting, completion imaging remains a matter of personal preference.

There are, however, data to recommend the use of patch angioplasty or eversion endarterectomy over standard endarterectomy with primary closure. Women and individuals with small ICAs are at most risk of early neurologic events and late restenosis if standard endarterectomy with primary closure is performed. Randomized studies have shown the benefit of patch closure over primary closure in patients undergoing standard CEA.¹⁷⁷ The type of patch material does not appear to have a significant effect on outcome. Prospective comparisons of eversion CEA with primary closure¹⁷⁸ have demonstrated a benefit of the eversion technique for reduction of early and late stroke. This has been borne out by low rates of early stroke and late restenosis in large single-center reports.¹⁷⁹

A number of investigations have studied the relationship of operative volume and specialty training with outcome. Although data suggest that there is some relationship between operative volume and outcome, the effect appears less than with other procedures.¹⁸⁰ In a large study of Medicare populations in Maryland and California, surgeons who perform 10 to 15 CEAs per year have better results than those who perform <5 procedures annually, but there was no added benefit to performing more than this relatively low threshold. There has been no consistent relationship between surgical specialty and outcome, and any effect seen is likely related to volume rather than specialty designation.^{8,180,181}

B. Carotid artery stenting

The periprocedural management of the CAS patient has been discussed in a previous section. Periprocedural antiplatelet therapy is mandatory, and appropriate attention to access vessels and the status of the aortic arch is required for optimal results. The technical conduct of the CAS involves access of the target vessel, crossing the target lesion, and stent deployment. Technical issues related to carotid stenting include achieving a stable platform for the procedure, use of embolic protection devices, stent dilation before deployment, stent selection, and postdeployment dilation.

Stable sheath access in the proximal CCA is required. This depends on appropriate patient selection, as described above. Once a stable platform is obtained, a decision must be made about use of a cerebral protection device. In general, cerebral protection device deployment has been suggested to reduce the incidence of distal embolization and, potentially, the risk of stroke.^{182,183} Although this position is not supported by robust data, it has been generally accepted by the medical community, and use of an embolic protection device has been required by Centers for Medicare and Medicaid Services to qualify for reimbursement.

Several embolic protection devices are available, and selection depends on lesion characteristics and anatomic considerations. Options include proximal or distal occlusion devices designed to interrupt forward flow during the

procedure and filter devices placed distal to the lesion designed to trap debris released during the procedure. Distal occlusion devices have the advantage of a smaller diameter than proximal occlusion devices, but the lesion must be crossed before the device is placed in the ICA, a maneuver that can itself cause embolization. At the end of the procedure, suction is applied between the sheath in the CCA and the balloon occluding the distal internal carotid artery to remove debris.

Proximal occlusion devices require placement of two occlusion balloons, one each in the common and external carotid artery, with flow reversal by suction or creation of a proximal arteriovenous connection.¹⁸⁴ Placement of a proximal occlusion device avoids crossing the lesion before protection is in place and has been associated with the lowest incidence of distal embolization as detected by transcranial Doppler imaging or postoperative MRI.¹⁸⁴⁻¹⁸⁶

The main procedural disadvantages of the current proximal occlusion devices are the relatively large size (9F) of the access sheath, the need to occlude both the common and external carotid artery, and the need to establish venous access for continuous flow reversal. Proximal and distal occlusion devices may both be problematic in patients with poor intracranial collateral circulation because they mandate cessation—and sometimes reversal—of antegrade flow in the ICA. This situation is generally encountered in ≤5% of patients and may be managed by short intermittent inflation times.

Distal filters are deployed in the distal ICA and trap debris released during angioplasty and stent deployment. Like distal occlusion devices, they have the advantage of a smaller diameter (6F), but the lesion must be initially crossed in an unprotected fashion. These filters come in a variety of configurations and pore sizes. Their efficacy is related to the degree with which they can reliably achieve complete apposition to the distal arterial wall. They have the advantage that antegrade ICA flow can be maintained throughout the procedure; however, the filter may become completely occluded if large amounts of debris are released, and debris may escape distally during filter recapture.

The choice of filter device is often related to individual preference and familiarity. Some authors believe proximal occlusion with flow reversal is preferable in nearly all circumstances; however, this technique has its greatest advantage in lesions with a high risk of embolization (markedly irregular plaque, echolucent lesions, active symptoms) or in those that may be difficult to cross due to tortuosity or severe narrowing because protection is in place before the lesion is manipulated. Use of a filter over proximal or distal occlusion is preferred if there is a likelihood that interruption of antegrade ICA flow will not be tolerated. Distal occlusion devices are preferred to filters when the distal ICA anatomy suggests that complete apposition of filter to the distal ICA wall may be difficult due to size or tortuosity.

Direct comparison of proximal occlusion with flow reversal vs distal protection shows that proximal protection with flow reversal results in the lowest embolic load.^{165,185} However, no device can completely eliminate the risk of

embolization during CAS. The fact that no embolic protection is completely effective and that some emboli originate during cannulation of the aortic arch and the proximal great vessels suggests that although improvements to embolization after CAS can be made, the problem cannot be eliminated.

Studies using postoperative diffusion-weighted MRI shown increased 17% incidence of MRI-identified infarcts in patients undergoing CAS compared with CEA (adjusted risk ratio, 5.21).¹⁰ Although these are generally subclinical, recent reports suggest these lesions might be associated with subtle long-term neurologic changes. Echolucent lesions are more likely to be associated with increased embolic risk, whereas recurrent stenoses or fibrous lesions are associated with a decreased risk of procedural embolization.^{66,96,165,184}

Stent predilation is not recommended unless a filter cannot be passed. Stent selection is often based on physician preference. The only large study to test the effect of cell size suggests that closed-cell stents more effectively constrain the carotid plaque and reduce embolization,¹⁸⁷ but there is no consensus on that point. Open-cell stents are more conformable than closed-cell stents and are preferred by some in tortuous anatomy. Once the stent has been deployed, postdilation is used to ensure stent apposition to the plaque, but vigorous postdilation to achieve anatomic perfection is avoided.

The learning curve associated with CAS has been the object of considerable study. The Endarterectomy Versus Angioplasty in Patients With Symptomatic Severe Carotid Stenosis¹⁶² (EVA-3S) study was criticized because of the requirement that interventionalists perform only 25 procedures to qualify for participation in the trial. The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) study required a significant lead-in phase for interventionalists and documentation of low procedural morbidity.^{188,189} It is worth noting that CREST is associated with the lowest periprocedural complication rate in the literature. There are data in the literature that suggest achieving a low predictable complication rate after CAS requires a higher level of initial and ongoing experience than current guidelines suggest.^{97,190,191}

No relationship has been demonstrated between specialty and outcome. Data from CREST demonstrate that vascular surgeons, cardiologists, interventional radiologists, and interventional neurologists can all achieve comparable results with CAS and that experience is more important than specialty designation in assuring optimal outcomes.^{188,189}

● Recommendations regarding CEA and CAS technique

1. Patch angioplasty or eversion endarterectomy are recommended rather than primary closure to reduce the early and late complications of CEA (GRADE 1, Level of Evidence A).
2. Use of an embolic protection device (proximal or distal occlusion, distal filter) is recommended during CAS to

reduce the risk of cerebral embolization (GRADE 1, Level of Evidence B).

V. SELECTING THE APPROPRIATE THERAPY: MEDICAL MANAGEMENT, CAS, OR CEA

Once a patient with a clinically significant carotid stenosis is identified, appropriate treatment must be selected. Treatment is primarily directed at the reduction of stroke risk. The risks of an interventional treatment must be considered when treatment choices are made. In general, rates of stroke, MI, and death have been used when comparing CAS with CEA. In most clinical trials comparing CAS with CEA, stroke, MI, and death have been given equal weight in determining a composite end point to test overall efficacy.

Data from CREST,⁹ however, indicate that stroke has a more significant effect on quality of life at 1 year than nonfatal MI. Because the primary goal of intervention in carotid stenosis is stroke prevention, in developing its recommendations, the committee placed more emphasis on the prevention of stroke and procedurally related death than the occurrence of periprocedural MI. This may result in committee recommendations that differ from the published results of some trials where these three end points were given equal weight in analysis.

Treatment is chosen based on the assessment of risk associated with intervention and the likelihood that a particular intervention will favorably alter the course of the disease. The major determinants of the clinical course of patients with carotid bifurcation stenosis are the presence or absence of neurologic symptoms and the degree of carotid bifurcation stenosis. The threat of stroke in asymptomatic patients with <60% ICA stenosis and in symptomatic patients with 50% stenosis is generally considered to be small and does not warrant intervention. ECST and NASCET²⁻⁴ demonstrated that CEA was unable to reduce the subsequent neurologic event rates in patients with symptoms of cerebral ischemia and bifurcation stenosis of <50% diameter reduction and was actually associated with increased morbidity compared with medical management. Stenoses of <60% diameter reduction were excluded from the asymptomatic studies,^{5,6} assuming that asymptomatic patients with stenosis <60% would not benefit from carotid reconstruction. Given the findings of the symptomatic trials, this proved to be an appropriate decision. There have been no studies supporting either CEA or CAS for this cohort of patients.¹⁶

A. Assessing the risk associated with intervention

CEA and CAS are each associated with specific clinical scenarios that increase their respective risks. This section provides information to identify conditions that pose an increased risk for CAS or CEA and thereby help select the most appropriate therapy. When the risk of intervention is sufficiently increased due to the presence of one or more of these factors, medical therapy may be more appropriate than CEA or CAS.

In the initial CAS trials, a series of anatomic and physiologic criteria were developed by a consensus panel in an attempt to identify “high-risk” CEA patients who might be expected to benefit from CAS.¹⁹² Although these criteria were used to enroll patients in CAS trials and registries, their ability to define “high risk” was never validated in a prospective manner. In fact, some have suggested that CEA could be safely performed in most of these patients.^{193,194} As CAS experience matured, certain conditions have been shown to be associated with increased complications after CAS. Risk stratification can generally be divided into two categories: anatomic (including the lesion) characteristics and physiologic characteristics.

1. Anatomic and lesion characteristics.

a. Lesion location. CEA provides excellent access to the cervical carotid artery, but lesions that extend outside this zone can be difficult to treat surgically. Lesions at or above the level of the C2 cervical vertebra or below the clavicle are generally more difficult to expose surgically for CEA without increasing the morbidity of the operation. Lesions of the distal cervical carotid artery can be exposed by division of the digastric muscle and subluxation or division of the mandible, as required.^{195,196} Although rarely required, these high carotid exposures may be associated with increased difficulty in directly visualizing the end point of the endarterectomy and with increased incidence of cranial nerve injury, particularly cranial nerve IX.^{195,196} Lesions of the very proximal CCAs are difficult or impossible to expose without extending the incision into the chest. This must be considered when evaluating the morbidity of the procedure.

b. Lesion characteristics. Lesion-specific characteristics are thought to increase the risk of cerebral vascular events after CAS^{66,197} and include a “soft” lipid-rich plaque identified on noninvasive imaging, extensive (15 mm or more) disease, a preocclusive lesion, and circumferential heavy calcification. A recent publication using multivariate logistic regression analysis of a large patient cohort demonstrated increased periprocedural stroke risk (odds ratios, 2.5-5.6) among patients with lesions >15 mm, excessive calcification, and ulceration.¹⁹⁷ An earlier study has shown a periprocedural stroke risk (odds ratio, 7.1) among patients with a lipid-rich plaque treated with CAS.⁶⁶

The CAS procedure requires manipulation of a wire and a self-expanding stent through the carotid lesion. Unstable plaque increases the risk of embolization during placement of the wire or stent across the carotid lesion. This can be reduced, but not eliminated, by using flow-reversal embolic protection rather than distal filter protection.¹⁸⁵ Long segment lesions may require the placement of multiple stents, and this situation and preocclusive stenoses are both associated with a higher risk of acute or late stent occlusion. Heavy circumferential calcification makes lesion dilation more difficult and also increases the risk of embolization with CAS. There are no lesion specific characteristics that increase the risk of CEA.

c. Other anatomic considerations. Several anatomic situations may increase the difficulty of CEA. These include reoperation after prior CEA, existence of a cervical stoma, history of neck radiotherapy with resultant local fibrotic changes of the skin and soft tissues, and previous ablative neck surgery, such as radical neck dissection and laryngectomy.^{193-195,198}

While CEA can be successfully performed in these situations, particularly when the tissues of the ipsilateral neck are not scarred and fibrotic, these situations can increase the risk of wound infection, difficulty of dissection, and potentially, the incidence of cranial nerve injury. The presence of a short, thick neck in an obese patient may make dissection more tedious but has not in itself proven to be associated with increased operative risk.

Anatomic factors to consider with CAS are related to access issues. Successful CAS requires remote access of the ICA artery using a stable platform to avoid the intravascular motion of sheaths, stents, and protection devices during the procedure. Anatomic factors that may complicate this process include aortoiliac tortuosity, a sharply angulated aortic arch (type III), or a carotid lesion with more than two 90° bends within a short distance of the target lesion.¹⁹⁷ Significant distal ICA tortuosity may also complicate the placement and stabilization of a distal embolic protection device. An aortic arch with heavy calcium or a high atherosclerotic burden is also associated with an increased risk with CAS. This is felt to be the main reason that CAS results are worse in patients aged >80 years.^{199,200}

2. Patient characteristics. It seems intuitive that the risk of periprocedural events after CEA or CAS might be increased in patients presenting with severe comorbid conditions, including dialysis-dependent renal failure, New York Heart Association class III or IV heart disease, left ventricular ejection fraction <30%, class III or IV angina pectoris, left main or multivessel coronary disease, severe aortic valvular disease, oxygen- or steroid-dependent pulmonary disease, or both, contralateral carotid occlusion, and advanced age. However, little data exist to support one therapy over another in these patients.^{162,163} In fact, defining a high-risk patient is much more subjective than defining a high-risk lesion.^{193,194,201,202}

As will be seen later, CAS is associated with a lower incidence of cardiac events than is seen in CEA. Therefore, CAS would be preferred over CEA when severe cardiac comorbidities exist in neurologically symptomatic patients. Chronic renal insufficiency has been associated with increased risk of stroke and death after CAS^{203,204} and CEA.^{205,206} Univariate and multivariate analysis both show that the risk of death, stroke, and MI after CAS at 6 months was associated with hazard ratios >2.5 among patients with chronic kidney disease.²⁰⁴ Chronic renal insufficiency also increases the risk of stroke after CEA (1.08% to 5.56%). Among asymptomatic patients with cardiac or renal insufficiency, best medical therapy may be preferable to CAS or CEA. CEA or CAS may be considered among symptomatic high-risk patients with moderate to severe carotid stenosis,

but the effectiveness over medical therapy is not well established.

There are conflicting data on the influence of contralateral occlusion on the outcome of CEA or CAS. NASCET reported that a contralateral occlusion increased the risk of stroke after CEA from 5.8% to approximately 14%.²⁰⁷ However, most reports regarding contralateral occlusion do not bear this observation out, and a meta-analysis of the literature suggests a much more modest increase, from 2.4% to 3.7%.^{208,209} This was statistically significant, but the results remain within the AHA recommended guidelines. Several single-center studies have shown excellent results in patients with contralateral carotid occlusion.^{210,211} A possible explanation for this discrepancy is an inadequate sample size in the single-center studies. Alternatively, a more consistent technique of intraoperative management in single-center reports, including, algorithms for maintaining intraoperative cerebral perfusion, are more likely to occur in single-center experience than in multicentered studies.

CEA is associated with a lower stroke risk than CAS in patients aged >80 years.^{152,161,162} A combined death, stroke, and MI rate of $\geq 10\%$ has been seen in octogenarians treated with CAS.^{152,161} In the CREST study, CAS was associated with an increased stroke risk in patients aged >70 years⁹ and appeared to have a benefit compared with CEA in patients aged <70 years, although no other studies have reported this association to date.

Because there is a demonstrable incidence of cranial nerve injury after CEA that is absent after CAS, patients with a history of a contralateral vocal cord paralysis are at increased risk with CEA vs CAS; thus, CAS would be preferred in these patients.

B. Neurologically asymptomatic patients with carotid artery stenosis of 60% or more

1. CEA for asymptomatic lesions. Patients with asymptomatic lesions are currently responsible for nearly all of the carotid interventions performed in the United States.⁷ Controlled randomized trials have compared CEA with best medical therapy, but there are a paucity of data on the role of CAS in asymptomatic patients. The results of ACAS⁵ and ACST⁶ favored CEA in the management of these patients. ACAS demonstrated the superiority of CEA over antiplatelet therapy alone for asymptomatic patients with carotid stenosis of $\geq 60\%$. This trial recommended CEA for these patients (aged <80 years) as long as the expected combined stroke and mortality rate for the individual surgeon was not >3%.

The long-term effectiveness of CEA in asymptomatic patients was confirmed by the recently updated results of ACST I, as reported by Halliday et al.²¹² Compared with the randomized medical arm, where patients primarily received antithrombotic and antihypertensive therapy, the patients in the CEA arm (aged <75 years) experienced significantly lower perioperative and 10-year stroke rates (13.3% vs 17.9%). The strength of these conclusions have been questioned, based on the relatively modest

absolute benefits of CEA and the contention that the medical therapy arm did not reflect contemporary medical management.^{213,214}

The question of whether modern medical therapy (including statins) is equivalent or superior to CEA or CAS has not yet been addressed by well-designed, appropriately funded, prospective, multicenter, and randomized trials. An upcoming multicenter randomized trial designed to answer the role of modern pharmacologic therapy in the management of asymptomatic carotid stenosis is the Stent-Protected Angioplasty in Asymptomatic Carotid Artery Stenosis (SPACE-II) study,²¹⁵ which will include best medical therapy as the third arm of the trial together with CEA and CAS.

Concerns have also been raised about whether the results of the controlled trials could be attained in general practice. Critics pointed out that these trials were performed in centers of excellence and that the patients were highly selected. However, subsequent reports on patients who would have been excluded from these trials suggest that the exclusion criterion did not falsely lower complication rates. Combined stroke and death rates after CEA in patients defined as high-risk or eligible for high-risk carotid registries varied between 1.4% and 3.6%, well within the AHA guidelines.^{193,194,210} Similarly, studies of large National Surgical Quality Improvement Program, state, and Medicare databases of between 4,000 and 35,000 patients^{7,8,176,215} demonstrated stroke and death rates as low as 2.2% with a maximum of 6.9% (symptomatic patients only), suggesting that results that conform to national guidelines are achievable across large patient populations.

2. CAS in asymptomatic lesions. Very few studies have specifically addressed the outcome of carotid stenting in asymptomatic patients. CAS has been applied in asymptomatic patients based on the benefit seen for CEA, with the expectation that it would be equivalent or superior to CEA because of its less invasive nature. Many studies of CAS have been in the form of "high-risk" registries.^{96,97,163,216-219} Others, such as the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) trial not, only had a small overall usage of stents (26%), but only 16 of 504 patients (<5%) in the study population were asymptomatic.²²⁰ A single-institution study by Brook et al⁸⁵ comparing CEA with stenting in asymptomatic patients was also limited by the small number of patients and the lack of major postprocedural complications in either group.²²¹

Another trial that suffered from a limited number of patients (<100 asymptomatic CAS) in addition to lack of randomization was the Carotid Revascularization using Endarterectomy or Stenting Systems (CaRESS) study. The primary outcomes were not stratified according to the presence or absence of neurologic symptoms, probably because of the small number of enrollees. The overall 30-day composite of death/stroke/MI was not statistically significantly different for CEA (4.4%) or for CAS (2.1%), and noninferiority of CAS was not demonstrated by statistical methodology.²²²

In 2004, the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial, which included “high-risk” patients, 70% of whom were asymptomatic, demonstrated that the results of stenting with cerebral protection devices were not inferior to those obtained with CEA.⁹⁴ The primary end point of the study was the 30-day cumulative incidence of death/stroke/MI, which was 5.4% for asymptomatic patients who underwent CAS and 10.2% for CEA ($P = .20$).

The critics of this study raised several important issues, including the criteria used to define high-risk patients for CEA, the failure to randomize >50% of eligible patients, the unexpected high incidence of postoperative stroke, particularly in the asymptomatic patients, and questions about reporting bias. A number of critics suggested that the absolute complication rates of both CAS and CEA in this study could not be used to justify either intervention in asymptomatic patients.^{223,224} Murad et al¹¹ found that asymptomatic patients accounted for a minority of all patients entered in 13 trials of CAS vs CEA and that clear conclusions on the treatment of asymptomatic patients were not possible.

CREST⁹ has been the only recent multicenter randomized trial that entered a significant number of individuals (1181 patients) with asymptomatic carotid artery stenosis. The published results show that although the risk of stroke with CAS was greater than for CEA in the asymptomatic patients, this was not statistically significant. The difference between CAS and CEA in asymptomatic patients for any periprocedural stroke was 2.5% vs 1.4%, respectively, and any periprocedural stroke, death, or postprocedural ipsilateral stroke was 2.5% vs 1.4%, respectively. These results for CAS and CEA were both within the AHA recommended guidelines.¹³ In addition, the primary composite end point of the study that included any periprocedural stroke, death, MI, or postprocedural ipsilateral stroke was 3.5% for CAS and 3.6% for CEA ($P = 0.96$). These results are considerably better than any other large study, including ACAS and ACST for both procedures.²²⁵

The CREST results confirm that CEA and CAS can be done with relatively low complication rates in asymptomatic patients when performed by highly experienced practitioners who use their best judgment to select the most appropriate patient to be entered into the study. This study provides a benchmark to strive for, but no other large trials have achieved these results.

Unfortunately, the authors did not record the number of patients excluded from the study because they were not considered “good” candidates for any of the proposed procedures. Thus, the true applicability of CEA and CAS in the general population is unknown. This observation may lead one to believe that the CREST results reflect the best possible selection of candidates for CAS. This is particularly true when these results are compared with the considerably worse results presented in SAPPHIRE, the only other extant trial with a large number of asymptomatic patients.

Data published by the Society for Vascular Surgery Outcomes Committee demonstrated that real-world CAS

was associated with a significantly higher rate of major complications than CEA in asymptomatic patients.²²⁶ The 30-day outcome analysis of CAS and CEA in 2818 patients revealed the combined death, stroke, or MI rate for 1450 CAS patients was 4.6% vs 1.97% for 1368 CEA patients. Other studies of larger databases^{7,8,201,215} have yielded similar results.

Further conclusions on the role of intervention in asymptomatic patients await the results of two additional randomized prospective studies designed to compare the early and long-term results of CEA vs CAS and best medical management: The Carotid Stenting vs Surgery of Severe Carotid Artery Disease and Stroke Prevention in Asymptomatic Patients (ACT I) and, the Asymptomatic Carotid Surgery Trial (ACST-2).²²⁷ Results are not expected until at least 2018.

3. Medical management of asymptomatic carotid stenosis. There has been an increasing call for trials to compare modern medical management of carotid stenosis with both CEA and CAS.^{213,214} This is based on the relatively modest absolute stroke reduction in both ACAS and ACST,^{5,6} the effect of optimal medical management on stroke risk (see *Section III*), and the rates of stroke reported in SAPPHIRE and many carotid stent registries, all of which contain a significant number of asymptomatic patients. Operation for asymptomatic carotid stenosis should only be undertaken in good-risk patients where excellent results can be documented. In patients with a short life expectancy or multiple risk factors, medical management is likely to be superior to intervention. As noted, several studies have been designed to test the ultimate role of medical vs interventional management in asymptomatic carotid disease.

C. Neurologically symptomatic patients with 50% or greater carotid artery stenosis

1. CEA in symptomatic stenosis. NASCET and ECST both demonstrated the benefit of CEA in neurologically symptomatic patients with carotid stenosis that reduced diameter >50%.²⁻⁴ NASCET demonstrated an absolute risk reduction in stroke of 17% at 2 years (24% in medical arm vs 7% in surgical arm) for patients with >70% carotid stenosis. ECST demonstrated a similar stroke risk in this group after 3 years in the medical arm, 26.5% with a stroke risk in the surgical group of 7%, an absolute reduction of 14.9%. In both studies, the risk of stroke in the medical arm, and therefore the benefit of CEA, increased with the degree of stenosis. The results of these trials firmly established CEA as the treatment of choice for patients with severe carotid stenosis and are widely accepted throughout the medical community. The benefit of CEA in more moderate stenosis of 50% to 69% was more moderate—15.7% stroke after CEA vs 22.2% stroke with medical therapy at 5 years—but still statistically significant.³ Stenoses <50% were not benefited by CEA.

2. CAS in symptomatic stenosis. A number of trials have examined the role of CAS in the management of neurologically symptomatic patients with >50% diameter

stenosis. As previously mentioned, SAPPHERE demonstrated overall equivalence of CAS and CEA in the management of carotid stenosis, although the number of symptomatic patients was too small for subgroup analysis.⁹⁴ Two large prospective randomized European trials, EVA-3S¹⁶² and SPACE1,²²⁸ examined the role of CAS vs CEA in neurologically symptomatic patients. EVA-3S showed a statistically inferior outcome for CAS compared with CEA (stroke death, 9.5% vs 3.8%) in these patients. This study was criticized because of the relatively low level of experience (minimum of 25 CAS cases) required in the CAS arm.

The Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy (SPACE) trial was designed to test “equivalence” between CEA and CAS in patients with neurologic symptoms. This trial stopped after recruitment of 1200 patients due to the futility of proving equivalence between the two treatments. The rate of death or ipsilateral stroke at 30 days was 6.84% for CAS and 6.34% for CEA in 1183 randomized patients. However, the study was not powered appropriately and failed to show noninferiority of CAS compared with CEA ($P = .09$).

Subsequently the International Carotid Stenting Study Trial (ICST),¹⁰ which enrolled 1713 patients, demonstrated an increased stroke risk for CAS (7.7%) compared with CEA (4.1%) in neurologically symptomatic patients. This observed difference was significant ($P = .002$). The rate of any stroke or death ≤ 30 days of treatment in the stenting group was more than twice the rate recorded in the endarterectomy group (7.4% vs 3.4%, $P = .0004$). In addition, the composite end point of stroke, death, and MI significantly favored CEA (5.2%) vs CAS (8.5%; $P = .006$). It is of interest to note that the authors of this trial highlight the fact that they observed a higher rate of fatal MIs with CAS than with CEA. This observation has not been confirmed in other large studies, including CREST, and in meta-analysis, where the incidence of MI is higher in the CEA group.¹¹

D. Meta-analysis: CEA vs CAS

Murad et al¹¹ recently completed an updated meta-analysis of all published trials comparing CEA and CAS in the management of patients with carotid stenosis. This analysis included data from the most recently completed randomized studies, CREST and ICST, which comprised 56% of all reported patients. Their analysis concluded that, compared with CEA, CAS was associated with a significantly reduced risk of perioperative MI (relative risk reduction [RRR], 0.43) and a significantly increased risk of any periprocedural stroke (RRR, 1.48). CAS was associated with an increased risk of periprocedural death (RRR, 1.40) that did not reach statistical significance. The risk of ipsilateral major stroke did not differ between the two procedures (RRR, 1.00), although the studies were underpowered to test this effect.

● Recommendations for selecting therapy

1. For neurologically symptomatic patients with stenosis $< 50\%$ or asymptomatic patients with stenosis $< 60\%$

diameter reduction, optimal medical therapy is indicated. There are no data to support CAS or CEA in this patient group (GRADE 1, Level of Evidence B).

2. In most patients with carotid stenosis who are candidates for intervention, CEA is preferred to CAS for reduction of all-cause stroke and periprocedural death (GRADE 1, Level of Evidence B). Data from CREST suggest that patients aged < 70 years may be better treated by CAS, but these data need further confirmation.
3. Neurologically asymptomatic patients with $\geq 60\%$ diameter stenosis should be considered for CEA for reduction of long-term risk of stroke, provided the patient has a 3- to 5-year life expectancy and perioperative stroke/death rates can be $\leq 3\%$ (GRADE 1, Level of Evidence A).
4. CEA is preferred over CAS in patients aged > 70 years of age, with long (> 15 -mm) lesions, preocclusive stenosis, or lipid-rich plaques that can be completely removed safely by a cervical incision in patients who have a virgin, nonradiated neck (GRADE 1, Level of Evidence A).
5. CAS is preferred over CEA in *symptomatic* patients with $\geq 50\%$ stenosis and tracheal stoma, situations where local tissues are scarred and fibrotic from prior ipsilateral surgery or external beam radiotherapy, prior cranial nerve injury, and lesions that extend proximal to the clavicle or distal to the C2 vertebral body (GRADE 2, Level of Evidence B). CEA may be preferable in situations where ipsilateral tissue planes remain relatively intact.
6. CAS is preferred over CEA in *symptomatic* patients with $\geq 50\%$ stenosis and severe uncorrectable CAD, congestive heart failure, or chronic obstructive pulmonary disease (GRADE 2, Level of Evidence C). In making this a GRADE 2 recommendation, the committee recognized the difficulty in clearly defining this group of individuals, both in symptomatology and risk assessment, and acknowledged the potential increased role of aggressive medical management as primary therapy in this high-risk group.
7. Neurologically asymptomatic patients deemed “high risk” for CEA should be considered for primary medical management. CEA can be considered in these patients only with evidence that perioperative morbidity and mortality is $< 3\%$. CAS should not be performed in these patients except as part of an ongoing clinical trial (GRADE 1, Level of Evidence B).
8. There are insufficient data to recommend CAS as primary therapy for neurologically asymptomatic patients with 70% to 99% diameter stenosis. Data from CREST suggest that in properly selected asymptomatic patients, CAS is equivalent to CEA in the hands of experienced interventionalists. Operators and institutions performing CAS must exhibit expertise sufficient to meet the previously established AHA guidelines for treatment of patients with asymptomatic carotid stenosis. Specifically, the combined stroke and death rate must be $< 3\%$

to ensure benefit for the patient (GRADE 2, Level of Evidence B).

VI. UNUSUAL CONDITIONS ASSOCIATED WITH CAROTID STENOSIS

Vascular surgeons will encounter a number of clinical scenarios where the role of carotid intervention is not well established. Oftentimes the data regarding treatment are relatively sparse or represent single-center series rather than prospective randomized trials. These conditions, however, may still be associated with the development of cerebral symptoms, particularly cerebrovascular accident (CVA) and consequently warrant analysis and recommendation.^{46,229} For the most part, randomized controlled trials have not been performed to examine these conditions that occur infrequently, and consequently, Level I evidence is often not available to guide physician practice. Nonetheless, the task force members determined that it was appropriate to make some recommendations in areas where they could reach unanimous agreement. These recommendations should be taken as the best opinion of the task force given current available data. As stated earlier, they may well change in the future as therapy evolves and new data emerge.

A. Acute neurologic syndromes

Acute neurologic syndromes can be divided into several clinical categories: acute stroke, stroke in evolution, and crescendo TIAs. The pathophysiology and concerns in each category are somewhat different, as are the treatment algorithms and outcomes.

Acute stroke is often associated with intracranial thrombosis, although this is less common in patients with the other two clinical presentations. As a consequence, a major management goal is to identify those patients with intracranial occlusion and to reperfuse the ischemic brain as rapidly as possible. Therapy is primarily directed at the intracranial occlusion. Although carotid bifurcation stenosis may be present, occlusion of the ICA in the neck is unusual in patients who are candidates for intervention.

In contrast, patients with crescendo TIA, by definition, have not had a significant volume of brain infarcted but do have a significant amount of brain at risk from a very unstable lesion with multiple small emboli or a large ischemic brain penumbra due to hemodynamic compromise and poor cerebral autoregulation. In these cases attention is directed at the source of symptoms, usually the carotid bifurcation.

Patients with stroke in evolution occupy a middle ground. Often there has been a permanent area of infarction, but the remaining ischemic penumbra is significant and attention is directed at salvaging this ischemic area as rapidly as possible.

In each of these clinical scenarios, expeditious clinical evaluation, brain imaging, and rapid evaluation of the carotid bifurcation is important in optimizing results. Brain imaging, most often by diffusion-weighted MRI, allows a rapid assessment of the amount of brain in-

fracted and the amount at risk, whereas CDUS imaging can assess the status of the bifurcation. As will be discussed below, this information dictates the branch points in treatment algorithms that follow. In general, patients with preocclusive carotid stenosis or carotid occlusion are considered for emergency intervention, whereas those with lesser degrees of stenosis are initially managed medically with urgent, but not emergency intervention, according to the recommendations for symptomatic patients with carotid stenosis.

1. Management of acute stroke.

a. Presentation within 0-6 hours. The National Institute of Neurological Disorders and Stroke trial established the efficacy of intravenous recombinant tissue plasminogen activator in the treatment of acute stroke, if therapy could be initiated ≤ 3 hours of the onset of symptoms.²³⁰ Efficacy has also been established for transarterial intracranial infusion.²³¹ Factors that have been noted to influence results include the extent of hemispheric involvement, time to the initiation of therapy, time to reperfusion, age, blood glucose, and female sex.²³²⁻²³⁵ The most important of these appear to be the degree of hemispheric involvement ($>30\%$ by volume), time to reperfusion, and age. The more rapidly intracranial reperfusion occurred, the better the neurologic recovery, with minimal improvement seen if reperfusion was not established before 6 hours.²³⁴ Thrombolysis may be given by systemic (intravenous) or local (intracranial) routes, and both routes are used in some cases to facilitate rapid reperfusion.²³⁴

Intravenous recombinant tissue plasminogen activator (r-tPA) has the advantage of rapid onset of administration but the potential disadvantage of longer time to reperfusion. Administration of r-tPA into the intracranial thrombus requires assembling a neurointerventional team and therefore takes longer to implement but is more efficacious than systemic therapy alone. Data suggest that about 30% of patients will show neurologic improvement with intravenous r-tPA²³⁵ and that recanalization will occur in $>50\%$ of patients ≤ 6 hours when systemic lysis is supplemented by local intra-arterial infusion.²³⁴

Mechanical thrombectomy, ultrasound-facilitated lysis, and clot fragmentation or extraction have all been proposed as methods to accomplish rapid reperfusion without the increased risk of hemorrhage associated with chemical thrombolysis.²³⁶⁻²³⁸ Experience at this time is limited. The role of extracranial intervention in the form of CAS or CEA must be considered in the context of the treatment of intracranial thrombosis or obstruction. Angioplasty and stenting of the extracranial ICA may be performed as an adjunct to intracranial therapy. Treatment of extracranial disease offers the potential advantages of preventing further embolization from the extracranial carotid atherosclerosis, increasing perfusion to the ischemic penumbra surrounding the area of cerebral infarct, enhancing arterial flow to augment clot-dissolution therapies, improve access for intervention on the intracranial lesions, and potentially improve the patency of the intracranial intervention. The use

of CAS as an adjunct to intracranial catheter-directed therapies has been evaluated in several case series.²³⁹ Although the results initially reported have been favorable, the overall experience has been limited.

b. Presentation later than 6 hours. Only about 15% of acute stroke patients will present within the 6-hour time window for acute intervention.²⁴⁰ Reasons for delay include failure to recognize symptoms, delay in seeking medical assistance, and a lack of nearby facilities capable of emergency intervention. As a result, many patients present outside this therapeutic window. Intervention in these patients is directed at the carotid bifurcation, not the intracranial circulation, with the goal of preventing recurrent events rather than re-establishing intracranial flow in occluded arteries.

Patients with an acute fixed deficit of more than 6-hours' duration and a mild or moderate deficit may be considered for carotid intervention after a period of medical stabilization. It is generally accepted that intervention is safely performed early (≤ 2 weeks) after the event and is preferable to a delayed (4-6 weeks) intervention.²⁴¹⁻²⁴⁴ Advances in radiographic imaging have made possible the identification of a subset of patients who may benefit from carotid bifurcation intervention in the setting of acute stroke.^{245,246}

Urgent CEA may be considered for patients in whom the distal ICA as well as middle cerebral artery and other intracranial vessels remain patent, who have limited areas of infarct ($< 30\%$ of hemispheric volume), with significant areas of ischemic penumbra at risk for progression of the infarct, have a mild to moderate neurologic deficit, and are at risk for recurrent embolization and repeat stroke. Patients should be hemodynamically stable, with mild or moderate functional deficit, relatively preserved mental status, and a favorable prognosis.²⁴⁷⁻²⁵² Because these are symptomatic patients, CEA would be recommended unless the patients are at high risk for surgery due to medical morbidity or anatomic features.

There are separate groups of patients in whom the neurologic examination fluctuates under observation. These patients can be classified as having unstable neurologic syndromes, a category that includes both stroke in evolution and crescendo TIA. In these clinical syndromes, urgent or emergent therapy is often considered to reverse ischemia or salvage brain at risk.

2. Stroke in evolution (fluctuating neurologic deficits). This is a clinical syndrome that has been characterized by an evolving neurologic condition associated with an acute precipitating neurologic event. In these situations, the initial medical management of stroke, including antiplatelet agents, volume support, and blood pressure management, has not succeeded in stabilizing the patient's neurologic condition, which may "wax and wane" over the early course of disease. Although patients may never return to normal, their neurologic deficits will be mild to moderate in nature. These patients should have brain imaging to exclude hemorrhage as an etiology and to identify ischemic

but viable brain. Carotid imaging by DUS, CTA, or MRA should identify a tight lesion in the carotid bifurcation.

The presumption is that optimizing hemispheric blood flow will improve perfusion to the ischemic hemisphere and reduce the ultimate extent of neurologic deficit. This must be balanced by concern that restoring blood flow may result in hemorrhagic conversion of an infarction or a reperfusion injury.

There are no large series of patients treated in a standard manner from which to draw definitive conclusions regarding optimal therapy. In patients where hemorrhage has been excluded by brain imaging, some surgeons use a heparin infusion to try to stabilize these patients and prevent propagation of thrombus as part of their immediate management. Only a few reports have included outcomes of CEA in patients with stroke in evolution. In general the stroke/death rates range from 9.2% to 26.2%.^{230,248,250-252} This reflects the heterogeneous group of patients and lack of standard selection criterion for intervention. There are no data on unoperated-on controls for comparison. The lack of high-quality data on the treatment of stroke in evolution precludes any clear conclusions on the management of this group of patients. There has not been a significant experience with CAS in these patients, distinct from what is referenced above for acute stroke, to draw conclusions.

3. Crescendo TIA. This relatively rare clinical syndrome is characterized by repetitive episodes of transient neurologic ischemia, followed by return to a normal neurologic status. The definition of "crescendo" varies, but generally includes multiple repetitive events within a 24-hour period that do not respond to antiplatelet therapy. High-grade stenosis of the carotid bifurcation, often with associated ulceration or thrombus, is a common finding. Brain imaging does not reveal a significant area of infarcted brain, and there may or may not be a large ischemic penumbra. Symptoms are thought to arise from an unstable carotid plaque with recurrent emboli despite antiplatelet therapy or from unstable cerebral hemodynamics associated with the bifurcation lesion.

Therapy in these patients is directed at removing the causative lesion at the carotid bifurcation. Again, some surgeons advocate heparin therapy in the immediate preoperative period if intracranial hemorrhage has been excluded, but this is based on personal experience rather than reported data. Urgent CEA in these patients has been associated with an increased risk of stroke compared with "elective" interventions. Overall, however, the results of surgery in patients with crescendo TIA are better than that of stroke in evolution. Systematic reviews of the literature for crescendo TIA report rates of stroke and death of 6.5% (95% CI, 3.4%-10.4%) and stroke, MI, and death of 10.9% (95% CI, 5.5%-17.9%). The comparable end points for stroke in evolution include stroke and death rates of 16.9% (95% CI, 9.2%-26.2%), and stroke, MI and death rates of 20.8% (95% CI, 13.2%-29.6%).²⁵² Although there are no data comparing CAS and CEA in these patients, the presumptive increase in embolic potential of these plaques

suggests that CEA would be preferred to CAS when the former is feasible.

4. Acute postintervention stroke or occlusion. Patients who undergo carotid intervention may suffer stroke in the early postintervention period. Treatment aims at restoring intracranial blood flow to normal levels and depends on identifying the etiology of the stroke. In general, treatment decisions should be made as expeditiously as possible. Stroke that occurs immediately after CEA is considered secondary to a technical defect at the operative site, until proven otherwise. Other etiologies of stroke in the immediate postoperative period include embolization, intraoperative watershed infarction, and intracranial hemorrhage.

Of these four, early thrombosis at the endarterectomy site is the most common.²⁵³ The status of the endarterectomy site should be determined. In most cases, this can be done by emergency bedside ultrasound imaging. If thrombosis is confirmed, then operative exploration with repair of the defect is indicated. Early re-exploration of an occluded endarterectomy site with successful repair may reduce long-term neurologic sequelae. Although there are no control groups available for comparison, re-exploration for symptomatic thrombosis has been associated with resolution of neurologic deficit in half to three-quarters of patients.²⁵⁴⁻²⁵⁶

If imaging shows the endarterectomy site is patent, other etiologies should be considered, specifically, distal embolization or intracranial hemorrhage. Emergency head CT to exclude hemorrhage is followed by anticoagulation and angiography, with intracranial intervention according to acute stroke guidelines. If capability for acute stroke intervention is not available, then anticoagulation and blood pressure support is indicated.

Acute stroke complicating CAS may result from embolization to the intracranial circulation during the procedure, occlusion of the angioplasty and stent site, or intracranial hemorrhage. Because CAS procedures are performed on patients who are awake, ongoing neurologic assessment is possible to guide evaluation and management. Management of acute, symptomatic intracranial embolization commonly reflects the current standard for intervention for acute stroke, as detailed in the previous section. Management options, including catheter-directed intra-arterial thrombolysis, clot dissolution or fragmentation with evacuation, and potentially, intracranial stenting, may be used as appropriate.^{233,236-239,257} In selected cases, perfusion imaging may also be of utility in determining which patients will potentially benefit from intracranial revascularization.^{245,246}

Acute occlusion of the stent has rarely been reported. A total of 10 cases of stent thrombosis have been reported, with causes being attributed to the use of inappropriate, balloon-expandable stents, inadequate antiplatelet or anticoagulation therapy, or plaque protrusion through the stent or technical failure. Options for management are analogous to the techniques used for acute de novo occlusion of the internal carotid artery and include recanaliza-

tion, intra-arterial thrombolysis, and management of the underlying cause of the occlusion.

● Recommendations for management of acute neurologic syndromes

1. Patients who present ≤ 6 hours of the onset of stroke should be considered for acute intervention to reduce the ultimate neurologic deficit. Interventions may include local or systemic thrombolysis (GRADE 1, Level of Evidence A). The role of endoluminal mechanical lysis or extraction remains to be defined.
2. Patients who present with fixed neurologic deficit > 6 -hours' duration should be considered for CEA once their condition has been stabilized. CEA should be performed ≤ 2 weeks of the neurologic event (GRADE 1, Level of Evidence B).
3. Patients who present with repetitive (crescendo) episodes of transient cerebral ischemia unresponsive to antiplatelet therapy should be considered for urgent CEA. The risk of intervention is increased over elective surgery for neurologic symptoms, but not as much as for patients with stroke in evolution. CEA is preferred to CAS in these patients based on the presumptive increased embolic potential of bifurcation plaque in this clinical situation (GRADE 1 Level of Evidence C).
4. For acute stroke after CEA, emergent imaging (ultrasound or fast CTA) is indicated to evaluate the endarterectomy site. When imaging suggests thrombosis, is indeterminate, or not available, immediate operative re-exploration is indicated (GRADE 1, Level of Evidence B).
5. When the endarterectomy site is patent, other modalities such as CT and angiography should be used to better identify the cause of the stroke. If CT excludes intracranial hemorrhage, anticoagulation is reasonable until a definitive decision regarding the appropriate diagnosis and therapy can be made (GRADE 2, Level of Evidence C). The committee acknowledged the lack of robust data in this small group of patients but was unanimous in its endorsement of this recommendation based on the data available and the low likelihood that new data would emerge in the near future.
6. No firm recommendations can be made on treatment of stent thrombosis associated with CAS. It is reasonable to attempt to restore patency by use of chemical lysis or clot extraction (GRADE 2, Level of Evidence C). The committee acknowledged the lack of robust data in this small group of patients but was unanimous in its endorsement of this recommendation based on the data available and the low likelihood that new data would emerge in the near future.

B. ICA occlusion with persistent symptoms and external carotid stenosis

Some patients with documented chronic occlusion of the ICA may develop recurrent neurologic or ocular symptoms. Neurologic symptoms may be secondary to embolization from the distal aspect of the occluded ICA segment, intrinsic disease of the external carotid artery, or from

embolization from the proximal aspect of the occluded ICA. Ocular ischemia may arise from stenosis of the external carotid artery.²⁵⁸ These patients may be managed by endarterectomy of the common and external carotid artery with transection and flush ligation of the ICA to remove the “stump” as a cause of the symptoms.^{259,260} Alternatively, angioplasty and stenting of the external carotid artery has been used to enhance cerebral perfusion in patients with external carotid stenosis and occlusion of the ICA.²⁶¹

Oral anticoagulation administration has been used in the treatment of patients with a stroke associated with chronic occlusion of the ICA. On meta-analysis, anticoagulation resulted in a significant reduction in the incidence of recurrent CVA. In contrast, aspirin administration did not affect the recurrent stroke rate.²⁶²

● **Recommendations for management of symptomatic ICA occlusion**

1. Patients with known ICA occlusion and persistent ipsilateral neurologic symptoms can be treated by endarterectomy of the common and external carotid artery, with transection and ligation of the ICA origin. The addition of oral anticoagulation is likely to reduce the rate of recurrent CVA (GRADE 1, Level of Evidence C).

C. Carotid dissection

Carotid dissection may occur spontaneously or result from traumatic or iatrogenic injury. Historically, carotid dissection has been treated medically with antiplatelet agents or anticoagulation. Intervention has largely been reserved for patients with recurrent neurologic symptoms despite anti-thrombotic therapy, those who experience cerebral hypoperfusion due to hemodynamic effects of the dissection, or those in whom antithrombotic therapy is contraindicated. Open surgical therapy may be associated with significant rates of perioperative CVA and cranial nerve injury. The largest case series reported a 12.5% rate of combined recurrent stroke and death and a 58% rate of cranial nerve injury.²⁶³

More recently, endovascular techniques, including stent placement with or without adjunctive angioplasty, have been evaluated. Relatively few reports have been published on a small number of patients with dissection.²⁶⁴⁻²⁶⁶ These initial results provide some encouragement, with the development of new or progressive symptoms occurring infrequently. Endovascular therapies appear to provide significantly superior results compared with open surgical approaches, with lower stroke rates and no cranial nerve injuries.

A comprehensive literature review identified 62 patients treated by endovascular means. The technical success rate reported was 100%, and the 1-year patency rate was 100%. The rate of recurrent CVA was 11% with no deaths.²⁶⁴⁻²⁶⁶ No large series have been reported, and a multicenter trial appears to be warranted. With these considerations, endovascular treatment of patients when medical management fails appears to be justified.

● **Recommendations for management of carotid dissection**

1. Patients with carotid dissection should be initially treated with antithrombotic therapy (antiplatelet agents or anticoagulation) (GRADE 1, Level of Evidence C).
2. Patients who remain symptomatic on medical therapy may be considered for intervention. Although data are insufficient to make firm recommendations, the committee unanimously agreed that balloon angioplasty and stenting is currently preferred over open surgery after failed medical management (GRADE 2, Level of Evidence C).

D. Combined carotid and coronary disease

The incidence of concomitant carotid and coronary atherosclerosis is significant. Patients who have coronary disease amenable to percutaneous coronary intervention should be treated in that manner, followed by treatment of the carotid stenosis. The presence of carotid disease has been associated with an increase in the incidence of CVA in the perioperative period for cardiac surgery. The presence of a bruit increases the risk of CVA to 1.6% to 5.5%, and the presence of a carotid stenosis between 50% to 99% increases the risk to 2.0% to 8.4%.^{38,46,267} Consequently, the management of concomitant carotid and coronary disease has been the subject of considerable study.

For patients experiencing symptoms related to a carotid stenosis (TIA, CVA), the risk of CVA associated with cardiac surgery is increased to such a degree that concomitant management of the carotid disease is mandatory. Prior CVA or TIA increases the risk of perioperative stroke to 2.2% to 8.5%. If bilateral 50% to 99% stenoses are present, the risk of perioperative CVA increases to 5.2% (95% CI, 0%-10.8%). If carotid occlusion is present, the risk of perioperative CVA increases to 7% to 12% (95% CI, 2.1%-21.2%).²⁶⁸⁻²⁷¹ Alternative treatments, including combined CEA and CABG, staged CEA and CABG, or CAS and CABG have all been reported.

A review of the literature to date suggests that CEA, followed by CABG, is associated with the lowest stroke rate, whereas combined CEA and CABG carries a higher mortality rate, and delayed CEA is associated with the lowest mortality but the highest stroke rate. Most studies are retrospective reviews, and there is no evidence that patient groups are comparable. However, in a meta-analysis, Naylor et al²⁶⁹ found that the total stroke/MI/death rate associated with any combination CEA and CABG ranges from 9% to 12%.

In contrast to patients with neurologic symptoms and those with severe bilateral carotid bifurcation stenosis, the management of patients requiring cardiac surgery in whom unilateral asymptomatic carotid stenosis has been identified is not established. Documentation of an increase in the perioperative stroke rate in patients undergoing cardiac surgery who have been identified as having concomitant carotid disease has been well established for decades.²⁷² An increase in the incidence of CVA in the perioperative period for patients undergoing cardiac surgery has been demonstrated for patients with a carotid bruit, carotid stenosis >50%, or a history of TIA or CVA. Stenoses <70% do not appear to be associated with increased stroke.^{271,273}

Unfortunately, the literature is not consistent with regard to the degree of stenosis reported as “significant” or the criteria for screening and quantifying stenosis. As a result, accurate assessment of the stroke risk associated with an asymptomatic stenosis in CABG patients is not possible at this time. It remains uncertain if correction of carotid disease before cardiac surgery is effective in lowering the perioperative rate of CVA for those patients. Only two randomized controlled trials have compared combined CEA/CABG with a strategy of CABG first and delayed CEA in patients with unilateral asymptomatic carotid stenosis. Hertzler et al²⁷⁴ demonstrated reduced combined stroke/death rates for combined CEA/CABG compared to staged CEA (5.6% vs 17%). The stroke rate associated with the “unprotected” CABG was 7.4%, compared to a stroke rate of 2.8% with combined CEA/CABG. Recently, Illuminati et al²⁷⁵ reported randomizing 185 patients with unilateral severe (>80%) asymptomatic carotid stenosis, in whom aortic arch disease had been excluded by preoperative CT scan, between “protected” CABG (15 CEA first, 79 combined CEA and CABG) and “unprotected” CABG with CEA performed at a later time (within 3 months) (91 patients). There were no strokes in the “protected” group, compared to 7 strokes (3 early, 4 later) in the “unprotected” group. All strokes were ipsilateral to the stenosis and occurred before CEA was performed. These two reports suggest that patients with asymptomatic unilateral severe stenosis may benefit from CEA before or with CABG in centers with considerable experience. However, further studies are required before a general recommendation can be made. Other factors, including the specific nature of the cardiac surgery being performed, length of cardiopulmonary bypass, and the status of the aortic arch, among a variety of other risk factors, are important in determining overall stroke risk after CABG.^{271,276} The best results, stroke/death rates of 2.2%, have been reported for off-pump CABG and synchronous CEA, although there is likely a significant influence of patient selection in these series.²⁷⁷ It is also possible that the presence of carotid stenosis is a surrogate marker for stroke risk, rather than a preventable, direct cause (as evidenced by patients with unilateral carotid occlusion who exhibit the highest perioperative rates of CVA).²⁶⁹

In summary, significant indirect evidence suggests that treatment of neurologically symptomatic carotid stenosis or patients with bilateral asymptomatic severe disease may reduce the incidence of perioperative CVA in patients undergoing cardiac surgery. The data on treatment of unilateral asymptomatic stenosis >70% suggest CEA before or in combination with CABG is reasonable in centers of excellence but the data at this point are insufficient to make a firm recommendation. Local results are critical in determining appropriate therapy.

When coronary intervention can be performed percutaneously, this should precede carotid intervention. Data indicating trends toward improved outcomes for simultaneous performance of the surgical procedures at institutions that manage these conditions regularly are not suffi-

ciently robust to support a definitive recommendation. More recently, some studies suggested a potential role for CAS before CABG, with a trend toward decreased stroke rates in the patients treated with CAS.^{278,279} A review of the Nationwide Inpatient Sample found the risk of perioperative stroke was 62% higher for combined CEA and CABG (3.9%) compared with combined CAS and CABG (2.4%), with an OR of 1.62 (95% CI, 1.1-2.5).²⁷⁸

If a sequential strategy is planned, CABG may need to be deferred for 2 to 4 weeks because of the need for dual-antiplatelet therapy after CAS. This has resulted in some logistical difficulties in patients who require urgent coronary revascularization. A meta-analysis of all published results²⁸⁰ suggested that the stroke/death rate of 9.1% seen with CAS and CABG is not significantly different than the results with CEA and CABG. One must conclude that data are insufficient to support a clear recommendation for treating patients with unilateral asymptomatic carotid stenosis who need CABG.

● Recommendations for management of combined carotid and coronary disease

1. Patients with symptomatic carotid stenosis will benefit from CEA before or concomitant with CABG. The timing of the intervention depends on clinical presentation and institutional experience (GRADE 1, Level of Evidence B).
2. Patients with severe bilateral asymptomatic carotid stenosis, including stenosis and contralateral occlusion, should be considered for CEA before or concomitant with CABG (GRADE 2, Level of Evidence B).

AUTHOR CONTRIBUTIONS

Conception and design: JR, AA, EA, ME, PF, BL

Analysis and interpretation: JR, AA, EA, ME, PF, BL

Data collection: JR, AA, EA, ME, PF, BL

Writing the article: JR, AA, EA, ME, PF, BL

Critical revision of the article: JR, AA, EA, ME, PF, BL

Final approval of the article: JR, AA, EA, ME, PF, BL

Statistical analysis: JR, AA, EA, ME, PF, BL

Obtained funding: Not applicable.

Overall responsibility: JR

REFERENCES

1. Fields WS, North RR, Hass WK, Kircheff II, Chase NE, Bauer RB, et al. Joint study of extracranial arterial occlusion as a cause of Stroke. I. Organization of study and survey of patient population. *JAMA* 1968; 203:955-60.
2. North American Symptomatic Carotid Endarterectomy Trial Collaborators (NASCET). Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators *N Engl J Med* 1991;325:445.
3. Barnett HJ, Taylor DW, Eliasziw M, Fox AJ, Ferguson GG, Haynes RB, et al. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. *N Engl J Med* 1998;339: 1415-25.
4. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). *Lancet* 1998;351:1379-87.

5. Endarterectomy for the asymptomatic carotid artery stenosis. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. *JAMA* 1995;273:1421-8.
6. Halliday A, Mansfield A, Marro J, Peto C, Peto R, Potter J, et al. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. *Lancet* 2004;363:1491-502.
7. Eslami MH, McPhee JT, Simons JP, Schanzer A, Messina LM. National trends in utilization and postprocedure outcomes for carotid revascularization 2005 to 2007. *J Vasc Surg* 2011;53:307-15.
8. Cowan JA, Dimick JB, Thompson BC, Stanley JA, Upchurch GR. Surgeon volume as an indicator of outcomes after carotid endarterectomy: an effect independent of specialty practice and hospital volume. *JACS* 2002;195:814-21.
9. Brott TG, Hobson RW, 2nd, Howard G, Roubin GS, Clark WM, Brooks W, et al. Stenting versus endarterectomy for treatment of carotid-artery stenosis. *N Engl J Med* 2010;363:11-23.
10. International Carotid Stenting Study investigators, Ederle J, Dobson J, Featherstone RL, Bonati LH, van der Worp HB, et al. Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomised controlled trial. *Lancet* 2010;375:985-97.
11. Murad MH, Shahrour A, Shah ND, Montori VM, Ricotta JJ. A systematic review and meta-analysis of randomized trials of carotid endarterectomy vs stenting. *J Vasc Surg* 2011;53:792-97.
12. Hobson RW 2nd, Mackey WC, Ascher E, Murad MH, Calligaro KD, Comerota AJ, et al. Management of atherosclerotic carotid artery disease: clinical practice guidelines of the Society for Vascular Surgery. *J Vasc Surg* 2008;48:480-6.
13. Brott TG, Halperin JL, Abbara S, Bacharach JM, Barr JD, Bush RL, et al. 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. *J Am Coll Cardiol* 2011;57:e16-e94.
14. Murad MH, Montori VM, Sidawy AN, Ascher E, Meissner MH, Chaikof EL, et al. Guideline methodology of the Society for Vascular Surgery including the experience with the GRADE framework. *J Vasc Surg* 2011;53:1375-80.
15. Warlow CP, Dennis MS, van Gijn J. What caused the transient or persisting ischaemic event, In Warlow CP, et al, editors. *Stroke a practical guide to management*. Oxford, Engle: Blackwell Science; 2001. p. 223-300.
16. Chambers BR, Donnan GA. Carotid endarterectomy for asymptomatic carotid stenosis. *Cochrane Database Syst Rev* 2005;4:CD001923.
17. Abbott AL, Bladin CF, Levi CR, Chambers BR. What should we do with asymptomatic carotid stenosis? *Int J Stroke* 2007;2:27-39.
18. Hankey GJ. Impact of treatment of people with transient ischemic attacks on stroke incidence and public health. *Cerebrovasc Dis* 1996;6(suppl 1):26-33.
19. Chaturvedi S, Bruno A, Feasby T, Holloway R, Benavente O, Cohen SN, et al. Carotid Endarterectomy – an evidence based review: report of the Therapeutics and Technology Subcommittee of the American Academy of Neurology. *Neurology* 2005;65:794-801.
20. Benavente O, Eliasziw M, Streifler JY, Fox AJ, Barnett HJ, Meldrum H, et al. Prognosis after transient monocular blindness associated with carotid-artery stenosis. *N Engl J Med* 2001;345:1084-90.
21. Qureshi AI, Alexandrov AV, Tegeler CH, Hobson RW 2nd, Dennis Baker J, Hopkins LN, et al. Guidelines for screening of extracranial carotid artery disease: a statement for healthcare professionals from the multidisciplinary practice guidelines committee of the American Society of Neuroimaging: cosponsored by the Society of Vascular and Interventional Neurology. *J Neuroimaging* 2007;17:19-47.
22. Gorelick PB, Sacco RL, Smith DB, Alberts M, Mustone-Alexander L, Rader D, et al. Prevention of a first stroke: a review of guidelines and a multidisciplinary consensus statement from the National Stroke Association. *JAMA* 1999;281:1112-20.
23. Perry JR, Szalai JP, Norris JW. Consensus against both endarterectomy and routine screening for asymptomatic carotid artery stenosis. Canadian Stroke Consortium. *Arch Neurol* 1997;54:25-8.
24. U.S. Preventive Services Task Force. Screening for carotid artery stenosis: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2007;147:854-9.
25. Goldstein LB, Adams R, Alberts MJ, Appel LJ, Brass LM, Bushnell CD, et al. Primary prevention of ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council: cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and Metabolism Council; and the Quality of Care and Outcomes Research Interdisciplinary Working Group: the American Academy of Neurology affirms the value of this guideline. *Stroke* 2006;37:1583-633.
26. Bates ER, Babb JD, Casey DE Jr, Cates CU, Duckwiler GR, Feldman TE, et al. ACCF/SCAI/SVMB/SIR/ASITN 2007 clinical expert consensus document on carotid stenting: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents (ACCF/SCAI/SVMB/SIR/ASITN Clinical Expert Consensus Document Committee on Carotid stenting). *J Am Coll Cardiol* 2007;49:126-70.
27. Zhu CZ, Norris JW. Role of carotid stenosis in ischemic stroke. *Stroke* 1990;21:1131-4.
28. Sauvé JS, Thorpe KE, Sackett DL, Taylor W, Barnett HJ, Haynes RB, et al. Can bruits distinguish high-grade from moderate symptomatic carotid stenosis? The North American Symptomatic Carotid Endarterectomy Trial. *Ann Intern Med* 1994;120:633.
29. Ratchford EV, Jin Z, Di Tullio MR, Salameh MJ, Homma S, Gan R, et al. Carotid bruit for the detection of hemodynamically significant carotid stenosis: the Northern Manhattan Study. *Neurol Res* 2009;31:748-52.
30. Heyman A, Wilkinson WE, Heyden S, Helms MJ, Bartel AG, Karp HR, et al. Risk of stroke in asymptomatic persons with cervical arterial bruits: a population study in Evans County, Georgia. *N Engl J Med* 1980;302:383.
31. Wiebers DO, Whisnant JP, Sandok BA, O'Fallon WM. Prospective comparison of a cohort with asymptomatic carotid bruit and a population-based cohort without carotid bruit. *Stroke* 1990;21:984-8.
32. Shorr RI, Johnson KC, Wan JY, Sutton-Tyrrell K, Pahor M, Bailey JE, et al. The prognostic significance of asymptomatic carotid bruits in the elderly. *J Gen Intern Med* 1998;13:86.
33. Pickett CI, Jackson JL, Hemann BA, Atwood E. Carotid bruits as a prognostic indicator of cardiovascular death and myocardial infarction: a meta-analysis. *Lancet* 2008;371:1587-94.
34. Benavente O, Moher D, Pham B. Carotid endarterectomy for asymptomatic carotid stenosis: a meta-analysis. *BMJ* 1998;317:1477.
35. Jacobowitz GR, Rockman CB, Gagne PJ, Adelman MA, Lamparello PJ, Landis R, et al. A model for predicting occult carotid artery stenosis: screening is justified in a selected population. *J Vasc Surg* 2003;38:705-9.
36. Qureshi AI, Janardhan V, Bennett SE, Luft AR, Hopkins LN, Guterma LR. Who should be screened for asymptomatic carotid artery stenosis? Experience from the Western New York stroke screening program. *J Neuroimaging* 2001;11:105-11.
37. Ascher E, Hingorani A, Yorkovich W, Ramsey PJ, Salles-Cunha S. Routine preoperative carotid duplex scanning in patients undergoing open heart surgery: is it worthwhile? *Ann Vasc Surg* 2001;15:669-78.
38. Naylor AR, Mehta Z, Rothwell PM, Bell PR. Carotid artery disease and stroke after coronary artery bypass: a critical review of the literature. *Eur J Vasc Endovasc Sur* 2002;23:283-94.
39. D'Agostino RS, Svensson LG, Neumann DJ, Balkhy HH, Williamson WA, Shahian DM. Screening carotid ultrasonography and risk factors

- for stroke in coronary artery surgery patients. *Ann Thorac Surg* 1996;62:1714-23.
40. Fukuda I, Ohuchi H, Sato M, Sato F, Wada M. Carotid screening with duplex scanning before coronary artery bypass. *Nippon Kyobu Geka Gakkai Zasshi* 1996;44:478-83.
 41. Hill AB. Should patients be screened for asymptomatic carotid artery stenosis? *Can J Surg* 1998;41:208-13.
 42. Ascher E, DePippo P, Salles-Cunha S, Marchese J, Yorkovich W. Carotid screening with duplex ultrasound in elderly asymptomatic patients referred to a vascular surgeon: is it worthwhile? *Ann Vasc Surg* 1999;13:164-8.
 43. Hill AB, Obrand D, Steinmetz OK. The utility of selective screening for carotid stenosis in cardiac surgery patients. *J Cardiovasc Surg [Torino]* 1999;40:829-36.
 44. Durand DJ, Perler BA, Roseborough GS, Grega MA, Borowicz LM Jr, Baumgartner WA, et al. Mandatory versus selective preoperative carotid screening: a retrospective analysis. *Ann Thorac Surg* 2004;78:159-66.
 45. Tanimoto S, Ikari Y, Tanabe K, Yachi S, Nakajima H, Nakayama T, et al. Prevalence of carotid artery stenosis in patients with coronary artery disease in Japanese population. *Stroke* 2005;36:2094-8.
 46. Eagle KA, Guyton RA, Davidoff R, Edwards FH, Ewy GA, Gardner TJ, et al. ACC/AHA 2004 guideline update for coronary artery bypass graft surgery: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (committee to update the 1999 guidelines for coronary artery bypass graft surgery). *Circulation* 2004;110:1168-76.
 47. Marek J, Mills JL, Harvich J, Cui H, Fujitani RM. Utility of routine carotid duplex screening in patients who have claudication. *J Vasc Surg* 1996;24:572-7.
 48. Alexandrova NA, Gibson WC, Norris JW, Maggisano R. Carotid artery stenosis in peripheral vascular disease. *J Vasc Surg* 1996;23:645-9.
 49. Valentine RJ, Hagino RT, Boyd PI, Kakish HB, Clagett GP. Utility of carotid duplex in young adults with lower extremity atherosclerosis: how aggressive should we be in screening young patients? *Cardiovasc Surg* 1997;5:408-13.
 50. Cheng SW, Wu LL, Ting AC, Lau H, Wong J. Screening for asymptomatic carotid stenosis in patients with peripheral vascular disease: a prospective study and risk factor analysis. *Cardiovasc Surg* 1999;7:303-9.
 51. House AK, Bell R, House J, Mastaglia F, Kumar A, D'Antuono M. Asymptomatic carotid artery stenosis associated with peripheral vascular disease: a prospective study. *Cardiovasc Surg* 1999;7:44-9.
 52. Deville C, Kerdi S, Madonna F, de la Renaudiere DF, Labrousse L. Infrarenal abdominal aortic aneurysm repair: detection and treatment of associated carotid and coronary lesions. *Ann Vasc Surg* 1997;11:467-72.
 53. Cahan MA, Killewich LA, Kolodner L, Powell CC, Metz M, Sawyer R, et al. The prevalence of carotid artery stenosis in patients undergoing aortic reconstruction. *Am J Surg* 1999;178:194-6.
 54. Axelrod DA, Diwan A, Stanley JC, Jacobs LA, Henke PK, Greenfield LJ, et al. Cost of routine screening for carotid and lower extremity occlusive disease in patients with abdominal aortic aneurysms. *J Vasc Surg* 2002;35:754-8.
 55. Cheng SW, Wu LL, Ting AC, Lau H, Lam LK, Wei WI. Irradiation-induced extracranial carotid stenosis in patients with head and neck malignancies. *Am J Surg* 1999;178:323-8.
 56. Moritz MW, Higgins RF, Jacobs JR. Duplex imaging and incidence of carotid radiation injury after high-dose radiotherapy for tumors of the head and neck. *Arch Surg* 1990;125:1181-3.
 57. Dubec JJ, Munk PL, Tsang V, Lee MJ, Janzen DL, Buckley J, et al. Carotid artery stenosis in patients who have undergone radiation therapy for head and neck malignancy. *Br J Radiol* 1998;71:872-5.
 58. Carmody BJ, Arora S, Avena R, Curry KM, Simpkins J, Cosby K, et al. Accelerated carotid artery disease after high-dose head and neck radiotherapy: is there a role for routine carotid duplex surveillance? *J Vasc Surg* 1999;30:1045-51.
 59. Steele SR, Martin MJ, Mullenix PS, Crawford JV, Cuadrado DS, Andersen CA. Focused high-risk population screening for carotid arterial stenosis after radiation therapy for head and neck cancer. *Am J Surg* 2004;187:594-8.
 60. Kakkos SK, Sabetai M, Tegos T, Stevens J, Thomas D, Griffin M, et al. Silent embolic infarcts on computed tomography brain scans and risk of ipsilateral hemispheric events in patients with asymptomatic internal carotid artery stenosis. *J Vasc Surg* 2009;49:902-9.
 61. Risk of stroke in the distribution of an asymptomatic carotid artery. The European Carotid Surgery Trialists Collaborative Group. *Lancet* 1995;345:209.
 62. Ricotta JJ, Schenck EA, Hassett JM, Deweese JA. Lesion Width as a Discriminator of Plaque Characteristics. *J Cardiovasc Surg* 1996;4:124-9.
 63. Reilly LM, Lusby RJ, Hughes L, Ferrell LD, Stoney RJ, Ehrenfeld WK. Carotid plaque histology using real-time ultrasonography. Clinical and therapeutic implications. *Am J Surg* 1983;146:188-93.
 64. AbuRahma AF, Wulu JT, Crotty B. Carotid plaque ultrasonic heterogeneity and severity of stenosis. *Stroke* 2002;33:1772-5.
 65. Nicolaides AN. Asymptomatic carotid stenosis and risk of stroke: identification of a high risk group (ACRS): a natural history study. *Int Angio* 1995;14:21-3.
 66. Biasi GM, Froio A, Diethrich EB, Deleo G, Galimberti S, Mingazzini P, et al. Carotid plaque echolucency increases the risk of stroke in carotid stenting: the Imaging in Carotid Angioplasty and Risk of Stroke (ICAROS) Study. *Circulation* 2004;110:756-62.
 67. Nicolaides AN, Kakkos SK, Griffin M, Sabetai M, Dhanjil S, Thomas DJ, et al. Effect of image normalization on carotid plaque classification and the risk of ipsilateral hemispheric ischemic events: results from the asymptomatic carotid stenosis and risk of stroke study. *Vascular* 2005;13:211-21.
 68. Grant EG, Benson CB, Moneta GL, Alexandrov AV, Baker JD, Bluth EI, et al. Carotid artery stenosis: grayscale and Doppler ultrasound diagnosis – Society of Radiologists in Ultrasound Consensus Conference. *Ultrasound Q* 2003;19:190-8.
 69. AbuRahma AF, Srivastava M, Stone PA, Mousa AY, Jain A, Dean LS, et al. Critical appraisal of the carotid duplex consensus criteria in the diagnosis of carotid artery stenosis. *J Vasc Surg* 2011;53:53-60.
 70. Comerota AJ, Salles-Cunha SX, Daoud Y, Jones L, Beebe HG. Gender differences in blood velocities across carotid stenoses. *J Vasc Surg* 2004;40:939-44.
 71. Busuttill SJ, Franklin DP, Youkey JR, Elmore JR. Carotid duplex overestimation of stenosis due to severe contralateral disease. *Am J Surg* 1996;172:144-7.
 72. Lal BK, Hobson RW, Tofghi B, Kapadia I, Cuadra S, Jamil Z. Duplex ultrasound velocity criteria for the stented carotid artery. *J Vasc Surg* 2008;47:63-73.
 73. Sitzer M, Rose G, Fürst G, Siebler M, Steinmetz H. Characteristics and clinical value of an intravenous echo-enhancement agent in evaluation of high-grade internal carotid stenosis. *J Neuroimaging* 1997;7(suppl 1):S22-5.
 74. Ferrer JM, Samsó JJ, Serrando JR, Valenzuela VF, Montoya SB, Docampo MM. Use of ultrasound contrast in the diagnosis of carotid artery occlusion. *J Vasc Surg* 2000;31:736-41.
 75. Bude RO, Rubin JM, Adler RS. Power versus conventional color Doppler sonography: comparison in the depiction of normal intrarenal vasculature. *Radiology* 1994;192:777-80.
 76. Nederkoom PJ, van der Graaf Y, Hunink MG. Duplex ultrasound and magnetic resonance angiography compared with digital subtraction angiography in carotid artery stenosis: a systematic review. *Stroke* 2003;34:1324-32.
 77. Remonda L, Senn P, Barth A, Arnold M, Lövlblad KO, Schroth G. Contrast-enhanced 3D MR angiography of the carotid artery: comparison with conventional digital subtraction angiography. *AJNR Am J Neuroradiol* 2002;23:213-9.
 78. Yuan C, Mitsumori LM, Ferguson MS, Polissar NL, Echelard D, Ortiz G, et al. In vivo accuracy of multispectral magnetic resonance imaging for identifying lipid-rich necrotic cores and intraplaque hemorrhage in advanced human carotid plaques. *Circulation* 2001;104:2051-6.
 79. Hatsukami TS, Ross R, Polissar NL, Yuan C. Visualization of fibrous cap thickness and rupture in human atherosclerotic carotid plaque in

- vivo with high-resolution magnetic resonance imaging. *Circulation* 2000;102:959-64.
80. Bartlett ES, Walters TD, Symons SP, Fox AJ. Quantification of carotid stenosis on CT angiography. *AJNR Am J Neuroradiol* 2006;27:13.
 81. Koelmay MJ, Nederkoorn PJ, Reitsma JB, Majoie CB. Systematic review of computed tomographic angiography for assessment of carotid artery disease. *Stroke* 2004;35:2306-12.
 82. Grønholdt ML. B-mode ultrasound and spiral CT for the assessment of carotid atherosclerosis. *Neuroimaging Clin N Am* 2002;12:421-35.
 83. Hanky GJ, Warlow CP, Molyneux AJ. Complications of cerebral angiography for patients with mild carotid territory ischaemia being considered for carotid endarterectomy. *J Neurol Neurosurg, Psychiatry* 1990;53:542-8.
 84. Davies KN, Humphrey PR. Complications of cerebral angiography in patients with symptomatic carotid territory ischaemia screened by carotid ultrasound. *J Neurol Neurosurg, Psychiatry* 1993;56:967-72.
 85. Leonardi M, Cenni P, Simonetti L, Raffi L, Battaglia S. Retrospective study of complications arising during cerebral and spinal diagnostic angiography from 1998 to 2003. *Intervent Neuroradiol* 2005;11:213-21.
 86. Wardlaw JM, Chappell FM, Stevenson M, De Nigris E, Thomas S, Gillard J, et al. Accurate, practical and cost-effective assessment of carotid stenosis in the UK. *Health Technol Assess* 2006;10:iii-iv, ix-x, 1-182.
 87. Sadideen H, Taylor PR, Padayachee TS. Restenosis after carotid endarterectomy. *Int J Clin Pract* 2006;60:1265-30.
 88. Moore WS, Kempczinski RF, Nelson JJ, Toole JF. Recurrent carotid stenosis: results of the Asymptomatic Carotid Atherosclerosis Study. *Stroke* 1998;29:2018-25.
 89. Cao P, Giordano G, De Rango P, Zannetti S, Chiesa R, Coppi G, et al. Eversion versus conventional carotid endarterectomy: late results of a prospective multicenter randomized trial. *J Vasc Surg* 2000;31:19-30.
 90. Sundt TM Jr, Whisnant JP, Houser OW, Fode NC. Prospective study of the effectiveness and durability of carotid endarterectomy. *Mayo Clin Proc* 1990;65:625-35.
 91. Raman KG, Layne S, Makaroun MS, Kelley ME, Rhee RY, Tzeng E, et al. Disease progression in contralateral carotid artery is common after endarterectomy. *J Vasc Surg* 2004;39:52-7.
 92. Martin-Conejero A, Reina-Gutierrez T, Serrano-Hernando FJ, Sanchez-Hervas L, Blanco-Cañibano E, Ponce-Cano AI, et al. Disease progression in the contralateral carotid artery after endarterectomy. *Ann Vasc Surg* 2005;19:662-8.
 93. AbuRahma AF, Robinson PA, Mullins DA, Holt SM, Herzog TA, Mowery NT. Frequency of postoperative carotid duplex surveillance and type of closure: results from randomized trial. *J Vasc Surg* 2000;32:1043-51.
 94. Yadav JS, Wholey MH, Kuntz RE, Fayad P, Katzen BT, Mishkel GJ, et al. Protected carotid-artery stenting versus endarterectomy in high-risk patients. *N Engl J Med* 2004;351:1493-501.
 95. Chakhtoura EY, Hobson RW 2nd, Goldstein J, Simonian GT, Lal BK, Haser PB, et al. In-stent restenosis after carotid angioplasty-stenting: incidence and management. *J Vasc Surg* 2001;33:220-5.
 96. Roubin GS, New G, Iyer SS, Vitek JJ, Al-Mubarak N, Liu MW, et al. Immediate and late clinical outcomes of carotid artery stenting in patients with symptomatic and asymptomatic carotid artery stenosis: a 5-year prospective analysis. *Circulation* 2001;103:532-7.
 97. Wholey MH, Al-Mubarak N, Wholey MH. Updated review of the global carotid artery stent registry. *Catheter Cardiovasc Interv* 2003;60:259-66.
 98. McCabe DJ, Pereira AC, Clifton A, Bland JM, Brown MM, CAVATAS Investigators. Restenosis after carotid angioplasty, stenting, or endarterectomy in the carotid and vertebral artery transluminal angioplasty study (CAVATAS). *Stroke* 2005;36:281-6.
 99. AbuRahma AF, Abu-Halimah S, Bensenhaver J, Dean LS, Keiffer T, Emmett M, et al. Optimal carotid duplex velocity criteria for defining the severity of carotid in-stent restenosis. *J Vasc Surg* 2008;48:589-94.
 100. Sacco RL, Adams R, Albers G, Alberts MJ, Benavente O, Furie K, et al. Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke: co-sponsored by the Council on Cardiovascular Radiology and Intervention: the American Academy of Neurology affirms the value of this guideline. *Stroke* 2006;37:577-617.
 101. Rodgers A, MacMahon S, Gamble G, Slattery J, Sandercock P, Warlow C. Blood pressure and risk of stroke in patients with cerebrovascular disease. The United Kingdom Transient Ischaemic Attack Collaborative Group. *BMJ* 1996;313:147.
 102. Lawes CM, Bennett DA, Feigin VL, Rodgers A. Blood pressure and stroke: an overview of published reviews. *Stroke* 2004;35:1024.
 103. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003;289:2560-72.
 104. Wilson PW, Hoeg JM, D'Agostino RB, Silbershatz H, Belanger AM, Poehlmann H, et al. Cumulative effects of high cholesterol levels, high blood pressure, and cigarette smoking on carotid stenosis. *N Engl J Med* 1997;337:516-22.
 105. Heiss G, Sharrett AR, Barnes R, Chambless LE, Szklo M, Alzola C. Carotid atherosclerosis measured by B-mode ultrasound in populations: associations with cardiovascular risk factors in the ARIC study. *Am J Epidemiol* 1991;134:250-6.
 106. Howard G, Manolio TA, Burke GL, Wolfson SK, O'Leary DH. Does the association of risk factors and atherosclerosis change with age? An analysis of the combined ARIC and CHS cohorts. The Atherosclerosis Risk in Communities (ARIC) and Cardiovascular Health Study (CHS) investigators. *Stroke* 1997;28:1693-701.
 107. Smith NL, Barzilay JI, Shaffer D, Savage PJ, Heckbert SR, Kuller LH, et al. Fasting and 2-hour postchallenge serum glucose measures and risk of incident cardiovascular events in the elderly: the Cardiovascular Health Study. *Arch Intern Med* 2002;162:209-16.
 108. Wagenknecht LE, D'Agostino R Jr, Savage PJ, O'Leary DH, Saad MF, Haffner SM. Duration of diabetes and carotid wall thickness. The Insulin Resistance Atherosclerosis Study (IRAS). *Stroke* 1997;28:999-1005.
 109. Dobs AS, Nieto FJ, Szklo M, Barnes R, Sharrett AR, Ko WJ. Risk factors for popliteal and carotid wall thicknesses in the Atherosclerosis Risk in Communities (ARIC) Study. *Am J Epidemiol* 1999;150:1055-67.
 110. Laakso M. Benefits of strict glucose and blood pressure control in type 2 diabetes: lessons from the UK Prospective Diabetes Study. *Circulation* 1999;99:461-2.
 111. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008;358:2545-59.
 112. The ADVANCE Collaborative Group, Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008;358:2560-72.
 113. Effect of simvastatin on coronary atheroma: the Multicentre Anti-Atheroma Study (MAAS). *Lancet* 1994;344:633-8.
 114. Iso H, Jacobs DR Jr, Wentworth D, Neaton JD, Cohen JD. Serum cholesterol levels and six-year mortality from stroke in 350,977 men screened for the multiple risk factor intervention trial. *N Engl J Med* 1989;320:904-10.
 115. Bots ML, Elwood PC, Nikitin Y, Salonen JT, Freire de Concalves A, Inzitari D, et al. Total and HDL cholesterol and risk of stroke. EUROSTROKE: a collaborative study among research centres in Europe. *J Epidemiol Comm Health* 2002;56(suppl 1):19-24.
 116. Horenstein RB, Smith DE, Mosca L. Cholesterol predicts stroke mortality in the women's Pooling Project. *Stroke* 2002;33:1863-8.
 117. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005;366:1267-78.
 118. Bucher HC, Griffith LE, Guyatt GH. Effect of HMGCoA Reductase Inhibitors on stroke. A meta-analysis of randomized, controlled trials. *Ann Intern Med* 1998;128:89-95.
 119. Amarenco P, Goldstein LB, Szarek M, Silleisen H, Rudolph AE, Callahan A 3rd, et al. Effects of intense low-density lipoprotein cho-

- lesterol reduction in patients with stroke or transient ischemic attack: the Stroke Prevention by Aggressive Reduction in cholesterol Levels (SPARCL) trial. *Stroke* 2007;38:3198-204.
120. Crouse JR 3rd, Grobbee DE, O'Leary DH, Bots ML, Evans GW, Palmer MK, et al. Measuring Effects on intima media Thickness: an Evaluation Of Rosuvastatin in subclinical atherosclerosis—the rationale and methodology of the METEOR study. *Cardiovasc Drugs Ther* 2004;18:231-8.
 121. Taylor AJ, Kent SM, Flaherty PJ, Coyle LC, Markwood TT, Vernalis MN. ARBITER: Arterial Biology for the Investigation of the Treatment Effects of Reducing cholesterol: a randomized trial comparing the effects of atorvastatin and pravastatin on carotid intima medial thickness. *Circulation* 2002;106:2055-60.
 122. Smilde TJ, van Wissen S, Wollersheim H, Trip MD, Kastelein JJ, Stalenhoef AF. Effect of aggressive versus conventional lipid lowering on atherosclerosis progression in familial hypercholesterolemia (ASAP): a prospective, randomised, double-blind trial. *Lancet* 2001;357:577-81.
 123. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002;106:3143-421.
 124. van den Bogaard B, van den Born BJ, Fayyad R, Waters DD, DeMicco DA, LaRosa JC, et al. On-treatment lipoprotein components and risk of cerebrovascular events in the Treating to New Targets study. *Eur J Clin Invest* 2011;41:134-42.
 125. Avellone G, Di Garbo V, Guarnotta V, Scaglione R, Parrinello G, Purpura L, et al. Efficacy and safety of long-term ezetimibe/simvastatin treatment in patients with familial hypercholesterolemia. *Int Angiol* 2010;29:514-24.
 126. Shinton R, Beevers G. Meta-analysis of relation between cigarette smoking and stroke. *BMJ* 1989;298:789-94.
 127. Wolf PA, D'Agostino RB, Kannel WB, Bonita R, Belanger AJ. Cigarette smoking as a risk factor for stroke. The Framingham study. *JAMA* 1988;259:1025-9.
 128. Gordon T, Kannel WB, McGee D, Dawber TR. Death and coronary attacks in men after giving up cigarette smoking. A report from the Framingham Study. *Lancet* 1974;2:1345-8.
 129. Kawachi I, Colditz GA, Stampfer MJ, Willett WC, Manson JE, Rosner B, et al. Smoking cessation and decreased risk of stroke in women. *JAMA* 1993;269:232-6.
 130. Wannamethee SG, Shaper AG, Whincup PH, Walker M. Smoking cessation and the risk of stroke in middle-aged men. *JAMA* 1995;274:155-60.
 131. Fiore MC, Bailey WC, Cohen SJ, et al. Smoking cessation. Clinical Practice Guideline No. Rockville, MD: Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research; 1996, p. 18. AHCPR Publication 96-0692.
 132. Frank E, Winkleby MA, Altman DG, Rockhill B, Fortmann SP. Predictors of physician's smoking cessation advice. *JAMA* 1991;266:3139-44.
 133. Fiore MC, Smith SS, Jorenby DE, Baker TB. The effectiveness of the nicotine patch for smoking cessation. A meta-analysis. *JAMA* 1994;271:1940-7.
 134. Wolff T, Miller T, Ko S. Aspirin for the primary prevention of cardiovascular events: an update of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med* 2009;150:405-10.
 135. Pearson TA, Blair SN, Daniels SR, Eckel RH, Fair JM, Fortmann SP, et al. AHA Guidelines for Primary Prevention of Cardiovascular Disease and Stroke: 2002 Update: Consensus Panel Guide to Comprehensive Risk Reduction for Adult Patients without Coronary or other atherosclerotic Vascular Diseases. American Heart Association Science Advisory and Coordinating Committee. *Circulation* 2002;106:388-91.
 136. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;324:71-86.
 137. Albers GW, Amarenco P, Easton JD, Sacco RL, Teal P, et al. Anti-thrombotic and thrombolytic therapy for ischemic stroke: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008;33(6 suppl):630-69S.
 138. Wolf PA, Clagett GP, Easton JD, Goldstein LB, Gorelick PB, Kelly-Hayes M, et al. Preventing ischemic stroke in patients with prior stroke and transient ischemic attack: a statement for healthcare professionals from the Stroke Council of the American Heart Association. *Stroke* 1999;30:1991-4.
 139. Johnston SC, Nguyen-Huynh MN, Schwarz ME, Fuller K, Williams CE, Josephson SA, et al. National Stroke Association guidelines for the management of transient ischemic attacks. *Ann Neurol* 2006;60:301-13.
 140. Fox KA, Mehta SR, Peters R, Zhao F, Lakkis N, Gersh BJ, et al. Benefits and risks of the combination of clopidogrel and aspirin in patients undergoing surgical revascularization for non-ST segment elevation acute coronary syndrome: the clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) trial. *Circulation* 2004;110:1202-08.
 141. Steinhubl SR, Berger PB, Mann JT 3rd, Fry ET, DeLago A, Wilmer C, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2002;288:2411-20.
 142. Diener HC, Bogousslavsky J, Brass LM, Cimminiello C, Csiba L, Kaste M, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. *Lancet* 2004;364:331-7.
 143. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996;348:1329-39.
 144. Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med* 2006;354:1706-17.
 145. Alberts MJ, Bergman DL, Molner E, Jovanovic BD, Ushiwata I, Teruya J. Antiplatelet effect of aspirin in patients with with cerebrovascular disease. *Stroke* 2004;35:175-8.
 146. Kasotakis G, Pipinos II, Lynch TG. Current evidence and clinical implications of aspirin resistance. *J Vasc Surg* 2009;50:1500-10.
 147. Mega JL, Close SL, Wiviott SD, Shen L, Hockett RD, Brandt JT, et al. Cytochrome p-450 polymorphisms in response to clopidogrel. *N Engl J Med* 2009;360:354-62.
 148. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007;357:2001-15.
 149. De Miguel A, Ibanez B, Badimón JJ. Clinical implications of clopidogrel resistance. *Thromb Haemost* 2008;100:196-203.
 150. Mohr JP, Thompson JL, Lazar RM, Levin B, Sacco RL, Furie KL, et al. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. *N Engl J Med* 2001;345:1444-51.
 151. ESPRIT Study Group, Halkes PH, van Gijn J, Kappelle LJ, Koudstaal PJ, Algra A. Medium intensity anticoagulation vs. aspirin after cerebral ischemia or arterial origin (ESPRIT): a randomized controlled trial. *Lancet Neurol* 2007;6:6115-24.
 152. Nair A, Sealove B, Halperin JL, Webber G, Fuster V. Anticoagulation in patients with heart failure: who, when, and why? *Eur Heart J Suppl* 2006;8(suppl E):E32-8.
 153. Fleisher LA, Beckman JA, Brown KA, Calkins H, Chaikof EL, Fleischmann KE, et al. ACC/AHA 2007 Guidelines on Perioperative cardiovascular Evaluation and care for Noncardiac Surgery: a Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative cardiovascular Evaluation for Noncardiac Surgery) Developed in Collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. *J Am Coll Cardiol* 2007;50:e159-242.

154. American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines; American Society of Echocardiography; American Society of Nuclear Cardiology; Heart Rhythm Society; Society of Cardiovascular Anesthesiologists; Society for Cardiovascular Angiography and Interventions, et al. 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. *J Am Coll Cardiol* 2009;54:e13-118.
155. Eikelboom JW, Hirsh J. Bleeding and management of bleeding. *Eur Heart J Suppl* 2006;8 (suppl G):G38-45.
156. Merritt JC, Bhatt DL. The efficacy and safety of perioperative antiplatelet therapy. *J Thromb Thrombolysis* 2004;17:21-7.
157. Stone DH, Goodney PP, Schanzer A, Nolan BW, Adams JE, Powell RJ, et al. Clopidogrel is not associated with major bleeding complications during peripheral arterial surgery. *J Vasc Surg* 2011[E-pub ahead of print: doi:10.1016/j.jvs.2011.03.003].
158. Taylor DW, Barnett HJ, Haynes RB, Ferguson GG, Sackett DL, Thorpe KE, et al. Low-dose and high-dose acetylsalicylic acid for patients undergoing carotid endarterectomy: a randomised controlled trial. *ASA and Carotid Endarterectomy (ACE) Trial Collaborators. Lancet* 1999;353:2179-84.
159. Hindler K, Shaw AD, Samuels J, Fulton S, Collard CD, Riedel B. Improved postoperative outcomes associated with preoperative statin therapy. *Anesthesiology* 2006;105:1260-72; Quiz:1289-90.
160. Durazzo AE, Machado FS, Ikeoka DT, De Bernoche C, Monachini MC, Puech-Leão P, et al. Reduction in cardiovascular events after vascular surgery with atorvastatin: a randomized trial. *J Vasc Surg* 2004;39:967-75; discussion: 975-66.
161. Lindenauer PK, Peckow P, Wang K, Gutierrez B, Benjamin EM. Lipid-lowering therapy and in-hospital mortality following major noncardiac surgery. *JAMA* 2004;291:2092-9.
162. Mas JL, Chatellier G, Beyssen B, Branchereau A, Moulin T, Becquemin JP, et al. Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis. *N Engl J Med* 2006;355:1660-71.
163. Massop D, Dave R, Metzger C, Bachinsky W, Solis M, Shah R, et al. Stenting and angioplasty with protection in patients at high-risk for endarterectomy: SAPPHERE Worldwide Registry first 2,001 patients. *Catheter Cardiovasc Interv* 2009;73:129-36.
164. Momin TA, Ricotta JJ. Minimizing the Complications of Carotid Endarterectomy. *Perspect Vasc Surg Endovasc Ther* 2010;22:106-13.
165. Parodi FE, Schonholz C, Parodi JC. Minimizing Complications of Carotid stenting. *Perspect Vasc Surg Endovasc Ther* 2010;22:117-22.
166. GALA Trial Collaborative Group, Lewis SC, Warlow CP, Bodenham AR, Colam B, Rothwell PM, et al. General anaesthesia versus local anaesthesia for carotid surgery (GALA): a multicentre, randomized controlled trial. *Lancet* 2008;372:2132-42.
167. Rerkasem K, Rothwell PM (The Cochrane Collaboration). Local versus general anesthesia for carotid endarterectomy (Review). *The Cochrane Library* 2009;1:1-84.
168. Ballotta E, Saladini M, Gruppo M, Mazzalai F, Da Giau G, Baracchini C. Predictors of electroencephalographic changes needing shunting during carotid endarterectomy. *Ann Vasc Surg* 2010;24:1045-52.
169. Skelly CL, Meyerson SL, Curi MA, Desai TR, Bassiouny HS, McKinsey JF, et al. Routine early postoperative duplex scanning is unnecessary following uncomplicated carotid endarterectomy. *Vasc Endovasc Surg* 2002;36:115-22.
170. Bond R, Rerkasem K, Counsell C, Salinas R, Naylor R, Warlow CP, et al. Routine or selective carotid artery shunting for carotid endarterectomy (and different methods of monitoring in selective shunting). *Cochrane Database Syst Rev* 2002;2:CD000190.
171. Bandyk DF, Mills JL, Gahtan V, Esses GE. Intraoperative Duplex scanning of arterial reconstructions: fate of repaired and unrepaired defects. *J Vasc Surg* 1994;20:426-33.
172. Ascher E, Markevich N, Kallakuri S, Schutzer RW, Hingorani AP. Intraoperative carotid artery duplex scanning in a modern series of 650 consecutive primary endarterectomy procedures. *J Vasc Surg* 2004;39:416-20.
173. Burnett MG, Stein SC, Sonnad SS, Zager EL. Cost-effectiveness of intraoperative imaging in carotid endarterectomy. *Neurosurgery* 2005;57:478-85.
174. O'Brien-Irr RJ. Completion angiography, is it really necessary? *Am J Surg* 1997;174:181-4.
175. Rockman CB, Halm EA. Intraoperative imaging: does it really improve perioperative outcomes of carotid endarterectomy? *Semin Vasc Surg* 2007;20:236-43.
176. Chiriano J, Abou-Zamzam AM Jr, Molkara NK, Zhang WW, Bianchi C, Teruya TH. Preoperative carotid duplex findings predict carotid stump pressures during endarterectomy in symptomatic but not asymptomatic patients. *Ann Vasc Surg* 2010;24:1038-44.
177. Bond R, Rerkasem K, Naylor AR, Aburahma AF, Rothwell PM. Systematic Review of randomized controlled trials of patch angioplasty versus primary closure and different types of patch materials during carotid endarterectomy. *J Vasc Surg* 2004;40:1126-35.
178. Cao P, De Rango P, Zannetti S. Eversion vs. conventional carotid endarterectomy: a systematic review. *Eur J Vasc Endovasc Surg* 2002;23:195-201.
179. Darling RC 3rd, Mehta M, Roddy SP, Paty PS, Kreienberg PB, Ozsvath KJ, et al. Eversion carotid endarterectomy: a technical alternative that may obviate patch closure in women. *Cadivosc Surg* 2003;11:347-52.
180. Matsen SL, Chang DC, Perler BA, Roseborough GS, Williams GM. Trends in the in-hospital stroke rate following carotid endarterectomy in California and Maryland. *J Vasc Surg* 2006;44:488-95.
181. AbuRahma AF, Robinson P. Indications and complications of carotid endarterectomy as performed by four different surgical specialty groups. *J Cardiovasc Surg* 1988;29:277-82.
182. Garg N, Karagiorgos N, Pisimisis GT, Sohal DP, Longo GM, Johanning JM, et al. Cerebral protection devices reduce periprocedural strokes during carotid angioplasty and stenting: a systematic review of the current literature. *J Endovasc Ther* 2009;16:412-27.
183. Vos JA, van den Berg JC, Ernst SM, Suttorp MJ, Overtoom TT, Mauser HW, et al. Carotid angioplasty and stent placement: comparison of transcranial Doppler US data and clinical outcome with and without filtering cerebral protection devices in 509 patients. *Radiology* 2005;237:374-75.
184. Parodi JC, Schönholz C, Parodi FE, Sicard G, Ferreira LM. Initial 200 cases of carotid artery stenting using a reversal of flow cerebral protection device. *J Cardiovasc Surg* 2007;48:117-24.
185. Schnaudigel S, Gröschel K, Pilgram SM, Kastrup A. New brain lesions after carotid stenting versus carotid endarterectomy: a systematic review of the literature. *Stroke* 2008;39:1911-9.
186. Ansel GM, Hopkins LN, Jaff MR, Rubino P, Bacharach JM, Scheinert D, Myla S, et al. Safety and efficacy of the INVATEC MOMA proximal cerebral protection device during carotid artery stenting: results from the ARMOUR pivotal trial. *Catheter Cardiovasc Interv* 2010;76:1-8.
187. Hart JP, Peeters P, Verbist J, Deloosse K, Bosiers M. Do device characteristics impact outcome in carotid artery stenting? *J Vasc Surg* 2006;44:725-30.
188. Hopkins LN, Roubin GS, Chakhtoura EY, Gray WA, Ferguson RD, Katzen BT, et al. The Carotid revascularization Endarterectomy versus stenting trial: credentialing of interventionalists and final results of the lead-in phase. *J Stroke Cerebrovasc Dis* 2010;19:153-62.
189. Hobson RW 2nd, Howard VJ, Roubin GS, Ferguson RD, Brott TG, Howard G, et al. Credentialing of Surgeons as interventionalists for carotid artery stenting: experience from the lead-in phase of CREST. *J Vasc Surg* 2004;40:952-7.
190. Verzini F, De Rango P, Parlani G, Panuccio G, Cao P. Carotid artery stenting: technical issues and role of operator's experience. *Perspect Vasc Surg Endovasc Ther* 2008;20:247-57.
191. Lin PH, Bush RL, Peden EK, Zhou W, Guerrero M, Henao EA, et al. Carotid artery stenting with neuroprotection: assessing the learning curve and treatment outcome. *Am J Surg* 2005;190:850-57.
192. Ricotta JJ 2nd, Malgor RD. A review of the trials comparing carotid endarterectomy and carotid angioplasty and stenting. *Perspect Vasc Surg Endovasc Ther* 2008;20:299-308.
193. Mozes G, Sullivan TM, Torres-Russotto DR, Bower TC, Hoskin TL, Sampaio SM, et al. Carotid endarterectomy in SAPPHERE-eligible

- high-risk patients: implications for selecting patients for carotid angioplasty and stenting. *J Vasc Surg* 2004;39:958-65.
194. Gasparis AP, Ricotta L, Cuadra SA, Char DJ, Purtill WA, van Bemmel PS, et al. High-risk carotid endarterectomy (CEA): facts or fiction. *J Vasc Surg* 2003;37:40-6.
 195. Simonian GT, Pappas PJ, Padberg FT Jr, Samit A, Silva MB Jr, Jamil Z, et al. Mandibular subluxation for distal internal carotid exposure: technical considerations. *J Vasc Surg* 1999;30:1116-20.
 196. Jaspers GW, Witjes MJ, van den Dungen JJ, Reintsema H, Zeebregts CJ. Mandibular subluxation for distal internal carotid artery exposure in edentulous patients. *J Vasc Surg* 2009;50:1519-22.
 197. Setacci C, Chisci E, Setacci F, Iacoponi F, de Donato G, Rossi A. Siena carotid artery stenting score: a risk modeling study for individual patients. *Stroke* 2010;41:1259-65.
 198. AbuRahma AF, Abu-Halimah S, Bensenhaver J, Nanjundappa A, Stone PA, Dean LS, et al. Primary carotid artery stenting versus carotid artery stenting for postcarotid endarterectomy stenosis. *J Vasc Surg* 2009;50:1031-9.
 199. White RA, Sicard GA, Zwolak RM, Sidawy AN, Schermerhorn ML, Shackleton RJ, et al. Society of Vascular Surgery vascular registry comparison of carotid artery stenting outcomes for atherosclerotic vs nonatherosclerotic carotid artery disease. *J Vasc Surg* 2010;51:1116-23.
 200. Lam RC, Lin SC, DeRubertis B, Hyneczek R, Kent KC, Faries PL. The impact of increasing age on anatomic factors affecting carotid angioplasty and stenting. *J Vasc Surg* 2007;45:875-80.
 201. Kang JL, Chung TK, Lancaster RT, Lamuraglia GM, Conrad MF, Cambria RP. Outcomes after carotid endarterectomy: is there a high-risk population? A National Surgical Quality Improvement Program report. *J Vasc Surg* 2009;49:331-9.
 202. Bangalore S, Kumar S, Wetterslev J, Bavry AA, Gluud C, Cutlip DE, et al. Carotid artery stenting vs carotid endarterectomy: meta-analysis and diversity-adjusted trial sequential analysis of randomized trials. *Arch Neurol* 2011;68:172-84.
 203. Saw J, Gurm HS, Fathi RB, Bhatt DL, Abou-Chebl A, Bajzer C, et al. Effect of chronic kidney disease on outcomes after carotid artery stenting. *Am J Cardiol* 2005;94:1093-6.
 204. Jackson BM, English SJ, Fairman RM, Karmacharya J, Carpenter JP, Woo EY. Carotid artery stenting: identification of risk factors for poor outcomes. *J Vasc Surg* 2008;48:74-9.
 205. Hamdan AD, Pomposelli FB, Gibbons GW, Campbell DR, LoGerfo FW. Renal insufficiency and altered postoperative risk in carotid endarterectomy. *J Vasc Surg* 1999;29:1006-11.
 206. Ascher E, Marks NA, Schutzer RW, HIngorani AP. Carotid endarterectomy in patients with chronic renal insufficiency: a recent series of 184 cases. *J Vasc Surg* 2005;41:24-9.
 207. North American Symptomatic Carotid Endarterectomy Trial. Methods, patient characteristics, and progress. *Stroke* 1991;22:711-20.
 208. Maatz W, Köhler J, Botsios S, John V, Walterbusch G. Risk of stroke for carotid endarterectomy patients with contralateral carotid occlusion. *Ann Vasc Surg* 2008;22:45-51.
 209. Rockman CB, Su W, Lamparello PJ, Adelman MA, Jacobowitz GR, Gagne PJ, et al. A reassessment of carotid endarterectomy in the face of contralateral carotid occlusion: surgical results in symptomatic and asymptomatic patients. *J Vasc Surg* 2002;36:668-73.
 210. Mackey WC, O'Donnell TF Jr, Callow AD. Carotid Endarterectomy contralateral to an occluded carotid artery: perioperative risk and late results. *J Vasc Surg* 1990;11:778-83.
 211. Halliday A, Harrison M, Hayter E, Kong X, Mansfield A, Marro J, et al. 10-year stroke prevention after successful carotid endarterectomy for asymptomatic carotid stenosis (ACST-1): a multicentre randomised trial. *Lancet* 2010;376:1074-84.
 212. Schneider PA, Naylor AR. Asymptomatic Carotid artery stenosis—medical therapy alone versus medical therapy plus carotid endarterectomy or stenting. *J Vasc Surg* 2010;52:499-507.
 213. Marquardt L, Geraghty OC, Mehta Z, Rothwell PM. Low risk of ipsilateral stroke in patients with asymptomatic carotid stenosis on best medical treatment: a prospective, population-based study. *Stroke* 2010;41:e11-7.
 214. Reiff T, Stingele R, Eckstein HH, Fraedrich G, Jansen O, Mudra H, et al. Stent-protected angioplasty in asymptomatic carotid artery stenosis vs. endarterectomy: SPACE2 - a three-arm randomised-controlled clinical trial. *Int J Stroke* 2009;4:294-9.
 215. Bunch CT, Kresowik TF. Can randomized trial outcomes for carotid endarterectomy be achieved in community-wide practice? *Semin Vasc Surg* 2004;17:209-13.
 216. Gray WA, Hopkins LN, Yadav S, Davis T, Wholey M, Atkinson R, et al. Protected carotid stenting in high-risk surgical patients: the ARCHeR results. *J Vasc Surg* 2006;44:258-68.
 217. Gray WA, Gray WA, Chaturvedi S, Verta P; Investigators and the Executive Committees. Thirty-day outcomes for carotid artery stenting in 6320 patients from 2 prospective, multicenter, high-surgical-risk registries. *Circ Cardiovasc Interv* 2009;2:159-66.
 218. Zarins CK, White RA, Dietrich EB, Shackleton RJ, Siami FS, CaRESS Steering Committee and CaRESS Investigators. Carotid revascularization using endarterectomy or stenting systems (CaRESS): 4-year outcomes. *J Endovasc Ther* 2009;16:397-409.
 219. Higashida RT, Popma JJ, Apruzzese P, Zimetbaum P, MAVERIC I and II Investigators. Evaluation of the Medtronic exponent self-expanding carotid stent system with the Medtronic guardwire temporary occlusion and aspiration system in the treatment of carotid stenosis; combined form the MAVERIC (Medtronic AVE Self-expanding Carotid Stent System with distal protection In the treatment of Carotid stenosis) I and MAVERIC II trials. *Stroke* 2010;41:e102-9.
 220. CAVATAS Investigators. Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomised trial. *Lancet* 2001;357:1729-37.
 221. Brooks WH, McClure RR, Jones MR, Coleman TC. Carotid angioplasty and stenting versus carotid endarterectomy: randomized trial in a community hospital. *J Am Coll Cardiol* 2001;38:1589-95.
 222. CaRESS Steering Committee. Carotid revascularization Using Endarterectomy or stenting Systems (CaRESS) phase I clinical trial: 1-year results. *J Vasc Surg* 2005;42:213-9.
 223. Naylor AR, Bell PR. Treatment of asymptomatic carotid disease with stenting: con. *Semin Vasc Surg* 2008;21:100-7.
 224. LoGerfo FW. Carotid stents: unleashed, unproven. *Circulation* 2007;116:1596-601.
 225. Lal BK, Moore W, Timaran C, Jamil Z, Meschia-Thomas JF, Brott G. CEA Shows Improved Results in CREST when Compared to Previous Randomized Trials. Presented at The Vascular Annual Meeting; Boston, Mass; 2010.
 226. Sidawy AN, Zwolak RM, White RA, Siami FS, Schermerhorn ML, Sicard GA, et al. Outcomes Committee for the Society for Vascular Surgery. Risk-adjusted 30-day outcomes of carotid stenting and endarterectomy: results from the SVS Vascular Registry. *J Vasc Surg* 2009;49:71-9.
 227. Rudarakachana N, Dialynas M, Halliday A. Asymptomatic Carotid Surgery Trial. 2 (ACST-2): rationale for a randomized clinical trial comparing carotid endarterectomy with carotid artery stenting in patients with asymptomatic carotid stenosis. *J Vasc Endovasc Surg* 2009;38:239-42.
 228. SPACE Collaborative Group, Ringleb PA, Allenberg J, Brückmann H, Eckstein HH, Fraedrich G et al. 30 Day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomised non-inferiority trial. *Lancet* 2006;368:1239-47.
 229. Liapis CD, Bell PRF, Mikhailidis D, Sivenius J, Nicolaidis A, Fernandes e Fernandes J, et al. ESVS guidelines. Invasive treatment for carotid stenosis: indications, techniques. *Eur J Vasc Endovasc Surg* 2009;37:S1-S19.
 230. Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke. Rt-TPA Stroke Study Group. *N Engl J Med* 1995;333:1581-87.
 231. Furlan A, Higashida R, Wechsler L, Gent M, Rowley H, Kase C, et al. Intra-arterial prolyse for acute ischemic stroke. The PROACT II study: a randomized controlled trial. *Prolyse in Acute Cerebral Thromboembolism*. *JAMA* 1999;282:2003-11.

232. Suh DC, Kim JK, Choi CG, Kim SJ, Pyun HW, Ahn C, et al. Prognostic factors for neurologic outcome after endovascular revascularization of acute symptomatic occlusion of the internal carotid artery. *AJNR Am J Neuroradiol* 2007;28:1167-71.
233. Hacke W, Donnan G, Fieschi C, Kaste M, von Kummer R, Broderick JP, et al. Association of outcome with early stroke treatment: pooled analysis of Atlantis, ECASS, and NINDS Rt-PA stroke trials. *Lancet* 2004;363:768-74.
234. Khatri P, Abruazzo T, Yeatts SD, Nichols C, Broderick JP, Tomsick TA, et al. Good clinical outcome after ischemic stroke with successful revascularization is time dependent. *Neurology* 2009;73:1066-72.
235. Saposnik G, DiLegge S, Webster F, Hachinski V. Predictors of major neurologic improvement after thrombolysis in acute stroke. *Neurology* 2005;65:1165-74.
236. Josephson SA, Saver JL, Smith WS. MERCI and Multi MERCI Investigators. Comparison of mechanical embolectomy and intraarterial thrombolysis in acute ischemic stroke within the MCA: MERCI and Multi MERCI compared to PROACT II. *Neurocrit Care* 2009;11:43-9.
237. Sugg RM, Malkoff MD, Noser EA, Sugg RM, Malkoff MD, Noser EA et al. Endovascular recanalization of internal carotid artery occlusion in acute ischemic stroke. *AJNR Am J Neuroradiol* 2005;26:2591-4.
238. Smith WS. Safety of mechanical thrombectomy and intravenous tissue plasminogen activator in acute ischemic stroke. Results of the multi Mechanical Embolus Removal in Cerebral Ischemia (MERCI) trial, part I. *AJNR Am J Neuroradiol* 2006;27:1177-82.
239. Nedeltchev K, Brekenfeld C, Remonda L, Ozdoba C, Do DD, Arnold M, et al. Internal carotid artery stent implantation in 25 patients with acute stroke: preliminary results. *Radiology* 2005;237:1029-37.
240. Cloft HJ, Rabinstein A, Lanzino G, Kallmes DF. Intra-arterial stroke therapy: an assessment of demand and available work-force. *AJNR Am J Neuroradiol* 2009;30:453-8.
241. Keldahl ML, Eskandari MK. Timing of carotid surgery after stroke. *Expert Rev Cardiovasc Ther* 2010;8:1399-403.
242. Baron EM, Baty DE, Loftus IM. The timing of carotid endarterectomy post stroke. *Neurol Clin* 2006;24:669-80.
243. Rantner B, Pavelka M, Posch L, Schmidauer C, Fraedrich G. Carotid Endarterectomy after acute stroke-is there justification for delayed surgery? *Eur J Vasc Endovasc Surg* 2005;30:36-40.
244. Meyer FB, Sundt TM Jr, Piepgras DG, Sandok BA, Forbes G. Emergency carotid endarterectomy for patients with acute carotid occlusion and profound neurological deficits. *Ann Surg* 1986;203:82-9.
245. Barber PA, Darby DG, Desmond PM, Yang Q, Gerraty RP, Jolley D, et al. Prediction of stroke outcome with echoplanar perfusion- and diffusion-weighted MRI. *Neurology* 1998;51:418-26.
246. Wintermark M, Meuli R, Browaeys P, Reichhart M, Bogousslavsky J, Schnyder P, et al. Comparison of CT perfusion and angiography and MRI in selecting stroke patients for acute treatment. *Neurology* 2007;68:694-7.
247. Mussa FF, Aaronson N, Lamparello PJ, Maldonado TS, Cayne NS, Adelman MA, et al. Outcome of carotid endarterectomy for acute neurological deficit. *Vasc Endovasc Surg* 2009;43:364-9.
248. Baracchini C, Meneghetti G, Ballotta E. Early Carotid endarterectomy in acute stroke. *Cerebrovasc Dis* 2005;19:417-8.
249. Paty PS, Darling RC 3rd, Feustel PJ, Bernardini GL, Mehta M, Ozsvath KJ, et al. Early carotid endarterectomy after acute stroke. *J Vasc Surg* 2004;39:148-54.
250. Capoccia L, Sbarigia E, Speziale F, Toni D, Fiorani P. Urgent Carotid Endarterectomy to prevent recurrence and improve neurologic outcome in mild-to-moderate acute neurologic events. *J Vasc Surg* 2011;53:622-2.
251. Sbarigia E, Toni D, Speziale F, Acconcia MC, Fiorani P. Early carotid endarterectomy after ischemic stroke: the results of a prospective multicenter Italian study. *Eur J Vasc Endovasc Surg* 2006;32:229-35.
252. Karkos CD, Hernandez-Lahoz I, Naylor AR. Urgent carotid surgery in patients with crescendo transient ischaemic attacks and stroke-in-evolution: a systematic review. *Eur J Vasc Endovasc Surg* 2009;37:279-88.
253. Greenstein AJ, Chassin MR, Wang J, Rockman CB, Riles TS, Tuhirim S, et al. Association between minor and major surgical complications after carotid endarterectomy: results of the New York Carotid Artery Surgery study. *J Vasc Surg* 2007;46:1138-44.
254. Rockman CB, Jacobowitz GR, Lamparello PJ, Adelman MA, Woo D, Schanzer A, et al. Immediate reexploration for the perioperative neurologic event after carotid endarterectomy: is it worthwhile? *J Vasc Surg* 2000;32:1062-70.
255. Koslow AS, Ricotta JJ, Ouriel KO, O'Brien M, Green RM, DeWeese JA. Reexploration for thrombosis in carotid endarterectomy. *Circulation* 1989;80:1173-8.
256. Peer RM, Shah RM, Upson JF, Ricotta JJ. Carotid exploration for acute postoperative thrombosis. *Am J Surg* 1994;168:168-70.
257. Roth C, Papanagiotou P, Behnke S, Walter S, Haass A, Becker C, et al. Stent-assisted mechanical recanalization for treatment of acute intracerebral artery occlusions. *Stroke* 2010;41:2559-67.
258. Street DL, Ricotta JJ, Green RM, DeWeese JA. The role of external carotid revascularization in the treatment of ocular ischemia. *J Vasc Surg* 1987;6:280-2.
259. Harris LM, Pillai L, Ricotta JJ. External carotid endarterectomy with internal carotid artery transposition flap angioplasty for symptomatic internal carotid artery occlusion. *Cardiovasc Surg* 1995;3:625-9.
260. Nicolosi A, Klinger D, Bandyk D, Towne J. External carotid artery endarterectomy in the treatment of symptomatic patients with internal carotid artery occlusion. *Ann Vasc Surg* 1998;2:336-9.
261. Adel JG, Bendok BR, Hage ZA, Naidech AM, Miller JW, Batjer HH. External carotid artery angioplasty and stenting to augment cerebral perfusion in the setting of subacute symptomatic ipsilateral internal carotid artery occlusion. Case report. *J Neurosurg* 2007;107:1217-22.
262. Klijn CJ, Kappelle LJ, Algra A, van Gijn J. Outcome in patients with symptomatic occlusion of the internal carotid artery or intracranial arterial lesions: a meta-analysis of the role of baseline characteristics and type of antithrombotic treatment. *Cerebrovasc Dis* 2001;12:228-34.
263. Müller BT, Luther B, Hort W, Neumann-Haefelin T, Aulich A, Sandmann W. Surgical treatment of 50 carotid dissections: indications and results. *J Vasc Surg* 2000;31:980-8.
264. Donas KP, Mayer D, Guber I, Baumgartner R, Genoni M, Lachat M. Endovascular repair of extracranial carotid artery dissection: current status and level of evidence. *J Vasc Interv Radiol* 2008;19:1693-8.
265. Pham MH, Rahme RJ, Arnaout O, Hurley MC, Bernstein RA, Batjer HH, et al. Endovascular stenting of extracranial carotid and vertebral artery dissections: a systematic review of the literature. *Neurosurgery* 2011;68:856-66.
266. Anson J, Crowell RM. Cervicocranial arterial dissection. *Neurosurgery* 1991;29:89-96.
267. Li Y, Walicki D, Mathiesen C, Jenny D, Li Q, Isayev Y, et al. Strokes after cardiac surgery and relationship to carotid stenosis. *Arch Neurol* 2009;66:1091-6.
268. Naylor AR. Managing patients with symptomatic coronary and carotid artery disease. *Perspect Vasc Surg* 2010;22:70-6.
269. Naylor AR, Cuffe RL, Rothwell PM, Bell PR. A systematic review of outcomes following staged and synchronous carotid endarterectomy and coronary artery bypass. *Eur J Vasc Endovasc Surg* 2003;25:380-9.
270. Bucerius J, Gummert JF, Borger MA, Walther T, Doll N, Onnasch JF, et al. Stroke after cardiac surgery: a risk factor analysis of 16,184 consecutive adult patients. *Ann Thorac Surg* 2003;75:472-8.
271. Newman MF, Wolman R, Kanchuger M, Marschall K, Mora-Mangano C, Roach G, et al. Multicenter pre-operative stroke risk index for patients undergoing coronary artery bypass graft surgery: multicenter study of perioperative ischemia (mMcSPI) research group. *Circulation* 1996;94(9 suppl):1174-80.
272. Bernhard VM, Johnson WD, Peterson JJ. Carotid artery stenosis: association with surgery for coronary artery disease. *Arch Surg* 1972;105:837-40.
273. Cywinski JB, Koch CG, Krajewski LP, Smedira N, Li L, Starr NJ. Increased risk associated with combined carotid endarterectomy and coronary artery bypass graft surgery: a propensity-matched comparison with isolated coronary artery bypass graft surgery. *J Cardiothorac Vasc Anesth* 2006;20:796-802.

274. Ricotta JJ, Char DJ, Cuadra SA, Bilfinger TV, Wall LP, Giron F, et al. Modelling stroke risk after coronary artery bypass and combined coronary artery bypass and carotid endarterectomy. *Stroke* 2003;34:1212-7.
275. Hertzner NR, Loop FD, Been EG, O'Hara PJ, Krajewski LP. Surgical staging for simultaneous coronary and carotid disease: a study including prospective randomization. *J Vasc Surg* 1989;9:455-63.
276. Illuminati G, Ricco JB. Randomized controlled trial examining the timing of carotid endarterectomy in patients with asymptomatic carotid stenosis undergoing coronary artery bypass grafting [Abstract]. *J Vasc Surg* 2011;53:101S.
277. Fareed KR, Rothwell PM, Mehta Z, Naylor AR. Synchronous carotid endarterectomy and off-pump coronary bypass: an updated systematic review of early outcomes. *Eur J Vasc Endovasc Surg* 2009;37:375-8.
278. Timaran CH, Rosero EB, Smith St, Valentine RJ, Modrall JG, Clagett GP. Trends and outcomes of concurrent carotid revascularization and coronary bypass. *J Vasc Surg* 2008;48:355-61.
279. Van der Heyden J, Suttorp MJ, Bal ET, Ernst JM, Ackerstaff RG, Schaap J, et al. Staged carotid angioplasty and stenting followed by cardiac surgery in patients with severe asymptomatic carotid artery stenosis: early and long-term results. *Circulation* 2007;116:2036-42.
280. Naylor AR, Mehta Z, Rothwell PM. A systematic review and meta-analysis of 30-day outcomes following staged carotid artery stenting and coronary bypass. *Eur J Vasc Endovasc Surg* 2009;37:379-87.

Submitted Jun 20, 2011; accepted Jul 12, 2011.