The Society for Vascular Surgery implementation document for management of extracranial cerebrovascular disease

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TABLE OF CONTENTS

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INTRODUCTION

The management of extracranial cerebrovascular disease, including carotid endarterectomy (CEA), carotid stenting and medical management is performed by several specialists. Vascular surgeons perform a majority of CEA, whereas catheter-based therapies (eg, carotid artery stenting [CAS]) are performed by vascular surgeons, cardiologists, interventional radiologists, neurosurgeons, interventional neurologists, and other professionals.[1,2] Because multiple treatment modalities are available for extracranial cerebrovascular disease, defining optimal therapy can be challenging particularly when different specialtiesdoften with nonoverlapping expertised deliver these therapeutic options.

In 2011, the Society for Vascular Surgery (SVS) published clinical practice guidelines for the management of extracranial carotid artery disease in the Journal of VascularSurgery.[3] A multispecialty document was also published on the "Management of Patients with Extracranial Carotid and Vertebral Artery Disease."[4] However, since these documents came out, four large, randomized trials have been published that compared the efficacy of CAS and CEA in

management of extracranial carotid stenosis.[5-9] This led the European Society for Vascular Surgery to update its guidelines, "Management of Atherosclerotic Carotid and Vertebral Artery Disease" in 2017.[10] Similarly, the SVS felt an update of its 2011 document was needed.

Accordingly, the SVS selected a writing group consisting of leaders in vascular surgery with a major interest in this field. The group met in person and on several conference calls to identify the most important and/or controversial issues and questions it felt were of major interest to practicing clinicians and other specialists, and these issues are addressed in the revised Clinical Practice Guidelines. To support the guideline, a systematic review and meta-analysis was conducted by the Mayo Clinic Evidence Practice Center to address these issues, and these will be published separately in the Journal ofVascular Surgery. The following five issues/questions are addressed:

1. Is CEA recommended over maximal medical therapyfor asymptomatic carotid stenosis in low surgical risk patients?
2. Is CEA recommended over transfemoral CAS in lowsurgical risk patients for symptomatic carotid artery stenosis of greater than 50%?
3. What is the optimal timing of carotid intervention inpatients presenting with acute stroke?
4. Screening for carotid artery stenosis in asymptomaticpatients
   A. Is screening for asymptomatic carotid stenosis recommended in the general population?
   B. Is screening for carotid stenosis recommended forhigh-risk asymptomatic patients?
   C. What imaging test is best for screening for carotidstenosis in asymptomatic patients?
5. What is the optimal sequence for intervention in patients with combined carotid and coronary artery disease?

These questions are addressed in a separate Clinical Practice Guidelines document.

However, there are several additional topics in the management of extracranial cerebrovascular disease which the writing group felt needed to be updated. This Comprehensive Implementation Document was prepared to address those topics.

Each member of the writing group was assigned responsibility for compiling information on a specific topic and findings were distributed to all members for review. Each topic area was discussed and summary recommendations reflecting the unanimous opinion of the writing group was reached by consensus.

Prevalence and incidence of stroke. The prevalence of stroke prevalence in US adults (>18 years old) is currently 2.7%, a figure that is expected to increase to 3.9% by 2030 as the population ages. The American Heart Association (AHA) reports, "Every 40 seconds someone has a stroke and every 3 minutes and 45 seconds someone in the United States dies of a stroke."[11] With approximately 795,000 cases annually, stroke ranks fifth among all causes of death in the United States and second globally.[11,12]

The estimated prevalence of self-reported physiciandiagnosed transient ischemic attack (TIA) is 2.3% and also increases with advancing age. However, challenges with accurate diagnosis suggest that true prevalence is
likely greater.[13]

Definition of TIA and stroke. The original 1950s definition of TIA was time-based, relying on an arbitrary symptom duration of less than 24 hours.[14] At that time, TIA were defined as sudden, focal neurologic deficits of vascular origin, but if the neurologic deficit remained for more than 7 days then it was a stroke. Events between 24 hours and 7 days were classified as reversible ischemic neurologic deficits. This term is no longer used because most events lasting more than 24 hours are associated with cerebral infarction and should therefore carry a stroke diagnosis.

Advances in cerebral imaging yielded evidence that the arbitrary 24-hour time period for diagnosing a TIA was inaccurate, with up to 50% of patients showing brain injury on diffusion-weighted magnetic resonance imaging (MRI). The Stroke Council of the AHA/American Stroke Association removed time as a definitional factor and endorsed the current TIA definition in 2009: "A transient episode of neurologic dysfunction caused by focal cerebral, spinal cord or retinal ischemia, without acute infarction." This definition includes radiologic exclusion of stroke.[15] Stroke is subsequently defined as any episode of neurologic dysfunction caused by focal cerebral, spinal, or retinal infarction. Moving toward this radiologic demonstration of infarction or hemorrhage, the 2013 AHA/American Stroke Association definition of stroke included the silent infarctions. It defined them based on imaging or neuropathological evidence of central nervous system infarction, without a history of acute neurologic dysfunction attributable to the lesion.[16] This "tissue-based" definition represents a step forward in the characterization of cerebrovascular events. However, in everyday practice and across different hospital settings, tissuebased diagnosis of a TIA episode may vary depending on the availability and type of brain MRI machines.

The US tissue-based imaging definition of TIA and the silent pathology equivalence to stroke as described elsewhere in this article are at odds with time-based clinical definitions endorsed by the World Health Organization, European Stroke Organization, European Society for Vascular Surgery, and the World Stroke Organisation.[10,17-19] The implications of not arriving at a universal definition of TIA and stroke are far-reaching. They may include differences in reporting of incidence and prevalence rates and differences in reporting of neurologic events after interventions, as well as changes in life insurance premiums.[17] However, a recent population study demonstrated that the broad tissue-based TIA definition was associated with only a slight change in incidence compared with the traditional time-based definition.[20] Regardless, in the future it will be important for international organizations to reach a consensus

to standardize data reporting and research end points. In this guidelines, reported rates of TIA and stroke are based primarily on studies that used the earlier, time-based definitions.

Etiology. Approximately 87% of all strokes are due to ischemic cerebral infarction and 13% are hemorrhagic (intracerebral or subarachnoid).[21] The currently recognized ischemic stroke mechanisms are embolism, decreased perfusion, and thrombosis.

Embolism may be cardiac or arterial in origin. Commonly recognized cardiac sources for embolism include atrial fibrillation, recent acute myocardial infarction (MI), endocarditis, cardiac tumors, and valvular disorders. Arterial embolism is a common cause of cerebral infarction associated with plaques of the large extracranial (including the aortic arch) and intracranial arteries. Stroke owing to perfusion failure occurs with severe stenosis of the carotid and basilar artery, and when there is microstenosis of the small deep arteries, the latter being a common cause of lacunar infarction. In situ thrombosis may also occur owing to a severely stenotic lesion, plaque rupture, or less frequently to a prothrombotic state.

Atherosclerotic lesions are not randomly distributed along the cerebral arterial tree. The carotid artery system is mostly affected at the common carotid artery (CCA) bifurcation, the siphon, and the M1 segment of the middle cerebral artery (MCA). Along the vertebrobasilar circulation, the first and fourth segments of the vertebral artery and the first segment of the basilar artery are frequently affected. Factors that lead these lesions to become symptomatic are not well-understood, but stenoses are linearly associated with increased risk of distal brain infarct. Extra-cranial carotid artery disease (ipsilateral stenosis of $50%) has been linked to 9% to 36% of ischemic strokes.[22,23] Yet, carotid artery plaques that cause less severe stenosis have a potentially causative association with embolism of undetermined source (cryptogenic).[24]

CAROTID IMAGING INDICATIONS

Most experts believe that at least 20% of ischemic strokes are likely related to extracranial carotid artery atherosclerosis.[3,25] It is for this reason that the goal of carotid bifurcation imaging is to detect “high-risk” patients with significant carotid bifurcation plaque who would be likely to benefit from therapy to reduce their stroke risk.[3]

Many factors drive stroke risk, but among patients with atherosclerosis of the carotid bifurcation, the most important seem to be a history of prior neurologic symptoms, severity or degree of stenosis, and, to a lesser extent, plaque characteristics such as ulceration, intraplaque hemorrhage, and composition.[3]

Symptomatic patients

It is important to image the carotid bifurcation in all patients with symptoms of cerebral ischemia, whether they present in as a TIA or completed stroke.[3] Assuming significant carotid artery disease is the cause of symptoms, these patients are likely candidates for carotid artery intervention to prevent an initial or secondary stroke.[26]

Typical carotid territory focal ischemic symptoms include contralateral weakness of the face, upper extremity, lower extremity, or both; contralateral sensory deficit or paresthesia of the face, upper or lower extremity, or both; or transient ipsilateral blindness (amaurosis fugax).[3] Notably, more than 90% of people are right handed, and language-related functions are controlled by the left cerebral hemisphere in most of these individuals.[27] In most right-handed individuals, if the right cerebral hemisphere is involved, other ischemic manifestations may be observed. These include anosognosia, asomatognosia, neglect, visual, and sensory extinction. To be noted that, even in left-handed individuals, speech is most often controlled by the left hemisphere. If the left hemisphere is involved, patients may demonstrate aphasia, alexia, anomia, and agraphesthesia. Nonspecific neurologic symptoms that are not typically associated with carotid territory thromboembolic events include vertigo, ataxia, diplopia, other visual disturbances, dysarthria, decreased consciousness, weakness, syncope, and dizziness.[3] Although imaging is most often performed with a carotid duplex ultrasound examination, among patients presenting with stroke, the extracranial and intracranial vasculature may be imaged simultaneously with computed tomography (CT) or MRI studies.

Asymptomatic patients

Indications for imaging the carotid bifurcation in select groups of neurologically asymptomatic patients are controversial.[3] Although statistically significant in large trials including the Asymptomatic Carotid Atherosclerosis Study (ACAS),[28] the benefit of CEA and other carotid stenting interventions in preventing stroke in asymptomatic patients is much lower than among neurologically symptomatic individuals. Moreover, the magnitude of benefit depends on the assumption that interventions are performed with minimal morbidity. Populationlevel screening for asymptomatic carotid artery disease is not currently recommended by the US Preventive Services Task Force.[29] The identification of asymptomatic patients with “screening” should therefore be limited to high-risk individuals (see Clinical Practice Guidelines document), or those with relevant findings on physical examination or other imaging studies (ie, an audible carotid bruit, Hollenhorst plaque on fundoscopic examination, silent infarction on brain imaging examinations). Among these patients, the most appropriate screening test is a carotid duplex ultrasound examination.

The presence of an audible bruit in the neck may be an appropriate indication for carotid imaging in selected neurologically asymptomatic patients. Among patients with a neck bruit, the prevalence of carotid stenosis of more than 75% is 1.2%.[30] However, the presence of a neck bruit did not predict carotid stenosis of more than 60% in an asymptomatic patient population.[30] These observations contrast to those in symptomatic patients, in whom an ipsilateral bruit had a sensitivity of 63% and specificity of 61% for high-grade carotid stenosis (70%99%).[31] The presence of a bruit clearly increases the risk of MI and cardiovascular death.[32] However,

in population-based studies, the prevalence of severe stenosis is not high enough to make a bruit alone an indication for screening. Thus, screening for a bruit alone should not be done unless patients have other stenosis risk factors.[3]

It is reasonable to image the carotid bifurcation in patients with evidence of cerebral infarction on brain imaging, even without a relevant clinical history of stroke. Although these patients may not be "symptomatic" as defined in the NASCET trial (hemispheric TIA, monocular blindness or a nondisabling stroke within the previous 120 days),[33] prior silent cerebral infarction in the carotid territory noted on brain imaging studies may be considered a correlate of carotid territory neurologic symptoms.[34] Additionally, the finding of Hollenhorst plaque on fundoscopic examination of the retina is also correlated with presence of significant carotid bifurcation disease, and may therefore also warrant carotid artery evaluation.[3,35,36] Additional information regarding possible high-risk populations of neurologically asymptomatic patients who may be appropriate for screening is discussed elsewhere in this section.

Imaging modalities

The most important features of imaging of carotid bifurcation disease are the degree of stenosis and the character of the plaque.[3,26,28,37,38] It is common for clinicians to use multiple modalities when evaluating and planning intervention for patients with carotid artery stenosis. A greater degree of stenosis is generally thought to reflect an increased risk of future stroke.[26,37] However, plaque morphology also plays a significant role.[38] The morphologic features of the plaque include heterogeneity, measurement of plaque area and juxtaluminal black area, gray-scale median, and echogenicity.

Duplex ultrasound examination. Duplex ultrasound examination is safe, accurate, and reliable. Because results are heavily dependent on technique, it should be performed in an accredited ultrasound laboratory (consensus of writing group).[3] Duplex ultrasound examination is the first-line imaging modality for carotid artery imaging, screening, and identification of patients with 70% to 99% stenosis of the internal carotid artery (ICA).[39,40] The rationale for widespread use of duplex ultrasound examination include its low cost, ease of performance, and robust sensitivity (0.89; 95% confidence interval [CI], 0.85-0.92) and specificity (0.84; 95% CI, 0.770.89).[39,41] Consensus ultrasound criteria for diagnosing varying degrees of carotid artery stenosis have been extensively developed, widely used and validated.[42] Yet, duplex criteria that are used to categorize degree of stenosis can vary widely across centers, thereby impacting treatment decisions.[43,44] Duplex ultrasound examination may have a lower sensitivity and specificity for diagnosis of more moderate degrees of stenosis (50%69%).[40] Duplex ultrasound examination also has the ability to evaluate features of plaque morphology that may indicate patients at a high risk of stroke.[38]

Many surgeons use carotid duplex ultrasound examination as the primary and sole mode of imaging before planning and performing CEA.[45] These patients should have no evidence of arch disease on clinical examination (equal arm blood pressure), no abnormal waveform suggesting inflow as noticed by low peak systolic velocities or outflow disease as noted by low/absent diastolic flow and absence of extensive tortuosity, which may falsely elevate peak systolic velocities. This practice is in contrast with planning for carotid stenting procedures (CAS), for which additional imaging of the aortic arch and great vessels is typically considered mandatory.

The determination of the degree of carotid stenosis is based on analysis of hemodynamic parameters obtained from Doppler analysis, including peak systolic and end diastolic velocities. Ultrasound criteria describing the degree of carotid stenosis should be defined on angiographic/imaging correlation in each vascular laboratory. The most common consensus criteria include a cutoff peak systolic velocity of the ICA of 125 cm/second or greater to denote an angiographic stenosis of greater than 50%. A combination of peak systolic velocity of 230 cm/second and an end-diastolic velocity of greater than100 cm/second, or a peak systolic velocity ratio between the internal and CCA of greater than 4 can be used to predict a stenosis of greater than 70%.[42,46] Using these criteria, the reported sensitivity, specificity and accuracy of duplex in predicting 50% to 69% or a more than 70% stenosis are 93%, 68%, and 85% and 99%, 86%, and 95%, respectively.[42] Many surgeons have raised their threshold for intervention for asymptomatic carotid stenosis to 80% or greater. Typical duplex criteria to identify stenosis at this level include an end diastolic velocity of more than 140 cm/second.[47]

The major limitations of duplex ultrasound examination include dependence on a skilled operator and the inability to completely image the proximal and intracranial vasculature. Certain anatomic features such as severe vascular calcification and arterial tortuosity can also decrease the accuracy of duplex imaging.[3]

MR angiography. Current contrast-enhanced MR angiography (MRA) can provide three-dimensional images, which can rival those of formal arteriography.[40] The main advantages of MRA include the absence of radiation and the avoidance of iodinated-based contrast materials. Additionally, MRA can be combined with MR brain imaging to delineate clinically silent cerebral infarction, and it can also evaluate plaque morphology, particularly the presence of intraplaque hemorrhage.[48] However, bony landmarks are not typically present on the resulting images, and calcification of the vessels or plaque is not wellidentified.[40] Nevertheless, MRA has become widely used in evaluating patients with carotid artery disease. It can be used in combination with an initial duplex ultrasound scan for the planning of carotid artery intervention.

Contrast-enhanced MRA using gadolinium has been shown to be the most accurate noninvasive imaging modality for evaluation of carotid stenosis.[39] However, MRA has no role in screening for carotid artery disease owing to its considerable expense. Contraindications include the presence of metallic implants, including some pacemakers and defibrillators. In patients with significant renal failure, there is a rare but serious risk of nephrogenic systemic fibrosis following gadolinium contrast administration.[49] MRA using the time of flight technique has been reported to overestimate the degree of stenosis.[3]

CT angiography. Multidimensional CT angiography (CTA) can rapidly and accurately evaluate soft tissue, bone and vascular structures simultaneously. It is also able to evaluate the extent of vessel calcification, particularly in the aortic arch, and is less likely to overestimate the severity of carotid stenosis as compared with MRA.[3,40] Radiation and use of contrast remain its most significant limitations. CTA is not appropriate for widespread screening owing to its significant cost and degree of radiation exposure.[40] With regard to CEA planning, CTA is often used during preoperative evaluation in combination with an initial duplex ultrasound examination. In particular, if there is hemodynamic evidence of either proximal cerebrovascular disease or intracranial outflow disease on duplex ultrasound examination, CTA can be used to accurately image the aortic arch, great vessels, and intracranial circulation. However, MRA is likely better than CTA in the evaluation of plaque morphology.[50] Duplex criteria have also been validated using CTA as opposed to formal catheter-based arteriography to measure the degree of carotid artery stenosis.[47]

Conventional catheter arteriography. Catheter arteriography was previously considered the gold standard for the evaluation of carotid artery stenosis, particularly before CEA,[40] and it was used to measure the degree of carotid stenosis in most of the seminal studies comparing CEA with medical therapy.[26,28] However, it carries a small risk of complications. In the ACAS trial, angiographic-related stroke accounted for 50% of the procedural risk after CEA.[28,40] With current techniques, the risk of complications is likely much lower.

Currently, there is a limited role for routine use of arteriography in diagnostic evaluation of patients with carotid artery disease or in the planning of routine CEA. Although considered the gold standard for the evaluation of carotid artery stenosis, the current role of carotid angiography is to help to clarify conflicting results obtained from other imaging modalities, particularly with regard to the presence of carotid artery occlusion or “string sign.”

Clearly, carotid arteriography is an integral part of all carotid stenting procedures. Arteriography is also performed as a completion study following CEA by some practitioners, and it may be useful in evaluation and management of patients with post carotid intervention stroke to evaluate and potentially treat the intracranial circulation. Contraindications include anaphylaxis to contrast materials.

Indications for carotid screening: High-risk groups

This is covered in the Clinical Practice Guidelines document.[3]

Methods of measuring carotid stenosis

The degree of stenosis is still considered to be the most critical parameter in determining who will benefit from carotid artery intervention for stroke prevention. Accurately defining the degree of stenosis is essential to proper patient selection and management. As noted earlier, duplex ultrasound examination is the most widely used technique for evaluation of ICA stenosis. Velocities and other hemodynamic parameters obtained from the duplex ultrasound examination are used to infer degree of stenosis based upon validated data in comparison to formal arteriography. In most of the seminal trials comparing CEA with medical therapy, degree of stenosis was actually measured using arteriography.[26,28] There are several different methods for doing so.

The North American Symptomatic Carotid Endarterectomy Trial (NASCET) method, also used in the ACAS trial, measures the residual lumen at the point of greatest ICA stenosis with the lumen of the normal distal cervical ICA.[51] Percent stenosis is calculated as: (1 e minimal residual lumen/normal distal cervical ICA diameter) 100. However, an alternative method was used in the European Surgical Carotid Trial (ECST).[37] The ECST technique indexed minimal residual lumen to the diameter of the carotid bulb (as opposed to the normal distal cervical ICA). Both methods may have inherent inaccuracies.[51] The ECST technique must use arteriographic images to estimate the actual location of the carotid bulb wall and the NASCET technique may calculate a negative value for stenosis when minimal occlusive disease is present at the carotid bifurcation. Currently, the NASCET method is more widely used and accepted.[52] CTA has been shown to be a reliable substitute to formal arteriography in this regard.[53]

Summary and recommendations

(See also Clinical Practice Guidelines document.[3])

1. Duplex ultrasound examination preferably performedin an accredited vascular laboratory is the initial diagnostic imaging of choice for evaluating the severity of carotid stenosis in both symptomatic and asymptomatic patients. Unequivocal identification by duplex ultrasound examination of carotid stenosis 50% to 99% in neurologically symptomatic patients or 70% to 99% in asymptomatic patients is sufficient to make a decision regarding carotid a artery intervention in appropriately selected patients.
2. When duplex ultrasound results are equivocal or maybe inaccurate owing to the presence of significant calcification or other findings, additional imaging with MRA, CTA, or digital subtraction arteriography may be considered before consideration of carotid artery revascularization procedure.
3. When evaluation of the vessels proximal or distal tothe cervical carotid artery is required for diagnosis or to plan endovascular or surgical therapy, additional imaging with CTA, MRA, or digital subtraction angiography (DSA) is indicated. CTA is preferred to MRA for extreme calcification. When there is a discordance between two minimally invasive imaging techniques, DSA may be indicated to resolve conflicting results. DSA is generally reserved for situations where there is inconclusive evidence on minimally invasive studies, or when CAS procedures are planned.
4. Imaging of the carotid bifurcation is recommended inall patients with symptoms of cerebral ischemia. This is based on the increased incidence of clinically relevant carotid stenosis and future stroke in this patient group, and the efficacy of carotid intervention in reducing the risk of future stroke.
5. Imaging of the carotid bifurcation should be stronglyconsidered in patients who present with amaurosis fugax, evidence of

retinal artery embolization on fundoscopic examination, or asymptomatic cerebral infarction noted on imaging studies. This is based on the intermediate stroke risk in this patient population, and the efficacy of carotid intervention in reducing future stroke risk (see Clinical Practice Guidelines document).

OPTIMAL MEDICAL THERAPY AND RISK FACTOR MODIFICATION

Treatment of hypertension

Hypertension is a well-recognized risk factor for atherosclerotic cardiovascular disease, including carotid artery disease and stroke. The association between blood pressure and stroke is independent of other risk factors for stroke, and blood pressure reduction decreases this risk.[54,55] Each 10 mm Hg increase in blood pressure is associated with a 30% to 45% increased risk of stroke and each 10 mm Hg blood pressure reduction in hypertensive patients decreased the risk of stroke by 33%.[56] There is no Level 1 evidence from randomized clinical trials assessing the influence of blood pressure reduction on stroke prevention among patients with asymptomatic carotid stenoses. However, a meta-analysis of 25 randomized clinical trials including patients without documented vascular disease demonstrated significant decreases in the incidence of late strokes (relative risk reduction 45%; 95% CI, 35-55), and stroke reduction was proportional to the reduction in systolic blood pressure.[57] In addition, a meta-analysis of 147 randomized clinical trials of hypertensive therapy among patients with a history of stroke demonstrated a significant relative risk reduction in stroke incidence with antihypertensive therapy (34%; 95% CI, 15-32).[57]

However, there is no convincing evidence supporting systemic blood pressure decreased in the acute phase of a stroke; in fact, this may be potentially harmful among patients undergoing CEA. In one report, the benefit of preoperative blood pressure reduction increased stroke risk among recently symptomatic patients with bilateral 70% or greater ICA stenosis.[58] In contrast, severe hypertension, defined as a systolic blood pressure of greater than 180 mm Hg should be treated to decrease the risk of postoperative hyperperfusion syndrome, intracranial hemorrhage, and surgical bleeding.[59,60] Similarly, severe hypertension is associated with risk of hyperperfusion syndrome and intracranial hemorrhage after CAS procedures.[61] Post-CAS hypertension and hypotension are both associated with increased risk of periprocedural stroke and mortality. In an analysis of 5263 patients who underwent CAS in the Vascular Quality Initiative (VQI), beta blocker use for more than 30 days decreased the stroke/death rates after CAS, although the benefit may not have been related exclusively to blood pressure lowering.[62]

Similar to the general population, among patients with asymptomatic carotid disease or a remote symptomatic history, a blood pressure target of 140/90 mm Hg was accepted for some time as the standard. However, this target level was recently lowered to 130/80 in the 2017 guidelines released by the AHA and the American College of Cardiology.[63]

In addition to its clinical benefit, reduction of elevated blood pressure also has been demonstrated to have benefits pathologically. Several trials showed that elevated blood pressure is associated with development of carotid atherosclerosis,[64-66] and other research indicated that reduction in carotid pulse pressure was associated with a parallel reduction in intima-media thickness.[67] Further, there is evidence that antihypertensive therapy may slow progression of carotid atherosclerosis and possibly promote plaque regression.[68] However, a more recent meta-analysis demonstrated that calcium channel blockers reduce intima-medial thickness to a greater degree than diuretics, beta blockers, and angiotensin converting enzyme inhibitors, suggesting that the origin of this beneficial effect may be more complex than simple lowering of blood pressure.[69]

Treatment of diabetes mellitus

The relationship between blood glucose levels and cerebrovascular disease is complex. The Insulin Resistance Atherosclerosis Study and the Atherosclerosis Risk in the Community Study demonstrated associations between diabetes and carotid artery intima-media thickness as well as progression in intima-media thickness.[70,71] More recent work indicates that plaque burden and plaque instability are influenced by diabetes status.[72]

Among patients with documented carotid artery disease in the Cardiovascular Health Study, elevated fasting blood glucose level was associated with increased stroke risk,[73] and in the Northern Manhattan Study, diabetes was associated with a doubling of the stroke risk.[74] However, a recent meta-analysis of nine randomized clinical trials and nearly 60,000 patients did not confirm that tight control of glucose levels decreased stroke risk.[75] Further, no reduction in stroke risk was identified despite achieving a hemoglobin A_{1c} level of less than 6.5% in either the United Kingdom Prospective Diabetes Study, the Action to Control Cardiovascular Risk in Diabetes study, or the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation trial.[76-78] Nevertheless, among patients with carotid artery disease, hemoglobin A_{1c} of less than 7% is recommended to reduce the development of microvascular complications and possible macrovascular complications other than stroke.

Treatment of lipid abnormalities: Statin therapy

Although the relationship between hypercholesterolemia and coronary artery disease and MI are wellestablished, the data with respect to elevated cholesterol levels and stroke are somewhat conflicting.

Several studies identified increased incidence of stroke among men and women with elevated cholesterol levels,[79-81] but a meta-analysis of 45 studies of hypercholesterolemic patents did not indicate an increased risk of stroke.

Nonetheless, there is compelling evidence that decreasing low-density lipoprotein (LDL) levels through lipid-lowering therapy is

highly effective in decreasing stroke risk among patients with known atherosclerotic disease. A meta-analysis of 28 randomized clinical trials including more than 106,000 patients with nearly 50,000 randomized to statin medications, demonstrated that in hyperlipidemic patients without a prior history of stroke, statins were associated with a 15% to 30% decrease in stroke incidence.[82] A more recent meta-analysis of 26 trials including more than 90,000 patients with coronary artery or other atherosclerotic disease demonstrated a greater than 15% decrease in the rate of stroke for every 10% reduction in serum LDL.[83] The 2006 Stroke Prevention by Aggressive Reduction in Cholesterol Levels trial was the first study to demonstrate the benefits of statin therapy in preventing recurrent stroke. Among 4731 patients who had experienced a stroke or TIA within 1 to 6 months of randomization to atorvastatin 80 mg/day or placebo, there was a 33% decrease in the incidence of fatal or nonfatal stroke and a 42% decrease in the overall incidence of cardiovascular events.[84,85]

In the Heart Protection Study, which included 20,536 patients, 3280 had a history of nondisabling ischemic stroke or TIAs and were randomized to 40 mg of simvastatin or placebo. There was a 25% (95% CI, 15-34) proportional reduction in the first event rate for stroke (4.4% simvastatin vs 5.7% placebo) (P < .0001), indicating a 28% reduction in ischemic strokes (P < .0001).[86] A Cochrane review investigating the role of statins in primary prevention of cardiovascular disease included 18 randomized clinical trials of nearly 57,000 patients and demonstrated a significant reduction in incidence of fatal and nonfatal strokes among patients randomized to statin therapy.[87]

Although LDL levels are associated with stroke risk, there is also some evidence that high levels of highdensity lipoprotein (HDL) cholesterol may be protective, but to a lesser degree.[88] In 9247 patients with a mean age of 61 who received treatment to reduce LDL and raise HDL levels, an elevated total cholesterol/HDL ratio was associated with a 22% increased risk of stroke whereas an elevation in the HDL level was independently associated with a 14% reduction in stroke risk.[89]

The benefit of statin medications for stroke risk reduction is most likely due to their pleiotropic effects, and these effects are being recognized in the periprocedural period for patients undergoing CEA and CAS. A study from the Johns Hopkins Hospital was the first to investigate the impact of statins on CEA outcomes. In a series of nearly 1600 patients with either symptomatic or asymptomatic carotid stenoses undergoing CEA, statin use was associated with a 3-fold reduction in 30-day stroke (P¼ .019) and a 5-fold decrease in 30-day mortality (P ¼ .049).[90] Other studies confirmed the beneficial impact of statin use on perioperative CEA outcomes among symptomatic[91] and asymptomatic patients.[92] Most recently, a meta-analysis of seven studies and 21,387 patients demonstrated that administration of statin medications before CEA was associated with lower rates of perioperative stroke and superior overall survival.[93]

Less has been reported on the influence of statins on CAS outcomes, but available data parallel those for CEA. In a retrospective review of 53 patients who underwent CAS in a single institution, the 30-day stroke/death/ MI rate was 4% in patients on statins and 15% among those not on statins at the time of the CAS (odds ratio [OR], 0.23; 95% CI, 0.005-0.99; P ¼ .049).[94] This finding was confirmed in a study of 344 consecutive patients who underwent CAS from 2002 to 2012. Statins were associated with a periprocedural risk reduction in the incidence of ischemic stroke, MI, or death (OR, 0.31; 95% CI, 0.3-0.71; P ¼ .006).[95] The largest case series reported to date includes 1083 patients who underwent CAS from 2004 to 2009. In these patients, statin use was associated with reduced perioperative stroke and death (OR, 0.33; 95% CI, 0.13-0.80; P ¼ .016), and the impact of statins was more pronounced in reducing stroke and death in symptomatic patients (OR, 0.13; P¼ .032) and in males (OR, 0.27; P¼ .01).[96]

In addition, several studies have demonstrated regression in intima-media thickness in the carotid artery among statin users compared with controls.[97-99] Very recent MRI data from the population-based Rotterdam Study showed that among 1740 participants with carotid atherosclerosis and a mean age of 72.9 years, statin use was associated with a change in carotid plaque composition from vulnerable plaque with a lipid core to more stable calcified plaque.[100] However, there is no compelling evidence that statin therapy is associated with clinically significant carotid plaque regression.

When combined with lifestyle and dietary changes, statin therapy is the most effective pharmacologic therapy for lipid-lowering.[101] High intensity statin therapy includes daily atorvastatin 40 to 80 mg or rosuvastatin 20 to 40 mg. Moderate intensity statin therapy includes atorvastatin 10 to 20 mg/day, fluvastatin 40 mg twice daily, or fluvastatin XL 80 mg, lovastatin 40 mg, pitavastatin 2 to 4 mg, pravastatin 40 to 80 mg, rosuvastatin 5 to 10 mg, or simvastatin 20 to 40 mg.[101] For individuals age 75 or less with atherosclerotic disease, including carotid artery disease, recent evidence supports high-intensity statin therapy, or moderate-intensity statin therapy if highintensity therapy is not tolerated. For older individuals, moderate-intensity statin therapy is recommended.

Smoking cessation

Smoking is well-recognized as a powerful risk factor for atherosclerotic disease, including carotid artery disease and stroke. In the Framingham study of 4255 men and women aged 36 to 68 years, heavy cigarette smoking was associated with a two-fold increase in stroke risk compared with light smokers.[102] This finding was confirmed in a meta-analysis of 32 studies that demonstrated the risk of stroke is nearly doubled in smokers.[103] Moreover, early studies have documented that smoking cessation reduces stroke risk in both men and women.[104,105]

From a mechanistic point of view, recent studies have suggested that smoking-related stroke risk is related at least in part to the deleterious effect of smoking on plaque biology in the carotid

artery. In a population-based study of 4657 men in Sweden, a greater than 50% internal carotid stenosis was identified by duplex examination in 5%, 2%, and 1% of current, former, and never smokers, respectively.[106] In a pooled analysis of four population-based cohort studies (Malmö Diet and Cancer Study, Tromsø Study, Carotid Atherosclerosis Progression Study, and Cardiovascular Health Study) that included a total of 23,706 participants, there was a significant association between cigarette smoking and a greater than 50% ICA stenosis (OR, 2.3; 95% CI, 1.8-2.8) and greater than 70% ICA stenosis (OR, 3.0; 95% CI, 2.14.4).[107] More recently, in the Chinese intracranial atherosclerosis study of 2656 patients with acute ischemic stroke and 208 patients with TIA, current smoking was associated with extracranial carotid artery disease (OR, 1.47; 95% CI, 1.09-1.99, P < .001). With each additional year of smoking, the risk of extracranial carotid disease increased by 1.1% (OR, 1.011; 95% CI, 1.003-1.019; P ¼ .005). Even low levels of smoking increase risk: With one cigarette smoked per day increment, the risk of extracranial carotid disease increased by 1.0% (OR, 1.010; 95% CI, 1.001-1.020; P ¼ .03). Finally, with one pack-year of smoking increment, the risk of extracranial carotid disease increased by 0.7% (OR, 1.007; 95% CI, 1.002-1.012; P < .01).[108] Cigarette smoking has been demonstrated to be associated with plaque progression,[109] but no significant association was identified between cigarette smoking and intracranial carotid disease.[108]

As comprehensive vascular specialists, vascular surgeons should counsel patients regarding the deleterious impact of smoking on overall health as well as cerebrovascular well-being. There is clear evidence that counseling is an efficacious strategy that can be supported by a number of pharmacologic adjuncts.[110] In an analysis of 12 reviews including 267 studies and more than 101,000 participants, nicotine replacement therapy was superior to placebo (OR, 1.84; 95% CI, 1.71-1.99) and bupropion (Wellbutrin/Zyban) was also superior to placebo (OR, 1.82; 95% CI, 1.60-2.06). Varenicline (Chantix) was also superior to placebo in achieving quitting (OR, 2.88; 95% CI, 2.40-3.47). Bupropion and nicotine replacement therapy were found to be equally efficacious. Conversely, varenicline was superior to single forms of nicotine replacement therapy (OR, 1.57; 95% CI, 1.29-1.91), but was not superior to combination nicotine replacement therapy (OR, 1.06; 95% CI, 0.75-1.48). Nortriptyline was also effective in increasing smoking cessation (RR 1.26; 95% CI, 0.62-2.56).[111]

Antiplatelet and antithrombotic therapy

Although there is no compelling evidence to support a benefit of aspirin among patients with asymptomatic carotid artery disease, the US Preventive Services Task Force recommends initiating low-dose aspirin for primary prevention of cardiovascular disease in adults aged 50 to 59 years who have a 10-year risk of greater than 10% for cardiovascular disease, have a life expectancy 10 years or more, and are not at increased risk of bleeding. For individuals aged 60 to 69 years, the decision should be individualized. There is insufficient evidence to support aspirin recommendations for individuals less than 50 years of age.[112]

Aspirin studies focusing on individuals with asymptomatic carotid stenoses also show conflicting results. In the Asymptomatic Cervical Bruit study, 372 patients with asymptomatic stenosis greater than 50% internal carotid stenoses were randomized to daily aspirin (325 mg) or placebo. At a median follow-up of 2.3 years, there was no significant differences between groups in incidence of any ischemic event or death.[113] Conversely, in the Asymptomatic Carotid Emboli Study that focused on patients with a 70-99% asymptomatic stenosis, antiplatelet therapy was associated with lower rates of ipsilateral stroke/TIA and any stroke/cardiovascular death.[114] In addition, a multicenter stroke registry of 10,433 individuals of whom 1914 (18.3%) were taking aspirin, aspirin use was associated with reduced stroke severity and improved functional outcome.[115]

Several studies offer strong evidence supporting the efficacy of antiplatelet therapy for secondary prevention among patients with symptomatic carotid artery disease[116-122] and a meta-regression analysis of 11 trials demonstrated an approximate 15% reduction in stroke risk associated with aspirin use.[123] Because patients who have experienced a symptomatic episode are at greatest risk of a second event in the first few days after the initial event, it is important to initiate antiplatelet therapy as soon as possible. In a meta-analysis comparing aspirin vs control that included 12 randomized clinical trials with nearly 16,000 patients, at 6 weeks there was a 60% decrease in the risk of recurrent stroke (hazard ratio [HR], 0.42; 95% CI, 0.32-0.55, P < .0001) and a 70% decrease in the risk of a fatal stroke (HR, 0.29; 95% CI, 0.2-0.42; P< .0001).[124]

Breakthrough ischemic events may occur in some patients who are compliant with aspirin therapy owing to aspirin resistance. There is some evidence that aspirin's reduced antithrombotic efficacy may be more common in patients who take enteric coated aspirin or lower dose therapy (81 mg) compared with those taking uncoated aspirin (325 mg).[125] However, routine laboratory testing for platelet reactivity is not supported by the evidence.[126] Three randomized clinical trials compared aspirin with anticoagulation with warfarin among patients with noncardioembolic TIA or stroke. These studies failed to demonstrate superiority of anticoagulation over antiplatelet therapy in reducing the incidence of ischemic events, although there was an increased incidence of bleeding complications associated with anticoagulation.[127-129] A recent meta-analysis of eight clinical trials comparing anticoagulation with antiplatelet therapy for secondary prevention of stroke identified no difference in prevention of vascular events.[130]

In addition to aspirin, clopidogrel, the combination agent aspirin þ dipyridamole, and dual antiplatelet therapy have all been investigated in this clinical scenario but the optimal regimen is not clear. In the Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial, there was a small advantage of clopidogrel over aspirin in reducing overall ischemic events.[131] However, analysis of a subset of patients with a prior history of stroke in the

CAPRIE trial demonstrated no difference in incidence of vascular events.[131] In the European/Australasian Stroke Prevention in Reversible Ischemia Trial, patients were randomized to aspirin or aspirin þ extended release dipyridamole therapy within 6 months of a TIA or stroke. The study showed a statistically significant lower rate of vascular events in patients who received the combination regimen.[132]

In the Prevention Regimen for Effectively Avoiding Second Strokes trial, patients received either clopidogrel or aspirin þ extended release dipyridamole. This trial showed no difference in the rate of recurrent strokes, but there was a lower incidence of major hemorrhagic events in the clopidogrel group.[133] In a recent metaanalysis of 13 randomized clinical trials of patients with cerebral infarction, patients who received aspirin þ dipyridamole had lower mortality compared with those who received aspirin þ clopidogrel (OR , 0.46; 95% CI, 0.18-

0.99).[134]

There is considerable evidence supporting dual antiplatelet therapy in secondary stroke prevention. In the Clopidogrel in High Risk Patients with Acute Nondisabling Cerebrovascular events (CHANCE) trial, patients were randomized to aspirin þ clopidogrel or aspirin alone within 24 hours of experiencing a TIA or minor stroke. Stroke occurred in 8.2% of patients in the aspirin þ clopidogrel group, compared with 11.7% of patients who took aspirin alone (HR, 0.68; 95% CI, 0.57-0.81; P< .001). Moderate or severe hemorrhage occurred in seven patients (0.3%) in the clopidogrel-aspirin group and in eight (0.3%) in the aspirin group (P¼ .73) and the rate of hemorrhagic stroke was 0.3% in each group.[135] A subsequent meta-analysis assessed trials including the following regimens: Aspirin þ clopidogrel vs aspirin; aspirin þ clopidogrel vs clopidogrel; aspirin þ dipyridamole vs aspirin; aspirin þ dipyridamole vs dipyridamole; aspirin þ dipyridamole vs clopidogrel; and cilostazol þ aspirin vs aspirin. This meta-analysis concluded that dual antiplatelet therapy was associated with a 31% relative risk reduction in stroke incidence compared with monotherapy.[136] Finally, consistent with recognition that plaque instability is greatest early after an ischemic event, dual antiplatelet therapy appears clinically beneficial in the early weeks following these events. A meta-analysis of eight randomized clinical trials including 20,728 patients demonstrated that short-term (<3 months) dual antiplatelet therapy with aspirin and clopidogrel compared with aspirin alone significantly decreased risk of recurrent stroke but it did not increase risk of hemorrhagic complications. Relative to monotherapy with aspirin, dual therapy with aspirin and clopidogrel reduced risk of stroke recurrence (RR, 0.69; 95% CI, 0.59-0.81; P< .01) and did not increase the risk of hemorrhagic stroke (RR, 1.23; 95% CI, 0.50-3.04; P¼ .65) or major bleeding events (RR, 2.17; 95% CI, 0.1825.71; P¼ .54). However, short-term combination therapy was associated with a significantly lower risk of major vascular events (RR, 0.70; 95% CI, 0.69-0.82; P< .01). Longterm, however, dual antiplatelet therapy did not decrease the risk of stroke recurrence (RR, 0.92; 95% CI, 0.83-1.03; P¼ .15), but it was associated with a significantly higher risk of hemorrhagic stroke (RR, 1.67; 95% CI, 1.10-2.56; P¼

.02) and major bleeding events (RR, 1.90; 95% CI, 1.46-2.48; P < .01). Long-term combination therapy also failed to reduce the risk of major vascular events (RR, 0.92; 95% CI, 0.84-1.03; P¼ .09).[137]

Alternate antiplatelet agents are also being investigated for secondary prevention among patients with symptomatic carotid disease. In a recent meta-analysis of 36 randomized clinical trials, the efficacy of conventional antiplatelet agents (aspirin; clopidogrel) was compared with newer agents (cilostazol; triflusal). The major finding was a trend indicating cilostazol was associated with reduced risk of recurrent stroke compared with low-dose aspirin þ dipyridamole (OR, 0.75; 95% CI, 0.52-1.02) and clopidogrel (OR, 0.76; 95% CI, 0.51-1.05), but these differences were not statistically significant.[138]

Finally, some surgeons selectively use dextran 40 in the immediate postoperative period after CEA. The rationale for use relates to case series that identified transcranial Doppler (TCD)-detected microembolization which occurs during CEA and immediately postoperatively, and the reduced number of microemboli with dextran 40 infusion. For example, in a series of 163 patients who underwent CEA, dextran 40 was infused for any patient who manifested more than 25 emboli within 10 minutes. It was infused in nine patients (5%) and rapidly controlled embolization.[139] In a similar study, 156 patients undergoing CEA were randomized to receive dextran 40 or placebo. TCD detected embolic signals in 57% of placebo and 42% of dextran patients. At 2 to 3 hours postoperatively, embolic signals were detected in 45% of placebo and 27% of dextran patients, with embolic signal counts 64% lower for dextran patients (P ¼ .040).[140] In a report of 400 patients monitored with TCD during CEA, more than 25 emboli in 10 minutes after unclamping were detected in 216 patients (54%). Following initiation of dextran 40, embolization ceased in all cases and there were no strokes or acute carotid thromboses in these patients.[141] Another review reported a 46% decrease in emboli when dextran was administered during CEA.[142]

Previous work demonstrated increased platelet activation during CEA. In a study of 38 CEA patients who were taking aspirin and who received heparin intraoperatively, P-selectin binding index was assessed as a measure of platelet activation. P-selectin levels rose after incision, during carotid clamping, after clamp release, and at 1 hour and 24 hours postoperatively. Likewise, TCD revealed an increase in embolic signals compared with the rate of preoperative signals during the dissection, after clamp release, and during recovery. Six patients who had greater than 50 high intensity signals per 30 minutes received dextran 40 and a significant reduction in P-selectin levels (P< .05) was noted after dextran therapy in these patients.[143] These findings indicate that platelet aggregation occurs during CEA despite conventional antiplatelet therapy with aspirin and heparin administration, and that it may be ameliorated with dextran 40.[144] Recent work suggested that dextran may exert a combined therapeutic effect by enhancing endogenous fibrinolysis

as well as reducing platelet adhesion to von Willebrand factor and platelet activation by thrombin.[145]

Although these observations make a compelling case for the efficacy of dextran use among patients undergoing CEA, objective clinical benefit has not been definitively demonstrated. Further, in a recent review of the Vascular Study Group of New England, including 89 surgeons and 66641 CEA procedures performed from 2003 to 2020, intraoperative dextran administration did not decrease the rate of perioperative stroke, but it was associated with an increased incidence of postoperative MI and congestive heart failure.[146] Because this study investigated intraoperative dextran use, an objective assessment of the clinical risk/benefit ratio of postoperative dextran is not possible. There is clearly no Level 1 evidence to recommend for or against use of dextran among patients undergoing CEA, so this should be a clinical judgment made by the operating surgeon.

Perioperative medical management for patients undergoing CEA and carotid stenting

Carotid endarterectomy. Perioperative medical management of patients undergoing CEA should include blood pressure control, and beta blocker, statin, and antiplatelet therapy.

Postoperative hypertension is a well-recognized risk factor for stroke and TIAs, wound bleeding, and intracranial hemorrhage.[60,147-150] Therefore, strict attention to preoperative blood pressure control, as noted elsewhere in this article, is important in optimizing postoperative outcomes. Postoperative fluctuations of hypertension and hypotension are not uncommon.

If hypotension does not respond to a fluid infusion, phenylephrine is accepted therapy with the dose adjusted to maintain systolic blood pressure within 20 mm Hg of the preoperative level. Conversely, hypertensive episodes should be treated with an infusion of nitroprusside. The effect is immediate, and can be quickly removed with cessation of the infusion. Intravenous nitroglycerin may be administered for myocardial ischemia.

MI is the most frequent non-neurologic complication of CEA. Beta blockers should be continued in patients undergoing noncardiac surgery who have been on these drugs chronically. It may be reasonable to begin perioperative beta blockers for patients with intermediate or high risk for myocardial ischemia, or for patients with three or more Revised Cardiac Risk Index risk factors such as heart failure, coronary artery disease, renal insufficiency, diabetes mellitus, or cerebrovascular accident. It is important to recognize that initiation of any beta blocker therapy should be sufficiently in advance of surgery to assess safety and tolerability.[151] Perioperative beta blockade started within 1 day or less before noncardiac surgery prevents nonfatal MI, but increases risk of stroke, death, hypotension, and bradycardia.[151]

Several series have demonstrated that perioperative statins are associated with significant reductions in 30day stroke and death rates among patients undergoing CEA.[90-92] These findings are consistent with other studies of patients undergoing an array of other vascular procedures. In a randomized clinical trial of patients undergoing vascular surgical procedures, atorvastatin use was associated with a lower rate of perioperative stroke, MI, and death[152] and a meta-analysis identified a reduced rate of perioperative mortality among vascular surgery patients who were on statins.[153] In addition, an observational study of 780,591 patients undergoing noncardiac surgery showed that risk-adjusted mortality was significantly lower among patients taking a perioperative statin.[154] There is also some recent evidence suggesting that patients taking statin medications at the time of CEA may have reduced rates of perioperative spontaneous embolization compared with those not taking statins.[155] These clinical benefits may be partly due

to the anti-inflammatory and plaque-stabilizing pleiotropic effects of statin medications,[156,157] but is not clear how soon before surgery one should start a patient on statins to achieve these beneficial effects. However, the sudden withdrawal of statin medications in the perioperative period should be avoided, because there is evidence that sudden cessation may be associated with increas

ed perioperative cardiovascular morbidity and mortality.[158]

Patients should remain on aspirin therapy perioperatively,[159] and low-dose aspirin (81 mg or 325 mg) seems to be as effective as higher dose aspirin.[160] The benefit of aspirin in reducing the rate of perioperative stroke without increasing bleeding complications was demonstrated in a randomized trial.[161] However, some previous work also suggested that sudden cessation of chronic aspirin therapy may be associated with a rebound increased incidence of ischemic events but recent data do not support this observation.[162,163]

Continuation of dual antiplatelet therapy in the perioperative period should be individualized. In a metaanalysis of three randomized clinical trials including 36,881 patients undergoing CEA, dual antiplatelet therapy was not associated with reduced risk of perioperative stroke, TIA, or death, but it was associated with increased risk of neck hematoma and major bleeding complications.[164] Conversely, in a review of 10,46 patients undergoing vascular surgerydincluding 5264 undergoing CEAdthere was no difference in the risk of bleeding complications among patients on aspirin, clopidogrel, or dual aspirin þ clopidogrel therapy, or no antiplatelet therapy.[165] Clearly, among those patients with a specific indication for clopidogrel such as symptomatic carotid disease or recent stent placement, dual antiplatelet therapy is indicated. Intraoperative anticoagulation, and protamine reversal, is discussed in Section on Anticoagulation and protamine reversal.

Carotid stenting. Perioperative medical management of CAS patients is similar to those undergoing CEA, including blood pressure control and beta blocker use. Similarly, although there is currently no Level 1 evidence to inform on the efficacy of statins among patients undergoing CAS, individual case series support this approach. For example, in a series of 180 patients undergoing CAS, the 30-day risk of stroke, death, and MI was 4% among statin users vs 15% among nonusers (P < .05).[94] In another series of 344 CAS patients, multivariate analysis demonstrated that statin use was a significant predictor of reduced peri-interventional incidence of ischemic stroke, MI, or death (OR, 0.31; P ¼ .006).[95] Further, in the largest series reported to dated1083 patients undergoing CASdmultivariable analysis showed that statin use was associated with a reduction in the incidence of perioperative stroke and death (OR, 0.327, 95% CI, 0.13-0.80; P¼ .016).[96]

With respect to antiplatelet therapy, there also are no randomized clinical trials assessing the benefit of aspirin vs dual therapy with aspirin and clopidogrel for patients undergoing CAS. Current recommendations are therefore largely based on experience with coronary artery stents. Dual antiplatelet therapy including aspirin (325 mg) and clopidogrel (75 mg) should be initiated before CAS, and continued for 4 weeks after the procedure.[166] There is no evidence to indicate that continuing clopidogrel beyond four weeks improves coronary outcomes.[167]

Summary and recommendations

1. In patients with arteriosclerotic arterial disease, werecommend aggressive antihypertensive therapy.
2. In severely hypertensive patients undergoing CEA, werecommend aggressive blood pressure lowering.
3. In severely hypertensive patients undergoing carotidartery stent procedures, we recommend aggressive blood pressure lowering.
4. In patients with known atherosclerotic disease, werecommend reducing LDL levels with lipid-lowering agents.
5. In patients with a prior history of stroke or TIA, werecommend statin therapy.
6. In patients without a prior history of cardiovasculardisease, we recommend statins in the primary prevention of fatal and nonfatal strokes.
7. In active smokers, we recommend complete smokingcessation.
8. In active smokers, we recommend pharmacologic treatment in addition to counseling to achieve smoking cessation.
9. In patients with symptomatic carotid artery disease,we recommend antiplatelet therapy with aspirin for secondary prevention.
10. In patients with a history of noncardiogenic TIAs orstroke, we do not recommend anticoagulation over aspirin therapy.
11. In patients with a history of stroke or TIAs within 6 months, we recommend dual antiplatelet therapy with aspirin and dipyridamole.
12. In patients with a history of TIAs or minor stroke within24 hours, we also recommend dual antiplatelet therapy with aspirin and clopidogrel over aspirin alone as an alternative to aspirin and dipyridamole.
13. In patients with increased cardiac risk factors undergoing noncardiac surgery, we recommend starting beta blockade therapy. If not currently on the medication, it should be started as soon as possible preoperatively so that one has an opportunity to assess its hemodynamic effect. Therefore, beta blockers should not be started on the day of or 1 day before the procedure.
14. In patients undergoing CEA, we recommend statintherapy.

15. In patients undergoing CEA, we recommend continuing aspirin therapy.
16. In patients undergoing CEA, during the perioperativeperiod we recommend individualizing the continued use of dual antiplatelet therapy based on specific indications (eg, cardiac).
17. In patients with increased cardiac risk factors undergoing carotid stent procedures, we recommend starting beta blockade therapy. If not currently on the medication, it should be started as soon as possible preoperatively so that one has an opportunity to assess its hemodynamic effect. Therefore, beta blockers should not be started on the day of or 1 day before the procedure.
18. In patients undergoing CAS, we recommend statinuse.
19. In patients undergoing CAS, we recommend dual antiplatelet therapy with aspirin (325 mg) and clopidogrel (75 mg) initiated before the procedure and continued for 4 weeks after the procedure.

CAROTID INTERVENTION INDICATIONS

A. Is CEA recommended over maximal medical therapyin low surgical risk patients?

See the Clinical Practice Guidelines document.[3]

B. Is CEA recommended over transfemoral CAS in lowsurgical risk patients with symptomatic carotid artery stenosis of greater than 50%?

See the Clinical Practice Guidelines document.[3]

Once a patient with clinically significant carotid stenosis is identified, appropriate treatment must be selected. Treatment is primarily directed at reducing stroke risk. The risks associated with an interventional treatment must be compared with those of optimal medical therapy when treatment choices are made. In general, risk of stroke, MI, and death are used when comparing transfemoral CAS with CEA. In most clinical trials comparing transfemoral CAS with CEA, stroke, MI, and death have been given equal weight in determining a composite end point to test overall efficacy. Data from the Carotid Revascularization Endarterectomy vs Stenting Trial (CREST),[5] however, indicate that stroke has a more significant effect on quality of life at 1 year than nonfatal MI. In developing its recommendations, the committee placed greater emphasis on stroke prevention and procedurally related death than periprocedural MI because the primary goal of intervention in carotid stenosis is stroke prevention. This may result in committee recommendations that differ from the published results of some trials in which these three outcomes were allocated equal analytic weight.

The major determinants of the clinical course of patients with carotid bifurcation stenosis are the presence or absence of neurologic symptoms and the severity of stenosis. Treatment is chosen based on assessment of risk associated with the intervention and the likelihood that a particular intervention will favorably alter the course of disease.

The threat of stroke in asymptomatic patients with less than 60% ICA stenosis and in symptomatic patients with less than 50% stenosis is generally considered to be small and does not warrant intervention. ECST and NASCET demonstrated that CEA did not significantly reduce subsequent neurologic event rates in patients with symptoms of cerebral ischemia and bifurcation stenosis of less than 50% diameter reduction and it was actually associated with increased morbidity compared with medical management.[37,168] Notably, stenoses of less than 60% diameter reduction were excluded from the asymptomatic studies,[28,169] assuming that asymptomatic patients with stenosis less than 60% would not benefit from carotid reconstruction. Given findings of the symptomatic trials, this exclusion proved to be an appropriate decision. There have been no studies supporting either CEA or transfemoral CAS for asymptomatic patients with less than 60% ICA stenosis.[170]

Assessing the risk associated with carotid intervention

There are certain anatomic and physiologic conditions that can increase risk of specific carotid revascularization methodologies regardless of the patient's symptomatic status. For instance, high bifurcation or high cervical lesion above C2 may increase risk of CEA[171] and aortic arch tortuosity can increase risk of transfemoral CAS.[172,173] Accordingly, risk stratification can generally be divided into two categories: Anatomic (including the lesion) characteristics and patient-specific or physiologic characteristics.

Risk stratification based on anatomic and lesion characteristics

Lesion location and vessel tortuosity.

HighriskforCEA. CEA provides excellent access to the cervical carotid artery, but lesions that extend outside this zone can be difficult to treat surgically. It is generally understood that lesions at or above the level of the C2 cervical vertebra or at or below the clavicle are generally more difficult to expose surgically during CEA without increasing the morbidity associated with the procedure.[171] Lesions of the distal cervical carotid artery can be exposed by division of the posterior belly of the digastric muscle and subluxation or division of the mandible, as required.[171,174] Although rarely required, these high carotid exposures may be associated with increased difficulty in directly visualizing the end point of the endarterectomy as well as increased risk of cranial nerve injury (CNI), particularly cranial nerve IX.[171,174] Lesions of the very proximal CCA are difficult or impossible to expose without extending the incision into the chest. This must be considered when evaluating the morbidity of the procedure. There are no extracranial carotid lesion locations that increase risk of transfemoral CAS

HighriskfortransfemoralCAS. Tortuosity of the aortic arch and target vessel can decrease the technical success rate and increase risk of stroke and death among patients who undergo transfemoral CAS.[175] For example, increased aortic arch tortuosity in a type III arch can make sheath or guide catheter placement difficult or impossible.[172,173] In addition, significant CCA and/or ICA tortuosity can increase the risk of technical failure and stroke. In particular, the presence of ICA tortuosity can make crossing the lesion and positioning a distal embolic protection filter difficult. In the tortuous ICA it may be difficult to find a sufficient length of carotid artery above the lesion with parallel walls, a challenge that may decrease the effectiveness of distal embolic protection filters in trapping generated debris that can occur during the procedure.[172]

Atherosclerotic disease burden in the arch can directly impact stroke risk during transfemoral CAS because of catheter manipulations that need to be performed in the aortic arch to engage the target vessel. This risk can be best identified on preprocedure CTA.[172]

The presence of iliac artery occlusion, severe stenosis or tortuosity can make sheath placement into the aortic arch difficult if not impossible. Alternative access sites that traverse the aortic arch have been reported, such as brachial or radial arterial access. Limited data render assessment of the efficacy of these approaches unclear.

High risk for transcervical carotid stent. There are limited data examining the efficacy of transcarotid artery revascularization (TCAR) in symptomatic and asymptomatic patients with severe carotid occlusive disease. Since this procedure accesses the CCA above the clavicle, relative contraindications include lesions that are less than 5 cm cranial to the clavicle.[176] In addition, severe target vessel tortuosity and small (<6 mm) CCA, significantly diseased CCA (excess calcification or thrombus) and/or depth of CCA which make access difficult are also relative contraindications.[177,178]

Lesion morphology

Lesion morphology such as echolucency, calcification, long irregular plaques, the presence of fresh thrombus or a string sign can affect outcomes and alter decision making concerning carotid revascularization.[172,175] This section examines the impact of lesion morphology on outcome following carotid revascularization techniques.

High risk for CEA. Lesion-specific morphology generally does not have a significant impact on CEA outcome. The degree of lesion calcification, echolucency, and the presence of fresh thrombus have not been shown to impact risk of neurologic events following CEA as these lesions can be removed en bloc. Long complex lesions can also be treated with no increase in complication if they do not extend above the lower endplate of the C2 vertebral body. The presence of a carotid string sign in which the extra and intracranial ICA is diminutive may be a relative contraindication. In most instances the carotid artery is small because it is under pressurized, and patients with a proximal ICA atherosclerotic lesion can be treated safely.[179] However, it is important to acknowledge that there is little clinical evidence guiding treatment indications for patients with a carotid string sign, nor is there guidance on whether CEA or carotid stenting are equally effective in this setting. In a small series of patients undergoing intervention, the 30-day stroke risk for CEA was 2.1% vs 2.4% for CAS. Restenosis risk was 5% for both groups over 1 to 5 years of follow-up.[180]

High risk for transfemoral CAS. Lesion morphology has a significant impact on outcomes for patients undergoing transfemoral CAS. Very tight stenosis, irregular calcified stenosis, and long lesions can limit the ability to deliver the stent across the lesion.[172,175] Carotid bifurcation stent placement in heavily or circumferentially calcified lesions has been associated with a significant risk of stent fracture and deformation.[181] Fresh thrombus within the carotid bifurcation is a contraindication to carotid stent placement with distal embolic protection devices (EPDs) because of risk of embolization while crossing the lesion as well thrombus disruption and embolization after stent placement. Similarly, long, complex lesions can increase risk of embolization during placement of the distal EPD and should, therefore, be approached cautiously when considering transfemoral CAS.[175] It is unclear how the presence of a carotid string sign impacts patient outcomes after transfemoral CAS.

High risk for TCAR. Similar to transfemoral CAS, circumferential or large bulky carotid bifurcation plaques can limit the ability to deliver the stent across the lesion. Carotid bifurcation stent placement in heavily or circumferentially calcified lesions has been associated with significant risk of stent fracture and deformation. As a result, heavily calcified carotid bifurcation lesions are a relative contraindication to stent placement. Early data suggest that long, complex, and echolucent lesions may be treated safely with TCAR because of proximal flow reversal before crossing the stenosis. However, the level of evidence to support this observation is much lower than that for CEA and transfemoral CAS.

Risk stratification based on patient-specific characteristics

Patient-specific factors can influence outcome following carotid revascularization. These factors include nonvascular hostile anatomy such as previous neck surgery or radiation. The second category of patientspecific factors includes physiologic comorbidities such as congestive heart failure, chronic obstructive lung disease, and renal insufficiency. This section examines the influence of patient-specific factors on outcomes after various revascularization options.

High risk for CEA.

Hostilenonvascularanatomy. 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.[171,182-184] Previous cervical fusion or severe cervical kyphosis or immobility owing to arthritis can also make CEA more technically challenging. Although CEA can be performed successfully in these situations, particularly when the tissues of the ipsilateral

neck are not scarred and fibrotic, these circumstances can increase risk of wound infection, difficulty of dissection, and potentially, risk of CNI. Among obese patients, the presence of a short neck may make dissection more tedious but has not been associated with increased operative risk.

Medicalhighrisk. 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 functional class III or IV heart disease, a left ventricular ejection fraction of less than 30%, class III or IV angina pectoris, left main or multivessel coronary disease, severe aortic valvular disease, oxygen- or steroiddependent pulmonary disease, contralateral carotid occlusion, and advanced age. However, few data exist to support one therapy over another in these patients.[7,185] In fact, defining a high-risk patient is much more subjective than defining a high-risk lesion.[182,183,186,187] CAS is associated with a lower risk of cardiac events than CEA. Assuming appropriate anatomy for either procedure, CAS is therefore 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 transfemoral CAS[188,189] and CEA.[190,191] Univariate and multivariate analyses both show that among patients with chronic kidney disease, 6-month risk of death, stroke, and MI after transfemoral CAS were associated with HRs of greater than 2.5.[188] Chronic renal insufficiency also increases the risk of stroke after CEA (1.08%-5.56%). Among asymptomatic patients with cardiac or renal insufficiency, best medical therapy may be preferable to transfemoral CAS or CEA. CEA or transfemoral 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 CEA or transfemoral CAS outcomes. NASCET reported that a contralateral occlusion increased risk of stroke after CEA from 5.8% to approximately 14%.[33] However, most reports on contralateral occlusion do not support this observation, and a metaanalysis suggested a much more modest increase, from 2.4% to 3.7%.[192,193] Although this increase in stroke risk was statistically significant, the results remain within AHA recommended guidelines. Several single-center studies have shown excellent results in patients with contralateral carotid occlusion.[194,195] A possible explanation for this discrepancy may be linked to inadequate sample sizes in the single-center studies. Alternatively, more consistent intraoperative management techniques, including algorithms for maintaining intraoperative cerebral perfusion, are more likely to occur in a single-center experience than in multicentered studies.[5] AbuRahma et al[196] reported on perioperative and late stroke rates of CEA contralateral to carotid artery occlusion. In a trial of 399 CEAs with randomization done by arterial closure method, 49 patients had contralateral carotid artery occlusion (group A) and 350 patients did not (group B). Strokes were designated as contralateral if they arose from the occluded side and ipsilateral if they arose from the same CEA side. Risk of all strokes (operative and late) and perioperative strokes was 4.1% and 2% (2% contralateral and 2% ipsilateral) for group A and 3.4% (all ipsilateral) and 2.9% for group B (P ¼ .85 and P ¼.60, respectively). The risk of all neurologic events (stroke and TIA) and perioperative events was 18.4% and 2% for group A and 9.7% and 5.4% for group B (P¼ .113 and P¼.27, respectively). At 5 years, the cumulative stroke-free survival was 84% in group A and 77% in group B (P > .1). Notably, all patients were routinely shunted. In this report, survival rates and risk of perioperative and all late strokes were comparable in patients with contralateral occlusion and to those without.[196]

Because there is a demonstrable risk of CNI after CEA that is absent after transfemoral CAS, patients with a history of a contralateral vocal cord paralysis are at increased risk with CEA vs transfemoral CAS. Thus, transfemoral CAS may be preferred in these patients.

High risk for transfemoral CAS.

Hostilenonvascularanatomy. Because of the remote location in which the carotid bifurcation is accessed, the impact of hostile nonvascular anatomy on transfemoral-CAS stroke risk is minimal and in many instances is the preferred approach for treating these patients.

Medicalhighrisk. Transfemoral CAS is associated with higher stroke risk than CEA in patients aged more than 80 years,[5,197-199] and in the CREST study, transfemoral CAS was associated with increased stroke risk in patients aged more than 70 years.[5] This was confirmed in a metaanalysis of four randomized trials comparing CEA and transfemoral CAS.[199] Similarly, a study by Hicks et al[200] using VQI data demonstrated a higher risk of stroke and death in patients meeting Medicare high-risk criteria (HR, 1.65; 95% CI, 1.05-2.60; P¼ .03) undergoing transfemoral CAS vs CEA.

High risk for TCAR.

Hostile nonvascular anatomy. Although similar to CEA, several anatomic considerations that may increase the difficulty of CEA may not be as prohibitive for TCAR. For example, if the proximal CCA is not exposed during the primary CEA, there may be no increased risk for TCAR in the treatment of carotid restenosis after CEA. Additionally, because the magnitude of surgical exposure is less than standard CEA (carotid bifurcation exposure), exposure of the proximal CCA is not as prone to nerve injury. Nonetheless, 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,[171,182-184] would be relative contraindications for TCAR. Similar to CEA, TCAR can be performed successfully in these situations. However, it can be associated with an increased risk of wound infection, difficulty of dissection, and potentially, the incidence of vagus nerve injury (group consensus).

Neurologic symptoms.

Symptomatic with a greater than 50% ICA stenosis. CEAinsymptomaticstenosis. Both NASCET and ECST demonstrated the benefit of CEA in neurologically symptomatic patients with carotid stenosis that reduced diameter of greater than 50%.[28,37,168] NASCET demonstrated an absolute risk reduction of stroke of 17%

at 2 years (24% in medical arm vs 7% in surgical arm) for patients with a greater than 70% carotid stenosis. The ECST demonstrated a similar decrease in stroke risk in symptomatic patients after 3 years. The stroke risk in the medical arm was 26.5%, compared with 14.9% in the surgical group, an absolute reduction of 11.6%.[37] In both studies, the risk of stroke in the medical arm, and therefore the benefit of CEA, increased with degree of stenosis. The results of these trials established CEA as the treatment of choice for patients with severe carotid stenosis, and they are widely accepted throughout the medical community. At 5 years, the benefit of CEA among patients with stenosis of 50% to 69% was more moderate, but still statistically significantda 15.7% stroke rate after CEA vs 22.2% with medical therapy.[168] Stenoses of less than 50% do not benefit from CEA.

Transfemoral CAS in symptomatic stenosis. A number of trials examined transfemoral CAS in management of neurologically symptomatic patients with a greater than 50% diameter stenosis. Several early trials in high surgical risk patients such as Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE), demonstrated overall equivalence of transfemoral CAS and CEA in management of carotid stenosis, although the number of symptomatic patients was too small for subgroup analysis.[201] Two large randomized European trials, Endarterectomy vs Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S)[7] and Stent Protected Angioplasty vs CEA (SPACE1),[8] examined CAS vs CEA in neurologically symptomatic patients. EVA-3S showed a statistically inferior 30-day outcome for transfemoral CAS compared with CEA (stroke death, 9.5% vs 3.8%) in these patients. However, this study was criticized because of the relatively low level of operator experience (minimum of 12 transfemoral CAS cases or 35 supra-aortic trunk cases, of which 5 had to be transfemoral CAS procedures) required in the CAS arm. The Stent-Supported Percutaneous Angioplasty of the Carotid Artery vs Endarterectomy (SPACE) trial was designed to test "equivalence" between CEA and CAS in patients with neurologic symptoms but the trial was stopped after recruitment of 1200 patients owing to the futility of proving equivalence between the two treatments. The 30-day risk of death or ipsilateral stroke 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 transfemoral CAS compared with CEA (P< .09).

More recently, two large, randomized trials have been completed. The International Carotid Stenting Study Trial (ICST)[6] enrolled 1713 patients and demonstrated significantly increased periprocedural stroke risk for transfemoral CAS (7.7%) compared with CEA (4.1%) in neurologically symptomatic patients (P< .002). The risk of any stroke or death less than 30 days after treatment in the stenting group was more than twice that 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 transfemoral CAS (8.5%; P< .006). These findings are similar to those of the symptomatic patients in the CREST Trial. Periprocedural risk of stroke and death was significantly higher in transfemoral CAS vs CEA among symptomatic patients (6.0% 6 0.9% vs 3.2% 6 0.7%; HR, 1.89; 95% CI, 1.11-3.21; P< .02). The risk of MI was lower after transfemoral CAS vs CEA among symptomatic patients (1.0% 6 0.4% vs 2.3% 6 0.6%; HR, 0.45; 95% CI, 0.18-1.11; P< .08); however, these differences were not significant. If CREST patients older than 80 years are removed to allow CREST to be compared with other trials, results from the symptomatic cohort demonstrated that 30-day stroke and death risk was significantly lower among the patients undergoing CEA (2.6%þ0.7% for CEA and 5.6%þ1.0% for transfemoral CAS; P ¼ .006). A 2020 Cochrane Review showed that in symptomatic patients, transfemoral CAS was associated with higher risk of periprocedural death or stroke than CEA, (OR, 1.70; 95% CI, 1.31-2.19; P< .0001, I^2 ¼ 5%; 10 trials; 5396 participants; high certainty evidence).[202]

Long-term outcomes of transfemoral CAS vs CEA in symptomatic patients have been examined in a preplanned pooled analysis of data from the EVA-3S, SPACE, International Carotid Stenting Study (ICSS), and CREST Trials. Together, these trials randomized 4754 symptomatic patients with a greater than 50% ICA stenosis with median follow-up of 2.0 to 6.9 years. Risk of stroke or death within 120 days of the index procedure was 5.5% for CEA and 8.7% for transfemoral CAS (risk difference, 3.2%; 95% CI, 1.7-4.7). Beyond the periprocedural period of 120 days, there was no difference in annual risk of late ipsilateral stroke (annual event rate of 0.60% for CEA vs 0.64% for transfemoral CAS),[9] lending support to the conclusion that both procedures have similar midterm outcomes. However, long-term outcomes continue to favor CEA because of its lower periprocedural stroke and death rate. In addition, 10-year outcomes comparing CEA and transfemoral CAS have been published. In symptomatic patients from CREST, a combined end point of periprocedural stroke and death and 10-year ipsilateral stroke was 7.9% (95% CI, 5.9-10.0) in patients treated with CEA vs 11% (95% CI, 8.5-13.9; HR, 1.37; 95% CI, 1.01-1.86) in patients treated with CAS (P¼ .04).[203] A 2020 Cochrane Review also showed the combination end point of periprocedural death or stroke or ipsilateral stroke during follow-up was significantly lower with CEA.[202]

Despite the evidence, there is concern regarding whether data from randomized controlled trials of CAS can be extrapolated to real-world experience. In general, physicians who performed carotid stenting in these trials were highly experienced and their outcomes were rigorously assessed before they were allowed to enroll patients.[204] By contrast, in a review of physicians treating Medicare beneficiaries with CAS, fewer than 10% would meet criteria to participate in CREST based on low volume or high complication rate.[205] It is unclear if similar results will be obtained for CAS among clinicians who are less experienced or among patients who would not meet inclusion criteria for the clinical trial. Nolan et al[206] reviewed data from the Northern New England Vascular Registry and showed a higher risk of stroke and death in symptomatic patients treated with CAS compared with CEA (5.1% CAS vs 1.6% CEA; P¼ .001). Last, in a study by Hicks et al[200] looking

at almost 52,000 carotid procedures in the VQI, symptomatic high risk patients defined using Medicare criteria) had a 2.3% risk of stroke and death following CEA vs 3.6% for CAS (P < .001). The difference in stroke was two-fold higher for CAS in the general population as well as in propensity-matched patient cohorts (HR, 2.23; 95% CI,
1.58-3.15; P< .001).

Transcarotid artery revascularization. Early data suggest that TCAR may have a role in treatment of patients with symptomatic carotid occlusive disease. Numerous studies have shown that TCAR has a similar rate of diffusion-weighted infarcts (DWI) on postprocedure MRI compared with CEA while transfemoral CAS is associated with a two-to three-fold higher risk of DWI. Up to 50% of DWI and strokes that occur after transfemoral CAS are contralateral, suggesting arch pathology as the etiology. In two recently completed trials, Safety and Efficacy Study for Reverse Flow Used during CAS Procedure (ROADSTER-1) and (ROADSTER-2), the risk of periprocedural stroke in symptomatic patients from the two trials combined was 0.6% while mortality risk was
0.6% for a combined risk of stroke and death of 1.2%.[177,178] A more recent study comparing TCAR and transfemoral CAS examined 1829 propensity scorematched patients from the VQI with symptomatic carotid disease. This study demonstrated that TCAR was associated with significantly lower risk of in-hospital stroke or death compared with transfemoral CAS (2.1% vs 4.2%; absolute difference, 2.02% [95% CI, 3.21% to 0.83%]; RR, 0.51 [95% CI, 0.35 to 0.75]; P< .001).[207] There was no difference in MI between the groups. Last, Malas et al[208] examined a more recent cohort of patient from the VQI Trans-carotid Revascularization Project. These investigators propensity score-matched 6384 pairs of patients who had undergone either TCAR or CEA. In this cohort there were 3333 symptomatic patients that were compared. There was no difference in in-hospital stroke and death between symptomatic patients undergoing TCAR vs CEA (2.2% vs 2.6%; P¼ .46) and TCAR was associated with a lower incidence of CNI and shorter hospital stay. The impact of developing a TCAR program on overall carotid revascularization outcomes was examined by Columbo et al.[209] These investigators compared the risk of MACE defined as stroke, death and MI in centers who performed only CEA vs those centers that performed both CEA and TCAR. At 1 year, the incidence of MACE was 10% lower at centers that performed both TCAR and CEA vs CEA alone (OR, 0.9; 95% CI, 0.810.99; P¼.04).[209] These studies seem to be promising and have been supported by a clinical competency statement from the SVS[210] and although it is important to remember that to date the vast majority of TCAR procedures have been performed in patients at high anatomic or medical risk for CEA the procedure appears promising and further data in low-risk symptomatic patients are awaited.

Asymptomatic with a greater than 70% stenosis.

CEAforasymptomaticlesions. Patients with asymptomatic lesions currently account for a majority of carotid interventions performed in the United States.[1] As discussed elsewhere in this article, randomized controlled trials such as ACAS and ACST that compared CEA with best medical therapy showed favorable results for CEA.[28,169] ACAS demonstrated superiority of CEA over antiplatelet therapy alone for asymptomatic patients with carotid stenosis of greater than 60%, and these investigators recommended CEA for patients aged less than 80 years as long as the expected combined stroke and mortality risk for the surgeon was not more than 3%. The long-term effectiveness of CEA in asymptomatic patients was confirmed by ACST I, as reported by Halliday et al[194] compared with patients randomized to the medical arm which primarily involved antithrombotic and antihypertensive therapy, patients aged less than 75 years in the CEA arm had significantly lower 10-year stroke risk (13.3% vs 17.9%).

Some authorities suggest that CEA should be considered in average surgical risk patients with 60% to 99% asymptomatic carotid stenosis only in the presence of one or more risk factors that increase risk of late ipsilateral stroke. Those factors include stenosis progression, silent infarction on CTA/MRI, plaque echolucency, intraplaque hemorrhage on MRI, large plaque area or spontaneous embolization using TCD.[10]

Transfemoral CAS in asymptomatic lesions. Many CAS studies have been in the form of “high-risk” registries.[185,211-216] In 2004, the SAPPHIRE trial, which included “high-risk” patients (70% of whom were asymptomatic) demonstrated that stenting with cerebral protection devices was not inferior to CEA.[201] The primary end point of the study was 30-day cumulative incidence of death/stroke/MI, which was 5.4% for asymptomatic patients who underwent CAS and 10.2% for CEA (P ¼.20). Critics of this study raised several important issues, including the criteria used to define high-risk patients for CEA, the failure to randomize more than 50% of eligible patients, the unexpectedly high incidence of postoperative strokedparticularly in asymptomatic patientsdand questions about reporting bias. Notably, MI was defined only by enzymatic elevation. 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.[217,218]

CREST and Asymptomatic Carotid Trial (ACT-1) are two recent multicenter randomized trials that enrolled significant numbers of individuals with asymptomatic carotid artery stenosis. CREST showed that although stroke risk with CAS was greater than that for CEA in asymptomatic patients, the difference was not statistically significant. The actual risk 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. Results for transfemoral CAS and CEA were both within the AHA recommended guidelines.[219] In addition, the primary composite end point of the study, which included any periprocedural stroke, death, MI, or postprocedural ipsilateral stroke, was similar in the two groups: 3.5% for transfemoral CAS and 3.6% for CEA (P¼ .96).

The recently completed ACT-1 Trial randomized 1453 patients 3:1 transfemoral CAS (1089) and CEA (364) in a noninferiority design.[220]

There was no difference in the composite primary end point of death, stroke and MI between the transfemoral CAS group (3.8% 6 0.59% vs CEA 3.4% 6 0.98% (2.27% confidence interval [CI], P¼ .01 noninferior). Stroke and death risk was 2.9% for transfemoral CAS and 1.7% for CEA (P¼ .33), and major stroke and death was identical in both groups at 0.6%. These results are considerably better than any other large study, including ACAS and ACST, for both procedures. CREST and ACT-1 results confirm that CEA and CAS can be performed safely in carefully selected asymptomatic patients.

Similar to patients with symptomatic carotid stenosis, concerns remain whether the latter data can be translated into "real-world" experience in asymptomatic patients. In a 2009 study of asymptomatic patients using VQI data, transfemoral CAS was associated with a significantly higher risk of major complications compared with CEA.[221] The 30-day outcome analysis of CAS and CEA in 2,818 patients revealed the combined risk of death, stroke, or MI for 1450 CAS patients was 4.6% vs 1.97% for 1368 CEA patients. However, the recent VQI report by Hicks et al showed transfemoral CAS was not associated with a significant difference in stroke and death when compared with CEA among low-risk, propensity-matched patients (HR, 1.49; 95% CI, 0.76-2.90; P¼ .24).[200]

Transcarotidarteryrevascularization. The 30-day incidence of stroke and death in 485 asymptomatic patients from the ROADSTER 1 and 2 trials was 1% and the 30-day incidence of any stroke was 0.6%. Although these early results are promising, further studies are needed to determine if these results are robust in larger populations.[177,178] A recent study of VQI data compared propensity score matched asymptomatic patients and showed no difference in stroke and death risk between TCAR and transfemoral CAS (1.0% vs 1.5%; absolute difference, 0.42% [95% CI, 1.30% to 0.47%]; RR, 0.71 [95% CI, 0.37 to1.39]; P¼ .32).[207] A more recent study propensity scored patients from the VQI that had undergone either TCAR or CEA were compared. Of this cohort 9435 were asymptomatic. There was no difference in stroke and death between CEA and TCAR (1.3% vs 1.4%; P¼.49), although TCAR was associated with a lower incidence of MI and CNI, as well as a shorter length of stay.[208]

Summary and recommendations

1. For neurologically symptomatic patients with stenosisless than 50% or asymptomatic patients with stenosis less than 60% diameter reduction, optimal medical therapy is indicated. There are no data to support transfemoral CAS, TCAR, or CEA in this patient group.

Table I. Revascularization techniques with high-risk criteria

Revascularization techniques	High-risk criteria (based on clinical judgement)
CEA	Neck irradiation Previous CEA Previous neck surgery Tracheal stoma Lesion above C2 Contralateral vocal cord injury Hostile neck owing to obesity, immobility, or kyphosis Medical high risk
TCAR	Heavily calcified carotid lesion Lesion within 5 cm of clavicle CCA diameter <6 mm Neck irradiation Tracheal stoma Hostile neck owing to obesity, immobility or kyphosis Medical high risk
TF-CAS	Age > 75 years old Heavily calcified carotid stenosis Complex bifurcation stenosis >15 mm length Tortuous ICA Tortuous CCA Type 3 or tortuous aortic arch Heavy atherosclerotic burden of arch

Table II. High-risk surgical risk for carotid endarterectomy (CEA) based on the Medicare National Coverage Decision (20.7) on PTA including carotid artery stenting (CAS)

Physiologic risks	Anatomic risks
Age $75	Prior head/neck surgery or irradiation
Congestive heart failure	Spinal immobility
Left ventricular ejection fraction #35%	Restenosis after CEA
Two diseased coronaries with $70% stenosis	Surgically inaccessible lesion
Unstable angina	Laryngeal palsy; laryngectomy; permanent contralateral CNI
MI within 6 weeks	Contralateral occlusion
Abnormal stress test	Severe tandem lesions
Need for open heart surgery	
Need for major surgery (including vascular)	
Uncontrolled diabetes	
Severe pulmonary disease	

CNI, Cranial nerve injury; MI, myocardial infarction.

CCA, Common carotid artery; CEA, carotid endarterectomy; ICA, internal carotid artery; TCAR, transcervical carotid stent; TF-CAS, transfemoral carotid stent.

2. Neurologically asymptomatic patients with a 70% orgreater diameter stenosis should be considered for CEA, TCAR, or transfemoral CAS 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 3% or less. Perhaps future models to help estimate life expectancy based on calculating various physiologic comorbidities such as cardiac, pulmonary, renal, malignancy, will be available in the future. The determination for which technique to use should be based on the presence or absence of high risk criteria for CEA, TCAR, or transfemoral CAS (Table I).
3. CEA is preferred over transfemoral CAS in symptomatic patients with 50% or greater stenosis who are candidates for both procedures. TCAR is preferred over transfemoral CAS but not CEA in symptomatic patients with 50% or greater stenosis.
4. Transfemoral CAS is preferred over CEA in symptomatic patients with 50% or greater stenosis and tracheal stoma, situation where local tissues are scarred and fibrotic from prior ipsilateral surgery or external beam radiotherapy. CEA or TCAR may be preferable in situations where ipsilateral tissue planes remain relatively intact (Table II).
5. TCAR is preferred over CEA and transfemoral CAS insymptomatic patients with 50% or greater stenosis and lesion above C2 (Table II).
6. TCAR is preferred over CEA and transfemoral CAS inhigh surgical risk (both anatomically and physiologically).
7. CAS is preferred over CEA in symptomatic patients with 50% or greater stenosis and severe uncorrectable coronary artery disease, congestive heart failure, or chronic obstructive pulmonary disease. 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 (Table II).
8. Neurologically asymptomatic patients deemed highrisk for CEA, TCAR, and transfemoral CAS should be considered for primary medical management. Intervention can be considered in these patients only with evidence that perioperative morbidity and mortality is less than 3%. CAS should not be performed in these patients except as part of an ongoing clinical trial.
9. There are insufficient data to recommend transfemoral CAS as primary therapy for neurologically asymptomatic patients with 70% to 99% diameter stenosis. Data from CREST, ACT, and the VQI suggest that in properly selected asymptomatic patients, CAS may be 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 less than 3% to ensure benefit for the patient.

Table III. Local vs general anesthesia for carotid endarterectomy (CEA)

Study	Patient population/comparison	Outcome	Design
GALA Trial Collaborative Group, 2008[228]	patients (general) (local)	Primary outcome was proportion of patients with stroke/MI/death between randomization & 30 days after surgery. Composite end point was 4.8% (general) vs 4.5% (local).	RCT
Rerkasem et al, 2009[244] (Cochrane Database)	RCTs (812 procedures) Nonrandomized studies (24,181 procedures)	RCTs No evidence of reduction in operative strokes (2.7% local vs 2.7% general; P¼ .99) Nonrandomized studies: Local associated with significant reduction in: Risk of early 30-day perioperative stroke (38 studies) Stroke/death (27 studies) Death (42 studies) (27 studies) To be noted, methodologic quality of nonrandomized studies were felt to be questionable; concluded insufficient evidence from RCT to indicate superiority of local over general.	Systematic review of RCTs and nonrandomized studies
Vaniyapong et al, 2013[236] (Cochrane Database)	RCTs (4596 procedures)	No statistically difference in: 30-day stroke rate (3.2% local vs 3.5% general) 30-day stroke/death (3.6% local vs 4.2% general) Concluded stroke/death rates were similar	Systematic review of RCT
Aridi et al, 2018[238]	Retrospective analysis of VQI Database 2003-2017 (75,319 procures)	Compared real-world outcome of CEA under local vs general. No difference in perioperative death/ stroke. CEA with general was associated with: times the odds of acute CHF (OR, 3.92, 95% CI, 1.84-8.34; P< .001) times the odds of hemodynamic instability (OR, 1.54; 95% CI, 1.44-1.66; P< .001) Noted differences were clinically irrelevant, as overall risk of cardiac adverse events were low. Approach to choosing anesthesia should be based on patient risk factors, preference and team experience.	

CI, Confidence interval; MI, myocardial infarction; OR, odds ratio; RCT, randomized controlled trial; VQI, Vascular Quality Initiative.

CEA TECHNICAL CONSIDERATIONS

Local vs general anesthesia

An advantage of performing CEA on awake patients under local/regional anesthesia is the ability to perform an accurate neurologic assessment during the operation and in the immediate postoperative period. Local/ regional anesthesia also attenuates the hemodynamic swings both during induction of general anesthesia and upon awakening. It has been postulated that local anesthesia also has the benefit of increasing systemic blood pressure that may occur after carotid clamping,[222] helping to maintain cerebral perfusion. However, opponents of CEA under local anesthesia highlight that pain or anxiety during the procedure may increase stress, potentially resulting in increased risk of perioperative MI. However, this stress can be minimized by premedication and intraoperative sedation/analgesia. The patient's heightened stress level may also impact the performance of some surgeons. In addition, the ability to train fellows or residents in performing CEA may also be negatively impacted by use of local/regional anesthesia. This approach may also result in needle damage to important structures such as the vertebral artery during deep cervical plexus block, phrenic nerve block, or may result in intravascular injection with associated hematoma.[223] Therefore, many clinics use only superficial cervical plexus block for CEA.[224] It has also been suggested that general

anesthetics decrease the cerebral metabolic rate and may therefore have a neuroprotective effect in the presence of cerebral ischemia.[225]

Over the past several decades, a number of publications have shown conflicting results about anesthesia, some favoring general anesthesia, while others favor local anesthesia. Halm et al[226] conducted a retrospective analysis of 1972 patients undergoing CEA by 64 surgeons in six New York hospitals in 1997 and 1998. Death or stroke occurred in 2.3% in patients without carotid symptoms, 2.9% among those with carotid TIA, and 7.1% among patients with perioperative stroke. Two surgical techniques reduced the adjusted odds of death or stroke: Use of local anesthesia (OR, 0.3; 95% CI, 0.160.58) and patch closure (OR, 0.43; 95% CI, 0.24-0.76). Stoner et al[227] also reported outcome of 13,622 CEAs performed during a 3-year period at 123 Veteran's Administration and 13 private academic medical centers. The combined risk of stroke, death, or cardiac event was 4% and stroke/death risk was 3.4%. Regional anesthesia was used in 18% of cases with the following relative risk reductions: stroke 17%, death 24%, cardiac events 33%, and the composite outcome 31% (OR, 0.69; P ¼ .008). The authors concluded that the use of regional anesthesia significantly reduced perioperative complications, however did admit the low use of regional anesthesia may represent selection bias.

Results from randomized controlled trials, metaanalyses, and registries. One of the strongest Level 1 evidence sources on anesthesia is the General Anesthesia vs Local Anesthesia for Carotid Surgery (GALA) trial.[228] The two groups did not show any significant differences regarding primary outcome (stroke, MI, or death) (Table III), length of hospital stay, and quality of life. Additionally, there was no difference in the primary outcome in the subgroup analysis of age and baseline surgical risk. The primary outcome rate for patients over the age of 75 was 5.3% for general anesthesia vs 4.6% for local anesthesia (P¼ .741). This is in contrast with 4.5% for local anesthesia vs 4.6% for general anesthesia for patients younger than the age of 75 (P¼ .741). The primary outcome rate for patients with high surgical risk was 4.6% for local anesthesia vs 4.1% for general anesthesia, in contrast with 4.2% for local anesthesia vs 4.7% for general anesthesia in patients with low surgical risk (P ¼ .933). These results suggest that local anesthesia may be more effective than general anesthesia for patients with contralateral carotid occlusion. The primary outcome for stroke, MI, or death at 30 days was 5% for local anesthesia vs 10% for general anesthesia in patients with contralateral carotid occlusion (OR, 0.47; P¼.098) in contrast with 4.3% for general anesthesia and 4.5% for local anesthesia in patients without contralateral carotid occlusion.

A Cochrane Review of the several randomized trials[229-235] looking at anesthesia showed no evidence of decreased perioperative strokes (2.7% for local anesthesia vs 2.7% for general anesthesia; P¼ .99). Use of local anesthesia was also associated with a significant reduction in risk of 30-day perioperative local hemorrhage (OR, 0.3; 95% CI, 0.12-0.77; Table III).

A more recent Cochrane Review by Vaniyapong et al[236] reported results comparing local vs general anesthesia for CEA from 14 RCTs, concluding that risk of stroke or death within 30 days of surgery did not differ significantly between the two anesthetic techniques (Table III).

More recently, Hye et al[237] reported on anesthesia technique and risk of MI after CEA in the CREST trial. Between 2000 and 2008, 1151 patients underwent CEA (anesthetic type available for 1149 patients), and 1123 patients underwent CAS within 30 days of randomization in CREST. CEA patients were categorized by anesthetic type (regional anesthesia vs general anesthesia). The results showed that CREST patients undergoing CEA with regional anesthesia had a similar risk of periprocedural MI as those undergoing CAS, whereas the risk for CEA with general anesthesia was twice that of patients undergoing CAS.

Dakour Aridi et al[238] used VQI data for 2003 to 2017 to compare real-world outcomes of CEA under regional or local anesthesia vs general anesthesia. A retrospective analysis showed that compared with patients undergoing CEA with general anesthesia, the 6684 (9%) CEA cases of 75,319 that were were performed under local anesthesia/regional anesthesia were more likely to have a higher American Society of Anesthesiologists class (class 3-5, 94% vs 93%) and more likely to be older (median age, 72 years vs 71 years) (all P<.001). CEA with general anesthesia had higher crude rates of in-hospital cardiac events including arrhythmia (1.6% vs 1.2%; P < .001), hemodynamic instability (27% vs 20%; P < .001), MI (0.5% vs 0.2%; P¼.01), and acute congestive heart failure (0.5% vs 0.2%; P < .001) compared with CEA with local or regional anesthesia. However, there was no difference in perioperative death or stroke between the two groups. CEA with general anesthesia was associated with four times the odds of acute CHF (OR, 3.92; 95% CI, 1.84-8.34; P < .001), 1.5 times the odds of hemodynamic instability (OR, 1.54; 95% CI, 1.44-1.66; P < .001), and twice the odds of in-hospital MI (OR, 1.95; 95% CI, 1.06-3.59; P¼ .03). Patients who underwent CEA with general anesthesia had 1.8 times the odds of staying in the hospital for more than 1 day (OR, 1.80; 95% CI, 1.671.93; P < .001). These authors noted that differences were clinically irrelevant, because the overall risk of cardiac adverse events after CEA was low. Others felt that the approach to choosing anesthesia for CEA should be based on patient risk factors and preference, and by the team's experience.[239-241]

Local and regional anesthesia and the use of antiplatelet agents. Because many patients who undergo CEA take aspirin antiplatelet monotherapy and some also take dual antiplatelet therapy, there is some concern about hematoma formation. In a systemic review of 10,081 patients in 69 studies, the combined superficial and deep cervical plexus blockade was associated with a significantly higher risk of major complications (OR, 2.13; P¼ .006), when compared with superficial/intermediate blockade.[224] Most of the major complications reported were inadvertent intravascular injection and respiratory distress or failure secondary to phrenic nerve and/or recurrent laryngeal nerve paralysis. In most scenarios, the general guidelines recommend cessation of antiplatelet therapy, specifically clopidogrel, whenever possible.[242]

Presently, there are no published guidelines regarding whether it is safe to perform deep cervical plexus blockade in CEA patients who are taking dual antiplatelet therapy.[243] Therefore, because many

symptomatic patients will undergo CEA while on dual antiplatelet therapy, surgeons and anesthesiologists who perform this procedure must consider the risks and benefits of doing surgery under regional/local anesthesia while the patient is on perioperative antiplatelet therapy. It is generally not recommended to stop antiplatelet therapy and/or delay CEA for the usual recommendation of 7 days, as this may increase the risk of early recurrent embolic stroke.

Summary and recommendations. The choice of anesthesia local/regional vs general anesthesia is equivalent and should be left to surgeon's/anesthesiologist's preference because both techniques have similar outcomes and should be based on availability of expertise for effective block (Table III).

Decision for longitudinal versus transverse incision for CEA

Although the traditional approach to the carotid bifurcation is through a longitudinal incision just medial to the anterior border of the sternocleidomastoid muscle, a transverse incision can be performed. However, a key concern with a transverse incision is the cephalad extent of the atherosclerotic disease. As shown by Ascher et al,[245] if one were to undertake the transverse incision, the bifurcation should be analyzed by duplex ultrasound examination not only before surgery, but also at the time of surgery. This allows the surgeon to identify where the bifurcation is, as well as to confirm the extent of disease.[245] Other investigators have demonstrated that transverse incisions give better cosmetic results with fewer cranial nerve injuries.[246] However, Marcucci et al[247] reported that it is more difficult to shunt using the transverse incision, and saw no difference in the presence of cranial nerve injuries.

Summary and recommendations. In the absence of Level 1 data, a transverse crease incision may give the best cosmetic results if there is a focal stenosis with a relatively low bifurcation.

Anticoagulation and protamine reversal

In the last decade, numerous reports have documented increased use of anticoagulation reversal with protamine sulfate after CEA. The Vascular Study Group of Northern New England first noted safe use of protamine to reduce bleeding complication without increased stroke risk.[248] In 2013, the same group noted an increase in anticoagulation reversal among their surgeon cohort with decreased incidence of bleeding and no difference with respect to MI or stroke risk.[249] A meta-analysis by Kakisis et al[250] reported a 64% risk reduction in wound hematoma without an increase in stroke risk with anticoagulation reversal. These results were corroborated by a contemporaneous metaanalysis by Newhall et al,[251] showing similar favorable findings for use of protamine. Although there is no new Level 1 evidence in this area, the abundance of literature supports reasonable use of anticoagulation reversal at the end of CEA without an increase in perioperative stroke risk.

Summary and recommendations. In patients undergoing CEA, we suggest use of protamine sulfate (depending on heparin dose) to reduce risk of postoperative bleeding without an increase in other perioperative risk.

Intraoperative cerebral monitoring

The purpose of intraoperative cerebral monitoring is to assess the need for temporary arterial shunting during the ischemic portion of the procedure while the carotid artery flow is interrupted and to attempt to predict those patients who are most likely to suffer an ischemic postoperative event. Options for cerebral perfusion assessment include awake testing with local/regional anesthesia, somatosensory evoked potentials, measurement of stump pressures, TCD and infrared spectroscopy. Although numerous reports advocate for the overall effectiveness of each technique,[59] a comprehensive review in 2011 by AbuRahma et al,[252] and review of the recent literature has not identified a predominant technique to predict adequate cerebral perfusion.[253-255]

Summary and recommendations. We suggest judicious use of cerebral monitoring based on practitioner expertise and institutional standards, particularly if no routine shunting is used.

Shunting: routine versus selective

Based on the current literature, the use of shunting during CEA has not evolved. For many years, use of arterial shunts was considered in three broad categories: Always, never, or selective use with multiple alternatives available to provide temporary flow during periods of carotid clamping. These were mainly based on the preference and training of the operating surgeon. AbuRahma et al[252] conducted a comprehensive review of available approaches to cerebral monitoring and intraoperative shunting methods and found no discernible advantage with any technique. Since then, large series have also failed to report definitive differences in outcomes with any particular strategy.[255-258] In the most recent reported

Table IV. Patch closure vs primary closure for carotid endarterectomy (CEA) (randomized trials)

Study	Patient population/ comparison: No. patch/primary comparison	Early outcome: Perioperative stroke/death (%), patch/primary	Early outcome: OR (95% CI)	Late outcome: $50% restenosis rate (%), patch/ primary	Late outcome: OR (95% CI)	Late outcome: Follow-up, mo	Design
De Vleeschauwer et al, 1987[272]	90/84	0/0	———[a]	1.1/10.7	0.1 (0.0-0.8)	12	RCT
Eikelboom et al, 1988[273]	66/60	4.5/6.7	0.67 (0.15-3.06)	11.9/27.4	0.37 (0.16-0.89)	60	RCT
Lord et al, 1989[278]	90/50	1.1/6.0[b]	0.2 (0.0-1.7)	———[a]	———[a]	Hospital discharge	RCT
Ranaboldo et al, 1993[283]	96/91	3.2/7.7	0.41 (0.11-1.45)	5.5/16.3	0.33 (0.14-0.77)	12	RCT
Myers et al, 1994[280]	46/48	0/2.1	0.14 (0.00-7.12)	3.2/3.1	1.03 (0.14-7.51)	54	RCT
Katz et al, 1994[276]	43/44	2.3/4.5	0.52 (0.05-5.11)	0/5.9	0.14 (0.01-1.33)	29	RCT
AbuRahma et al, 1996[261]	264/135	2.3/6.7	0.3 (0.10-0.8 ;)	5.3/33.3	0.11 (0.06-0.19)	30	RCT
AbuRahma et al, 1999[264]	74/74	0/4.0	———[a]	7/45	0.09 (0.03-0.25)	29	RCT
Malas et al, 2015[290]	753/329 CEA Arm of CREST	1.2/4.0	0.35 (0.15-0.82)	3.1/10.7[c]	0.27 (0.15-0.48)	24	RCT

CI, Confidence interval; OR, odds ratio; RCT, randomized controlled trial.
[a] Not available or not applicable. [b] Only 30-day risk of ipsilateral stroke only.
[c] For $70%.

series, Wiske et al[257] reviewed 28,457 CEAs in the VQI from 2012 to 2015 and found no difference in inhospital death or stroke among the different types of cerebral monitoring and shunt strategies. However, the authors did report shorter length of stay among patients undergoing awake assessment with local anesthesia.[257]

Summary and recommendations. Owing to the paucity of suitable data on when to shunt or best shunting methods during CEA, specific recommendations cannot be provided. The committee suggests consideration of arterial shunting during CEA based on practitioner expertise and institutional standards.

Carotid closure: primary versus patching

The type of closure after CEA, whether primary closure vs patching remains somewhat controversial.[259-285] However, most authorities agree that in a small carotid artery (#4 mm), particularly in women, and in the presence of technical difficulties at the ICA end of the arteriotomy, patching may decrease the risk of future restenosis. It has been suggested that a flow characteristic of patched arteries may be superior to those of primary closure for minimizing early perioperative carotid thrombosis.[283,286,287] Other investigators have attributed this improvement to widening the artery with a corresponding reduction of intimal hyperplasia.[288] Therefore, many suggest that CEA with patch angioplasty decreases the chance of technical errors. It has been shown to be more effective than primary closure in multiple clinical trials in decreasing the risk of perioperative carotid thrombosis, perioperative stroke and late restenosis.[261-264,267,268,271-273,276,278,289] Others believe that inclusion of a patch prolongs the operative, shunt and clamping time and makes the procedure more technically demanding and that it may also be unnecessary in some patients.[270]

Results from randomized trials. Several randomized controlled trials published over the past two decades compared CEA with primary closure vs patch angioplasty.[261,263,264,266,267,271-273,276,278,280,283] As noted in Table IV, most studies showed that patch closure was superior to primary closure in all perioperative parameters including risk of perioperative stroke, stroke/death, and restenosis.

In contrast, Al-Rawi et al[266] reported results supporting primary (direct) closure. In this study, the 30-day perioperative stroke risk was similar for microscopic patch angioplasty (3.9%) and direct arteriotomy closure (2.9%). In

Table V. Meta-analysis of primary closure vs carotid endarterectomy (CEA) with patching

Systemic/Meta-analysis	Patient Population/Comparison	Outcome	Design

Bond et al, 2004[269,292,a] (Cochrane review)	7 RCTs 1281 CEAs (1193 patients)	Patch angioplasty associated with reduction in: Stroke/death (2.5% vs 6.1%;Any stroke (1.6% v 4.5%;Arterial occlusion (0.5% vs 3.6%;Ipsilateral stroke (1.6% vs 4.8%;P¼P.004)¼P.07)P¼¼.001).0001) Long-term follow-up reduction in: Late post-CEA stenosis (4.8% vs 18.6%;Ipsilateral stroke (1.6% vs 4.8%;Stroke/death (14.6% vs 24%;Any stroke (1.9% vs 5.9%; P¼P.0009)¼P.004)¼ .001)P< .0001)	Systemic analysis of RCTs
Rerkasem et al, 2011[293]	10 RCTs 2157 CEAs (1967 patients)	Routine patching associated with reduction in: Ipsilateral stroke (1.5% vs 4.5%; P¼ .001) Carotid thrombosis (0.5% vs 3.1%; P< .0011) Return to operating room (3.1% vs 1.1%; P¼ .01) Long-term outcome reduction in: Ipsilateral stroke (1.6% vs 4.8%; P¼ .001) Any stroke (1.4% vs 4.6%; P¼ .002) Rate of restenosis (4.3% vs 13.8%; P< .01)	Systemic analysis of RCTs
Cao et al, 2001[294]	5 RCTs 2,590 CEAs (2,465 patients)	ECEA vs CCEA: Perioperative stroke/death rate of 2.1% (1.7% vs 2.6%) No significant differences in rate of early carotid thrombosis, MI and local complications: Neck hematoma (4.2% vs 5.5%) CNI (3.8% vs 5.6%) No significant difference in restenosis at later follow-up (1-69 months) or stroke rate (2.0% vs 2.4%)	RCS
Schneider et al, 2015[295]	2365 ECEAs 17155 CCEAs	ECEA vs CCEA: Perioperative ipsilateral neuro events (1.3% vs 1.2%; P¼ .86) Any ipsilateral stroke (0.8% vs 0.9%; P¼ .84) Return to the operating room for bleeding (1.4% vs 0.8%; P¼ .002) 1-year freedom from recurrent stenosis >50% (89% vs 94%; P< .001) 1-year freedom from reoperation (99.5% vs 99.6%; P¼ .67)	VQI

Paraskevas et al, 2018[296]	25 studies (20 Observational Studies, 5 RCTs) 49,500 CEAs (33,251 CCEAs/16,249 ECEAs)	RCT Data CCEA, ECEA did not confer significant reductions in 30 day perioperative stroke, death, stroke/death, stroke/death/MI or neck hematoma ECEA was associated with reduced late restenosis (OR, 0.40; P¼ .001) OS Data ECEA (compared with CCEA) associated with significant reduction in: 30-day perioperative stroke (OR, 0.58; P<.0001) Death (OR, 0.46; P< .0001) Stroke/death (OR, 0.52; P< .0001) Stroke/death/MI (OR, 0.50; P< .0001) Late restenosis (OR, 0.49; P¼ .032) RCT and OS Data Combined ECEA (compared with CCEA) associated with significant reduction in: 30-day death (OR, 0.55; P< .0001) Stroke (OR, 0.63; P¼ .004) Stroke/death (OR, 0.58; P< .0001) Late restenosis (OR, 0.45; P¼ .004) ECEA vs patched CCEA: there were no differences between the two procedures, except for neck hematoma, where ECEA was better than patched CCEA	RCS and observation studies

Table V. Continued.

Systemic/Meta-analysis	Patient Population/Comparison	Outcome	Design
Huizing et al, 2019[297]	29 studies (20 Observational Studies, 9 RCTs) 13,219 CEAs	PRC group had higher overall 30-day stroke risk (OR, 1.9; 95% CI, 1.2-2.9) Difference was not statistically significant anymore, after exclusion of nonrandomized studies (OR, 1.8; 95% CI, 0.8-3.9) Restenosis rate was higher after PRC (OR, 2.2; 95% CI, 1.4-3.4) Concluded that compared with PRC, perioperative stroke rate was lower after patch closure Restenosis rate was higher after PRC, although the clinical significance of this finding remained unclear in terms of long-term stroke prevention To be noted, many of these primary closures were selected in relatively larger arteries	RCS and observation studies

CCEA, Conventional carotid endarterectomy; CI, confidence interval; CNI, cranial nerve injury; ECEA, eversion carotid endarterectomy; MI, myocardial infarction; OR, odds ratio; OS, overall survival; PRC, primary closure; RCT, randomized controlled trial; VQI, Vascular Quality Initiative.
[a] This is meta-analysis of several randomized trials.

CREST, patching was also associated with a significant reduction in 30-day risk of perioperative stroke (1.2% vs 4% for no patching; P¼ .02), reduction in perioperative stroke and death (1.2% vs 4%; P¼ .02).[290] At 4 years, patching was associated with a significant reduction in late stroke (3.5% vs 6.6% for no patching; P¼ .047), and stroke and death (3.5% vs 6.6%; P¼ .047). Restenosis risk was also significantly higher at 2 years in patients with no patching (10.7% vs 3.1% with patching) (Table IV). Recently, Edenfield et al[291] reported on the long-term impact of the Vascular Study Group of New England carotid patch quality initiative (14,636 CEA), showing that patch use increased from 71% to 91% (P< .001) between 2003 and 2014. The rate of return to the operating room for bleeding (P< .001), 1-year restenosis or occlusion (P< .001), and 1-year stroke or TIA (P< .003) were statistically lower with patch closure. High-volume surgeons increased patch use from 50% to 90%, and decreased their 1-year stroke or TIA risk from 4.9% to 1.9% (P < .001) and restenosis risk from 9.0% to 1.2%. The VSGNE carotid patch quality initiative successfully increased CEA patch closure rates.

Meta-analysis of primary closure vs CEA with patching. A meta-analysis of randomized controlled trials showed patching was superior to primary closure in lowering risk of perioperative stroke, perioperative stroke and death, late restenosis[292,298,299] (Table V).

Role of selective patching. Selective patching has been proposed for certain patients such as those with tortuous or exceptionally small carotid artery. Although there is no Level 1 evidence supporting

selective patching vs primary closure or routine patching. Golledge et al[300] reported data for patients with selective patching of carotid arteries that were less than 5.5 to 6.0 mm. They found no significant difference in stroke or restenosis and advocated selective patching of carotid arteries. Cikrit et al[301] reported similar results, but patching was selectively applied to small arteries.

Recently, Maertens et al[302] reported complication rates after CEA with selective patch angioplasty and primary closure. Primary closure was performed when the carotid artery had a diameter of greater than 5 mm or there was a high carotid bifurcation, and when the contralateral carotid artery was occluded. The study concluded that primary closure was equivalent to patch angioplasty when used in selected patients.

Avgerinos et al[303] compared perioperative and longterm outcomes of different CEA closure techniques in a large single-center retrospective study (1737 CEA). Onehalf of the patients had patch closure, with the rest evenly distributed between eversion closure and primary longitudinal arteriotomy closure. Although more men had primary closure, other demographic characteristics and baseline symptoms were similar among groups, and risk of stroke and death were also similar.

Patch material during CEA. CEA patch material is also controversial with supporters for both vein patches (saphenous or neck veins) and synthetic patches (polytetrafluoroethylene [PTFE], Dacron) or pericardial patches. Data from randomized controlled trials suggest that the type of patch, whether vein or prosthetics, has no effect on short or long-term outcomes.[269,271,281,304] Bond et al[304] reported from the Cochrane Database on several randomized clinical trials,[259,260,263,274,278,281,282,305,306] but found insufficient data to enable a definitive conclusion (Table VI) about optimal patch material because of the small number of adverse events. In the early period, carotid patching was performed using conventional Dacron or PTFE patches; however, a main criticism of the conventional PTFE patch was a prolonged hemostasis time. Thus, a modified PTFE patch was introduced (ACUSEAL, W. L. Gore & Associates, Flagstaff, Ariz), which claims to have better hemostatic properties. Similarly, a new ultrathin Dacron graft patch was introduced to minimize thrombosis (Finesse; Boston Scientific, Natick, Mass). AbuRahma et al[259,260] reported the results of a randomized trial comparing conventional PTFE and conventional collagen-impregnated Hemashield in CEA. Perioperative stroke risk was 0% for PTFE vs 7% for Dacron graft (P¼ .02). There were five cases of perioperative carotid thrombosis in the Dacron group vs none in the PTFE group, and restenosis risk was also higher in patients with Dacron graft (P# .001). However, PTFE had longer intraoperative needle hole bleeding time. Subsequently, AbuRahma et al[265] reported the results of randomized trial of 200 CEA patients, 100 ACUSEAL vs 100 Finesse Dacron patching, in which the perioperative stroke risk (2%) and stroke-free survival rate were comparable for both patches. However, freedom from 70% or greater restenosis at 1, 2, and 3 years for ACUSEAL was 98%, 96%, and 89% vs 92%, 85%, and 79%, respectively, for the Finesse patch (P¼ .04).

Satisfactory outcomes were also reported using pericardial patching after CEA by Biasi et al.[307] Stone et al[308] reported results of prospective randomized trial of ACUSEAL vs Vascu-Guard patching in 200 CEA and they concluded that there was no significant differences in perioperative/late neurologic events and late restenosis in the two groups.

Oldenburg et al[309] reported on durability of CEA with a bovine pericardial patch in a retrospective analysis of 874 consecutive patients who underwent CEA at the Mayo Clinic in Florida. A bovine pericardial patch was used in 680 patients (group I) and other CEA techniques were used in 194 patients (group II) (standard without patch, 78; standard with vein patch, 16; standard with Dacron, 74; and other techniques: bypasses, 26). There were no significant differences in 30-day mortality or morbidity between the 2 groups, except that group I had a lower 30-day stroke risk (0.1%) than group II (1.5%; P¼ .03). Ten-year freedom from stroke/TIA and freedom from restenosis was also similar between groups. The authors concluded that CEA with bovine pericardium angioplasty had excellent early and late outcomes with minimal morbidity and mortality.

More recently, Texakalidis et al[310] reported the results of a meta-analysis of 18 randomized trials comparing bovine pericardium and other patch materials for CEA, noting similar findings when comparing synthetic patches vs bovine pericardium. As noted in Table VI, the outcome for various patches in CEA were also somewhat similar.

Carotid eversion: eversion CEA versus traditional endarterectomy

Eversion CEA (ECEA) is a technique that can be used for most carotid bifurcation disease. It may be best indicated in patients with short bifurcation lesions, those with elongated ICAs (coils and kinks) and in cases with high bifurcations. The most commonly-accepted technique is that the ICA is transected while removing the bulk of the plaque from the CCA as the ICA is transected. This is followed by everting the distal media or the external elastic lamina and the adventitia around the core of atherosclerotic plaque until the end point is reached. Visualization of the end point is mandatory and in about 25% of cases, the ICA can be shortened as it is reanastomosed to the CCA.[294,311-318]

Multiple studies have documented the numerous advantages of this technique. These include no risk of prosthetic infection, less operative time and cerebral ischemic clamp time than patched CEA, preservation of the anatomic and hemodynamic geometry of the ICA/CCA, and possibly a decreased risk of restenosis.[319] Although early studies reported decreased restenosis risk, in meta-analyses it has been shown to be equivalent to traditional patch angioplasty, and both patched and eversion endarterectomies are superior to primary arterial closure. Patients with small internal carotid arteries, such as women, may benefit from eversion or patched endarterectomy.[320] Disadvantages of this approach are that it may be difficult to evaluate the end point in extensive and long ICA disease. If shunting in ECEA is necessary, shunts are usually inserted after the endarterectomy is

Table VI. Comparing various patch closures after carotid endarterectomy (CEA) (randomized trials)

Study	Comparison	Early outcome		Late outcome			
	No.	Perioperative stroke/death (%)	OR (95% CI)	$50% restenosis/occlusion rate (%) at 1 year		OR (95% CI)	
Author/Year/Ref	Dacron/vein patch	Dacron/vein patch	Dacron/vein patch	Dacron/vein patch		Dacron/vein patch	Design
Katz et al, 1996[306]	107/100	2.8/1.0	2.9 (0.3->10)	———[a]		———[a]	RCT
Hayes et al, 2001[274]	135/136	2.2/2.2	1.0 (0.2-5.1)	———[a]		———[a]	RCT
O'Hara et al, 2002[282]	94/101	3.2/3.9	0.8 (0.2-3.7)	6.3/4.3		1.0 (0.3-3.1)	RCT
Naylor et al, 2004[281]	136/137	2.2/3.7	0.6 (0.14-2.54)	12.4/7.2		1.8 (0.8-4.1)	RCT
		ePTFE/vein patch	ePTFE/vein patch	ePTFE/vein patch			
Lord et al, 1989[278]		47/43	2.1/0	———[a]	———[a]	———[a]	RCT
Gonzalez-Fajardo et al, 1994[305]		39/35	5.1/0	199 (0.0->10)	4/0	19.7 (0.0->50)	RCT
AbuRahma et al, 1998[263]		134/130	2.2/2.3	1.0 (0.2-4.9)	2.2/8.5	0.2 (0.1-0.9)	RCT
		Dacron/ePTFE patch	Dacron/ePTFE patch	Dacron/ePTFE patch			
AbuRahma et al, 2002[260,b]		100/100	7/0	———[a]	12/2	6.68 (1.46-30.69)	RCT
AbuRahma et al, 2008[265,c]		100/100	2/2	1.0 (0.14-7.24)	4/0	———[a]	RCT
		ACUSEAL (PTFE)/Vascu-Guard patch					
Stone et al, 2014[308]		100/100	3/1[d]	———[a]	0/2[e]	———[a]	RCT
Systemic/meta-analysis		Patch material during CEA					
Bond et al, 2004[304,c] (Cochrane review)		1280 patients 7 RCTs	No obvious differences in perioperative stroke/death rate using synthetic or vein patch No differences in long-term follow-up Risk of major arterial complications (patch infection/rupture) <1% on vein and synthetic patches 3 of 348 (0.9%) had vein patch blowout, 1 fatal 2 of 359 (0.6%) had synthetic patch rupture, 1 fatal				
Texakalidis et al, 2018[310]		3,234 patients 18 studies	30 day stroke, MI, wound infection, death, cranial nerve palsy, carotid artery thrombosis and death, long-term stroke and restenosis were similar between venous vs synthetic patch No differences in 30-day stroke, death, TIA, carotid artery thrombosis and long-term restenosis were detected between Dacron and synthetic polytetrafluoroethylene patch				

CI, Confidence interval; ePTFE, expanded polytetrafluoroethylene; MI, myocardial infarction; OR, odds ratio; RCT, randomized controlled trial; TIA, transient ischemic attack.
[a] Not available or not applicable. [b] Conventional PTFE vs collagen-impregnated Dacron patch (Hemashield).
[c] ACUSEAL vs Finesse (Ultrathin Dacron) (PTFE). [d] Transient ischemic attack/stroke. [e] Restenosis of $70%.

performed. This technique can be very useful in patients who have carotid kinks or coils by shortening the ICA.

Several randomized trials compared conventional CEA (CCEA) with eversion,[311-317] and all provided Level 1 evidence confirming the equivalence of ECEA and CCEA with patching in regard to perioperative results. The largest Level 1 study was a multicenter randomized trial comparing CCEA and eversion came from the EVERsion CEA vs Standard Trial (EVEREST) (1353 patients).[314,315] Risk of 30-day perioperative major stroke/death was similar for both groups at 1.3%. The risk of 30-day all stroke was also similar: 1.9% for CCEA vs 2.2% for ECEA (P ¼ .80). At 33 months, carotid restenosis rate was noted in 2.8% with eversion, 7.9% for primary closure and 1.5% for CEA with patching. The cumulative, 4-year postcarotid stenosis was lower in the ECEA comparted to primary closure: 3.6% vs 9.2% (P¼ .01). However, the difference in postCEA stenosis was comparable when eversion was compared with patching (2.8% for eversion vs 1.5% for patching). There was no significant difference in cumulative risk of ipsilateral stroke (2.2% for standard vs 3.9% for eversion; P¼ .2) or death (13.1% vs 12.7%). Of 18 variables that were analyzed for their effect on risk of post-CEA stenosis, ECEA (HR, 0.3; P¼ .0004) and patch CEA (HR, 0.2; P¼ .002) were negative predictors (protective) of postCEA stenosis. Also, in the CREST trial, patients undergoing eversion endarterectomy had lower risk of cranial nerve injuries than those with patched CEA.

Observational studies also show somewhat similar results. Shah et al[321] reported data on one of the largest

samples of eversion endarterectomy in which 1855 patients underwent 2244 CEAs using the eversion technique. In this study, 410 patients had 474 CEAs by the standard technique. Operative mortality risk was 1% on the eversion group vs 2.2% in the standard group and incidence of perioperative stroke was 2.3% in standard CEA vs 0.8% for ECEA. Risk of 60% or greater post-CEA stenosis was 0.3% for ECEA vs 1.1% for standard CEA.

Schneider et al[295] compared results with ECEA (2365) vs

CCEA (17,155) using data from the VQI and the MidAmerica Vascular Study Group. compared with eversion, CCEA was more often performed with general anesthesia (92% vs 80%; P< .001) and with a shunt (59% vs 24%; P < .001). Perioperative ipsilateral neuro events (ECEA, 1.3% vs CCEA, 1.2%; P¼ .86) and any ipsilateral stroke (ECEA, 0.8% vs CCEA, 0.9%; P¼ .84) were similar in the two groups. ECEA tended to take less time (median 99 minutes vs 114 minutes; P < .001). However, ECEA was more like to require a return to the operating room for bleeding (1.4% vs 0.8%; P¼.002). Estimated survival and freedom from stroke at 1 year were similar, but the 1-year freedom from recurrent stenosis of greater than 50% was lower for ECEA (89% vs 94%; P < .001).

The authors concluded that ECEA and CCEA appear to yield similar outcomes.

Recently, Deser et al[322] conducted a study to determine whether there is a difference in postoperative blood pressure changes, stroke risk and postoperative complications after CCEA and ECEA. Mean operative and cross-clamping time were shorter for ECEA (72 6 14.3 minutes vs 115 6 17.4 minutes; P< .001) and (22 6 7.7 vs 34 6 6.3; P< .001), respectively. No significant difference was noted between the groups in incidence of perioperative stroke (P¼ .501) or postoperative blood pressure difference at the 6th hour or 24th hour after surgery.

Meta-analysis of standard CEA vs ECEA. A Cochrane Review[316] of five randomized trials[311-315,317] of 2465 patients (2590 arteries) also provided Level 1 evidence. In this review (except for the EVEREST trial in which where the ECEA was compared with both patch angioplasty and primary closure), only CEA with patch angioplasty was considered for comparison to ECEA. Results showed an overall risk of any perioperative stroke/death of 2.1% (1.7% for ECEA vs 2.6% for CCEA) with no significant difference between techniques. Nor were there significant differences risk of early carotid thrombosis, MI, and local complications (neck hematoma 4.2% for eversion vs 5.5% for CCEA; CNI 3.8% for eversion vs 5.6% for CCEA). Additionally, no differences were noted in restenosis at followup ranging from 1 to 69 months nor did stroke risk during follow-up differ between groups (2% vs 2.4%). A metaanalysis of randomized trials also reported that ECEA was associated with significantly higher incidence of post-CEA hypertension (OR, 2.75; 95% CI, 1.82-4.16), compared with CCEA. However, CCEA was associated with significantly higher incidence of perioperative hypotension (OR, 11.37; 95% CI, 1.95-66.46)[323] (Table V).

Carotid artery bypass. If the distal end point cannot be assessed adequately or is incomplete, a transverse incision in the ICA can be chosen for completion of the eversion endarterectomy to evaluate the rest of the end point and also to tack down the distal intima.[318] Alternatively, if the disease extends or the end point is not well tacked down, a more commonly used approach is to transect the ICA distally and perform a common carotid to ICA bypass. This can be done in numerous ways.[324-329] The most common technique calls for transection of the ICA at the distal end point and an anastomosis performed with greater saphenous vein or appropriately sized prosthetic, usually 6 mm. By performing a distal first, the length of the bypass can be judged so there is no kinking. One option is to close the arteriotomy on the CCA preserving the external carotid artery into and end-to-side anastomosis more proximally on the CCA. Alternatively, one can use the area with which one did an endarterectomy and place the heel of the bypass on the external carotid artery and trying to preserve it.[326] Last, in extreme circumstances, the external carotid artery can be ligated. Summary and recommendations.

1. There is Level 1 evidence to support a recommendation in favor of routine carotid patching.
2. Primary closure may be safely practiced in a large ICAof greater than 6 mm.
3. There is also no difference between preferential use ofvarious patch materials, whether saphenous vein, jugular vein or synthetic patches (ACUSEAL, PTFE, Dacron, or pericardial patches).
4. Based on available data, there is no difference in stroke/death rates between CCEA with patch closure and ECEA.
5. The rate of significant post-CEA stenosis with CEA with patching is somewhat similar with ECEA; however, ECEA had a lower post-CEA stenosis rate than patients undergoing CEA with primary closure.

Technical tips for high carotid lesions

High bifurcation or stenosis extending above C2 can present a technical challenge, as well as an increased risk of cranial nerve injuries. Although this is not a common problem, clinicians must be prepared to approach these high lesions. The first indication of an unusually high lesion could be inability to image above the lesion when performing the ultrasound assessment. In these instances, corroborative CTA and/or MR imaging must be performed to fully evaluate operative approaches. In highly select cases, the presence of distal disease extension may prompt the surgeon to reconsider whether CAS is more appropriate (especially in asymptomatic patients), or whether medical therapy would be more appropriate.

In the presence of distal disease extension, advanced planning is essential. Nasal pharyngeal intubation enables the mouth to be closed which then opens up the angle between the jaw and mastoid process to facilitate distal access.[330] Subluxation (not dislocation) of the temporal mandible joint has to be undertaken preoperatively because it cannot be performed once the

operation is underway.[171,331,332] An alternative strategy involves extending the incision anterior to the ear and mobilization of the superficial lobe of the parotid. This greatly increases access to the upper ICA, but usually requires assistance of an ENT specialist or parotid surgeon.[330] Intraoperatively, there are several techniques to

optimize access to the more distal ICA. These include division of the posterior belly of the digastric muscle, division of the occipital branch of the external carotid artery, which tethers the hypoglossal nerve; transection of the ansa-cervicalis, which also tethers the hypoglossal nerve; and transection of the styloid process. One simple maneuver can be transection of the ansa-cervicalis with division of the digastric and keeping a suture on the ansa-cervicalis and using it as a retractor to move the hypoglossal nerve out of the field and protect it.[171,330-332]

Summary and recommendations.

1. Surgeons should anticipate the presence of distal disease extension preoperatively and plan for this in advance in case a high exposure of the ICA is necessary.

Wound drainage and hematoma after CEA

Stone et al[165] reported that reexploration for neck hematomas were required in 1.3% of CEA patients on aspirin, 0.9% on clopidogrel, and 1.5% of patients taking aspirin and clopidogrel. There is no evidence that dual antiplatelet therapy significantly increases hematoma risk.[165,333-335] In one study, protamine reversal demonstrated a statistically significant reduction of neck hematoma formation after CEA. However, the amount of heparin that was used was not mentioned, and this may also be a mitigating factor. There are further data for comparison. A vast majority of hematomas occur in the first six hours after CEA, often after a period of poorly controlled hypertension. The rationale for placing a wound drain after CEA is that it should prevent hematoma formation as well as resultant, and potential major complications such as respiratory compromise or potential nidus for abscess formation, which may cause patch infection. Small caliber suction drains (#10F) do not seem to decrease the incidence or prevalence of hematoma, whereas larger drains (14F) may help.[336] Despite findings from this single randomized trial, there are not enough convincing data to support mandating drain or no drainage of CEA incisions. Any evidence of stridor or tracheal deviation mandates immediate wound exploration and hematoma evacuation. Summary and recommendations.

1. The decision for use of drainage post CEA should beleft up to the operating surgeon.
2. Patients on heparin anticoagulation may benefit from perioperative suction drainage; however, there are no Level 1 data to confirm this.

Completion imaging

The previous carotid guideline document highlighted uncertainty regarding use of completion imaging after CEA to prevent restenosis or stroke.[3] Despite numerous reports of postendarterectomy intraoperative lesion detection with completion imaging,[337-339] there were also several series that reported favorable outcomes without use of routine imaging.[340,341] In 2013, a Vascular Study Group of Northern New England report of 6115 CEAs with variable use of completion imaging did not show risk-adjusted improvement in outcome, with possible deleterious effects on mortality and stroke with resultant reexploration based on imaging findings.[342] However, a recent German study of 142,074 CEAs from 2009 to 2014 reported an independent risk reduction with use of completion ultrasound examination orangiography.[256] This finding has not been reproduced in a large series and in the absence of a prospective trial, it remains difficult to advocate for compulsory completion imaging after CEA for the purpose of reducing future events. However, if there is concern about the end point, abnormal Doppler findings or neurologic deterioration completion studies should be performed.

Summary and recommendations. There is insufficient evidence to recommend routine use of completion imaging after CEA.

Management of carotid coils and kinks

In the absence of significant stenosis, management of patients with ICA coils and kinks remains controversial. Incidental coils and kinks are found in up to 16% of patients, and one-half will have histologic features consistent with fibromuscular dysplasia. One randomized trial compared surgical correction and medical therapy in 182 patients with hemispheric/nonhemispheric symptoms in an isolated coil and kink in the ICA. At a mean follow-up of almost 6 years, patients randomized to surgical correction had 0% risk of occlusion compared with 5.5% of those randomized to medical treatment (P ¼ .002). Late stroke was 0% in surgically treated patients compared with 6.6% in medically treated patients (P¼ .01). Unfortunately, 41% of the medical patients crossed over to surgical treatment because of recurrent hemispheric or ongoing nonhemispheric symptoms, thus making interpretation difficult.[343] Despite these data, it is difficult to recommend operative therapy of asymptomatic patients with kinks or coils other than how clinicians would normally treat their underling hemodynamically significant atherosclerotic disease. Summary and recommendations.

1. Surgical intervention for asymptomatic isolated coilsor kinks of the ICA is not recommended.
2. Symptomatic patients with isolated coils and kinksmay be considered for surgical correction but only after all other etiologies for TIA or stroke symptoms can be identified.

TIMING OF CAROTID INTERVENTION IN STROKE

Acute stroke. See the Clinical Practice Guidelines document.[3]

Stroke in evolution. Stroke in evolution is a clinical syndrome that has been characterized as an evolving neurologic condition associated with an acute precipitating neurologic event. In these situations, initial medical management of stroke including antiplatelet therapy, volume support and blood pressure management has not succeeded in stabilizing the patient's neurologic outcome, which may wax and wane over the early course of the presentation. Patients may never return to normal and their neurologic deficit will be mild to moderate in nature. 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.

Expeditious clinical evaluation, brain imaging, and rapid evaluation of the carotid bifurcation is important to optimize result. Brain imaging, most often by diffusion-weighted MRI, allows rapid

assessment of the amount of brain infarcted and the amount at risk. After brain imaging to exclude hemorrhage as an etiology and to identify ischemic but viable brain, carotid imaging by duplex ultrasound examination, CTA, or MRI should be used to identify the offending lesion at the carotid bifurcation. If other etiologies are excluded, urgent CEA is warranted. In general, patients with preocclusive ICA stenosis or carotid occlusion are considered for emergency intervention, whereas those with less severe stenosis are initially medically optimized with urgent, but not emergent, intervention, planned during the admission.[344-349]

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

There are no large series of patients treated in 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 the immediate management, although there are no conclusive data supporting this approach. There are scant reports outlining the outcomes of CEA among patients who present with stroke in evolution. In general, risk of stroke/death have been reported from 9.2% to 26%. However, this reflects patient heterogeneity and lack of standard selection criteria for intervention.[350] The lack of high-quality data in the treatment of stroke in evolution precludes any clear conclusions regarding management of these patients. However, many extrapolate data for improved results with early CEA for stroke because these patient populations may overlap.

Crescendo TIA. Patients with crescendo TIAs, by definition, have not experienced a significant volume of brain infarcted. However, they do have a significant amount of brain at risk from a very unstable lesion with multiple small emboli or a large ischemic brain penumbra owing to hemodynamic compromise and poor cerebral autoregulation. In these cases, attention is directed at the source of the symptoms: the carotid bifurcation disease. This relatively rare clinical syndrome is characterized by repetitive episodes of transient neurologic ischemia followed by return to normal neurologic status. The definition of crescendo varies, but generally includes multiple 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 may not reveal a significant area of infarcted brain and there may not be a large ischemic penumbra. Symptoms are thought to arise from unstable carotid plaque with recurrent emboli despite antiplatelet therapy, or from unstable cerebral hemodynamics. Therapy in these patients is directed at removing the causative lesion at the carotid bifurcation.[351-354]

Some surgeons advocate heparin therapy during the preoperative period if intracranial hemorrhage has been excluded. There are no randomized trial data for determining whether intravenous heparin administration is superior to antiplatelet therapy in preventing early recurrent stroke in patients with stroke in evolution or crescendo TIAs. Two trials compared low-molecular-weight heparin vs aspirin monotherapy in acute stroke patients where antiplatelet/antithrombotic therapy was commenced within 48 hours of onset of symptoms. There was no significant difference in early outcomes between therapies in either study. However, in one trial, the post hoc analysis analyzed the incidence of neurologic deterioration at 10 days and found that low-molecular-weight heparin therapy was associated with a significant decrease in ischemic stroke progression (5%) compared with aspirin (12.7%) without an excess risk of cerebral hemorrhage.[353] Another study demonstrated that early administration of aspirin and clopidogrel, once parenchymal hemorrhage was excluded by CT scan and or MRI, was associated with significant reduction of spontaneous embolization (21% to 5%) and a significant reduction of recurrent events before CEA (13% to 3%). In the absence of high-quality evidence, it may seem reasonable to offer heparin plus aspirin or dual antiplatelet therapy in patients with a recurrent TIAs or crescendo TIAs before urgent CEA.

Urgent CEA in these patients has been associated with an increased risk of stroke compared with elective interventions. However, results of surgery in patients with crescendo TIAs are better than those for stroke in evolution.[355,356] CEA in neurologically unstable patients (ie, stroke in evolution, crescendo TIA) carries a higher than average procedural risk when performed in the elective setting. However, without surgery there is a significant chance of another major neurologic event. A meta-analysis reported that stroke and death risk after CEA were 20.2% in patients undergoing CEA for stroke in evolution and 11.4% in patients undergoing CEA for crescendo TIA. However, in select patients with an area of infarction volume less than 30% of the MCA territory, emergency CEA can be performed with a 2% to 8% risk of stroke/death among patients with stroke in evolution and 0% to 2% among patients presenting with crescendo TIAs.[357] Although there were no data comparing CAS with CEA in these patients, the presumptive increase in embolic potential of these plaques suggested that CEA would be preferred to CAS when the former is feasible.

Acute postoperative stroke or occlusion. Patients who undergo carotid intervention may suffer stroke in the early post intervention period. The goal of treatment is to expeditiously restore intracranial blood flow to normal levels and to identify the etiology of the stroke.

Until proven otherwise, a stroke that occurs immediately after CEA is considered secondary to a technical defect at the operative site. Other etiologies of stroke in the immediate postoperative period include embolization, intraoperative watershed infarct and intracranial hemorrhage. The status of the endarterectomy site should be determined expeditiously, and in most cases, this can be done by emergency bedside ultrasound imaging. If thrombosis is confirmed, operative exploration with repair of defect is urgently indicated. Early reexploration of an occluded CEA site with successful

repair may reduce long-term neurologic sequelae.[358] Although there is no control group available for comparison, reexploration for symptomatic thrombosis has been associated with resolution of neurologic defects in up to three quarters of patients. Reconstructions include reendarterectomy and patch with extension of the arteriotomy cephalad and caudad, as well as bypass of the endarterectomized segment with a prosthetic or vein conduit, especially in cases when platelet aggregates have been seen.

If imaging shows the endarterectomy site is patent without debris, other etiologies should be considered, including distal embolization or intracranial hemorrhage. An emergency head CT scan to exclude hemorrhage followed by anticoagulation and angiography with intracranial intervention according to acute stroke guidelines is indicated. If capability for acute stroke intervention is not available, then anticoagulation and blood pressure support is indicated. Meticulous blood pressure control in the periprocedure period has been identified as an important predictor of positive outcomes for all acute stroke interventions.[60]

Summary and recommendations for management of acute neurologic syndrome.

1. Patients who present in less than 6 hours of onset ofstroke should be considered for acute intervention to reduce the ultimate neurologic deficit. Interventions may include local or systemic thrombolysis (see Clinical Practice Guidelines).
2. Patients who present with fixed neurologic deficit greater than 6 hours in duration should be considered for CEA once their condition has been stabilized. CEA should be performed less than 14 days after the index neurologic event.
3. Patients who present with repetitive (crescendo episodes of transient cerebral ischemia) unresponsive to antiplatelet therapy should be considered for urgent CEA.
4. Patients with a stenosis or more than 50% who present with stroke in evolution or crescendo TIAs should be considered for urgent CEA, preferably within 24 hours. Early CEA within 14 days should be considered after intravenous thrombolysis in symptomatic patients if they make a rapid neurologic recovery (modified Rankin 0-2), the area of infarction is less than 30% of the ipsilateral MCA territory, a previously occluded MCA has been recanalized, there is a greater than 50% carotid stenosis and no evidence of parenchymal hemorrhage or significant brain edema.
5. For acute strokes after CEA, immediate imaging ultrasound examination or CTA is indicated for the evaluation of the endarterectomized site, if it can be done expeditiously. When imaging suggests thrombosis or is indeterminate, immediate operative reintervention is indicated. Immediate exploration is mandated if imaging is delayed.
6. When the endarterectomy site is patent, other modalities of CT scanning and angiography should be used to better identify as a cause of stroke. If CT scanning excludes intracranial hemorrhage, anticoagulation is reasonable until definitive decision regarding the appropriate diagnosis and therapy can be made.
7. Revascularization should not be considered in patients with any stenosis who suffered a disabling stroke, modified Rankin score of greater than 3 whose area of infarction exceeds 30% of the ipsilateral MCA territory or who have altered consciousness to minimize the risk of postoperative parenchymal hemorrhage.
8. It is recommended that patients undergoing early carotid interventions after thrombolysis should have postinterventional hypertension actively treated to reduce the risk of parenchymal hemorrhage.

CAROTID ARTERY STENTING

Access: Femoral, radial, cervical (TCAR)

Appropriate patient selection for CAS was discussed in prior sections of these guidelines. In summary, there is strong evidence that aortic arch tortuosity (type III arch) and severe atherosclerosis are associated with a significant increase in risk of stroke during CAS.[175,359] Moreover, longer and more extensive carotid lesions are associated with dramatic increase in adverse outcomes.[175] Patients over age 80 tend to have more tortuous anatomy and more advanced lesions. Prior studies showed better outcomes for these patients with CEA vs transfemoral CAS.[197,199,360,361] There is also strong evidence that dual antiplatelet therapy, statins, beta blockers, and tight diabetes control can reduce risk of stroke and death during CAS.[62,164,362,363]

CAS has the advantage of percutaneous access and should be performed under local anesthesia with conscious sedation because local anesthesia reduces risk of cardiac complications and allows for continuous neurologic monitoring.[238,364,365]

Transfemoral access. CAS is commonly performed via a retrograde transfemoral approach using 5F to 9F access sheath in a right-handed operator. This approach is advantageous in that the femoral artery can accommodate larger diameter devices. Duplex ultrasound examination should be used to guide access to the common femoral artery. Micropuncture (5F) access is used for initial access and exchanged to 0.035 access with a 90-cm 6F sheath (Cook Medical, Bloomington, Ind). The patient is subsequently heparinized before any arch instrumentation to keep an activated clotting time of greater than 250 and up to 300 seconds. An aortic arch angiogram using long pigtail catheter and 45 left anterior oblique projection is useful in identifying and cannulating the ostia of the great vessels.[366] Roadmap or overlay techniques are useful to guide access into the major vessels' origin. An arch angiogram may not be necessary when preoperative CTA or MRA is available. Several catheters are available for selecting the CCA. The most common are JB1 or vertebral shape catheters for simple arch anatomy and VTEK or SIM2 catheters for complex arch anatomy. In general, a double curved catheter is used for carotid cannulation. A cervical carotid angiogram is performed through the catheter to confirm selection of the CCA. A glide wire is advanced into the mid CCA. Some catheters are compatible with the 6F guiding sheath, which allow for telescoping the sheath over the catheter and the glide wire without exchange to dilator. The sheath

is advanced into the mid to distal CCA, avoiding the lesion. The use of a stiff wire into the ECA may facilitate advancing the sheath into the mid/distal CCA. The sheath should be flushed carefully with heparinized saline to avoid air embolization.[367]

Certain anatomic conditions such as severe aortoiliac disease, unfavorable aortic arch configuration (type II or III), bovine arch anatomy, and supra-aortic vessel takeoff can render Transfemoral CAS more difficult.[175,359,368] Patients with complex aortic arch anatomy and patients greater than 80 years of age are at high risk of cerebral embolization during CAS owing to manipulation of the aortic arch and major vessels before placement of an EPD. In an MRI-based, prospective single-center study, 40% of patients undergoing transfemoral CAS had evidence of cerebral embolization with 60% of the cerebral infarcts being outside the vascular territory of the treated lesion, observations suggesting that emboli originated from the aortic arch.[369] In the Carotid ACCULINK/ACCUNET Post Approval Trial to Uncover Unanticipated or Rare Events (CAPTURE) postapproval study, nearly one in five strokes occurred in a nonipsilateral distribution, with the exception of intraprocedural events, which were all ipsilateral to the stent being implanted.[370]

Radial and brachial access. CAS from upper extremity approaches can be performed safely and is effective in treating both left- and right-sided carotid lesions in patients with type III and bovine arch anatomy. These approaches are patient selective, and used based on the operator's experience. A preprocedural Allen's test and careful review of all imaging studies should be performed before considering these approaches.[371] However, such access is technically difficult for catheterization of a nonbovine left ICA take-off (owing to its sharp angle) and does not solve the problem of ostial stenosis.[372]

Multiple studies analyzing large cohorts demonstrate low complication risk from radial approaches, while others have noted benefits of both radial and brachial approaches.[371,373-377] In particular, excellent results have been achieved with right brachial approaches in patients with left ICA lesions and bovine arch anatomy,[373] and with transradial access in patients undergoing CAS with bovine and type III aortic arch anatomy.[371] Although some investigators have found it beneficial to approach CAS from a contralateral radial access,[371] others reserve the left radial access to treat left-sided lesions in patients with previous debranching procedures (eg, left common-to-subclavian bypasses, because this method allows access to the ipsilateral ICA). The latter avoids crossing all three great vessels and minimizes arch manipulation; therefore, decreasing risk of embolic events. The RADCAR (Radial access for Carotid artery stenting) study randomized patients to transradial (n ¼ 130) and transfemoral (n ¼ 130) groups and showed no differences in major adverse events and hospitalization between the two approaches. However, with transradial access, crossover and radiation dose were higher. Moreover, hospitalization was shorter with transradial access in the per-protocol analysis.[378]

Techniqueforradial/brachialapproach. A micropuncture access set is used for brachial artery access, whereas a Glidesheath hydrophilic-coated nitinol micropuncture set (Terumo Medical, Somerset, NJ), is used for radial artery access.[378] Patients undergoing radial artery access are given both verapamil (0.075-0.15 mg/kg) and nitroglycerin (100200 mg for a 70-kg patient) as boluses through the sheath as antispasmodics. Anticoagulation during the procedure is achieved upon access to the target vessel with unfractionated heparin with the goal of keeping activated clotting time of greater than 250 up to 300 seconds. The target CCA is initially cannulated using standard techniques, and an angled catheter (ie, Cobra, Headhunter) is usually used. A 0.035-inch hydrophilic coated wire is then used to position the catheter into the CCA or external carotid artery, depending on anatomy. Once access is secured with a medium body wire, the 5F sheath is exchanged for a 6F shuttle sheath and advanced over the wire once the target CCA or external carotid artery is engaged.

CAS is then performed using standard techniques. Once the procedure is complete, the heparin is actively reversed with protamine sulfate. Manual pressure is applied for brachial access, and a TR Band assisted compression device (Terumo Interventional Systems, Irvine, Calif) is used for radial access.

Transcarotid artery revascularization. Direct open cervical access of the CCA offers the advantage of avoiding the atherosclerotic arch and crossing the major vessels. It can be performed under general, regional or local anesthesia with conscious sedation. Preoperative duplex ultrasound examination and/or CTA is needed to evaluate the CCA and its bifurcations. The proximal cervical CCA must be free of severe calcification and atheroma. A minimal 6mm luminal diameter is required. Proper distance between the clavicle and bifurcation (5-cm landing zone) is required for TCAR. The depth of the CCA should be also evaluated. The ratio of depth/landing zone should be less than 1:2. In anatomies where the ratio is greater than one, TCAR is not recommended. Details of this technique have been described elsewhere.[379] In brief, a 2- to 4-cm transverse or longitudinal incision is made in the triangle between the two heads of the sternocleidomastoid muscle and clavicle. The proximal CCA is dissected free and vessel loop or umbilical tape is placed proximally. A purse-string or U 5.0 Prolene pre-suture is placed and the CCA is punctured directly with a 21G micropuncture needle. Using a standard approach, the CCA access is secured and placed at a 45 angle, and a 0.018-inch soft tip microwire is advanced 3 to 4 cm into the external carotid artery. Next, a 5F soft microsheath is placed only 2 cm into the CCA over the microwire. The microwire and dilator are removed and a cervical carotid angiography with road mapping or fade in and out digital subtraction is performed with different oblique views to delineate the bifurcation. If the external carotid artery is open with no lesion at the bifurcation, the wire is advanced into ECA followed by the 5-F microsheath with dilator (ECA engaging technique). The 0.035-inch wire is then advanced in the microsheath into the ECA. This technique allows a for few additional centimeters of purchase. If the lesion involves the bifurcation or if the ECA is significantly narrowed, stay short technique is recommended with advancing of the microsheath followed by the 0.035 wire into distal CCA but staying short of the lesion. Next, an 8F sheath is advanced over a 0.035 wire carefully with gentle traction on the umbilical tape on the CCA. At least two angiography views are performed through

the sheath to confirm proper position. Technical advantages of this technique include ease of direct access, use of short wire and catheters, and the ability to clamp the proximal CCA providing CEA-like cerebral protection before lesion manipulation. Prior studies demonstrate a significant decrease in the incidence of silent ischemic lesions after TCAR compared with transfemoral CAS using diffusionweighted MRI.[380,381] The risk of DWI in the ICSS study was 17% in the CEA arm vs 73% in the transfemoral CAS arm.[382] The PROOF study showed 18% risk of DWI after TCAR with flow reversal and proximal CCA clamping.[380]

Summary and recommendations. Access.

1. Proper imaging of the aortic arch and carotid bifurcation are recommended preoperatively.

2. Transfemoral access can be used in younger patientsand aortic arch free of obvious disease.

3. Transradial and transbrachial access is especially beneficial in left ICA lesions in patients with bovine anatomy or prior carotid subclavian bypass.

4. TCAR has advantages of avoiding the diseased tortuous arch and providing CEA like protection.

Technical considerations

Use of cerebral protection devices/TCAR. Cerebral protection devices have resulted in lower risk of distal embolization. The results from the EVA-3S reported significantly lower 30-day stroke risk in patients undergoing transfemoral CAS with EPD compared with those without EPD (7.5% vs 25%; P¼ .03). An EPD was required in all patients enrolled in the CREST, and the Centers for Medicare and Medicaid Services requires an EPD in all patients undergoing CAS to be considered for reimbursement. A meta-analysis of more than 15,000 CAS procedures showed a 45% decrease in stroke and death with an EPD.[359] Currently, cerebral embolic protection can be achieved via distal microporous filters, distal occlusion devices, proximal occlusion with flow reversal, and with the TCAR with the dynamic flow reversal neuroprotection system. The choice of device is often dependent on physician preference and familiarity. The distal ICA with minimal tortuosity and adequate diameter and length must be available for suitable placement of a distal EPD.

Evidence regarding the superiority of one protection device over another is limited. The Prevention of Cerebral Embolization by Proximal Balloon Occlusion compared with Filter Protection during Carotid Artery Stenting (PROFI) study is the only randomized trial that compared filter-protected vs proximal balloonprotected transfemoral CAS. The study reported a significantly lower incidence of ischemic lesions after proximal occlusion compared with distal filters (6.5% vs 29%; P¼ .05) with a DWI risk of 87% with distal filters vs 45% with proximal occlusion.[383] In a meta-analysis of eight studies comparing filter protection vs proximal occlusion, Stabile et al[384] a reported lower incidence of newer ischemic lesions in patients undergoing proximal occlusion.

Distal filter devices. Distal filter devices are most commonly used for CAS, and they have the advantage of smaller diameter and maintaining the antegrade ICA flow throughout the procedure. Several distal filters are available and each is compatible with a stent system such as the Emboshield Nav6, Rx Accunet (Abott Laboratories, Abott Park, Ill), Angioguard Rx (Cordis, Melpitas, Calif), and FilterWire EZ (Boston Scientific) and Spider FX (Medtronic, Dublin, Ireland). However, there is no evidence of the superiority of one distal filter over another.[385]

The microporous filter must be deployed in a straight segment of the ICA to allow apposition of the filter to the vessel wall. It must be placed in the distal ICA at a sufficient distance to allow safe deployment of the distal end of the stents without trapping of the filter. Visualization of the sheath should be maintained at all times to prevent prolapse of the sheath into the arch, which could dislodge the filter and pull it through the carotid lesion.[366]

The main disadvantage of using distal filters is that the lesion must be passed initially which increases risk of cerebral embolization. The filters can also become occluded if a large amount of debris is released. Moreover, small particulate debris (<100 mm) can pass through the pores of the filter. Improper movement of the device might damage the surrounding vessel wall and lead to dislodgement of fragments and debris around the filter. In the case of very tight or extremely tortuous lesions, systems that are advanced over an independent wire and not attached to a wire itself may be preferable. These systems first advance the guidewire and then track the EPD over that wire. An angiogram is usually obtained before completion and removal of the EPD. If extensive amounts of debris are trapped within the EPD, blood flow in the ICA might stop. In this case, the resultant standing column of blood and any embolic debris should be aspirated to prevent embolization when the EPD is withdrawn.[366] An aspiration catheter with a side port might be needed to evacuate the standing column of debris.

Distalocclusiondevices. Distal occlusion devices are not commonly used and have largely been abandoned in current practice. Similar to distal filters, a distal occlusion device initially requires the crossing of the lesion, which can result in increased embolization. Also, this device has the disadvantage of stopping blood flow during stenting. However, it does have an advantage of smaller diameter than proximal occlusion devices. If these devices used, it is crucial to aspirate adequately after stenting and before balloon deflation to remove all debris. Vasospasm may be encountered before or just after filter or occlusion balloon removal, and this is usually managed by watchful waiting. Rarely, the administration of a vasodilatordmost commonly nitroglycerine in 100mg aliquotsdis necessary to relieve flow-limiting vasospasm.[366]

Proximal occlusion. Proximal occlusion with transfemoral CAS can be achieved with the MoMa device by placement of two occlusion

balloons in common and external carotid artery (Medtronic). Disadvantages of this system are the larger sheath size (9F), the need for
ECA selection and balloon placement.

TCARwithcerebralflowreversal. The ENROUTE system for TCAR allows for dynamic cerebral flow reversal by connecting the arterial sheath to a venous sheath placed in the common femoral vein. The connecting tubing allows for low and high flow reversal options. After clamping of the proximal CCA, active flow reversal carries embolic debris, released during or immediately after angioplasty and stent placement, away from the cerebral circulation. The main advantage of this technique, in addition to avoiding the arch, is the ability to perform the entire procedure (lesion crossing, ballooning, and stenting) under complete protection. The disadvantages of this technique include the need to cutdown compared with the percutaneous approach, the inability to use it in patients with calcified and atherosclerotic proximal CCA and proximal CCA diameter of less than 6 mm or in patients with less than 5 cm distance from the clavicle to the carotid bifurcation. Short-term results from the ROADSTER study of high-risk patients undergoing TCAR with the ENROUTE neuroprotection and stent system showed the lowest stroke risk (1.4%) compared with all other prospective and randomized clinical trials of endovascular carotid intervention.[177] These findings persisted up to 1 year with a 0.6% incidence of ipsilateral stroke and 3.7% overall mortality after TCAR with dynamic flow reversal.[178] A recent study by Malas et al from the VQI/SVS TCAR Surveillance Project (TSP) showed that transfemoral CAS is associated with twice the odds of in-hospital neurologic events compared with TCAR.[207,386,387] Another study by Schermerhorn et al[388] from the TSP, showed no significant difference in stroke and death rate between TCAR and CEA. A more recent and larger analysis by Malas et al[208] from TSP showed a significant reduction in risk of CNI and MI in TCAR in comparison with CEA.

Although the transfemoral approach remains the most commonly used access in daily practice, advances in endovascular technology may result in shifting the access site to TCAR to optimize CAS safety, especially in elderly patients and those with unfavorable aortic arch anatomy. However, long-term follow-up is needed to validate the benefits of these new technologies.

Summary and recommendations.

1. Transfemoral CAS should be performed with distal orproximal protection devices.
2. There is no evidence of superiority of one DEP devicevs the others.
3. There is some evidence that proximal protection offers advantage over DEP by avoiding unprotected lesion crossing.
4. TCAR with cerebral flow reversal had the lowest reported stroke rate to date compare to all transfemoral
   CAS studies.

Timing of PTA during stenting. A key step during CAS, percutaneous transluminal angioplasty (PTA) can be performed after establishing distal or proximal protection. Both prestent and poststent deployment PTA can be performed. Pre-dilatation allows the stent delivery system to be advanced without being constrained or trapped. In pre-PTA, a balloon with 2- to 4-mm diameter and 15- to 20-mm length is used to prepare a stenosed vessel for stent deployment. However, predilatation might increase the risk for embolic stroke. Risk of perioperative stroke in the CAPTURE study was significantly higher in patients with pre-PTA vs without PTA (OR, 3.68, 95% CI, 2.26-6.0, P< .001).[198] However, a real-world analysis of all CAS cases in the VQI database between 2005 and 2016 showed a similar risk of stroke and death after primary CAS without angioplasty compared with conventional CAS with angioplasty, as long as an EPD is used.[389] Balloon inflation should, therefore, be slow, bearing in mind not to exceed the nominal pressure, which is then followed by immediate gradual deflation. This practice helps to prevent negative pressure formation and helps to minimize embolic showering.

In contrast, post-PTA is largely user dependent. It is commonly used to mitigate residual stenosis after stent deployment. However, post-PTA is associated with an increased risk of intraoperative and postoperative hemodynamic depression, and a significant increase in the risk of stroke and death. The latter might be secondary to fracturing of the atheromatous plaque and liberation of a large amount of particulate debris.[390] Obeid et al[391] compared pre-PTA vs post-PTA using the SVSVQI dataset and reported a 2-fold higher odds of periprocedural stroke/death rate following poststent PTA compared with prestent PTA. However, patient selection may be biased in this analysis. Nonetheless, PTA is generally reserved for select cases with severe residual stenosis. Stents used in CAS are self-expanding and continue to expand after the procedure.[392] A mild to moderate residual stenosis (<30%) of the target lesion may be accepted in an effort to avoid generating excessive embolic debris and potentially severe embolic
complications.[366]

A recent systematic review/meta-analysis of predilation and postdilation in transfemoral CAS by Ziapour et al[393] showed avoiding post-PTA reduces the perioperative hemodynamic instability which can last up to 30 days. Regardless of the type, fewer PTA during CAS particularly decreases neurologic events during and 30 days after the procedure.

Summary and recommendations. Pre-PTAandpost-PTA.

1. Protection should be established before PTA duringCAS.
2. Prestent PTA can be performed safely with small diameter balloon to nominal pressure.
3. Post-PTA should only be used for patients with significant residual stenosis.

Stent selection.

Openclosedcells. Depending on the density of the struts, carotid stents can be classified into open vs closed cells. Generally, a free cell area of more than 7 mm^2 is considered an open cell and is thought to leave larger gaps uncovered. Closed-cell design stents have small cell areas and may provide effective plaque coverage, reducing the risk of debris embolization. However, they are less conformable to the

carotid anatomy and thus cannot be used in tortuous arteries. In contrast, open cell designs are more flexible and can accommodate tortuous carotid anatomy but have large cell sizes that might increase risk of plaque protrusion and potential embolization. Current evidence on specific stent design remains controversial, but largely supports benefits of close cell design. One small randomized clinical trial of 40 patients showed no difference in embolization between open and close cell design based on TCD and DWI-MRI evaluations.[394] A meta-analysis by Kouvelos et al[395] found no difference in 30-day cerebrovascular complications after CAS using open vs closed cell designs. Results from the SVS Registry also found no association between perioperative stroke and stent type.[396] By contrast, a multicenter study looking at CAS free cell area of greater than 7.5 mm^2 found a higher stroke risk compared with less than 7.5 mm^2, suggesting closed cells are more protective of stroke than open cells.[397] A recent pooled analysis of 1557 patients from three large randomized trials (EVA-3S, SPACE, and ICSS) showed an independent association between closed-cell design and reduced risk of periprocedural stroke or death.[398] However, in a systemic review and comprehensive meta-analysis of 33 studies (including 2 randomized trials), use of an open cell stent design in CAS was associated with decreased risk of restenosis compared with the closed-cell stent without significant differences in periprocedural outcomes.[399]

Mesh-coveredstents. A new generation of dual layered carotid stents has been designed. These consist of thin struts of nitinol wires covered with nitinol or polyethyleneterephthalate mesh, which helps to stabilize the plaque and reduce risk of distal embolization.[400] The Roadsaver Carotid Artery Stent System (Microvention/Terumo), the Gore Carotid Stent (W. L. Gore & Associates) and the CGuard Carotid Stent System (InspireMD) feature different constructions, but all have a mesh covering with an open or closed cell design, and a pore size that ranges from 180 to 500 mm. However, studies on the efficacy and safety of these stents are still inconclusive. Assessment of 41 procedures of ICA and CCA stenting using the Roadsaver double nitinol layer micromesh stent in 40 nonconsecutive patients with symptomatic or high-risk carotid artery stenosis showed favorable outcomes with one minor stroke occurring after CCA selection with a guiding catheter (before stent deployment) and one transient postprocedural TIA of the ipsilateral cerebral hemisphere. No restenosis or thrombosis were observed. Angiographic stenosis decreased from 82.9 6 9.1% (range, 61%-97%) to 19.3 6 7.3% (range, 0%-34%) (P< .05).[401]

The CGuard CARENET (Carotid Embolic Protection Using MicroNet) trial included 30 consecutive patients from four centers in Germany and Poland. The 30-day major adverse cardiac or cerebrovascular event risk was 0%. New silent ipsilateral ischemic lesions on diffusionweighted MRI at 48 hours occurred in 37.0% of patients. Thirty-day diffusion-weighted MRI showed complete resolution of all but one periprocedural lesion and only one new minor lesion in relation to the 48-hour scan.[402] In contrast, in patients at high risk for CEA, data from the SCAFFOLD trial showed a low risk of major adverse events at 30 days as well as a low risk of ipsilateral stroke from 31 days to 1 year with the Gore carotid stent (W. L. Gore & Associates). The trial enrolled 312 patients, but only 265 were included in the primary analysis. Thirtyday mortality risk was 0.6% (out of 265) and 30-day stroke risk was 2.9% in the entire cohort. The two deaths reported in the study were not stroke related.

Numberofcarotidstents. The number of stents used are associated with risk of perioperative stroke, and this is likely a surrogate for the length of the lesion and difficulty of the case. Data from the CAPTURE trial demonstrated a higher 30-day stroke risk of 9.7% after the use of multiple stents compared with 4.5% in patients with only one stent.[198] In a secondary analysis from the CREST study, lesions longer than 12.85 mm had a 3.4-fold higher risk of stroke and death in CAS compared with CEA.[175] In contrast, a recent study by AbuRahma et al[403] of 409 patients who underwent CAS between 2004 and 2015 found no significant difference in stroke and major adverse events in regards to the stent length, number of stents or stent diameter after CAS.[403] However, these results may be explained by the small number of strokes/adverse events.

In summary, proper patient selection, careful preprocedural planning, including performing adequate imaging studies to evaluate patient's anatomy and lesion characteristics and optimal medical management, are crucial in improving CAS outcomes. Advances in protection devices, membrane- and mesh-covered stents, alternative hybrid approach such as TCAR and reversal of flow also offer promising tools to improve outcomes.[404]

Summary and recommendations. Pre-PTAandpost-PTA.

1. Embolic protection should be established before PTA/CAS
2. There is conflicting evidence on the risk of stroke based on stent cell design.
3. Early studies of covered stents showed favorable results. Larger studies are needed.
4. An increased number of stents or longer lesions isassociated with a significant increase in the risk of stroke.

EXTERNAL CEA INDICATIONS AND TECHNIQUES

The external carotid artery is an integral part of the collateral circulation in the setting of a known ICA occlusion. As such, referable neurologic symptoms may arise from embolization of the proximal aspect of the occluded ICA or from external carotid artery stenosis via the usual thromboembolic mechanism.[405,406] For many decades, external CEA has been discussed in the setting of new or recurrent neurologic or ocular symptoms given the aforementioned pathophysiology.[407-413] Other than small series and case reports, there has been no new reporting in the literature with respect to treatment recommendations.[414-416] Treatment consists of flush ligation of the internal carotid and common and external CEA to remove the embolic source. Despite the lack of confirmatory evidence, use of this technique in the appropriate setting of symptoms and relevant anatomy seems reasonable.

Summary and recommendations. In the appropriate clinical setting, external CEA and flush ligation of the ICA is suggested to minimize further neurologic sequelae.

COMPLICATIONS OF CAROTID INTERVENTION

Early complications of carotid intervention

1. Stroke after CEA (intraoperative and immediate postoperative stroke): therapy
2. Stroke after CAS
3. Hemodynamic instability: post CEA hypertension andhypotension
4. Post-CAS hemodynamic depression
5. CNI after CEA
6. Myocardial infarction/renal insufficiency
7. Wound hematoma after CEA

Late complications after carotid intervention

1. Prosthetic patch infection
2. Restenosis following CEA3. Restenosis following CAS

Early complications of CEA

Stroke after CEA. Stroke is one of the most serious complications following CEA, and its incidence must be minimized to achieve appropriate CEA efficacy in stroke prevention, particularly among neurologically asymptomatic patients. More than 20 different mechanisms of perioperative stroke have been identified.[417] The most common mechanism of stroke is perioperative arterial thrombosis and embolization, frequently related to a technical deficit at the endarterectomy site.[417,418] Examples of technical deficits can include inadvertently leaving behind residual intimal flaps, atheromatous disease, or luminal thrombus.[417,418] Additional examples of technical complications include vascular clamp injuries or damage caused by intra-arterial shunt placement. Other potential causes of perioperative stoke include cerebral ischemia during carotid clamping and intracerebral hemorrhage (ICH),[417,418] but these less common etiologies of perioperative stroke are not typically dependent on technical imperfections that may occur during the operation itself.

Some authors have recommended intraoperative completion imaging studies to minimize risk of leaving technical imperfections at the endarterectomy site.[3,417] These completion studies can include continuous wave Doppler, duplex ultrasound examinaton, or intraoperative arteriography, and they are operator and technique dependent. There is controversy concerning what technical deficits noted on completion imaging studies warrant intraoperative reexploration of the artery because not all technical imperfections will cause strokes.[3,417] Additionally, attempts to revise lesions have the potential to cause additional morbidity from repeated manipulation of the vessel. Some authors believe that intraoperative completion studies may be particularly useful following eversion endarterectomy, because the distal end point may not be sufficiently visualized with this technique. Other authors have found no significant benefit to completion imaging, and report excellent results without routinely using any type of completion studies.[3,341,417] Therefore, the routine use of completion imaging after CEA remains controversial. The clinical significance of many observed abnormalities is uncertain, and it has not been definitively proven that routine performance of completion studies reduces perioperative stroke risk. The decision generally remains a matter of surgeon experience and preference.[3]

When a patient sustains a stroke during or immediately following CEA, the chance of maximizing recovery depends on early recognition of the neurologic event, establishing its likely etiology, and immediate institution of appropriate therapy or rescue measures.[358,417] Establishing the diagnosis of a perioperative stroke is typically a clinical diagnosis, but may be supported by appropriate imaging studies.

Intraoperative stroke recognized upon awakening fromgeneralanesthesia. When CEA is performed under general anesthesia, a stroke is typically recognized when the patient awakes after wound closure. If a new focal ipsilateral neurologic deficit is identified, the incision should be reopened immediately.[417] The ICA can be assessed with intraoperative Doppler in addition to visual inspection and palpation. If the arteryseemsto bepatent with flow present, further evaluation for technical deficits should be performed with either intraoperative duplex ultrasound examinaton or arteriography to identify correctable deficits. Angiography should include intracranial imaging to evaluate for distal intracerebral embolization. If the ICA is without flow, completely thrombosed, or an imaging study reveals a significant technical deficit, the endarterectomy site itself must be reexplored.[417] The distal ICA should not be clamped initially to appropriately perform repeat thromboendarterectomy without causing fracturing and intracerebral embolization of any local thrombus or debris. The clot is carefully extracted with the hope that existing backpressure will help to achieve complete removal of the existing thrombus from the cervical ICA. If there is no back bleeding, gentle meticulous balloon catheter thrombectomy can be performed, but there is a risk of causing a carotid-cavernous sinus fistula.[419] Once thrombus has been extracted and back bleeding occurs, the ICA can be safely clamped. The endarterectomy site must be meticulously inspected for any technical deficits that may have caused the thrombosis or embolization and these should be repaired as necessary.[358,417,418] Most surgeons recommend shunt insertion during reexploration for a perioperative stroke to limit the ischemic event during repair, but this must be done extremely carefully under direct visualization.[358]

If no defect or thrombosis is noted at the endarterectomy site, the stroke is likely related to either ischemia that occurred while the carotid artery was clamped or intraoperative embolization during the dissection. Intraoperative arteriography may demonstrate an intracerebral embolus. Catheter-directed thrombolysis or other

neurologic rescue techniques can be used to salvage these situations and restore flow to the intracerebral vessels. However, if the ICA seems to be normal at reexploration, and no large intracerebral embolus can be identified, this finding suggests that the patient may have experienced either embolization before carotid clamping or sustained a significant period of ischemia during the clamping period. These etiologies may not be formally treatable with surgical or endovascular techniques. Therefore, treatment is primarily medical, including supportive care, hemodynamic monitoring, and anticoagulation or antiplatelet agents as deemed clinically appropriate.

Intraoperative stroke recognized during regional anesthesia. If a perioperative stroke or TIA occurs during CEA while the patient is awake under local/regional anesthesia, stroke etiology can typically be elucidated based on its timing during the operation. A neurologic deficit that occurs during dissection of the carotid bulb before carotid clamping is almost certainly related to embolization of atheromatous debris. This deficit can be minimized by avoiding significant manipulation of the bulb during dissection of the carotid artery until heparinization and control of the ICA has been established. If a neurologic deficit does occur during the preclamping period, the patient should be expeditiously heparinized, and the operation should be completed in an expedient fashion with the placement of an intra-arterial shunt. If the deficit does not reverse with shunt placement and completion of the surgery, additional assessment should proceed as above, including intracerebral arteriography. If, during local/regional anesthesia, neurologic changes occur with test clamping of the artery, this is an indication for placement of an intra-arterial shunt. Neurologic changes that occur during initial carotid clamping will typically reverse with successful shunt placement. If they do not, one must again consider the possibility that intracerebral embolization has occurred.

Perioperativestrokerecognizedinthepostoperative period. If a patient awakens neurologically intact after CEA under general anesthesia, or is initially neurologically intact during and after CEA under local anesthesia, and subsequently develops a new neurologic deficit in the postoperative period, the differential diagnosis may be more complex. The likely etiology and treatment may depend on the timing of the deficit. Neurologic deficits that occur within the first few hours after completion of CEA after an initially normal period are typically related to thromboembolization and technical defects at the endarterectomy site. If the operation was performed under locoregional anesthesia with the patient being tolerant of carotid clamping, it is almost certain that an early deficit is related to embolization, and not complete thrombosis of the artery. Although duplex scanning can be considered if it can be performed expeditiously, these patients will likely benefit from immediate return to the operating room for reexploration and assessment of the ICA and endarterectomy site, as described elsewhere in this article. Alternatively, a neurologic deficit that occurs later in the postoperative course (1-3 days) is more likely to be related to ICH or another cause of stroke. A CT scan of the brain should be performed in these patients to rule out ICH, particularly in patients at increased risk.

As reported in an analysis of 2024 CEAs from a single institution, the causes of 38 (1.9%) perioperative neurologic deficits were clamping ischemia (13.2%), thromboembolic events (63.2%), ICH (13.2%), and miscellaneous etiologies not directly related to the operated artery (10.5%).[358] Neurologic events that occurred in the initial 24 hours after surgery were significantly more likely to be caused by thromboembolic events, most commonly related to technical imperfections at the endarterectomy site. Most patients who experienced early events postoperatively underwent reexploration and intraluminal thrombus was noted in 83.3% of these cases. After reexploration, there was either complete resolution of, or significant improvement in the neurologic deficit that prompted reexploration.[358]

Cerebral hyperperfusion syndrome is a rare and potentially fatal cause of perioperative stroke after CEA. It is characterized by severe ipsilateral headache, seizures, and possible intracranial hemorrhage.[420] A recent analysis showed that the overall risk of this syndrome was an extremely low 0.18% of 51,001 CEAs.[420] However, the associated mortality was 38.2%. Multivariate analysis revealed that female sex, recent ipsilateral stroke, and contralateral stenosis of 70% or greater, postoperative hypertension and postoperative hypotension were all independently associated with cerebral hyperperfusion syndrome, but postoperative blood pressure lability had the strongest association.[420]

Summary and recommendations for the management of intraoperative or perioperative stroke with CEA.

1. If a patient awakens from CEA under general anesthesia with a new focal neurologic deficit related to the ipsilateral cerebral hemisphere, immediate reopening of the incision and evaluation of the ICA is indicated.
2. If a patient awakens from CEA under general anesthesia, and reexploration and evaluation of the ICA reveals either thrombosis of the ICA or a technical deficit, the artery must be reexplored and repaired as clinically warranted.
3. If technically feasible, a shunt should be inserted carefully and at the appropriate time during reexploration of the artery for a perioperative stroke to limit the extent of cerebral ischemia.
4. Treatment of the artery at reexploration can includethrombectomy, thromboendarterectomy, correction of any noted technical deficits and/or intracerebral arteriography based on the operative findings.
5. If there are no relevant findings at the endarterectomy site on reexploration, and cerebral arteriography reveals intracerebral embolization, catheter directed thrombolysis and/or other intracranial endovascular “neurologic rescue” techniques can be considered as deemed clinically warranted.
6. If a patient who is initially normal after CEA undergeneral anesthesia develops a new neurologic deficit in the early postoperative period, immediate evaluation and reexploration of the artery is indicated, unless another cause of stroke is confirmed.

7. If a patient who is initially normal after CEA undergeneral anesthesia develops a new neurologic deficit later in the postoperative period, additional evaluation including a CT scan of the brain to rule out ICH is indicated before consideration of reexploration.
8. If reexploration for an intraoperative or perioperativestroke following CEA does not reveal any cause at the endarterectomy site or on intracerebral arterial imaging, medical management is indicated.
9. If a patient develops a new neurologic deficit intraoperatively during CEA under locoregional anesthesia, surgical management should proceed as appropriate based upon the timing of the event as related to the intraoperative course of the operation.
10. If a patient who is initially normal after CEA underlocoregional anesthesia with tolerance of carotid clamping develops an ipsilateral focal neurologic deficit, immediate reexploration of the artery and appropriate treatment is indicated, unless another cause of stroke can be strongly considered.
11. For early acute stroke (1-2 days) after CEA, immediateimaging (ultrasound examination or CTA) is indicated to evaluate the endarterectomy site. When imaging suggests thrombosis, is indeterminate, or not available, immediate operative reexploration is indicated.
12. For early acute stroke after CEA, if the endarterectomysite is found to be patent without abnormalities, other modalities such as a CT scan and/or arteriography should be used to better identify the cause of the stroke. If no definitive cause of stroke is found, anticoagulation is appropriate if a CT scan has excluded intracranial hemorrhage.

Stroke after CAS

Stroke after stenting: the role of thrombectomy and thrombolysis. The most feared complication after CAS is stroke, which can be due to cerebral embolism or intracranial hemorrhage. In most clinical trials, stroke presentation occurred in the first 24 hours following CAS. It is for this reason that it is imperative to monitor all CAS patients in the intensive care setting postoperatively. Stroke diagnosis is usually clinical. In patients with postoperative neurologic changes, carotid ultrasound examination, CTA, or MRI/MRA should be obtained immediately to evaluate stent patency, and determine if there is distal embolization or ICH. Management of acute stroke is described in the Acute Stroke section of these guidelines. However, acute stroke during or immediately after CAS might require immediate reintervention.

Distal embolization. If the embolic material is large enough to cause MCA occlusion, catheter-based thrombolysis with recombinant tissue plasminogen activator (tPA), GPIIB/IIIA inhibitor, and thrombectomy with stent retrieval should be considered. There is strong evidence that recanalizing the MCA with mechanical thrombectomy dramatically increases survival and functional outcomes.[421] However, the latter studies included patients with acute stroke in general, not after CAS specifically. Updated AHA guidelines recommend endovascular intervention with stent retriever/ aspiration within 6 hours of onset of stroke for patients with an occluded ICA or middle MCA.[422]

Intracranial hemorrhage. This complication of CAS is rare. In the National Impatient Sample database, the risk of intracranial hemorrhage is 6-fold higher in CAS compared with CEA.[423] However, these results have not been confirmed in large clinical trials.[8] Hypertensive patients with symptomatic and bilateral carotid artery stenoses have been shown to have increased risk of developing intracranial hemorrhage after CAS.[424] One study showed that patients on beta blockers before CAS had 65% lower risk of stroke and death if they developed hypertension postoperatively.[62] Before the initiation of the CAS procedure, all patients should be fully anticoagulated with intravenous unfractionated heparin, preferably at 80 to 100 U/kg of dose. The activated clotting time should be followed not to exceed 300 seconds to prevent risk of hemorrhagic stroke secondary to reperfusion after CAS.[425] Acute stent thrombosis. This complication is an acute emergency with an increased risk of embolic stroke, and it can be due to carotid artery recoiling, stent misplacement, poor sizing or massive plaque protrusion through stent struts. Treatment of acute stent thrombosis usually involves conversion to CEA. However, because many of these patients are at high risk for CEA, endovascular intervention with catheter-based thrombolysis and thrombectomy may be considered. This allows use of cerebral angiography to evaluate distal embolization as well as the use of stent retrieval thrombectomy.

Carotid artery dissection

Dissection can be largely avoided with meticulous techniques. This complication should be identified on the completion angiogram. If the dissection occurs distally and is flow limiting, a second stent can be placed in the true lumen overlapping with the initial stent. In CCA dissection after TCAR, the same stent or an additional stent can be extended as proximal as possible to the tip of the sheath. Conversion to CEA is rarely needed. Engaging the ECA when possible, dilatation of the anterior wall of CCA with a 9F dilator as well as maintaining the 0.035 wire access, reduce risk of dissection during insertion of the arterial sheath during TCAR.

Cerebral hyperperfusion

This complication is rare, occurring in 1% to 2% of patients undergoing CAS. Patients typically present with headache. Diagnosis can be made on CT imaging revealing ipsilateral cerebral edema without any evidence of stroke. Treatment is largely supportive, focusing on controlling blood pressure and maintaining adequate cerebral perfusion. Additional details concerning management of hyperperfusion syndrome are discussed in other sections of these guidelines.

Summary and recommendations for treatment of stroke after CAS.
AcuteCAScomplication.

1. Stroke owing to MCA occlusion owing to embolization after CAS should be treated with mechanical thrombectomy and thrombolysis.
2. Acute carotid stent occlusion should be treated withimmediate recanalization and cerebral angiography with potential mechanical thrombectomy and thrombolysis, which may include thrombus aspiration and filter removal.
3. Aggressive post-PTA should be avoided when possible to decrease hemodynamic depression and the risk of stroke.

Hemodynamic instability: Post-CEA hypertension and hypotension

Blood pressure instability after CEA is a risk factor for cerebrovascular and cardiovascular complications.[323] Carotid baroreceptors are mainly localized in the adventitial layer of the proximal ICA,[323,426] and these receptors play a significant role in moderating increases and decreases in blood pressure.[427] Denervation of the carotid sinus nerve during CEA can significantly increase risk of postoperative hypertension.[323] Hypertension in the postoperative period is much more common than hypotension. ECEA has been shown to increase risk of hypertension, while CCEA may increase overall risk of hypotension.[323]

Hemodynamic instability is common after CEA, and can result either from significant cardiac-related complications or, more commonly, from disordered baroreceptor function.[417] Both hypertension and hypotension can be associated with impaired clinical outcome.[227,323,428,429] Hypotension is less common and is often accompanied by bradycardia. Removal of plaque from the carotid bifurcation has been hypothesized to impair normal baroreceptor mechanisms. Reflex hypotension following endarterectomy can persist until the carotid sinus mechanisms has readjusted. CEA can result in direct surgical damage to the baroreceptor nerves located at the carotid bifurcation[323,430] or to the compensatory restoration of the baroreflex mechanism caused by removal of the bifurcation plaque.[323,430,431] Significant hypotension can result in postoperative global cerebral ischemia in predisposed patients. A recent meta-analysis found that post-CEA hypertension requiring vasodilator therapy was 53.8% after ECEA and 40.3% after conventional endarterectomy.[323]

Postoperative hypertension is closely related to presence of preoperative hypertension, but its mechanism following CEA is not well-characterized. Significant postoperative hypertension can increase risk of other postCEA complications, including myocardial ischemia, ICH, and wound hematoma.[432] Appropriate management of both postoperative hypertension and hypotension can help decrease the incidence of other associated postoperative morbidities.

To appropriately treat hemodynamic instability after CEA, patient observation in a monitored unit with either an indwelling radial artery catheter of systemic blood pressure monitoring is generally recommended in the initial postoperative period.[417] Hypotension should be treated initially with fluid administration to achieve a euvolemic state. If hypotension persists without other hemodynamic causes, blood pressure support with an intravenous infusion of phenylephrine is generally recommended.[417] Vasoconstrictors can typically be weaned within 24 hours after surgery.

Postoperative hypertension is generally treated with intravenous sodium nitroprusside.[417] Associated myocardial ischemia should be treated as appropriate. Most patients can resume their preoperative oral antihypertensive medications within 24 hours following surgery, and this often reduces the need for additional intravenous pharmacological management.[417]

Summary and recommendations for the management of postoperative hemodynamic instability after CEA.

1. Significant postoperative hypertension or hypotension should be evaluated carefully by appropriate hemodynamic monitoring during the initial post-CEA period.
2. Postoperative hypotension without other obvious hemodynamic etiologies should be treated with intravenous vasoconstrictors, typically phenylephrine, to achieve a normal blood pressure until hypotension resolves.
3. Postoperative hypertension should be treated withintravenous vasodilators, typically sodium nitroprusside, to achieve a normal blood pressure until hypertension resolves.
4. Selected patients with significant hemodynamic instability post-CEA should be carefully monitored for associated complications including myocardial ischemia and ICH.

Post-CAS hemodynamic depression

Hypotension with bradycardia is not uncommon after CAS owing to stretching of the carotid baroreceptors with angioplasty and stenting. This complication is increased four-fold with poststent balloon dilatation.[390] Therefore, careful monitoring of the patient's blood pressure and heart rate is necessary. An arterial pressure monitor connected to the intervention sheath or a separate arterial line allows for continuous blood pressure monitoring.[366] Hemodynamic depression can increase stroke risk owing to cerebral hypoperfusion in general and inadequate flow reversal in TCAR specifically. Atropine (0.4 to 1.0 mg) is often used to prevent hemodynamic depression during angioplasty of the carotid bulb. Glycopyrrolate (0.4 mg) is an alternative to atropine because it is associated with fewer coronary side effects. Volume resuscitation followed by epinephrine or dopamine can be used in patients with persistent or refractory postoperative hypotension. Some risk factors for persistent hypotension include type of stenosis, echogenic plaque morphology, carotid calcification and distance from carotid bifurcation to maximum stenotic lesion (#10 mm).[433] It is unusual for patients who have had prior CEA to have significant bradycardia because the normal innervation of the carotid baroreceptor is interrupted during

the initial procedure.[434] In these cases, glycopyrrolate or atropine is administered only if hypotension or bradycardia ensue.[366]

CNI after CEA

Although a CNI is likely the most common complication after CEA, it is typically mild, self-limited, and without prolonged or significant clinical sequelae. The reported incidence ranges from 5% to 20%.[417,435-438] In a prospective study of patients who underwent CEA and postoperative laryngoscopy evaluations, cranial nerve injuries were found in 11.4% of 656 carotid operations.[436] However, approximately one-third of the patients with documented cranial nerve injuries diagnosed by otolaryngology examination were clinically asymptomatic. In the CREST trial, the incidence of CNI was 4.7%. However, there was no significant adverse impact of CNI on patient quality of life at 1 year after surgery.[5,439] The most commonly injured nerves include, in decreasing order of incidence, the hypoglossal, recurrent laryngeal, superior laryngeal, marginal mandibular, glossopharyngeal, and spinal accessory nerves.[417,435]

In another study, a vast majority of CNIs were transient. Only 47 patients (0.7%) had a persistent CNI at their follow-up visit (median, 10.0 months; range, 0.3-
15.6 months). Predictors for CNI included urgent procedures (OR, 1.6), immediate reexploration after closure under the same anesthetic (OR, 2.0), and return to the operating room for a neurologic event or bleeding (OR,
2.3).[435]

The most appropriate way to avoid CNI is with appropriate knowledge of the relevant anatomy and meticulous identification and protection of the nervous structures during the conduct of the operation. Sharp dissection close to the arterial wall, and strict adherence to some general surgical rules, including careful use of forceps, retractors, cautery, and arterial clamps is mandatory. Perioperative dexamethasone administration has been shown to reduce risk of temporary CNIs during CEA without reducing the prevalence of permanent CNIs.[440] However, there is a remarkable paucity of data concerning treatment of CNIs once they have happened.[250]

Nerve injury is most often caused by blunt stretch injury to the nerves, which can occur with excessive traction; frank nerve transection is extremely rare. Injury can also result from electrocautery damage, inadvertent clamping, or from direct nerve transection.[417] Nerve injury may be more common during reoperative carotid surgery. Use of an intraoperative vagal nerve stimulator may be helpful during reoperative carotid surgery to try to avoid injury related to scar tissue.[417]

Iatrogenic CNI that occurs during CEA is most often managed expectantly. Unilateral hypoglossal injury is rarely serious.[417] Vagus or recurrent laryngeal nerve injury can result in paralysis of the ipsilateral vocal cord, and typically manifests as hoarseness. Superior laryngeal nerve injury can manifest by voice fatigue and difficulty with voice modulation. The marginal mandibular branch of the facial nerve may be injured from traction during surgery or from administration of cervical block anesthetic, and manifests as dropping of the ipsilateral lip.[417] Importantly, this should not be confused with a postoperative stroke that may produce facial asymmetry. Transient paresthesia of the marginal mandibular nerve can be cosmetically upsetting to the affected patient.

Summary and recommendations for the management of CNI after CEA. Cranial nerve injuries are best avoided by meticulous knowledge of the relevant anatomy and careful dissection to prevent injury to contiguous nervous structures.

1. Once a CNI is diagnosed, expectant management istypically indicated.
2. In rare cases, vocal cord paralysis may require otolaryngologic intervention, and bilateral vocal cord paralysis may require tracheotomy.
3. Vocal cord evaluation might be advisable in patientswith bilateral carotid stenosis post first CEA and before contralateral CEA.
4. In rare cases, critical glossopharyngeal nerve injury may produce severe dysphagia and/or aspiration and may require placement of a feeding gastrostomy tube.

Myocardial infarction and renal insufficiency

Patients undergoing CEA have a high prevalence of concomitant coronary artery disease. Although frank MI is unusual after CEA, MI is responsible for 25% to 50% of perioperative deaths following CEA.[441,442] The incidence of perioperative MI and resultant mortality has likely decreased in the past several decades owing to improved screening and treatment of pre-existing coronary disease as well as improved perioperative medical management.[417] Appropriate medical management of the CEA patient is critical to reduce risk of perioperative MI and cardiac mortality, and should include standard antihypertensive medications, statin medications, and antiplatelet therapy.[417] Although beta blockers should be continued in patients who have been on the medication chronically, routine use of routine beta blockers is controversial. It may be reasonable to begin perioperative beta blockers in specific patient groups (see section on the perioperative management of patients undergoing CEA).

Either single or dual antiplatelet therapy should be continued in the perioperative period for CEA to decrease the risk of both stroke and perioperative MI, particularly in patients with known preexisting coronary artery disease or prior percutaneous coronary procedures. The American College of Cardiology Perioperative Guidelines endorses continuation of aspirin during the period surrounding CEA.[443] The risk of periprocedural MI from aspirin withdrawal likely outweighs risk of severe bleeding from aspirin continuation.[3] Patients on clopidogrel may require individualized management. Clopidogrel may be safely continued through the perioperative period without a significantly increased risk of major bleeding.[165] Discontinuation of dual antiplatelet therapy may significantly increase risk of coronary stent thrombosis and MI, particularly in the setting of drug-eluting stents.[444]

Preoperative statin therapy can significantly reduce perioperative mortality and MI after CEA.[152,153] In a systematic review and meta-analysis, statin users undergoing CEA were at significantly lower risk

of perioperative death compared with statin-naïve patients.[445] However, a corresponding difference in risk of perioperative MI was not observed. Nevertheless, use of perioperative statin medications is generally recommended.

Labile blood pressure is common in the postoperative period following CEA. Aggressive monitoring and appropriate pharmacologic treatment of both hypotension and hypertension is recommended to reduce risk of related morbidity, including myocardial ischemia. For patients with known severe preexisting coronary artery disease, obtaining routine postoperative electrocardiograms and cardiac enzymes may be considered.[446] Patients with clinical, electrocardiogram or other evidence of myocardial ischemia or infarction in the postoperative period following CEA should be treated by accepted pharmacologic techniques, and urgent cardiac catheterization should be considered in appropriate patients.[447]

The risk of cardiovascular complications after CAS is very minimal compared with CEA. Data from randomized trials demonstrate significantly lower numbers of periprocedural MIs after stenting.[5,7,8] Performing CAS under local anesthesia is associated with significantly lower risk of MI and other cardiac complications.[365]

The use of a higher contrast load with CAS, as opposed to CEA, can lead to contrast-induced nephropathy, especially in CKD patients. The amount of contrast used during the procedure should be minimized and not exceed 60 mL. Adequate fluid resuscitation should be provided to minimize risk of acute kidney failure.

Summary and recommendations for the management of perioperative MI risk after CEA.

1. Perioperative MI after CEA is best avoided by appropriate preoperative treatment of relevant atherosclerotic risk factors, screening for coronary artery disease when appropriate, and standard pharmacologic management of atherosclerosis during the perioperative period.
2. All patients undergoing CEA should be treated with astatin medication, unless a contraindication exists.
3. All patients undergoing CEA should be maintainedon either single or dual antiplatelet medication throughout the perioperative period, unless a contraindication exists.
4. Patient with a coronary drug-eluting stent should bemaintained on dual antiplatelet medications whenever feasible.
5. Early recognition of perioperative MI should occur toallow appropriate individualized therapy including medical or pharmacologic interventions, or urgent cardiac catheterization/percutaneous coronary intervention when deemed appropriate.

Wound hematoma after CEA

The reported incidence of significant perioperative bleeding after CEA is 0.7% to 3.0%.[417] Most cases of clinically significant bleeding result from diffuse capillary or soft tissue oozing owing to intraoperative heparinization and/or antiplatelet agents. At the completion of CEA, administration of protamine to achieve heparin reversal seems to decrease the incidence of significant wound hematoma.[248] Although many vascular surgeons routinely use drains after CEA, there has been no demonstrable decrease in risk of reexploration for bleeding when drains are used.[45]

In a retrospective study of 384 patients, preoperative clopidogrel therapy and not using protamine sulfate after heparin were identified as risk factors for hematoma.[448] Upon reexploration, venous bleeding or capillary oozing were more common findings than arterial bleeding from the site of vascular repair, and difficulty with intubation because of tracheal deviation was prevalent. The authors recommend that airway management for reexploration should include a laryngeal mask airway, partial wound reexploration with hematoma evacuation under initial local anesthesia, subsequent intubation for general anesthesia, and finally complete wound exploration to achieve hemostasis.[448]

Although small asymptomatic wound hematomas or ecchymosis may be carefully observed, larger hematomas that result from frank surgical bleeding can be catastrophic. The presence of an enlarging hematoma may result in stridor and airway compromise, and mandates emergency evacuation to avoid respiratory arrest. A relatively small amount of blood in the closed space of the neck may cause airway compromise. If the patient is in clear respiratory distress, opening the incision at the bedside to evacuate the hematoma and relieve airway obstruction can be lifesaving. Under more controlled circumstances, emergency transport to the operating room is advised. Awake fiberoptic endotracheal intubation may be required to safely intubate the patient in the presence of a compressed airway. Rarely, emergency cricothyroidotomy may be required. Once the airway has been secured, reexploration should proceed in an organized fashion with assessment and appropriate surgical treatment of any hemorrhage sources.

Summary and recommendations for the management of wound hematoma after CEA. Avoidance of wound hematoma is best accomplished using meticulous surgical technique and appropriate methods of achieving hemostasis.

1. Protamine should be considered to reverse heparinization; decisions on its use may depend on how much heparin was administered, clinical examination of the wound for appropriate hemostasis, and other factors including the use of antiplatelet medications.
2. Small, asymptomatic hematomas in the perioperativeperiod may be safely observed.
3. Symptomatic or enlarging hematomas should undergo operative reexploration and treatment to avoid airway compromise.
4. Patients with large hematomas in respiratory distressmay require reopening of the incision at the bedside to evacuate the hematoma and prevent respiratory arrest.
5. Intubation in the setting of a large neck hematomamay require awake fiberoptic intubation or other techniques to manage airway compromise.

Late complications after CEA

Prosthetic patch infection. Infectious complications are extremely rare after CEA. The reported risk of wound infection or cellulitis ranges from 0.09% to 0.15%.[417] Prosthetic patch infection is even rarer, but true incidence is unknown. In a systematic review, 77 cases of graft infection were reported.[449] There are reported associations between postoperative wound hematoma and early prosthetic patch infections.[449] In one series, 80% of patients who presented with prosthetic patch infection within 9 weeks of surgery had documented wound complications in the perioperative period.[450] Other patient-related factors that may increase risk of patch infection include immunosuppression, and poor general or dental hygiene. Patch infection has been reported after dental or other procedures, which may carry a risk of transient bacteremia.[451] As a result, some practitioners recommend routine antibiotic prophylaxis for patients with prosthetic carotid patches before undergoing invasive or dental procedures.[452]

There seems to be a bimodal distribution of time to presentation.[449,451] Early patch infections may present with typical wound cellulitis. The signs associated with late patch infection may be more insidious, and can include localized edema, facial swelling, the appearance of a draining sinus tract, or a neck mass owing to inflammation or phlegmonous changes, or the formation of a related pseudoaneurysm. The most commonly involved organisms are Staphylococcusepidermidis and Staphylococcusaureus.[449,451]

Untreated prosthetic patch infections can result in localized sepsis and ultimately in pseudoaneurysm formation with rupture of the patch and uncontrolled hemorrhage. Therefore, surgical management is imperative when a documented prosthetic patch infection has been diagnosed. Preoperative imaging studies should include appropriate blood cultures and imaging, typically with duplex scanning and CTA. Presumptive antibiotics directed toward common organisms should be started.

Surgical intervention should include removal of all infected prosthetic material and establishing revascularization with autologous materials. Autologous vein patch angioplasty or interposition vein graft reconstruction are commonly used. Rarely, carotid artery ligation may be required. Surgical management can be challenging, and it is complicated by inflammation and scar tissue related to the primary surgical procedure, as well as localized sepsis and inflammatory changes. In some cases where the soft tissue or skin is severely compromised, a rotational muscle or myocutaneous flap should be considered to achieve adequate coverage of the vascular reconstruction or ligated vessels.

Summary and recommendations for the management of prosthetic patch infection after CEA.

1. In patients who have undergone CEA with prostheticpatch angioplasty reconstruction, empirical prophylactic antibiotics should be considered during dental and other procedures with a reasonable risk of transient bacteremia.
2. Perioperative antibiotics should be administered routinely during primary CEA.
3. Wound cellulitis in the immediate perioperative period should be treated with appropriate antibiotic therapy and close monitoring.
4. The presence of atypical wound edema, swelling, amass, or sinus in the neck should be evaluated promptly in patients with prior CEA.
5. Investigative studies for suspected prosthetic patchinfection should include duplex scanning and CTA, as well as appropriate laboratory and infectious disease studies.
6. Presumptive antibiotics directed toward common pathogens should be started in patients with suspected prosthetic patch infection.
7. In patients with a documented patch infection, operative management is indicated. Prosthetic material must be excised, and arterial reconstruction performed using autologous material. Appropriate soft tissue coverage must be assured, using rotational muscle flaps or myocutaneous flaps if necessary.
8. Temporary use of covered stent in cases of infectionand patch blowout as a bridge to a more controlled operation may be considered.

Restenosis after CEA

Recurrent carotid artery stenosis following CEA is reported to occur in 5% to 22% of patients.[417] However, very few (3%) of these recurrent stenoses are symptomatic, and few typically require reintervention.[417,453-455] As reported in the CREST study, the risk of significant restenosis or occlusion was 6.3% at 2 years.[453]

Recurrent stenosis is more likely to occur in certain patient subgroups, including women, active smokers, patients who undergo initial endarterectomy at a young age, and in patients with hypercholesterolemia, diabetes, and hypertension.[455-458] Additionally, some technical factors at the time of the initial CEA may contribute to the development of residual stenosis or subsequent restenosis. These include clamp injury, use of an intraluminal shunt, or placement of tacking sutures at the distal end point of the endarterectomy site.[459]

With regard to decreasing the incidence of significant restenosis, there are significant data in the literature to substantiate a recommendation for patch angioplasty or eversion endarterectomy over standard endarterectomy with primary closure of the artery.[3] A metaanalysis of randomized trials comparing bovine pericardium and other patch materials for CEA did not find any significant differences in the rates of late restenosis.[310] A systematic review of randomized controlled trials of patch angioplasty vs primary closure found that patch angioplasty seemed to decrease the risk of perioperative death or stroke, late ipsilateral stroke, and late recurrent stenosis.[269]

Recurrent stenosis after CEA seems to have two distinct patterns of presentation. Early recurrent stenosis usually develops within two years of primary CEA and typically results from neointimal hyperplasia.[3,417,455] This usually develops at the site of

endarterectomy and is felt to have a lower thromboembolic potential to cause stroke than recurrent frank atherosclerotic disease. Therefore, the threshold for reintervention is high, and these lesions are typically observed unless they become pre-occlusive or symptomatic, which is infrequent. Restenoses that occur after 2 to 3 years after primary CEA typically represent recurrent atherosclerotic lesions.[417,455] Indications for treatment of late recurrent carotid stenosis owing to atherosclerotic disease are typically similar to those for de novo carotid lesions.

Before the advent of carotid stenting, repeat carotid surgery was the standard treatment for symptomatic or severe recurrent stenosis that required reintervention for stroke prevention. However, scar tissue in the reoperative field can make the operation more technically demanding, and a higher incidence of CNI and other complications have been reported.[417] However, in general, reoperative carotid surgery can be performed safely, and has good durability.[455]

Nevertheless, the increased technical difficulty with reoperative carotid surgery has led many to recommend CAS as the preferred procedure for recurrent carotid stenosis.[417] A recent systematic review and meta-analysis of 4399 patients who underwent either redo carotid surgery or CAS for recurrent carotid stenosis found no differences in risk of perioperative mortality or stroke.[460] Patients who underwent redo CEA had higher risk of cranial nerve injuries, but most recovered in three months. However, risk of a secondary episode of recurrent stenosis was greater in patients whose initial restenosis was treated with CAS.

Several studies addressed perioperative and late outcomes of open surgical and endovascular treatment of post-CEA restenosis, and demonstrated acceptable results with either technique.[461] However, in many of these studies, CAS was typically used for early lesions related to neointimal hyperplasia, while redo CEA was preferred in cases of late restenosis owing to recurrent atherosclerotic lesions. Early restenosis is typically a fibrous lesion that is thought to have a low potential for embolization and stroke. By contrast, late recurrent stenoses owing to atherosclerotic lesions are typically associated with a higher embolic risk. Many authors recommend reintervention in cases of moderate and severe symptomatic recurrent stenosis, as well as severe preocclusive or progressive asymptomatic restenosis.

There seems to be an established relationship between restenosis and late ipsilateral stroke.[461,462] In a systematic review and meta-analysis of studies with a mean of 37 months of surveillance, 13 of 141 CEA patients (9.2%) with a restenosis of greater than 70% or occlusion suffered a late ipsilateral stroke compared with 33 of 2669 patients (1.2%) who did not have a restenosis of greater than 70% or occlusion. Nevertheless, 97% of all late ipsilateral strokes after CAS and 85% after CEA occurred in patients without evidence of significant restenosis or occlusion.[462]

Summary and recommendations for the management of restenosis after CEA.

1. The use of patch angioplasty or eversion endarterectomy is generally preferred over conventional endarterectomy with primary closure to reduce the incidence of recurrent carotid stenosis, particularly in women or patients with small diameter ICAs.
2. Early recurrent stenosis after CEA can generally bemanaged expectantly unless it is symptomatic, progressive or a very high grade/preocclusive lesion ($80%).
3. Late recurrent stenosis after CEA should be considered for reintervention with similar parameters as primary CEA in both symptomatic and asymptomatic cases.
4. Reintervention for recurrent stenosis after CEA caninvolve either redo endarterectomy/carotid artery reconstruction or carotid stenting procedures based upon the particular patient, clinical scenario and relevant anatomy.

Restenosis after CAS

Incidence. In-stent restenosis can be identified on routine follow-up by duplex ultrasound examination. Factors predisposing to in-stent restenosis are both mechanical and patient-related, but the most important is the neointimal thickening within stent struts, leading to lumen reduction.[463] Late de novo atherosclerosis or progressive atherosclerosis is also a common cause. Available data on incidence, predictors, diagnostic approach, and therapeutic strategies of restenosis after CAS are poor and inconsistent.[463] The incidence of carotid in-stent stenosis has been reported to vary between 1% and 30%, and might be slightly overestimated by conventional duplex ultrasound examination.[464,465] In the EVA-3S trial, recurrent carotid stenosis (>70% as defined by duplex ultrasound examination), was 11.1% at 2 years after CAS, significantly higher than after CEA (4.6%; P¼ .001).[465] In contrast, a secondary analysis of the Carotid Revascularization Endarterectomy vs Stenting Trial (CREST) trial showed no significant difference in restenosis or revascularization risk at 2 or 10 years after CAS (12.2%) and CEA (9.7%).[453] The systematic review and meta-analysis done by Kumar et al[462] on restenosis after carotid intervention and its relationship with recurrent ipsilateral stroke showed that in 11 randomized trials (4249 patients) of CEA that followed patients over a mean of 47 months, the occurrence of greater than 70% restenosis or occlusion was 5.8% (95% CI, 4.1-8.2). In five randomized trials (1078 patients), restenosis risk of greater than 70%/occlusion after patch CEA over a mean of 32 months was 4.1% (95% CI, 2-8.4).[462] In six randomized trials (2916 patients) over a mean follow-up of 60 months, the occurrence of restenosis greater than 70%/occlusion in patients undergoing CAS or PTA was 10.3% (95% CI, 6.0-16.4). In five trials (2,716 patients) and over a mean follow-up of 62 months restenosis risk greater than 70%/occlusion was 10% (95% CI, 6.0-16.3) in patients having CAS. The same study showed that over a mean of 50 months of surveillance, 1 of 125 CAS patients (0.8%) with restenosis greater than 70%/occlusion suffered a late ipsilateral stroke compared with 37 of 1839 CAS patients (2%) who did not have greater than 70% restenosis. Female sex, diabetes, and dyslipidemia were independent predictors of restenosis or occlusion after the two procedures.[453]

Diagnosis

Duplex ultrasound examination is frequently used for routine follow-up after CAS. The degree of lumen diameter reduction, peak systolic velocity, end-diastolic velocity, and the ratio of peak ICA to CCA velocity (ICA/CCA ratio) are the most common parameters used to quantify stenosis. In selected cases when results of duplex ultrasound examination are inconclusive, CTA is required. Discrepancies in results with either of these techniques should be confirmed using DSA.[463]

However, definitive criteria for diagnosis of restenosis after CAS have not yet been established and there are few data on the natural history of in-stent restenosis. Evidence from recent studies suggests that criteria used for diagnosing an atherosclerotic stenosis of the carotid artery cannot be easily applied to in-stent restenosis.[464] This is due to the distinct biomechanical properties of the stented artery and its enhanced stiffness which results in increased flow velocity. Recent analysis proposed adjusted criteria for defining stenosis in stented arteries.[464,466,467] A review of 14 studies suggested recording Doppler parameters of the recently stented vessel soon after CAS and using these values as the patient's reference point. This new reference point will guide future routine surveillance scans.[468]

Clinical impact

The clinical impact of significant restenosis after CAS is uncertain, but neointimal hyperplasia seems to be associated with reduced potential for embolization compared with native lesions.[467,469] In most trials, a higher incidence of in-stent restenosis during follow-up did not impact complication rates, suggesting that it might be a relatively benign disease.[465,470,471] However, analysis of the CREST trial showed greater risk for ipsilateral stroke after the periprocedural period up to the end of follow-up period in patients who had restenosis or occlusion within 2 years compared with those who did not have restenosis (HR, 4.37; 95% CI, 1.91-10.03; P¼ .0005, adjusted for age, sex, and symptomatic status).[453] A meta-analysis of surveillance data from a randomized trial involving CEA/CAS demonstrated that patients who had CAS had a 10% incidence of greater than 70% stenosis/occlusion at mean follow-up of 62 months. Notably, only 1 of 125 were associated with an ipsilateral stroke.[462]

Management

The management of patients with recurrent stenosis after CAS is clinically challenging, and no consensus on the best treatment modality is currently available.[472] Owing to its low incidence, no prospective study has compared treatment options for in-stent restenosis. The choice should therefore be made on a case-by-case basis with careful analysis of lesion features and the patient's profile. In the future, adequately powered trials using a uniform definition and standardized workup for in-stent restenosis are s necessary to determine the appropriateness of interventions for in-stent restenosis.

According to the available literature, in-stent restenosis can be successfully treated with surgical interventions (endarterectomy with stent removal in some cases) as well as with endovascular techniques.[472] Tight management of diabetes, dyslipidemia, and smoking cessation remain potent targets for preventing and improving outcomes for patients with in-stent restenosis.[473] However, medical therapy alone should be chosen only in asymptomatic patients and patients with high-risk lesions where invasive treatment is high-risk based on the patient's clinical status and comorbidities.

Endovascular treatment, such as PTA with simple balloon, cutting-balloon, drug-eluting balloon, and stenting, is recommended as the first choice wherever possible, mainly because it is the less invasive option and has good results. Although PTA is a common treatment for in-stent restenosis, recurrent restenosis seems to limit the durability, leading to recurrent interventions and associated cost implications.[472] An analysis of the VQI database showed no significant differences in 1year stroke, death, and stroke/death between primary CAS and redo CAS. Moreover, the odds of bradycardia and hypotension were lower after redo CAS compared with primary CAS.[434] Drug-eluting techniques are emerging and may become the preferred treatment option, but long-term follow-up is needed to evaluate their efficacy.[472]

In contrast, CEA should be avoided in asymptomatic patients with serious systemic disease. Analysis of 645 patients with in-stent restenosis in the VQI database showed no significant differences in perioperative and 1year outcomes between CEA vs restenting or PTA. However, CEA was offered to patients who are more severely ill than redo CAS, resulting in significantly higher mortality (3.7% vs 0.9%; P¼ .02).[473]

Summary and recommendations for treatment of restenosis following CAS.

1. Most asymptomatic patients (>70% restenosis) should be treated with aggressive medical management.
2. Symptomatic patients and progressive lesions shouldbe offered an endovascular option first.
3. Evidence on PTA vs drug-coated balloon vs restenting is lacking.

MISCELLANEOUS

Acute carotid occlusion

Acute carotid occlusion commonly presents with cerebral or retinal ischemia, and is associated with poor clinical outcomes.[474-476] Acute carotid occlusion represents 6% to 15% of patients with acute ischemic stroke.[477] Patients usually bear high National Institutes of Health Stroke Scale scores because of severe neurologic deficits, with only 2% to 12% achieving good recovery, 40% to 69% having a severe deficit, and 16% to 55% dying from infarction.[478-480] Carotid occlusion can occur after carotid stenting or endarterectomy owing to technical problems or it may result from underlying cardiac pathology such as atrial fibrillation. Female sex, age, history of embolism, and higher B-type natriuretic peptide levels have been identified as risk factors for proximal carotid axis occlusion in patients with atrial fibrillation.[481]

Acute ICA occlusion is a therapeutic challenge because of poor neurologic outcome and paucity of effective therapeutic options.[482] Treatment of acute ICA occlusion needs to be individualized. No large, controlled trials have examined the efficacy of any treatment approach. Patients presenting with stroke should be admitted to a stroke unit. Hypotension should be avoided because it might severely compromise cerebral perfusion in the context of ICA occlusion. In contrast, hypertension should not be corrected in the acute phase unless it is in a malignant range. Short-term (approximately 6 weeks) anticoagulation with heparin and warfarin followed by antiplatelet drugs might be used to decrease embolization from the fresh clot. However, evidence for this strategy is unavailable.[482]

In patients presenting early (<3 hours) and up to 5 to 6 hours after the onset of stroke with no evidence of cerebral hemorrhage or a large infarction on brain imaging, intravenous thrombolysis using recombinant tPA may be considered. Thrombolytic treatment using a combination of intravenous and intra-arterial routes or using the intra-arterial only route has been reported to be effective in distal ICA occlusion, particularly when given soon after the onset of stroke. However, the efficacy of IV tPA has been debated because it is associated with poor recanalization in the case of large clots and secondary to the slow distal flow in patients with acute ICA occlusion.[475,477,483] Several factors may influence IV tPA treatment outcomes among patients with ICA occlusion. First, because the rate of fibrinolysis depends on the pressure gradient to which the clot is exposed, effective delivery and distribution of thrombolytic drug into the clot is needed to accelerate fibrinolysis.[484] Second, the presence of an ipsilateral MCA occlusion along with the ICA occlusion, is generally caused by artery-to-artery embolism, with a platelet-rich, lytic-resistant clot proceeding from the carotid plaque. These clots have a poorer propensity for lysis with tPA compared with fibrin-rich clots.[485] Third, because of the high clot burden and poor collateral circulation, functional ICA occlusions show poor response to IV thrombolysis.[486]

With advances in stent retrievers, recanalization rates in patients with ICA occlusion are increasing. Optimal endovascular strategies for patients with acute carotid occlusion are being elucidated. Despite the complex classification of occlusion sites, different underlying etiologies, huge clot burden and high risk of ICH, endovascular treatment of acute ICA occlusion seems to be effective and safe.[487] However, the time to treatment should be as short as possible.

A high revascularization rate has been reported with angioplasty and stenting (endovascular treatment) for acute carotid occlusions. Sugg et al[488] reported a 64% immediate recanalization risk with endovascular treatment in patients with ICA occlusion treated within 3 hours of onset of stroke. The most challenging step involves catheterization of the lumen of the total occluded artery. In a large case series involving stenting of the proximal ICA followed by thrombectomy, Cohen et al reported successful reperfusion in 79% of patients. These data supported use of this approach because most acute occlusion lesions are due to atherosclerotic lesions with fresh thrombus.[489]

Summary and recommendations.

1. Intravenous thrombolysis should be administered asfirst-line treatment in symptomatic patients with early acute ICA occlusion.
2. Endovascular treatment might be considered and has acceptable clinical outcomes.

Carotid artery dissection

Carotid dissection may occur spontaneously, or it may result from traumatic or iatrogenic injury. Diagnosis is made with contrast-enhanced CTA, MRA or catheterbased angiography. The choice of appropriate therapy remains controversial because most carotid dissections heal on their own and there are no randomized trials to compare treatment options.[490] Antithrombotic treatment with either an anticoagulant (heparin, low molecular weight heparin or warfarin) or a platelet inhibitor (aspirin, clopidogrel or the combination of extendedrelease dipyridamole plus aspirin) for at least 3 to 6 months is reasonable in patients with carotid artery dissection associated with ischemic stroke or TIA. The number of adverse events does not significantly differ based on the medical therapy.[491] The safety and effectiveness of therapy with alpha-adrenergic antagonist, angiotensin inhibitor, or nondihydropyridine calcium channel antagonist to lower blood pressure to normal and reduce arterial wall stress are not well-established.

By contrast, intervention is reserved for symptomatic patients with recurrent neurologic symptoms whose symptoms have not responded to antithrombotic therapy after acute carotid dissection. Although open surgical repair with saphenous vein interposition graft is the therapy of choice, it is associated with increased risk of perioperative cerebrovascular events and CNI.[492]

With recent advances in endovascular technology, percutaneous therapy with stent placement has become increasingly common. The indications for stent placement are poorly defined. Failure or contraindications to medical therapy is the most common reason for endovascular management. In a retrospective review of 53 patients who underwent endovascular treatment for symptomatic traumatic carotid dissection, risk of postoperative symptoms, luminal narrowing, and asymptomatic stent occlusion were 6.4%, 2.1% and 2.0%, respectively.[493] Although there are no studies comparing open vs endovascular repair, endovascular treatment of patients who failed medical management seems to be justified.

TREATMENT OF PROXIMAL VERTEBRAL ARTERY DISEASE

Proximal vertebral artery disease (V1 segment) is a less common cause of cerebrovascular pathology than internal carotid stenosis, but atherosclerosis of the vertebral artery may occur in up to 30% of patients presenting with TIA or stroke.[494-498] In addition, these patients may have concomitant ICA disease. Less common etiologies include dissection, trauma, fibromuscular dysplasia, Takayasu's disease, spinous bony compression, aneurysms, and arteritis. Patients with vertebral-basilar TIAs with a diseased vertebral artery have a 5-year stroke risk of 22% to 35%.[495,499-501] In addition, patients with posterior circulation strokes have higher mortality (20%-30%)

than patients with anterior circulation strokes.[502-504] The proximal vertebral artery origin (V1 segment) is the most common site of atherosclerotic stenosis (20%40% of patients), but lesions are typically smooth with low embolic risk.[505]

Despite the relatively high stroke risk, only 5%-8% of operations for cerebrovascular disease are performed for proximal vertebral disease.[506] Before treatment of symptomatic vertebral artery lesions, other overlapping causes of symptoms, such as orthostatic hypotension, aggressive use of antihypertensive medications, inner ear pathology, and cardiac causes must be excluded. The most common open surgical treatment is vertebral artery to CCA transposition, with a low morbidity and mortality akin to CEA. However, these procedures are reserved for symptomatic patients.[506-508] Outcomes of combined stroke and death are less than 1% for vertebral artery operation alone, but 5.7% when combined with carotid disease intervention.[507] Endovascular treatment for proximal vertebral artery disease has been reported in multiple small case series, often with a high risk of restenosis (40%-50%)[498,509-512] Distal embolic protection is often difficult because of the small size of the vertebral artery,[494,513] and both angioplasty alone and in combination with stent has been described.[494,509-512] The randomized series (CAVATAS)[510] and other small descriptive series[494,509,511] failed to demonstrate superior outcome in the endovascular management of vertebral artery disease, with a higher incidence of carotid territory stroke, MI, and restenosis in patients having stent placement.

Summary and recommendations. In patients presenting with symptomatic vertebral disease causing vertebrobasilar TIA or stroke, open surgical treatment with vertebral artery to common carotid transposition is recommended in low-risk surgical candidates.

TREATMENT OF BRACHIOCEPHALIC DISEASE AND PROXIMAL CCA OCCLUSIVE DISEASE

Significant stenosis or occlusion of the great vessel origins is rare with an incidence of 0.5% to 6.4%. Disease occurs in the innominate or left subclavian artery more frequently than the left carotid.[514] Many of these arch lesions are asymptomatic, although tandem lesions in the carotid bifurcation can occur in up to 17% of patients with arch origin lesions.[514,515] Although the indications for intervention in patients with great vessel branch disease are similar to those for CEA, there is no evidence supporting treatment in asymptomatic patients. The treatment of symptomatic patients with stroke/TIA or arm ischemia is logical, but in patients without symptoms the natural history of the disease is unknown.

Intervention can be performed by open direct repair with possible sternotomy (mini), cervical extra-anatomic bypass or transposition, hybrid open/endovascular, or endovascular intervention alone. Endarterectomy and bypass procedures with sternotomy or trap-door incisions may be considered with equally excellent longterm patency, although small series suggest direct reconstruction with endarterectomy may be superior to bypass.[516,517] In some cases, when all three arch vessels are diseased, the ascending aorta must be used as inflow, requiring sternotomy. In general, a transthoracic approach provides significantly better long-term patency than the cervical approach.[518] However, these reconstructions require invasive incisions and longer recovery. When there is a patent arch vessel to act as inflow, cervical open reconstructions may be less invasive, but they also carry a risk of nerve or thoracic duct injury. Prosthetic conduit can be used with excellent long term patency if direct transposition of vessels is not possible.[519] If grafts are tunneled from the contralateral side, a retroesophageal tunnel can be used to avoid a graft in the anterior neck.[520] Because of the decreased morbidity compared with the transthoracic approach, cervical reconstruction is recommended in patients with multiple comorbidities.[520]

Endovascular options include antegrade and retrograde angioplasty and stent with bare and covered stents, as well as hybrid procedures of cervical endarterectomy with retrograde stenting.[514] In the series from van de Weijer et al,[514] 144 lesions in 114 patients were treated, including 117 undergoing primary stenting for symptomatic arch lesions. The authors reported a technical success rate of 94% and no stroke or death at 30 days. At a mean follow-up of 52 months, symptom-free survival was 95% and 78% at 12 and 60 months, respectively.[514] Embolic protection should be used if anatomically feasible.

Tandem lesions include patients with significant ICA stenosis in combination with proximal ipsilateral common carotid or innominate stenosis of greater than 50%. Although open reconstructions may be technically feasible, small case series suggest that a hybrid approach with CEA and retrograde CCA/innominate stent may have improved morbidity and mortality compared with an open approach.[521-523]

Summary and recommendations.

1. Interventions (open or endovascular) to treat proximalCCA or innominate artery critical lesions are not suggested in asymptomatic patients.
2. In symptomatic patients, the choice of open (cervicalvs transthoracic), hybrid, or endovascular treatment is dependent on patient anatomy and comorbidities. Embolic protection is suggested for endovascular intervention if feasible.

THERAPY OF CONCURRENT CORONARY AND CAROTID DISEASE

(See also Clinical Practice Guidelines document.)

Carotid stenosis of greater than 50% occurs in 9% of coronary artery bypass (CABG) patients, and carotid stenosis of greater than 80% stenosis occurs in 7% of CABG patients.[524] Although overall perioperative stroke prevalence with CABG is 1% to 2%, stroke risk increases as high as 7% to 9% in patients with 50% to 100% carotid stenosis,[524,525] and 18% and 26% after CABG in patients with symptomatic unilateral and bilateral carotid stenosis, respectively.[526] If carotid occlusion is present, risk of perioperative stroke increases to 7% to 12%.[527-530] It is unknown whether carotid stenosis itself specifically increases stroke risk in patients undergoing CABG or

whether carotid stenosis is a marker of diffuse atherosclerotic disease. Even the presence of a bruit increases the risk of stroke to 1.6% to 5.5%.[524,531,532]

If possible, patients with coronary disease amenable to percutaneous coronary intervention should be treated in that manner, followed by treatment of the carotid stenosis. Options for management of both carotid and coronary disease include staged CEA followed by CABG, CABG followed by CEA, simultaneous CABG and CEA, staged CAS followed by CABG, or even CAS with CABG or coronary percutaneous intervention the same day.[533,534] A review of the current literature suggests that the lowest stroke risk occurs when CEA is performed first, followed by staged CABG. Understandably, combined CEA and CABG has the highest mortality risk, whereas CABG first followed by CEA has the lowest mortality risk, but the highest stroke risk, as suggested by older studies.[535,536] However, these studies were not prospectively randomized because of the complex decisionmaking involved in caring for these patients. A meta-analysis, however, by Naylor et al[527] reported the total stroke/MI/death risk with any combination CEA and CABG ranges from 9% to 12%. In addition, Klarin et al[537] reviewed the Society of Thoracic Surgeons Adult Cardiac database, assessing 22,355 patients with CABG between 2011 and 2016. Results showed that concomitant CEA did not reduce stroke risk regardless of the patient having an off-pump or on-pump CABG, although a directly comparison to a staged approach was not possible.[537] An additional meta-analysis of 21,710 synchronous CABG-CEA patients and 23,185 staged patients, found that the simultaneous CABG-CEA group had higher 30-day mortality and stroke, but a lower risk of MI compared with the staged group.[538] These large meta-analyses suggest that combined CABG-CEA may not be indicated in most patients (see Clinical Practice Guidelines document).

Although one may consider intervention in patients with asymptomatic disease in some cases, a logical follow-up question is whether all CABG patients should be preoperatively screened for carotid disease. The prevalence of asymptomatic carotid artery disease (>70%) is 5% to 10% in patients undergoing CABG, but it is less clear whether identifying the stenosis before CABG will affect patient outcomes.[539,540] However, when assessing the literature in aggregate, screening for carotid stenosis results in improved mortality (see Clinical Practice Guidelines). Several society guidelines, including those from the American College of Cardiology Foundation, recommend screening among asymptomatic patients with planned CABG. In addition, patients with clinical factors that may increase the likelihood of identifying severe carotid stenosis including increased age, carotid bruit, history of prior stroke/TIA, and left main stem disease, should undergo carotid imaging.[525,541,542]

CAS may be an option to reduce stroke risk before CABG. Several studies demonstrate a trend toward decreased stroke risk in patients treated with CAS before CABG.[543-545] A review of the Nationwide Inpatient Sample found a 62% higher perioperative stroke risk after 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).[543] A more recent meta-analysis from Paraskevas et al included 2,727 patients who had staged or sameday CAS-CABG with an overall 30-day combined stroke/ death risk of 7.9%. However, 80% had asymptomatic unilateral carotid artery stenosis.[533] Shishehbor et al[546] assessed three groups in mostly asymptomatic patients: staged CEA-CABG, staged CAS-CABG, and combined CEA-CABG. Staged CEA-CABG had the least favorable risks of death, stroke and MI compared with the other 2 groups, which were similar. Overall, CAS-CABG was favored for long-term outcomes after 1 year.[546]

Summary and recommendations. See Clinical Practice Guidelines.

THERAPY OF CAROTID DISEASE AND OTHER MAJOR NONCARDIAC SURGERY

Overall, less than 0.1% to 4.3% of patients undergoing noncardiac surgery will have a clinically overt perioperative stroke.[547-550] Stroke risks range from 0.08% to 0.7% of patients undergoing general surgery, 0.2% to 0.9% with orthopaedic surgery, 0.6% to 0.9% lung operations, and 0.8% to 3.0% of patients undergoing peripheral vascular procedures.[551,552] However, perioperative stroke in these circumstances have devastating effects with as high as 32% 30-day mortality and 58% major disability in the POISE trial.[550] Multivariate analysis of 523,059 patients identified age, history of MI within 6 months, acute renal failure, a history of stroke or TIA, dialysis, hypertension, chronic obstructive pulmonary disease, and current tobacco use to be independent predictors of stroke.[549] A high body mass index corresponded with a lower stroke risk.[549]

Patients scheduled for noncardiac surgery should be queried about stoke or TIA symptoms. If there is clinical evidence of a symptomatic cerebrovascular event within the last 6 months, the patient should have imaging of the carotid and brain and undergo carotid revascularization, thereby postponing the noncardiac surgery.[549,553] In patients with peripheral arterial disease, the rate of asymptomatic carotid stenosis of greater than 70% is 14%.[554,555] Therefore, clinical judgement may dictate the need for preoperative imaging in patients with peripheral arterial disease underdoing noncardiac surgery. Most important, carotid stenosis may be just one sign that the patient has diffuse atherosclerosis, in particular, coronary disease. In a prospective series of 390 patients undergoing elective carotid stenting, 22% had three-vessel disease, and 7% had left main disease, emphasizing the importance of risk factor reduction and optimal medical management with antiplatelet agents, statins, and blood pressure control.[151,556] However, there are other predictors of postoperative stroke, such as female gender or renal failure that are nonmodifiable.[557] If not absolutely contraindicated, statin and antiplatelet therapy should continue in the perioperative period of noncardiac surgery in patients with asymptomatic moderate to severe carotid stenosis, as long as bleeding risk is not excessive.[554] Although most literature assesses symptomatic stroke and TIA, there is also an ongoing trial to identify covert stroke after noncardiac surgery by evaluation of MRI and cognitive assessments.[558]

Summary and recommendations.

1. Before noncardiac surgery, preoperative carotid andcerebral imaging is suggested in patients with stroke or TIA within preceding 6 months.
2. Patients with carotid artery disease undergoing noncardiac surgery should have the same indications for intervention as the general population.
3. If possible, statin and antiplatelet therapy should becontinued perioperatively in patients with 50% to 99% asymptomatic stenosis.
4. If a patient has asymptomatic carotid stenosis andcritical limb ischemia, the limb ischemia should be addressed first.

OPERATIVE VOLUME AND SPECIALTY AND CAROTID INTERVENTION: CEA AND CAS

Carotid endarterectomy

Several studies concluded that higher surgeon volume is associated with lower complication rates after CEA,[2,559-562] and others have noted high-volume centers are associated with better outcomes.[563-565] It has also been reported that surgeon specialty may play a role in perioperative outcomes after CEA, with some studies noting advantages of one surgical specialty over another.[559,566,567] Only a few studies have examined the combined impact of the surgeon's specialty and volume as they relate to CEA outcomes.[559,567] Healthcare reform and related issues concerning comparative and costeffectiveness are driving the need to define outcomerelated interventions. This is especially true for asymptomatic CEA because some authorities question the value of stroke prevention vs optimal medical therapy.

A meta-analysis of 25 studies (936,436 CEA) noted a significant correlation between CEA in higher-volume centers and lower risk of 30-day perioperative death, stroke, and stroke/death. The critical threshold was 79 cases per year per center.[568] Similarly, a British study of 18,248 CEAs showed there was a significant relationship between volume and outcomes that favored higher volume centers. These were associated with a lower mortality risk and shorter length of stay.[569] In this study, the critical threshold was 35 CEA per center per year.

Enomoto et al[570] reported on surgical specialty and outcomes for CEA using data for 34,493 CEAs from 2005 to 2010 in the NSQIP database. After controlling for patient/surgical characteristics, patients treated by general surgeons did not have significant differences in length of stay or 30-day mortality than those treated by vascular surgeons. However, general surgery patients had nearly twice the risk of acquiring a surgical site infection (OR, 1.9; P¼ .012) and greater than 1.5 times the risk of stroke (OR, 1.6; P¼.008) than vascular surgery patients. But general surgery patients had less than half the risk of MI (OR, 0.34; P¼ .031) compared with vascular surgery patient. The authors concluded that surgical specialty was associated with a wide range of postoperative clinical outcomes after CEA.[570]

Lieber et al[571] reported on the impact of surgical specialty on outcomes following CEA. using the National Surgical Quality Inpatient database that included 42,369 patients across all specialties. Patient demographics were similar between the specialty groups. Results showed that compared with vascular surgeons, general surgery patients had significantly a higher postoperative stroke risk (2.3% vs 1.5%; OR, 1.6; 95% CI, 1.172.21). However, surgical specialty was not a significant risk factor for 30-day postoperative mortality (0% for cardiothoracic surgeons; 0.8% for vascular surgeons; 1.1% for general surgeons; and 1.8% for neurosurgeons; P ¼ .995). Length of stay (P< .001), operative duration (P<.001), and postoperative requirement for a ventilator greater than 48 hours (P¼ .004) were all greatest among neurosurgeons. The authors concluded that although there was a difference in postoperative stroke and other secondary outcomes, no differences in mortality risk were observed among specialties after CEA.[571]

AbuRahma et al[572] reported on the effect of surgeon's specialty and volume on CEA perioperative outcomes in a retrospective analysis of 953 CEA during a 2-year period. Surgeons were classified into general surgeons, cardiothoracic surgeons, and vascular surgeons, and their volume was categorized into low volume (<10 CEAs), medium volume (10 to <30 CEAs) and high volume ($30 CEAs). Perioperative stroke and death risk were 1.3%, 2.9%, and 4.1% for vascular surgeons, cardiothoracic surgeons, and general surgeons, respectively (P¼ .126). A subgroup analysis showed that perioperative stroke risks for asymptomatic patients were 0.7%, 3%, and 3.6% (P¼ .099) and for symptomatic patients were 2.3%, 2.3%, and 5.3% (P¼ .511) for vascular surgeons, cardiothoracic surgeons, and general surgeons, respectively. Perioperative stroke risks were higher for nonvascular surgeons (general surgeons and cardiothoracic surgeons combined) vs vascular surgeons in asymptomatic patients (3.2% vs 0.7%; P ¼ .033). Additionally, perioperative stroke/death was also significantly lower for highvolume surgeons: 1.3% vs 4.1% and 4.3% for mediumand low-volume surgeons (P ¼ .019) (1.3% vs 4.15% for high vs low/medium combined; P¼ .005). A univariate logistic analysis showed that the OR of having a perioperative stroke was 0.4 (95% CI, 0.16-1.07; P ¼ .069) for vascular surgeons vs cardiothoracic surgeons and general surgeons, 0.3 for high-volume surgeons vs low-/medium-volume surgeons (95% CI, 0.1-0.7; P ¼ .008), and 0.2 (95% CI, 0.06-0.45; P ¼ .0004) when patching was used. A multivariate analysis showed that the OR of having a perioperative stroke for low-volume surgeons (vs high-volume) was 3.4 (95% CI, 0.96-11.8; P¼ .0581). The authors concluded that high-volume surgeons had significantly better perioperative stroke/death rate for CEA than low-/medium-volume surgeons. The perioperative stroke/death rate were also higher for nonvascular surgeons in asymptomatic patients.[572]

Recently, Meltzer et al[573] analyzed the impact of provider characteristics on outcomes of CEA for asymptomatic carotid stenosis in New York State. In this study, 36,495 patients underwent CEA for asymptomatic disease performed by vascular surgeons (76%), general surgeons (16%), cardiac surgeons (6%), and neurosurgeons (2%). Unadjusted outcomes improved with increasing surgeon annual

CEA volume. Patients of mid-career surgeons had lower stroke and mortality risk than those of early or late-career surgeons. The odds of mortality were increased when surgery was performed by the lowest volume providers (quintile 1, 0-11 CEA/year; OR, 2.61; 95% CI, 1.3-5.3) or a nonspecialty trained general surgeon (OR, 1.64; 95% CI, 1.0-2.7). After adjustment for all patient-level factors, provider volume remained an independent predictor of outcome, with significantly increased odds of mortality for volume quintile 1 (OR, 2.6; 95% CI, 1.3-5.2) and quintile 2 (12-22 CEA/year) (OR, 2.1; 95% CI, 1-4.3) surgeons. The authors concluded that surgeon characteristics impact outcomes, with the best results offered by high-volume, mid-career, specialty trained surgeons.[573]

Kuehnl et al[574] also reported on the association of annual hospital volume with risk of in-hospital stroke or death following CEA and carotid stenting by analyzing the Statutory German Carotid Quality Assurance database. Hospitals were categorized into empirically determined quintiles according to annual case volume. The resulting volume thresholds were 10, 25, 46, and 79 for CEA and 2, 6, 12, and 26 for CAS procedures, and the analysis included 17,575 CAS procedures and 161,448 CEA. For CEA patients, the crude risk of stroke or death decreased from 4.2% (95% CI, 3.6%-4.9%) in low-volume hospitals (first quintile 1-10 CEA per year) to 2.1% (2.0%-2.2%) in hospitals providing 80 or more CEA per year (fifth quintile; P< .001 for trend). The overall risk of any death or stroke in CAS patients was 3.7% (3.5%-4%), but no trend was observed for annual volume (P¼ .304). Riskadjusted analysis confirmed a significant inverse relationship between hospital volume and risk of stroke or death after CEA but not CAS.[574]

Using administrative claims databases, Hussain et al[575] reported on the association between operator specialty and outcome after carotid artery revascularization in a population-based, observational cohort study of all patients who underwent CEA or CAS in Ontario, Canada, between 2002 and 2015. In this report, 16,544 patients were analyzed (14,301 CEA and 2243 CAS). Vascular surgeons performed a majority of CEA (56%) followed by neurosurgeons (21%), general surgeons (15%), cardiac surgeons (8%), radiologists (82.5%), and neurosurgeons (17.5%) performed CAS. In the CEA group, risk of stroke or death was higher among patients treated by nonvascular surgeons (4%) compared with vascular surgeons (2.9%; adjusted OR, 1.3; 95% CI, 1.1-1.6; P¼ .008) but risk of death was similar in the two groups. The 30-day risk of stroke or death was higher in CEA patients treated by neurosurgeons (4.1%; adjusted OR, 1.3; 95% CI, 1.001.6) and cardiac surgeons (4.4%; adjusted OR, 1.5; 95% CI, 1.0-2.3) compared with vascular surgeons (2.9%). Patients who underwent CAS by radiologists and neurosurgeons experienced similar 30-day stroke or death risk (8% vs 7.9%, respectively; adjusted OR, 1.1; 95% CI, 0.7-1.7; P¼ .79).[575]

Carotid artery stenting

CAS volume. Several prospective multicenter studies evaluated operator experience to determine if it predicts outcomes after CAS, yielding mixed results.[5,198,576-580] The Carotid ACCULINK/ACCUNET Post Approval Trial to Uncover Rare Events (CAPTURE 2) Study which included 5297 patients and CHOICE (Evaluating Outcomes Through the Collection of Clinical Evidence) Study of 5841 patients both showed that physician experience impacted CAS outcomes.[577,580] However, neither the CABANA (Carotid Stenting Boston Scientific Surveillance Program) Study of 1025 patients nor the CAPTURE Study of 3500 patients found that operator experience affected outcomes.[198,578] The CHOICE Study found that increased time interval between the first CAS and subsequent CAS procedures was the only independent predictor of 30day perioperative stroke, death, and MI after CAS.[580] The CAPTURE 2 Study showed an inverse relationship between operator volume and adverse events.[577] Other studies used regional and national database to evaluate if annual CAS volume impacts outcome and demonstrated decreased complication risk when CAS was performed by high-volume surgeons.[205,581,582] However, a study of 4001 CAS procedures by Steppacher et al[583] did not show a difference in in-patient stroke/death risk based on operator volume. However physician categories were defined as low (<10 cases/year), medium (9-23 cases/year) and high (>23 cases/year), although other studies defined this factor differently.

Calvert et al[576] reported the results of pooled analysis from the Carotid Stenting Trialists Collaboration. This included the EVA-3S trial, the SPACE trial, and the ICSS. In this study of 1546 CAS patients, neither lifetime stenting experience excluding the carotid nor lifetime CAS experience impacted 30-day risk of death or stroke. However, annual in-trial CAS operator volume significantly impacted outcomes such that low-volume providers (mean of #3.2 CAS/year) had a 30-day stroke/death risk of 10%, intermediate-volume providers (3.2-5.6 CAS/ year) had a 30-day stroke/death risk of 8.4%, and with high-volume providers (>5.6 CAS/year), had 30-day stroke/death risk of 5.1%.

In a systematic review of outcomes from a registry and four large case series, it was noted that in active CAS centers it took almost 2 years of experience before 30-day stroke/death risk fell below 5%.[584] A large high-risk for CEA registry, showed that a lifetime experience of 72 CAS procedures was needed to achieve 30-day stroke/ death risk of less than 3% in asymptomatic patients less than 80 years of age.[577] In an analysis of Medicare beneficiaries, Nallamothu et al[205] showed that 30-day mortality was significantly higher when practitioners performed fewer than six CAS procedures per year, compared with more than 24 (OR, 1.9; 95% CI, 1.4-2.7; P < .001). Setacci et al[585] reported data from a large single-center series involving 2124 CAS procedures and showed that a lifetime experience of more than 100 CAS procedures was associated with significantly fewer perioperative strokes (OR, 0.81; 95% CI, 0.7-0.95), whereas a lifetime experience of fewer than 50 CAS procedures was a significant predictor of increased risk of perioperative stroke (P< .001).

As noted elsewhere in this article, Calvet et al[576] concluded that CAS practitioners should be performing at least six CAS procedures each year. The Society for Cardiovascular Angiography and Interventions and the Society for Vascular Medicine both advise that in the setting of low CAS volumes, 25 lifetime CAS procedures is reasonable to

achieve competence, along with annual 10 to 15 CAS procedures to maintain competency.[586] These numbers assume that 3% asymptomatic and 6% for symptomatic thresholds are maintained.

CAS provider specialty

The CREST study noted no differences in outcome for CAS based on operator specialty.[5] The CAPTURE 2 study noted that patients of interventional cardiologists tended to have a lower 30-day stroke/death risk than those of other specialties, but the difference was not statistically significant.[577] The CHOICE study, which separated specialties into surgery, radiology/neurology, and cardiology,[580] demonstrated that cardiologists had reduced EPD dwell times (the time during which the cerebral protection devices were deployed in place), compared with surgery and radiology/neurology. However, the 30-day stroke/death/MI risk did not differ among the three specialties. Similarly, the CAPTURE study found no difference in 30-day stroke/death/MI based on specialty.[577] Vogel et al[587] evaluated the State Inpatient Database for New Jersey and found that in 625 CAS patients, stroke risk was not significantly different between specialties. Interestingly, vascular surgeons did have a lower mean hospital cost with radiology and cardiology. Similarly, Steppacher et al[583] used the State In-Patent Databases from New York and Florida to evaluate 4001 CAS procedures, demonstrating no difference in inpatient stroke or death risk between interventional cardiology, interventional radiology, and vascular surgery. Additionally, Sgroi et al[588] evaluated 20,663 CAS patients from the National Impatient Sample database, where operators were classified into surgeons and interventionalists, and demonstrated that the 30-day stroke/death/MI risks were not significantly different between the two groups.[588] However, the study showed that the interventionalists did have increased hospital charges and length of stay compared with the surgeons.

Recently, AbuRahma et al[589] reported on the clinical outcome of CAS according to provider specialty and volume. Four hundred fourteen CAS procedures (44% for symptomatic indications) were analyzed. Clinical characteristics and demographics were similar between specialties. Major adverse events rates (stroke/MI/death) were not significantly different between specialties: 7.1% for interventional radiologists, 6.7% for interventional vascular medicine, 6.3% for vascular surgeons, and 3.1% for interventional cardiologists (P¼ .3121; 6.3% for vascular surgeons and 3.8% for others combined; P ¼ .2469). When physicians with less than 5 CAS/year were excluded: the major adverse event rates were 6.7% for interventional vascular medicine, 4.7% for vascular surgeons, and 3.1% for interventional cardiologists (P ¼ .5633). When physicians performing fewer than five CAS per year were excluded, and the vascular surgeons alone were compared with others, the MAE rates were 3.6% for non-vascular surgeons vs 4.7% for vascular surgeons (P¼ .5958). The major adverse event rate for high-volume providers was 4.0% vs 9.5% for low-volume providers, regardless of their specialty (P ¼ .1002). Logistic regression analysis showed that for high-volume providers, the OR of major adverse event rate was 0.4 (95% CI, 0.15-1.1; P¼ .0674). The authors concluded that perioperative major adverse event risks for CAS, regardless of specialties, were similar across various providers, particularly for vascular surgeons with similar volumes as nonvascular surgeons. Low-volume providers had higher major adverse event rates.

POSTCAROTID INTERVENTION SURVEILLANCE: POST CEA AND POST STENTING

Surveillance after a carotid intervention is common practice established on historical ipsilateral restenosis, contralateral disease progression and associated stroke risk. Traditional surveillance protocols for both CEA and CAS have been very rigorous, including ultrasound examination follow-up at 1, 3, 6, 12, and 18 months and annually thereafter, with some variation in early postoperative surveillance.[590-593]

Early surveillance (eg, at 1-3 months), particularly when intraoperative completion imaging has not been performed, helps to identify technical errors and establishes a baseline for subsequent comparisons. Follow-up can detect ipsilateral carotid restenosis and contralateral disease progression, thereby providing an opportunity for timely intervention to reduce stroke risk. This notion, however, is increasingly challenged because of the decreasing and selective role for intervention in otherwise asymptomatic patients.[462,590,594-596] A surveillance protocol is meaningful when anticipated results are likely to alter a medical or interventional treatment plan in a cost-effective manner.

Duplex ultrasound examination is the standard technique to observe patients treated with CEA or CAS. The advantages of duplex ultrasound examination for follow-up of patients undergoing carotid revascularization are well recognized. It is noninvasive, free of complications, and readily available in vascular laboratories. CTA and MR angiography are alternative methods for determining restenosis after carotid procedures. The attendant radiation, nephrotoxic contrast agents, and expense incurred with these modalities means that they are more frequently used to confirm a suspected severe restenosis after CEA or CAS when a therapeutic intervention is being considered.[597]

Surveillance for restenosis

As described in Section COMPLICATIONS OF CAROTID INTERVENTION, carotid restenosis occurs in a bimodal distribution. Restenosis is generally attributed to neointimal hyperplasia when occurring within the first 2 years after revascularization or to recurrence of underlying atherosclerotic disease thereafter. As demonstrated in a recent meta-analysis of randomized trials, the anticipated, clinically relevant incidence of restenosis 70% or more is 5.8% after any CEA and 10% after CAS within 4 to 5 years of follow-up.[462]

Although an increased risk of stroke has been shown in patients with at least moderate ($50%) stenosis, the mechanism of the stroke is not clear and may be of cardiac origin or a lacunar stroke.[595,598] Without high-quality evidence, that patients who suffer a stroke or TIA in the presence of carotid restenosis 50% to 99% should be considered for CEA or CAS. For asymptomatic stenoses however,

intervention should not be considered before restenosis exceeds 70%, because the value is uncertain and the associated risk is high (see Section COMPLICATIONS OF CAROTID INTERVENTION).

A vast majority of the few patients who develop restenosis will remain asymptomatic. In the meta-analysis cited above, 1.5% and 5.2% of CEA patients with 0% to 69% and 70% to 99% stenosis, respectively, developed a late ipsilateral stroke. The corresponding stroke risks for CAS were 2.2% and 0.8%, suggesting a lower restenosis-mediated risk compared with CEA.[462] Even with the higher restenosis-mediated risk of CEA, the absolute risk reduction in late ipsilateral stroke is small. The 2% to 3% stroke risk of reintervention (CEA or CAS)[460,599] needs to be considered in the cost of any surveillance protocol, given that the annual risk of ipsilateral (nonprocedure-related) stroke is only about 1% to 2%.[600]

A cost-effectiveness analysis of post-CEA ultrasound examination surveillance estimated total hospital charges of $1,408,320 with a reimbursement of $702,400 for 489 CEAs followed up at 24 hours, 1, 6, and 12 months, and annually thereafter. This surveillance protocol detected only four patients with a greater than 80% restenosis, raising concerns about overuse of surveillance ultrasound assessments. The authors challenged the need for surveillance as not cost-effective and suggested decision making based on severity of the contralateral carotid.[596]

Surveillance for contralateral carotid disease

Contralateral carotid disease progression after CEA and its clinical significance have been controversial in terms of the need and frequency of surveillance as well as the need for prophylactic surgical management among asymptomatic patients.[590,593,601-604]

Irrespective of baseline contralateral ICA stenosis, by 2 years, 5% to 15% of patients will progress by one duplex defined categorical range (from <50% to 50%-69% or from 50%-69% to >70%).[590,593,603,605,606] More important than the progression itself is the associated risk of stroke with higher grades of stenosis. Many studies have confirmed associations between disease progression and stroke. However, the low overall risk, partly related to the protective role of the index CEA and partly to optimization of medical treatment, challenge the need for carotid intervention in patients with asymptomatic carotid stenosis with prior contralateral CEA.[590,593,602,603,605,606] In the most recent retrospective study, late stroke risk in patients with disease progression of the contralateral ICA was almost double that of those without progression (7.0% vs 3.3%). However, the difference did not reach significance even when only progression to severe stenosis was considered, an observation that points to other stroke sources (eg, cardiac origin or a lacunar stroke). The authors concluded that 95% of patients who undergo CEA will take at least 2 years to progress to clinically relevant severe ($70%) ipsilateral or contralateral stenosis and that risk of stroke, even for those who progress is very low.[590]

There are no robust data regarding intervals for followup imaging, and existing recommendations vary from “no surveillance” to selective to rigorous follow-up.[607] Targeted imaging surveillance programs based on a patient’s individual risk factors may be more cost effective. Female gender, diabetes, renal insufficiency, continued smoking, and impaired cerebrovascular reactivity (eg, electrophysiological changes during clamping or neurologic symptoms during balloon inflation) have been associated with disease progression and/or symptomatic conversion.[453,590,595,608,609]

If cost effectiveness is considered in developing policies to guide perioperative duplex scan surveillance, it is reasonable to scan at 1 year and annually thereafter until disease seems to be stable, defined as no restenosis is observed in two consecutive annual scans. Annual follow-up also allows careful reassessment of risk factors and medical treatment optimization. More frequent follow-up can be considered for higher risk groups. Summary and recommendations.

1. After CEA or CAS, we recommend surveillance withduplex ultrasound examination at baseline (#3 months) and annually thereafter until stable (ie, until no restenosis observed in two consecutive annual scans). Subsequent interval or regular surveillance (eg, every 2 years) can be selectively maintained based on the stenosis of the contralateral ICA, the risk profile and life expectancy of the patient.
2. For patients combining multiple risk factors for restenosis after CEA or CAS (eg, female gender, diabetes, renal insufficiency, continued smoking, and impaired cerebrovascular reactivity) we recommend surveillance with duplex ultrasound examination every 6 months until a stable clinical pattern is established and annually thereafter.

CAROTID INTERVENTION: CEA OR CAS AND COGNITIVE FUNCTION

Carotid disease and cognitive function. As medical advances increase the average lifespan of the world population, the prevalence of dementia will increase and place additional economic burdens on caregivers and the healthcare system as a whole.[610,611] Many factors influence dementia risk.[612] Current literature suggests an association between carotid occlusive disease and increased risk for cognitive deterioration.[613-615] Both chronic hypoperfusion and embolization are implicated in cognitive deterioration.[616]

The association between stroke and cognitive dysfunction has been clearly documented, Cognitive impairment following stroke ranges from 20% to 40%.[617,618] The relationship between asymptomatic carotid stenosis and cognitive function is still controversial. Multiple large population-based cross-sectional and cohort studies including the Tromsø Study, Rotterdam Study, Framingham Study, and Cardiovascular Health Study show that subjects with asymptomatic carotid stenosis preform significantly worse on cognitive measures than control subjects without carotid stenosis.[614-616,619] These population-based studies show an overall trend of decreased cerebral blood flow and increased silent infarcts on the hemisphere of the brain ipsilateral to the carotid artery with various degree of

asymptomatic stenosis. More specifically, decreased cerebral blood flow and decreased brain volume have been associated with deterioration in various cognitive domains.[620-622] In addition, studies have shown that 10% to 20% of asymptomatic patients with severe carotid stenosis have embolic signals and these signals are higher for symptomatic patients.[623,624] A linear relationship between the process of mechanically unstable areas of carotid plaques and cognitive decline suggests a contributory role of microembolization in silent strokes.[613] Several studies showed that embolic signals are associated with faster cognitive deterioration and dementia in elderly despite an absence of neurologic symptoms.[625-627] Although patients with evidence of carotid stenosis have impaired cognitive function compared with healthy controls independent of common vascular risk factors,[615,628] vascular disease shares common risk factors with cognitive decline. These common factors include hypertension, diabetes, and smoking, making it difficult to differentiate between causation and correlation.

The effects of revascularization procedures on cognition. Both CEA and stenting, particularly CEA, decrease stroke risk,[5,203] but the effect of carotid intervention on cognitive function has been long debated.[629]

Many studies show an improvement in cognitive function after carotid revascularization procedures. Presumably, improved cerebral perfusion and removal of embolic source have a positive impact on brain health. Qu et al[630] showed that CEA for severe carotid stenosis following a minor stroke improved neurocognitive, ophthalmic, and acoustic functions compared with those did not receive treatment. Several prospective case-control studies showed that successful revascularization improves long-term cognitive performance measured by cognitive batteries compared with those who did not receive treatment,[631,632] and by P300 auditory evoked potentials.[633] Auditory evoked potentials present changes of brain electrical activity caused by auditory stimulus and the P300 wave is a measurable direct reaction of the brain to a certain sensory, cognitive, or mechanical stimulus.[634,635]

Fierstra et al[636] also showed increased cerebral blood flow and cortical thickness measured by MRI for those who received successful revascularization for severe occlusive cerebrovascular disease in whom affected brain areas exhibited “steal physiology.” However, owing to rich intracranial collaterals, unilateral severe carotid stenosis may not correspond with severe cortical ischemia.[637] Therefore, the benefit of improved perfusion cannot be generalized. Although the aforementioned prospective longitudinal studies followed relatively vigorous study protocols, the cognitive benefit of carotid intervention has not been definitely established and thus, cannot be recommended owing to relatively small sample sizes.

In addition, procedure-related subclinical microembolization is common and carotid stenting is associated with a higher incidence of microembolization.[382,638-641] The cognitive impact of microembolization may be significant, but the effects are difficult to decipher.[642-645] Although many studies show procedure-related microembolization is associated with deterioration in cognitive domains after carotid revascularization procedures; others do not.[639,642-645] Owing to differing sizes of embolic particles, locations of these micro-embolic lesions, it is challenging to select the appropriate cognitive batteries to test the true cognitive impacts of embolic lesions.[646] Studies have shown improved cognitive function despite an evidence of microembolization and that size of emboli play a significant role in neuronal death and long-term cognitive outcomes.[646,647]

It is important to recognize that the confluence of factors contributing to poorer vascular health may also affect cognition, and many other factors may also contribute to which patients experience procedurerelated cognitive changes. Baseline brain connectivity[648] and inflammatory status[649] have been shown to contribute to cognitive changes following carotid interventions. Physical activity[650,651] also contributes to cognitive health.

COST ANALYSIS OF CEA AND CAS

Although health insurance coverage has been extended to millions of previously uninsured individuals in the United States, out of pocket expenses have risen more rapidly than at any time in our history. From 2004 through 2014, for example, deductibles increased by 256% and coinsurance has increased by 106%.[652] As a result, many healthcare facilities are asking patients to pay out-of-pocket expenses up front.[653] In fact, there is evidence that many patients are delaying or foregoing medical/surgical treatment because of out-of-pocket costs.[654] Massachusetts became the first state in the United States to require hospitals to post healthcare prices.[655] Of particular relevance to vascular surgeons, the Centers for Medicare and Medicaid Services proposed that hospitals post prices online.[656] It seems undeniable that patients will be increasingly focused on the cost of proposed procedures as well as the potential clinical benefits and risks. As a result, several organizations have determined that it is now appropriate for clinical practice guidelines to factor in cost in determining best practices.[657,658] The respective costs of CEA vs CAS have been studied in several institutional series, population database studies, meta-analyses, randomized clinical trials, and through models of cost efficacy.

In an early institutional series, 45 patients with symptomatic carotid stenoses who were considered high risk (NASCET-ineligible) for CEA underwent CAS between 1996 and 2002, and their costs were compared with a control series of 391 patients with comparable risk factors who underwent CEA. Median total costs were $10,628 vs $10,148 (P¼ .495) for CAS and CEA patients, respectively. However, these results are confounded by a length of stay of 4.1 days for CEA, which is not the standard of care in current domestic practice, compared with a length of stay of 1.6 days for CAS. When data were adjusted for length of stay, CEA was less costly than CAS.[659] In another early institutional series of 46 patients undergoing CAS and 48 patients undergoing CEA, CAS was associated with higher total procedural costs ($17,402 vs $12,112; P¼ .029) and direct costs ($10,522 vs $7227; P¼.017). Of note, the hospital length of stay was 1.2 days for CAS and 2.1 days for CEA. The major driver of the difference was supply costs for CAS and CEA ($15,407 vs $1953; P¼

.001), respectively.[660] In a similar institutional study from Korea (in which costs are expressed in thousands of Korean won, TW) that included 28 patients who underwent CEA and 19 patients who underwent CAS, procedure and resource costs were higher in CAS patients (5122 6 674 TW vs 2622 6 332 TW; P<
.001), although total hospital costs were similar owing to higher postprocedure costs among CEA cases. This reflected the excessive length of stay for both procedures, but especially CEA patients, compared with contemporary American standards (9.4 6 3.0 for CEA vs 4.8 6
3.2 days for CAS).[661] In another single institution study of 31 patients undergoing CAS and 31 patients undergoing CEA, total direct costs for CAS and CEA were $8219 6 $2958 and $3765 6 $2170 (P< .001), respectively.[662] The largest single institution study reported to date included 174 patients who underwent CEA and 132 patients who underwent CAS. Data showed that mean hospital costs were $9426 6 5775 for CAS and $6734 6 3935 for CEA
(P< .0001). As in other reports, the major driver of this differential was supply costs which were $5634 for CAS vs $1967 for CEA (P < .0001). Hospital length of stay was 2.1 days for both groups.[663]

Population database analyses provide generally comparable results. In the most recent analysis from the Premier Perspective Database that used propensity score matching, total hospital costs among asymptomatic patients were 40% higher for CAS compared with CEA ($11,814 vs $8378; P<.001); and 37% higher among symptomatic patients $19,426 vs $14,190; P<.001).[664] These findings parallel an earlier study from the National Inpatient Sample of 404,256 patients who underwent either CEA or CAS from 2005 through 2007. Median charges were significantly higher for patients who underwent CAS (P < .0001).[1] Conversely, a recent meta-analysis of 17 studies found that procedure costs were 51% higher for CAS compared with CEA, largely owing to the costs of devices and supplies. However, costs of the index admission in total were comparable owing to higher postprocedure CEA costs.[665] The relative costs of CAS and CEA will clearly impact hospital profitability. An analysis of the National Inpatient Sample from 2001 through 2008 identified 181,200 CEA and 12,485 CAS procedures. Median costs for uncomplicated CEA and CAS cases were $1466 and $3272 higher than the average Medicare reimbursement, respectively. Median costs for patients with intermediate levels of comorbid conditions for CEA and CAS cases were $2847 and $4926 higher than Medicare reimbursements, respectively. For patients with the highest levels of comorbid conditions, the median costs for CEA and CAS were $23,399 and $21,750 higher than Medicare reimbursements, respectively.[666] These findings were supported by a single institution study of 169 patients undergoing CEA and 132 patients undergoing CAS. Hospital reimbursement was 16% higher for CAS compared with CEA ($12,000 6 $7372 vs $10,160 6 6840; P¼ .02). However, hospital net revenue was 29% higher ($3487 vs $2603) among patients undergoing CEA compared with CAS owing to much higher CAS supply costs.[667]

Several investigators have reported long-term cost efficacy analyses of CAS and CEA. In one report, outcomes of 447 patients undergoing CEA in a single institution were compared with CAS outcomes in the literature. A Markov decision model was constructed that included procedural costs and long-term cost of morbidities such as stroke. Procedural costs of CEA and CAS were $7871 and $10,133, respectively. Assuming a procedural stroke rate of 0.9% for CEA and 5.0% for CAS, and a 30-day mortality rate of 0% for CEA and 1.2% for CAS, CEA was found to be associated with a lifetime saving of $7017 per patient and an increase in quality-adjusted life years saved of 0.16.[668] In another report, a cost utility analysis using a Markov model was carried out using a Korean database which included 346 CAS and 331 CEA procedures performed for symptomatic disease. CAS produced 6.49 quality-adjusted life-years compared with 6.71 qualityadjusted life-years for CEA, with significantly higher costs for CAS.[669] Similarly, the Canadian health system database was used to carry out a cost utility analysis among symptomatic patients using a Markov analytical model. In the base case analysis, CAS was noted to be more costly (incremental cost of $6107) and have a lower utility (e0.12 quality-adjusted life-years). The drivers of these results were the costs of the procedures and the incidence of periprocedural complications. CAS was only cost effective among high-surgical risk patients.[670]

In the CREST, estimated net costs were $18,335 and $13,276 for CAS and CEA, respectively.[671] However, in another report, a Markov disease simulation model was used to analyze CREST data to project 10-year costs and quality-adjusted life-year expectancy for the two patient populations. CAS was associated with a mean incremental cost of $524 per patient and a reduction in quality-adjusted life expectancy of 0.008 years. It is unclear whether the practitioners who participated in CREST through a rigorous selection process reflect what can be expected in general practice of CAS and CEA.[672] The authors of the latter study also noted that although CEA and CAS provided comparable overall results, more widespread performance of CAS may be limited by the costs associated with CAS.[672] Other investigators also conducted a cost utility analysis of the results of the ICSS over a 5-year horizon. This analysis found that there were no significant differences in adjusted costs between the two procedures or in adjusted outcomes. However, the authors of this report noted that the study was limited by failure to capture the costs of managing strokes in the study, and the fact that the costs of supplies may not apply to other
countries.[673]

Although the clinical results of CAS continue to improve, it seems clear from objective evidence accumulated to date that more broad-based applicability may be limited by economic considerations. This should be considered by clinicians when electing how to treat patients with carotid artery disease, and it may also influence patient decision-making. It seems clear that a reduction in the costs associated with carotid stents and associated other necessary endovascular tools may be necessary,[674] and/or reimbursement by payors will need to match associated costs.

REFERENCES

1. Eslami MH, McPhee JT, Simons JP, Schanzer A, Messina LM. National trends in utilization and postprocedure outcomes for carotid artery revascularization 2005 to 2007. J Vasc Surg 2011;53:307-15.
2. Cowan JA Jr, Dimick JB, Thompson BG, Stanley JC, Upchurch GR Jr. Surgeon volume as an indicator of outcomes after carotid endarterectomy: an effect independent of specialty practice and hospital volume. J Am Coll Surg 2002;195:814-21.
3. Ricotta JJ, Aburahma A, Ascher E, Eskandari M, Faries P, Lal BK. Updated Society for Vascular Surgery guidelines for management of extracranial carotid disease. J Vasc Surg 2011;54:e1-31.
4. 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 managehttp://refhub.elsevier.com/S0741-5214(21)00894-6/sref4ment 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 Surhttp://refhub.elsevier.com/S0741-5214(21)00894-6/sref4geons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Sohttp://refhub.elsevier.com/S0741-5214(21)00894-6/sref4ciety of Interventional Radiology, Society of NeuroInterventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery. J Am Coll Cardiol 2011;57:e16-94.
5. 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.
6. Ederle J, Dobson J, Featherstone RL, Bonati LH, van der Worp HB, de Borst GJ, 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.
7. 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.
8. Ringleb PA, Allenberg J, Bruckmann H, Eckstein HH, Fraedrich G, Hartmann M, et al. 30 day results from the SPACE trial of stentprotected angioplasty versus carotid endarterectomy in symphttp://refhub.elsevier.com/S0741-5214(21)00894-6/sref8tomatic patients: a randomised non-inferiority trial. Lancet 2006;368:1239-47.
9. Brott TG, Calvet D, Howard G, Gregson J, Algra A, Becquemin JP, et al. Long-term outcomes of stenting and endarterectomy for symptomatic carotid stenosis: a preplanned pooled analysis of individual patient data. Lancet Neurol 2019;18:348-56.
10. Naylor AR, Ricco JB, de Borst GJ, Debus S, de Haro J, Halliday A, et al. Editor's Choice - Management of Atherosclerotic Carotid and Vertebral Artery Disease: 2017 Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS). Eur J Vasc Endovasc Surg 2018;55:3-81.
11. Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, et al. Heart disease and stroke statistics-2018 update: a report from the American Heart Association. Circulation 2018;137: e67-492.
12. Feigin VL, Roth GA, Naghavi M, Parmar P, Krishnamurthi R, Chugh S, et al. Global burden of stroke and risk factors in 188 countries, during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet Neurol 2016;15:913-24.
13. Johnston SC, Fayad PB, Gorelick PB, Hanley DF, Shwayder P, van Husen D, et al. Prevalence and knowledge of transient ischemic attack among US adults. Neurology 2003;60:1429-34.
14. Acheson J, Hutchinson EC. Observations on the natural history of transient cerebral ischaemia. Lancet 1964;2:871-4.
15. Easton JD, Saver JL, Albers GW, Alberts MJ, Chaturvedi S, Feldmann E, et al. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. Stroke 2009;40:2276-93.
16. Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/ American Stroke Association. Stroke 2013;44:264-89.
17. Coupland AP, Thapar A, Qureshi MI, Jenkins H, Davies AH. The definition of stroke. J R Soc Med 2017;110:9-12.
18. Liapis CD, Bell PR, Mikhailidis D, Sivenius J, Nicolaides A, Fernandes e Fernandes J, et al. ESVS guidelines. Invasive treatment for carotid stenosis: indications, techniques. Eur J Vasc Endovasc Surg 2009;37(4 Suppl):1-19.
19. Aho K, Harmsen P, Hatano S, Marquardsen J, Smirnov VE, Strasser T. Cerebrovascular disease in the community: results of a WHO collaborative study. Bull World Health Organ 1980;58: 113-30.
20. Degan D, Ornello R, Tiseo C, De Santis F, Pistoia F, Carolei A, et al. Epidemiology of transient ischemic attacks using time- or tissuebased definitions: a population-based study. Stroke 2017;48:530-6.
21. Kleindorfer DO, Khoury J, Moomaw CJ, Alwell K, Woo D, Flaherty ML, et al. Stroke incidence is decreasing in whites but not in blacks: a population-based estimate of temporal trends in stroke incidence from the Greater Cincinnati/Northern Kentucky Stroke Study. Stroke 2010;41:1326-31.
22. Marnane M, Duggan CA, Sheehan OC, Merwick A, Hannon N, Curtin D, et al. Stroke subtype classification to mechanism-specific and undetermined categories by TOAST, A-S-C-O, and causative classification system: direct comparison in the North Dublin population stroke study. Stroke 2010;41:1579-86.
23. Abbott AL, Bladin CF, Levi CR, Chambers BR. What should we do with asymptomatic carotid stenosis? Int J Stroke 2007;2:27-39.
24. Bulwa Z, Gupta A. Embolic stroke of undetermined source: The role of the nonstenotic carotid plaque. J Neurol Sci 2017;382:49-52.
25. Rockman CB. Cerebrovascular diseases. In: Sidawy AN, editor. Rutherford's vascular surgery and endovascular therapy. 9th ed. Philadelphia: Elsevier; 2018. p. 1121-39.
26. Barnett HJM, Taylor DW, Haynes RB, Sackett DL, Peerless SJ, Gerguson GG, et al; North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. N Engl J Med 1991;325:445-53.
27. Toraman S, Tuncer SA, Balgetir F. Is it possible to detect cerebral dominance via EEG signals by using deep learning? Med Hypotheses 2019;131:109315.
28. Endarterectomy for asymptomatic carotid artery stenosis. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. JAMA 1995;273:1421-8.
29. Guirguis-Blake J, Weber E, Coppolu E. Screening for asymptomatic carotid artery stenosis: a systematic review and meta-analysis for the U.S. Preventive Services Task Force. Publication No. 20-05268(EF-1). Rockville (MD): U.S. Preventive Services Task Force; 2020.
30. Zhu CZ, Norris JW. Role of carotid stenosis in ischemic stroke. Stroke 1990;21:1131-4.
31. Sauve 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;120:633-7.
32. Pickett CA, Jackson JL, Hemann BA, Atwood JE. Carotid bruits as a prognostic indicator of cardiovascular death and myocardial infarction: a meta-analysis. Lancet 2008;371:1587-94.
33. North American Symptomatic Carotid Endarterectomy Trial. Methods, patient characteristics, and progress. Stroke 1991;22:711-20.
34. Finn C, Giambrone AE, Gialdini G, Delgado D, Baradaran H, Kamel H, et al. The Association between carotid artery atherosclerosis and silent brain infarction: a systematic review and meta-analysis. J Stroke Cerebrovasc Dis 2017;26:1594-601.
35. Benavente O, Eliasziw M, Streifler JY, Fox AJ, Barnett HJ, Meldrum H. Prognosis after transient monocular blindness associated with carotid-artery stenosis. N Engl J Med 2001;345:1084-90.

36. McCullough HK, Reinert CG, Hynan LS, Albiston CL, Inman MH, Boyd PI, et al. Ocular findings as predictors of carotid artery occlusive disease: is carotid imaging justified? J Vasc Surg 2004;40: 279-86.
37. MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70-99%) or with mild (0-29%) carotid stenosis. European Carotid Surgery Trialists' Collaborative Group. Lancet 1991;337:1235-43.
38. 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.
39. 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.
40. Naylor AR, Adair W. Cerebrovascular Disease: Diagnostic Evaluation. In: Sidawy AN, Perler BA, editors. Rutherford's textbook of vascular surgery and endovascular therapy. 9th ed. Philadelphia: Elsevier; 2018. p. 1149-65.
41. Loftus IM, McCarthy MJ, Pau H, Hartshorne T, Bell PR, London NJ, et al. Carotid endarterectomy without angiography does not compromise operative outcome. Eur J Vasc Endovasc Surg 1998;16: 489-93.
42. 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;53:53-9; discussion: 59-0.
43. Arous EJ, Simons JP, Flahive JM, Beck AW, Stone DH, Hoel AW, et al. National variation in preoperative imaging, carotid duplex ultrasound criteria, and threshold for surgery for asymptomatic carotid artery stenosis. J Vasc Surg 2015;62:937-44.
44. Columbo JA, Zwolak RM, Arous EJ, Goodney PP, Lilly MP, Welch HG. Variation in ultrasound diagnostic thresholds for carotid stenosis in the United States. Circulation 2020;141:946-53.
45. AbuRahma AF, Srivastava M, Hass SM, Chong B, AbuRahma Z, Dean LS, et al. Practice patterns of carotid endarterectomy as performed by different surgical specialties at a single institution and the effect on perioperative stroke and cost of preoperative imaging. J Vasc Surg 2014;60:1232-7.
46. 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.
47. Kim AH, Augustin G, Shevitz A, Kim H, Trivonovich MR, Powell AR, et al. Carotid Consensus Panel duplex criteria can replace modified University of Washington criteria without affecting accuracy. Vasc Med 2018;23:126-33.
48. Altaf N, Daniels L, Morgan PS, Auer D, MacSweeney ST, Moody AR, et al. Detection ofintraplaquehemorrhage bymagnetic resonance imaging in symptomatic patients with mild to moderate carotid stenosis predicts recurrent neurological events. J Vasc Surg 2008;47:337-42.
49. Kuo PH, Kanal E, Abu-Alfa AK, Cowper SE. Gadolinium-based MR contrast agents and nephrogenic systemic fibrosis. Radiology 2007;242:647-9.
50. Saba L, Sanfilippo R, Pirisi R, Pascalis L, Montisci R, Mallarini G. Multidetector-row CT angiography in the study of atherosclerotic carotid arteries. Neuroradiology 2007;49:623-37.
51. Gagne PJ, Matchett J, MacFarland D, Hauer-Jensen M, Barone GW, Eidt JF, et al. Can the NASCET technique for measuring carotid stenosis be reliably applied outside the trial? J Vasc Surg 1996;24: 449-55; discussion: 455-6.
52. Abbott AL, Paraskevas KI, Kakkos SK, Golledge J, Eckstein HH, DiazSandoval LJ, et al. Systematic review of guidelines for the management of asymptomatic and symptomatic carotid stenosis. Stroke 2015;46:3288-301.
53. Bartlett ES, Walters TD, Symons SP, Fox AJ. Diagnosing carotid stenosis near-occlusion by using CT angiography. AJNR Am J Neuroradiol 2006;27:632-7.
54. 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.
55. 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.
56. Lawes CM, Bennett DA, Feigin VL, Rodgers A. Blood pressure and stroke: an overview of published reviews. Stroke 2004;35:1024.
57. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ 2009;338:b1665.
58. Rothwell PM, Howard SC, Spence JD. Relationship between blood pressure and stroke risk in patients with symptomatic carotid occlusive disease. Stroke 2003;34:2583-90.
59. Bond R, Narayan SK, Rothwell PM, Warlow CP. Clinical and radiographic risk factors for operative stroke and death in the European carotid surgery trial. Eur J Vasc Endovasc Surg 2002;23:108-16.
60. Naylor AR, Sayers RD, McCarthy MJ, Bown MJ, Nasim A, Dennis MJ, et al. Closing the loop: a 21-year audit of strategies for preventing stroke and death following carotid endarterectomy. Eur J Vasc Endovasc Surg 2013;46:161-70.
61. Abou-Chebl A, Reginelli J, Bajzer CT, Yadav JS. Intensive treatment of hypertension decreases the risk of hyperperfusion and intracerebral hemorrhage following carotid artery stenting. Catheter Cardiovasc Interv 2007;69:690-6.
62. Obeid T, Arhuidese I, Gaidry A, Qazi U, Abularrage C, Goodney P, et al. Beta-blocker use is associated with lower stroke and death after carotid artery stenting. J Vasc Surg 2016;63:363-9.
63. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/ APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2018;71:e127-248.
64. 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.
65. 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.
66. 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.
67. Boutouyrie P, Bussy C, Hayoz D, Hengstler J, Dartois N, Laloux B, et al. Local pulse pressure and regression of arterial wall hypertrophy during long-term antihypertensive treatment. Circulation 2000;101:2601-6.
68. Sutton-Tyrrell K, Wolfson SK Jr, Kuller LH. Blood pressure treatment slows the progression of carotid stenosis in patients with isolated systolic hypertension. Stroke 1994;25:44-50.
69. Wang JG, Staessen JA, Li Y, Van Bortel LM, Nawrot T, Fagard R, et al. Carotid intima-media thickness and antihypertensive treatment: a meta-analysis of randomized controlled trials. Stroke 2006;37: 1933-40.
70. 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.
71. 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.
72. Scholtes VP, Peeters W, van Lammeren GW, Howard DP, de Vries JP, de Borst GJ, et al. Type 2 diabetes is not associated with an altered plaque phenotype among patients undergoing carotid revascularization. A histological analysis of 1455 carotid plaques. Atherosclerosis 2014;235:418-23.
73. 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.
74. Banerjee C, Moon YP, Paik MC, Rundek T, Mora-McLaughlin C, Vieira JR, et al. Duration of diabetes and risk of ischemic stroke: the Northern Manhattan Study. Stroke 2012;43:1212-7.
75. Zhang C, Zhou YH, Xu CL, Chi FL, Ju HN. Efficacy of intensive control of glucose in stroke prevention: a meta-analysis of data from 59,197 participants in 9 randomized controlled trials. PLoS One 2013;8: e54465.
76. 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.
77. Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545-59.

78. 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.
79. 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.
80. 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 Community Health 2002;56(Suppl 1):i19-24.
81. Horenstein RB, Smith DE, Mosca L. Cholesterol predicts stroke mortality in the Women's Pooling Project. Stroke 2002;33:1863-8.
82. 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.
83. 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.
84. Amarenco P, Bogousslavsky J, Callahan A 3rd, Goldstein LB, Hennerici M, Rudolph AE, et al. High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med 2006;355: 549-59.
85. Amarenco P, Goldstein LB, Szarek M, Sillesen H, Rudolph AE, Callahan A 3rd, et al. Effects of intense low-density lipoprotein cholesterol 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.
86. Collins R, Armitage J, Parish S, Sleight P, Peto R. Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20536 people with cerebrovascular disease or other high-risk conditions. Lancet 2004;363:757-67.
87. Taylor F, Huffman MD, Macedo AF, Moore TH, Burke M, Davey Smith G, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev 2013:Cd004816.
88. 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.
89. 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.
90. McGirt MJ, Perler BA, Brooke BS, Woodworth GF, Coon A, Jain S, et al. 3-hydroxy-3-methylglutaryl coenzyme A reductase inhttp://refhub.elsevier.com/S0741-5214(21)00894-6/sref90hibitors reduce the risk of perioperative stroke and mortality after carotid endarterectomy. J Vasc Surg 2005;42:829-36; dishttp://refhub.elsevier.com/S0741-5214(21)00894-6/sref90cussion: 836-7.
91. Kennedy J, Quan H, Buchan AM, Ghali WA, Feasby TE. Statins are associated with better outcomes after carotid endarterectomy in symptomatic patients. Stroke 2005;36:2072-6.
92. Heyer EJ, Mergeche JL, Bruce SS, Ward JT, Stern Y, Anastasian ZH, et al. Statins reduce neurologic injury in asymptomatic carotid endarterectomy patients. Stroke 2013;44:1150-2.
93. Ironside N, Brenner D, Heyer E, Chen CJ, Robison T, Christophe B, et al. Systematic review and meta-analysis of perioperative and long-term outcomes in patients receiving statin therapy before carotid endarterectomy. Acta Neurochir (Wien) 2018;160:1761-71.
94. Groschel K, Ernemann U, Schulz JB, Nagele T, Terborg C, Kastrup A. Statin therapy at carotid angioplasty and stent placement: effect on procedure-related stroke, myocardial infarction, and death. Radiology 2006;240:145-51.
95. Reiff T, Amiri H, Rohde S, Hacke W, Ringleb PA. Statins reduce periprocedural complications in carotid stenting. Eur J Vasc Endovasc Surg 2014;48:626-32.
96. Verzini F, De Rango P, Parlani G, Giordano G, Caso V, Cieri E, et al. Effects of statins on early and late results of carotid stenting. J Vasc Surg 2011;53:71-9; discussion: 79.
97. 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.
98. 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.
99. 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 hyperhttp://refhub.elsevier.com/S0741-5214(21)00894-6/sref99cholesterolaemia (ASAP): a prospective, randomised, double-blind trial. Lancet 2001;357:577-81.
100. Mujaj B, Bos D, Selwaness M, Leening MJG, Kavousi M, Wentzel JJ, et al. Statin use is associated with carotid plaque composition: The Rotterdam Study. Int J Cardiol 2018;260:213-8.
101. Lloyd-Jones DM, Morris PB, Ballantyne CM, Birtcher KK, Daly DD Jr, DePalma SM, et al. 2017 focused update of the 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: a report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. J Am Coll Cardiol 2017;70:1785-822.
102. 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.
103. Shinton R, Beevers G. Meta-analysis of relation between cigarette smoking and stroke. BMJ 1989;298:789-94.
104. 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.
105. Wannamethee SG, Shaper AG, Whincup PH, Walker M. Smoking cessation and the risk of stroke in middle-aged men. JAMA 1995;274:155-60.
106. Hogberg D, Kragsterman B, Bjorck M, Tjarnstrom J, Wanhainen A. Carotid artery atherosclerosis among 65-year-old Swedish men - a population-based screening study. Eur J Vasc Endovasc Surg 2014;48:5-10.
107. de Weerd M, Greving JP, Hedblad B, Lorenz MW, Mathiesen EB, O'Leary DH, et al. Prediction of asymptomatic carotid artery stenosis in the general population: identification of high-risk groups. Stroke 2014;45:2366-71.
108. Ji R, Pan Y, Yan H, Zhang R, Liu G, Wang P, et al. Current smoking is associated with extracranial carotid atherosclerotic stenosis but not with intracranial large artery disease. BMC Neurol 2017;17:120.
109. Herder M, Johnsen SH, Arntzen KA, Mathiesen EB. Risk factors for progression of carotid intima-media thickness and total plaque area: a 13-year follow-up study: the Tromso Study. Stroke 2012;43: 1818-23.
110. Steliga MA. Smoking cessation in clinical practice: how to get patients to stop. Semin Thorac Cardiovasc Surg 2018;30:87-91.
111. Cahill K, Stevens S, Perera R, Lancaster T. Pharmacological inhttp://refhub.elsevier.com/S0741-5214(21)00894-6/sref111terventions for smoking cessation: an overview and network metaanalysis. Cochrane Database Syst Rev 2013:Cd009329.
112. Bibbins-Domingo K. Aspirin use for the primary prevention of cardiovascular disease and colorectal cancer: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med 2016;164: 836-45.
113. Cote R, Battista RN, Abrahamowicz M, Langlois Y, Bourque F, Mackey A. Lack of effect of aspirin in asymptomatic patients with carotid bruits and substantial carotid narrowing. The Asymptomatic Cervical Bruit Study Group. Ann Intern Med 1995;123:649-55.
114. King A, Shipley M, Markus H. The effect of medical treatments on stroke risk in asymptomatic carotid stenosis. Stroke 2013;44:542-6.
115. Park JM, Kang K, Cho YJ, Hong KS, Lee KB, Park TH, et al. Comparative effectiveness of prestroke aspirin on stroke severity and outcome. Ann Neurol 2016;79:560-8.
116. 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 prohttp://refhub.elsevier.com/S0741-5214(21)00894-6/sref116fessionals 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.
117. 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.
118. Albers GW, Amarenco P, Easton JD, Sacco RL, Teal P. Antithrombotic and thrombolytic therapy for ischemic stroke: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133(6 Suppl):630s-69s.
119. 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.
120. 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.
121. van Gijn J, Algra A, Kappelle J, Koudstaal PJ, van Latum A. A comparison of two doses of aspirin (30 mg vs. 283 mg a day) in patients after a transient ischemic attack or minor ischemic stroke. N Engl J Med 1991;325:1261-6.
122. Goli RR, Contractor MM, Nathan A, Tuteja S, Kobayashi T, Giri J. Antiplatelet therapy for secondary prevention of vascular disease complications. Curr Atheroscler Rep 2017;19:56.
123. Johnson ES, Lanes SF, Wentworth CE 3rd, Satterfield MH, Abebe BL, Dicker LW. A metaregression analysis of the dose-response effect of aspirin on stroke. Arch Intern Med 1999;159:1248-53.
124. Rothwell PM, Algra A, Chen Z, Diener HC, Norrving B, Mehta Z. Effects of aspirin on risk and severity of early recurrent stroke after transient ischaemic attack and ischaemic stroke: time-course analysis of randomised trials. Lancet 2016;388:365-75.
125. Alberts MJ, Bergman DL, Molner E, Jovanovic BD, Ushiwata I, Teruya J. Antiplatelet effect of aspirin in patients with cerebrovascular disease. Stroke 2004;35:175-8.
126. Kasotakis G, Pipinos II, Lynch TG. Current evidence and clinical implications of aspirin resistance. J Vasc Surg 2009;50:1500-10.
127. A randomized trial of anticoagulants versus aspirin after cerebral ischemia of presumed arterial origin. The Stroke Prevention in Reversible Ischemia Trial (SPIRIT) Study Group. Ann Neurol 1997;42: 857-65.
128. 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.
129. Halkes PH, van Gijn J, Kappelle LJ, Koudstaal PJ, Algra A. Medium intensity oral anticoagulants versus aspirin after cerebral ischaemia of arterial origin (ESPRIT): a randomised controlled trial. Lancet Neurol 2007;6:115-24.
130. De Schryver EL, Algra A, Kappelle LJ, van Gijn J, Koudstaal PJ. Vitamin K antagonists versus antiplatelet therapy after transient ischaemic attack or minor ischaemic stroke of presumed arterial origin. Cochrane Database Syst Rev 2012:Cd001342.
131. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. Lancet 1996;348:1329-39.
132. Halkes PH, van Gijn J, Kappelle LJ, Koudstaal PJ, Algra A. Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial. Lancet 2006;367:1665-73. 133. Sacco RL, Diener HC, Yusuf S, Cotton D, Ounpuu S, Lawton WA, et al. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. N Engl J Med 2008;359:1238-51.
134. Zhang JJ, Liu X. Aspirin plus dipyridamole has the highest surface under the cumulative ranking curves (SUCRA) values in terms of mortality, intracranial hemorrhage, and adverse event rate among 7 drug therapies in the treatment of cerebral infarction. Medicine (Baltimore) 2018;97:e0123.
135. Wang Y, Wang Y, Zhao X, Liu L, Wang D, Wang C, et al. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. N Engl J Med 2013;369:11-9.
136. Wong KS, Wang Y, Leng X, Mao C, Tang J, Bath PM, et al. Early dual versus mono antiplatelet therapy for acute non-cardioembolic ischemic stroke or transient ischemic attack: an updated systematic review and meta-analysis. Circulation 2013;128:1656-66.
137. Zhang Q, Wang C, Zheng M, Li Y, Li J, Zhang L, et al. Aspirin plus clopidogrel as secondary prevention after stroke or transient ischemic attack: a systematic review and meta-analysis. Cerebrovasc Dis 2015;39:13-22.
138. Niu PP, Guo ZN, Jin H, Xing YQ, Yang Y. Antiplatelet regimens in the long-term secondary prevention of transient ischaemic attack and ischaemic stroke: an updated network meta-analysis. BMJ Open 2016;6:e009013.
139. Lennard N, Smith JL, Hayes P, Evans DH, Abbott RJ, London NJ, et al. Transcranial Doppler directed dextran therapy in the prevention of carotid thrombosis: three hour monitoring is as effective as six hours. Eur J Vasc Endovasc Surg 1999;17:301-5.
140. Levi CR, Stork JL, Chambers BR, Abbott AL, Cameron HM, Peeters A, et al. Dextran reduces embolic signals after carotid endarterectomy. Ann Neurol 2001;50:544-7.
141. Hayes P, Lennard N, Smith J, Abbott R, Evans D, London N, et al. Vascular surgical society of great britain and ireland: transcranial Doppler-directed dextran therapy in the prevention of postoperative carotid thrombosis. Br J Surg 1999;86:692.
142. Abir F, Barkhordarian S, Sumpio BE. Efficacy of dextran solutions in vascular surgery. Vasc Endovascular Surg 2004;38:483-91.
143. Robless P, Okonko D, Tegos T, Mansfield A, Stansby G. Vascular surgical society of great britain and ireland: platelet function during carotid endarterectomy and the antiplatelet effect of dextran 40. Br J Surg 1999;86:709.
144. Robless PA, Tegos TJ, Okonko D, Mansfield AO, Nicolaides AN, Mikhailidis DP, et al. Platelet activation during carotid endarterectomy and the antiplatelet effect of Dextran 40. Platelets 2002;13:231-9.
145. Jones CI, Payne DA, Hayes PD, Naylor AR, Bell PR, Thompson MM, et al. The antithrombotic effect of dextran-40 in man is due to enhanced fibrinolysis in vivo. J Vasc Surg 2008;48:715-22.
146. Farber A, Tan TW, Rybin D, Kalish JA, Hamburg NM, Doros G, et al. Intraoperative use of dextran is associated with cardiac complications after carotid endarterectomy. J Vasc Surg 2013;57:635-41.
147. Asiddao CB, Donegan JH, Whitesell RC, Kalbfleisch JH. Factors associated with perioperative complications during carotid endarterectomy. Anesth Analg 1982;61:631-7.
148. Towne JB, Bernhard VM. The relationship of postoperative hypertension to complications following carotid endarterectomy. Surgery 1980;88:575-80.
149. Payne DA, Twigg MW, Hayes PD, Naylor AR. Antiplatelet agents and risk factors for bleeding postcarotid endarterectomy. Ann Vasc Surg 2010;24:900-7.
150. Naylor AR, Evans J, Thompson MM, London NJ, Abbott RJ, Cherryman G, et al. Seizures after carotid endarterectomy: hyperperfusion, dysautoregulation or hypertensive encephalopathy? Eur J Vasc Endovasc Surg 2003;26:39-44.
151. Wijeysundera DN, Duncan D, Nkonde-Price C, Virani SS, Washam JB, Fleischmann KE, et al. Perioperative beta blockade in noncardiac surgery: a systematic review for the 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. J Am Coll Cardiol 2014;64:2406-25.
152. 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.
153. Durazzo AE, Machado FS, Ikeoka DT, De Bernoche C, Monachini MC, Puech-Leao P, et al. Reduction in cardiovascular events after vascular surgery with atorvastatin: a randomized trial. J Vasc Surg 2004;39:967-75; discussion: 975-6.
154. Lindenauer PK, Pekow P, Wang K, Gutierrez B, Benjamin EM. Lipid-lowering therapy and in-hospital mortality following major noncardiac surgery. JAMA 2004;291:2092-9.
155. Molloy KJ, Thompson MM, Schwalbe EC, Bell PR, Naylor AR, Loftus IM. Comparison of levels of matrix metalloproteinases, tissue inhibitor of metalloproteinases, interleukins, and tissue necrosis factor in carotid endarterectomy specimens from patients on versus not on statins preoperatively. Am J Cardiol 2004;94:144-6.
156. Biccard BM. A peri-operative statin update for non-cardiac surgery. Part II: Statin therapy for vascular surgery and peri-operative statin trial design. Anaesthesia 2008;63:162-71.

157. Perler BA. The effect of statin medications on perioperative and long-term outcomes following carotid endarterectomy or stenting. Semin Vasc Surg 2007;20:252-8.
158. Schouten O, Kertai MD, Bax JJ, Durazzo AE, Biagini E, Boersma E, et al. Safety of perioperative statin use in high-risk patients undergoing major vascular surgery. Am J Cardiol 2005;95:658-60.
159. Merritt JC, Bhatt DL. The efficacy and safety of perioperative antiplatelet therapy. J Thromb Thrombolysis 2004;17:21-7.
160. 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.
161. Lindblad B, Persson NH, Takolander R, Bergqvist D. Does low-dose acetylsalicylic acid prevent stroke after carotid surgery? A doubleblind, placebo-controlled randomized trial. Stroke 1993;24:1125-8.
162. Gerstein NS, Schulman PM, Gerstein WH, Petersen TR, Tawil I. Should more patients continue aspirin therapy perioperatively?: clinical impact of aspirin withdrawal syndrome. Ann Surg 2012;255:
811-9.
163. Biccard BM, Sigamani A, Chan MTV, Sessler DI, Kurz A, Tittley JG, et al. Effect of aspirin in vascular surgery in patients from a randomized clinical trial (POISE-2). Br J Surg 2018;105:1591-7.
164. Barkat M, Hajibandeh S, Hajibandeh S, Torella F, Antoniou GA. Systematic review and meta-analysis of dual versus single antiplatelet therapy in carotid interventions. Eur J Vasc Endovasc Surg 2017;53:53-67.
165. 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;54: 779-84.
166. McKevitt FM, Randall MS, Cleveland TJ, Gaines PA, Tan KT, Venables GS. The benefits of combined anti-platelet treatment in carotid artery stenting. Eur J Vasc Endovasc Surg 2005;29:522-7.
167. Navarese EP, Andreotti F, Schulze V, Kolodziejczak M, Buffon A, Brouwer M, et al. Optimal duration of dual antiplatelet therapy after percutaneous coronary intervention with drug eluting stents: metaanalysis of randomised controlled trials. BMJ 2015;350:h1618.
168. 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.
169. 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.
170. Chambers BR, Donnan GA. Carotid endarterectomy for asymphttp://refhub.elsevier.com/S0741-5214(21)00894-6/sref170tomatic carotid stenosis. Cochrane Database Syst Rev 2005: Cd001923.
171. 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.
172. Wyers MC, Powell RJ, Fillinger MF, Nolan BW, Cronenwett JL. The value of 3D-CT angiographic assessment prior to carotid stenting. J Vasc Surg 2009;49:614-22.
173. Faggioli G, Ferri M, Gargiulo M, Freyrie A, Fratesi F, Manzoli L, et al. Measurement and impact of proximal and distal tortuosity in carotid stenting procedures. J Vasc Surg 2007;46:1119-24.
174. 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. 175. Moore WS, Popma JJ, Roubin GS, Voeks JH, Cutlip DE, Jones M, et al. Carotid angiographic characteristics in the CREST trial were major contributors to periprocedural stroke and death differences between carotid artery stenting and carotid endarterectomy. J Vasc Surg 2016;63:851-7.8.e1.
176. Wu WW, Liang P, O'Donnell TFX, Swerdlow NJ, Li C, Wyers MC, et al. Anatomic eligibility for transcarotid artery revascularization and transfemoral carotid artery stenting. J Vasc Surg
2019;69:1452-60.
177. Kwolek CJ, Jaff MR, Leal JI, Hopkins LN, Shah RM, Hanover TM, et al. Results of the ROADSTER multicenter trial of transcarotid stenting with dynamic flow reversal. J Vasc Surg 2015;62:1227-34.
178. Malas M, Nejim BJ, Kwolek CJ, Leal Lorenzo J, Hanover T, Mehta M, et al. One-year results of the ROADSTER multicenter trial of transcarotid stenting with dynamic flow reversal. J Vasc Surg 2018;67:e5.
179. Archie JP Jr. Carotid endarterectomy for string sign internal carotid arteries. Annual Meeting Abstracts. J Vasc Surg 1993;17:1114-5.
180. Koutsoumpelis A, Kouvelos G, Peroulis M, Tzilalis V, Matsagkas M. Surgical and endovascular intervention on internal carotid artery near occlusion. Int Angiol 2015;34:172-81.
181. Chang CK, Huded CP, Nolan BW, Powell RJ. Prevalence and clinical significance of stent fracture and deformation following carotid artery stenting. J Vasc Surg 2011;54:685-90.
182. Gasparis AP, Ricotta L, Cuadra SA, Char DJ, Purtill WA, Van Bemmelen PS, et al. High-risk carotid endarterectomy: fact or fiction. J Vasc Surg 2003;37:40-6.
183. Mozes G, Sullivan TM, Torres-Russotto DR, Bower TC, Hoskin TL, Sampaio SM, et al. Carotid endarterectomy in SAPPHIRE-eligible high-risk patients: implications for selecting patients for carotid angioplasty and stenting. J Vasc Surg 2004;39:958-65; discussion: 965-6.
184. 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.
185. 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: SAPPHIRE Worldwide Registry first 2,001 patients. Catheter Cardiovasc Interv 2009;73:129-36.
186. 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;49:331-8.9.e1; discussion: 338-9.
187. Bangalore S, Kumar S, Wetterslev J, Bavry AA, Gluud C, Cutlip DE, et al. Carotid artery stenting vs carotid endarterectomy: metahttp://refhub.elsevier.com/S0741-5214(21)00894-6/sref187analysis and diversity-adjusted trial sequential analysis of randomized trials. Arch Neurol 2011;68:172-84.
188. 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.
189. 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 2004;94:1093-6.
190. 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.
191. Hamdan AD, Pomposelli FB Jr, Gibbons GW, Campbell DR, LoGerfo FW. Renal insufficiency and altered postoperative risk in carotid endarterectomy. J Vasc Surg 1999;29:1006-11.
192. Maatz W, Kohler 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.
193. 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 symphttp://refhub.elsevier.com/S0741-5214(21)00894-6/sref193tomatic and asymptomatic patients. J Vasc Surg 2002;36:668-73.
194. Halliday A, Harrison M, Hayter E, Kong X, Mansfield A, Marro J, et al. 10-year stroke prevention after successful carotid endarterectomy for asymptomatic stenosis (ACST-1): a multicentre randomised trial. Lancet 2010;376:1074-84.
195. 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; discussion: 784-5.
196. AbuRahma AF, Robinson P, Holt SM, Herzog TA, Mowery NT. Perioperative and late stroke rates of carotid endarterectomy contralateral to carotid artery occlusion : results from a randomized trial. Stroke 2000;31:1566-71.
197. Bonati LH, Fraedrich G. Age modifies the relative risk of stenting versus endarterectomy for symptomatic carotid stenosis–a pooled analysis of EVA-3S, SPACE and ICSS. Eur J Vasc Endovasc Surg

2011;41:153-8.
198. Gray WA, Yadav JS, Verta P, Scicli A, Fairman R, Wholey M, et al. The CAPTURE registry: predictors of outcomes in carotid artery stenting with embolic protection for high surgical risk patients in the early post-approval setting. Catheter Cardiovasc Interv 2007;70:1025-33.
199. Howard G, Roubin GS, Jansen O, Hendrikse J, Halliday A, Fraedrich G, et al. Association between age and risk of stroke or death from carotid endarterectomy and carotid stenting: a metaanalysis of pooled patient data from four randomised trials. Lancet 2016;387:1305-11.
200. Hicks CW, Nejim B, Locham S, Aridi HD, Schermerhorn ML, Malas MB. Association between Medicare high-risk criteria and outcomes after carotid revascularization procedures. J Vasc Surg 2018;67:1752-61.e2.
201. 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.
202. Müller MD, Lyrer P, Brown MM, Bonati LH. Carotid artery stenting versus endarterectomy for treatment of carotid artery stenosis. Cochrane Database Syst Rev 2020;2:Cd000515.
203. Brott TG, Howard G, Roubin GS, Meschia JF, Mackey A, Brooks W, et al. Long-term results of stenting versus endarterectomy for carotid-artery stenosis. N Engl J Med 2016;374:1021-31.
204. 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 lead-in phase. J Stroke Cerebrovasc Dis 2010;19:153-62.
205. Nallamothu BK, Gurm HS, Ting HH, Goodney PP, Rogers MA, Curtis JP, et al. Operator experience and carotid stenting outcomes in Medicare beneficiaries. JAMA 2011;306:1338-43.
206. Nolan BW, De Martino RR, Goodney PP, Schanzer A, Stone DH, Butzel D, et al. Comparison of carotid endarterectomy and stenting in real world practice using a regional quality improvement registry. J Vasc Surg 2012;56:990-6.
207. Schermerhorn ML, Liang P, Eldrup-Jorgensen J, Cronenwett JL, Nolan BW, Kashyap VS, et al. Association of transcarotid artery revascularization vs transfemoral carotid artery stenting with stroke or death among patients with carotid artery stenosis. JAMA 2019;322:2313-22.
208. Malas MB, Dakour-Aridi H, Kashyap VS, Eldrup-Jorgensen J, Wang GJ, Motaganahalli RL, et al. TransCarotid revascularization with dynamic flow reversal versus carotid endarterectomy in the Vascular Quality Initiative Surveillance Project. Ann Surg 2020. doi: 10.1097/SLA.0000000000004496.
209. Columbo JA, Martinez-Camblor P, O'Malley AJ, Stone DH, Kashyap VS, Powell RJ, et al. Association of adoption of transcarotid artery revascularization with center-level perioperative outcomes. JAMA Network Open 2021;4:e2037885.
210. Lal BK, Jordan W, Kashyap VS, Kwolek CJ, Moore WS, Mukherjee D, et al. Clinical competence statement of the Society for Vascular Surgery on training and credentialing for transcarotid artery revascularization. J Vasc Surg 2020;72:779-89.
211. 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.
212. Wholey MH, Al-Mubarek N, Wholey MH. Updated review of the global carotid artery stent registry. Catheter Cardiovasc Interv 2003;60:259-66.
213. Gray WA, Chaturvedi S, Verta P. 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.
214. Gray WA, Hopkins LN, Yadav S, Davis T, Wholey M, Atkinson R, et al. Protected carotid stenting in high-surgical-risk patients: the ARCHeR results. J Vasc Surg 2006;44:258-68.
215. Higashida RT, Popma JJ, Apruzzese P, Zimetbaum P. 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 from 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.
216. Zarins CK, White RA, Diethrich EB, Shackelton RJ, Siami FS. Carotid revascularization using endarterectomy or stenting systems (CaRESS): 4-year outcomes. J Endovasc Ther 2009;16:397-409.
217. LoGerfo FW. Carotid stents: unleashed, unproven. Circulation 2007;116:1596-601; discussion: 601.
218. Naylor AR, Bell PR. Treatment of asymptomatic carotid disease with stenting: con. Semin Vasc Surg 2008;21:100-7.
219. 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: executive summary. Stroke 2011;42:e420-63.
220. Rosenfield K, Matsumura JS, Chaturvedi S, Riles T, Ansel GM, Metzger DC, et al. Randomized Trial of Stent versus Surgery for Asymptomatic Carotid Stenosis. N Engl J Med 2016;374:1011-20.
221. Sidawy AN, Zwolak RM, White RA, Siami FS, Schermerhorn ML, Sicard GA. Risk-adjusted 30-day outcomes of carotid stenting and endarterectomy: results from the SVS Vascular Registry. J Vasc Surg 2009;49:71-9.
222. McCleary AJ, Dearden NM, Dickson DH, Watson A, Gough MJ. The differing effects of regional and general anaesthesia on cerebral metabolism during carotid endarterectomy. Eur J Vasc Endovasc Surg 1996;12:173-81.
223. Hakl M, Michalek P, Sevcik P, Pavlikova J, Stern M. Regional anaesthesia for carotid endarterectomy: an audit over 10 years. Br J Anaesth 2007;99:415-20.
224. Pandit JJ, Satya-Krishna R, Gration P. Superficial or deep cervical plexus block for carotid endarterectomy: a systematic review of complications. Br J Anaesth 2007;99:159-69.
225. Wells BA, Keats AS, Cooley DA. Increased tolerance to cerebral ischemia produced by general anesthesia during temporary carotid occlusion. Surgery 1963;54:216-23.
226. Halm EA, Hannan EL, Rojas M, Tuhrim S, Riles TS, Rockman CB, et al. Clinical and operative predictors of outcomes of carotid endarterectomy. J Vasc Surg 2005;42:420-8.
227. Stoner MC, Abbott WM, Wong DR, Hua HT, Lamuraglia GM, Kwolek CJ, et al. Defining the high-risk patient for carotid endarterectomy: an analysis of the prospective National Surgical Quality Improvement Program database. J Vasc Surg 2006;43:285-95; discussion: 295-6.
228. Lewis SC, Warlow CP, Bodenham AR, Colam B, Rothwell PM, Torgerson D, et al. General anaesthesia versus local anaesthesia for carotid surgery (GALA): a multicentre, randomised controlled trial. Lancet 2008;372:2132-42.
229. Binder M, Dreiseitl S. The interpretation of test results. J Cutan Med Surg 2000;4:19-25.
230. Forssell C, Takolander R, Bergqvist D, Johansson A, Persson NH. Local versus general anaesthesia in carotid surgery. A prospective, randomised study. Eur J Vasc Surg 1989;3:503-9.
231. Kasprzak PM, Altmeppen J, Angerer M, Mann S, Mackh J, Topel I. General versus locoregional anesthesia in carotid surgery: a prospective randomised trial. Vasa 2006;35:232-8.
232. Pluskwa F, Bonnet F, Abhay K, Touboul C, Rey B, Marcandoro J, et al. [Comparison of blood pressure profiles with flunitrazepam/fentanyl/nitrous oxide vs cervical epidural anesthesia in surgery of the carotid artery]. Ann Fr Anesth Reanim 1989;8:26-32.
233. Prough DS, Scuderi PE, McWhorter JM, Balestrieri FJ, Davis CH Jr, Stullken EH. Hemodynamic status following regional and general anesthesia for carotid endarterectomy. J Neurosurg Anesthesiol 1989;1:35-40.
234. JM R, Trigg R, John C, Gough MJ, Horrocks M. Patient satisfaction for carotid endarterectomy performed under local anaesthesia. Eur J Vasc Endovasc Surg 2004;27:654-9.
235. Sbarigia E, DarioVizza C, Antonini M, Speziale F, Maritti M, Fiorani B, et al. Locoregional versus general anesthesia in carotid surgery: is there an impact on perioperative myocardial ischemia? Results of a prospective monocentric randomized trial. J Vasc Surg 1999;30: 131-8.
236. Vaniyapong T, Chongruksut W, Rerkasem K. Local versus general anaesthesia for carotid endarterectomy. Cochrane Database Syst Rev 2013:Cd000126.
237. Hye RJ, Voeks JH, Malas MB, Tom M, Longson S, Blackshear JL, et al. Anesthetic type and risk of myocardial infarction after carotid endarterectomy in the Carotid

Revascularization Endarterectomy versus Stenting Trial (CREST). J Vasc Surg 2016;64:3-8.e1.
238. Dakour Aridi H, Paracha N, Nejim B, Locham S, Malas MB. Anesthetic type and hospital outcomes after carotid endarterectomy from the Vascular Quality Initiative database. J Vasc Surg 2018;67: 1419-28.
239. Hussain AS, Mullard A, Oppat WF, Nolan KD. Increased resource utilization and overall morbidity are associated with general versus regional anesthesia for carotid endarterectomy in data collected by the Michigan Surgical Quality Collaborative. J Vasc Surg 2017;66: 802-9.
240. Kfoury E, Dort J, Trickey A, Crosby M, Donovan J, Hashemi H, et al. Carotid endarterectomy under local and/or regional anesthesia has less risk of myocardial infarction compared to general anesthesia: An analysis of national surgical quality improvement program database. Vascular 2015;23:113-9.
241. Leichtle SW, Mouawad NJ, Welch K, Lampman R, Whitehouse WM Jr, Heidenreich M. Outcomes of carotid endarterectomy under general and regional anesthesia from the American College of Surgeons' National Surgical Quality Improvement Program. J Vasc Surg 2012;56:81-88.e3.
242. Horlocker TT, Wedel DJ, Rowlingson JC, Enneking FK, Kopp SL, Benzon HT, et al. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Third Edition). Reg Anesth Pain Med 2010;35:64-101.
243. Stoneham MD, Stamou D, Mason J. Regional anaesthesia for carotid endarterectomy. Br J Anaesth 2015;114:372-83.
244. Rerkasem K, Rothwell PM. Local versus general anaesthesia for carotid endarterectomy. Cochrane Database Syst Rev 2008: Cd000126.
245. Ascher E, Hingorani A, Marks N, Schutzer RW, Mutyala M, Nahata S, et al. Mini skin incision for carotid endarterectomy (CEA): a new and safe alternative to the standard approach. J Vasc Surg 2005;42: 1089-93.
246. Bastounis E, Bakoyiannis C, Cagiannos C, Klonaris C, Filis C, Bastouni EE, et al. A short incision for carotid endarterectomy results in decreased morbidity. Eur J Vasc Endovasc Surg 2007;33: 652-6.
247. Marcucci G, Antonelli R, Gabrielli R, Accrocca F, Giordano AG, Siani A. Short longitudinal versus transverse skin incision for carotid endarterectomy: impact on cranial and cervical nerve inhttp://refhub.elsevier.com/S0741-5214(21)00894-6/sref247juries and esthetic outcome. J Cardiovasc Surg (Torino) 2011;52: 145-52.
248. Stone DH, Nolan BW, Schanzer A, Goodney PP, Cambria RA, Likosky DS, et al. Protamine reduces bleeding complications associated with carotid endarterectomy without increasing the risk of stroke. J Vasc Surg 2010;51:559-64.e1.
249. Patel RB, Beaulieu P, Homa K, Goodney PP, Stanley AC, Cronenwett JL, et al. Shared quality data are associated with increased protamine use and reduced bleeding complications after carotid endarterectomy in the Vascular Study Group of New England. J Vasc Surg 2013;58:1518-24.e1.
250. Kakisis JD, Antonopoulos CN, Mantas G, Moulakakis KG, Sfyroeras G, Geroulakos G. Cranial nerve injury after carotid endarterectomy: incidence, risk factors, and time trends. Eur J Vasc Endovasc Surg 2017;53:320-35.
251. Newhall KA, Saunders EC, Larson RJ, Stone DH, Goodney PP. Use of protamine for anticoagulation during carotid endarterectomy: a meta-analysis. JAMA Surg 2016;151:247-55.
252. Aburahma AF, Mousa AY, Stone PA. Shunting during carotid endarterectomy. J Vasc Surg 2011;54:1502-10.
253. Nwachuku EL, Balzer JR, Yabes JG, Habeych ME, Crammond DJ, Thirumala PD. Diagnostic value of somatosensory evoked potential changes during carotid endarterectomy: a systematic review and meta-analysis. JAMA Neurol 2015;72:73-80.
254. Jonsson M, Lindstrom D, Wanhainen A, Djavani Gidlund K, Gillgren P. Near infrared spectroscopy as a predictor for shunt requirement during carotid endarterectomy. Eur J Vasc Endovasc Surg 2017;53:783-91.
255. Udesh R, Natarajan P, Thiagarajan K, Wechsler LR, Crammond DJ, Balzer JR, et al. Transcranial Doppler monitoring in carotid endarterectomy: a systematic review and meta-analysis. J Ultrasound Med 2017;36:621-30.
256. Knappich C, Kuehnl A, Tsantilas P, Schmid S, Breitkreuz T, Kallmayer M, et al. Intraoperative completion studies, local anesthesia, and antiplatelet medication are associated with lower risk in carotid endarterectomy. Stroke 2017;48:955-62.
257. Wiske C, Arhuidese I, Malas M, Patterson R. Comparing the efficacy of shunting approaches and cerebral monitoring during carotid endarterectomy using a national database. J Vasc Surg 2018;68:416-25.
258. Chongruksut W, Vaniyapong T, Rerkasem K. Routine or selective carotid artery shunting for carotid endarterectomy (and different methods of monitoring in selective shunting). Cochrane Database Syst Rev 2014:Cd000190.
259. AbuRahma AF, Hannay RS, Khan JH, Robinson PA, Hudson JK, Davis EA. Prospective randomized study of carotid endarterectomy with polytetrafluoroethylene versus collagen-impregnated Dacron (Hemashield) patching: perioperative (30-day) results. J Vasc Surg 2002;35:125-30.
260. AbuRahma AF, Hopkins ES, Robinson PA, Deel JT, Agarwal S. Prospective randomized trial of carotid endarterectomy with polyhttp://refhub.elsevier.com/S0741-5214(21)00894-6/sref260tetrafluoroethylene versus collagen-impregnated dacron (Hemashield) patching: late follow-up. Ann Surg 2003;237:885-92; discussion: 892-3.
261. AbuRahma AF, Khan JH, Robinson PA, Saiedy S, Short YS, Boland JP, et al. Prospective randomized trial of carotid endarterectomy with primary closure and patch angioplasty with saphenous vein, jugular vein, and polytetrafluoroethylene: perihttp://refhub.elsevier.com/S0741-5214(21)00894-6/sref261operative (30-day) results. J Vasc Surg 1996;24:998-1006; discushttp://refhub.elsevier.com/S0741-5214(21)00894-6/sref261sion: 1007.
262. AbuRahma AF, Robinson P, Richmond B. Reanalysis of factors predicting recurrent stenosis in a prospective randomized trial of carotid endarterectomy comparing primary closure and patch closure. Vasc Surg 2000;34:319-29.
263. AbuRahma AF, Robinson PA, Saiedy S, Kahn JH, Boland JP. Prospective randomized trial of carotid endarterectomy with primary closure and patch angioplasty with saphenous vein, jugular vein, and polytetrafluoroethylene: long-term follow-up. J Vasc Surg 1998;27:222-32; discussion: 233-4.
264. AbuRahma AF, Robinson PA, Saiedy S, Richmond BK, Khan J. Prospective randomized trial of bilateral carotid endarterectomies: primary closure versus patching. Stroke 1999;30:1185-9.
265. Aburahma AF, Stone PA, Elmore M, Flaherty SK, Armistead L, AbuRahma Z. Prospective randomized trial of ACUSEAL (Gore-Tex) vs Finesse (Hemashield) patching during carotid endarterectomy: long-term outcome. J Vasc Surg 2008;48:99-103.
266. Al-Rawi PG, Turner CL, Waran V, Ng I, Kirkpatrick PJ. A randomized trial of synthetic patch versus direct primary closure in carotid endarterectomy. Neurosurgery 2006;59:822-8; discussion: 828-9.
267. Archie JP Jr. Prospective randomized trials of carotid endarterectomy with primary closure and patch reconstruction: the problem is power. J Vasc Surg 1997;25:1118-20.
268. Archie JP Jr. A fifteen-year experience with carotid endarterectomy after a formal operative protocol requiring highly frequent patch angioplasty. J Vasc Surg 2000;31:724-35.
269. 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.
270. Clagett GP, Patterson CB, Fisher DF Jr, Fry RE, Eidt JF, Humble TH, et al. Vein patch versus primary closure for carotid endarterectomy. A randomized prospective study in a selected group of patients. J Vasc Surg 1989;9:213-23.
271. Counsell CE, Salinas R, Naylor R, Warlow CP. A systematic review of the randomised trials of carotid patch angioplasty in carotid endarterectomy. Eur J Vasc Endovasc Surg 1997;13:345-54.
272. De Vleeschauwer P, Wirthle W, Holler L, Krause E, Horsch S. Is venous patch grafting after carotid endarterectomy able to reduce the rate of restenosis? Prospective randomized pilot study with stratification. Acta Chir Belg 1987;87:242-6.
273. Eikelboom BC, Ackerstaff RG, Hoeneveld H, Ludwig JW, Teeuwen C, Vermeulen FE, et al. Benefits of carotid patching: a randomized study. J Vasc Surg 1988;7:240-7.
274. Hayes PD, Allroggen H, Steel S, Thompson MM, London NJ, Bell PR, et al. Randomized trial of vein versus Dacron patching during carotid endarterectomy: influence of patch type on postoperative embolization. J Vasc Surg 2001;33:994-1000.
275. Hertzer NR, Mascha EJ. A personal experience with coronary artery bypass grafting, carotid patching, and other factors influencing the outcome of carotid endarterectomy. J Vasc Surg 2006;43:959-68.

276. Katz D, Snyder SO, Gandhi RH, Wheeler JR, Gregory RT, Gayle RG, et al. Long-term follow-up for recurrent stenosis: a prospective randomized study of expanded polytetrafluoroethylene patch angioplasty versus primary closure after carotid endarterectomy. J Vasc Surg 1994;19:198-203; discussion: 204-5.
277. Kresowik TF, Bratzler DW, Kresowik RA, Hendel ME, Grund SL, Brown KR, et al. Multistate improvement in process and outcomes of carotid endarterectomy. J Vasc Surg 2004;39:372-80.
278. Lord RS, Raj TB, Stary DL, Nash PA, Graham AR, Goh KH. Comparison of saphenous vein patch, polytetrafluoroethylene patch, and direct arteriotomy closure after carotid endarterectomy. Part I. Perioperative results. J Vasc Surg 1989;9:521-9.
279. Mannheim D, Weller B, Vahadim E, Karmeli R. Carotid endarterectomy with a polyurethane patch versus primary closure: a prohttp://refhub.elsevier.com/S0741-5214(21)00894-6/sref279spective randomized study. J Vasc Surg 2005;41:403-7; discussion: 407-8.
280. Myers SI, Valentine RJ, Chervu A, Bowers BL, Clagett GP. Saphenous vein patch versus primary closure for carotid endarterectomy: longterm assessment of a randomized prospective study. J Vasc Surg 1994;19:15-22.
281. Naylor R, Hayes PD, Payne DA, Allroggen H, Steel S, Thompson MM, et al. Randomized trial of vein versus dacron patching during carotid endarterectomy: long-term results. J Vasc Surg 2004;39: 985-93; discussion: 993.
282. O'Hara PJ, Hertzer NR, Mascha EJ, Krajewski LP, Clair DG, Ouriel K. A prospective, randomized study of saphenous vein patching versus synthetic patching during carotid endarterectomy. J Vasc Surg 2002;35:324-32.
283. Ranaboldo CJ, Barros D'Sa AA, Bell PR, Chant AD, Perry PM. Randomized controlled trial of patch angioplasty for carotid endarterectomy. The Joint Vascular Research Group. Br J Surg 1993;80:1528-30.
284. Rerkasem K, Rothwell PM. Systematic review of the operative risks of carotid endarterectomy for recently symptomatic stenosis in relation to the timing of surgery. Stroke 2009;40:e564-72.
285. Rockman CB, Halm EA, Wang JJ, Chassin MR, Tuhrim S, Formisano P, et al. Primary closure of the carotid artery is associated with poorer outcomes during carotid endarterectomy. J Vasc Surg 2005;42:870-7.
286. Archie JP Jr. Prevention of early restenosis and thrombosishttp://refhub.elsevier.com/S0741-5214(21)00894-6/sref286occlusion after carotid endarterectomy by saphenous vein patch angioplasty. Stroke 1986;17:901-5.
287. Dirrenberger RA, Sundt TM Jr. Carotid endarterectomy. Temporal profile of the healing process and effects of anticoagulation therapy. J NeuroSurg 1978;48:201-19.
288. Deriu GP, Ballotta E, Bonavina L, Grego F, Alvino S, Franceschi L, et al. The rationale for patch-graft angioplasty after carotid endarterectomy: early and long-term follow-up. Stroke 1984;15:972-9.
289. Rerkasem K, Rothwell PM. Patch angioplasty versus primary closure for carotid endarterectomy. Cochrane Database Syst Rev 2009: Cd000160.
290. Malas M, Glebova NO, Hughes SE, Voeks JH, Qazi U, Moore WS, et al. Effect of patching on reducing restenosis in the carotid revascularization endarterectomy versus stenting trial. Stroke 2015;46: 757-61.
291. Edenfield L, Blazick E, Healey C, Hawkins R, Bloch P, Eldruphttp://refhub.elsevier.com/S0741-5214(21)00894-6/sref291Jorgensen J, et al. Long-term impact of the Vascular Study Group of New England carotid patch quality initiative. J Vasc Surg 2019;69: 1801-6.
292. Bond R, Rerkasem K, AbuRahma AF, Naylor AR, Rothwell PM. Patch angioplasty versus primary closure for carotid endarterectomy. Cochrane Database Syst Rev 2004:Cd000160.
293. Rerkasem K, Rothwell PM. Systematic review of randomized controlled trials of patch angioplasty versus primary closure and different types of patch materials during carotid endarterectomy. Asian J Surg 2011;34:32-40.
294. Cao P, De Rango P, Zannetti S. Eversion vs conventional carotid endarterectomy: a systematic review. Eur J Vasc Endovasc Surg 2002;23:195-201.
295. Schneider JR, Helenowski IB, Jackson CR, Verta MJ, Zamor KC, Patel NH, et al. A comparison of results with eversion versus conventional carotid endarterectomy from the Vascular Quality Initiative and the Mid-America Vascular Study Group. J Vasc Surg 2015;61: 1216-22.
296. Paraskevas KI, Robertson V, Saratzis AN, Naylor AR. Editor's choice http://refhub.elsevier.com/S0741-5214(21)00894-6/sref296an updated systematic review and meta-analysis of outcomes following eversion vs. conventional carotid endarterectomy in randomised controlled trials and observational studies. Eur J Vasc Endovasc Surg 2018;55:465-73.
297. Huizing E, Vos CG, van den Akker PJ, Schreve MA, de Borst GJ, Ünlü Ç. A systematic review of patch angioplasty versus prihttp://refhub.elsevier.com/S0741-5214(21)00894-6/sref297mary closure for carotid endarterectomy. J Vasc Surg 2019;69: 1962-74.e4.
298. Counsell C, Salinas R, Warlow C, Naylor R. Patch angioplasty versus primary closure for carotid endarterectomy. Cochrane Database Syst Rev 2000:Cd000160.
299. Ren S, Li X, Wen J, Zhang W, Liu P. Systematic review of randomized controlled trials of different types of patch materials during carotid endarterectomy. PLoS One 2013;8:e55050.
300. Golledge J, Cuming R, Davies AH, Greenhalgh RM. Outcome of selective patching following carotid endarterectomy. Eur J Vasc Endovasc Surg 1996;11:458-63.
301. Cikrit DF, Larson DM, Sawchuk AP, Thornhill C, Shafique S, Nachreiner RD, et al. Discretionary carotid patch angioplasty leads to good results. Am J Surg 2006;192:e46-50.
302. Maertens V, Maertens H, Kint M, Coucke C, Blomme Y. Complication rate after carotid endarterectomy comparing patch angioplasty and primary closure. Ann Vasc Surg 2016;30:248-52.
303. Avgerinos ED, Chaer RA, Naddaf A, El-Shazly OM, Marone L, Makaroun MS. Primary closure after carotid endarterectomy is not inferior to other closure techniques. J Vasc Surg 2016;64:678-83.e1.
304. Bond R, Rerkasem K, Naylor R, Rothwell PM. Patches of different types for carotid patch angioplasty. Cochrane Database Syst Rev 2004:Cd000071.
305. Gonzalez-Fajardo JA, Perez JL, Mateo AM. Saphenous vein patch versus polytetrafluoroethylene patch after carotid endarterectomy. J Cardiovasc Surg (Torino) 1994;35:523-8.
306. Katz SG, Kohl RD. Does the choice of material influence early morbidity in patients undergoing carotid patch angioplasty? Surgery 1996;119:297-301.
307. Biasi GM, Sternjakob S, Mingazzini PM, Ferrari SA. Nine-year experience of bovine pericardium patch angioplasty during carotid endarterectomy. J Vasc Surg 2002;36:271-7.
308. Stone PA, AbuRahma AF, Mousa AY, Phang D, Hass SM, Modak A, et al. Prospective randomized trial of ACUSEAL versus Vascu-Guard patching in carotid endarterectomy. Ann Vasc Surg 2014;28:1530-8.
309. Oldenburg WA, Almerey T, Selim M, Farres H, Hakaim AG. Durability of carotid endarterectomy with bovine pericardial patch. Ann Vasc Surg 2018;50:218-24.
310. Texakalidis P, Giannopoulos S, Charisis N, Giannopoulos S, Karasavvidis T, Koullias G, et al. A meta-analysis of randomized trials comparing bovine pericardium and other patch materials for carotid endarterectomy. J Vasc Surg 2018;68:1241-56.e1.
311. Ballotta E, Da Giau G, Saladini M, Abbruzzese E, Renon L, Toniato A. Carotid endarterectomy with patch closure versus carotid eversion endarterectomy and reimplantation: a prospective randomized study. Surgery 1999;125:271-9.
312. Ballotta E, Renon L, Da Giau G, Toniato A, Baracchini C, Abbruzzese E, et al. A prospective randomized study on bilateral carotid endarterectomy: patching versus eversion. Ann Surg 2000;232:119-25.
313. Balzer K, Guds I, Heger J, Jahnel B. [Conventional thrombendarterectomy with carotid patch plasty vs. eversion endarterectomy: technique, indications and results]. Zentralbl Chir 2000;125:228-38.
314. 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.
315. Cao P, Giordano G, De Rango P, Zannetti S, Chiesa R, Coppi G, et al. A randomized study on eversion versus standard carotid endarterectomy: study design and preliminary results: the Everest Trial. J Vasc Surg 1998;27:595-605.
316. Cao PG, de Rango P, Zannetti S, Giordano G, Ricci S, Celani MG. Eversion versus conventional carotid endarterectomy for preventing stroke. Cochrane Database Syst Rev 2001:Cd001921.

317. Vanmaele RG, Van Schil PE, DeMaeseneer MG, Meese G, Lehert P, Van Look RF. Division-endarterectomy-anastomosis of the internal carotid artery: a prospective randomized comparative study. Cardiovasc Surg 1994;2:573-81.
318. Darling RC 3rd, Paty PS, Shah DM, Chang BB, Leather RP. Eversion endarterectomy of the internal carotid artery: technique and results in 449 procedures. Surgery 1996;120:635-9; discussion: 639-40.
319. Entz L, Járányi Z, Nemes A. Comparison of perioperative results obtained with carotid eversion endarterectomy and with conventional patch plasty. Cardiovasc Surg 1997;5:16-20.
320. 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. Cardiovasc Surg 2003;11:347-52.
321. Shah DM, Darling RC 3rd, Chang BB, Paty PS, Kreienberg PB, Lloyd WE, et al. Carotid endarterectomy by eversion technique: its safety and durability. Ann Surg 1998;228:471-8.
322. Deser SB, Demirag MK, Kolbakir F. Does surgical technique influence the postoperative hemodynamic disturbances and neurohttp://refhub.elsevier.com/S0741-5214(21)00894-6/sref322logical outcomes in carotid endarterectomy? Acta Chir Belg 2019;119:78-82.
323. Demirel S, Goossen K, Bruijnen H, Probst P, Bockler D. Systematic review and meta-analysis of postcarotid endarterectomy hyperhttp://refhub.elsevier.com/S0741-5214(21)00894-6/sref323tension after eversion versus conventional carotid endarterectomy. J Vasc Surg 2017;65:868-82.
324. Koncar I, Ribac JZ, Ilic NS, Dragas M, Mutavdzic P, Tomic IZ, et al. Carotid replacement with Dacron graft in 292 patients. Vascular 2016;24:580-9.
325. Branchereau A, Pietri P, Magnan PE, Rosset E. Saphenous vein bypass: an alternative to internal carotid reconstruction. Eur J Vasc Endovasc Surg 1996;12:26-30.
326. Roddy SP, Darling RC 3rd, Ozsvath KJ, Mehta M, Chang BB, Paty PS, et al. Choice of material for internal carotid artery bypass grafting: vein or prosthetic? Analysis of 44 procedures. Cardiovasc Surg 2002;10:540-4.
327. Lauder C, Kelly A, Thompson MM, London NJ, Bell PR, Naylor AR. Early and late outcome after carotid artery bypass grafting with saphenous vein. J Vasc Surg 2003;38:1025-30.
328. Dorafshar AH, Reil TD, Ahn SS, Quinones-Baldrich WJ, Moore WS. Interposition grafts for difficult carotid artery reconstruction: a 17year experience. Ann Vasc Surg 2008;22:63-9.
329. Ricco JB, Marchand C, Neau JP, Marchand E, Cau J, Fébrer G. Prosthetic carotid bypass grafts for atherosclerotic lesions: a prospective study of 198 consecutive cases. Eur J Vasc Endovasc Surg 2009;37:272-8.
330. Naylor AR, Moir A. An aid to accessing the distal internal carotid artery. J Vasc Surg 2009;49:1345-7.
331. Fisher DF Jr, Clagett GP, Parker JI, Fry RE, Poor MR, Finn RA, et al. Mandibular subluxation for high carotid exposure. J Vasc Surg 1984;1:727-33.
332. Coll DP, Ierardi R, Mermer RW, Matsumoto T, Kerstein MD. Exposure of the distal internal carotid artery: a simplified approach. J Am Coll Surg 1998;186:92-5.
333. Liu L, Wong KS, Leng X, Pu Y, Wang Y, Jing J, et al. Dual antiplatelet therapy in stroke and ICAS: Subgroup analysis of CHANCE. Neurology 2015;85:1154-62.
334. Batchelder A, Hunter J, Cairns V, Sandford R, Munshi A, Naylor AR. Dual antiplatelet therapy prior to expedited carotid surgery reduces recurrent events prior to surgery without significantly increasing peri-operative bleeding complications. Eur J Vasc Endovasc Surg 2015;50:412-9.
335. Youssef F, Jenkins MP, Dawson KJ, Berger L, Myint F, Hamilton G. The value of suction wound drain after carotid and femoral artery surgery: a randomised trial using duplex assessment of the volume of postoperative haematoma. Eur J Vasc Endovasc Surg 2005;29:162-6.
336. Beard JD, Mountney J, Wilkinson JM, Payne A, Dicks J, Mitton D. Prevention of postoperative wound haematomas and hyperhttp://refhub.elsevier.com/S0741-5214(21)00894-6/sref336perfusion following carotid endarterectomy. Eur J Vasc Endovasc Surg 2001;21:490-3.
337. Bandyk DF, Mills JL, Gahtan V, Esses GE. Intraoperative duplex scanning of arterial reconstructions: fate of repaired and unrepaired defects. J Vasc Surg 1994;20:426-32; discussion: 432-3.
338. 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.
339. Burnett MG, Stein SC, Sonnad SS, Zager EL. Cost-effectiveness of intraoperative imaging in carotid endarterectomy. Neurosurgery 2005;57:478-85; discussion: 485.
340. Ricotta JJ, O'Brien-Irr MS. Completion angiography, is it really necessary? Am J Surg 1997;174:181-4.
341. Rockman CB, Halm EA. Intraoperative imaging: does it really improve perioperative outcomes of carotid endarterectomy? Semin Vasc Surg 2007;20:236-43.
342. Wallaert JB, Goodney PP, Vignati JJ, Stone DH, Nolan BW, Bertges DJ, et al. Completion imaging after carotid endarterectomy in the Vascular Study Group of New England. J Vasc Surg 2011;54: 376-85.e1-3.
343. Ballotta E, Thiene G, Baracchini C, Ermani M, Militello C, Da Giau G, et al. Surgical vs medical treatment for isolated internal carotid artery elongation with coiling or kinking in symptomatic patients: a prospective randomized clinical study. J Vasc Surg 2005;42:838-46; discussion: 846.
344. Rantner B, Schmidauer C, Knoflach M, Fraedrich G. Very urgent carotid endarterectomy does not increase the procedural risk. Eur J Vasc Endovasc Surg 2015;49:129-36.
345. 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.
346. Ali M, Stephenson J, Naylor AR. Delay prior to expedited carotid endarterectomy: a prospective audit of practice. Eur J Vasc Endovasc Surg 2013;46:404-10.
347. Baracchini C, Meneghetti G, Ballotta E. Early carotid endarterectomy in acute stroke. Cerebrovasc Dis 2005;19:417-8.
348. Mussa FF, Aaronson N, Lamparello PJ, Maldonado TS, Cayne NS, Adelman MA, et al. Outcome of carotid endarterectomy for acute neurological deficit. Vasc Endovascular Surg 2009;43:364-9.
349. 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;53:622-7; discussion: 627-8.
350. Capoccia L, Sbarigia E, Speziale F, Toni D, Biello A, Montelione N, et al. The need for emergency surgical treatment in carotid-related stroke in evolution and crescendo transient ischemic attack. J Vasc Surg 2012;55:1611-7.
351. Karkos CD, Hernandez-Lahoz I, Naylor AR. Urgent carotid surgery in patients with crescendo transient ischaemic attacks and stroke-inevolution: a systematic review. Eur J Vasc Endovasc Surg 2009;37: 279-88.
352. Hao Q, Chang HM, Wong MC, Wong KS, Chen C. Frequency of microemboli signal in stroke patients treated with low molecular weight heparin or aspirin. J Neuroimaging 2010;20:118-21.
353. Wong KS, Chen C, Ng PW, Tsoi TH, Li HL, Fong WC, et al. Low-molecular-weight heparin compared with aspirin for the treatment of acute ischaemic stroke in Asian patients with large artery occlusive disease: a randomised study. Lancet Neurol 2007;6:407-13.
354. Dorigo W, Pulli R, Nesi M, Alessi Innocenti A, Pratesi G, Inzitari D, et al. Urgent carotid endarterectomy in patients with recent/crescendo transient ischaemic attacks or acute stroke. Eur J Vasc Endovasc Surg 2011;41:351-7.
355. Naylor AR. Thrombolysis and expedited carotid revascularization. J Cardiovasc Surg (Torino) 2015;56:159-64.
356. Wang Q, Chen C, Chen XY, Han JH, Soo Y, Leung TW, et al. Lowmolecular-weight heparin and early neurologic deterioration in acute stroke caused by large artery occlusive disease. Arch Neurol 2012;69:1454-60.
357. Lennard NS, Vijayasekar C, Tiivas C, Chan CWM, Higman DJ, Imray CHE. Control of emboli in patients with recurrent or crescendo transient ischaemic attacks using preoperative transcranial Doppler-directed Dextran therapy. Br J Surg 2003;90:166-70.
358. 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.
359. Naggara O, Touze E, Beyssen B, Trinquart L, Chatellier G, Meder JF, et al. Anatomical and technical factors associated with stroke or death during carotid angioplasty and stenting: results from the endarterectomy versus angioplasty in patients with symptomatic severe carotid stenosis (EVA-3S) trial and systematic review. Stroke 2011;42:380-8.

360. Nejim B, Alshwaily W, Dakour-Aridi H, Locham S, Goodney P, Malas MB. Age modifies the efficacy and safety of carotid artery revascularization procedures. J Vasc Surg 2019;69:1490-503.e3.
361. Dakour-Aridi H, Kashyap VS, Wang GJ, Eldrup-Jorgensen J, Schermerhorn ML, Malas MB. The impact of age on in-hospital outcomes after transcarotid artery revascularization, transfemoral carotid artery stenting, and carotid endarterectomy. J Vasc Surg 2020;72:931-42.
362. Huibers A, Halliday A, Bulbulia R, Coppi G, de Borst GJ. Antiplatelet therapy in carotid artery stenting and carotid endarterectomy in the Asymptomatic Carotid Surgery Trial-2. Eur J Vasc Endovasc Surg 2016;51:336-42.
363. Rizwan M, Faateh M, Aridi HD, Nejim B, Alshwaily W, Malas MB. Statins reduce mortality and failure to rescue after carotid artery stenting. J Vasc Surg 2018;69:112-9.
364. Dakour-Aridi H, Gaber MG, Khalid M, Patterson R, Malas MB. Examination of the interaction between method of anesthesia and shunting with carotid endarterectomy. J Vasc Surg 2020;71:1964-71.
365. Dakour-Aridi H, Rizwan M, Nejim B, Locham S, Malas MB. Association between the choice of anesthesia and in-hospital outcomes after carotid artery stenting. J Vasc Surg 2019;69:1461-70.e4.
366. Malik RK, Vouyouka A, Salloum A, Marin ML, Faries PL. Tips and techniques in carotid artery stenting. J Vasc Surg 2009;50:216-20.
367. Hicks CW, Malas MB. Cerebrovascular disease: carotid artery stenting. In: Sidawy AN, Perler BA, editors. Rutherford's vascular surgery and endovascular therapy. Philadelphia: Elsevier; 2019.
368. Schneider PA, Kasirajan K. Difficult anatomy: what characteristics are critical to good outcomes of either CEA or CAS? Semin Vasc Surg 2007;20:216-25.
369. Hammer FD, Lacroix V, Duprez T, Grandin C, Verhelst R, Peeters A, et al. Cerebral microembolization after protected carotid artery stenting in surgical high-risk patients: results of a 2-year prospective study. J Vasc Surg 2005;42:847-53; discussion: 853.
370. Fairman R, Gray WA, Scicli AP, Wilburn O, Verta P, Atkinson R, et al. The CAPTURE registry: analysis of strokes resulting from carotid artery stenting in the post approval setting: timing, location, severity, and type. Ann Surg 2007;246:551-6; discussion: 556-8.
371. Patel T, Shah S, Ranjan A, Malhotra H, Pancholy S, Coppola J. Contralateral transradial approach for carotid artery stenting: a feasibility study. Catheter Cardiovasc Interv 2010;75:268-75.
372. Folmar J, Sachar R, Mann T. Transradial approach for carotid artery stenting: a feasibility study. Catheter Cardiovasc Interv 2007;69:355-61.
373. Ventoruzzo G, Biondi-Zoccai G, Maioli F, Liistro F, Bolognese L, Bellandi G. A tailored approach to overcoming challenges of a bovine aortic arch during left internal carotid artery stenting. J Endovasc Ther 2012;19:329-38.
374. Montorsi P, Galli S, Ravagnani PM, Tresoldi S, Teruzzi G, Caputi L, et al. Carotid artery stenting with proximal embolic protection via a transradial or transbrachial approach: pushing the boundaries of the technique while maintaining safety and efficacy. J Endovasc Ther 2016;23:549-60.
375. Etxegoien N, Rhyne D, Kedev S, Sachar R, Mann T. The transradial approach for carotid artery stenting. Catheter Cardiovasc Interv 2012;80:1081-7.
376. Mendiz OA, Sampaolesi AH, Londero HF, Fava CM, Lev GA, Valdivieso LR. Initial experience with transradial access for carotid artery stenting. Vasc Endovascular Surg 2011;45:499-503.
377. Wu CJ, Cheng CI, Hung WC, Fang CY, Yang CH, Chen CJ, et al. Feasibility and safety of transbrachial approach for patients with severe carotid artery stenosis undergoing stenting. Catheter Cardiovasc Interv 2006;67:967-71.
378. Ruzsa Z, Nemes B, Pinter L, Berta B, Toth K, Teleki B, et al. A randomised comparison of transradial and transfemoral approach for carotid artery stenting: RADCAR (RADial access for CARotid artery stenting) study. EuroIntervention 2014;10:381-91.
379. Malas MB, Leal J, Kashyap V, Cambria RP, Kwolek CJ, Criado E. Technical aspects of transcarotid artery revascularization using the ENROUTE transcarotid neuroprotection and stent system. J Vasc Surg 2017;65:916-20.
380. Alpaslan A, Wintermark M, Pinter L, Macdonald S, Ruedy R, Kolvenbach R. Transcarotid artery revascularization with flow reversal. J Endovasc Ther 2017;24:265-70.
381. Palombo G, Stella N, Faraglia V, Rizzo L, Fantozzi C, Bozzao A, et al. Cervical access for filter-protected carotid artery stenting: a useful tool to reduce cerebral embolisation. Eur J Vasc Endovasc Surg 2010;39:252-7.
382. Bonati LH, Jongen LM, Haller S, Flach HZ, Dobson J, Nederkoorn PJ, et al. New ischaemic brain lesions on MRI after stenting or endarterectomy for symptomatic carotid stenosis: a substudy of the International Carotid Stenting Study (ICSS). Lancet Neurol 2010;9: 353-62.
383. Bijuklic K, Wandler A, Hazizi F, Schofer J. The PROFI study (Prevention of Cerebral Embolization by Proximal Balloon Occlusion Compared to Filter Protection During Carotid Artery Stenting): a prospective randomized trial. J Am Coll Cardiol 2012;59:1383-9.
384. Stabile E, Sannino A, Schiattarella GG, Gargiulo G, Toscano E, Brevetti L, et al. Cerebral embolic lesions detected with diffusionweighted magnetic resonance imaging following carotid artery stenting: a meta-analysis of 8 studies comparing filter cerebral protection and proximal balloon occlusion. JACC Cardiovasc Interv 2014;7:1177-83.
385. Dhillon AS, Li S, Lewinger JP, Shavelle DM, Matthews RV, Clavijo LC. Comparison of devices used in carotid artery stenting: a vascular quality initiative analysis of commonly used carotid stents and embolic protection devices. J Vasc Surg 2018;68:1609-10.
386. Malas MB, Dakour-Aridi H, Wang GJ, Kashyap VS, Motaganahalli RL, Eldrup-Jorgensen J, et al. Transcarotid artery revascularization versus transfemoral carotid artery stenting in the Society for Vascular Surgery Vascular Quality Initiative. J Vasc Surg 2018;69: 92-103.
387. Naazie IN, Cui CL, Osaghae I, Murad MH, Schermerhorn M, Malas MB. A systematic review and meta-analysis of transcarotid artery revascularization with dynamic flow reversal versus transfemoral carotid artery stenting and carotid endarterectomy. Ann Vasc Surg 2020;69:426-36.
388. Schermerhorn ML, Aridi HD, Kashyap VS, Wang GJ, Nolan B, Cronenwett J, et al. VESS05. In-hospital outcomes of transcarotid artery revascularization and carotid endarterectomy in the Society for Vascular Surgery Vascular Quality Initiative. J Vasc Surg 2018;67: e50-1.
389. Hicks CW, Nejim B, Obeid T, Locham SS, Malas MB. Use of a primary carotid stenting technique does not affect perioperative outcomes. J Vasc Surg 2018;67:1736-43.e1.
390. Qazi U, Obeid TE, Enwerem N, Schneider E, White JR, Freischlag JA, et al. The effect of ballooning following carotid stent deployment on hemodynamic stability. J Vasc Surg 2014;59:756-60.
391. Obeid T, Arnaoutakis DJ, Arhuidese I, Qazi U, Abularrage CJ, Black J, et al. Poststent ballooning is associated with increased periprocedural stroke and death rate in carotid artery stenting. J Vasc Surg 2015;62:616-23.e1.
392. Qazi U, Obeid T, Arhuidese I, Malas M. Carotid artery stent continued expansion days after deployment, without post stent deployment angioplasty. Clin Pract 2015;5:767.
393. Ziapour B, Schermerhorn ML, Iafrati MD, Suarez LB, TourSavadkohi S, Salehi P. A systematic review and meta-analysis of predilation and postdilation in transfemoral carotid artery stenting. J Vasc Surg 2020;72:346-55.e1.
394. Timaran CH, Rosero EB, Higuera A, Ilarraza A, Modrall JG, Clagett GP. Randomized clinical trial of open-cell vs closed-cell stents for carotid stenting and effects of stent design on cerebral embolization. J Vasc Surg 2011;54:1310-6.e1; discussion: 1316.
395. Kouvelos GN, Patelis N, Antoniou GA, Lazaris A, Matsagkas MI. Metaanalysis of the effect of stent design on 30-day outcome after carotid artery stenting. J Endovasc Ther 2015;22:789-97.
396. Jim J, Rubin BG, Landis GS, Kenwood CT, Siami FS, Sicard GA. Society for Vascular Surgery Vascular Registry evaluation of stent cell design on carotid artery stenting outcomes. J Vasc Surg 2011;54:71-9.
397. Bosiers M, de Donato G, Deloose K, Verbist J, Peeters P, Castriota F, et al. Does free cell area influence the outcome in carotid artery stenting? Eur J Vasc Endovasc Surg 2007;33:135-41; discussion: 142-3.
398. Wodarg F, Turner EL, Dobson J, Ringleb PA, Mali WP, Fraedrich G, et al. Influence of stent design and use of protection devices on outcome of carotid artery stenting: a pooled analysis of individual patient data. J Neurointerv Surg 2018;10:1149-54.
399. Texakalidis P, Giannopoulos S, Kokkinidis DG, Lanzino G. Effect of open- vs closed-cell stent design on periprocedural outcomes and restenosis after carotid artery stenting: a systematic review and comprehensive meta-analysis. J Endovasc Ther 2018;25:523-33.
400. Sannino A, Giugliano G, Toscano E, Schiattarella GG, Franzone A, Tesorio T, et al. Double layered stents for carotid angioplasty: a meta-analysis of available clinical data. Catheter Cardiovasc Interv 2018;91:751-7.

401. Machnik R, Paluszek P, Tekieli L, Dzierwa K, Maciejewski D, Trystula M, et al. Mesh-covered (Roadsaver) stent as a new treatment modality for symptomatic or high-risk carotid stenosis. Postepy w kardiologii interwencyjnej 2017;13:130-4.
402. Schofer J, Musialek P, Bijuklic K, Kolvenbach R, Trystula M, Siudak Z, et al. A prospective, multicenter study of a novel mesh-covered carotid stent: the CGuard CARENET Trial (Carotid Embolic Protection Using MicroNet). JACC Cardiovasc Interv 2015;8:1229-34.
403. AbuRahma AF, DerDerian T, Hariri N, Adams E, AbuRahma J, Dean LS, et al. Anatomical and technical predictors of perioperative clinical outcomes after carotid artery stenting. J Vasc Surg 2017;66: 423-32.
404. Paraskevas KI, Veith FJ. Transcervical access, reversal of flow and mesh-covered stents: New options in the armamentarium of carotid artery stenting. World J Cardiol 2017;9:416-21.
405. 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.
406. Nicolosi A, Klinger D, Bandyk D, Towne J. External carotid endarterectomy in the treatment of symptomatic patients with internal carotid artery occlusion. Ann Vasc Surg 1988;2:336-9.
407. Connolly JE, Stemmer EA. Endarterectomy of the external carotid artery. Its importance in the surgical management of extracranial cerebrovascular occlusive disease. Arch Surg 1973;106:799-802.
408. Machleder HI, Barker WF. External carotid artery shunting during carotid endarterectomy. Evidence for feasibility. Arch Surg 1974;108: 785-8.
409. Lindberg B. Acute carotid occlusion. Indication for surgery? J Cardiovasc Surg (Torino) 1980;21:315-20.
410. Donaldson MC, Drezner AD. Surgery for acute carotid occlusion. Therapy in search of predictability. Arch Surg 1983;118:1266-8.
411. Lamberth WC. External carotid endarterectomy: indications, operative technique, and results. Surgery 1983;93:57-63.
412. Gertler JP, Cambria RP. The role of external carotid endarterectomy in the treatment of ipsilateral internal carotid occlusion: collective review. J Vasc Surg 1987;6:158-67.
413. Sterpetti AV, Schultz RD, Feldhaus RJ. External carotid endarterectomy: indications, technique, and late results. J Vasc Surg 1988;7: 31-9.
414. Fokkema M, Reichmann BL, den Hartog AG, Klijn CJ, Schermerhorn ML, Moll FL, et al. Selective external endarterectomy in patients with ipsilateral symptomatic internal carotid artery occlusion. J Vasc Surg 2013;58:145-51.e1.
415. Nicolas K, Hubert L, Leclere FM, Etienne M, Robert M. Stroke from an external carotid: lesion pattern and mechanisms. Ann Vasc Surg 2016;32:129.e13-5.
416. Dwivedi AJ, Yancey AE, Ross CB, Morris ME. Symptomatic external carotid artery stenosis. Am Surg 2011;77:E238-9.
417. Arnold M, Perler BA. Cerebrovascular diseases. In: Sidawy AN, editor. Rutherford's vascular surgery and endovascular therapy. 9th ed. Philadelphia: Elsevier; 2018. p. 1194-214.
418. Riles TS, Imparato AM, Jacobowitz GR, Lamparello PJ, Giangola G, Adelman MA, et al. The cause of perioperative stroke after carotid endarterectomy. J Vasc Surg 1994;19:206-14; discussion: 215-6.
419. Alan N, Nwachuku E, Jovin TJ, Jankowitz BT, Jadhav AP, Ducruet AF. Management of iatrogenic direct carotid cavernous fistula occurring during endovascular treatment of stroke. World Neurosurg 2017;100:710.e15-20.
420. Wang GJ, Beck AW, DeMartino RR, Goodney PP, Rockman CB, Fairman RM. Insight into the cerebral hyperperfusion syndrome following carotid endarterectomy from the national Vascular Quality Initiative. J Vasc Surg 2017;65:381-9.e2.
421. Badhiwala JH, Nassiri F, Alhazzani W, Selim MH, Farrokhyar F, Spears J, et al. Endovascular thrombectomy for acute ischemic stroke: a meta-analysis. JAMA 2015;314:1832-43.
422. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2018;49:e46-110.
423. McDonald RJ, Cloft HJ, Kallmes DF. Intracranial hemorrhage is much more common after carotid stenting than after endarterectomy: evidence from the National Inpatient Sample. Stroke 2011;42: 2782-7.
424. Abou-Chebl A, Yadav JS, Reginelli JP, Bajzer C, Bhatt D, Krieger DW. Intracranial hemorrhage and hyperperfusion syndrome following carotid artery stenting: risk factors, prevention, and treatment. J Am Coll Cardiol 2004;43:1596-601.
425. Saw J, Bajzer C, Casserly IP, Exaire E, Haery C, Sachar R, et al. Evaluating the optimal activated clotting time during carotid artery stenting. Am J Cardiol 2006;97:1657-60.
426. Toorop RJ, Ousrout R, Scheltinga MR, Moll FL, Bleys RL. Carotid baroreceptors are mainly localized in the medial portions of the proximal internal carotid artery. Ann Anat 2013;195:248-52.
427. Lanfranchi PA, Somers VK. Arterial baroreflex function and cardiovascular variability: interactions and implications. Am J Physiol Regul Integr Comp Physiol 2002;283:R815-26.
428. Demirel S, Attigah N, Bruijnen H, Hakimi M, Burgmer B, Bockler D. Perioperative blood pressure alterations after eversion and conventional carotid endarterectomy sustain in the midterm. Langenbecks Arch Surg 2013;398:303-12.
429. Wennberg DE, Lucas FL, Birkmeyer JD, Bredenberg CE, Fisher ES. Variation in carotid endarterectomy mortality in the Medicare population: trial hospitals, volume, and patient characteristics. JAMA 1998;279:1278-81.
430. Chung J, Kim BM, Paik HK, Hyun DK, Park H. Effects of carotid artery stenosis treatment on blood pressure. J Neurosurg 2012;117:755-60.
431. Cafferata HT, Merchant RF Jr, DePalma RG. Avoidance of posthttp://refhub.elsevier.com/S0741-5214(21)00894-6/sref431carotid endarterectomy hypertension. Ann Surg 1982;196:465-72.
432. Greenstein AJ, Chassin MR, Wang J, Rockman CB, Riles TS, Tuhrim 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; discussion: 1145-6.
433. Nonaka T, Oka S, Miyata K, Mikami T, Koyanagi I, Houkin K, et al. Prediction of prolonged postprocedural hypotension after carotid artery stenting. Neurosurgery 2005;57:472-7; discussion: 7.
434. Arhuidese IJ, Rizwan M, Nejim B, Malas M. Outcomes of primary and secondary carotid artery stenting. Stroke 2017;48:3086-92.
435. Fokkema M, de Borst GJ, Nolan BW, Indes J, Buck DB, Lo RC, et al. Clinical relevance of cranial nerve injury following carotid endarterectomy. Eur J Vasc Endovasc Surg 2014;47:2-7.
436. Forssell C, Kitzing P, Bergqvist D. Cranial nerve injuries after carotid artery surgery. A prospective study of 663 operations. Eur J Vasc Endovasc Surg 1995;10:445-9.
437. Forssell C, Takolander R, Bergqvist D, Bergentz SE, Gramming P, Kitzing P. Cranial nerve injuries associated with carotid endarterectomy. A prospective study. Acta Chir Scand 1985;151:595-8.
438. Schauber MD, Fontenelle LJ, Solomon JW, Hanson TL. Cranial/cervical nerve dysfunction after carotid endarterectomy. J Vasc Surg 1997;25:481-7.
439. Hye RJ, Mackey A, Hill MD, Voeks JH, Cohen DJ, Wang K, et al. Incidence, outcomes, and effect on quality of life of cranial nerve injury in the Carotid Revascularization Endarterectomy versus Stenting Trial. J Vasc Surg 2015;61:1208-14.
440. Regina G, Angiletta D, Impedovo G, De Robertis G, Fiorella M, Carratu MR. Dexamethasone minimizes the risk of cranial nerve injury during CEA. J Vasc Surg 2009;49:99-102; discussion: 103.
441. Hertzer NR, Lees CD. Fatal myocardial infarction following carotid endarterectomy: three hundred thirty-five patients followed 6-11 years after operation. Ann Surg 1981;194:212-8.
442. O'Donnell TF Jr, Callow AD, Willet C, Payne D, Cleveland RJ. The impact of coronary artery disease on carotid endarterectomy. Ann Surg 1983;198:705-12.
443. 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: executive summary: 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;50:1707-32.
444. Smilowitz NR, Berger JS. Perioperative management to reduce cardiovascular events. Circulation 2016;133:1125-30.

445. Texakalidis P, Giannopoulos S, Kokkinidis DG, Jabbour P, ReaveyCantwell J, Rangel-Castilla L. Outcome of carotid artery endarterectomy in statin users versus statin-naive patients: a systematic review and meta-analysis. World Neurosurg 2018;116:444-450.e1.
446. Marston N, Brenes J, Garcia S, Kuskowski M, Adabag S, Santilli S, et al. Peak postoperative troponin levels outperform preoperative cardiac risk indices as predictors of long-term mortality after vascular surgery Troponins and postoperative outcomes. J Crit Care 2012;27:66-72.
447. Ujueta F, Berger JS, Smilowitz N. Coronary angiography in patients with perioperative myocardial injury after non-cardiac surgery. J Invasive Cardiol 2018;30:E90-2.
448. Tamaki T, Morita A. Neck haematoma after carotid endarterectomy: risks, rescue, and prevention. Br J Neurosurg 2019;33:156-60.
449. Knight BC, Tait WF. Dacron patch infection following carotid endarterectomy: a systematic review of the literature. Eur J Vasc Endovasc Surg 2009;37:140-8.
450. Naylor AR, Payne D, London NJ, Thompson MM, Dennis MS, Sayers RD, et al. Prosthetic patch infection after carotid endarterectomy. Eur J Vasc Endovasc Surg 2002;23:11-6.
451. Rockman CB, Su WT, Domenig C, Lamparello PJ, Adelman MA, Jacobowitz GR, et al. Postoperative infection associated with polyester patch angioplasty after carotid endarterectomy. J Vasc Surg 2003;38:251-6.
452. Fok KC, Chan YC, Law Y, Cheng SW. Septic carotid endarterectomy patch as a result of preoperative tooth extraction. Ann Vasc Surg 2018;50:299.e1-4.
453. Lal BK, Beach KW, Roubin GS, Lutsep HL, Moore WS, Malas MB, et al. Restenosis after carotid artery stenting and endarterectomy: a secondary analysis of CREST, a randomised controlled trial. Lancet Neurol 2012;11:755-63.
454. Lattimer CR, Burnand KG. Recurrent carotid stenosis after carotid endarterectomy. Br J Surg 1997;84:1206-19.
455. Rockman CB, Riles TS, Landis R, Lamparello PJ, Giangola G, Adelman MA, et al. Redo carotid surgery: an analysis of materials and configurations used in carotid reoperations and their influence on perioperative stroke and subsequent recurrent stenosis. J Vasc Surg 1999;29:72-80; discussion: 81.
456. Rockman CB, Svahn JK, Willis DJ, Lamparello PJ, Adelman MA, Jacobowitz GR, et al. Carotid endarterectomy in patients 55 years of age and younger. Ann Vasc Surg 2001;15:557-62.
457. Salvian A, Baker JD, Machleder HI, Busuttil RW, Barker WF, Moore WS. Cause and noninvasive detection of restenosis after carotid endarterectomy. Am J Surg 1983;146:29-34.
458. Reina-Gutierrez T, Serrano-Hernando FJ, Sanchez-Hervas L, Ponce A, Vega de Ceniga M, Martin A. Recurrent carotid artery stenosis following endarterectomy: natural history and risk factors. Eur J Vasc Endovasc Surg 2005;29:334-41.
459. Callow AD. Recurrent stenosis after carotid endarterectomy. Arch Surg 1982;117:1082-5.
460. Texakalidis P, Giannopoulos S, Jonnalagadda AK, Kokkinidis DG, Machinis T, Reavey-Cantwell J, et al. Carotid artery endarterectomy versus carotid artery stenting for restenosis after carotid artery endarterectomy: a systematic review and meta-analysis. World Neurosurg 2018;115:421-9.e1.
461. Dorigo W, Fargion A, Giacomelli E, Pulli R, Masciello F, Speziali S, et al. A propensity matched comparison for open and endovascular treatment of post-carotid endarterectomy restenosis. Eur J Vasc Endovasc Surg 2018;55:153-61.
462. Kumar R, Batchelder A, Saratzis A, AbuRahma AF, Ringleb P, Lal BK, et al. Restenosis after carotid interventions and its relationship with recurrent ipsilateral stroke: a systematic review and meta-analysis. Eur J Vasc Endovasc Surg 2017;53:766-75.
463. Di Gioia G, Scordino D, Campanale C, Miglionico M, Creta A, Proscia C, et al. In-stent restenosis after carotid artery stenting: from diagnosis to treatment. EMJ 2016;1:118-24.
464. AbuRahma AF, AbuRahma ZT, Scott G, Adams E, Mata A, Beasley M, et al. The incidence of carotid in-stent stenosis is underestimated >/¼50% or >/¼80% and its clinical implications. J Vasc Surg 2019;69:1807-14.
465. Arquizan C, Trinquart L, Touboul PJ, Long A, Feasson S, Terriat B, et al. Restenosis is more frequent after carotid stenting than after endarterectomy: the EVA-3S study. Stroke 2011;42:1015-20.
466. Lal BK, Hobson RW 2nd, Tofighi B, Kapadia I, Cuadra S, Jamil Z. Duplex ultrasound velocity criteria for the stented carotid artery. J Vasc Surg 2008;47:63-73.
467. Lal BK, Kaperonis EA, Cuadra S, Kapadia I, Hobson RW 2nd. Patterns of in-stent restenosis after carotid artery stenting: classification and implications for long-term outcome. J Vasc Surg 2007;46:833-40.
468. Pizzolato R, Hirsch JA, Romero JM. Imaging challenges of carotid artery in-stent restenosis. J Neurointerv Surg 2014;6:32-41.
469. Van Laanen J, Hendriks JM, Van Sambeek MR. Factors influencing restenosis after carotid artery stenting. J Cardiovasc Surg (Torino) 2008;49:743-7.
470. Naylor AR. Stenting versus endarterectomy: the debate continues. Lancet Neurol 2008;7:862-4.
471. Eckstein HH, Ringleb P, Allenberg JR, Berger J, Fraedrich G, Hacke W, et al. Results of the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) study to treat symptomatic stenoses at 2 years: a multinational, prospective, randomised trial. Lancet Neurol 2008;7:893-902.
472. Pourier VE, de Borst GJ. Technical options for treatment of in-stent restenosis after carotid artery stenting. J Vasc Surg 2016;64:1486-96. 473. Arhuidese IJ, Nejim B, Chavali S, Locham S, Obeid T, Hicks CW, et al. Endarterectomy versus stenting in patients with prior ipsilateral carotid artery stenting. J Vasc Surg 2017;65:1418-28.
474. Bhatia R, Hill MD, Shobha N, Menon B, Bal S, Kochar P, et al. Low rates of acute recanalization with intravenous recombinant tissue plasminogen activator in ischemic stroke: real-world experience and a call for action. Stroke 2010;41:2254-8.
475. Paciaroni M, Inzitari D, Agnelli G, Caso V, Balucani C, Grotta JC, et al. Intravenous thrombolysis or endovascular therapy for acute ischemic stroke associated with cervical internal carotid artery occlusion: the ICARO-3 study. J Neurol 2015;262:459-68.
476. Buslovich S, Hines GL. Spontaneous recanalization of chronic internal carotid artery occlusions: report of 3 cases. Vasc Endovascular Surg 2011;45:93-7.
477. Rubiera M, Ribo M, Delgado-Mederos R, Santamarina E, Delgado P, Montaner J, et al. Tandem internal carotid artery/middle cerebral artery occlusion: an independent predictor of poor outcome after systemic thrombolysis. Stroke 2006;37:2301-5.
478. 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.
479. Jones HJ, Millikan CH. Temporal profile (clinical course) of acute carotid system cerebral infarction. Stroke 1976;7:64-71.
480. Grillo P, Patterson RH Jr. Occlusion of the carotid artery: prognosis (natural history) and the possibilities of surgical revascularization. Stroke 1975;6:17-20.
481. Sakamoto Y, Sato S, Kuronuma Y, Nagatsuka K, Minematsu K, Toyoda K. Factors associated with proximal carotid axis occlusion in patients with acute stroke and atrial fibrillation. J Stroke Cerehttp://refhub.elsevier.com/S0741-5214(21)00894-6/sref481brovasc Dis 2014;23:799-804.
482. Thanvi B, Robinson T. Complete occlusion of extracranial internal carotid artery: clinical features, pathophysiology, diagnosis and management. Postgrad Med J 2007;83:95-9.
483. Christou I, Felberg RA, Demchuk AM, Burgin WS, Malkoff M, Grotta JC, et al. Intravenous tissue plasminogen activator and flow improvement in acute ischemic stroke patients with internal carotid artery occlusion. J Neuroimaging 2002;12:119-23.
484. Blinc A, Francis CW. Transport processes in fibrinolysis and fibrinolytic therapy. Thromb Haemost 1996;76:481-91.
485. Molina CA, Montaner J, Arenillas JF, Ribo M, Rubiera M, AlvarezSabin J. Differential pattern of tissue plasminogen activatorhttp://refhub.elsevier.com/S0741-5214(21)00894-6/sref485induced proximal middle cerebral artery recanalization among stroke subtypes. Stroke 2004;35:486-90.
486. Saqqur M, Uchino K, Demchuk AM, Molina CA, Garami Z, Calleja S, et al. Site of arterial occlusion identified by transcranial Doppler predicts the response to intravenous thrombolysis for stroke. Stroke 2007;38:948-54.
487. Li W, Yin Q, Xu G, Liu X. Treatment strategies for acute ischemic stroke caused by carotid artery occlusion. Interv Neurol 2016;5:148-56.
488. Sugg RM, Malkoff MD, Noser EA, Shaltoni HM, Weir R, Cacayorin ED, et al. Endovascular recanalization of internal carotid artery occlusion in acute ischemic stroke. AJNR Am J Neuroradiol 2005;26:2591-4.

489. Cohen JE, Leker RR, Eichel R, Gomori M, Itshayek E. Emergency endovascular revascularization of tandem occlusions: Internal carotid artery dissection and intracranial large artery embolism. J Clin Neurosci 2016;28:157-61.
490. Patel RR, Adam R, Maldjian C, Lincoln CM, Yuen A, Arneja A. Cervical carotid artery dissection: current review of diagnosis and treatment. Cardiol Rev 2012;20:145-52.
491. Georgiadis D, Arnold M, von Buedingen HC, Valko P, Sarikaya H, Rousson V, et al. Aspirin vs anticoagulation in carotid artery dissection: a study of 298 patients. Neurology 2009;72:1810-5.
492. Muller BT, Luther B, Hort W, Neumann-Haefelin T, Aulich A, Sandmann W. Surgical treatment of 50 carotid dissections: inhttp://refhub.elsevier.com/S0741-5214(21)00894-6/sref492dications and results. J Vasc Surg 2000;31:980-8.
493. Seth R, Obuchowski AM, Zoarski GH. Endovascular repair of traumatic cervical internal carotid artery injuries: a safe and effective treatment option. AJNR Am J Neuroradiol 2013;34:1219-26.
494. Shutze W, Gierman J, McQuade K, Pearl G, Smith B. Treatment of proximal vertebral artery disease. Vascular 2014;22:85-92.
495. Searls DE, Pazdera L, Korbel E, Vysata O, Caplan LR. Symptoms and signs of posterior circulation ischemia in the new England medical center posterior circulation registry. Arch Neurol 2012;69:346-51.
496. Wehman JC, Hanel RA, Guidot CA, Guterman LR, Hopkins LN. Atherosclerotic occlusive extracranial vertebral artery disease: indications for intervention, endovascular techniques, short-term and long-term results. J Interv Cardiol 2004;17:219-32.
497. Albuquerque FC, Fiorella D, Han P, Spetzler RF, McDougall CG. A reappraisal of angioplasty and stenting for the treatment of vertebral origin stenosis. Neurosurgery 2003;53:607-14; discussion: 614-6.
498. Jenkins JS, White CJ, Ramee SR, Collins TJ, Chilakamarri VK, McKinley KL, et al. Vertebral artery stenting. Catheter Cardiovasc Interv 2001;54:1-5.
499. Markus HS, van der Worp HB, Rothwell PM. Posterior circulation ischaemic stroke and transient ischaemic attack: diagnosis, investigation, and secondary prevention. Lancet Neurol 2013;12: 989-98.
500. Savitz SI, Caplan LR. Vertebrobasilar disease. N Engl J Med 2005;352: 2618-26.
501. Gulli G, Marquardt L, Rothwell PM, Markus HS. Stroke risk after posterior circulation stroke/transient ischemic attack and its relationship to site of vertebrobasilar stenosis: pooled data analysis from prospective studies. Stroke 2013;44:598-604.
502. Stayman AN, Nogueira RG, Gupta R. A systematic review of stenting and angioplasty of symptomatic extracranial vertebral artery stenosis. Stroke 2011;42:2212-6.
503. Al-Ali F, Barrow T, Duan L, Jefferson A, Louis S, Luke K, et al. Vertebral artery ostium atherosclerotic plaque as a potential source of posterior circulation ischemic stroke: result from borgess medical center vertebral artery ostium stenting registry. Stroke 2011;42: 2544-9.
504. Feng H, Xie Y, Mei B, Liu Y, Li B, Yin C, et al. Endovascular vs. medical therapy in symptomatic vertebral artery stenosis: a meta-analysis. J Neurol 2017;264:829-38.
505. Caplan LR, Wityk RJ, Glass TA, Tapia J, Pazdera L, Chang HM, et al. New England Medical Center Posterior Circulation registry. Ann Neurol 2004;56:389-98.
506. Edwards WH, Edwards WH Jr. Vertebral-carotid transposition. Semin Vasc Surg 2000;13:70-3.
507. Molnar RG, Naslund TC. Vertebral artery surgery. Surg Clin North Am 1998;78:901-13.
508. Berguer R, Flynn LM, Kline RA, Caplan L. Surgical reconstruction of the extracranial vertebral artery: management and outcome. J Vasc Surg 2000;31:9-18.
509. Mukherjee D, Pineda G. Extracranial vertebral artery intervention. J Interv Cardiol 2007;20:409-16.
510. Coward LJ, McCabe DJ, Ederle J, Featherstone RL, Clifton A, Brown MM. Long-term outcome after angioplasty and stenting for symptomatic vertebral artery stenosis compared with medical treatment in the Carotid And Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomized trial. Stroke 2007;38:1526-30.
511. Jenkins JS. Percutaneous treatment of vertebral artery stenosis. Interv Cardiol Clin 2014;3:115-22.
512. Thomas CS, Habib F, Varghese K, Abraham MT, Hayat NJ, Cherian G. Disease of proximal part of vertebral artery in patients with coronary artery disease. Angiology 2003;54:205-9.
513. Espinosa de Rueda M, Parrilla G, Zamarro J, Garcia-Villalba B, Hernandez F, Moreno A. Treatment of acute vertebrobasilar occlusion using thrombectomy with stent retrievers: initial experience with 18 patients. AJNR Am J Neuroradiol 2013;34: 1044-8.
514. van de Weijer MA, Vonken EJ, de Vries JP, Moll FL, Vos JA, de Borst GJ. Technical and clinical success and long-term durability of endovascular treatment for atherosclerotic aortic arch branch origin obstruction: evaluation of 144 procedures. Eur J Vasc Endovasc Surg 2015;50:13-20.
515. Klonaris C, Kouvelos GN, Kafeza M, Koutsoumpelis A, Katsargyris A, Tsigris C. Common carotid artery occlusion treatment: revealing a gap in the current guidelines. Eur J Vasc Endovasc Surg 2013;46: 291-8.
516. Cherry KJ Jr, McCullough JL, Hallett JW Jr, Pairolero PC, Gloviczki P. Technical principles of direct innominate artery revascularization: a comparison of endarterectomy and bypass grafts. J Vasc Surg 1989;9:718-23; discussion: 723-4.
517. Cherry KJ. Direct reconstruction of the innominate artery. Carhttp://refhub.elsevier.com/S0741-5214(21)00894-6/sref517diovasc Surg 2002;10:383-8.
518. Takach TJ, Reul GJ, Cooley DA, Duncan JM, Livesay JJ, Gregoric ID, et al. Brachiocephalic reconstruction I: operative and long-term results for complex disease. J Vasc Surg 2005;42:47-54.
519. Fry WR, Martin JD, Clagett GP, Fry WJ. Extrathoracic carotid reconstruction: the subclavian-carotid artery bypass. J Vasc Surg 1992;15: 83-8; discussion: 88-9.
520. Berguer R, Morasch MD, Kline RA, Kazmers A, Friedland MS. Cervical reconstruction of the supra-aortic trunks: a 16-year experience. J Vasc Surg 1999;29:239-46; discussion: 246-8.
521. Barilla D, Massara M, Alberti A, Volpe A, Cutrupi A, Versace P, et al. Old and new techniques as a safe hybrid approach for carotid tandem lesions. Ann Vasc Surg 2016;32:132.e9-12.
522. de Borst GJ, Hazenberg CE. How should I treat a patient with a tandem carotid artery atherosclerotic stenosis involving the internal carotid artery and the innominate/proximal common carotid artery? Eur J Vasc Endovasc Surg 2015;50:257-8.
523. Illuminati G, Pizzardi G, Pasqua R, Frezzotti F, Palumbo P, Macrina F, et al. Hybrid treatment of tandem, common carotid/ innominate artery and ipsilateral carotid bifurcation stenoses by simultaneous, retrograde proximal stenting and eversion carotid endarterectomy: preliminary results of a case series. Int J Surg 2018;52:329-33.
524. Naylor AR, Mehta Z, Rothwell PM, Bell PR. Carotid artery disease and stroke during coronary artery bypass: a critical review of the literature. Eur J Vasc Endovasc Surg 2002;23:283-94.
525. Naylor AR, Bown MJ. Stroke after cardiac surgery and its association with asymptomatic carotid disease: an updated systematic review and meta-analysis. Eur J Vasc Endovasc Surg 2011;41:607-24.
526. 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.
527. 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.
528. 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.
529. Newman MF, Wolman R, Kanchuger M, Marschall K, Mora-Mangano C, Roach G, et al. Multicenter preoperative stroke risk index for patients undergoing coronary artery bypass graft surgery. Multicenter Study of Perioperative Ischemia (McSPI) Research Group. Circulation 1996;94(9 Suppl):Ii74-80.
530. Naylor AR. Managing patients with symptomatic coronary and carotid artery disease. Perspect Vasc Surg Endovasc Ther 2010;22:70-6.
531. 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.
532. 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.
533. Paraskevas KI, Nduwayo S, Saratzis AN, Naylor AR. Carotid stenting prior to coronary bypass surgery: an updated systematic review and meta-analysis. Eur J Vasc Endovasc Surg 2017;53:309-19.

534. Bertrand OF, Ruzsa Z, Barria Perez A, De Larochelliere R. Same-day discharge after transradial percutaneous coronary intervention and carotid stenting in a single session. Can J Cardiol 2017;33:830.e1-3.
535. Hertzer NR, Loop FD, Beven 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.
536. Ricotta JJ, Char DJ, Cuadra SA, Bilfinger TV, Wall LP, Giron F, et al. Modeling stroke risk after coronary artery bypass and combined coronary artery bypass and carotid endarterectomy. Stroke 2003;34:1212-7. 537. Klarin D, Patel VI, Zhang S, Xian Y, Kosinski A, Yerokun B, et al. Concomitant carotid endarterectomy and cardiac surgery does not decrease postoperative stroke rates. J Vasc Surg 2020;72:589-96.e3.
538. Tzoumas A, Giannopoulos S, Texakalidis P, Charisis N, Machinis T, Koullias GJ. Synchronous versus staged carotid endarterectomy and coronary artery bypass graft for patients with concomitant severe coronary and carotid artery stenosis: a systematic review and meta-analysis. Ann Vasc Surg 2020;63:427-38.e1.
539. Berens ES, Kouchoukos NT, Murphy SF, Wareing TH. Preoperative carotid artery screening in elderly patients undergoing cardiac surgery. J Vasc Surg 1992;15:313-21; discussion: 322-3.
540. Lin JC, Kabbani LS, Peterson EL, Masabni K, Morgan JA, Brooks S, et al. Clinical utility of carotid duplex ultrasound prior to cardiac surgery. J Vasc Surg 2016;63:710-4.
541. Aboyans V, Lacroix P. Indications for carotid screening in patients with coronary artery disease. Presse Med 2009;38:977-86.
542. 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. Vasc Med 2007;12:35-83.
543. 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;48:355-60; discussion: 360-1.
544. 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.
545. Naylor AR, Mehta Z, Rothwell PM. A systematic review and metaanalysis of 30-day outcomes following staged carotid artery stenting and coronary bypass. Eur J Vasc Endovasc Surg 2009;37:379-87.
546. Shishehbor MH, Venkatachalam S, Sun Z, Rajeswaran J, Kapadia SR, Bajzer C, et al. A direct comparison of early and late outcomes with three approaches to carotid revascularization and open heart surgery. J Am Coll Cardiol 2013;62:1948-56.
547. Larsen SF, Zaric D, Boysen G. Postoperative cerebrovascular accidents in general surgery. Acta Anaesthesiol Scand 1988;32:698-701.
548. Popa AS, Rabinstein AA, Huddleston PM, Larson DR, Gullerud RE, Huddleston JM. Predictors of ischemic stroke after hip operation: a population-based study. J Hosp Med 2009;4:298-303.
549. Mashour GA, Shanks AM, Kheterpal S. Perioperative stroke and associated mortality after noncardiac, nonneurologic surgery. Anesthesiology 2011;114:1289-96.
550. Devereaux PJ, Yang H, Yusuf S, Guyatt G, Leslie K, Villar JC, et al. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. Lancet 2008;371:1839-47.
551. Macellari F, Paciaroni M, Agnelli G, Caso V. Perioperative stroke risk in nonvascular surgery. Cerebrovasc Dis 2012;34:175-81.
552. Selim M. Perioperative stroke. N Engl J Med 2007;356:706-13.
553. Kristensen SD, Knuuti J, Saraste A, Anker S, Botker HE, De Hert S, et al. 2014 ESC/ESA Guidelines on non-cardiac surgery: cardiovascular assessment and management: The Joint Task Force on noncardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA). Eur J Anaesthesiol 2014;31:517-73.
554. Tendera M, Aboyans V, Bartelink ML, Baumgartner I, Clement D, Collet JP, et al. ESC Guidelines on the diagnosis and treatment of peripheral artery diseases: document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries: the Task Force on the Diagnosis and Treatment of Peripheral Artery Diseases of the European Society of Cardiology (ESC). Eur Heart J 2011;32:2851-906.
555. Ahmed B, Al-Khaffaf H. Prevalence of significant asymptomatic carotid artery disease in patients with peripheral vascular disease: a meta-analysis. Eur J Vasc Endovasc Surg 2009;37:262-71.
556. Hofmann R, Kypta A, Steinwender C, Kerschner K, Grund M, Leisch F. Coronary angiography in patients undergoing carotid artery stenting shows a high incidence of significant coronary artery disease. Heart 2005;91:1438-41.
557. Jorgensen ME, Torp-Pedersen C, Gislason GH, Jensen PF, Berger SM, Christiansen CB, et al. Time elapsed after ischemic stroke and risk of adverse cardiovascular events and mortality following elective noncardiac surgery. JAMA 2014;312:269-77.
558. Mrkobrada M, Chan MTV, Cowan D, Spence J, Campbell D, Wang CY, et al. Rationale and design for the detection and neurological impact of cerebrovascular events in non-cardiac surgery patients cohort evaluation (NeuroVISION) study: a prospective international cohort study. BMJ Open 2018;8:e021521.
559. Hannan EL, Popp AJ, Feustel P, Halm E, Bernardini G, Waldman J, et al. Association of surgical specialty and processes of care with patient outcomes for carotid endarterectomy. Stroke 2001;32:
2890-7.
560. Kucey DS, Bowyer B, Iron K, Austin P, Anderson G, Tu JV. Dehttp://refhub.elsevier.com/S0741-5214(21)00894-6/sref560terminants of outcome after carotid endarterectomy. J Vasc Surg 1998;28:1051-8.
561. Nazarian SM, Yenokyan G, Thompson RE, Griswold ME, Chang DC, Perler BA. Statistical modeling of the volume-outcome effect for carotid endarterectomy for 10 years of a statewide database. J Vasc Surg 2008;48:343-50; discussion: 350.
562. Takagi H, Kawai N, Umemoto T. Regarding "provider volume and outcomes for abdominal aortic aneurysm repair, carotid endarterectomy, and lower extremity revascularization procedures.". J Vasc Surg 2008;47:1123-4. author reply 1124.
563. Karthikesalingam A, Hinchliffe RJ, Loftus IM, Thompson MM, Holt PJ. Volume-outcome relationships in vascular surgery: the current status. J Endovasc Ther 2010;17:356-65.
564. Cebul RD, Snow RJ, Pine R, Hertzer NR, Norris DG. Indications, outcomes, and provider volumes for carotid endarterectomy. JAMA 1998;279:1282-7.
565. Perler BA, Dardik A, Burleyson GP, Gordon TA, Williams GM. Influence of age and hospital volume on the results of carotid endarterectomy: a statewide analysis of 9918 cases. J Vasc Surg 1998;27: 25-31; discussion: 33.
566. Killeen SD, Andrews EJ, Redmond HP, Fulton GJ. Provider volume and outcomes for abdominal aortic aneurysm repair, carotid endarterectomy, and lower extremity revascularization procedures. J Vasc Surg 2007;45:615-26.
567. O'Neill L, Lanska DJ, Hartz A. Surgeon characteristics associated with mortality and morbidity following carotid endarterectomy. Neurology 2000;55:773-81.
568. Holt PJ, Poloniecki JD, Loftus IM, Thompson MM. Meta-analysis and systematic review of the relationship between hospital volume and outcome following carotid endarterectomy. Eur J Vasc Endovasc Surg 2007;33:645-51.
569. Holt PJ, Poloniecki JD, Loftus IM, Thompson MM. The relationship between hospital case volume and outcome from carotid endartectomy in England from 2000 to 2005. Eur J Vasc Endovasc Surg
2007;34:646-54.
570. Enomoto LM, Hill DC, Dillon PW, Han DC, Hollenbeak CS. Surgical specialty and outcomes for carotid endarterectomy: evidence from the National Surgical Quality Improvement Program. J Surg Res
2014;188:339-48.
571. Lieber BA, Henry JK, Agarwal N, Day JD, Morris TW 3rd, Stephens ML, et al. Impact of surgical specialty on outcomes following carotid endarterectomy. Neurosurgery 2017;80:217-25.
572. AbuRahma AF, Stone PA, Srivastava M, Hass SM, Mousa AY, Dean LS, et al. The effect of surgeon's specialty and volume on the perioperative outcome of carotid endarterectomy. J Vasc Surg 2013;58: 666-72.
573. Meltzer AJ, Agrusa C, Connolly PH, Schneider DB, Sedrakyan A. Impact of Provider characteristics on outcomes of carotid endarterectomy for asymptomatic carotid stenosis in New York state. Ann Vasc Surg 2017;45:56-61.
574. Kuehnl A, Tsantilas P, Knappich C, Schmid S, Konig T, Breitkreuz T, et al. Significant association of annual hospital volume with the risk of inhospital stroke or death following carotid endarterectomy but likely not after carotid stenting: secondary data analysis of the Statutory German Carotid Quality Assurance Database. Circ Cardiovasc Interv 2016;9:e004171.
575. Hussain MA, Mamdani M, Tu JV, Saposnik G, Salata K, Bhatt DL, et al. Association between operator specialty and outcomes after carotid artery revascularization. J Vasc Surg 2018;67:478-89.e6.
576. Calvet D, Mas JL, Algra A, Becquemin JP, Bonati LH, Dobson J, et al. Carotid stenting: is there an operator effect? A pooled analysis from the carotid stenting trialists' collaboration. Stroke 2014;45:527-32.
577. Gray WA, Rosenfield KA, Jaff MR, Chaturvedi S, Peng L, Verta P. Influence of site and operator characteristics on carotid artery stent outcomes: analysis of the

CAPTURE 2 (Carotid ACCULINK/ACCUNET Post Approval Trial to Uncover Rare Events) clinical study. JACC Cardiovasc Interv 2011;4:235-46.
578. Hopkins LN, White CJ, Foster MT, Powell RJ, Zemel G, Diaz-Cartelle J. Carotid artery stenting and patient outcomes: the CABANA surveillance study. Catheter Cardiovasc Interv 2014;84:997-1004.
579. Modrall JG, Chung J, Kirkwood ML, Baig MS, Tsai SX, Timaran CH, et al. Low rates of complications for carotid artery stenting are associated with a high clinician volume of carotid artery stenting and aortic endografting but not with a high volume of percutaneous coronary interventions. J Vasc Surg 2014;60:70-6.
580. Shishehbor MH, Venkatachalam S, Gray WA, Metzger C, Lal BK, Peng L, et al. Experience and outcomes with carotid artery stenting: an analysis of the CHOICE study (Carotid Stenting for High SurgicalRisk Patients; Evaluating Outcomes Through the Collection of Clinical Evidence). JACC Cardiovasc Interv 2014;7:1307-17.
581. Badheka AO, Chothani A, Panaich SS, Mehta K, Patel NJ, Deshmukh A, et al. Impact of symptoms, gender, co-morbidities, and operator volume on outcome of carotid artery stenting (from the Nationwide Inpatient Sample [2006 to 2010]). Am J Cardiol 2014;114:933-41.
582. Vogel TR, Dombrovskiy VY, Graham AM. Carotid artery stenting in the nation: the influence of hospital and physician volume on outcomes. Vasc Endovascular Surg 2010;44:89-94.
583. Steppacher R, Csikesz N, Eslami M, Arous E, Messina L, Schanzer A. An analysis of carotid artery stenting procedures performed in New York and Florida (2005-2006): procedure indication, stroke rate, and mortality rate are equivalent for vascular surgeons and non-vascular surgeons. J Vasc Surg 2009;49:1379-85; discussion: 1385-6.
584. Smout J, Macdonald S, Weir G, Stansby G. Carotid artery stenting: relationship between experience and complication rate. Int J Stroke 2010;5:477-82.
585. Setacci C, Chisci E, Setacci F, Iacoponi F, de Donato G, Rossi A. Siena carotid artery stenting score: a risk modelling study for individual patients. Stroke 2010;41:1259-65.
586. Aronow HD, Collins TJ, Gray WA, Jaff MR, Kluck BW, Patel RA, et al. SCAI/SVM expert consensus statement on carotid stenting: Training and credentialing for carotid stenting. Catheter Cardiovasc Interv 2016;87:188-99.
587. Vogel TR, Dombrovskiy VY, Haser PB, Graham AM. Carotid artery stenting: impact of practitioner specialty and volume on outcomes and resource utilization. J Vasc Surg 2009;49:1166-71.
588. Sgroi MD, Darby GC, Kabutey NK, Barleben AR, Lane JS 3rd, Fujitani RM. Experience matters more than specialty for carotid stenting outcomes. J Vasc Surg 2015;61:933-8.
589. AbuRahma AF, Campbell JE, Hariri N, AbuRahma J, Dean LS, Bates MC, et al. Clinical outcome of carotid artery stenting achttp://refhub.elsevier.com/S0741-5214(21)00894-6/sref589cording to provider specialty and volume. Ann Vasc Surg 2017;44:361-7.
590. Avgerinos EDGC, Ling J, Naddaf A, Steinmetz AL, Makaroun MS, Chaer RA. Carotid artery disease progression and related neurologic events following carotid endarterectomy. J Vasc Surg 2014;59:2.
591. Iafrati MD, Salamipour H, Young C, Mackey WC, O'Donnell TF Jr. Who needs surveillance of the contralateral carotid artery? Am J Surg 1996;172:136-9.
592. Patel ST, Kuntz KM, Kent KC. Is routine duplex ultrasound surveillance after carotid endarterectomy cost-effective? Surgery 1998;124: 343-51; discussion: 351-2.
593. 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.
594. Al Shakarchi J, Lowry D, Nath J, Khawaja AZ, Inston N, Tiwari A. Duplex ultrasound surveillance after carotid artery endarterectomy. J Vasc Surg 2016;63:1647-50.
595. Chaturvedi S. Is surveillance for restenosis justified after carotid revascularisation? Lancet Neurol 2018;17:570-1.
596. AbuRahma AF, Srivastava M, AbuRahma Z, Jackson W, Mousa A, Stone PA, et al. The value and economic analysis of routine postoperative carotid duplex ultrasound surveillance after carotid endarterectomy. J Vasc Surg 2015;62:378-83.
597. Zierler RE, Jordan WD, Lal BK, Mussa F, Leers S, Fulton J, et al. The Society for Vascular Surgery practice guidelines on follow-up after vascular surgery arterial procedures. J Vasc Surg 2018;68:256-84.
598. Bonati LH, Gregson J, Dobson J, McCabe DJH, Nederkoorn PJ, van der Worp HB, et al. Restenosis and risk of stroke after stenting or endarterectomy for symptomatic carotid stenosis in the International Carotid Stenting Study (ICSS): secondary analysis of a randomised trial. Lancet Neurol 2018;17:587-96.
599. Fokkema M, Vrijenhoek JE, Den Ruijter HM, Groenwold RH, Schermerhorn ML, Bots ML, et al. Stenting versus endarterectomy for restenosis following prior ipsilateral carotid endarterectomy: an individual patient data meta-analysis. Ann Surg 2015;261:598-604.
600. Naylor AR, Saratzis A. The fate of severe restenosis after carotid interventions. Lancet Neurol 2018;17:842-3.
601. AbuRahma AF, Cook CC, Metz MJ, Wulu JT Jr, Bartolucci A. Natural history of carotid artery stenosis contralateral to endarterectomy: results from two randomized prospective trials. J Vasc Surg 2003;38:1154-61.
602. Ballotta E, Da Giau G, Meneghetti G, Barbon B, Militello C, Baracchini C. Progression of atherosclerosis in asymptomatic carotid arteries after contralateral endarterectomy: a 10-year prohttp://refhub.elsevier.com/S0741-5214(21)00894-6/sref602spective study. J Vasc Surg 2007;45:516-22.
603. Fluri F, Engelter ST, Wasner M, Stierli P, Merlo A, Lyrer PA. The probability of restenosis, contralateral disease progression, and late neurologic events following carotid endarterectomy: a long-term follow-up study. Cerebrovasc Dis 2008;26:654-8.
604. Kallmayer M, Tsantilas P, Zieger C, Ahmed A, Sollner H, Zimmermann A, et al. Ultrasound surveillance after CAS and CEA: what's the evidence? J Cardiovasc Surg (Torino) 2014;55(2 Suppl 1):33-41.
605. Diaz-Duran C, Clara A, Roig L, Ruiz-Carmona C, Mellado Joan M, Elosua R. Disease progression in the contralateral carotid artery is still common after endarterectomy. Ann Vasc Surg 2018;50:225-30.
606. Kakkos SK, Nicolaides AN, Charalambous I, Thomas D, Giannopoulos A, Naylor AR, et al. Predictors and clinical significance of progression or regression of asymptomatic carotid stenosis. J Vasc Surg 2014;59:956-67.e1.
607. Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/ American Stroke Association. Stroke 2014;45:2160-236.
608. Zapata-Arriaza E, Moniche F, Gonzalez A, Bustamante A, EscuderoMartinez I, De la Torre Laviana FJ, et al. Predictors of restenosis following carotid angioplasty and stenting. Stroke 2016;47:2144-7.
609. Halsey JH, McDowell HA, Gelmon S, Morawetz RB. Blood velocity in the middle cerebral artery and regional cerebral blood flow during carotid endarterectomy. Stroke 1989;20:53-8.
610. Abbott A. Dementia: a problem for our age. Nature 2011;475:S2-4.
611. Wimo A, Jonsson L, Bond J, Prince M, Winblad B. Alzheimer disease I. The worldwide economic impact of dementia 2010. Alzheimers Dement 2013;9:1-11.e3.
612. Snowdon DA, Greiner LH, Mortimer JA, Riley KP, Greiner PA, Markesbery WR. Brain infarction and the clinical expression of Alzheimer disease. The Nun Study. JAMA 1997;277:813-7.
613. Dempsey RJ, Vemuganti R, Varghese T, Hermann BP. A review of carotid atherosclerosis and vascular cognitive decline: a new understanding of the keys to symptomology. Neurosurgery 2010;67: 484-93; discussion: 493-4.
614. Mathiesen EB, Waterloo K, Joakimsen O, Bakke SJ, Jacobsen EA, Bonaa KH. Reduced neuropsychological test performance in asymptomatic carotid stenosis: the Tromso Study. Neurology 2004;62:695-701.
615. Johnston SC, O'Meara ES, Manolio TA, Lefkowitz D, O'Leary DH, Goldstein S, et al. Cognitive impairment and decline are associated with carotid artery disease in patients without clinically evident cerebrovascular disease. Ann Intern Med 2004;140:237-47.
616. Poels MM, Ikram MA, Vernooij MW, Krestin GP, Hofman A, Niessen WJ, et al. Total cerebral blood flow in relation to cognitive function: the Rotterdam Scan Study. J Cereb Blood Flow Metab 2008;28:1652-5.
617. Zhu L, Fratiglioni L, Guo Z, Aguero-Torres H, Winblad B, Viitanen M. Association of stroke with dementia, cognitive impairment, and functional disability in the very old: a population-based study. Stroke 1998;29:2094-9.

618. Sun JH, Tan L, Yu JT. Post-stroke cognitive impairment: epidemiology, mechanisms and management. Ann Transl Med 2014;2:80.
619. Romero JR, Beiser A, Seshadri S, Benjamin EJ, Polak JF, Vasan RS, et al. Carotid artery atherosclerosis, MRI indices of brain ischemia, aging, and cognitive impairment: the Framingham study. Stroke 2009;40:1590-6.
620. Rabbitt P, Scott M, Thacker N, Lowe C, Jackson A, Horan M, et al. Losses in gross brain volume and cerebral blood flow account for age-related differences in speed but not in fluid intelligence.
Neuropsychology 2006;20:549-57.
621. Binnewijzend MA, Benedictus MR, Kuijer JP, van der Flier WM, Teunissen CE, Prins ND, et al. Cerebral perfusion in the predementia stages of Alzheimer's disease. Eur Radiol 2016;26:506-14.
622. Alosco ML, Gunstad J, Jerskey BA, Xu X, Clark US, Hassenstab J, et al. The adverse effects of reduced cerebral perfusion on cognition and brain structure in older adults with cardiovascular disease. Brain Behav 2013;3:626-36.
623. Markus HS, King A, Shipley M, Topakian R, Cullinane M, Reihill S, et al. Asymptomatic embolisation for prediction of stroke in the Asymptomatic Carotid Emboli Study (ACES): a prospective observational study. Lancet Neurol 2010;9:663-71.
624. Liberman AL, Zandieh A, Loomis C, Raser-Schramm JM, Wilson CA, Torres J, et al. Symptomatic carotid occlusion is frequently associated with microembolization. Stroke 2017;48:394-9.
625. Purandare N, Burns A, Morris J, Perry EP, Wren J, McCollum C. Association of cerebral emboli with accelerated cognitive deterioration in Alzheimer's disease and vascular dementia. Am J Psychiatry 2012;169:300-8.
626. Purandare N, Voshaar RC, Morris J, Byrne JE, Wren J, Heller RF, et al. Asymptomatic spontaneous cerebral emboli predict cognitive and functional decline in dementia. Biol Psychiatry 2007;62:339-44.
627. Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and the risk of dementia and cognitive decline. N Engl J Med 2003;348:1215-22.
628. Lal BK, Dux MC, Sikdar S, Goldstein C, Khan AA, Yokemick J, et al. Asymptomatic carotid stenosis is associated with cognitive impairment. J Vasc Surg 2017;66:1083-92.
629. De Rango P, Caso V, Leys D, Paciaroni M, Lenti M, Cao P. The role of carotid artery stenting and carotid endarterectomy in cognitive performance: a systematic review. Stroke 2008;39:3116-27.
630. Qu L, Feng J, Zou S, Bai J, Hu Z, Guo M, et al. Improved visual, acoustic, and neurocognitive functions after carotid endarterechttp://refhub.elsevier.com/S0741-5214(21)00894-6/sref630tomy in patients with minor stroke from severe carotid stenosis. J Vasc Surg 2015;62:635-44.e2.
631. Carta MG, Lecca ME, Saba L, Sanfilippo R, Pintus E, Cadoni M, et al. Patients with carotid atherosclerosis who underwent or did not undergo carotid endarterectomy: outcome on mood, cognition and quality of life. BMC Psychiatry 2015;15:277.
632. Watanabe J, Ogata T, Higashi T, Inoue T. Cognitive change 1 year after CEA or CAS compared with medication. J Stroke Cerebrovasc Dis 2017;26:1297-305.
633. Czerny M, Schuch P, Sodeck G, Balassy C, Hoelzenbein T, Juraszek A, et al. Sustained cognitive benefit 5 years after carotid endarterectomy. J Vasc Surg 2010;51:1139-44.
634. Johnson R Jr. On the neural generators of the P300 component of the event-related potential. Psychophysiology 1993;30:90-7.
635. Medvidovic S, Titlic M, Maras-Simunic M. P300 evoked potential in patients with mild cognitive impairment. Acta Inform Med 2013;21: 89-92.
636. Fierstra J, Maclean DB, Fisher JA, Han JS, Mandell DM, Conklin J, et al. Surgical revascularization reverses cerebral cortical thinning in patients with severe cerebrovascular steno-occlusive disease. Stroke 2011;42:1631-7.
637. Reinhard M, Muller T, Guschlbauer B, Timmer J, Hetzel A. Dynamic cerebral autoregulation and collateral flow patterns in patients with severe carotid stenosis or occlusion. Ultrasound Med Biol 2003;29:
1105-13.
638. Tedesco MM, Dalman RL, Zhou W, Coogan SM, Lane B, Lee JT. Reduction of postprocedure microemboli following retrospective quality assessment and practice improvement measures for carotid angioplasty and stenting. J Vasc Surg 2009;49:607-12; discussion:
612-3.
639. Hitchner E, Baughman BD, Soman S, Long B, Rosen A, Zhou W. Microembolization is associated with transient cognitive decline in patients undergoing carotid interventions. J Vasc Surg 2016;64:
1719-25.
640. Montorsi P, Caputi L, Galli S, Ciceri E, Ballerini G, Agrifoglio M, et al. Microembolization during carotid artery stenting in patients with high-risk, lipid-rich plaque. A randomized trial of proximal versus distal cerebral protection. J Am Coll Cardiol 2011;58:1656-63.
641. Schnaudigel S, Groschel 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.
642. Bossema ER, Brand N, Moll FL, Ackerstaff RG, van Doornen LJ. Perioperative microembolism is not associated with cognitive outcome three months after carotid endarterectomy. Eur J Vasc Endovasc Surg 2005;29:262-8.
643. Ghogawala Z, Westerveld M, Amin-Hanjani S. Cognitive outcomes after carotid revascularization: the role of cerebral emboli and hypoperfusion. Neurosurgery 2008;62:385-95; discussion: 393-5.
644. Zhou W, Hitchner E, Gillis K, Sun L, Floyd R, Lane B, et al. Prospective neurocognitive evaluation of patients undergoing carotid inhttp://refhub.elsevier.com/S0741-5214(21)00894-6/sref644terventions. J Vasc Surg 2012;56:1571-8.
645. Laza C, Popescu BO, Popa M, Roceanu AM, Tiu C, Antochi FA, et al. Microemboli detection in patients with carotid artery stenting–a potential marker for future cognitive impairment? J Neurol Sci
2013;326:96-9.
646. Zhou W, Baughman BD, Soman S, Wintermark M, Lazzeroni LC,
Hitchner E, et al. Volume of subclinical embolic infarct correlates to long-term cognitive changes after carotid revascularization. J Vasc Surg 2017;65:686-94.
647. Rapp JH, Pan XM, Sharp FR, Shah DM, Wille GA, Velez PM, et al. Atheroemboli to the brain: size threshold for causing acute neuronal cell death. J Vasc Surg 2000;32:68-76.
648. Soman S, Prasad G, Hitchner E, Massaband P, Moseley ME, Zhou W, et al. Brain structural connectivity distinguishes patients at risk for cognitive decline after carotid interventions. Hum Brain Mapp
2016;37:2185-94.
649. Zuniga MC, Tran TB, Baughman BD, Raghuraman G, Hitchner E, Rosen A, et al. A Prospective evaluation of systemic biomarkers and cognitive function associated with carotid revascularization. Ann Surg 2016;264:659-65.
650. Hillman CH, Erickson KI, Kramer AF. Be smart, exercise your heart: exercise effects on brain and cognition. Nat Rev Neurosci 2008;9: 58-65.
651. Vaynman S, Ying Z, Gomez-Pinilla F. Hippocampal BDNF mediates the efficacy of exercise on synaptic plasticity and cognition. Eur J Neurosci 2004;20:2580-90.
652. Kaiser Family Foundation. Payments for cost sharing increasing rapidly over time. October 5, 2017. Available at: https://www.kff.org/ health-costs/issue-brief/payments-for-cost-sharing-increasing-rapidlyover-time/. Accessed September 4, 2018.
653. Mincer J. Ballooning bills. More US hospitals pushing patients to pay before care. Reuters; 2007. Available at: https://www.reuters.com/ article/us-usa-healthcare-hospital-payments/ballooning-bills-moreu-s-hospitals-pushing-patients-to-pay-before-care-idUSKBN17F1 CM. Accessed July 30, 2021.
654. Hudec W. Massachusetts becomes first state to publish prices of health care services. December 4, 2017. Available at: https://www.advisory.com/research/medical-group-strategy-council/practicenotes/2014/december/mass-price-transparency. Accessed September 4, 2018.
655. Hurtubise S. Gallop: Peak number of Americans delaying medical care over costs. November 2, 2014. Available at: http://dailycaller. com/2014/11/28/gallup-peak-number-of-americans-delaying-medicalcare-over-costs/. Accessed September 4, 2018.
656. Abraham T. CMS finalizes rule requiring hospitals to post prices online. August 3, 2018. Available at: https://www.healthcaredive. com/news/cms-finalizes-rule-requiring-hospitals-to-post-pricesonline/529261/. Accessed September 11, 2018.
657. Garrison LP Jr. Cost-effectiveness and clinical practice guidelines: have we reached a tipping point? An overview. Value Health 2016;19:
512-5.
658. Anderson JL, Heidenreich PA, Barnett PG, Creager MA, Fonarow GC, Gibbons RJ, et al. ACC/AHA statement on cost/value methodology in clinical practice guidelines and performance measures: a report of the American College of Cardiology/American Heart Association
Task Force on Performance Measures and Task Force on Practice

Guidelines. Circulation 2014;129:2329-45.
659. Ecker RD, Brown RD Jr, Nichols DA, McClelland RL, Reinalda MS, Piepgras DG, et al. Cost of treating high-risk symptomatic carotid artery stenosis: stent insertion and angioplasty compared with endarterectomy. J NeuroSurg 2004;101:904-7.
660. Park B, Mavanur A, Dahn M, Menzoian J. Clinical outcomes and cost comparison of carotid artery angioplasty with stenting versus carotid endarterectomy. J Vasc Surg 2006;44:270-6.
661. Kim JH, Choi JB, Park HK, Kim KH, Kuh JH. Cost-effectiveness of carotid endarterectomy versus carotid artery stenting for treatment of carotid artery stenosis. Korean J Thorac Cardiovasc Surg 2014;47: 20-5.
662. Pawaskar M, Satiani B, Balkrishnan R, Starr JE. Economic evaluation of carotid artery stenting versus carotid endarterectomy for the treatment of carotid artery stenosis. J Am Coll Surg 2007;205:
413-9.
663. Sternbergh WC 3rd, Crenshaw GD, Bazan HA, Smith TA. Carotid endarterectomy is more cost-effective than carotid artery stenting. J Vasc Surg 2012;55:1623-8.
664. Obeid T, Alshaikh H, Nejim B, Arhuidese I, Locham S, Malas M. Fixed and variable cost of carotid endarterectomy and stenting in the United States: a comparative study. J Vasc Surg 2017;65:1398-1406.e1.
665. de Vries EE, Baldew VGM, den Ruijter HM, de Borst GJ. Meta-analysis of the costs of carotid artery stenting and carotid endarterectomy. Br J Surg 2017;104:1284-92.
666. McDonald RJ, Kallmes DF, Cloft HJ. Comparison of hospitalization costs and Medicare payments for carotid endarterectomy and carotid stenting in asymptomatic patients. AJNR Am J Neuroradiol
2012;33:420-5.
667. Donovan MJ, Ramirez DE, Crenshaw GD, Smith TA, Bazan HA, Sternbergh WC 3rd. Hospital reimbursement for carotid stenting and endarterectomy. J Endovasc Ther 2014;21:296-302.
668. Kilaru S, Korn P, Kasirajan K, Lee TY, Beavers FP, Lyon RT, et al. Is carotid angioplasty and stenting more cost effective than carotid endarterectomy? J Vasc Surg 2003;37:331-9.
669. Oh SH, You JH, Lee JY, Park JJ, Shin S. Cost-utility analysis of carotid artery stenting versus endarterectomy for symptomatic carotid stenosis patients. Value Health 2014;17:A491.
670. Almekhlafi MA, Hill MD, Wiebe S, Goyal M, Yavin D, Wong JH, et al. When is carotid angioplasty and stenting the cost-effective alternative for revascularization of symptomatic carotid stenosis? A Canadian health system perspective. AJNR Am J Neuroradiol 2014;35: 327-32.
671. Khan AA, Chaudhry SA, Sivagnanam K, Hassan AE, Suri MF, Qureshi AI. Cost-effectiveness of carotid artery stent placement versus endarterectomy in patients with carotid artery stenosis. J NeuroSurg 2012;117:89-93.
672. Vilain KR, Magnuson EA, Li H, Clark WM, Begg RJ, Sam AD 2nd, et al. Costs and cost-effectiveness of carotid stenting versus endarterectomy for patients at standard surgical risk: results from the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST). Stroke 2012;43:2408-16.
673. Morris S, Patel NV, Dobson J, Featherstone RL, Richards T, LuengoFernandez R, et al. Cost-utility analysis of stenting versus endarterectomy in the International Carotid Stenting Study. Int J Stroke
2016;11:446-53.
674. Rinaldo L, Brinjikji W, Cloft H, DeMartino RR, Lanzino G. Investigation into drivers of cost of stenting for carotid stenosis. J Vasc Surg 2017;66:786-93.

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