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Authors

Ooi, Yinn Cher

Gonzalez, Nestor R

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Management of Extracranial Carotid Artery Disease



Yinn Cher Ooi, MD^a, Nestor R. Gonzalez, MD^{a,b,*}

KEYWORDS

- Carotid disease • Carotid stenosis • Atherosclerotic disease • Stroke • Carotid endarterectomy
- Carotid angioplasty and stenting • Antiplatelet therapy

KEY POINTS

- Asymptomatic patients without risk factors should not be screened for carotid atherosclerotic disease.
- Carotid ultrasonography should be the initial screening tool for symptomatic patients.
- Medical management, including antiplatelet therapy, is indicated in all symptomatic patients with carotid atherosclerotic disease, independent of degree of stenosis.
- In general, carotid revascularization is indicated in symptomatic patients with nonocclusive moderate to severe stenosis (>50%) and asymptomatic patients with severe stenosis (>70%).
- When revascularization is indicated, patient anatomy, risk factors, and plaque factors should be considered in the decision for carotid endarterectomy versus angioplasty and stenting.

INTRODUCTION

Epidemiology

When considered as an independent diagnosis separate from other cardiovascular diseases, stroke is the third leading cause of death in developed nations and a leading cause of long-term disability.¹ Approximately 87% of all strokes are ischemic, 10% are hemorrhagic, and 3% are subarachnoid hemorrhages.^{2–10}

Based on the Framingham Heart Study and Cardiovascular Health Study populations, the prevalence of greater than 50% carotid stenosis is approximately 9% in men and 6% to 7% in women.^{11,12} Carotid stenosis or occlusion as a cause of stroke has been more difficult to determine from population studies. Approximately 7%

to 18% of all first strokes were associated with carotid stenosis.^{13,14} The risk for recurrent strokes among survivors is 4% to 15% within a year after the initial stroke, and 25% by 5 years.⁸

Extracranial atherosclerotic disease accounts for up to 15% to 20% of all ischemic strokes.^{15,16} Whereas intracranial atherosclerotic disease has been shown to be consistently more common among Blacks, Hispanics, and Asians in comparison with Whites,^{15,17} the racial differences for extracranial atherosclerotic disease are less apparent. The Northern Manhattan Stroke study reported equal incidence of extracranial atherosclerotic disease among patients of all races presenting with an acute ischemic stroke.¹⁵ However, a smaller study reported that Whites were

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^a Department of Neurosurgery, University of California, Los Angeles, 300 Stein Plaza, Suite 562, Los Angeles, CA 90095-69, USA; ^b Department of Radiology, University of California, Los Angeles, 300 Stein Plaza, Suite 562, Los Angeles, CA 90095-69, USA

* Corresponding author. Department of Neurosurgery, University of California, Los Angeles, 300 Stein Plaza, Suite 562, Los Angeles, CA 90095-69.

E-mail address: NGonzalez@mednet.ucla.edu

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more likely than Blacks to have extracranial carotid artery lesions (33% vs 15%, $P = .001$).¹⁶ Male gender appears to be an independent predictor for intracranial atherosclerotic disease, whereas no gender differences were reported for extracranial disease.¹⁶

Natural History

Stroke associated with extracranial carotid atherosclerotic disease could occur via several mechanisms¹⁸:

- Atheroembolism of cholesterol crystals or other debris
- Artery to artery embolism of thrombus
- Structural disintegration of the wall (dissection)
- Acute thrombotic occlusion
- Reduced cerebral perfusion with plaque growth

In symptomatic patients, there is a clear correlation between the degree of stenosis and the risk of stroke.¹⁹ In the North America Symptomatic Carotid Endarterectomy Trial (NASCET), the stroke rate after 18 months of medical therapy without revascularization was 19% in patients with 70% to 79% stenosis, 28% in patients with 80% to 89% stenosis, and 33% in patients with 90% to 99% stenosis.¹⁹

This correlation is less apparent in asymptomatic patients. In the Asymptomatic Carotid Atherosclerosis Study (ACAS) and the Asymptomatic Carotid Surgery Trial (ACST), asymptomatic patients with 60% to 80% stenosis had higher strokes rates compared with those with more severe stenosis.^{20,21} The presence of a carotid bruit also does not appear to be a reliable predictor of stroke risk in asymptomatic patients. Despite the Framingham Heart Study population showing that asymptomatic patients with carotid bruit had a 2.6-fold increased incidence of strokes in comparison with those without carotid bruit, less than half of these stroke events involved the ipsilateral cerebral hemisphere.³

Although the degree of carotid stenosis remains the main determinant of disease severity, additional imaging markers of plaque vulnerability are also important in determining the risk for transient ischemic attack (TIA) and strokes.^{22–24} Imaging markers for plaque vulnerability on ultrasonography (US) include^{22,23}:

- Ulceration
- Echolucency
- Intraplaque hemorrhage
- High lipid content

Thin or ruptured fibrous caps, intraplaque hemorrhage and large lipid-rich or necrotic plaque cores, and overall plaque thickness seen on MRI have also been associated with subsequent ischemic events.²⁵

The utility of biomarkers and imaging makers for inflammation in predicting plaque vulnerability and the risk for stroke has also been investigated. Carotid plaques from patients with ipsilateral stroke demonstrated infiltration of the fibrous cap by inflammatory cells.^{26,27} ¹⁸F-Fluorodeoxyglucose measured by PET is believed to reflect inflammation.^{28,29} Macrophage activity quantified by PET has been observed in experimental models. In addition, biomarkers such as C-reactive protein and different matrix metalloproteinases are currently being studied for their predictive value of plaque instability.^{30–32} However, the reliability of these markers remains uncertain.

EVALUATION OF CAROTID ATHEROSCLEROTIC DISEASE

Carotid Ultrasonography

When performed by well-trained, experienced technologists, carotid US is accurate and relatively inexpensive.^{33–38} Carotid US is also noninvasive, and does not require a venipuncture or exposure to contrast material or radiation. As such, carotid US is recommended for the initial evaluation of symptomatic and asymptomatic patients with suspicion for carotid atherosclerotic disease.³⁹

Carotid US should be performed in asymptomatic patients with 2 or more of the following risk factors:

- Hypertension
- Hyperlipidemia
- Family history of atherosclerosis or ischemic stroke before 60 years of age
- Tobacco smoking

US remains an appropriate screening tool for high-risk, asymptomatic patients irrespective of auscultation findings, because the sensitivity and positive predictive value of a carotid bruit for a hemodynamically significant carotid stenosis are relatively low.

Carotid US is not recommended, however, for routine screening of asymptomatic patients without risk factors for atherosclerotic disease, owing to the lack of data from health economic studies to support mass screening of the general population.^{40,41}

Carotid US should also be performed annually to assess the progression or regression of disease and response to therapeutic measures in patients with greater than 50% stenosis. Once stability has

been established or a patient's candidacy for further intervention has changed, longer intervals may be appropriate.³⁹

Carotid US does not directly measure the luminal diameter of the artery or stenotic section. Instead, it relies on blood flow velocity as an indicator for the degree of stenosis. Several schemes have been developed for assessment of carotid stenosis.^{42–44} Measuring the internal carotid artery (ICA) peak systolic velocity and the ratio of ICA peak systolic velocity over the ipsilateral common carotid artery velocity correlate best with angiographic stenosis. Potential pitfalls of velocity-based estimation of stenosis are the higher velocities in women than in men, and elevated velocities in the presence of a contralateral occlusion.^{45,46} Subtotal arterial occlusion may also sometimes be mistaken for total occlusion, a crucial differentiation in determining management strategies. Other factors that may further reduce the accuracy of carotid US include highly operator-dependent reliability, obesity, high carotid bifurcation, severe arterial tortuosity, extensive calcifications, and presence of a carotid stent.^{33–35,39,47}

Despite varying results between imaging centers and operators, the overall sensitivity and specificity for detection of occlusion or stenosis greater than 70% have been reported to be 85% to 90% when compared with catheter angiography.^{48–50}

Computed Tomography Angiography and Magnetic Resonance Angiography

Both magnetic resonance angiography (MRA) and computed tomography angiography (CTA) are able to generate high-resolution images of the cervical arteries.^{51–57} In comparison with catheter angiography, MRA has a sensitivity range of 97% to 100% and a specificity range of 82% to 96%,^{58–62} whereas CTA has 100% sensitivity and 63% specificity (95% confidence interval [CI] 25%–88%).⁶³ Both are indicated in symptomatic patients when carotid US cannot be obtained, yield equivocal results, or show complete occlusion.³⁹ In patients with high pretest probability for disease, MRA and CTA may be used as the initial test. MRA and CTA of the intracranial vessels should be done when an extracranial source cannot be identified in symptomatic patients or in patients with risk factors for intracranial atherosclerotic disease. MRA and CTA are helpful in determining the exact severity of stenosis and anatomic details that will influence treatment decisions.

MRA has the benefit of its relative insensitivity to arterial calcification. Contrast-enhanced MRA allows for more detailed evaluation of the

cervical arteries, especially in lesions with a slow blood flow, in comparison with noncontrast studies.^{58–61,64,65} However, if contrast is contraindicated, non-contrast-enhanced MRA may be used.⁵¹

Potential pitfalls for MRA include a tendency to overestimate the degree of stenosis, and an inability to discriminate between total occlusion and subtotal occlusion. This effect is reduced with the use of contrast-enhanced MRA. Additional barriers of MRA include patients who are claustrophobic, extreme obesity, or incompatible implanted devices, such as pacemakers or defibrillators. For these patients, CTA is a good alternative.³⁹

Unlike both MRA and carotid US, CTA provides direct imaging of the arterial lumen, making it suitable for evaluation of stenosis. It is an accurate test to determine severity of stenosis, and is also highly accurate for the detection or exclusion of complete occlusions.⁵⁵ However, CTA exposes patients to radiation, and the relatively high volume of iodinated contrast needed for the study precludes patients with impaired renal function. The presence of heavily calcified plaques may affect the accuracy of CTA in determining the degree of stenosis.⁵⁶ In addition, foreign metal objects, such as dental implants and surgical clips in the neck, can generate artifacts, which may obscure the targeted vessels.

Catheter Angiography

Although noninvasive imaging can provide the information needed in guiding the choice of medical, endovascular, or surgical treatment in most cases,³⁹ catheter angiography remains the gold standard for diagnosing and grading of carotid atherosclerotic disease.

Owing to its inherent cost and risk for complications, such as ischemic strokes, catheter angiography should be reserved for patients in whom noninvasive imaging is contraindicated, inconclusive, or yields discordant results. The risks of catheter angiography include allergic reactions to contrast, kidney dysfunction resulting from contrast toxicity, femoral artery injuries, infections or hematomas of the puncture site, strokes, or death, typically at a rate lower than 1 in 1000 for the most serious complications and less than 5% for the minor events in specialized centers with high volumes.^{67,68}

Catheter angiography is useful in patients with renal insufficiency. Selective angiography of a single suspected vascular territory could provide definitive imaging with limited exposure to contrast material, and is unlikely to exacerbate renal insufficiency.³⁹

Several methods to measure stenosis have been described, producing marked variability in measurements of vessels with the same degree of actual anatomic narrowing. Measurement methods based on the NASCET have been used in most modern clinical trials, taking into account the luminal diameter at the section with highest degree of stenosis (A), and the luminal diameter of a normal section just distal to the stenosis (B).²⁰

$$\% \text{ Stenosis} = (B - A)/B \times 100$$

MEDICAL MANAGEMENT

Pharmacologic therapy for patients with carotid atherosclerotic disease consists mainly of antiplatelet therapy and medical management of the risk factors for atherosclerotic disease.

Antithrombotic Therapy

The use of antiplatelet agents has been shown to reduce the risk of stroke in patients with TIA or a previous stroke.^{40,69–71} Single-agent antiplatelet therapies are recommended for all symptomatic patients, independent of whether they are candidates for revascularization. Aspirin 75 to 325 mg daily should be the first line of therapy. Clopidogrel 75 mg daily or ticlopidine 250 mg daily are reasonable alternatives when aspirin is contraindicated by factors other than active hemorrhage.^{39,69,70,72}

Several randomized, controlled, double-blinded studies have shown that dual-antiplatelet combination therapy is not superior to single agents. The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial and Management of Atherothrombosis with Clopidogrel in High-Risk Patients (MATCH) both showed that combination therapy of aspirin plus clopidogrel did not reduce stroke risk significantly compared with either drug alone.^{73,74} The Second European Stroke Prevention Study (ESPS-2), which included 6602 patients, showed that the combination of aspirin and extended-release dipyridamole was superior to aspirin alone in patients with prior TIA or stroke.⁷⁵ However, a much larger study, with more than 20,000 patients, The Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS) trial, showed that combination therapy of aspirin and extended-release dipyridamole was not superior to clopidogrel alone in recurrent stroke prevention.⁷⁶ Furthermore, there was an increased risk for major hemorrhagic events, including intracranial hemorrhage, in the combination therapy group.⁷⁶ Despite clopidogrel monotherapy showing equal efficacy and lower hemorrhage risk than aspirin plus extended-release dipyridamole, and equal

efficacy with aspirin plus clopidogrel, the variations in response to clopidogrel attributable to genetic factors and drug interactions makes it crucial for individualized treatment selection for optimum stroke prevention.

Variability in response to clopidogrel is a result of both clinical and genetic factors. Conversion of clopidogrel to its active form by the cytochrome P450 system depends highly on CYP enzyme, which has significant genetic variability. CYP2C19*2 is the most common genetic variant associated with impaired response to clopidogrel.³⁹ However, other genetic polymorphisms may also contribute to poor response. Aspirin resistance has also been described, and was more frequent in patients taking low-dose aspirin (81 mg daily) and the enteric-coated preparations.⁷⁷ Clopidogrel or aspirin resistance resulting from the inability of these agents to inhibit platelet function is a potential cause of failure in stroke prevention. However, whether variations in response to antiplatelet therapy are associated with greater stroke risk and whether treatment of resistance improves outcomes have not been established. There is also a lack of consensus regarding which platelet function test should be used to determine such resistance.³⁹

The efficacy of antiplatelet therapy in stroke prevention for asymptomatic patients is less apparent.^{40,69,70,78} In the randomized, double-blinded Asymptomatic Cervical Bruit Study, the annual rate of ischemic events and death from any cause in patients with greater than 50% carotid stenosis was 11.0% in the aspirin group compared with 12.3% in the placebo group during a 2-year follow-up. However, the sample size of 372 patients may have been insufficient to detect a clinically meaningful difference.⁷⁹

Anticoagulation with warfarin, along with its potential risk for increased hemorrhagic complications, has not been shown to be superior to antiplatelet agents. Antiplatelet therapy is recommended over anticoagulation for both symptomatic and asymptomatic patients in whom antithrombotic therapy is indicated.³⁹ The Warfarin-Aspirin Recurrent Stroke Study (WARSS), a randomized, double-blinded trial with 2206 patients, compared warfarin to aspirin for stroke prevention or recurrent ischemic stroke in patients with a recent stroke.⁸⁰ No significant benefit of warfarin over aspirin was found after 2 years. Parental anticoagulation with unfractionated heparin or low molecular weight heparin is also not recommended for patients with extracranial carotid atherosclerosis with acute ischemic stroke or TIA.^{81–83} In patients who have other indications for anticoagulation, such as a mechanical prosthetic valve or atrial fibrillation, a vitamin K antagonist such as warfarin may be

preferred to antiplatelet therapy. The target international normalized ratio should be 2.0 to 3.0.⁸⁴

Treatment of Hypertension

Antihypertensive therapy has shown to reduce the risk of stroke, with a 33% reduction in stroke risk for every 10-mm Hg decrease in systolic blood pressure up to 115/75 mm Hg.^{85,86} Antihypertensive therapy also reduces the risk for recurrent strokes by 24%.⁸⁷ These effects appear to be consistent between Whites and Blacks across a wide age range⁸⁸ and between sexes, regions, and stroke subtypes.⁸⁵ As such, antihypertensive treatment is recommended for all patients with concurrent hypertension and asymptomatic extracranial carotid atherosclerotic disease, with a target blood pressure lower than 140/90 mm Hg.^{85–87,89,90} The protective value of antihypertensive therapy also seems to extend to patients without concurrent hypertension, as demonstrated by the Heart Outcomes Protection Evaluation (HOPE) trial.⁹¹

The exact benefits of antihypertensive treatment in symptomatic patients with severe carotid stenosis remain unclear because of concerns for reduction in cerebral perfusion and exacerbation of cerebral ischemia. Patients with severe carotid stenosis may have impaired cerebrovascular reactivity caused by chronic hypoperfusion, thereby increasing the risk for ipsilateral ischemic events.⁹² Antihypertensive treatment is likely indicated in patients with hypertension and symptomatic extracranial atherosclerosis after the hyperacute period.³⁹ However, a specific blood pressure goal has yet to be established.

Treatment of Hyperlipidemia

According to the 2011 American Heart Association guidelines on the management of extracranial carotid and vertebral artery disease, statins are recommended for all patients with extracranial carotid stenosis to reduce low-density lipoprotein (LDL) levels to less than 100 mg/dL.^{39,70,89,93} A target LDL level of 70 mg/dL is reasonable in patients who have sustained an ischemic stroke. Niacin and bile acid sequestrants are reasonable alternatives in patients who do not tolerate statins,^{94–96} and can also be used in combination with a statin if treatment with a statin does not achieve target LDL levels.^{94,95,97,98}

Epidemiologic studies have consistently shown a positive association between cholesterol levels and carotid artery atherosclerosis.^{99–101} Lipid-lowering therapy with statins has been shown to reduce the risk of ischemic stroke in patients with atherosclerosis.^{102,103} A meta-analysis of 26 trials

involving approximately 90,000 patients showed that statins reduced the risk for all stroke by 21% (odds ratio [OR] 0.79, 95% CI 0.73–0.85), with a 15.6% reduction in stroke risk for every 10% decrease in serum LDL levels (95% CI 6.7–23.6).¹⁰³ Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL), a randomized, prospective trial, showed that 80 mg daily of atorvastatin reduced the absolute risk for stroke at 5 years by 2.2%, the relative risk (RR) of all stroke by 16%, and the RR of ischemic stroke by 22%.⁹³ Statins also reduce the progression and induce regression of carotid atherosclerosis.¹⁰⁴ A meta-analysis of 9 randomized trials showed that statins reduced stroke risk by 15.6% and intima-media thickness (IMT) by 0.73% per year for every 10% reduction in LDL levels.¹⁰³ In the Atorvastatin versus Simvastatin on Atherosclerosis Progression (ASAP) trial involving patients with familial hypercholesterolemia, 80 mg daily of atorvastatin decreased carotid IMT after 2 years of treatment, but carotid IMT increased in patients randomized to simvastatin 40 mg daily.¹⁰⁵ Atorvastatin's effects on IMT were further supported by the Arterial Biology for Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) trial, which showed that carotid IMT regressed after 12 months of treatment with atorvastatin 80 mg daily, but remained unchanged with pravastatin 40 mg daily.¹⁰⁶ The Measuring Effects of Intima-Media Thickness: An Evaluation of Rosuvastatin (METEOR) trial showed that in patients with elevated LDL levels and a low Framingham risk score, rosuvastatin reduced the progression of carotid IMT over 2 years when compared with placebo.¹⁰⁷

The effects of nonstatin lipid-modifying therapies on reduction of stroke risk are less apparent.³⁹ Niacin only showed a small benefit in reduction of risk of death caused by cerebrovascular disease in patients participating in the Coronary Drug Project.¹⁰⁸ Fenofibrate did not reduce stroke rates in patients with diabetes mellitus in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study.¹⁰⁹ Gemfibrozil reduced the risk of total strokes and ischemic strokes in patients with coronary artery disease and low high-density lipoprotein (HDL) levels in the Veteran Affairs HDL Intervention trial.¹¹⁰

The ARBITER-2 and Effect of Combination Ezetimibe and High-Dose versus Simvastatin Alone on the Atherosclerosis Process in Patients with Heterozygous Familial Hypercholesterolemia (ENHANCE) studies showed that the addition of extended-release niacin and ezetimibe, respectively, to statin therapy did not affect progression of carotid IMT more than statin therapy alone.^{106,111} The Cholesterol Lowering Atherosclerosis (CLAS)

trial, however, showed that combination therapy of niacin and colestipol reduced the progression of carotid IMT.¹¹²

Management of Diabetes Mellitus

Elevated fasting and postchallenge glucose levels were associated with an increased risk of stroke.¹¹³ The risk of ischemic stroke in diabetic patients is increased 2- to 5-fold compared with nondiabetic patients.^{114–116} The Cardiovascular Health Study showed that diabetes was associated with carotid IMT and severity of carotid stenosis.¹² Both the Atherosclerosis Risk in Communities (ARIC) study and Insulin Resistance Atherosclerosis Study and Epidemiology of Diabetes Interventions and Complications (EDIC) showed that diabetes was associated with progression of carotid IMT.^{116–122} Several randomized, controlled, double-blinded studies have shown that the use of pioglitazone leads to substantial regression of carotid IMT.^{123,124} The effect of pioglitazone appears to be independent of improved glycemic control.¹²³

Smoking Cessation

Cigarette smoking increases the RR for ischemic stroke by 25% to 50%.^{125–131} This risk decreases substantially within 5 years among those who quit smoking.^{126,128} The Framingham Heart Study showed that the degree of extracranial carotid stenosis correlated with the quantity of cigarettes smoked over time.¹³² These findings were corroborated by the Cardiovascular Health Study, in which the severity of carotid stenosis was greater among current smokers than in former smokers, and there was a significant association between pack-years of tobacco exposure with the severity of carotid stenosis.¹³³ The ARIC study revealed that current and past cigarette smoking was associated with a 50% and 25% increase, respectively, in risk of progression of IMT over a 3-year period when compared with nonsmokers.¹³⁰ Smoking cessation counseling and interventions should be offered to patients with extracranial carotid atherosclerosis to reduce the risk for disease progression and stroke.^{125–128,134}

Obesity and Physical Inactivity

Abdominal adiposity has a strong positive association with the risk for stroke or TIA.¹³⁵ Adjusted OR for the waist-to-hip ratio showed successive increases in stroke/TIA risk for every successive tertile. There was also significant association with waist circumference and waist-to-stature ratio with the risk of stroke/TIA.

Physical inactivity is a significant modifiable risk factor for stroke, with 25% prevalence, 30%

attributable risk, and an RR of 2.7.^{40,136} However, the risk reduction associated with intervention remains unclear. Several observational studies and meta-analyses have suggested a lower risk for stroke among individuals engaging in regular moderate to high levels of physical activity.¹³⁷ However, it is unclear whether exercise alone has a significant risk reduction for stroke in the absence of effects on other risk factors, such as reduction in obesity and improvement in glycemic control and serum lipid levels.

INTERVENTIONAL MANAGEMENT

Atherosclerotic disease of the extracranial carotid arteries carries significant morbidity and mortality risk despite maximal medical therapy. NASCET demonstrated a stroke rate of 19% to 33% after 18 months of medical therapy without intervention among symptomatic patients, depending on the degree of stenosis.¹⁹ Interventional management, consisting mainly of carotid endarterectomy (CEA) and carotid angioplasty and stenting (CAS), has been shown to decrease the stroke rate among these patients.^{8,19,138–146}

In general, intervention when indicated should be done within 6 months of original presentation.^{8,19,147,148} However, intervention within 2 weeks of the index event is reasonable for patients with no contraindications for early revascularization.¹⁴⁹

The indications for intervention are discussed in detail in the following sections. The general contraindications for interventions include:

- Severe, disabling stroke (modified Rankin Scale [mRS] score ≤ 3)
- Chronic total carotid artery occlusion
- Carotid stenosis less than 50%
- Extreme high risk for periprocedural complications

Carotid revascularization is not recommended for patients with near-complete occlusion or stenosis less than 50% because the risk for stroke is low in these patients.¹⁹ Revascularization has also not been shown to have any benefit in these patients.¹⁹ Moreover, carotid revascularization is also not recommended for patients with cerebral infarction causing severe disability that precludes preservation of useful function.

Carotid Endarterectomy

Carotid endarterectomy in symptomatic patients

CEA has been shown to significantly reduce the risk for ipsilateral stroke beyond the 30-day

perioperative period in symptomatic patients. However, the inherent risk for periprocedural complications, such as stroke and myocardial infarction (MI), must be considered in the overall assessment of safety and efficacy.

Patients with a nondisabling ischemic stroke (mRS >3) or TIA and greater than 70% stenosis of the ipsilateral ICA by noninvasive imaging, or greater than 50% stenosis by catheter angiography, should undergo CEA.^{8,147}

In NASCET, a randomized trial comparing stroke risk in symptomatic patients receiving CEA and medical management with medical management alone, patients were stratified according to severity of stenosis.¹⁹ The trial for the high-grade stenosis group (70%–99%) was stopped after 18 months after randomizing 328 patients, because a significant benefit for CEA was evident. There was 17% absolute reduction in stroke risk with CEA at 2 years.¹⁹ At the end of NASCET, the investigators also reported a benefit for CEA in patients with 50% to 69% stenosis. The rate of ipsilateral stroke including perioperative events was 15.7% at 5 years, compared with 22% in the medical management only group. The rate of operative mortality or perioperative stroke at 30 days was 6.7%. CEA had no benefit in patients with carotid stenosis less than 50%.

The European Carotid Surgery Trial (ECST), which randomized 2518 patients over a 10-year period, showed similar results to those of NASCET in symptomatic patients with 70% to 99% stenosis, showing a highly significant benefit for CEA, but did not show any benefit in patients with milder stenosis.^{150,151} The lack of benefit of CEA in symptomatic patients with 50% to 69% stenosis based on ECST was attributed to the difference in angiographic measurement of stenosis.

The Veterans Affairs Cooperative Study (VACS) was stopped before completion, after only randomizing 189 symptomatic patients with a mean follow-up of 11.9 months, because of the significant benefit of CEA over medical therapy alone. The primary end point of death, stroke, or TIA occurred in 7.7% of CEA patients, compared with 19.4% of patients receiving medical therapy alone.¹⁵²

A meta-analysis of these 3 trials showed that CEA was most effective in patients with greater than 70% stenosis without complete or near occlusion.¹⁵⁰ Benefits of CEA in patients with 50% to 69% stenosis were only modest, but increased with time. Surgery offered little to no long-term benefits in patients with complete or near occlusion. When the combined outcome of perioperative stroke or death and fatal or disabling ipsilateral ischemic stroke was considered, the

clinical benefits of CEA were only evident in patients with 80% to 99% stenosis.

Carotid endarterectomy in asymptomatic patients

The benefits of CEA for reduction of stroke risk in asymptomatic patients are less profound than in symptomatic patients. CEA is reasonable in asymptomatic patients who have greater than 70% ICA stenosis if the risk of perioperative MI, stroke, and death is low.^{138,153–156} Whereas CEA in symptomatic patients showed an increased benefit of surgery with increased degree of stenosis, CEA in asymptomatic patients did not show a similar trend. Equal benefits were seen in all patients within the 60% to 99% stenosis range.¹⁵⁶

The VACS group conducted the first major trial of CEA in asymptomatic patients.¹⁵³ A total of 444 patients with 50% or greater stenosis were randomized over a 54-month period into either the CEA group or the medical therapy group. The 30-day mortality rate among patients undergoing CEA was 1.9% and the incidence of stroke was 2.4%. The study showed a statistically significant reduction in TIA, stroke, and death 5 years post-CEA, with a 10% overall rate of adverse events in the surgical group compared with 20% in the group given medical therapy alone. However, the inclusion of TIA in the primary composite end point remains controversial, given that the study was underpowered to detect a difference in a composite end point of death and stroke without TIA.^{153,157,158}

ACAS also sought to determine whether the addition of CEA to medical management reduced the incidence of cerebral infarction in asymptomatic patients, but excluded TIA in its primary end point.¹³⁸ The trial was stopped before completion after randomizing 1662 patients, owing to the apparent advantage of CEA among patients with greater than 60% carotid stenosis. After a mean follow-up of 2.7 years, the projected 5-year risk for ipsilateral stroke and any perioperative stroke or death was estimated as 5.1% for surgical patients and 11.0% for patients treated medically. The aggregate risk reduction was 53% (95% CI 22%–72%).

These findings were further corroborated by the ACST, which randomized 3120 asymptomatic patients with greater than 60% stenosis to immediate CEA versus delayed surgery with initial medical management.²¹ The 30-day stroke risk was 3.1% in both groups, but the 5-year rates were 6.4% in the early surgery group compared with 11.8% in the group initially managed medically.¹³⁹

The benefits of CEA for asymptomatic patients are even less apparent in women, because of the

higher operative risk and lower stroke risk without intervention among asymptomatic women compared with men.¹⁵⁶ Such benefits remain unclear despite a meta-analysis combining the data from both ACST and ACAS.¹⁵⁶

Interpretation of carotid endarterectomy trials

The interpretation of CEA trials for both symptomatic and asymptomatic patients should be done in the context of the evolution of medical therapy for atherosclerotic disease. Although pharmacotherapy was included in most trials, guidelines and strategies for medical management have changed over the years. Best medical therapy during the period of older trials such as NASCET was scant by modern standards. In NASCET, only approximately 70% of patients were placed on antihypertensive drugs and an even smaller proportion were given lipid-lowering agents.⁸ Medical therapy was not described in ACAS. The ACST investigators reported a change in medical therapy over the 10-year trial period.¹³⁹ Toward the end of the trial in 2003, 70% of patients were on lipid-lowering agents and 81% were on antihypertensive drugs. However, the outcomes for CEA were only reported for the first 5 years of the trial, ending in 1998, during which such medical therapy was considerably less frequent. In addition, 60% of patients had systolic blood pressure (SBP) greater than 160 mm Hg while 33% had total serum cholesterol greater than 250 mg/dL.

Concurrently surgical outcomes of CEA have improved over time, with advances in training, increased hospital and surgeon volumes, and improved perioperative medical management.^{159–162}

Therefore, with advances in both medical management and operative/perioperative management and outcomes over time, which has led to a decline in rates of adverse events, the comparative outcomes of CEA over medical therapy must be interpreted with caution.

Demographic and clinical considerations

Advanced age does not preclude CEA in appropriately selected patients. Despite several reports showing a higher risk for complications among older patients,^{163,164} patients 75 years and older with few cardiovascular risk factors have been shown to have comparable risk for perioperative stroke and death in comparison with younger patients.¹⁶⁵ However, in ACST no benefit from CEA was observed in patients 80 years of age and older.²¹ In NASCET, the greatest benefit of CEA was observed in older patients up to 80 years of age.¹⁹ Patients older than 80 years were excluded from NASCET (before 1991) and ACAS.^{19,138}

Women undergoing CEA have a higher risk than men for complications.^{147,166–168} In both ACAS and NASCET, women had a higher risk for surgical mortality, neurologic morbidity, recurrent stenosis, or gaining little to no benefit from surgery.^{19,138}

There are insufficient data to determine the effects of ethnicity on outcomes.³⁹

Anatomic considerations

Several factors that affect patient anatomy must be taken into account when considering the safety and technical challenges associated with CEA. Unfavorable factors include:

- High carotid bifurcation or arterial stenosis above the level of the second cervical vertebra
- Arterial stenosis below the clavicle (intrathoracic)
- Contralateral carotid occlusion
- Contralateral vocal cord paralysis
- Previous ipsilateral CEA
- Prior radical neck surgery or radiation
- Prior tracheostomy

A high carotid bifurcation or arterial stenosis above the level of the second vertebra may require high cervical exposure, which increases the risk for cranial nerve injury.^{169,170} The risk for cranial nerve injury is also higher in patients with prior radical neck surgery or tracheostomy. In these cases, there usually is added difficulty in exposing the artery and increased risk for perioperative infection. Contralateral laryngeal nerve palsy is a relative contraindication for CEA because bilateral laryngeal nerve palsy can lead to significant compromise of the airway.¹⁷¹ Prior radiation can make CEA technically challenging, but several series have shown that CEA can still be performed safely.¹⁷² Although in this situation CAS may be a safer option, the rate of restenosis is high, ranging from 18% to 80% over 3 years.^{173–175}

Technical considerations

There have been considerable variations in surgical technique with CEA over the past 50 years. Local anesthesia was initially recommended to permit observation of patients' level of consciousness during temporary carotid artery clamping. Several investigators also advocated local anesthesia because of the possibility of less perioperative adverse cardiac events.³⁹ However, there have been no significant data demonstrating an advantage of local anesthesia over general anesthesia.

Patients undergoing general anesthesia for CEA should undergo intraoperative monitoring of cerebral function to determine the need for

shunting during arterial clamping.^{176–178} Selective shunting of patients is preferable, owing to the potential complications associated with shunting such as mechanical injury to distal ICA, air embolism, or thromboembolism through the shunt, and obscuring the distal arterial anatomy during endarterectomy.³⁹ Intraoperative monitoring includes:

- Electroencephalography (EEG)
- Somatosensory evoked potential (SSEP)
- Transcranial Doppler US
- Computed topographic brain mapping, measurement of residual collateral perfusion pressure, or ICA back pressure

Shunting was generally indicated when EEG abnormalities associated with ischemia appeared.¹⁷⁹ In the authors' institution, shunts are used when a depression of at least 50% of EEG amplitude or SSEP P25 amplitude is observed. Shunts are used in all patients with contralateral carotid occlusion.

Patch closure of the arteriotomy may reduce the incidence of residual or recurrent stenosis. However, there is increased operative time and increased carotid clamp time. Multiple studies have failed to demonstrate a consistent difference in outcomes between patch closure and primary closure.^{180–190} A Cochrane meta-analysis of the combined results of 10 trials showed that patch closure reduces the risk of perioperative arterial occlusion and ipsilateral stroke. There was also reduction in the subsequent risk of restenosis, death, or stroke.¹⁷⁹ As such, most surgeons now advocate for patch closure. Several different patch materials have been described in the literature, including the use of bovine pericardium, vein, polyethylene terephthalate, and polytetrafluoroethylene.^{191–194} However, the outcomes have appeared to be similar independent of the patch material used.

The use of perioperative antiplatelet therapy such as aspirin or clopidogrel reduces the risk for adverse cardiac and neurologic events without a significant increase in risk for postoperative bleeding.^{195,196} However, perioperative combination therapy consisting of aspirin and clopidogrel was associated with increased risk for postoperative bleeding or incisional hematoma.^{197,198}

Perioperative management

Antiplatelet therapy with aspirin 81 to 325 mg daily is recommended before CEA, and should be continued indefinitely postoperatively.^{71,199} In the Acetylsalicylic Acid and Carotid Endarterectomy (ACE) study, where 2849 patients were randomized to 4 different daily doses of aspirin, the

risk of stroke, MI, and death within 30 days and 3 months after CEA was higher in patients taking higher doses of aspirin (650 or 1300 mg daily) compared with those taking lower doses (81 mg or 325 mg daily). The risk at 30 days was 7.0% vs 5.4%, (RR 1.31, 95% CI 0.98–1.75), and at 3 months 8.4% vs 6.2%, (RR 1.34, 95% CI 1.03–1.75).¹⁹⁹ Clopidogrel 75 mg daily or a combination of low-dose aspirin plus extended-release dipyridamole 25 to 200 mg twice daily are reasonable alternatives.^{72,74,80}

The use of perioperative lipid-lowering drugs such as statins for prevention of ischemic events regardless of serum lipid levels after CEA is reasonable.²⁰⁰ However, the optimum agents and doses for prevention of restenosis have not been established. A retrospective review of 1566 patients undergoing CEA at a single large academic center performed by 13 surgeons revealed that receiving statin medication at least 1 week before surgery (42% of total patients reviewed) was associated with lower rates of:

- Perioperative stroke (1.2% vs 4.5%; $P < .01$)
- TIA (1.5% vs 3.6%; $P < .01$)
- All causes of mortality (0.3% vs 2.1%; $P < .01$)
- Median (interquartile range) length of hospitalization (2 days [2–5 days] vs 3 days [2–7 days]; $P < .05$)

Antihypertensive medication is recommended before CEA and should be resumed postoperatively.³⁹

Perioperative management pearls based on the authors' institutional experience are as follows:

- General anesthesia
- Continue EEG and SSEP monitoring
- Discuss with anesthesia the potential need for barbiturates in the reduction of cerebral metabolic demand
- Intravenous antibiotics: cefazolin or vancomycin
- Patient is kept normocapnic (35–45 mm Hg)
- Patient is kept normotensive with permissive hypertension to 20% above baseline during carotid clamping
- Strict control of blood pressure to avoid hypertension is initiated immediately after removal of carotid clamps
- Patient is kept normothermic
- Goal hematocrit of at least 30%
- Shunt is used with any reduction in 50% in EEG amplitude or 50% in the P25 median nerve SSEP activity, or in cases of contralateral occlusion
- A single dose of intravenous heparin is given before cross-clamping, usually 5000 U. In

smaller patients or more heavy-set patients, an alternative dose of 85 U/kg can be used

- During dissection of the carotid bulb, arrhythmias may occur. Atropine or glycopyrrrolate should be ready

Complications

Complications associated with CEA are listed here, and include neurologic and nonneurologic complications²⁰¹:

- Cranial nerve palsy
- Infection
- Hemorrhage
- Stroke
- Venous thromboembolism
- Acute arterial occlusion
- Arterial restenosis
- MI
- Hemodynamic instability (hypertension or hypotension)
- Death

Risk factors associated with increased perioperative stroke and death include^{201–203}:

- Symptomatic before CEA (OR 1.62, $P < .0001$)
- Hemispheric symptoms (OR 2.31, $P < .001$ vs retinal symptoms)
- Urgent operations (OR 4.9, $P < .001$)
- Reoperation (OR 1.95, $P < .018$)
- Contralateral carotid arterial occlusion (RR 2.2, CI 1.1–4.5)

A large, retrospective, cohort study reviewing CEAs performed at 6 different hospitals by 64 different surgeons in a 2-year period revealed a 30-day postoperative stroke or death rate of 2.28% in asymptomatic patients, 2.93% in patients with TIA, and 7.11% among patients presenting with stroke.²⁰⁴ These results were similar to those of NASCET, which had a 30-day postoperative stroke or mortality rate of 6.7% among symptomatic patients.¹⁹ The pooled analysis of NASCET, ECST, and VACS revealed a 30-day stroke and death rate after CEA of 7.1%.¹⁵⁰ The results for asymptomatic patients were also similar to those of prospective trials such as ACAS and ACST, which had 30-day stroke and mortality rates of 2.3% and 3.1%, respectively.^{21,138} High-risk anatomic criteria, such as restenosis after CEA and contralateral carotid occlusion, further increase this risk, as seen in NASCET and ACAS.^{138,201} The perioperative stroke and death rate have been reported to be as high as 19.9% in patients undergoing reoperative CEA and 14.3% among patients with contralateral carotid occlusion.²⁰⁵

However, more recent reports suggest a much lower risk than was previously reported. Case volume and surgical training are important factors in determining the clinical outcomes after a CEA. A population-based study in the state of Virginia investigating all CEAs performed from 1997 to 2001, with approximately 14,000 procedures, reported a cumulative stroke rate of 1.0% and mortality rate of 0.5%.²⁰⁶ There was a progressive decline in these rates in each successive year. Similar results were found in Maryland from 1994 to 2003, which included 23,237 CEA procedures. The cumulative stroke rate was 0.73%; 2.12% in 1994, 1.47% in 1995, and 0.29% to 0.65% from 1996 to 2003.²⁰⁷ The cumulative stroke rate in California from 1999 to 2003 was similar, at 0.54%. During this time 51,231 CEA procedures were performed.²⁰⁷ Mortality rates in both states were relatively stable over the reported years.

Intracerebral hemorrhage can also occur as a result of hyperperfusion syndrome despite adequate control of blood pressure, which occurs in less than 1% of patients with a stable preoperative blood pressure and well-managed blood pressure perioperatively.^{208–211}

Cranial nerve injury occurs in up to 7% of patients undergoing CEA; however, permanent injury remained in less than 1% of patients.^{150,171,212} Cranial neuropathy typically appeared early in the postoperative period, with most patients showing complete resolution over time.¹⁷¹ Only 3.7% had residual cranial nerve deficits. In decreasing order of frequency, cranial nerves or their branches involved are^{171,201,213–215}:

1. Hypoglossal
2. Marginal mandibular
3. Recurrent laryngeal
4. Spinal accessory
5. Cervical sympathetic chain (Horner syndrome)

Cardiovascular events have been reported in up to 20% of patients undergoing CEA, with hypotension occurring in 5%, hypertension in 20%, and perioperative MI in 1%.³⁹ Local anesthesia and cervical block may lessen cardiovascular instability in selected patient groups.²¹⁶ Myocardial ischemia, including nonfatal MI, is a major cause of morbidity in patients undergoing CEA because carotid bifurcation atherosclerosis is commonly associated with coronary atherosclerosis.³⁹ In NASCET and ECST, respectively, the incidence of MI was 0.3% and 0.2%.^{19,147} The risk for cardiopulmonary complications is associated with^{217–219}:

- Advanced age
- Active angina pectoris

- New York Heart Association (NYHA) functional class III or IV heart failure
- Left ventricular ejection fraction 30% or less
- MI within 30 days
- Urgent cardiac surgery 30 days prior
- Severe chronic lung disease
- Severe renal insufficiency

Wound infections occur in 1% or fewer patients.^{220,221} Wound hematoma occurred in 5% or fewer patients and was associated with perioperative antiplatelet therapy,²²² duration of surgery, perioperative use of heparin and protamine, and other factors.³⁹

Carotid Angioplasty and Stenting

CAS has shown varying outcome differences when compared with CEA, based on different patient factors. CAS seems to be a good alternative to CEA in certain patient groups, such as those with unfavorable surgical anatomy (noted previously). When performed with an embolic protection device (EPD), the risk associated with CAS may be lower than that of CEA in patients at increased risk for surgical complications.

Carotid angioplasty and stenting in asymptomatic patients

CAS has been reported to have superior outcomes when compared with CEA in patients at high surgical risk. In a selected group of asymptomatic patients with unfavorable surgical anatomy and significant comorbidities, it is reasonable to recommend CAS over CEA when intervention is indicated. Patients at high surgical risk were defined as having 1 or more of following criteria^{223,224}:

- NYHA class III or IV heart failure
- Chronic obstructive pulmonary disease
- Greater than 50% contralateral carotid artery stenosis
- Prior CEA or CAS
- Prior coronary artery bypass graft surgery

The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPHIRE) trial randomized high-risk patients into CEA and CAS with EPD groups, with inclusion criteria of symptomatic stenosis greater than 50% or asymptomatic stenosis greater than 80%. The primary end point was defined as death, stroke, or MI within 30 days plus death from neurologic causes or ipsilateral stroke between 31 days and 1 year. The secondary end point was defined as the primary end point events plus death or ipsilateral stroke between 1 and 3 years. Technical success was achieved in 95.6% of patients who

underwent CAS. However, the study incurred a selection bias by excluding patients from the CEA arm who were considered a priori to have exceedingly high risk for complication. The trial was stopped before completion after randomizing 334 patients, owing to a sharp decline in enrollment rate. Three-year follow-up data were available for only 85.6% of patients.^{143,144} In asymptomatic patients, the occurrence of the primary end point was greater after CEA (21.5%) than after CAS (9.9%). The periprocedural death, MI, or stroke rate was also greater after CEA (10.2%) than after CAS (5.4%). The 3-year stroke rates were comparable between CEA and CAS, at 9.2% and 10.3%, respectively.

CAS does not appear to be superior to CEA in asymptomatic patients with conventional surgical risk for intervention. The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) was a multicenter, randomized trial comparing CAS with CEA in both symptomatic (carotid stenosis >50%) and asymptomatic (carotid stenosis >60%) patients.^{141,225,226} Among 2502 patients followed for 2 years, the estimated 4-year rate of stroke, death, or MI was similar in both CAS and CEA (7.2% and 6.8%, respectively; stenting hazard ratio [HR] 1.11, 95% CI 0.81–1.51; $P = .51$). However, periprocedural stroke alone was more frequent after CAS (4.1% vs 2.3%; $P = .01$), whereas periprocedural MI alone was more frequent after CEA (2.3% vs 1.1%; $P = .03$). In the subgroup of asymptomatic patients, the 4-year stroke and death rates were higher after CAS (4.5% and 2.7%, respectively; HR 1.86, $P = .07$). In addition, CREST also showed that quality of life was significantly affected by major and minor stroke but not by MI, based on quality-of-life studies done at 1 year. The outcomes with CEA and CAS also appeared to be affected by age, with a crossover occurring at approximately 70 years. CEA showed greater efficacy at older ages and CAS at younger ages.¹⁴¹ The comparative primary results did not vary by sex or symptom status. As seen in previous randomized trials, cranial nerve palsy was more common after CEA.

The Asymptomatic Carotid Surgery Trial 2 (ACST-2) is an ongoing, large, multicenter, randomized trial comparing CAS with CEA in asymptomatic patients with severe carotid stenosis. The trial aims to randomize 5000 patients. After randomizing 986 patients, interim safety results show that the combined CAS and CEA outcome is on a par with other recent trials; however, comparison results between CAS and CEA are not currently available.²²⁷ CREST-2 is another study that will evaluate intensive medical management versus CEA or CAS in asymptomatic patients.

The study is designed as two independent, multicenter, randomized controlled trials evaluating medical management versus CEA in one and CAS in the other.²²⁸

Carotid angioplasty and stenting in symptomatic patients

In symptomatic patients, CEA has been reported to have superior outcomes over CAS in patients at both conventional and high surgical risk. In symptomatic patients at high surgical risk, SAPHIRE showed that despite a similar occurrence of the primary end point at 1 year (CAS 16.8% vs CEA 16.5%), the secondary end point at 3 years was higher after CAS (32% vs 21.7%). Of note, a smaller proportion of symptomatic patients underwent 3-year follow-up in comparison with asymptomatic patients.^{143,144}

Several studies have compared the outcomes of CEA and CAS in symptomatic patients with conventional surgical risk. One of the most comprehensive and better designed is CREST, a multicenter, randomized trial comparing CAS with CEA in both symptomatic (carotid stenosis >50%) and asymptomatic (carotid stenosis >60%) patients.^{141,225,226} The 4-year stroke and death rate was higher after CAS in symptomatic patients (8.0% vs 6.4%, HR 1.37; $P = .14$). As mentioned earlier, although periprocedural MI was more frequent after CEA, the study showed that quality of life was significantly affected by major and minor stroke but not by MI.

Other studies comparing CAS with CEA in symptomatic patients with conventional surgical risk for intervention include the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS), which was a multicenter randomized trial comparing CAS with CEA. A total of 504 patients were randomized, 90% of whom were symptomatic.^{229–231} Of note, EPDs were not used and only 22% of CAS patients were stented. The combined stroke and death rate at 30 days was similar in both groups (10%). However, cranial neuropathy occurred more frequently in CEA patients (8.7% vs 0%; $P < .0001$). Major incisional hematoma after CEA occurred more frequently than access-site hematoma after CAS (6.7% vs 1.2%; $P < .0015$). The rate of ipsilateral stroke after 3 years of follow-up was similar in both groups (adjusted HR 1.04, 95% CI 0.63–1.70; $P = .9$). However, the 8-year incidence and HR for ipsilateral non-perioperative stroke was 11.3% versus 8.6% (HR 1.22, 95% CI 0.59–2.54). There was also a higher rate of restenosis associated with CAS, with an estimated 5-year incidence of 30.7% compared with 10.5% after CEA. The investigators found that several factors were associated with the

higher incidence of restenosis, including longer segments of stenosis at baseline and performing a balloon angioplasty alone without stenting.^{231,232}

The Endarterectomy Versus Angioplasty in Symptomatic Severe Carotid Stenosis (EVA-3S) trial randomized patients with a completed stroke or TIA within the past 120 days and an ipsilateral carotid stenosis greater than 60%.²³³ Patients with disabling stroke were excluded from the trial (mRS >3). After randomizing 520 patients, the trial was stopped before completion for reasons of safety and futility. The 30-day incidence of stroke or death was 9.6% after CAS versus 3.9% after CEA, with an RR of 2.5 (95% CI 0.5–4.2). However, there were several factors in the EVA-3S trial that may have confounded its results, including inadequate training requirements for operators performing CAS and no uniform requirement for the use of EPDs.²³⁴ In addition, 5 different carotid stent devices and 7 EPDs were used. Although experts have agreed that the EVA-3S trial results should not affect management guidelines, the trial has highlighted the importance of rigorous and standardized training criteria required for interventionists performing carotid stent placement.²³⁴

The Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) study was a randomized, noninferiority trial comparing CAS with CEA in symptomatic patients with a stroke or TIA within the past 180 days and ipsilateral carotid stenosis greater than 70%.^{142,235} Patients with severe disabling stroke (mRS >3) were excluded. The initial planned sample size of 1900 was not met; only 1214 patients were successfully randomized owing to the inability to further enroll patients. Surgeons were required to have at least 25 CEAs done with acceptable rates of mortality and morbidity in the past year; and CAS operators were required to have performed at least 25 successful angioplasties or stenting procedures, although not necessarily in the carotid artery. The rate of ipsilateral stroke and death were similar in both groups within 30 days (6.8% CAS vs 6.3% CEA) and also within 2 years (9.5% vs 8.8%, HR 1.10, 95%, CI 0.75–1.61). Recurrent stenosis of at least 70% was more frequent in CAS patients than in CEA patients (10.7% vs 4.6%; $P = .0009$).

The International Carotid Stenting Study (ICSS) is a multicenter randomized trial comparing the safety and efficacy of CAS and CEA in symptomatic patients with ipsilateral carotid stenosis of 50% and greater.²³⁶ The clinical phase of the trial is complete. In ICSS, participating centers were classified into experienced or supervised. Experienced centers were defined as having at least 1 surgeon and 1 interventionist who have performed 50 CEA (minimum of 10 per year) or 50 CAS (at

least 10 involving the carotid), respectively. Supervised centers were designated as experienced after randomization and treatment of 20 cases of CEA or CAS, if the results were acceptable to a proctor and credentialing committee. In total, 88% of patients were treated at an experienced center. Interim safety analysis reported that the risk for stroke and death by all causes was higher in the CAS group (stroke: 7.6% after CAS vs 4.1% after CEA, HR 1.92, 95% CI 1.27–2.89; death: 2.2% vs 0.8%, HR 2.76, 95% CI 1.16–6.56). In the MRI substudy, CAS was associated with more acute and persisting ischemic brain lesions.²³⁷ Periprocedural hemodynamic instability, including bradycardia, asystole, or hypotension requiring treatment, were more likely to cause ischemic brain lesions in CAS patients than in CEA patients (RR 3.36; 95% CI 1.73–6.50).²³⁸

Anatomic considerations

Several anatomic factors are considered to be unfavorable for endovascular intervention, including²³⁹:

- Type II or III aortic arch
- Arch vessel origin stenosis greater than 50%
- Common and ICA tortuosity greater than 30°
- Significant plaque calcifications
- Long segment stenosis

These factors increase the technical difficulty of CAS, and also increase the risk for perioperative stroke; they are more prevalent in the elderly (>80 years of age), but may also be found in patients of all ages.

Prevention of cerebral embolism

The outcomes associated with the use of EPDs have not been studied in randomized trials. Several observational studies have suggested that EPDs, when used by experienced operators, lead to reduced rates of adverse events, including major and minor strokes.^{240,241} An international survey involving 53 sites with a total of 11,392 CAS procedures performed by experienced operators reported a combined stroke and death rate of 2.8% when EPDs were used and 6.2% when they were not.²⁴⁰ Several other studies have also shown an improvement in outcome with the use of EPDs.^{143,144,242–244}

However, when used by operators who are not experienced with the device, EPDs have been associated with worse clinical outcome^{229,233,235} and increased incidence of ischemic abnormalities seen on postprocedural brain imaging.²⁴⁵ The AC-CULINK for Revascularization of Carotids in High-Risk Patients (ARChER) trial, a nonrandomized, multiphase trial that included experienced

operators, did not show an improvement in outcome with the use of EPDs.

Periprocedural management

Dual-antiplatelet therapy consisting of aspirin 81 to 325 mg daily and clopidogrel 75 mg daily is recommended before CAS and for a minimum of 30 days after CAS, after which at least 1 antiplatelet agent should be continued long term. Ticlopidine 250 mg twice daily is an acceptable alternative for patients intolerant of clopidogrel. Adequate intraprocedural anticoagulation can be achieved with unfractionated heparin with a target activated clotting time of 250 to 300 seconds. Alternatively bivalirudin may be used, which has an added advantage over heparin in that there is no need to monitor activated clotting time.^{246,247}

CAS is associated with hemodynamic instability, including hypotension and vasovagal responses. Several intraprocedural steps can be taken to minimize the associated risk³⁹:

- Continuous electrocardiogram and blood pressure monitoring
- Adequate hydration and adjustment of antihypertensive medication immediately before CAS to avoid persistent intraprocedural hypotension
- Prophylactic administration of atropine 0.5 to 1 mg intravenously before angioplasty and stenting
- Temporary transvenous pacemaker for persistent bradycardia
- Phenylephrine 1 to 10 µg/kg/min or dopamine 5 to 15 µg/kg/min for persistent hypotension
- To minimize risk of intracerebral hemorrhage or hyperperfusion syndrome, the SBP should be maintained at below 180 mm Hg before and during the procedure. In the authors' experience, strict control of SBP lower than 140 mm Hg immediately after revascularization has consistently prevented hemorrhages.

Complications

Complications associated with CAS include:

- Cardiovascular: baroreflex responses, MI, arterial dissection, target vessel perforation, vasospasm, restenosis
- Neurologic: TIA, stroke, hemorrhage, seizure
- Device failure
- Access-site injury

Baroreflex responses such as hypotension, bradycardia, and vasovagal reactions occur in 5% to 10% of cases, but have been reported to be as high as 33%.^{248–250} Most are transient and do not require additional treatment after the

Table 1
Summary of key randomized clinical trials

Trial, Year ^{Ref.}	Study Population, Degree of Stenosis	Intervention	Comparison	No. of Patients		Event	Events (%)	
				Treatment Group	Comparison Group		Treatment Group	Control Group
NASCET, 1991 ¹⁴⁰	S (70%–90% by angio)	CEA	Med	328	321	Ipsilateral stroke at 2 y	9.00	26.00
NASCET, 1998 ⁸	S (50%–69% by angio)	CEA	Med	320	428	Ipsilateral stroke at 5 y	15.70	22.20
ECST, 2003 ¹⁵¹	S (70%–99% by angio)	CEA	Med	429	850	Stroke or surgical death	6.80	NA
		CEA	Med	646	850	Stroke or surgical death	10.00	NA
ACAS, 1995 ¹³⁸	AS (>60% by angio)	CEA	Med	825	834	Ipsilateral stroke, periprocedural stroke, or death	5.10	11.0
ACST, 2004 ¹³⁹	AS (>60% by angio)	Immediate CEA	Delayed CEA	1560	1560	5-y stroke risk	3.8	11.0
SPACE, 2008 ¹⁴²	S (≥70% by US)	CEA	CAS	589	607	All stroke at 2 y	10.10	10.90
						All periprocedural strokes or deaths and ipsilateral strokes up to 2 y	8.80	9.50
						Ipsilateral stroke between 31 d and 2 y	1.90	2.20
EVA-3S, 2008 ¹⁴⁵	S (≥60%)	CEA	CAS	262	265	All stroke at 4 y	3.40	9.10
						Ipsilateral stroke at 4 y	1.50	1.50
						All periprocedural stroke, death, and nonprocedural ipsilateral stroke at 4 y	6.20	11.10
SAPHIRE, 2004 and 2008 ^{143,144}	S (≥50% by US) + AS (≥80% by US)	CEA	CAS	167	167	All strokes at 1 y	7.90	6.20
						Ipsilateral stroke at 1 y	4.80	4.20
						All stroke, death, or MI within 30 d of procedure, ipsilateral stroke between 31 d and 1 y	20.10	12.20
						All strokes at 3 y	9.00	9.00
						Ipsilateral stroke at 3 y	5.40	6.60
						All stroke, death, or MI within 30 d of procedure, ipsilateral stroke between 31 and 1080 d	26.90	24.60

ICSS, 2010 ¹⁴⁶	S (≥50% by angio or 2 noninvasive imaging)	CEA	CAS	858	855	All strokes within 30 d of randomization	3.30	7.00
						All strokes within 120 d of randomization	4.10	7.70
CREST, 2010 ¹⁴¹	S (≥50% by angio, ≥70% by US)	CEA	CAS	653	688	All periprocedural strokes, MI, death, and postprocedural ipsilateral strokes up to 4 y	8.40	8.60
						All periprocedural strokes, death, and postprocedural ipsilateral strokes up to 4 y	6.40	8.00
						All periprocedural strokes and postprocedural ipsilateral strokes up to 4 y	6.40	7.60
	AS (≥60% by angio, ≥70% by US)	CEA	CAS	587	594	All periprocedural strokes, MI, death, and postprocedural ipsilateral strokes up to 4 y	4.90	5.60
						All periprocedural strokes, death, and postprocedural ipsilateral strokes up to 4 y	2.70	4.50
						All periprocedural strokes and postprocedural ipsilateral strokes up to 4 y	2.70	4.50
						All strokes up to 4 y	7.90	10.20
S + AS	CEA	CAS	1240	1262				

Abbreviations: angio, catheter angiography; AS, asymptomatic; CAS, carotid angioplasty and stenting; CEA, carotid endarterectomy; d, days; Med, medical therapy; MI, myocardial infarction; NA, no data available; S, symptomatic; US, ultrasonography; y, years.

procedure. With the introduction of appropriate preprocedural management, rates can be kept in the lower range.^{249,251–256}

The risk for MI is approximately 1%, with rates as low as 0.9%, as reported in the CAPTURE registry of 3500 patients. However, this may be higher among high-risk patients, with up to 2.4% reported in the ARChER trial.^{154,250,257–266}

In one study, the risk for arterial dissection or thrombosis was less than 1% and the risk for target vessel perforation was also less than 1%.³⁹ External carotid stenosis or occlusion occurred in 5% to 10% of cases, but were usually benign, with no further intervention required.^{154,250,257–264,267} Transient vasospasm occurred in 10% to 15% of cases and was associated with vessel manipulation by guide wires, catheters, and capture devices. This occurrence is also more common among smokers and patients with hypertension.^{268–271} Restenosis occurs in 3% to 5% of cases, and can be minimized by avoiding multiple or high-pressure balloon angioplasties, particularly in heavily calcified vessels.^{174,272–289}

The CAPTURE registry reported an overall stroke rate of 4.9%, with disabling strokes occurring in 2% of patients.^{267,290–298} The ARChER trial reported similar results, with an overall stroke rate of 5.5% and disabling strokes occurring in 1.5% of patients.^{154,258–260,262,263,265,266} TIA occurs in up to 1% to 2% of patients undergoing CAS. Subclinical ischemic injury detected by MRI has also been reported.^{146,299,300}

Intracranial hemorrhage associated with hyperperfusion, hypertension, and anticoagulation occurs in less than 1% of cases.^{301–304} Seizures, which are predominantly associated with hyperperfusion, occur in less than 1% of cases.³⁰⁵

Device malfunction occurs in less than 1% of procedures and includes^{268,269,306,307}:

- Stent malformation
- Stent migration
- Failure of deployment of device
- EPD failure (inability to deliver EPD to target zone, reduced steerability, and ischemia caused by EPD overloaded by embolic material)

EPDs can reduce the stroke risk associated with CAS, but the device itself is also associated with failures.^{244,266,267,306,308–314} The use of appropriately sized EPDs is crucial, because undersized EPDs may allow passage of debris into distal circulation while oversized EPDs may cause endothelial injury or vasospasm.

Access-site injuries occur in up to 5% of cases and mostly consist of local pain and hematoma,

which are largely self-limited and require no further intervention.^{315–318} Other access-site injuries include:

- Groin infection (<1%)
- Pseudoaneurysm (1%–2%)
- Puncture-site bleeding or retroperitoneal hematoma requiring blood transfusion (2%–3%)

Contrast nephropathy is rare and has been reported in less than 1% of cases, largely because CAS is generally avoided in patients with severe renal dysfunction.³¹⁹

EVALUATION FOR RECURRENCE AND RECURRENCE MANAGEMENT

Noninvasive imaging at the 1-month interval, followed by the 6-month interval, and then annually after revascularization, is recommended for both CAS and CEA patients. Regular imaging allows for adequate assessment of ipsilateral carotid patency and to exclude development of contralateral lesions. Once stability has been established, surveillance at longer intervals may be appropriate. Surveillance may not be indicated when the patient is no longer a candidate for intervention.

The mechanism responsible for arterial restenosis after CEA is related to the postoperative interval. Early stenosis within 2 years is largely attributed to intimal hyperplasia, whereas later restenosis is usually due to progression of the atherosclerotic disease. Very early stenosis, detected on the first postoperative duplex US, usually represents an unsatisfactory or incomplete CEA, which usually occurs in less than 1% of cases and can be minimized by using intraoperative duplex US or a completion angiography.³⁹

The CAVATAS investigators reported that long-segment carotid stenosis (>0.65 times common carotid artery diameter) was associated with an increased risk for long-term restenosis. The risk for restenosis in long-segment carotid stenosis was significantly greater in CAS patients than in CEA patients.^{231,232} In CAS patients, performing an angioplasty alone without stenting was also associated with increased rates of restenosis.^{231,232}

The reported incidence of recurrent stenosis depends on the methods used for detection. When assessed by US, the rate of restenosis has been reported to be 5% to 10%. However, in more recent series where patch closures were used, the restenosis rate has consistently been less than 5%.^{191,192,203,215,320–323} When duplex US was used, hemodynamically significant restenosis occurred in 5% to 7% of cases.^{181,188,189,203,321,324–339}

Comparison data on restenosis after CAS and CEA should be interpreted with caution.³⁹ Most studies use US as the follow-up imaging modality, which introduces potential bias. Although stent placement has been shown to be associated with decreased rates of restenosis,^{231,232} the role of stent-generated artifacts in US velocity measurements have yet to be resolved with angiographic comparison. In the authors' experience, this effect may be partially overcome by performing intraprocedural carotid US immediately after CAS, which allows for a direct comparison of carotid US results with postprocedural catheter angiography results for future reference. In the CAVATAS study, a carotid US at 1 year detected 70% to 99% stenosis in 4% of CEA patients and 14% of CAS patients ($P < .001$). Of note, only 22% of CAS patients had stent placement.²²⁹⁻²³¹ In the SAPHIRE trial, where all CAS patients had stent placement, carotid US at 1 year was available in 218 patients (96 CEA, 122 CAS), and the rate of restenosis greater than 70% was 4.2% in CEA patients and 0.8% in CAS patients ($P = .17$).^{143,144} In the SPACE trial, carotid US at 1 year showed recurrent stenosis greater than 70% in 4.6% of CEA patients and 10.7% of CAS patients ($P = .0009$).^{142,235}

In patients with recurrent symptomatic carotid stenosis, a repeat CEA or CAS can be considered, using the same criteria as recommended for initial revascularization (see earlier discussion). Repeat intervention is also recommended when duplex US and additional confirmatory imaging (MRA, CTA, or catheter angiography) shows rapidly progressive restenosis, indicating risk of complete occlusion.³⁹ A repeat CEA can be considered under the hands of an experienced surgeon. CAS is an alternative to repeat CEA in patients with recurrent stenosis after CEA, and may be appropriate in asymptomatic patients with restenosis greater than 80% or symptomatic restenosis greater than 50%. Repeat intervention can also be considered in patients with asymptomatic recurrent stenosis, using the same criteria for initial intervention, but should not be performed in patients with less than 70% stenosis.

SUMMARY

There are several imaging modalities available for the screening and diagnosis of carotid atherosclerotic disease, and treatment consists mainly of medical and interventional management.

Carotid US has a relatively low cost, minimal side effects and discomfort, and is widely available. It should be used as the initial screening tool for both symptomatic and asymptomatic

patients with suspected carotid disease. Other more advanced noninvasive imaging, such as MRA and CTA, can be used when US yields equivocal results or is not available. MRA and CTA are helpful in determining the exact severity of stenosis and anatomic details in patients undergoing interventional management. Catheter angiography remains the gold standard for diagnosing carotid atherosclerotic disease and for grading the degree of stenosis. However, owing to its inherent cost and risk for complications such as ischemic strokes, it should be reserved for patients in whom noninvasive imaging is contraindicated, inconclusive, does not provide adequate delineation of the disease, or yields discordant results.

Medical therapy consists mainly of antithrombotic therapy and risk-factor modification. Dual-antiplatelet combination therapy has not been

Table 2
Factors influencing the decision of CEA versus CAS

CEA	CAS
Anatomic factors	
<ul style="list-style-type: none"> • Normal location of carotid bifurcation • Independent of aortic arch • Independent of vessel tortuosity 	<ul style="list-style-type: none"> • High (cervical) or low (intrathoracic) carotid bifurcation • Type I aortic arch • Reduced vessel tortuosity ($<30^\circ$)
Plaque factors	
<ul style="list-style-type: none"> • Independent of aortic arch atherosclerosis • Independent of length of segment occlusion^a • Independent of degree of calcification • Independent of stability of the plaque • Independent of presence of acute thrombus 	<ul style="list-style-type: none"> • No arch atherosclerosis • Short segment stenosis • Lack of extensive circumferential calcification • Stable plaque • Absence of acute thrombus
Patient factors	
<ul style="list-style-type: none"> • Independent of age (up to 80 y old) • Male gender • Low cardiac risk • Independent of patient's renal function 	<ul style="list-style-type: none"> • Younger patients • Independent of gender • Prior CEA • Prior neck surgery or tracheostomy • Prior neck radiation

^a As long as distal segment can be surgically reached below the angle of the mandible.

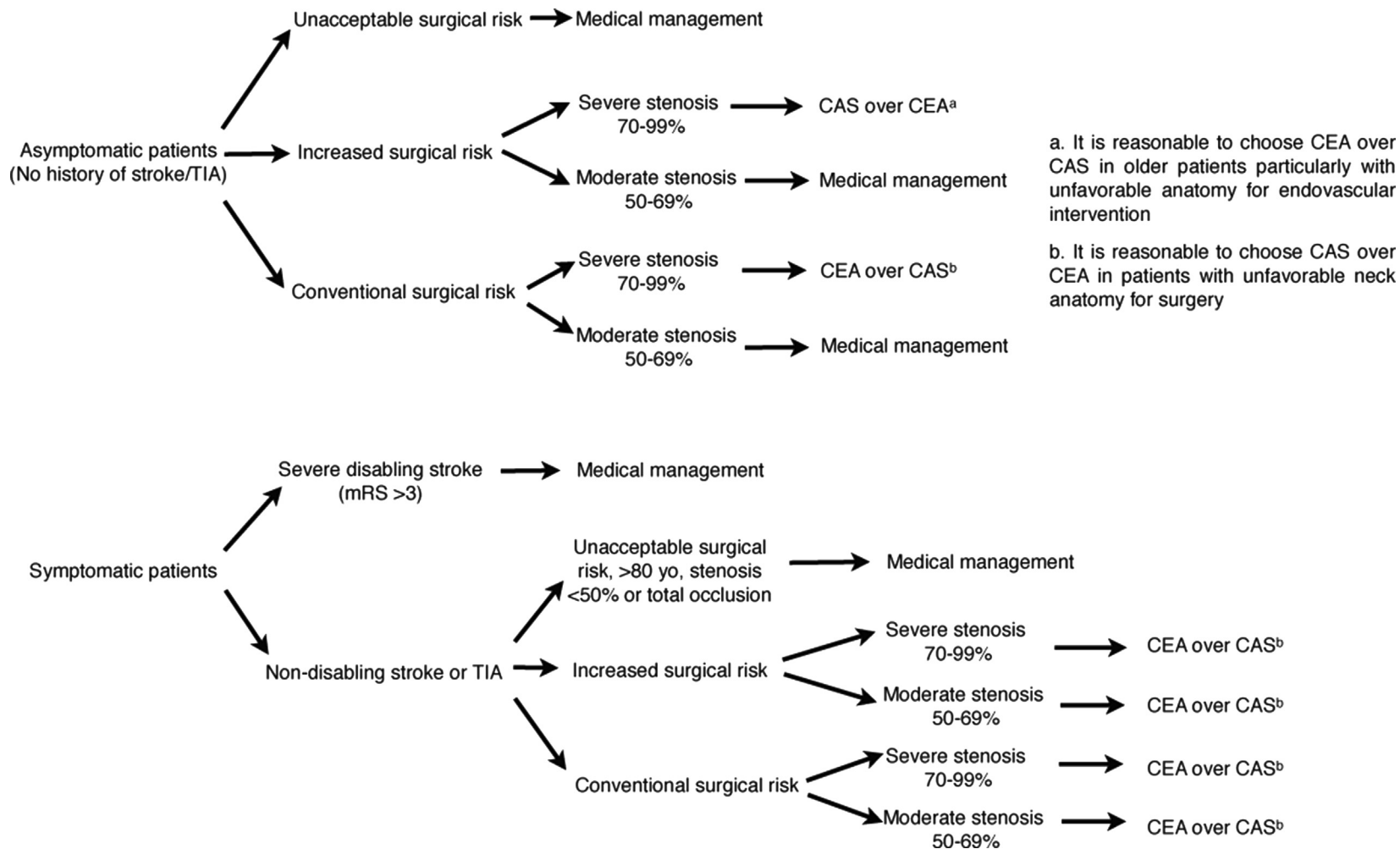


Fig. 1. Flow chart for the management of carotid disease. Medical management should be started on all patients with carotid atherosclerotic disease independent of intervention. Carotid endarterectomy (CEA) should be considered in all patients who require intervention. Carotid angioplasty and stenting (CAS) may be a better alternative to CEA in asymptomatic patients with severe stenosis and increased risk for surgery. mRS, modified Rankin Scale; TIA, transient ischemic attack; yo, years old.

shown to be superior to single agents. Anticoagulation with warfarin, along with its potential risk for increased hemorrhagic complications, also has not been shown to be superior to antiplatelet agents. Comprehensive risk-factor management should be used in these patients, including blood pressure control, cholesterol management, diabetes management, weight loss, cessation of smoking, and other lifestyle modifications.

Randomized trials such as NASCET, ECST, ACAS, ACST, SPACE, EVA-3S, SAPHIRE, and CREST (**Table 1**) have shown that revascularization decreases the long-term risk for adverse ischemic events in both asymptomatic patients with nonocclusive severe stenosis (>70%) and symptomatic patients without a devastating stroke (mRS >3), and with moderate to severe stenosis (>50%). However, patient comorbidities, overall life expectancy, and risk for periprocedural complications such as ischemic stroke, MI, and death must be taken into account (**Table 2**). The decision-making algorithm for medical treatment and types of revascularization is presented in **Fig. 1**.

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