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# Management of Extracranial Carotid Artery Disease

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## Abstract

Stroke is the third leading cause of death in developed nations. Up to 88% of strokes are ischemic in nature. Extracranial carotid artery atherosclerotic disease is the third leading cause of ischemic stroke in the general population and the second most common non-traumatic cause among adults <45 years of age. The aim of this paper is to provide comprehensive, evidence-based recommendations for the management of extracranial atherosclerotic disease, including imaging for screening and diagnosis, medical management and interventional management.

### Keywords

Carotid disease; Carotid stenosis; Atherosclerotic disease; Stroke; Carotid endarterectomy; Carotid angioplasty and stenting; Antiplatelet therapy

## 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 >50% carotid stenosis is approximately 9% in men and 6–7% in women.[11,12] Carotid stenosis or occlusion as a cause of stroke has been more difficult to determine from population studies. Approximately 7–18% of all first strokes were associated with carotid stenosis.[13,14] The risk for recurrent strokes among survivors is 4–15% within a year after the initial stroke and 25% by 5 years.[8]

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Extracranial atherosclerotic disease accounts for up to 15–20% of all ischemic strokes.[15,16] While intracranial atherosclerotic disease has shown to be consistently more common among Blacks, Hispanics and Asians compared to Whites,[15,17] the racial differences for extracranial atherosclerotic disease is 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 more likely than Blacks to have extracranial carotid artery lesions (33% versus 15%, p=0.001).[16] While the male gender appears to be an independent predictor for intracranial atherosclerotic disease, no gender differences were reported for extracranial disease.[16]

## Natural History

Stroke associated with extracranial carotid atherosclerotic disease could occur via several mechanisms:[18]

- 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 70–79% stenosis, 28% in patients with 80–89% stenosis, and 33% in patients with 90–99% 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 60–80% stenosis had higher strokes rates compared to 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 compared to those without carotid bruit, less than half of these stroke events involved the ipsilateral cerebral hemisphere.[3]

While 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 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 magnetic resonance imaging (MRI) have also been associated with subsequent ischemic events.[25]

Recently, the utility of biomarkers and imaging makers for inflammation in predicting plaque vulnerability and 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] F-fluorodeoxyglucose measured by positron emission tomography (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 metalloproteinase 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 Ultrasound

When performed by well-trained, experienced technologist, carotid ultrasound (US) is accurate and relatively inexpensive.[33–38] Carotid US is also noninvasive, 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 two 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, however, is not recommended for routine screening of asymptomatic patients without risk factors for atherosclerotic disease due 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 >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 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, which is crucial to differentiate 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 >70% have been reported to be 85–90% when compared to catheter angiography.[48–50]

## Computed Tomography Angiography (CTA) and Magnetic Resonance Angiography (MRA)

Both MRA and CTA are able to generate high-resolution images of the cervical arteries.[51–57] When compared to catheter angiography, MRA has a sensitivity range of 97–100% and a specificity range of 82–96%,[58–62] while CTA has 100% sensitivity and 63% specificity (95% 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 anatomical 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 when compared to non-contrasted 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 highly accurate for detection or exclusion of complete occlusions as well.[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.[66] 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

While non-invasive 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.

Due 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 due to contrast toxicity, femoral artery injuries, infections or hematomas of the puncture site, strokes, or death, typically at a rate lower than 1/1000 for the most serious complications and <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 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]

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

## 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 or not they are candidates for revascularization. Aspirin 75–325 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 to either drug alone.[73,74] The Second European Stroke Prevention Study (ESPS-2), which included 6,602 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 over 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 due 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 due to the inability of these agents to inhibit platelet function is a potential cause for failure in stroke prevention. However, whether or not variations in response to antiplatelet therapy are associated with greater stroke risk and whether or not treatment of resistance improves outcomes have not been established. There also a lack in consensus on 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 Asymptomatic Cervical Bruit Study, a randomized, double-blinded study, the annual rate of ischemic events and death due to any cause in patients with >50% carotid stenosis was 11.0% in the aspirin group compared to 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 where 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 used over antiplatelet therapy. The goal international normalized ratio (INR) should be 2.0–3.0.[84]

## Treatment of Hypertension

Antihypertensive therapy has shown to reduce the risk of stroke, with a 33% reduction in stroke risk for every 10 mmHg decrease in systolic blood pressure up to 115/75 mmHg.[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 range[88] 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 goal blood pressure below 140/90 mmHg.[85–87,89,90] The protective value of antihypertensive therapy also appears to extend to patients without concurrent hypertension, as demonstrated by the Heart Outcomes Protection Evaluation trial (HOPE).[91]

The exact benefits of antihypertensive treatment in symptomatic patients with severe carotid stenosis remain unclear due to concerns for reduction in cerebral perfusion and exacerbation of cerebral ischemia. Patients with severe carotid stenosis may have impaired cerebrovascular reactivity due to 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 below 100mg/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] They can also be used in combination with a statin if treatment with a statin does not achieve targeted LDL levels.[94,95,97,98]

Epidemiological 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% confidence interval (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 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] 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 40 mg daily of simvastatin.[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 80 mg daily of atorvastatin but remained unchanged with 40 mg daily of pravastatin.[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 to placebo.[107]

The effects of non-statin lipid-modifying therapies on stroke risk reduction 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] Genfibrozil reduced the risk of total strokes and ischemic strokes in patients with coronary artery disease and low HDL levels in the Veteran Affairs HDL Intervention trial.[110]

The ARBITER-2 and Effect of Combination Ezetimibe and High-Dose vs. 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 niacin and colestipol combination therapy reduced progression of carotid IMT.[112]

## Diabetes Mellitus Management

Elevated fasting and post challenge 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 non-diabetic 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 has lead to substantial regression of carotid IMT.[123,124] The affect of pioglitazone appears to be independent of improved glycemic control.[123]

## Smoking Cessation

Cigarette smoking increases the relative risk for ischemic stroke by 25–50%.[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 compared to former smokers and there was a significant association between pack-years of tobacco exposure to the severity of carotid stenosis.[133] The ARIC study revealed that current and past cigarette smoking were associated with a 50% and 25%

increase, respectively, in risk of progression of IMT over a 3-year period when compared to 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 of stroke or TIA.[135] Adjusted odds ratio 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 ration with the risk of stroke/TIA.

Physical inactivity is a significant modifiable risk factor for stroke, with a 25% prevalence, a 30% attributable risk, and a 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 stroke risk reduction 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 19–33% 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 will be discussed in detail in the sections below. The general contraindications for interventions include:

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

Carotid revascularization is not recommended for patients with near–complete occlusion or stenosis <50% since the risk for stroke is low in these patients.[19] Revascularization has also not shown to have any benefit in these patients.[19] 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 for safety and efficacy.

Patients with a non-disabling ischemic stroke (mRS >3) or TIA and >70% stenosis of the ipsilateral internal carotid artery by noninvasive imaging, or >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 versus medical management alone, patients were stratified according to severity of stenosis.[19] The trial for 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 stroke risk reduction with CEA at 2 years.[19] At the end of NASCET, the investigators also reported a benefit for CEA in patients with 50–69% stenosis. The rate of ipsilateral stroke including perioperative events was 15.7% at 5 years compared to 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 <50%.

The European Carotid Surgery Trial (ECST), which randomized 2518 patients over a 10-year period, showed similar results to that of NASCET in symptomatic patients with 70–99% 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 50–69% stenosis based on ECST was attributed to the difference in angiographic measurement of stenosis.

The Veterans Affairs Cooperative Study (VASC) was stopped before completion, after only randomizing 189 symptomatic patients with a mean follow-up of 11.9 months, due to significant benefit of CEA over medical therapy alone. The primary endpoint of death, stroke or TIA occurred in 7.7% of CEA patients versus 19.4% of patients receiving medical therapy alone.[152]

A meta-analysis of these three trials showed that CEA was most effective in patients with >70% stenosis without complete or near occlusion.[150] Benefits of CEA in patients with 50–69% 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 80–99% stenosis.

**Carotid Endarterectomy in Asymptomatic Patients—**The benefits of CEA for stroke risk reduction in asymptomatic patients is less profound compared to symptomatic patients. CEA is reasonable in asymptomatic patients who have >70% internal carotid artery stenosis if the risk of perioperative MI, stroke and death is low.[138,153–156] While 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 60–99% stenosis range.[156]

The Veterans Affair Cooperative Study (VACS) group was the first major trial of CEA in asymptomatic patients.[153] A total of 444 patients with ≥50% stenosis were randomized over a 54-month period into either the CEA group or the medically therapy group. The 30-day mortality rate among patients undergoing CEA was 1.9% and 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 endpoint remains controversial given that the study was underpowered to detect a difference in a composite endpoint 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 their primary endpoint.[138] The trial was stopped before completion after randomizing 1662 patients, due to the apparent advantage of CEA among patients with >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 to be 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 >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 to 11.8% in the group initially managed medically.[139]

The benefits of CEA for asymptomatic patients are even less apparent in women. This is due to the higher operative risk and lower stroke risk without intervention among asymptomatic women compared to men.[156] Such benefits remain unclear despite a meta-analysis done combining the data from both ACST and ACAS.[156]

**Interpretation of CEA 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 over the years. 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 of patients 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] Towards 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.

Additionally, 60% of patients had systolic blood pressure (SBP) >160 mmHg, while 33% had total serum cholesterol >250 mg/dL.

Concurrently, surgical outcomes of CEA have improved over time with advances in training, increased hospital and surgeon volumes, and improved peri-operative medical management.[159–162]

Therefore, with advances in both medical management and operative/peri-operative management and outcomes over time, which has lead to 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 of age with few cardiovascular risk factors have been shown to have comparable risk for perioperative stroke and death when compared to younger patients.[165] However, in ACST, no benefit from CEA was observed in patients ≥80 years of age.[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 of age were excluded from NASCET (prior to 1991) and ACAS.[19,138]

Women undergoing CEA have a higher risk for complications than men.[147,166–168] Both in ACAS and NASCET, women had a higher risk for surgical mortality, neurologic morbidity, recurrent stenosis or gaining little to no benefit form surgery.[19,138]

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

**Anatomical 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, but the rate of restenosis is high, ranging from 18–80% over 3 years.[173–175]

**Technical Consideration—**There have been considerable variations in surgical technique with CEA over the past 50 years. Local anesthesia was initially recommended to permit observation of patient's level of consciousness during temporary carotid artery clamping. Several authors also advocated local anesthesia due to the possibility of less perioperative adverse cardiac events.[39] However, there has 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 due to potential complications associated with shunting, such as mechanical injury to distal ICA, air embolism or thromboembolism through the shunt, and obscuring of distal arterial anatomy during endarterectomy.[39] Intraoperative monitoring include:

- Electroencephalography (EEG)
- Somasosentory evoked potential (SSEP)
- Transcranial Doppler ultrasonography
- Computerized topographic brain mapping, measurement of residual collateral perfusion pressure or internal carotid artery (ICA) back pressure

Shunting was generally indicated when EEG abnormalities associated with ischemia appeared.[190] In our institution, shunts are used when a depression of ≥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.[179–189] A Cochrane meta-analysis, analyzing the combined results of 10 trials showed that patch closure reduces the risk of peri-operative arterial occlusion and ipsilateral stroke. There was also reduction in the subsequent risk of restenosis, death or stroke.[190] 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 polytertrafluoroethyelene.[191–194] However, the outcomes have appeared to be similar independent of the patch material used.

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

**Peri-operative Management—**Antiplatelet therapy with aspirin 81–325 mg daily is recommended before CEA, and should be continued indefinitely post-operatively.[71,199] In the Acetylsalicylic Acid and Carotid Endarterectomy (ACE) study, where 2849 patients were randomized into 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) when compared to those taking lower doses (81 mg or 325 mg daily). (At 30 days, 7.0% versus 5.4%, RR 1.31 [95% CI 0.98−1.75]; and at 3 months, 8.4% versus 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 25–200 mg twice daily are reasonable alternatives as well.[72,74,80]

The use of peri-operative 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 by 13 surgeons of 1566 patients undergoing CEA at a single, large academic center, 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% versus 4.5%; $p < 0.01$)
- TIA (1.5% versus 3.6%; $p < 0.01$)
- All causes of mortality (0.3% versus 2.1%; $p < 0.01$)
- Median (interquartile range) length of hospitalization (2 days [2–5 days] versus 3 days [2–7 days]; $p < .05$)

Antihypertensive medication is recommended before CEA and should be resumed post-operatively.[39]

A summary of peri-operative management pearls based on our institution’s experience:

- General anesthesia
- Continues EEG and SSEP monitoring
- Discuss with anesthesia the potential need for barbiturates in the reduction of cerebral metabolic demand
- Intravenous antibiotics: ancef or vancomycin
- Patient is kept normocapnic (35–45 mmHg)
- 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 nomothermic
- Goal hematocrite of ≥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 5,000 units. In smaller patients or more heavyset patients, an alternative dosing of 85 units/kg can be used. If small patient or too large can use 85U/Kg (?)
- During dissection of the carotid bulb, arrhythmias may occur. Atropine or glycopyrrolate should be ready

**Complications—**Complications associated with CEA are listed below, and include neurological and non-neurological complications:[201]

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

Risk factors associated with increased perioperative stroke and death include:[201–203]

- Symptomatic before CEA (OR 1.62, $p < 0.0001$)
- Hemispheric symptoms (OR 2.31, $p < 0.001$ versus retinal symptoms)
- Urgent operations (OR 4.9, $p < 0.001$)
- Reoperation (OR 1.95, $p < 0.018$)
- 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 post-operative 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 post-operative 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 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 re-operative 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 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 0.29–0.65% 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 <1% of patients with a stable pre-operative blood pressure and blood pressure well managed peri-operatively.[208–211]

Cranial nerve injury occurs in up to 7% of patients undergoing CEA; however, permanent injury remained in <1% of patients.[150,171,212] Cranial neuropathy typically appeared early in the post-operative period, with most patients showing complete resolution over time.[171] Only 3.7% had residual cranial nerve deficits. Listed below in decreasing order of frequency, the involvement of cranial nerves or their branches:[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 20% of patients undergoing CEA, with hypotension occurring in 5%, hypertension in 20%, and peri-operative MI in 1%.[39] Local anesthesia and cervical block may lessen cardiovascular instability in selected patient groups..[216] Myocardial ischemia including non-fatal MI is a major cause of morbidity in patients undergoing CEA due to carotid bifurcation atherosclerosis commonly being 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 class III or IV heart failure
- Left ventricular ejection fraction ≤30%
- MI within 30 days

- Urgent cardiac surgery 30 days prior
- Severe chronic lung disease
- Severe renal insufficiency

Wound infections occur in ≤1% of patients.[220,221] Wound hematoma occurred in ≤5% of 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 to CEA based on different patient factors. CAS appears 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 compared to that of CEA in patients with increased risk for surgical complications.

**Carotid Angioplasty and Stenting in Asymptomatic Patients—**CAS has been reported to have superior outcomes when compared to CEA in high surgical risk patients. In a selected group of asymptomatic patients with unfavorable surgical anatomy and significant co-morbidities, it is reasonable to recommend CAS over CEA when intervention is indicated. High surgical risk patients were defined as having one or more of following criteria:[223,224]

- New York Heart Association class III or IV heart failure
- Chronic obstructive pulmonary disease
- >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 an inclusion criteria of symptomatic stenosis >50% or asymptomatic stenosis >80%. The primary endpoint was defined as death, stroke or MI within 30 days plus death due to neurological causes or ipsilateral stroke between 31 days and 1 year. The secondary endpoint was defined as the primary endpoint 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, due to a sharp decline in enrolment rate. Three-year follow up data were available in only 85.6% of patients.[143,144] In asymptomatic patients, the occurrence of the primary endpoint was greater after CEA (21.5%) versus after CAS (9.9%). The peri-procedural death, MI or stroke rate was also greater after CEA (10.2%) versus 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 to CEA in both symptomatic (carotid stenosis >50%) and asymptomatic patients (carotid stenosis >60%).[141,225,226] Among 2502 patients followed for 2 years, the estimated 4-year rate of stroke, death of MI was similar in both CAS and CEA (7.2% and 6.8%, respectively; stenting HR: 1.11, 95% CI: 0.81−1.51, p=0.51). However, peri-procedural stroke alone was more frequent after CAS (4.1% versus 2.3%, p=0.01), while peri-procedural MI alone was more frequent after CEA (2.3% versus 1.1%, p=0.03). 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=0.07). In addition, CREST also showed that quality of life was significantly impacted 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 to 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 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 both conventional- and high surgical risk patients. In high surgical risk symptomatic patients, SAPHIRE showed that despite a similar occurrence of the primary endpoint at 1 year (CAS 16.8% versus CEA 16.5%), the secondary endpoint at 3 years was higher after CAS (32% versus 21.7%). Of note, only a smaller portion of symptomatic patients underwent 3-year follow-up compared to asymptomatic patients.[143,144]

Several studies have compared the outcomes of CEA and CAS in conventional surgical risk symptomatic patients. One of the most comprehensive and better designed is CREST, a multicenter, randomized trial comparing CAS to CEA in both symptomatic (carotid stenosis >50%) and asymptomatic patients (carotid stenosis >60%).[141,225,226] The 4-year stroke and death rate was higher after CAS in symptomatic patients (8.0% versus 6.4%, HR: 1.37, p=0.14). As mentioned above, although peri-procedural MI was more frequent after CEA, the study showed that quality of life was significantly impacted by major and minor stroke but not by MI.

Other studies comparing CAS to 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% versus 0%, p <0.0001). Major incisional hematoma after CEA occurred more frequently than access site hematoma after CAS (6.7% versus 1.2%, p <0.0015). The rate of ipsilateral stroke after 3 years of follow up was similar in both groups (adjusted hazard ratio=1.04, 95% CI 0.63–1.70, p=0.9). 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 to 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 >60%.[233] Patients with disabling stroke were excluded from the trial [mRS score >3]. After randomizing 520 patients, the trial was stopped before completion due to both safety and futility reasons. The 30-day incidence of stroke or death was 9.6% after CAS versus 3.9% after CEA, with a RR of 2.5 (95% CI 0.5−4.2). However, there were several factors in the EVA-3S trial, which 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. While 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 interventionalists performing carotid stent placement.[234]

The Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) study was a randomized, non-inferiority trial comparing CAS to CEA in symptomatic patients with a stroke or TIA within the past 180 days and ipsilateral carotid stenosis >70%.[142,235] Patients with severe disabling stroke (mRS score >3) were excluded. The initial planned sample size of 1900 was not met; only 1214 patients were successfully randomized due 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, 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 versus 6.3% CEA) and also within 2 years (9.5% versus 8.8%, HR: 1.10, 95%, CI 0.75−1.61). Recurrent stenosis of ≥70% was more frequent in CAS patients compared to CEA (10.7% versus 4.6%, p=0.0009).

The International Carotid Stenting Study (ICSS) is a multicenter, randomized trial comparing the safety and efficacy of CAS to CEA in symptomatic patients with ipsilateral

carotid stenosis ≥50%.[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 interventionalist 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 versus 4.1% after CEA, HR 1.92, 95% CI: 1.27–2.89; death: 2.2% versus 0.8%, HR 2.76, 95% CI: 1.16–6.56). In the MRI sub-study, CAS was associated with more acute and persisting ischemic brain lesions.[237] Peri-procedural hemodynamic instability, including bradycardia, asystole, or hypotension requiring treatment, were more likely to cause ischemic brain lesions in CAS patients versus CEA patients (RR, 3.36; 95% CI: 1.73–6.50).[238]

**Anatomical Considerations—**Several patient anatomic factors are considered to be unfavorable for endovascular intervention, including:[239]

- Type II or III aortic arch
- Arch vessel origin stenosis >50%
- Common and internal carotid artery tortuosity >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.

**Cerebral Embolism Prevention—**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 11392 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 in post-procedural brain imaging.[245] The ACCULINK for Revascularization of Carotids in High-Risk Patients (ARCHeR) trial, a non-randomized, multiphase trial that included experienced operators, did not show an improvement in outcome with the use of EPDs.

**Peri-procedural Management—**Dual antiplatelet therapy consisting of aspirin 81–325 mg daily and clopidogrel 75 mg daily is recommended before CAS and for a minimum of 30

days after. 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 intra-procedural anticoagulation can be achieved with unfractionated heparin with a goal activated clotting time of 250–300 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 intra-procedural steps can be taken to minimize the associated risk:[39]

- Continuous electrocardiogram and blood pressure monitoring
- Adequate hydration and adjustment of antihypertensive medication immediately prior to CAS to avoid persistent intra-procedural hypotension
- Prophylactic administration of atropine 0.5 to 1 mg intravenously prior to angioplasty and stenting
- Temporary transvenous pacemaker for persistent bradycardia
- Phenylephrine 1–10mcg/kg/min or dopamine 5–15mcg/kg/min for persistent hypotension
- To minimize risk of intracerebral hemorrhage or hyperperfusion syndrome, the SBP should be maintained below 180 mmHg before and during the procedure. In our experience, strict control of SBP below 140 mmHg 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 5–10% 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 procedure. With the introduction of appropriate pre-procedural 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]

The risk for arterial dissection or thrombosis was <1%. The risk for target vessel perforation was also <1% in what study.[39] External carotid stenosis or occlusion occurred in 5–10% of cases, but were usually benign with no further intervention required.[154,250,257–264,267] Transient vasospasm occurred in 10–15% of cases and was associated with vessel

manipulation by guide wires, catheters and capture devices. This is also more common among smokers and patients with hypertension.[268–271] Restenosis occurs in 3–5% 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 1–2% of patients undergoing CAS. Subclinical ischemic injury detected by magnetic resonance imaging (MRI) has also been reported.[146,299,300]

Intracranial hemorrhage associated with hyperperfusion, hypertension and anticoagulation occurs in <1% of cases.[301–304] Seizures, which are predominantly associated with hyperperfusion occur in <1% of cases.[305]

Device malfunction occurs in <1% of procedures and include:[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 due to 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 cause vasospasm.

Access-site injuries occur in up to 5% of cases and mostly consist of local pain and hematoma, which are largely self-limited requiring 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 <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. This usually occurs in <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 compared to 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 ultrasonography, the rate of restenosis has been reported to be 5–10%. However, in more recent series in which patch closures were used, the restenosis rate has consistently been below 5%.[191,192,203,215,320–323] When duplex US is used, hemodynamically significant restenosis occurred in 5–7% of cases.[180,187,188,203,321,324–339]

Comparison data on restenosis after CAS and CEA should be interpreted with caution.[39] Most studies utilize ultrasonography as the follow-up imaging, which introduces potential bias. While 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 our experience, this effect may be partially overcome by performing an intra-procedural carotid ultrasonography immediately after CAS. This allows for a direct comparison of carotid US results with post-procedural catheter angiography results for future reference. In the CAVATAS study, a carotid US at 1 year detected 70–99% stenosis in 4% of CEA patients and in 14% of CAS patients ($p < 0.001$). 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 >70% was 4.2% in CEA patients and 0.8% in CAS patients ($p=0.17$).[143,144] In the SPACE trial, carotid US at 1 year showed recurrent stenosis >70% in 4.6% of CEA patients and in 10.7% of CAS patients ($p=0.0009$).[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 (discussed previously). Repeat intervention is also recommended when duplex ultrasonography and an 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 >80% or symptomatic restenosis >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 <70% stenosis.

## Summary

In summary, there are several imaging modalities that are 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 utilized as the initial screening tool for both symptomatic and asymptomatic patients with suspected carotid disease. Other more advanced non-invasive imaging, such as MRA and CTA, can be employed when US yields equivocal results, or is not available. MRA and CTA are helpful in determining the exact severity of stenosis and anatomical details in patients undergoing interventional management. Catheter angiography remains the gold standard for diagnosing carotid atherosclerotic disease and for grading stenosis degree. However, due 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 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 employed 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 non-occlusive severe stenosis (>70%) and symptomatic patients without a devastating stroke (mRS >3), and moderate to severe stenosis (>50%). However, patient comorbidities, overall life expectancy and risk for peri-procedural 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 are summarized in Figure 1.

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**Key Points**

- Asymptomatic patients without risk factors should not be screened for carotid atherosclerotic disease.
- Carotid ultrasound 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 non-occlusive 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.

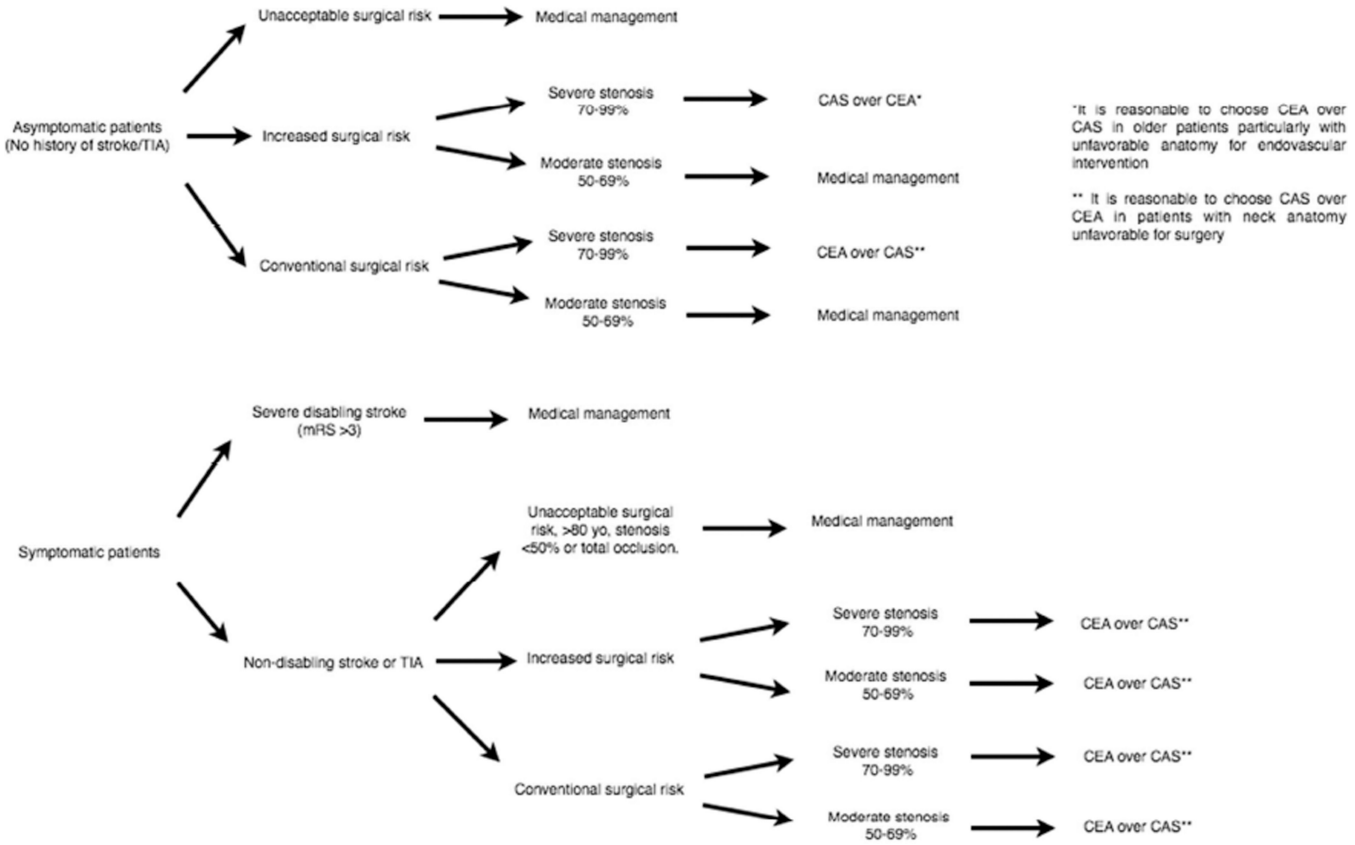


**Figure 1.**

Carotid disease management flow chart. 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. CAS may be a better alternative to CEA in asymptomatic patients with severe stenosis and increased risk for surgery.

**Table – 1**

Summary of key randomized clinical trials

| Trial, Year (Reference) | 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 yr | 9.00 | 26.00 |
| NASCET 1998[8] | S (50–69% by angio) | CEA | Med | 320 | 428 | Ipsilateral stroke at 5 yr | 15.70 | 22.20 |
| ECST 2003[151] | S (70–99% by angio) | CEA | Med | 429 | 850 | Stroke or surgical death | 6.80 | NA |
| | S (50–69% by angio) | CEA | Med | 646 | 850 | Stroke or surgical death | 10.00 | NA |
| ACAS 1995[138] | AS (>60% by angio) | CEA | Med | 825 | 834 | Ipsilateral stroke, peri-procedural stroke or death | 5.10 | 11.0 |
| ACST 2004[139] | AS (>60% by angio) | Immediate CEA | Delayed CEA | 1560 | 1560 | 5-yr stroke risk | 3.8 | 11.0 |
| SPACE 2008[142] | S (≥70% by US) | CEA | CAS | 589 | 607 | All stroke at 2 yr | 10.10 | 10.90 |
| | | | | | | All peri-procedural strokes or deaths and ipsilateral strokes up to 2 yr | 8.80 | 9.50 |
| | | | | | | Ipsilateral stroke between 31d and 2 yr | 1.90 | 2.20 |
| EVA-3S 2008[145] | S (≥60%) | CEA | CAS | 262 | 265 | All stroke at 4 yr | 3.40 | 9.10 |
| | | | | | | Ipsilateral stroke at 4 yr | 1.50 | 1.50 |
| | | | | | | All peri-procedural stroke, death and non-procedural ipsilateral stroke at 4 yr | 6.20 | 11.10 |
| SAPHIRE 2004 and 2008[143,144] | S (≥50% by US) + AS (≥80% by US) | CEA | CAS | 167 | 167 | All strokes a 1 yr | 7.90 | 6.20 |
| | | | | | | Ipsilateral stroke at 1 yr | 4.80 | 4.20 |
| | | | | | | All stroke, death or MI within 30d of procedure, ipsilateral stroke between 31d and 1 yr | 20.10 | 12.20 |
| | | | | | | All strokes at 3 yr | 9.00 | 9.00 |
| | | | | | | Ipsilateral stroke at 3 yr | 5.40 | 6.60 |
| | | | | | | All stroke, death or MI within 30d of procedure, ipsilateral stroke between 31d and 1080 d | 26.90 | 24.60 |
| ICSS 2010[146] | S (≥50% by angio or 2 non-invasive 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 |

| Trial, Year (Reference) | Study population, degree of stenosis | Intervention | Comparison | No. of patients | | Event | Events (%) | |
|---|---|---|---|---|---|---|---|---|
| | | | | Treatment group | Comparison group | | Treatment group | Control Group |
| CREST 2010[141] | S (≥50% by angio, ≥70% by US) | CEA | CAS | 653 | 688 | All peri-procedural strokes, MI, death and post-procedural ipsilateral strokes up to 4 yr | 8.40 | 8.60 |
| | | | | | | All peri-procedural strokes, death and post-procedural ipsilateral strokes up to 4 yr | 6.40 | 8.00 |
| | | | | | | All peri-procedural strokes and post-procedural ipsilateral strokes up to 4 yr | 6.40 | 7.60 |
| | AS (≥60% by angio, ≥70% by US) | CEA | CAS | 587 | 594 | All peri-procedural strokes, MI, death and post-procedural ipsilateral strokes up to 4 yr | 4.90 | 5.60 |
| | | | | | | All peri-procedural strokes, death and post-procedural ipsilateral strokes up to 4 yr | 2.70 | 4.50 |
| | | | | | | All peri-procedural strokes and post-procedural ipsilateral strokes up to 4 yr | 2.70 | 4.50 |
| | S + AS | CEA | CAS | 1240 | 1262 | All stroke up to 4 yr | 7.90 | 10.20 |

*US = ultrasonography, angio = catheter angiography, yr = year(s), d = day(s), S = symptomatic, AS = asymptomatic, NNT = number needed to treat; CEA = carotid endarterectomy; CAS = carotid angioplasty and stenting.

**Table 2**

Factors Influencing the Decision of CEA versus CAS

| CEA | CAS |
|---|---|
| Anatomic factors<br>• Normal location of carotid bifurcation<br>• Independent of aortic arch<br>• Independent of vessel tortuosity | Anatomic factors<br>• High (cervical) or low (intrathoracic) carotid bifurcation<br>• Type I aortic arch<br>• Reduced vessel tortuosity (<30°) |
| Plaque factors<br>• Independent of aortic arch atherosclerosis<br>• Independent of length of segment occlusion*<br>• Independent of degree of calcification<br>• Independent of stability of the plaque<br>• Independent of presence of acute thrombus | Plaque factors<br>• No arch atherosclerosis<br>• Short segment stenosis<br>• Lack of extensive circumferential calcification<br>• Stable plaque<br>• Absence of acute thrombus |
| Patient factors<br>• Independent of age (up to 80 years of age)<br>• Male gender<br>• Low cardiac risk<br>• Independent of patient's renal function | Patient factors<br>• Younger patients.<br>• Independent of gender<br>• Prior CEA<br>• Prior neck surgery or tracheostomy<br>• Prior neck radiation |

* As long as distal segment can be surgically reached below the angle of the