Carotid Endarterectomy: Current Concepts and Practice Patterns

Sibu P. Saha, MD, MBA[1] Subhajit Saha, MBBS[2] Krishna S. Vyas, MD, MHS[1]

[1] Division of Cardiothoracic Surgery, Department of Surgery, University of Kentucky College of Medicine, Lexington, Kentucky
[2] MediCiti Institute of Medical Science, Hyderabad, India

Address for correspondence Sibu P. Saha, MD, MBA, Cardiothoracic and Vascular Surgery, Room 407 Charles T Wethington Building, University of Kentucky, 900 South Limestone, Lexington, KY 40536-0200 (e-mail: ssaha2@email.uky.edu).

Int J Angiol 2015;24:223–235.

Abstract

Background Stroke is the number one cause of disability and third leading cause of death among adults in the United States. A major cause of stroke is carotid artery stenosis (CAS) caused by atherosclerotic plaques. Randomized trials have varying results regarding the equivalence and perioperative complication rates of stents versus carotid endarterectomy (CEA) in the management of CAS.

Objectives We review the evidence for the current management of CAS and describe the current concepts and practice patterns of CEA.

Methods A literature search was conducted using PubMed to identify relevant studies regarding CEA and stenting for the management of CAS.

Results The introduction of CAS has led to a decrease in the percentage of CEA and an increase in the number of CAS procedures performed in the context of all revascularization procedures. However, the efficacy of stents in patients with symptomatic CAS remains unclear because of varying results among randomized trials, but the perioperative complication rates exceed those found after CEA.

Conclusions Vascular surgeons are uniquely positioned to treat carotid artery disease through medical therapy, CEA, and stenting. Although data from randomized trials differ, it is important for surgeons to make clinical decisions based on the patient. We believe that CAS can be adopted with low complication rate in a selected subgroup of patients, but CEA should remain the standard of care. This current evidence should be incorporated into practice of the modern vascular surgeon.

Keywords
- carotid artery disease
- stroke
- carotid artery stenosis
- atherosclerosis
- carotid endarterectomy
- carotid artery stents
- endovascular carotid

Stroke/cerebrovascular accident (CVA) is the third leading cause of death in the developed nations, and is the leading cause of long-term disability.[1] This accounts for a substantial cost to the patient and to the healthcare system. Carotid artery stenosis (CAS) is responsible for 20 to 30% of ischemic strokes in the United States.[2] Understanding of the relationship between carotid artery disease and stroke began with autopsy findings in the early part of last century. Carotid endarterectomy (CEA) was introduced in the 1950s to prevent stroke. Several trials have proven CEA to be superior to medical therapy and CAS for stroke prevention in symptomatic lesions. Its value in the management of asymptomatic carotid artery disease is also shown to be of great value as long as the combined morbidity and mortality is less than 3%. In spite of these clinical trials, controversy continues regarding the best management for patients, particularly in the asymptomatic group. Medical therapy has significantly improved and so has the outcome of CEA. In this report, we describe current concepts and practice patterns of CEA.

Historical Perspective

Before 1900, knowledge regarding the pathophysiology of stroke was largely unknown. Chiari in 1906 and Hunt in 1914

published online
August 14, 2015

DOI http://dx.doi.org/10.1055/s-0035-1558645.
ISSN 1061-1711.

performed autopsies of the carotid arteries in the necks of patients who had cerebral infarction.[3] Hunt noted that there was no intracranial obstruction, and that the probable lesion was in the cervical carotid artery. These findings would go largely unrecognized until Miller Fisher reported cases of internal carotid artery occlusion from subintimal atheromas, thrombosis, and embolization as a cause of cerebral infarction in 1951.[4] Neurologist Egas Moniz is credited with the introduction of cerebral angiography in 1927, with use significantly rising in the 1950s for the diagnosis of atherosclerotic lesions.[5] The first carotid artery reconstruction was done in 1951 by Carrea, Mollins, and Murphy in Buenos Aires,[6] followed by Eastcott et al in 1954.[7] Eastcott et al performed resection of thrombus from the internal carotid artery followed by reconstruction. These ventures are worth mentioning and truly serve as landmarks in the evolution of CEA. The first successful CEA was performed by Michael DeBakey at Methodist Hospital in Houston, Texas in 1953,[8] although the first published report was by Eastcott et al in 1954.[7] Cooley et al used the first intravascular shunt during endarterectomy.[9] He also introduced the practice of induced hypertension to avoid shunting.

In the 1970s and 1980s, CEA became the most popular procedure in the United States for treating CAS, although questions were raised about associated perioperative morbidity and mortality in community hospitals.[10] After that report, many neurologists began treating their patients with aspirin only and avoided surgery. This led to large randomized clinical trials such as NASCET and ACAS in the 1990s. These studies clinically showed the superiority of CEA over the medical treatment group. Since then, CAS was introduced as a treatment for CAS. Multiple studies have failed to show its superiority over CEA, however, it has found its place in certain clinical situations where surgery would be of greater risk, such as in high-risk patients with comorbidities and in unfavorable necks such as restenosis after CEA.

Pathophysiology and Risk Factors

Atherosclerosis is a generalized disease but it tends to more pronounced and progressive at certain locations of the arterial tree, such as the carotid bifurcation and the aortic bifurcation. Significant atherosclerosis causing luminal narrowing is often limited to the proximal 2 cm of the internal carotid artery and the carotid bulb. The concept that atherosclerotic changes in the carotid bifurcation leads to ischemic changes in the brain was first postulated by Miller Fisher in 1951.[4] The plaque is usually stable and asymptomatic, but small pieces can embolize and lodge in small arteries in the brain, causing temporary symptoms such as a transient ischemic attack (TIA), amaurosis fugax or more permanent damage via thromboembolic stroke/cerebral infarction.[11] The degree of carotid stenosis is strongly associated with stroke risk. As the internal carotid artery is in continuity with the vessels in the circle of Willis, occlusion may be silent. Occlusion of the carotid artery may also result in ischemia in the watershed region.

Plaque morphology and the degree of stenosis matter in the pathophysiology of this disease.[12] Currently, ultrasound (US) studies are used to assess the plaque morphology, however, it fails to identify the most vulnerable plaque. Hopefully, technology will evolve to understand the type and variety of plaque in this region to select the best form of treatment, that is, CEA versus CAS.

Several modifiable and nonmodifiable risk factors contribute to the risk of stroke with carotid stenosis, including age, hypertension, carotid artery disease, previous stroke/TIA, absent collateral flow, irregular or ulcerated plaque morphology, and microembolic signals on transcranial Doppler.[13,14] Factors contributing to carotid artery disease and atherosclerosis include age, hypertension, diabetes, high levels of low-density lipoprotein cholesterol, low levels of high density lipoprotein cholesterol, family history of atherosclerosis, smoking, obesity, hyperhomocystinemia, and sedentary lifestyle.[15]

Clinical manifestations of atherosclerotic disease of the carotid artery are variable; patients may have a bruit in the affected carotid artery, amaurosis fugax, retinal infarctions or cholesterol emboli, or may not have any symptoms. Ischemia involving specific vascular territories results in specific clinical stroke syndromes. Patients often present with one or more of the following symptoms: amaurosis, aphasia, dysphasia, hemiparesis, and hemiplegia. Presence of a carotid bruit in the neck is not specific for CAS and may be due to causes. However, finding of a bruit should lead to further investigation, such as scanning of the neck vessels with carotid artery duplex.

Diagnosis

Preoperative evaluation should include a thorough history and assessment of medical risk factors, neurologic risk factors, and angiographic risk factors as determined by radiologic diagnostics. Medical risk factors include obesity, chronic obstructive pulmonary disease (COPD), advanced peripheral vascular disease, uncontrolled hypertension, congestive heart failure (CHF), angina and myocardial infarction (MI). Neurologic risk factors include neurologic deficit within 24 hours, active TIA, and cerebral infarction within 7 days. Angiographic risk factors include contralateral occlusion of the internal carotid artery, thrombus extending from an ulcerative lesion, plaque extension over 3 cm distally or over 5 cm proximally, and ipsilateral carotid siphon disease. These factors should be evaluated and worked up before the surgery. Patients should have a comprehensive cardiac evaluation before surgical intervention.

Patients with a history stroke should have evaluation of the brain with computed tomographic angiography (CTA) and/or magnetic resonance angiography (MRA) to rule out intracranial pathology such as hemorrhagic stroke.

There are many radiologic diagnostic options available for evaluating patients for CEA. Most surgeons rely on carotid artery duplex alone before CEA. Cerebral angiography is rarely used. Our center uses duplex US to assess the degree of carotid stenosis and CTA or MRA for further analysis. Advantages and disadvantages of various radiologic diagnostic tools are described in ►**Table 1**.

Medical Therapy

Medical management has advanced significantly as our understanding of carotid artery disease has improved. Aspirin was the only drug of choice in the 1980s. Now, we know that the management of risk factors matters for short- and long-term outcomes after CEA.

Management of risk factors such as hypertension, diabetes, or hyperlipidemia is essential in patients with CAS, in addition to lifestyle modification, medical optimization of comorbidities, and smoking cessation to reduce both early and long-term risks of vascular events and death.[16] Aspirin and aspirin with clopidogrel, extended-release dipyridamole, and ticlopidine have been shown to be effective antiplatelet agents in long-term prevention of ischemic stroke.[17,18]

The clinical trials of carotid revascularization must be assessed with respect to the evolution of medical therapies for atherosclerotic disease. Medical therapies have evolved throughout the duration of clinical trials, improving the therapeutic options available for clinicians to treat patients. The application of best medical practice and standards of care differ from those in published trials, and reduces the generalizability of those trials to our current practice. Future randomized controlled trials are needed to explore how revascularization interventions compare with current best-available medical therapy.[19] Surgical outcomes have also

Table 1 Radiologic diagnostics

Radiologic diagnostic imaging	Advantages	Disadvantages
Duplex ultrasound (US)	• Noninvasive • Rapid • Widely available • Inexpensive • Painless • Sensitive and accurate test for assessing the degree and location of stenosis and characteristics of plaque • Can calculate flow velocity and turbulence • Used during CEA to identify intimal flaps and assess flow • Used for screening in patients presenting with ipsilateral TIA or stroke and in follow-up postoperatively to detect restenosis	• Operator dependent • Does not provide anatomic detail of the neck or intracranial vessels • Cannot detect tandem or isolated lesions near the distal carotid artery • Calcium may obscure lesion
Computed tomographic angiography (CTA)	• Less invasive than conventional angiography • More accessible than MRA • More precise than US or MRA	• Risk of nephrotoxicity or allergy to iodinated contrast • More expensive than US • More rapidly available in emergencies • Motion artifacts may limit interpretation • Cannot detect intramural hematoma • Calcium deposits at the carotid bifurcation may limit quantification of luminal stenosis
Magnetic resonance angiography (MRA)	• Noninvasive and safer than CTA • No exposure to high levels of radiation like CTA • Most accurate of the noninvasive techniques • Used for diagnosis and therapy • Can evaluate and quantify luminal restenosis postoperatively • Can detect intramural hematoma and intracranial arteries	• Interaction with pacemakers, cerebral aneurysm clips and metal implants • Less rapidly available • Costly • Does not image calcium well • May overestimate degree of vessel stenosis • Same accuracy as US • Requires sedation since it is highly motion sensitive
Carotid cerebral angiography	• Clear vessel visualization	• Outcomes may depend on skill and experience of provider • More invasive and expensive compared with other diagnostic tools • Does not provide information about plaque characteristics • Risk of stroke and bleeding • Risk of iodinated contrast nephrotoxicity and allergy • Most expensive method of carotid stenosis evaluation

Abbreviations: CEA, carotid endarterectomy; CTA, computed tomographic angiography; MRA, magnetic resonance angiography; TIA, transient ischemic attack; US, ultrasound.

improved with better perioperative medical management, including the use of statins and blood pressure medications. Current recommendations are as follows:

- Aspirin (81–325 mg daily) is recommended before CEA and should be continued indefinitely postoperatively (LOE A).
- Aspirin (81–325 mg daily), clopidogrel (75 mg daily), or combined aspirin (25 mg daily) plus extended release dipyridamole (200 mg daily) should be used for long-term prophylaxis against ischemic cardiovascular events (LOE B).
- Lipid-lowering statins for prevention of ischemic events is reasonable for patients who have undergone CEA irrespective of serum lipid levels (LOE B).

Surgical Considerations

CEA has been established as the gold standard for treatment of CAS for many decades, but surgical and anesthetic techniques have evolved over time. There is a great degree of variability of this procedure across the country and even among providers in the same center.[20,21] Traditional endarterectomy employs a longitudinal arteriotomy, while eversion endarterectomy employs a transverse arteriotomy with reimplantation of the carotid artery.[22] A Cochrane review of five randomized controlled trials showed no statistically significant difference in the rates of perioperative stroke or death when comparing eversion and conventional endarterectomy with either patch angioplasty or primary closure. To reduce the risk of restenosis, autologous vein or synthetics can be used to close the artery and enlarge the lumen. A 2009 Cochrane review of 10 randomized and quasirandomized trials comparing carotid angioplasty with primary closure in over 1,900 patients revealed limited evidence of reduced risk of perioperative and long-term ipsilateral stroke, reduced risk of perioperative arterial occlusion and decreased restenosis during long-term follow-up in patients undergoing carotid patch angioplasty.[23] While the patch can increase operative time, it can also reduce the perioperative stroke or mortality by 60% and the risk of long-term vessel restenosis by 80% in long-term follow-up,[24] although some studies do not reflect these same outcomes.[25] Temporary intraluminal shunts can also be employed, but data from a 2014 Cochrane Review concluded that the data were too limited to support or refute the use of routine or selective shunting in CEA[23]; large randomized controlled trials are indicated. Perioperative mortality associated with CEA ranges from 0.5 to 3% with a 30-day unplanned readmission rate is 6.5%. Factors related to readmission include prior coronary artery bypass grafting, in-hospital postoperative stroke, bleeding/hematoma, and CHF.[26]

Anesthetic Considerations

The goals of anesthetic management in CEA are to maintain cerebral and myocardial perfusion. With general anesthesia, methods of assessing cerebral perfusion include electroencephalography, somatosensory-evoked potential monitoring, transcranial Doppler US, and carotid artery stump pressure monitoring. There are no controlled studies that explore the outcomes between regional and general anesthesia. In an analysis of the American College of Surgeons (ACS), National Surgical Quality Improvement Program (NSQIP) database, general anesthesia was used in approximately 85% and regional anesthesia was used in approximately 15% of cases.[27] The choice of general anesthesia or local anesthesia with or without cervical block for CEA is determined by surgeon preference and patient presentation and preference,[28] although most surgeons perform CEA under general anesthesia. A 2013 Cochrane review including results from the General Anesthesia versus Local Anesthesia (GALA) trial along with 14 randomized trials found no difference in perioperative stroke, MI, or death among patients receiving local and general anesthesia.[29]

Blood pressure is more largely affected by general anesthesia compared with local anesthesia, resulting in more variability and manipulation of blood pressure postoperatively.[28,30] Local anesthesia may be considered in select patients. Further analysis of the GALA trials found that local anesthesia might also be more cost-effective than general anesthesia.[31] The NSQIP data suggest that this could be because of the shorter operative time and anesthesia time and sooner discharge.[30] Other issues such as cost-effectiveness and length of hospitalization should also be considered.[32]

Asymptomatic Carotid Artery Stenosis

A meta-analysis of over 23,000 participants showed the prevalence of severe asymptomatic stenosis in the general population to be 3.1%.[33] In patients with stenosis greater than 60% treated medically, the annual incidence of stroke has been reported to be 2.5%.[34]

The risk of stroke and death in patients undergoing CEA for asymptomatic CAS is significantly increased in certain patients, particularly those with dependent functional status, recent MI, CHF, hypoalbuminemia, angina, dialysis dependence, steroid dependence, COPD, and American Society of Anesthesiologists Score more than 3.[35] Other factors that increase the risk of postoperative stroke and death include age $\geq$ 80 years, active smoking, contralateral internal CAS of 80 to 99%, emergency procedure status, preoperative stroke, presence of one or more ACS NSQIP-defined high-risk characteristics (including New York Heart Association class III/IV CHF, left ventricular ejection fraction less than 30%, recent unstable angina, or recent MI), and operative time $\geq$ 150 minutes.[36] A validated risk index can help to identify asymptomatic patients at greatest risk for 30-day stroke, MI, and death after CEA.[37]

Indications for CEA in patients with asymptomatic CAS are controversial. Medical management may be an alternative to CEA for patients with asymptomatic stenosis; therapy includes statins, β-blockers and antiplatelets along with management of risk factors such as hypertension, smoking, and diabetes. CEA in addition to best medical management should be the best in the management of patients with severe CAS.

Randomized controlled trials have established that CEA is beneficial for patients with asymptomatic CAS greater than 60%, although the degree of benefit is not as profound as for symptomatic stenosis. Neither the ACST nor the ACAS trials established a correlation between the degree of stenosis and the risk of stroke for patients with asymptomatic stenosis greater than 60%.

The Asymptomatic Carotid Surgery Trial (ACST) explored whether the addition of CEA to aspirin influenced the incidence of TIA or infarctions in patients with severe (> 60%) asymptomatic stenosis.[38] Over 3,100 patients were enrolled in this study from 1993 to 2003, with patients assigned to CEA or deferral of any carotid procedure. The study found that CEA in asymptomatic patients younger than 75 years reduced the 10-year stroke risk. The ACST-2 trial will compare CEA with CAS in the prevention of stroke in patients with asymptomatic stenosis.[39]

The Asymptomatic Carotid Atherosclerosis Study (ACAS) of 1987 to 1993 determined that the incidence of ipsilateral stroke and any perioperative stroke or death after a median follow-up of 2.7 years in patients with asymptomatic stenosis greater than 60% was 5.1% for those receiving CEA compared with 11.0% for those treated medically.[34] Although the perioperative complication rates were 2.3%, the reliability of the effect size is reduced because of the extrapolation of data from 2-year follow-up. Therefore, patients with asymptomatic stenosis greater than 60% will have a reduced 5-year risk of ipsilateral stroke if CEA is performed, done in conjunction with aggressive risk factor and medical management, and given that perioperative morbidity and mortality risk is less than 3%.

The Asymptomatic Carotid Emboli Study (ACES) determined that transcranial Doppler could be used to detect embolization and help stratify patients with asymptomatic stenosis in a higher and lower vascular event risk group.[40]

The data from these trials suggest that although surgery reduces the incidence of ipsilateral stroke and any stroke, the benefit is small (~ 1% per year), whereas the perioperative risk of stroke or death is high (3%). Therefore, medical management may be the most appropriate option in most asymptomatic patients, and only centers with a perioperative complication rate of less than 3% should consider surgery, although patients with a high risk of stroke (> 80% stenosis and a life expectancy more than 5 years) may benefit from surgery.[38,41] Resources should be invested in identifying asymptomatic patients at high risk for stroke who can benefit from best medical therapy and CEA or CAS.[42] These trials have helped to establish practice guidelines for the management of asymptomatic stenosis.

Symptomatic Carotid Artery Stenosis

Symptomatic CAS is defined as sudden onset focal neurologic symptoms within the previous 6 months that affect the carotid artery distribution (caused by carotid atherosclerosis). These symptoms may include TIA, amaurosis fugax, or ischemic stroke. The risk of stroke increases with higher degrees of symptomatic stenosis (hazard ratio of 1.18 per 10% increase in stenosis),[43,44] although patients with severely narrowed or collapsed carotid arteries (near occlusion) have a relatively lower risk of stroke on best medical therapy compared with carotid arteries with moderate degrees of stenosis.[45]

The North American Symptomatic Carotid Endarterectomy Trial (NASCET) trial of the 1980s was a large randomized controlled class I study and the first major study that compared CEA to medical therapy in patients with symptomatic stenosis.[44] It compared CEA with medical therapy in over 650 patients with recent TIA or nondisabling stroke and varying degrees of stenosis. It was terminated early in the severe stenosis group (> 70%) because of the significant benefit of surgery compared with medical therapy at 3-month follow-up. Clinically significant benefits of CEA versus medical therapy included lower risk of any major stroke or death (8.0 vs. 19.1%) and lower risk of any stroke or death (15.8 vs. 32.3%). CEA decreased the absolute risk of ipsilateral stroke by 17% at 2 years compared with medical management. A smaller but clinically important benefit was also evident in the group with 49 to 70% stenosis, with a 6.5% absolute risk reduction at 5 years compared with medical management. In patients with greater than 80% stenosis, CEA had an absolute risk reduction of 11.6% in stroke at 3 years. The major conclusion of the NASCET trial was that CEA was very beneficial in patients with recent symptomatic stenosis with ipsilateral stenosis greater than 70%.

The European Carotid Surgery Trial (ECST) was a large randomized controlled class I study that examined outcomes of CEA in stroke prevention in patients with symptomatic stenosis.[43] Over 3,000 patients of any age who had a symptomatic ischemic vascular event in the carotid artery distribution over the previous 6 months were enrolled and examined between 1981 and 1995. Major stroke or death occurred in 37.0% of the CEA group and 36.5% of the control group, and risk of major stroke or death complicating surgery (7.0%) did not vary with the degree of stenosis. However, the risk of major stroke ipsilateral to the unoperated symptomatic stenosis increased in stenosis above 70% of the original luminal diameter. The authors concluded that CEA was indicated for most patients with a recent nondisabling ischemic event in the carotid artery distribution with symptomatic stenosis greater than 80%.[46] This study demonstrated an absolute risk reduction of 6.5% for ipsilateral stroke and a relative reduction of 39%. CEA was only helpful in patients with greater than 50% narrowing of the internal carotid artery, with more severe narrowing receiving greater benefit from surgical intervention.

Current recommendations indicate CEA for symptomatic patients with stenosis from 70 to 99%; CEA may be indicated in patients with stenosis between 50 and 69% without neurologic deficit; CEA is not recommended for patients with stenosis less than 50% and should not be performed in centers with complication rates higher than the 6% rate observed in NASCET and ECST. In some patients with asymptomatic stenosis between 60 and 99%, CEA may be indicated if there is a very low-complication risk and if the patient has a life expectancy of at least 5 years.

To determine the effect of timing on operative risk and benefit of CEA, data from NASCET and ECST were examined.[47] The results found that CEA performed within 2 weeks of nondisabling stroke or TIA significantly improved outcomes compared with delayed CEA and without increasing operative risk. In patients with CAS > 70%, CEA reduced the absolute risk of stroke by 30.2% if performed within 2 weeks of the last ischemic event, and in patients with CAS between 50 and 69%, benefits of CEA were only observed within two weeks of the last ischemic event. More recent trials show that carotid revascularization performed within 15 days after symptom onset versus delayed CEA in symptomatic patients have no difference in outcomes.[48] A 2009 systematic review showed that the rate of perioperative stroke or mortality is significantly higher in emergent CEA (14.0%) compared with nonemergent CEA (4.0%).[49] Studies suggest that urgent CEA can be safely performed in symptomatic patients to improve neurologic outcome[50] without increased procedural risk,[51] although the poorest outcomes occur in patients with an evolving stroke, and urgent CEA should be offered with caution in these patients,[52] and can perhaps be offered within 48 hours after TIA or SIE to prevent recurrent stroke.[53]

Studies have also suggested gender differences in CEA outcomes. The benefit of CEA for women also declined more rapidly compared with men. Furthermore, the risk of ipsilateral stroke in symptomatic CAS is significantly lower for women treated medically than men, and the perioperative mortality risk from CEA is significantly higher in women compared with men. Therefore, CEA is considered beneficial for women with symptomatic stenosis more than 70%, and is not beneficial for most women with stenosis between 50 and 69%.[54] A 10-year national study on CEA outcomes in men and women hospitalized for carotid artery disease showed a lower perioperative cardiac morbidity and mortality rate in women compared with men and no difference in timing of CEA based on sex.[55] Sex differences in outcomes of treatment for carotid artery disease have been controversial.[56] A 2014 retrospective study of over 1,000 patients showed no difference in perioperative stroke and mortality rates after CEA in women.[57] A 2014 study of over 9,800 patients contrasted previous reports by concluding that while men and women demonstrated similar results after CEA and CAS, women did not have a higher risk of adverse events after carotid revascularization.[58]

According to results from NASCET, patients with symptomatic contralateral stenosis are benefit from CEA compared with medical management. Medically treated patients with occluded contralateral carotid artery were twice as likely to have an ipsilateral stroke at 2 years compared with patients with severe or mild-to-moderate contralateral stenosis. The perioperative risk of stroke and mortality were higher in patients with an occluded contralateral carotid artery (4.0% risk) or mild-to-moderate contralateral stenosis (5.1% risk). Despite the higher perioperative morbidity with an occluded contralateral carotid artery, patients with CEA performed on the recently symptomatic, severely stenosed ipsilateral carotid artery benefit compared with medically treated patients.[59]

It is important to note that the NASCET trial enrolled only patients younger than 80 years of age, and so results must be extrapolated to the elderly. The decision to treat elderly patients surgically depends in part on the operative risk, which includes stroke and cardiac risk. The American Heart Association suggests that the upper limits for stroke and cardiac risk for CEA after TIA be less than 5%. The NASCET trial showed a combined risk of 5.8%. Many studies have explored these risks in the elderly and suggest that there is no increased operative risk from age. However, a selection bias exists in these studies that disfavor patients who are ineligible to receive the procedure due to excessive risk or illness. The NASCET trial bias was applied to both the medical and surgical groups, so all patients were appropriate for surgical management. Nonetheless, most studies suggest that the operative risk for CEA in the elderly is not significantly increased.[60–62]

Operative Technique

Operative technique varies widely across the country. The type of anesthesia, cerebral monitoring, and the technique eversion versus direct feathering technique, patch versus primary closure, and stent utilization all vary widely. Variability exists even within the same institution, however, there is no evidence that one technique is superior to another, and probably depends on the surgeons experience.

Complications

Complications related to CEA have significantly declined over the years because of the advances in intraoperative management and postoperative care. CEA is effective in low-risk surgical patients and decreases the risk of stroke, but there are risks of general anesthesia, infection, MI, hyperperfusion syndrome, cervical hematoma, cranial nerve injury, restenosis, embolization, stroke, and even death.

Stroke: Stroke is the second most common cause of death following CEA. The rate of stroke after CEA ranges from 0.25 to 3%,[63,64] with symptomatic patients having a higher rate. Factors contributing to postoperative stroke after CEA include plaque emboli, platelet aggregates, and poor cerebral perfusion. Cerebral ischemia can be because of the following: hypotension associated with hypovolemia from blood loss; embolization or formation of a thrombus at the surgical site; and vasospasm from prolonged clamp time during surgery.

Neurologic changes after CEA should prompt immediate evaluation, including rule out of intracranial hemorrhage and assessment of the operative site for technical errors. Duplex US can be utilized to evaluate flow throughout the carotid artery; if no thrombosis or intimal flap is identified a head CT should be performed to rule out intracranial bleeding and heparin can be subsequently administered. Some surgeons prefer to return to the operating room (OR) to explore the operative site for technical errors.

There are no controlled trials to justify the use of intra-arterial thrombolytic therapy with tissue-type plasminogen activator (alteplase) for postoperative embolic stroke patients given the risk of intracranial hemorrhage from this treatment. Intravenous tPA is an independent risk factor for subarachnoid hemorrhage after CEA.[65,66]

Although intraoperative use of an intraluminal shunt may reduce the risk of stroke by increasing cerebral blood flow in the carotid artery, it may also increase the risk of arterial wall damage with subsequent stroke after CEA. Use of an intraluminal shunt is a risk factor for new magnetic resonance diffusion-weighted image lesions after CEA, supporting their selective use.[67]

Myocardial infarction: The risk of MI after CEA (range, 0–2%) is higher than CAS. Risk factors for and management of perioperative MI are important to consider.

Hyperperfusion syndrome: Hyperperfusion syndrome has an incidence of 1 to 3% but is the cause of most seizures and intracerebral hemorrhages after CEA. Hyperperfusion is a consequence of changes that occur to ischemic carotid vasculature. To maintain cerebral blood flow, the small vessels dilate; after CEA, blood flow is restored to normal perfusion pressures, and the dilated vessels are unable to autoregulate and vasoconstrict, resulting in elevated perfusion pressures, edema, and hemorrhage. Hyperperfusion is likely with revascularization of lesions with over 80% stenosis, from reduced cerebral flow before CEA, or after recent cerebral infarction. Clinically, the syndrome is characterized by ipsilateral headache with improvement on upright posture, focal motor seizures, and intracerebral hemorrhage. Transcranial Doppler can be used to monitor flow velocities of the middle cerebral artery to predict the occurrence of hyperperfusion syndrome. However, hyperperfusion syndrome may occur with only moderate increases in ipsilateral cerebral blood flow as measured by perfusion magnetic resonance imaging (MRI), even if middle cerebral artery flow velocity as measured by transcranial Doppler is normal. Systolic blood pressure should be strictly maintained below 150 mm Hg immediately and for weeks postoperatively. Blood pressure should be controlled to prevent rupture of the vessel and to reduce the risk of embolization of a thrombus. Patients with a sudden or severe headache following CEA should be evaluated with head CT. Antithrombotics should be discontinued.

Neck hematoma: Postoperative neck hematoma can result in loss of the airway; uncontrolled intraoperative or postoperative hypertension can contribute to hematoma formation. Bedside tracheostomy kit should be available for evacuation of neck hematomas that may compromise the airway. If a neck hematoma develops, return to the OR and reexploration of the neck is necessary. Patients receiving antiplatelet therapy preoperatively or anticoagulant therapy postoperatively have a higher incidence of neck hematoma. Anticoagulation can be reversed intraoperatively with protamine.

Nerve injury: Surgical trauma, inadvertent or improper retraction and transection of nerves, or compression of nerves from edema, hematoma, or inflammation can result in nerve injury. The risk of nerve injury in patients undergoing CEA is 5 to 6%, and the majority of these nerve injuries resolve after surgery. Nerves that can be affected are VII, XII, IX, X, and XI. Hypoglossal nerve injury is the most common (tongue deviation to affected side), followed by the marginal mandibular branch of the facial nerve (paresis of the ipsilateral orbicularis oris) and inferior laryngeal nerve (unilateral vocal cord paralysis) injury. Injury to the glossopharyngeal and sympathetic nerves has also been reported.

Restenosis: Restenosis rates are variable but are more common after primary closure than patch closure.

Readmission: In a study of over 235,000 carotid interventions, readmission rates for patients undergoing CEA and CAS were 8.8 and 11.1% (30 days), 13.3 and 17.9% (60 days), and 16.8 and 22.6% (90 days). Patients older than 80 years, those with renal failure, CHF, diabetes, or CAS were more likely to be readmitted.[68] In an NSQIP study of over 8,400 patients, preoperative bleeding disorder, history of a CVA/stroke, and increasing age were statistically significant predictors for readmission. Postoperatively, surgical site infection, MI, sepsis/septic shock, CVA/stroke, pneumonia, and urinary tract infection were associated with a greater rate of readmission.[69] In a study of 840 patients at a single institution, increased length of stay was associated with preadmission, history of CHF, female gender, history of COPD, electroencephalography change, OR start time after 12:00 PM, total OR time, transfer to intensive care unit, number of in-hospital postoperative complications, and Foley catheter placement. Over 1 year, increased length of stay was associated with increased hospital readmission and decreased survival.[70]

Postoperative Care

The most important part of postoperative care is strict control of blood pressure. Patients should continue on antiplatelet therapy. Perioperative use of aspirin has been associated with reduced postoperative complications. Most patients are kept in the hospital for 1 day postoperatively, although length of stay in the intensive care unit and hospital varies nationally. Some surgeons prefer to use a drain, however, drains should be removed on the first postoperative day and there is no study to support superiority of drain versus no drain. Follow-up with carotid duplex is typically performed 4 weeks postoperatively to establish a new baseline, and is performed at 6 months and then annually.

Carotid Artery Stenting

Certain anatomic features and comorbidities are considered contraindications, including complex bifurcation disease, string sign, or long, multifocal, heavy calcifications of the aortic arch, brachiocephalic trunk, or carotid bifurcation, and tortuous aortic arch. CAS is indicated in patients with high surgical risk, multiple comorbidities, contralateral laryngeal nerve palsy, previous neck dissection, cervical irradiation, previous CEA, or those at high risk of cerebral ischemia during carotid clamping. CAS is also an option for patients with high carotid bifurcation or intracranial extension of the carotid lesions, where access would be surgically difficult. It also avoids the risk of general anesthesia and cranial nerve

damage. CAS in symptomatic patients should only be considered in centers with perioperative risk of stroke or mortality less than 6%.

Four major studies, Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS), Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy (SPACE), Endarterectomy versus Stenting in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial and Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trials showed CAS to have either similar or inferior results when compared with CEA. These studies have been criticized for design, suboptimal medical therapy, and variability in operator and use of cerebral protection devices, but they are important studies. Recently, the International Carotid Stenting Study (ICSS) and the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) were published, yielding differing results. Although no difference was noted for disabling stroke between CEA and CAS in the ICSS, there were significantly more strokes of any severity in the CAS group (2.9 vs. 1.85% at 1 year). There was also a lower combined stroke/death and MI rate for CEA (5.2 vs. 8.5%). CREST showed no end point difference between CEA and CAS, and most guidelines subsequently included CAS as a valid alternative to CEA. However, the CREST study is criticized for its use of a combined end point of stroke and MI, and critics argue that stroke should be the only primary end point for both interventions. In addition, as strokes are more disabling than MI, the combined end point inflates the disadvantages associated with CEA, although patients who suffered from perioperative MI had a higher 4-year mortality than those who did not (19.1 vs. 6.7%). It is also important to note that medical therapy was not standard between the two trials and may have influenced outcomes.

The CAVATAS[71] was a randomized controlled trial designed to assess the safety and efficacy of CAS compared with CEA for carotid stenosis, and found that more patients had stroke during follow-up in the CAS group compared with the CEA group, but the rate of ipsilateral non-perioperative stroke was low in both the groups and none of the differences in the stroke outcome measures was significant.

The SPACE[72] trial found no significant difference between CAS and CEA in terms of 30-day ipsilateral ischemic stroke or mortality and 2-year perioperative stroke, mortality, or ipsilateral ischemic stroke. However, recurrent stenosis greater than 70% was significantly higher in the CAS group. No difference was found in the rates of ischemic stroke or mortality among patients treated with and without embolic protection. The SPACE-2 trial will address the question of intervention versus maximal medical therapy in asymptomatic patients.[73]

The EVA-3S trial randomly assigned patients with severe symptomatic stenosis to either CAS or CEA and found the incidence of any stroke or death at 30 days was significantly higher in the CAS group (9.6%) compared with the CEA group (3.9%), and the trial was stopped prematurely because of the excessive mortality in the CAS group. The secondary outcome of any perioperative stroke or mortality and any nonoperative ipsilateral stroke up to 4 years was also significantly higher in the CAS group (11.1%) compared with the CEA group (6.2%). Results of the trial are criticized because of the heterogeneity of stent types and interventionalists.

The SAPPHIRE trial tested the hypothesis that CAS was not inferior to CEA in patients at high risk for carotid surgery with symptomatic or asymptomatic stenosis.[74] Although there was a significant reduction in the primary composite end point (perioperative mortality, MI, or stroke) for CAS (12.2%) versus CEA (20.1%), there was no significant difference in major secondary end points (primary end points in addition to mortality or stroke between years 1 and 3) for CAS (24.6%) compared with CEA (26.2%), leading to the conclusion that CAS was not inferior to CEA in patients with asymptomatic disease.

The European International Carotid Stenting Study (ICSS/CAVATAS 2)[75] found that CAS had significantly higher rates for end points of any stroke (7.7 vs. 4.1%), any stroke and mortality (8.5 vs. 4.7%), and all-cause mortality (2.3 vs. 0.8%) compared with CEA, although there was no significant difference between CAS and CEA for disabling stroke (4.0 vs. 3.2%). The combined complications of stroke, MI, and death were significantly higher in the CAS group compared with the CEA group (8.5 vs. 5.2%). There was also a greater overall stroke risk with CAS (15.2%) compared with CEA (9.4%) after several years.[76] Therefore, in symptomatic patients with CAS, CEA remains the treatment of choice over CAS.

The CREST randomized over 2,500 patients to either CEA or CAS and was the first prospective, randomized controlled trial to indicate similar estimated 4-year rates of stroke, MI, or death between the CAS and CEA among men and women with either symptomatic or asymptomatic stenosis.[77] The incidence of perioperative stroke was higher in the CAS group, whereas the rate of perioperative MI was higher in the CEA group.

CREST also showed worse outcomes in elderly patients with CAS compared with CEA, leading to the recommendation that CAS could be reserved for younger patients and CEA for older patients in most clinical scenarios. In a meta-analysis comparing CAS to CEA in patients older than 80 years, the relative risk of MI or death at 30 days was similar, but the stroke rate was nearly three times higher for patients undergoing CAS (7.0%) compared with CEA (1.9%).[78] In addition, the risk of silent cerebral infarction on MRI after CAS is higher than CEA, but without measurable change in cognitive function.[79]

In a study of 17,716 patients with asymptomatic carotid stenosis treated with CEA and 3,962 treated with stenting, CAS was associated with a significantly higher risk of postoperative stroke or in-hospital death than CEA.[80] CAS has also been associated with a higher risk of perioperative mortality and stroke compared with CEA for all ages and clinical presentations.[81]

The efficacy of CAS in patients with symptomatic stenosis remains unclear because of the varying results in randomized trials, and rates of perioperative stroke and mortality exceeds those found in CEA.[82] Some studies suggest that the inconsistent results from randomized controlled trials of CAS are

related to variability in operator experience, utilization of embolic protection devices, and patient selection.[83] However, data may overestimate the efficacy of CAS in high-risk symptomatic patients.[84] Several advances in stenting are underway, including bare metal versus covered stents, tapering, and free cell, drug-eluting and cutting balloon. These all have conflicting evidence for risks and benefits and outcomes will need to be assessed.[85]

Systematic analysis of 4,399 patients comparing outcomes of repeated CEA and CAS for carotid restenosis after CEA showed no difference in the 30-day perioperative mortality, stroke, or TIA rates. Patients undergoing redo CEA had a higher incidence of cranial nerve injury and MI compared with CAS, but most cranial nerve injuries were reversible; furthermore, patients treated with CAS were more likely to develop restenosis than those treated with CEA in long-term follow-up.[86] In a similar study utilizing the Vascular Study Group of New England database, CEA and CAS showed statistically equivalent outcomes of stroke, death, MI within 30 days, cranial nerve injury, and restenosis $\geq$ 70% at 1-year follow-up in symptomatic and asymptomatic patients treated for restenosis after previous CEA. The risk of reintervention was increased compared with primary CEA.[87]

Systematic literature reviews revealed that CEA had lower rates of complications (such as minor stroke) compared with CAS and should remain the gold standard in the treatment of CAS in patients older than 80 years.[61,88,89] Large, controlled clinical trials are warranted to understand the safety and efficacy of CAS in the elderly. The relative risk of all-cause 5-year mortality is significantly higher in elderly patients with asymptomatic CAS who have atrial fibrillation or chronic renal failure undergoing carotid revascularization.[90]

Embolic protection devices can be either occlude or filter the blood to catch debris that is dislodged during stent placement and are categorized as either proximal or distal. Distal embolic protection devices must pass the stenosis, and therefore may dislodge emboli or require predilation before placement. Placement of the device may also result in vessel wall injury or induce vasospasm that can narrow the outflow and result in stroke. Proximal devices deploy occlusion balloons in the external and common carotid artery. After the stent is inserted, the proximal internal carotid artery is suctioned to remove debris before deflation. These devices may cause vessel wall injury or cerebral ischemia. In a study of over 10,000 stenting procedures, the use of proximal embolic protection devices during stenting was associated with low rates of perioperative stroke or mortality similar to distal devices.[91] A 2015 study suggests that there may be better cerebral embolic protection with proximal filters compared with distal filters in stenting, although this needs to be confirmed by larger studies.[92]

Broad application of CAS may also be limited by the higher initial procedural costs associated with this procedure,[93] only trivial differences in overall healthcare costs and quality-adjusted life expectancy exist between the CEA and CAS based on CREST data, and factors other than cost-effectiveness should be considered when deciding between treatment options in patients at standard risk for surgical complications.[94] CEA should be the standard of care for symptomatic patients unless medical comorbidities or unacceptable high risk for surgical therapy.

Trends

Despite the numerous randomized clinical trials and research dedicated to the study of revascularization techniques and outcomes of the management of carotid artery disease, there is little international consensus on optimal management. Professional society guidelines in the United States (American Heart Association, American Surgical Association) differ and sometimes contradict international guidelines.[95,96]

CEA is currently performed by various specialties with variable outcomes on perioperative stroke, mortality, and cost.[97] A lack of consensus among primary care physicians, cardiologists, vascular surgeons, neurologists, and interventionalists exists, likely because of the inability to identify high-risk stroke patients who will benefit from invasive therapies. It is critical that we establish randomized high-powered trials comparing CEA with both CAS and best medical therapy.[98] Appropriate stratification of patients by risk factor and diagnostic imaging is essential.

The utilization of CAS parallels the publication of randomized trials. After the SAPPHIRE trial of 2004, utilization of CAS doubled. After the publication of the CEA-favorable EVA-3S and SPACE in 2007, CAS decreased by 22%.[99] The introduction of CAS has lead to a decrease in the percentage of CEA and an increase in the number of CAS procedures performed in the context of all revascularization procedures, particularly after the CREST publication.[100,101]

Recommendations for Practice Guidelines

- Risk factors should be managed and medical management should be optimized.
- Best medical therapy should be offered to all patients.
- Until randomized controlled trials demonstrate that best medical therapy is superior to CEA or CAS in the prevention of stroke, guidelines should remain unchanged.
- Selection of patients for revascularization depends on comorbidities, life expectancy, and risks and benefits associated with the procedure.
- Screening for carotid disease can identify patients with significant asymptomatic stenosis who can undergo either CEA or CAS to prevent avoidable stroke.
- Prophylactic CEA can be performed in patients with $<$ 3% morbidity and mortality risk in asymptomatic patients with stenosis $>$ 60% by angiography or $>$ 70% by Doppler US.
- Prophylactic CAS can be performed in patients with asymptomatic stenosis $>$ 60% by angiography, 70% on Doppler US, or 80% on CTA or MRA.
- The data on CAS as an alternative to CEA in asymptomatic patients at high risk is unclear.
- For patients with symptomatic ipsilateral CAS $>$ 70%, CEA is recommended if the perioperative morbidity and mortality risk is $<$ 6%.

- For patients with symptomatic ipsilateral CAS between 50 and 69%, CEA is recommended if perioperative morbidity and mortality risk is < 6%.
- When the degree of stenosis is < 50%, there is no indication for revascularization by CEA or CAS.
- CEA should be performed within 2 weeks in symptomatic patients (TIA or stroke) and as early as 48 hours after onset of symptoms.
- CAS should be considered in patients with significant comorbidities (such as class III/IV angina or CHF, multivessel coronary artery disease, ejection fraction < 30%, recent MI, and severe COPD) and/or anatomic factors (high cervical lesion, intrathoracic lesion, prior CEA, prior radical neck, prior radiation therapy to neck, and contralateral occlusion).
- Practice guidelines should favor CEA over CAS and best medical therapy until recent randomized trials demonstrate their superiority over CEA for management of high-grade carotid stenosis.

Conclusion

Vascular surgeons are uniquely positioned to treat carotid artery disease through medical therapy, CEA, and carotid stenting. While the benefits of CEA with medical therapy have been described in several systematic reviews and randomized controlled trials, none compares CAS with medical therapy or CEA with current standard medical therapy. The application of best medical practice and current standards of care differ from those in published trials, and reduces the generalizability of those trials to our current practice. Future randomized controlled trials are needed to explore how revascularization interventions compare with current best available medical therapy.

The current evidence and position of the authors and the Society for Vascular Surgery is that CEA is superior to CAS. CREST, ICSS, and NSQIP data have demonstrated improved outcomes of CEA compared with previously published trials such as NASCET and ECST. ICSS showed that CEA had a fewer complications than CAS and was the preferred modality of treatment. CREST showed equivalency between CEA and CAS with respect to combined outcomes, with more MIs occurring after CEA and more strokes occupying after CAS. MIs appeared to be minor and affect quality of life less than strokes as determined by the SF-36 study in CREST. As the primary end points of the studies were to prevent stroke, it is recommended that CEA be employed for the majority of patients.

Although the CREST and ICSS results differ, it is important for surgeons to make clinical decisions based on the individual condition of each patient. The evidence shows that CEA is more effective in preventing stroke and stroke-related mortality than medical therapy alone in symptomatic patients with over 70% stenosis. Most vascular surgeons will perform CEA in symptomatic patients with stenosis less than 70%. Some patients who are unwilling or unable to undergo CEA may benefit from CAS. We believe that CAS can be adopted with a low complication rate in a selected subgroup of high-risk patients with significant comorbidities or anatomic risk factors, but CEA should remain the gold standard for revascularization. This current evidence should be incorporated into practice of the modern vascular surgeon.

Acknowledgments

This was an unfunded study. The authors have no conflicts of interest to disclose. We acknowledge the technical assistance of Christy Speer in the Division of Cardiothoracic Surgery at the University of Kentucky.

References

1 Centers for Disease Control and Prevention (CDC). Prevalence of disabilities and associated health conditions among adults—United States, 1999. MMWR Morb Mortal Wkly Rep 2001; 50(7):120–125 [Erratum in: MMWR Morb Mortal Wkly Rep 2001;50(8):149]
2 Fairhead JF, Rothwell PM. The need for urgency in identification and treatment of symptomatic carotid stenosis is already established. Cerebrovasc Dis 2005;19(6):355–358
3 Hunt JR. Hunt: the role of the carotid arteries: the role of the carotid arteries, in the causation of vascular lesions of the brain, with remarks on certain special features of the symptomatology. 1914. Am J Med Sci 2013;346(6):504–509
4 Fisher M. Occlusion of the internal carotid artery. AMA Arch Neurol Psychiatry 1951;65(3):346–377
5 Moniz E. Moniz E. L'encephalographie arterielle, son importance dans la localization des tumeurs cerebrales. Rev Neurol (Paris) 1927;2:72–90
6 Carrea RMM, Murphy G. Surgical treatment of spontaneous thrombosis of the internal carotid artery in the neck: carotid-carotidal anastomosis: report of a case. Acta Neurol Latinoam 1955;1:71–78
7 Eastcott HH, Pickering GW, Rob CG. Reconstruction of internal carotid artery in a patient with intermittent attacks of hemiplegia. Lancet 1954;267(6846):994–996
8 DeBakey ME. Successful carotid endarterectomy for cerebrovascular insufficiency. Nineteen-year follow-up. JAMA 1975; 233(10):1083–1085
9 Cooley DA, Al-Naaman YD, Carton CA. Surgical treatment of arteriosclerotic occlusion of common carotid artery. J Neurosurg 1956;13(5):500–506
10 Easton JD, Sherman DG. Stroke and mortality rate in carotid endarterectomy: 228 consecutive operations. Stroke 1977;8(5): 565–568
11 Easton JD, Saver JL, Albers GW, et al; American Heart Association; American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; Interdisciplinary Council on Peripheral Vascular Disease. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. Stroke 2009;40(6):2276–2293
12 Rohde LE, Lee RT. Pathophysiology of atherosclerotic plaque development and rupture: an overview. Semin Vasc Med 2003; 3(4):347–354

13 Poppert H, Sadikovic S, Sander K, Wolf O, Sander D. Embolic signals in unselected stroke patients: prevalence and diagnostic benefit. Stroke 2006;37(8):2039–2043
14 Hart RG, Ng KH. Stroke prevention in asymptomatic carotid artery disease: revascularization of carotid stenosis is not the solution. Pol Arch Med Wewn 2015;125(5):363–369
15 Saha SPWT, Whayne TF Jr, Mukherjee D. Evidence-based management of carotid artery disease. Int J Angiol 2010;19(1):e21–e24
16 Brott TG, Halperin JL, Abbara S, et al. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of NeuroInterventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery. J Am Coll Cardiol 2011;57(8):1002–1044
17 O'Donnell MJ, Hankey GJ, Eikelboom JW. Antiplatelet therapy for secondary prevention of noncardioembolic ischemic stroke: a critical review. Stroke 2008;39(5):1638–1646
18 Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002;324(7329):71–86
19 Raman G, Moorthy D, Hadar N, et al. Management strategies for asymptomatic carotid stenosis: a systematic review and meta-analysis. Ann Intern Med 2013;158(9):676–685
20 Saha SP, Rodgers-Fischl PM, Minion DJ, Ferraris VA, Davenport DL. Variability in carotid endarterectomy at a single medical center: an outcome and cost analysis. Int J Angiol 2012;21(4):209–212
21 Kansara A, Miller D, Damani R, Fuerst D, Silver B, Chaturvedi S. Variability in carotid endarterectomy practice patterns within a metropolitan area. Stroke 2012;43(11):3105–3107
22 Cao PG, de Rango P, Zannetti S, Giordano G, Ricci S, Celani MG. Eversion versus conventional carotid endarterectomy for preventing stroke. Cochrane Database Syst Rev 2001;(1):CD001921
23 Rerkasem K, Rothwell PM. Patch angioplasty versus primary closure for carotid endarterectomy. Cochrane Database Syst Rev 2009;(4):CD000160
24 Rerkasem K, Rothwell PM. Systematic review of randomized controlled trials of patch angioplasty versus primary closure and different types of patch materials during carotid endarterectomy. Asian J Surg 2011;34(1):32–40
25 Malas M, Glebova NO, Hughes SE, et al. Effect of patching on reducing restenosis in the carotid revascularization endarterectomy versus stenting trial. Stroke 2015;46(3):757–761
26 Ho KJ, Madenci AL, Semel ME, et al. Predictors and consequences of unplanned hospital readmission within 30 days of carotid endarterectomy. J Vasc Surg 2014;60(1):77–84
27 Leichtle SW, Mouawad NJ, Welch K, Lampman R, Whitehouse WM Jr, Heidenreich M. Outcomes of carotid endarterectomy under general and regional anesthesia from the American College of Surgeons' National Surgical Quality Improvement Program. J Vasc Surg 2012;56(1):81–8.e3
28 Lewis SC, Warlow CP, Bodenham AR, et al; GALA Trial Collaborative Group. General anaesthesia versus local anaesthesia for carotid surgery (GALA): a multicentre, randomised controlled trial. Lancet 2008;372(9656):2132–2142
29 Vaniyapong T, Chongruksut W, Rerkasem K. Local versus general anaesthesia for carotid endarterectomy. Cochrane Database Syst Rev 2013;12:CD000126
30 Schechter MA, Shortell CK, Scarborough JE. Regional versus general anesthesia for carotid endarterectomy: the American College of Surgeons National Surgical Quality Improvement Program perspective. Surgery 2012;152(3):309–314
31 Gomes M, Soares MO, Dumville JC, et al; GALA Collaborative Group. Cost-effectiveness analysis of general anaesthesia versus local anaesthesia for carotid surgery (GALA Trial). Br J Surg 2010;97(8):1218–1225
32 Paraskevas KI, Mikhailidis DP, Oikonomou K, Verhoeven EL. Local versus general anesthesia for carotid endarterectomy: issues beyond stroke, myocardial infarction, and death rates. Angiology 2012;63(6):405–408
33 de Weerd M, Greving JP, Hedblad B, et al. Prevalence of asymptomatic carotid artery stenosis in the general population: an individual participant data meta-analysis. Stroke 2010;41(6):1294–1297
34 Endarterectomy for asymptomatic carotid artery stenosis. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. JAMA 1995;273(18):1421–1428
35 Wu TY, Akopian G, Katz SG. Patients at elevated risk of major adverse events following endarterectomy for asymptomatic carotid stenosis. Am J Surg 2015;209(6):1069–1073
36 Bennett KM, Scarborough JE, Shortell CK. Predictors of 30-day postoperative stroke or death after carotid endarterectomy using the 2012 carotid endarterectomy-targeted American College of Surgeons National Surgical Quality Improvement Program database. J Vasc Surg 2015;61(1):103–111
37 Gupta PK, Ramanan B, Mactaggart JN, et al. Risk index for predicting perioperative stroke, myocardial infarction, or death risk in asymptomatic patients undergoing carotid endarterectomy. J Vasc Surg 2013;57(2):318–326
38 Halliday A, Mansfield A, Marro J, et al; MRC Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. Lancet 2004;363(9420):1491–1502
39 Rudarakanchana N, Dialynas M, Halliday A. Asymptomatic Carotid Surgery Trial-2 (ACST-2): rationale for a randomised clinical trial comparing carotid endarterectomy with carotid artery stenting in patients with asymptomatic carotid artery stenosis. Eur J Vasc Endovasc Surg 2009;38(2):239–242
40 Markus HS, King A, Shipley M, et al. Asymptomatic embolisation for prediction of stroke in the Asymptomatic Carotid Emboli Study (ACES): a prospective observational study. Lancet Neurol 2010;9(7):663–671
41 Chambers BR, Donnan GA. Carotid endarterectomy for asymptomatic carotid stenosis. Cochrane Database Syst Rev 2005;(4):CD001923
42 Naylor AR. Why is the management of asymptomatic carotid disease so controversial? Surgeon 2015;13(1):34–43
43 MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70-99%) or with mild (0-29%) carotid stenosis. European Carotid Surgery Trialists' Collaborative Group. Lancet 1991;337(8752):1235–1243
44 North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. N Engl J Med 1991;325(7):445–453
45 Morgenstern LB, Fox AJ, Sharpe BL, Eliasziw M, Barnett HJ, Grotta JC; North American Symptomatic Carotid Endarterectomy Trial (NASCET) Group. The risks and benefits of carotid endarterectomy in patients with near occlusion of the carotid artery. Neurology 1997;48(4):911–915
46 Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). Lancet 1998;351(9113):1379–1387
47 Rothwell PM, Eliasziw M, Gutnikov SA, Warlow CP, Barnett HJ. Sex difference in the effect of time from symptoms to surgery on benefit from carotid endarterectomy for transient ischemic attack and nondisabling stroke. Stroke 2004;35(12):2855–2861

48 Charmoille E, Brizzi V, Lepidi S, et al. Thirty-day outcome of delayed versus early management of symptomatic carotid stenosis. Ann Vasc Surg 2015
49 Rerkasem K, Rothwell PM. Systematic review of the operative risks of carotid endarterectomy for recently symptomatic stenosis in relation to the timing of surgery. Stroke 2009;40(10): e564–e572
50 Capoccia L, Sbarigia E, Speziale F, Toni D, Fiorani P. Urgent carotid endarterectomy to prevent recurrence and improve neurologic outcome in mild-to-moderate acute neurologic events. J Vasc Surg 2011;53(3):622–627, discussion 627–628
51 Rantner B, Schmidauer C, Knoflach M, Fraedrich G. Very urgent carotid endarterectomy does not increase the procedural risk. Eur J Vasc Endovasc Surg 2015;49(2):129–136
52 Barbetta I, Carmo M, Mercandalli G, et al. Outcomes of urgent carotid endarterectomy for stable and unstable acute neurologic deficits. J Vasc Surg 2014;59(2):440–446
53 Ferrero E, Ferri M, Viazzo A, et al. A retrospective study on early carotid endarterectomy within 48 hours after transient ischemic attack and stroke in evolution. Ann Vasc Surg 2014;28(1): 227–238
54 Alamowitch S, Eliasziw M, Barnett HJ; North American Symptomatic Carotid Endarterectomy Trial (NASCET); ASA Trial Group; Carotid Endarterectomy (ACE) Trial Group. The risk and benefit of endarterectomy in women with symptomatic internal carotid artery disease. Stroke 2005;36(1):27–31
55 Kuy S, Dua A, Desai SS, et al. Carotid endarterectomy national trends over a decade: does sex matter? Ann Vasc Surg 2014; 28(4):887–892
56 Hedayati N, Humphries MD, Zhou W. Gender and outcomes of carotid artery interventions. Vasc Endovascular Surg 2014;48(2): 99–105
57 Guzman RP, Weighell W, Guzman C, Rodriguez-Leyva D. Female sex does not influence 30-day stroke and mortality rates after carotid endarterectomy. Ann Vasc Surg 2014;28(1): 245–252
58 Jim J, Dillavou ED, Upchurch GR Jr, et al; SVS Outcomes Committee. Gender-specific 30-day outcomes after carotid endarterectomy and carotid artery stenting in the Society for Vascular Surgery Vascular Registry. J Vasc Surg 2014;59(3):742–748
59 Gasecki AP, Eliasziw M, Ferguson GG, Hachinski V, Barnett HJ; North American Symptomatic Carotid Endarterectomy Trial (NASCET) Group. Long-term prognosis and effect of endarterectomy in patients with symptomatic severe carotid stenosis and contralateral carotid stenosis or occlusion: results from NASCET. J Neurosurg 1995;83(5):778–782
60 Ballotta E, Toniato A, Da Roit A, Lorenzetti R, Piatto G, Baracchini C. Carotid endarterectomy for asymptomatic carotid stenosis in the very elderly. J Vasc Surg 2015;61(2):382–388
61 Reichmann BL, van Lammeren GW, Moll FL, de Borst GJ. Is age of 80 years a threshold for carotid revascularization? Curr Cardiol Rev 2011;7(1):15–21
62 Saha SPRA, Earle GF. Carotid endarterectomy in octagenarians and nonagenarians in a community hospital: An outcome analysis. Int J Angiol 2002;11:38–40. Available at http://link.springer.com/article/10.1007%2Fs00547-001-0051-y
63 Wu TY, Anderson NE, Barber PA. Neurological complications of carotid revascularisation. J Neurol Neurosurg Psychiatry 2012; 83(5):543–550
64 Hill MD, Brooks W, Mackey A, et al; CREST Investigators. Stroke after carotid stenting and endarterectomy in the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST). Circulation 2012;126(25):3054–3061
65 Vellimana AK, Yarbrough CK, Blackburn S, et al. Intravenous tissue-type plasminogen activator therapy is an independent risk factor for symptomatic intracerebral hemorrhage after carotid endarterectomy. Neurosurgery 2014;74(3): 254–261
66 Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. N Engl J Med 1995;333(24):1581–1587
67 Orlický M, Vachata P, Bartoš R, Waldauf P, Sameš M. A selective carotid artery shunting for carotid endarterectomy: prospective MR DWI monitoring of embolization in a group of 754 patients. J Neurol Surg A Cent Eur Neurosurg 2015;76(2):89–92
68 Galiñanes EL, Dombroviskiy VY, Hupp CS, Kruse RL, Vogel TR. Evaluation of readmission rates for carotid endarterectomy versus carotid artery stenting in the US Medicare population. Vasc Endovascular Surg 2014;48(3):217–223
69 Rambachan A, Smith TR, Saha S, Eskandari MK, Bendok BR, Kim JY. Reasons for readmission after carotid endarterectomy. World Neurosurg 2014;82(6):e771–e776
70 Ho KJ, Madenci AL, McPhee JT, et al. Contemporary predictors of extended postoperative hospital length of stay after carotid endarterectomy. J Vasc Surg 2014;59(5):1282–1290
71 Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomised trial. Lancet 2001; 357(9270):1729–1737
72 Ringleb PA, Allenberg J, Brückmann H, et al; SPACE Collaborative Group. 30 day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomised non-inferiority trial. Lancet 2006; 368(9543):1239–1247
73 Reiff T, Stingele R, Eckstein HH, et al; SPACE2-Study Group. Stent-protected angioplasty in asymptomatic carotid artery stenosis vs. endarterectomy: SPACE2 - a three-arm randomised-controlled clinical trial. Int J Stroke 2009;4(4):294–299
74 Yadav JS, Wholey MH, Kuntz RE, et al; Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy Investigators. Protected carotid-artery stenting versus endarterectomy in high-risk patients. N Engl J Med 2004;351(15): 1493–1501
75 Ederle J, Dobson J, Featherstone RL, et al; International Carotid Stenting Study investigators. Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomised controlled trial. Lancet 2010;375(9719): 985–997 [Erratum in Lancet 2010;376(9735):90]
76 Bonati LH, Dobson J, Featherstone RL, et al; International Carotid Stenting Study investigators. Long-term outcomes after stenting versus endarterectomy for treatment of symptomatic carotid stenosis: the International Carotid Stenting Study (ICSS) randomised trial. Lancet 2015;385(9967):529–538
77 Brott TG, Hobson RW II, Howard G, et al; CREST Investigators. Stenting versus endarterectomy for treatment of carotid-artery stenosis. N Engl J Med 2010;363(1):11–23
78 Usman AA, Tang GL, Eskandari MK. Metaanalysis of procedural stroke and death among octogenarians: carotid stenting versus carotid endarterectomy. J Am Coll Surg 2009;208(6):1124–1131
79 Kuliha M, Roubec M, Procházka V, et al. Randomized clinical trial comparing neurological outcomes after carotid endarterectomy or stenting. Br J Surg 2015;102(3):194–201
80 Choi JC, Johnston SC, Kim AS. Early outcomes after carotid artery stenting compared with endarterectomy for asymptomatic carotid stenosis. Stroke 2015;46(1):120–125
81 McDonald RJ, McDonald JS, Therneau TM, Lanzino G, Kallmes DF, Cloft HJ. Comparative effectiveness of carotid revascularization therapies: evidence from a National Hospital Discharge Database. Stroke 2014;45(11):3311–3319
82 Kolkert JL, Meerwaldt R, Geelkerken RH, Zeebregts CJ. Endarterectomy or carotid artery stenting: the quest continues part two. Am J Surg 2015;209(2):403–412
83 Al-Damluji MS, Nagpal S, Stilp E, Remetz M, Mena C. Carotid revascularization: a systematic review of the evidence. J Interv Cardiol 2013;26(4):399–410

84 Yoshida S, Bensley RP, Glaser JD, et al. The current national criteria for carotid artery stenting overestimate its efficacy in patients who are symptomatic and at high risk. J Vasc Surg 2013;58(1): 120–127
85 Morr S, Lin N, Siddiqui AH. Carotid artery stenting: current and emerging options. Med Devices (Auckl) 2014;7:343–355
86 Tu J, Wang S, Huo Z, Wu R, Yao C, Wang S. Repeated carotid endarterectomy versus carotid artery stenting for patients with carotid restenosis after carotid endarterectomy: Systematic review and meta-analysis. Surgery 2015;157(6):1166–1173
87 Fokkema M, de Borst GJ, Nolan BW, et al; Vascular Study Group of New England. Carotid stenting versus endarterectomy in patients undergoing reintervention after prior carotid endarterectomy. J Vasc Surg 2014;59(1):8–15.e1, 2
88 Kastrup A, Schulz JB, Raygrotzki S, Gröschel K, Ernemann U. Comparison of angioplasty and stenting with cerebral protection versus endarterectomy for treatment of internal carotid artery stenosis in elderly patients. J Vasc Surg 2004;40(5):945–951
89 Seretis K, Goudakos I, Vlachakis I, Anthimidis G, Papadimitriou D. Carotid artery disease in octogenarians: endarterectomy or stenting? Int Angiol 2007;26(4):353–360
90 Qureshi AI, Chaudhry SA, Qureshi MH, Suri MF. Rates and predictors of 5-year survival in a national cohort of asymptomatic elderly patients undergoing carotid revascularization. Neurosurgery 2015;76(1):34–40, discussion 40–41
91 Giri J, Parikh SA, Kennedy KF, et al. Proximal versus distal embolic protection for carotid artery stenting: a national cardiovascular data registry analysis. JACC Cardiovasc Interv 2015;8(4):609–615
92 Gargiulo G, Stabile E, Sannino A, Perrino C, Trimarco B, Esposito G. Embolic protection devices during carotid artery stenting: Is there a difference between proximal occlusion and distal filter? Int J Cardiol 2015;187:592–593
93 Khan AA, Chaudhry SA, Sivagnanam K, Hassan AE, Suri MF, Qureshi AI. Cost-effectiveness of carotid artery stent placement versus endarterectomy in patients with carotid artery stenosis. J Neurosurg 2012;117(1):89–93
94 Vilain KR, Magnuson EA, Li H, et al; CREST Investigators. Costs and cost-effectiveness of carotid stenting versus endarterectomy for patients at standard surgical risk: results from the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST). Stroke 2012;43(9):2408–2416
95 Meschia JF, Bushnell C, Boden-Albala B, et al; American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Functional Genomics and Translational Biology; Council on Hypertension. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/ American Stroke Association. Stroke 2014;45(12):3754–3832
96 Liapis CD, Bell PR, Mikhailidis D, et al; ESVS Guidelines Collaborators. ESVS guidelines. Invasive treatment for carotid stenosis: indications, techniques. Eur J Vasc Endovasc Surg 2009;37(4, Suppl):1–19
97 AbuRahma AF, Srivastava M, Hass SM, et al. Practice patterns of carotid endarterectomy as performed by different surgical specialties at a single institution and the effect on perioperative stroke and cost of preoperative imaging. J Vasc Surg 2014;60(5): 1232–1237
98 Naylor AR, Gaines PA, Rothwell PM. Who benefits most from intervention for asymptomatic carotid stenosis: patients or professionals? Eur J Vasc Endovasc Surg 2009;37(6):625–632
99 Dumont TM, Rughani AI. National trends in carotid artery revascularization surgery. J Neurosurg 2012;116(6):1251–1257
100 McDonald JS, McDonald RJ, Fan J, Lanzino G, Kallmes DF, Cloft HJ. Effect of CREST Findings on Carotid Revascularization Practice in the United States. J Stroke Cerebrovasc Dis 2015;24(6):1390–1396
101 Ali A, O'Callaghan A, Moloney T, Kelly C, Monoley D, Leahy A. The effect of carotid stenting on endarterectomy practice - A single institution experience. Surgeon 2014