Review Article

Carotid Artery Stenting, Endarterectomy, or Medical Treatment Alone: The Debate Is Not Over

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Abstract

The management of carotid artery stenosis reduces the risk of stroke and its related deaths. Management options include risk factor modification and medical therapy, carotid endarterectomy (CEA), and carotid artery stenting (CAS). Although several randomized controlled trials (RCTs), mostly conducted in late-1980s and mid-1990s, have proved CEA to be effective in the prevention of ipsilateral ischemic events in selected patients with carotid artery stenosis, aggressive risk factor modification and medical therapy with recently introduced antiplatelet agents, statins, and more effective antihypertensive medications may have reduced compelling indications for immediate surgery in asymptomatic populations. Also recently, due to improvements in percutaneous techniques and carotid stents, CAS has received wide attention as a potential alternative to CEA. Herein, we review the recent data on the management options of carotid artery stenosis and seek to identify the most appropriate treatment strategy in selected patients with carotid artery stenosis.

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Introduction

Stroke is the third leading cause of death in the United States and the leading cause of death and hospitalization in nearly all European countries.[1, 2] Prevention of stroke constitutes an important medical concern because patients who survive a stroke are often left with significant disabilities. The incidence of stroke in Iran is considerably greater than that in most Western countries, with stroke occurring at younger ages;[3] the burden of stroke, therefore, appears even more challenging in this country. Not only is it associated with poor patient outcomes, but it also increases resource consumption and overall costs.[4, 5]

Carotid stenosis is defined as a narrowing of the common or internal carotid artery; it is a progressive narrowing of the carotid arteries in a process called atherosclerosis. Carotid artery atherosclerosis is a major cause of ischemic stroke and its related morbidity and mortality.[6] Among patients with carotid artery stenosis, the risk of stroke mostly depends on symptom status and stenosis severity.[7]

The risk of stroke in patients with carotid artery stenosis is also influenced by other factors, including the clinical features of transient ischemic attack (TIA), presence of silent cerebral infarction, contralateral disease, intracranial disease, extent of intracranial collaterals, and plaque morphology. The 3-year risk of ipsilateral stroke was found to be 10% following retinal TIAs and 20.3% after hemispheric TIAs in the North American Symptomatic Carotid Endarterectomy

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Trial (NASCET) study.[8] The three-year risk of stroke in patients with carotid stenosis in the range of 85% to 99% has shown a raise from 25% to 46% in the presence of concomitant intracranial disease.[9] The presence of silent cerebral infarction in patients with asymptomatic carotid stenosis, with the estimated prevalence of 15% to 20%, seems to be related to a higher risk of subsequent stroke.[10] The annual stroke risk in patients with internal carotid artery (ICA) occlusion is affected by the number of intracranial collaterals.[11] In patients with severe carotid stenosis (70% to 99%), the risk of stroke in the presence of contralateral carotid occlusion may rise up to more than twofold,[12] while collateral circulation may decrease the risk by over twofold.[13] In patients with carotid stenosis, the influence of carotid plaque morphology, including the presence of hypoechoic or echolucent plaque[14, 15] and plaque ulceration,[16, 17] on the risk of stroke has been suggested, irrespective of the degree of stenosis.

The management of carotid stenosis, therefore, lies in reducing the risk of stroke and its related deaths.[18] Management strategies for carotid atherosclerosis include risk factor modification and medical therapy, carotid endarterectomy (CEA), and carotid artery stenting (CAS). Several randomized controlled trials (RCTs), mostly conducted in late-1980s and mid-1990s, have proved CEA to be effective in the prevention of ipsilateral ischemic events in selected patients with carotid stenosis.[19] However, aggressive risk factor modification and medical therapy with recently introduced antiplatelet agents, statins, and more effective antihypertensive medications may have reduced compelling indications for immediate surgery in asymptomatic populations. Also recently, due to improvements in percutaneous techniques and carotid stents, CAS has received wide attention as a potential alternative to CEA. The main aims of this review are to summarize the current data on the management strategies of carotid artery stenosis and to identify the most appropriate treatment option in selected patients with carotid artery stenosis.

Symptomatic vs. asymptomatic carotid-artery atherosclerosis

With the advancing age of the general population and the availability of noninvasive imaging studies, carotid artery stenosis is currently commonly observed in general medical practice. In the general population, the prevalence of asymptomatic carotid artery stenosis of 50% or greater increases with age from 0.5% in individuals below 50 years to 5% to 10% in individuals over 65 years of age.[20, 21] A clear distinction between symptomatic and asymptomatic carotid artery stenosis is of crucial importance because the treatment course differs markedly. Stenosis is considered symptomatic on condition that transient or permanent focal neurologic symptoms associated with the ipsilateral retinal or cerebral ischemia has occurred. Symptoms include ipsilateral transient visual obscuration (amaurosis fugax) from retinal ischemia; contralateral weakness or numbness of a limb or the face, or both; dysarthria; defect in visual field; and aphasia if the dominant (mostly left) hemisphere is involved. Stenosis is considered asymptomatic when these symptoms do not occur. Moreover, nonspecific symptoms found in daily clinical practice during the assessment of ill-defined episodes of syncope or near-syncope, dizziness, generalized subjective weakness, blurry vision, or transient positive visual phenomena (such as "floaters" or "stars") do not qualify as symptomatic ischemic events even in the presence of high-grade carotid artery stenosis.

As mentioned before, in patients with carotid artery stenosis, the risk of stroke is mostly dependent on symptom status and stenosis severity. In symptomatic patients, the stroke risk is much higher than asymptomatic patients, and the risk is highest immediately following the initial ischemic event.[7] In the NASCET the risk of stroke in the first year was 11% for carotid stenosis 70% to 79% and 35% for carotid stenosis ≥ 90%.[22, 23] Surprisingly, patients with near total occlusion showed a stroke risk of 11% at 1 year.[24] In asymptomatic patients, the annual risk of stroke was quite lower; it was less than 1% for carotid stenosis ≤ 60% and 1% to 2.4% for carotid stenosis > 60%,[10, 25] and in the ACST (Asymptomatic Carotid Surgery Trial),[25] no relationship was found between the risk of stroke with increasing stenosis severity from 60% to 99%. The low risk of ischemic stroke in patients with a high degree of stenosis suggests that low post-stenotic flow may protect the brain from infarction by lowering the frequency of cerebral embolism.[26]

In addition to the degree of stenosis, a high frequency of micro-emboli at transcranial Doppler,[27] a rapid progression of stenosis,[28, 29] and morphology of carotid plaques by ultrasound[30] have been associated with a higher risk of stroke.

However, the condition is quite different for the perioperative stroke rate in the coronary artery bypass graft (CABG) candidates in whom the high incidence of asymptomatic carotid stenosis can be found with a prevalence of 17% to 22% for carotid stenosis > 50% and 6% to 12% for carotid stenosis > 80%.[7] In a review of the literature, Naylor et al.[31] showed that the overall risk of perioperative stroke after CABG was 2%; the risk of stroke was 1.0% for patients undergoing CABG with normal carotid arteries (or for carotid stenosis < 50%); the risk increased to 3% among patients with asymptomatic ipsilateral carotid stenosis of 50 to 99%, 5% among those with bilateral stenoses of 50 to 99%, and 7% among those with carotid occlusion. In patients with carotid stenosis, 60% of perioperative infarcts were attributed to causes other than carotid disease.[31] Currently, few data provide support for the routine use of preoperative prophylactic revascularization in patients with asymptomatic carotid stenosis undergoing major cardiovascular surgery.[31]

In a previous study on symptomatic patients with > 60% stenosis and asymptomatic patients with > 80% stenosis in either internal or common carotid artery, one of the authors found the risk of stroke to be 7% in patients scheduled to undergo staged carotid stenting after CABG.[32]

Risk factor modification

With the growing availability of different noninvasive diagnostic imaging, most patients with carotid artery disease are asymptomatic. The typical therapeutic option in asymptomatic patients is intensive medical treatment for reducing the risk factors of atherosclerosis. Hypertension, cigarette smoking, diabetes mellitus, and hyperlipidemia are among the preventable causes of stroke.

Hypertension has been considered an underlying modifiable risk factor in almost 70% of strokes.[33] Elevation in systolic blood pressure (SBP) or diastolic blood pressure (DBP) increases the incidence of ischemic or hemorrhagic stroke in individuals of both sexes and all ages.[34] Antihypertensive therapy should be targeted at maintaining the blood pressure below 130/80 mm Hg, especially if there is evidence of diabetes or kidney disease, to obtain the maximal stroke-prevention benefit.[35]

A clear link between lower lipid levels with the development of carotid stenosis and prevention of stroke is also apparent; for every 10 mg/dl rise in cholesterol level, the relevant odds ratio for carotid stenosis would be 1.10.[36] Although the extent of benefit is still unclear, another advantage of statins may be related to the secondary effects that potentially contribute to carotid plaque regression, suggesting the possibility of vascular remodeling as a causative factor.[37]

Cigarette smoking has been associated with a higher risk of accelerated atherosclerosis, and it approximately doubles the risk of ischemic and hemorrhagic stroke being directly proportional to the number of cigarettes smoked.[38, 39] Smoking cessation is imperative, and registration in a formal effective smoking cessation program, including nicotine replacement, bupropion, social support, and skills training should be considered.

Diabetes is a potent independent risk factor for stroke; however, an association exists between the interaction of diabetes and hypertension and higher risk of stroke; sixfold higher than in normal patients, and twofold higher than normotensive diabetics.[7] The usefulness of tight glycemic control in patients with diabetes mellitus and established atherosclerotic plaque for stroke reduction is less certain.

Antiplatelet therapy

Once aggressive risk factor modification has been performed, all patients with carotid artery disease should take antiplatelet therapy. For asymptomatic patients, the main treatment approach for the primary prevention of cardiovascular events is antiplatelet therapy. For symptomatic patients, antiplatelet therapy is indicated on the basis of large stroke prevention studies, including patients with different stroke etiologies.[40-44] Aspirin therapy using different doses has been demonstrated to lower the risk of TIA, stroke, and death as single therapy in high-risk patients.[45] The Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) trial further showed that in symptomatic patients, placing patients on combination therapy with clopidogrel and aspirin may reduce the incidence of asymptomatic embolization in comparison with aspirin alone.[46] Based on the clinical outcomes in the Clopidogrel Versus Aspirin in Patients at Risk for Ischemic Events (CAPRIE) trial,[47] clopidogrel was more effective than ASA in preventing the primary study endpoint, a composite of ischemic stroke, myocardial infarction, or vascular death. The investigators found a significant 8.7% relative-risk reduction for clopidogrel over ASA.

Optimal medical treatment

Since 2002, new important findings of the stroke prevention offered by existing and new drugs have revolutionized the concept of "Optimal Medical Treatment".[48-54]Most important have been antiplatelet drugs (clopidogrel),[47] angiotensin converting enzyme inhibitors with possible unique cardioprotective properties,[55] and the anti-inflammatory effects of statins as effective and better tolerated lipid-lowering drugs[56] appear to be as significant as their lipid lowering effects.[57, 58] With regards to these new information, one recently published systematic review concluded that medical intervention alone is currently best for prevention of stroke associated with asymptomatic severe carotid stenosis.[59] Therefore, to compare CEA with optimal medical therapy in prevention of stroke among both symptomatic and asymptomatic patients, further studies are required to include treatment arm of medical therapy alone using new drugs with optimal dose.

Revascularization: CEA or CAS?

Qualifying and independent neurology audit

As stroke is a recognized risk of CAS and CEA, operators must have appropriate experience to achieve better outcomes. Especially for relatively new technique like CAS operators should previously have obtained a high level of proficiency in catheter-based intervention, complete dedicated training, and be credentialed at their hospital to maximize patient safety. Physicians interested in CAS represent a variety of subspecialties with different backgrounds, experience, and expertise. Another important issue in outcome assessment

is that reports in CAS studies should be independently neurologically evaluated because without this neurologic audit, neurologic events will be underestimated. A meta-analysis[60] of published CEA outcomes on ~16,000 patients showed overall risk of stroke and/or death of 5.6% in line with present guidelines; however, the risk varied systematically with the methods and the authorship of the study. The risk of stroke and/or death was highest (7.7%) in studies wherein patients were audited by a neurologist after surgery and lowest (2.3%) in studies with single surgeon author(s); this heterogeneity of risk of stroke and/or death was statistically significant ($P < 0.001$). As Rothwell et al.[60] mentioned the most likely possible explanation for this disparity is diagnostic bias. Surgeons may simply fail to diagnose minor or unusual strokes as compared to neurologists. A separate analysis using a various data-set confirmed the necessity of neurologic audit in outcomes assessment.[61] Participants are required to be assessed before, after (typically within 24 hours or prior to discharge), and at pre-specified endpoint intervals (e.g., 30 days, 6 months, 1 year, etc).

Carotid endarterectomy

Eastcott, Pickering, and Rob[62] reported the first successful CEA in1954; since then surgery has been a longstanding treatment option for carotid atherosclerosis along with risk factor modification and medical therapy. The first follow-up results were reported by Michael DeBakey[63] in 1975 which suggested the durability of surgery over a 19-year period. The first published trials comparing surgery versus medical therapy for treatment of carotid atherosclerosis came via the Mayo Asymptomatic Carotid Endarterectomy (MACE) trial[64] and the Carotid Artery Stenosis with Asymptomatic Narrowing Operation Versus Aspirin (CASANOVA) trial,[65] which both ultimately were considered suboptimal because of failure in study design.

Well-designed RCTs have demonstrated CEA to diminish the incidence of stroke and death both in symptomatic and asymptomatic patients.[66, 67] In patients with symptomatic carotid artery stenosis, CEA surgery has been established as the gold standard of care according to 2008 practice guidelines from the National Institute for Health and Clinical Excellence[68] and the Society for Vascular Surgery,[69] as well as strong published evidence.[22, 70, 71] However, it is less clear how to approach asymptomatic patients with carotid artery stenosis. In patients with carotid artery stenosis and no symptom, risk for stroke is not as great as patients with symptoms but greater than patients without stenosis. The question is that whether the benefits of CEA justify the risks of surgery patient in asymptomatic patients?

The efficacy of surgery for critical asymptomatic stenosis was first truly evidenced in the Veterans Affairs Cooperative Trial, which randomly assigned a sample of 444 asymptomatic men with > 50% carotid stenosis to aspirin alone or aspirin plus CEA. The study evaluated the primary endpoints of TIA, amaurosis fugax, and cerebrovascular accident (CVA) for 48 months. The findings indicated a statistically significant reduce in the incidence of ipsilateral stroke and TIA in the combination group with no significant difference in mortality at 30 days and 48 months;[72] however, the best outcome-based data for patients with asymptomatic carotid stenosis come from the Asymptomatic Carotid Atherosclerosis Study (ACAS)[10] and the Asymptomatic Carotid Surgery Trial (ACST),[25] and guidelines have been largely based on the ACAS[10] findings in conjunction with other smaller trials.[72, 73]

The ACAS[10] assigned 1662 patients with > 60% stenosis per ultrasound or arteriography to receive either aspirin alone or aspirin and CEA. The primary endpoint was assessment of cerebral infarction in the study artery or perioperative stroke or death for a median follow-up period of 2.7 years. The study reported a 47% relative reduction in the risk of ipsilateral stroke and perioperative death in favor of surgery group, although a 5-year risk of ipsilateral stroke without the operation of only 11% (5.1% vs. 11%). Preliminary evidence also suggested that men appreciated a more absolute risk lowering from surgery than women but this difference did not reach statistical significance.[10] The findings resulted in marked rise in the rates of endarterectomy for asymptomatic stenosis in some countries, most notably in the United States that at least half of the approximate 150, 000 endarterectomies in total are performed for asymptomatic stenoses.[74] There were two concerns with regards to ACAS results. First, very low operative risks in ACAS (1.5% for stroke and death; and 0.14% for death) could not be matched in routine clinical practice (the study only accepted surgeons with an excellent safety record, rejecting 40% of initial applicants and subsequently disapproving surgeons who had adverse operative outcomes during the trial).[75] Second, it was believed not to be cost-effective (it was estimated that 40 operations were needed to prevent 1 disabling or fatal stroke after 5 years). As a result, the degree to which the ACAS findings can be generalized to routine clinical practice remained uncertain.

From 1993 to 2003, the largest multicenter trial studying the benefit of surgery for asymptomatic patients, i.e. ACST,[25] randomized 3120 patients with > 60% stenosis per ultrasound (mainly asymptomatic; only 12% had symptoms at least 6 month previously) and assigned groups to immediate CEA (88% by 1 year) versus postponed surgery with a mean follow-up of 3.4 years. Surgeons were asked to provide evidence of an operative risk of ≤ 6% for their last 50 patients having an endarterectomy for asymptomatic stenosis, but none were excluded during the trial based on their operative risk. Selection of patients was on the basis of "Uncertainty Principle," with very few exclusion criteria. Carotid stenosis evaluated by Doppler ultrasonography. Despite the differences in methods, ACST[25] replicated the

results of ACAS[10] demonstrating a 5-year risk reduction for perioperative stroke or death in the immediate CEA group as compared to the deferral group (6.4% vs. 11.8%).A similar reduction in fatal or disabling stroke was also found in the immediate CEA group whereas in ACAS,[10] there was a 2.7% reduction in the absolute risk of disabling or fatal stroke with surgery but not statistically significant (P = 0.26). A notable finding in this study was a 2-year delayed benefit in the surgery group, with worse outcomes previous to this period.

ACAS[10] and ACST[25] trials revealed benefit for CEA in asymptomatic patients with carotid stenosis greater than 60%. However, even with the newly published ACST[25] the definition of optimal medical treatment evolved during study but the rate for taking drugs such as lipid-lowering agents was still quite low; the patients in the final cohort were given antiplatelet therapy (up to 90%), antihypertensive therapy (81%), and lipid-lowering therapy (70%). Given the low risk of stroke in asymptomatic patients, some experts recommend surgery only when the degree of stenosis is more than 80 percent, as was demonstrated by the investigators of European Carotid Surgery Trial (ECST).[70] Moreover, while evaluating the operational advantage in patients with carotid stenosis, other inherent risk of surgery, including postoperative complications such as wound hematomas, hypotension, cranial nerve injuries, seizures, hyperperfusion syndrome, and intracerebral hemorrhage need to be taken into consideration.[76]

Patients at high risk for CEA

Serious risks are associated with carotid endarterectomy. Even though the primary purpose of carotid artery revascularization is stroke prevention, stroke is the most serious postoperative risk. Other major complications include heart attack or other heart problems, death, breathing difficulties, high blood pressure, nerve injury, intracranial hemorrhage, and restenosis. The risks of carotid endarterectomy surgery are dependent on factors which listed in Table 1.

Internal and external evaluation

The skill and experience levels of the surgeons treating the patient are of most importance. When the surgeon performing the operation has acknowledged skills and experience, the possibility of complications is lower. According to the American Heart Association (AHA) expert consensus panel, surgery is not recommended while the predicted perioperative risk of stroke or death be greater than 3% for asymptomatic patients, greater than 6% for symptomatic patients, and greater than 10% for repeat CEA Hospitals should also be able to prove that fewer than 3% of their patients undergoing endarterectomy have had complications. Thus, both internal and external evaluations are needed in assessment for every single operator and for each hospital, and the same is true for CAS.

Carotid artery stenting

The benefits of CAS are numerous. Stenting is performed under local anesthesia which permits continuous neurologic monitoring, and involves only a small opening (< 3 mm in diameter) in the femoral artery comparing the much larger open incision in the neck needed for CEA. Wound infection, scarring, and other major surgical complications are significantly less frequent and complete recovery time is

Table 1. High-risk criteria for carotid endarterectomy (CEA) operation*

Category I Anatomic and lesion-related risk factors	Category II Medical risk factors	Category III Surgeon- and institutional-related risk factors
Previous radiation treatment to the neck or radical neck dissection	Age ≥ 80 years	Surgeon complication rates
Target lesion is at or above the second vertebral body (level of jaw)	Congestive Heart failure New York Heart Association (NYHA) Functional Class III or higher	> 3% for asymptomatic patients
Inability to extend the head due to cervical arthritis or other cervical disorders	Dialysis dependent renal failure (serum creatinine level of ≥ 3)	> 6% for symptomatic patients
Tracheostomy or tracheal stoma	Canadian Cardiovascular Society Angina Classification III or higher, or unstable angina	> 10% for repeat CEA
Laryngectomy	Requires coronary artery bypass surgery, cardiac valve surgery, peripheral vascular surgery, or abdominal aortic aneurysm repair within 60 days	
Contralateral laryngeal nerve palsy	MI within previous 6 wks	
Severe tandem lesions	Severe pulmonary disease, including at least one of the following: requires chronic O_2 therapy; resting $PO_2 \leq 60$ mm Hg, Hematocrit ≥ 50%, FEV1 or DLCO ≤ 50% of normal	
Occlusion after carotid stenting	Left ventricular ejection fraction < 35%	
Previous CEA with significant restenosis		
Distal aneurysm		
Total occlusion of the contralateral carotid artery		
Common carotid artery stenosis below the clavicle		

*The subject must fulfill at least one of the criteria in either category listed above to be considered high-risk for CEA
MI, Myocardial infarction; FEV1, Forced expiratory volume in 1 second; DLCO, Diffusing capacity of the lung for carbon monoxide

much shorter with stenting (averaging 2 to 4 days, vs. 2 to 4 weeks with surgery). As a result, CAS is progressively being considered as a minimally invasive alternative to surgery, particularly in patients at high risk for CEA. The first carotid balloon angioplasty was performed in 1979 but the first balloon-expandable stent was deployed in the carotid artery in 1989; risk of embolic stroke and compression of the stent restricted early enthusiasm.[77-80] Since then, as the design of both stents and distal-protection devices and in turn the outcomes have improved, there has been a rapid growth in the number of CAS for routine clinical use worldwide.[81] Notably, there are no randomized studies comparing CAS with and without distal protection devices; however, the use of these embolic devices seems to be essential in diminishing the risk of stroke during CAS.[82] Also, the same as for CEA, careful neurological audit is required before and after CAS.

RCTs comparing CAS vs. CEA

The first prospective randomized singe-center study comparing coronary angioplasty versus CEA in symptomatic patients was the Leicester trial.[79] The trial randomized low risk patients with carotid stenoses >70% but the study was stopped after allocation of only 17 participants because interim analysis revealed that 70% of all patients in the angioplasty arm had neurologic complications while CEA was performed uneventfully.

The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) was the first international multicenter trial comparing the late results of angioplasty with CEA in symptomatic patients. The study involved the random assignment of 504 patients with symptomatic or asymptomatic carotid stenosis who were equally suitable for endovascular treatment or surgery to undergo either angioplasty, with or without stenting, or surgery. Notably, stents were applied in only 26% of patients treated endovascularly and most patients included were symptomatic (96% for CEA arm and 97% for CAS arm). The 30-day rates of stroke and death were not significantly different in the two groups. However, the study lacked strict inclusion and exclusion criteria.[83] At 1 year follow-up, severe carotid restenosis by using ultrasonography was detected more commonly in CAS as compared to CEA group (14% vs. 4%, $p < 0.001$).[84] Although in the first year, the incidence of recurrent ipsilateral stroke seemed to be higher in cases of stenoses occurring after CAS vs. those after CEA; survival analysis at 3-year follow-up demonstrated no difference in the occurrence of ipsilateral stroke between two groups. The authors suggested that there was a comparable major risk and effectiveness for CAS and CEA in treatment of carotid stenosis but minor complications were lower with CAS treatment. Noteworthy, the wide confidence intervals of stroke rate in this study indicate that it is not possible to rule out a potentially significant advantage of one treatment over another.

The results of Kentucky study, a single-center randomized trial comparing CAS and CEA, were published in 2001 (Kentucky 1)[85] and 2004 (Kentucky 2).[86] Kentucky 1 and Kentucky 2 focused on symptomatic and asymptomatic patients, respectively. The trial consisted of a symptomatic arm and an asymptomatic arm; in either of these two arms patients were randomized between stenting and surgery. In the symptomatic arm, one patient died because of myocardial infarction immediately after carotid endarterectomy. There were no other deaths or strokes in symptomatic or asymptomatic patients treated with stenting or surgery. Even though both reports suggested low complication rates for either treatment options, the small sample size make the results hard to interpret.

The WALLSTENT study was another multicenter trial which enrolled patients with symptomatic carotid stenosis to either CAS or CEA.[87] Two hundred nineteen patients were randomized to CAS (n = 107) or CEA (n = 112). The 30-day periprocedural rates of stroke and death was significantly higher in the CAS group than in those with CEA (12.1% vs. 4.5%; $P = 0.049$). The study suspended prematurely and no further results from this trial have been published.

In the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial,[88] 334 dominantly asymptomatic patients (71%) were randomly assigned to undergo either CAS or CEA. The primary end point of stroke, death, or myocardial infarction within 30 days after the procedure, or ipsilateral stroke between 31 days and 1 year after, strongly favored stenting over surgery. The cumulative incidence of a major cardiovascular event during 1 year including myocardial infarction within 30 days following the procedure and death or ipsilateral stroke between 31 days and 1 year after either intervention was the primary endpoint of the study. The authors obtained follow-up data at 3 years for 78% of the participants, and they did not find a significant difference in the cumulative incidence of major cardiovascular events between the two treatment groups. The 3-year incidence of stroke (7.1% vs. 6.7%; p = NS) and target vessel revascularization (3.0% vs. 7.1%; p = NS) was similar for CAS and CEA.

The SAPPHIRE[88, 89] is the only randomized clinical trial in high-risk patients (defined as those with age > 80 years, congestive heart failure, chronic obstructive lung disease, previous endarterectomy with restenosis, previous radiation or neck surgery, or distal or proximal lesions) that compared contemporary CAS with protected device against CEA. The results of the study; however, may not be generalizable to patients at low-to-moderate surgical risk for CEA. In addition, since most of the patients initially considered for the trial were too high risk for CEA and excluded later, recruitment slowed and the trial was terminated prematurely; this fact may have influenced the power of the study and interpretation of findings.The study was also limited by the low rate of follow-up not equally distributed between two

groups.

In 2005, a Cochrane analysis assessing data from theses initial RCTs, i.e. Leicester, CAVATAS, Kentucky, WALLSTENT, and SAPPHIRE, indicated that all were equivocal with regard to differences in outcome or major risks between CAS versus CEA.[87] However, among them, SAPPHIRE[88, 89] was truly a landmark study that more clearly defined the role of CAS in carotid disease. SAPPHIRE study is now the standard for the acceptance of CAS by the Food and Drug Administration (FDA) for both symptomatic and asymptomatic patients with carotid atherosclerosis who are high-risk surgical candidates and are enrolled in postapproval studies.

Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) and Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) trials are two recently reported European trials on patients with normal risk for CEA which unlike SAPPHIRE showed poorer outcomes for CAS than for CEA.[90, 91] More recently, the International Carotid Stenting Study (ICSS), a multicenter, international, randomized controlled trial, suggested a clear superiority of CEA over CAS.[92] However, there are important drawbacks in designs and results of these three European trials regarding use of emboli-protection devices, use of dual antiplatelet drugs, and required experience level for CAS operators.

The EVA-3S was a randomized trial comparing CAS with CEA in patients with symptomatic (TIA or nondisabling stroke within 120 days prior to enrolment) ipsilateral carotid artery stenosis ≥ 60% at 30 sites in France.[90] The primary outcome was any stroke or death during 30 days of enrolment, seeking non-inferiority within a 2% margin. The protocol did not mandate the use of cerebral protection devices. A higher risk of stroke was seen early in the trial while these devices were not applied, and the protocol was amended to recommend their use. To have a statistical power of 80%, the investigators estimated that 872 patients would have to be enrolled. However, enrolment suspended while only 527 patients had been randomized to treatment due to safety and futility concerns. The 30-day incidence of any stroke or death was significantly lower among those assigned CEA versus CAS (3.9% vs. 9.6%, $p < 0.01$) with a relative risk (RR) of 2.5 (95% CI: 1.2-5.1). The 6-month incidence of any stroke or death was 11.7% in the CAS group and 6.1% in the CEA group ($P = 0.02$). At 4-year follow-up, the death or stroke rate still favored CEA, driven by the 30-day events. Stroke risk beyond the perioperative period (30 days) did not vary significantly and was low by either two forms of treatment.[91]

In EVA-3S, operators were required to have performed 12 or more CAS procedures or five CAS procedures and 30 endovascular procedures in the supra-aortic trunk to undertake CAS whereas to undertake CEA, the surgeon was required to have performed at least 25 endarterectomies before entering the trial. Some of the high 30-day complication rate in the CAS arm in this study may be explained by the lack of experience among trial CAS operators. Therefore, the trial did not compare the methods CAS and CEA, and the conclusion from the trial could be that CEA done by experienced surgeons had better outcomes than CAS performed by inexperienced operators.

Not only was training and experience severely limited but also was coverage with dual antiplatelet therapy. It is documented that dual antiplatelet therapy has an essential role in the safety of CAS.[93] In EVA-3S, only 69% and 38% of patients were on antiplatelet therapy pre-procedure and post-procedure, respectively. Not surprisingly, then, the outcomes after CAS were poor.

The SPACE trial[94] enrolled patients with ischemic stroke or TIA at 35 centers in Germany, Austria, and Switzerland. Ipsilateral carotid stenosis of > 50% was required with the mean degree of stenosis between 80% and 89%. Excluding patients at high surgical risk, a total of 1183 patents with severe symptomatic carotid stenosis, were randomly assigned to CAS or CEA. The primary endpoint of the study was ipsilateral stoke and death. Despite the early termination of the trial because of financial considerations, the 30-day results showed no significant difference in primary endpoint outcomes comparing CAS and CEA, as did the occurrence of stroke or death after 2 years.[95] Cerebral protection device was employed in only 27% of endovascular procedures, and multiple types of protection devices as well as multiple types of stents were used.

This trial was particularly criticized for its optional use of embolic protection devices in the CAS group. Although the effectiveness of embolic protection devices in preventing procedural complications has not sufficiently been evident on prospective randomized trials, a recent review of outcomes suggested that such devices resulted in a lower incidence of minor and major CVA.[82]

In the ICSS (or CAVATAS-II) trial,[92] 1713 patients with normal risk for CEA and with recently symptomatic stenosis greater than 70% were randomly assigned to receive CAS or CEA. The primary outcome measure of the study is the 3-year incidence of fatal or disabling stroke in any territory, and results are expected in 2012. The investigators most recently reported on an interim safety analysis that the incidence for composite of stroke, death, or procedural myocardial infarction was 8.5% in the CAS group compared with 5.2% in the CEA group (HR = 1.69, $p = 0.006$). Risks of any stroke and all-cause death were also higher in the stenting group than in the CEA group. Three procedural myocardial infarctions were recorded in the stenting group, all of which were fatal, compared with four, all non-fatal, in the endarterectomy group. The authors concluded that CEA should remain the treatment of choice for patients suitable for surgery at the time long-term follow-up is not established the efficacy of CAS as compared to CEA.

Because of limitations in SPACE, EVA3S and ICSS study design and conduct, the inferiority of CAS to CEA remains inconclusive. In fact, it may be concluded from these trials that CAS operated by inexperienced interventionalists has higher periprocedural complication rates than CEA performed by experienced surgeons. Moreover, surprisingly the dual antiplatelet use before and after CAS was not mandatory in ICSS and EVA3S (but not in SPACE), and it should be considered a serious limitation in the CAS arm of these two studies. It might be responsible for some strokes because the advantage of antiplatelet therapy against white thrombi occurring on foreign bodies such as stents is documented. Based on the results of these 3 trials, the European Stroke Organization (2008) reported that CAS should be limited to the subgroups of patients with severe symptomatic carotid artery stenosis with contra-indications to CEA, those with stenosis at a surgically inaccessible site, and re-stenosis after earlier CEA as well as post-radiation stenosis.[96] Further, it is not recommended for patients with asymptomatic carotid stenosis.[96] However, stop performing of CAS in centers with good and independently controlled track records on the basis of data from these studies could harm future patients who would have had the opportunity to take advantage of this procedure.

After a rigorous training and evaluating interventionalists in CAS arm during credentialing lead-in phase, Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) final findings, long-awaited and the largest prospective randomized trial to date, published most recently.[97] The study enrolled 2502 patients with symptomatic (n = 1326) and asymptomatic (n = 1196) extracranial carotid stenosis from 117 US and Canadian centers. The primary end point was the composite of any stroke, myocardial infarction, or death within the periprocedural period (from randomization up to 30 days after the procedure or if no procedure was performed up to 36 days after randomization) or ipsilateral stroke during 4 years following randomization. Two independent neurologists blindly adjudicated endpoints.

At 4-year follow-up including periprocedural period, the CREST results showed that both procedures, CAS and CEA, were associated with similar rates of the primary composite outcome among both sex with either symptomatic or asymptomatic carotid stenosis (7.2% and 6.8%, respectively; $p = 0.51$). At 30 day, although major stroke was not different at < 1% in both group, the periprocedural stroke rate was lower in the CEA group than in the CAS group (2.3% vs. 4.1%, $p = 0.01$), whereas the incidence of periprocedural myocardial infarction was higher in the CEA group (2.3% vs. 1.1%, $p = 0.03$).

In quality-of-life analyses among survivors at 1 year, the investigators of CREST trial revealed that patients who had an MI reported a better quality of life after recovery than those who had a stroke indicating that stroke had a greater adverse effect on a broad range of health-status domains. Even though other previous studies have shown that both stroke and MI are associated with major morbidity and mortality.[98, 99]

Another important finding was that, during the lead-in phase, the study authors noted differences in outcome with age, i.e. patients approximately older than 70 had higher risk for event with CAS than CEA.[100] The association of age with outcome also seen in the RCT itself, with those approximately 70 years and over having better outcome with CEA and those younger than 70 years having slightly better outcomes with CAS.[97] This trend has also been shown in other earlier trials[92, 94, 101] that may be explained by higher technical challenges of CAS in older patients due to increased arterial tortuosity, and burden in the internal carotid artery and carotid arch.[102]

Moreover, in CREST, CEA showed a clear-cut superiority over CAS with respect to the secondary end point of stroke or death despite that embolic protection devices were used in 96.1% of patients.[97] It indicates that although CAS may offer a reasonable alternative to CEA, particularly in younger patients and in those who prefer less invasive procedure, this technique has its own risks. The potential for distal embolization of established plaque with subsequent neurological events (TIA or stroke) is the most important complication associated with CAS.

A strategy for minimizing the risk of CAS procedural stroke would involve appropriate case selection. It is worth noting that factors which render patients at higher risk from CAS are different from those for CEA. Outcomes of CAS are mainly influenced by local vessels anatomy and lesion characteristics (Table 2) while comorbidities are the major risk factors for CEA, and both factors should be considered in case selection. The Risks are likely additive; for example, risks appear to be higher in a patient with type 3 arch, thrombotic lesion, and diseased external carotid artery. In addition, as mentioned before like any interventional procedure, CAS is dependent on operator expertise and experience.

Table 2. High-risk carotid stenting

Anatomic factors
Unable to place sheath
Difficult aortic arch
Proximal tortuosity and calcification
Tandem CCA and ICA lesions
Occluded ECA
Aorto-ostial lesions
Lesion Characteristics
Echolucent “vulnerable” plaque
Heavily calcified lesion
String sign
Visible lesion thrombus

CCA, Common carotid artery; ICA, Internal carotid artery; ECA, External carotid artery

One of the CREST study limitations was that the investigators performed the CAS procedures using a standardized protocol of neuroprotection and stent use (RX AccuNet and RX Acculink [Abbott Vascular]). Thus, external validity may have been affected by their prohibition on the use of other stent systems. Furthermore, RX Acculink is an open-cell design stent with big cell size and high probability of prolapse particularly in symptomatic plaques; the filter, RX AccuNet, has also a big pore size, which increases the risk of passing microemboli thorough them. Now, therefore, this first-generation stent and embolic protection device system has lost its popularity among operators. Proximal embolic occlusion (PEO) devices have revolutionized the field by lowering postprocedural complication rates.[103] These PEO devices have a benefit in that for the whole procedure no antegrade flow occurs while the carotid lesion is crossed with a guidewire; therefore, the patient is protected against procedure-related emboli.

Fortunately, a new study, Transatlantic Asymptomatic Carotid Intervention Trial (TACIT) is under way to compare revascularization with current optimal medical therapy in high- and low-risk individuals with a greater than 70% asymptomatic carotid stenosis and should provide invaluable data.[104] In total, approximately 2,400 patients from more than 130 sites will be enrolled in TACIT. This trial first involved a three-way randomization with medical therapy plus CEA, medical therapy plus CAS, and medical therapy alone arms. The executive committee later revised the protocol and redefined TACIT as a two-way trial on the basis of early data from CREST and other studies suggesting there is no difference between CEA and CAS in asymptomatic patients. TACIT is now a two-arm trial comparing CAS using distal protection (with commercially available devices) versus optimal medical therapy alone with a regimented, rigorously defined and targeted medical therapeutic plan in both arms of the study. The primary outcome is a composite of 30-day mortality, all strokes within the 5-year study period, and a component of neurocognitive function measuring a reduction in neurocognitive decline-what which is called vascular dementia or vascular depression using predominantly depression scales.

Conclusion

Based on the aforementioned studies, despite that management of carotid artery stenosis is complex and risk-benefit issue need to be discussed with individual patients, we believe it is safe to make following conclusions:

Since both CEA and CAS are being compared with the medical treatment for over one decade ago, available data from the clinical trials probably underestimate the benefits of medical intervention. Currently, medical treatment has evolved with newer antihypertensive drugs including modern angiotensin-converting enzymes inhibitors, newer antiplatelet drugs, and in particular statin medications. The anti-inflammatory effects of statins provided a means for not only delaying plaque progression, but also possibly degenerating already formed lesions. The most definitive evidence suggests that for disease management in asymptomatic patients, regardless of the degree of disease, optimal medical treatment alone, as compared to aggressive revascularization approaches, is now best with particular emphasis on statin medications.

As most patients with stenotic carotid disease are asymptomatic, there is a large clinical gap that needs to be overcome to finally define the role of revascularization in this population.

Based on the risk of CEA and patients' symptoms, we suggest four different treatment strategies for the carotid lesions (Table 3):

For standard risk asymptomatic patients, CEA should be recommended if there is at least one predictor of embolization risk (hypoechoic plaque, ulcerated plaque, high risk transcranial Doppler) and a severe (> 70%) stenosis, and procedural risks (of surgery as well as angiography) are expected to be < 3.0%. According to CREST study findings, CAS could be considered if the anatomy is favorable and in hands of a well-experienced operator (< 3% complication risk), and only in a well-designed clinical study not in outside study.

For high-risk asymptomatic patients (with at least one predictor of embolization risk), as long as suitable anatomy exists CAS would be the first option; otherwise, CEA would be considered. In case of poor anatomy and periprocedural risk > 3.0%, medical therapy is the best choice.

In symptomatic carotid disease, CEA has long been clearly approved as a safe and viable option. The potential advantages of surgery must be weighed against the relative risks, considering the presence of a contralateral lesion, complications of surgery, gender, and age. CAS performed with embolic distal-protection devices can be an effective

Table 3. Summary of treatment options in selected patients

	Asymptomatic		Symptomatic	
	Low risk	High risk	Low risk	High risk
First choice	OMT	OMT	CEA	CAS
Second choice	CEA	CAS	CAS	CEA
Third choice	CAS	CEA	OMT	OMT

OMT, Optimal medical treatment; CEA, Carotid endarterectomy; CAS, Carotid artery stenting

treatment for these symptomatic patients but presently there is no evidence that CAS provides better stroke prevention compared with CEA. Therefore, in patients with normal risk, CEA still remains the "gold standard" of treatment particularly in those with advanced age (> 70 years). CAS is suggested as a potential alternative to CEA in patients with less than 70 years of age, and in symptomatic patients with moderate to severe (≥ 50%) carotid stenosis and a high perioperative surgical risk. Same with other endovascular interventions, as the technology and operator experience in percutaneous techniques continue to advance; in particular, use of PEO devices and hybrid or closed-cell stents, the role of CAS will undoubtedly expand.

Additionally, evolving optimal medical therapy, timely intervention, and analysis of plaque composition may have an important effect on the future management of patients with carotid artery stenosis.

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