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What Is the Role for Carotid Stenting Versus Endarterectomy?

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Keywords

• Carotid stenosis • Carotid endarterectomy • Carotid stenting
• Carotid atherosclerosis

Key points

- There have been significant advances in medical management of carotid atherosclerosis since early trials comparing endarterectomy to medical therapy were performed.
- Carotid endarterectomy is strongly recommended for patients with symptomatic 70% to 99% carotid stenosis, preferentially within 14 days of symptom onset, but less strongly recommended for symptomatic 50% to 69% stenosis.
- Carotid endarterectomy may be recommended for patients with asymptomatic 60% to 99% stenosis, especially if they have certain imaging characteristics placing them at higher risk of embolic stroke.
- Carotid stenting may be an acceptable alternative to endarterectomy, but should not be performed in symptomatic patients who are greater than 70 years of age or in patients whose revascularization procedure occurs within 14 days of symptom onset.
- Ongoing clinical trials may help to further define the role of endarterectomy and stenting in the management of carotid stenosis.

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INTRODUCTION

The optimal management of atherosclerotic carotid arterial disease has been studied extensively over the past 3 decades. From the landmark trials comparing carotid endarterectomy (CEA) to medical therapy in the late 1980s, through the large trials comparing CEA to carotid arterial stenting (CAS) in the 1990s and 2000s, to the present day comparisons of both interventions with modern medical management, carotid stenosis has remained one of the most intensely investigated disease processes in surgery.

Despite the considerable attention allotted to carotid stenosis management in the literature, the recommended therapeutic approach to patients who have this condition has not changed dramatically, especially among those who have sustained symptoms attributable to their carotid disease. In this analysis, the authors will review the major clinical trials that have focused on carotid stenosis management and discuss the increasingly nuanced guidelines for carotid revascularization.

ORIGINAL TRIALS COMPARING ENDARTERECTOMY TO MEDICAL THERAPY

Traditional indications for carotid arterial revascularization originate from several well-known randomized clinical trials performed in the late 1980s and early 1990s. Consistent with the differential risk of subsequent stroke according to the presence or absence of symptoms attributable to carotid stenosis, these trials compared CEA with usual medical therapy in either symptomatic or asymptomatic study populations.

Asymptomatic carotid stenosis: asymptomatic carotid atherosclerosis study and the first asymptomatic carotid surgery trial

Before recent developments in medical management of atherosclerotic disease, the management of asymptomatic patients was largely informed by the results of 2 landmark randomized clinical trials, the Asymptomatic Carotid Atherosclerosis Study (ACAS) and the first Asymptomatic Carotid Surgery Trial (ACST-1).

The ACAS study randomized 1662 patients aged 40 to 79 years with 60% to 99% asymptomatic carotid artery stenosis to either CEA and daily aspirin or BMT (which consisted of daily aspirin and stroke risk factor modification, including lipid-lowering therapy in 13% of patients at trial entry) [1]. The trial excluded patients with comorbid conditions that were deemed likely to produce disability or death within 5 years. The primary outcome for the trial was ipsilateral stroke or any perioperative stroke or death. The estimated 5-year incidence of this outcome was 5.1% for CEA patients compared with 11.0% for BMT patients ($P = .004$), with an aggregate risk reduction of 53% associated with CEA. Subgroup analysis of trial data demonstrated that men aged $\leq$68 years, and those who had prior contralateral CEA or stroke, had the greatest estimated 5-year benefit from CEA.

The ACST-1 study randomized 3120 patients with 70% to 99% asymptomatic stenosis to either immediate CEA or indefinite deferral of any carotid procedure [2]. There were no age exclusions in this trial. The primary outcomes of the trial were 30-day death or stroke, and nonperioperative stroke. The 30-day death or stroke rate for patients undergoing immediate CEA was 3.0%. At 5 years, the risk of stroke was 4.1% in the immediate CEA group compared with 10.0% in the deferred CEA group, and this benefit for immediate CEA persisted at 10 years (stroke risk 10.8% for immediate CEA patients compared with 16.9% for deferred CEA patients). Although medical management of the patients in the ACST-1 trial was left to the discretion of the individual participating clinicians, most of the patients in both arms of the study were on antithrombotic and antihypertensive therapy, and the use of lipid-lowering agents increased significantly over the course of the study period. The investigators in this trial noted that the benefits of immediate CEA were significant for patients who were on lipid-lowering therapy, and for patients of either gender up to 75 years of age.

Symptomatic carotid stenosis: North American symptomatic carotid endarterectomy trial and european carotid surgery trial

The North American Symptomatic Carotid Endarterectomy Trial (NASCET) was performed at 50 centers in the United States and Canada, and included patients less than 80 year old who had sustained symptoms attributable to carotid stenosis within the 120 days preceding enrollment [3]. Patients were randomized to either BMT alone, or BMT and CEA. Patients with high-grade (70%–99%) stenosis were considered separately from those with lower-grade (30%–69%) stenosis. For the high-grade stenosis group, the trial was stopped prematurely at 18 month follow-up because of interim discovery of a clear benefit for CEA, which had an estimated 2-year ipsilateral stroke rate of 9% compared with 26% with BMT alone. The trial was continued for patients with lower-grade stenosis for an average follow-up of 5 years [4]. The NASCET investigators found that the 5-year ipsilateral stroke rate was 15.7% among patients treated with CEA who had 50% to 69% stenosis, compared with 22.2% among patients treated medically ($P = .45$). There were no significant differences between the 2 treatment arms for patients with 30% to 49% stenosis (14.9% for CEA patients vs 18.7% for medical therapy patients, $P = .16$).

Results from the later European Carotid Surgery Trial (ECST) largely confirmed the findings from NASCET [5]. The ECST randomized 3024 patients of any age with carotid stenosis and ipsilateral symptoms within 6 months of enrollment to either CEA or usual medical care. For this trial, patients were stratified by degree of stenosis (0%–19%, 20%–29%, 30%–39%, and so on). Investigators found that the risk of perioperative major stroke or death was 7.0% in patients undergoing CEA, and noted that this adverse perioperative event rate did not vary substantially by the degree of stenosis. Conversely, the investigators found that the major stroke rate for patients who were treated medically did increase with degree of stenosis for approximately 3 years after randomization, especially for patients with ≥80% stenosis. Comparison of the 2 treatment arms in patients with ≥80% stenosis demonstrated an estimated 3-year major stroke or death rate of 14.9% in CEA patients compared with 26.5% in medical therapy patients. For patients with lesser degrees of stenosis, the benefit of CEA was less clear.

Because the methods used to measure degree of stenosis were different in NASCET and ECST, a pooled analysis of these trials and an additional Veterans Administration trial was conducted in which degree of stenosis for ECST patients was recalculated according to NASCET methodology [6]. This study found CEA to increase the 5-year risk of ipsilateral stroke in patients with less than 30% stenosis, have no effect in patients with 50% to 69% stenosis, and have a large benefit (with an absolute risk reduction of 16.0%) in patients with 70% to 99% stenosis.

Summary of original trials

Based on the results of these landmark trials, a standard approach to carotid revascularization developed whereby symptomatic patients with ≥50% stenosis and asymptomatic patients with ≥70% stenosis would be recommended for CEA as long as their anticipated risk of major perioperative stroke or death was sufficiently low (<6% and <3%, respectively, for symptomatic and asymptomatic disease) [7].

CAROTID ARTERIAL STENTING

Although CEA has been considered the mainstay for patients needing carotid revascularization due to atherosclerotic stenosis, the aforementioned trials that established its efficacy over usual medical therapy tended to exclude patients who might be at higher risk for perioperative intervention, either because of significant comorbidity or because of anatomic characteristics that might increase the risk of intraoperative complications during endarterectomy (Table 1). Specific physiologic criteria that have been perceived to place patients at higher risk of perioperative morbidity during CEA include advanced age, class III or

Table 1
Physiologic and anatomic characteristics perceived to place patients at higher risk for complications during carotid endarterectomy

Physiologic high-risk characteristics	Anatomic high-risk characteristics
• Age >80 y	• Contralateral carotid occlusion
• Recent myocardial infarction	• Contralateral laryngeal nerve palsy
• Class III/IV congestive heart failure	• Prior ipsilateral radical neck surgery
• Severe pulmonary disease	• Prior radiation therapy to the neck
• Abnormal stress test	• Prior ipsilateral endarterectomy
• Need for open-heart surgery	

Data from Yadav JS, Wholey MH, Kuntz RE, Fayad P, Katzen BT, Mishkel GJ, et al. Protected carotid-artery stenting versus endarterectomy in high-risk patients. N Engl J Med 2004;351:1493–1501.

IV congestive heart failure, unstable angina or significant multivessel coronary artery disease, recent myocardial infarction, or severe chronic pulmonary or renal disease [8]. Specific anatomic criteria, meanwhile, include stenotic lesions located at or above the second cervical verterbral level, a prior history of ipsilateral radical neck surgery or radiation, occlusion of the contralateral carotid artery, previous ipsilateral CEA, contralateral laryngeal nerve palsy, or tracheostoma [8]. Although CAS was initially proposed as an alternative treatment option for patients who possessed 1 or more of these high-risk characteristics, the early clinical trials that compared this intervention to CEA were applied to the broader population of carotid stenosis patients who met traditional criteria for endarterectomy.

Early trials comparing carotid arterial stenting to carotid endarterectomy

The Carotid and Vertebral Artery Transluminal Angioplasty Study, published in 2001, was the first major randomized trial to compare the 2 interventions [9]. The trial was conducted at 22 centers in Europe, Australia, and Canada, and included patients with any degree of carotid stenosis, with or without symptoms, who were considered to be eligible for both procedures. Stenting after carotid angioplasty was not required. A total of 504 patients were assigned to either CEA (n = 253) or endovascular treatment (n = 251), and the mean degree of stenosis in these patients was 85.1% and 86.4%, respectively. The 30-day rate of disabling stroke or death did not differ between the 2 groups (9.9% after CEA vs 10.0% after endovascular treatment). At 1-year follow-up, patients undergoing endovascular treatment had a significantly greater incidence of severe (70%–99%) ipsilateral carotid stenosis (14% after endovascular therapy vs 4% after CEA; $P<.001$), but the estimated 3-year rate of ipsilateral stroke did not differ between the 2 groups. Importantly, only 26% of patients in the endovascular arm of this trial received a stent.

The Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial, published in 2006, was performed across 30 centers starting in November 2000, but was stopped prematurely for safety reasons in 2005 after enrolling 527 patients [10]. Patients were eligible for this trial if they had 60% to 99% carotid stenosis and ipsilateral symptoms within 120 days before enrollment. All patients in the endovascular arm of this trial received stents, and 91.9% of the endovascular procedures used a distal embolic protection device. The primary outcome of the trial was 30-day postoperative death or any stroke, a composite endpoint which occurred in 9.6% of CAS patients and 3.9% of CEA patients (relative risk with CAS 2.5; 95% CI, 0.5–4.2). Notably, investigators in this trial reported that the rate of periprocedural stroke or death was significantly higher in the small group of CAS patients whose procedure was performed without a distal embolic protection device (25% without vs 7.9% with embolic protection; $P = .03$), a finding that emphasizes the importance of such devices for perioperative stroke prevention during stenting procedures. Longer-term follow-up demonstrated that the cumulative probability of any procedural stroke or death or any ipsilateral stroke after randomization remained statistically higher at 5 years (11.0% after CAS vs 6.3%; $P = .04$), but not at 10 years (11.5% vs 7.6%; $P = .07$) [11].

The Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) trial randomized patients with symptomatic severe ($\geq$70%) stenosis to CEA or CAS, and was designed as a noninferiority study [12]. The use of embolic protection devices during this trial were left to the discretion of the proceduralist. A total of 1183 patients were included in the analysis. The 30-day rate of death or ipsilateral stroke was 6.84% in CAS patients and 6.34% in CEA patients, which resulted in a 1-sided *P* value for noninferiority of .09. Despite failing to demonstrate noninferiority at 30 days, the SPACE investigators did find the estimated 2-year incidence of death or stroke to be no different in the 2 treatment groups, although they found recurrent severe ($\geq$70%) restenosis at 2 years to be significantly higher after stenting (10.7% after CAS vs 4.6% after CEA; $P = .0009$) [13].

The International Carotid Stenting Study (ICSS) enrolled 1713 patients worldwide who had $\geq$50% symptomatic stenosis and who were deemed to be well-suited for either revascularization intervention [14]. Use of embolic protection devices was recommended but not mandated in this trial, with 72% of stenting procedures ultimately using such devices. At 120 days after randomization, the ICSS investigators found a significantly higher incidence of stroke, death, or myocardial infarction in the CAS group (8.5% after CAS vs 5.2% after CEA; $P = .006$), although the rate of disabling stroke or death did not differ between the 2 groups. Longer-term follow-up demonstrated no difference between the 2 groups in terms of cumulative 5-year risk of fatal or disabling stroke, but a significantly higher risk of any stroke in the CAS group [15]. Importantly, the functional outcomes of patients who sustained strokes did not differ between the 2 groups, as determined by distribution of modified Rankin scores, suggesting that the higher stroke rate observed among CAS patients did not translate into increased disability.

The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy trial was unique among carotid revascularization trials in that it has been the only one to date to confine its study population to those patients with one of the previously described physiologic and/or anatomic characteristics that presumably place them at higher risk for endarterectomy [16]. Symptomatic patients with $\geq$50% stenosis and asymptomatic patients with $\geq$80% stenosis were eligible for enrollment if they were deemed to be suitable candidates for either revascularization technique. All stenting procedures used distal embolic protection. The median total stenting experience of the proceduralists in this trial was 64 (range 20–700) procedures. The primary endpoint for the study was the composite incidence of death, stroke, or myocardial infarction within 30 days after the intervention, or death by ipsilateral stroke between 31 days and 1 year. This endpoint occurred in 12.2% of CAS patients and 20.1% of CEA patients ($P = .004$ for noninferiority, and $P = .053$ for superiority). When extended to 3 years, the incidence of the primary endpoint did not differ significantly between the 2 groups [17].

Although the previously described trials included either only symptomatic patients, or a combination of symptomatic and asymptomatic patients, the Asymptomatic Carotid Trial-1 has been the only large randomized trial to compare revascularization techniques in an exclusively asymptomatic population of carotid stenosis patients [18]. This trial randomized 1453 patients aged less than 80 years with asymptomatic 70% to 99% carotid stenosis to either CAS or CEA. All CAS procedures were performed using distal embolic protection. The primary endpoint for the trial, composite death, stroke, or myocardial infarction during the first 30 postprocedure days or ipsilateral stroke within the first postprocedure year, occurred in 3.8% of CAS patients and 3.4% of CEA patients, indicating noninferiority for stenting. The rate of ipsilateral stroke in the 2 groups was also statistically similar from 30 days to 5 years postprocedure.

The carotid revascularization endarterectomy versus stenting trial

Perhaps unavoidably, the aforementioned trials have faced critique since their publications. The major criticisms of this group of trials involve issues of heterogeneity in patient-eligibility criteria, experience levels of the interventionalists in the CAS arms, and technical aspects of the stenting procedures performed.

Because of its size, ample funding, and meticulous design, the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) is widely considered the preeminent study for comparison of revascularization techniques for carotid stenosis [19]. Importantly, the protocol for this trial seemed to overcome many of the notable weaknesses of earlier comparisons of revascularization techniques. The trial was conducted at 108 centers in the United States and 9 in Canada. Surgeons who participated in the trial required a minimum annual volume of CEA of 13 procedures pear year and documented perioperative death and complication rates of less than 3% in asymptomatic patients and less than 5% in symptomatic patients. Interventionists, meanwhile, were required to certification based on evaluation of previous endovascular experience, review of prior carotid stenting outcomes, pretrial hands-on training, and performance of stenting procedures during a lead-in phase before being able to participate in the trial. The same type of stent was used for all CAS procedures, and distal embolic protection use was protocolized when technically feasible.

Patients were considered eligible if they were symptomatic within 180 days before randomization and had a minimum threshold degree of stenosis based on imaging technique ($\geq$50% by angiography, $\geq$70% by ultrasonography, or $\geq$70% on computed tomographic angiography [CTA] or magnetic resonance angiography [MRA] if the stenosis was 50%–69% on ultrasound). Although not included in the original study protocol, asymptomatic patients became eligible in 2005 if they had $\geq$60% stenosis on angiography, $\geq$70% on ultrasonography, or $\geq$70% on CTA or MRA if stenosis on ultrasound was 50% to 69%. Patients also had to be suitable for management by either technique to be eligible for participation in this trial, whereas patients with a recent history of atrial fibrillation, myocardial infarction, or unstable angina were excluded from participation. A total of 2522 patients were randomized (1271 to CAS and 1251 to CEA).

The primary outcome of the CREST was the composite of any stroke, myocardial infarction, or death within 30 days of procedure or ipsilateral stroke within 4 years after randomization. The incidence of the primary outcome was 7.2% in CAS patients and 6.8% in CEA patients (hazard ratio with stenting 1.11; 95% CI, 0.81–1.51; $P = .51$). Analysis of the individual components of the periprocedural outcomes demonstrated that CAS patients had a higher risk of stroke (4.1% after CAS vs 2.3% after CEA; $P = .01$), but a lower risk of myocardial infarction (1.1% after CAS vs 2.3% after CEA; $P = .03$). The incidence of stroke after the periprocedural period was similar for both groups. Subgroup analyses of the primary endpoint in this trial revealed no differences between treatment groups based on preoperative symptom status or patient gender, although women in the CAS group did seem to have a higher risk of perioprocedural adverse events compared with women in the CEA group [20,21]. Investigators also found that the primary endpoint increased with patient age in CAS patients but not CEA patients, primarily due to age-related increase in stroke [22]. Perhaps in testament to the rigorous training and credentialing requirements contained within the CREST protocol, investigators failed to find an association between periprocedural event rates and the enrollment volume of the different centers that participated in this trial [23].

After 10-year follow-up, there was not a significant difference in the rate of the trial's composite endpoint between groups (11.8% for CAS patients and 9.9% for CEA patients [hazard ratio with CAS 1.10; 95% CI, 0.83–1.44]), either as a whole or once stratified by preoperative symptom status [24]. There was also no difference in the primary long-term endpoint of postprocedural ipsilateral stroke over the 10-year follow-up (6.9% after CAS and 5.6% after CEA). A prominent criticism of CREST was its inclusion of myocardial infarction (MI) as a component of the primary endpoint, which contributed to the ultimate trial conclusion that there was no difference in overall outcome between the 2 procedures [25,26]. Concern was raised because the criteria used to define MI in the trial allowed for the possibility that some asymptomatic infarcts would be captured, and that such events could therefore be weighted equally with stroke and death in terms of clinical import. However, CREST investigators showed that even those patients with biomarker elevation only (without electrocardiographic changes or chest pain) had increased mortality at 4 years, and that the 4-year risk of death after CREST-defined MI (hazard ratio = 3.4; 95% CI, 1.7–6.9) was similar to that observed for patients who sustained CREST-defined perioperative stroke of 2.78 (95% CI, 1.63–4.76) [27,28]. At the same time, the investigators also found that periprocedural stroke had a greater and more prolonged impact on health-related quality of life than MI at 1-year post-procedure [29].

BEYOND THE TRIALS

Improvements in medical therapy

There have been dramatic improvements in the medical management of carotid stenosis since the landmark trials of the 1980s and 1990s comparing CEA with usual medical therapy. Typical specified medical therapy in those trials consisted only of daily aspirin. In the interim, however, numerous studies have demonstrated the important impact that lipid-lowering agents and control of hypertension have on stroke prevention in patients with atherosclerotic disease.

In the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin trial, 17,802 healthy patients with low-density lipoprotein (LDL) cholesterol levels of less than 130 mg/dL and high C-reactive protein levels were randomized to receive either 20 mg rosuvastatin or placebo daily [30]. After this trial was stopped at a median follow-up of 1.9 years, patients in the treatment arm had a reduction in LDL cholesterol levels of 50%, and had a significantly lower incidence of stroke compared with patients in the placebo arm (0.18 stroke events per 100 person-years of follow-up in the rosuvastatin group versus 0.34 in the placebo group [hazard ratio = 0.52; 95% CI, 0.34–0.79; $P = .002$]). In a meta-analysis of 18 randomized controlled trials comparing statins versus placebo or usual care, and which had $\leq$10% of participants with a history of cerebrovascular disease, Taylor and colleagues [31] found that the use of statins was associated with a relative risk of combined fatal and nonfatal stroke of 0.78 (95% CI, 0.68–0.89; vs placebo or usual care). Additional evidence exists for a strong benefit for blood pressure-lowering medications in terms of stroke prevention. As a result, present day BMT for patients with asymptomatic carotid disease consists of statin therapy, antihypertensive medication to maintain long-term blood pressure less than 140/90 mm Hg, and aspirin therapy (or clopidogrel in patients who cannot tolerate aspirin) [32].

This important advance in BMT for carotid stenosis has essentially made trials such as ACAS and NASCET, which relied primarily on antiplatelet therapy for stroke prevention in their nonsurgical arms, obsolete. On the other hand, general awareness of the importance of statin therapy for patients with atherosclerotic carotid disease increased over the longer study period of the ACST-1, as demonstrated by the fact that the percentage of patients in that trial who were taking lipid-lowering therapy increased from less than 10% at the beginning of the trial to 80% by the end of the follow-up period [2]. As improved BMT has reduced the annual stroke risk for patients with asymptomatic carotid stenosis who forego revascularization, it is now necessary to conduct new trials that compare revascularization (using endarterectomy or stenting) with modern BMT [32,33].

Identification of high-risk characteristics of asymptomatic stenosis

Advances in medical therapy for atherosclerosis, and the resulting reduction in stroke risk with modern medical management of carotid stenosis, have led some to reconsider whether carotid revascularization need be performed in patients with asymptomatic disease. Nevertheless, from prospective multicenter studies, several imaging characteristics (which are summarized in Box 1) have been associated with increased stroke risk among patients with asymptomatic carotid disease.

In a prospective, multicenter cohort study of patients undergoing medical therapy for asymptomatic 50% to 99% carotid stenosis, investigators from the Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) Study Group found contralateral ischemic symptoms, large plaque area, large juxta-luminal hypoechoic area on ultrasonography to be independent predictors of ipsilateral cerebrovascular or retinal ischemic events [34,35]. This same group performed a multicenter natural history study of 821 patients with asymptomatic stenosis who were monitored with head computed tomography scans every 6 months for a maximum of 8 years, finding that the presence of silent embolic infarcts in the setting of 60% to 99% stenosis placed patients at higher risk of subsequent stroke [36]. Later analysis of a larger cohort from this study also demonstrated that 19.8% of patients with 50% to 99% asymptomatic stenosis sustained progression of their stenosis at a mean follow-up of 4 years, and that the stroke rate in the presence of progression was 21% compared with 12% in the absence of progression [37]. A separate retrospective of data from medically treated patients from ACST confirmed the prognostic import of fast progression of carotid stenosis, but the ACSRS investigators stopped short of recommending screening for progression in the absence of cost-effectiveness data [37,38].

The Asymptomatic Carotid Emboli Study (ACES) performed transcranial Doppler ultrasounds and then followed 106 patients with ≥70% asymptomatic stenosis, and found a nonsignificant trend toward increased stroke risk in patients with severely impaired cerebrovascular reactivity [39]. Given that their study was underpowered, they then completed a meta-analysis of the

Box 1: Imaging characteristics that increase the risk of stroke in patients with asymptomatic carotid stenosis

- Silent infarction on computed tomography of head
- Progression of stenosis on serial ultrasonography
- Large plaque area on computerized plaque analysis
- Large juxta-luminal hypoechoic area on ultrasonography
- Intraplaque hemorrhage on magnetic resonance imaging
- Impaired cerebrovascular reactivity on transcranial Doppler ultrasonography
- Plaque lucency on Duplex ultrasonography
- Spontaneous embolization on transcranial Doppler ultrasonography
- Contralateral transient ischemic attack or stroke

Data from Naylor AR, Ricco JB, de Borst GJ, Debus S, de Haro J, Halliday A, et al. Editor's choice - Management of atherosclerotic and verterbral disease: 2017 Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS). Eur J Vasc Endovasc Surg 2018;55:3–81.

ACES data with previous analysis, and found a significant association between reactivity and subsequent stroke risk. Similar analyses by the same group also demonstrated increased stroke risk for patients with spontaneous embolization during transcranial Doppler ultrasound [40]. Other investigators have demonstrated an increased risk of stroke for asymptomatic patients who demonstrate intraplaque hemorrhage on magnetic resonance imaging or plaque lucency on ultrasound to be associated with increased stroke risk [41,42].

Although the import of the above characteristics in terms of stroke risk prediction, and the subsequent usefulness of carotid revascularization in reducing that risk, has not been validated in randomized, multicenter trials, the presence of one or more of these characteristics is presently considered as potential justification for considering carotid revascularization for patients with asymptomatic carotid disease.

Age-associated increase in risk of periprocedural stroke with carotid arterial stenting

The Carotid Stenting Trialists' Collaboration (CSTC) conducted a meta-analysis of symptomatic patients from 4 of the stenting versus endarterectomy trials (EVA-3S, SPACE, ICSS, and CREST) to determine whether patient age was associated with treatment differences between the 2 revascularization techniques [43]. The CSTC investigators found no evidence of increased periprocedural risk of ipsilateral stroke or death by age in patients undergoing CEA, but did note that the risk of periprocedural stroke increased in patients undergoing CAS beyond the age of 70 years. The investigators concluded that CEA was superior to CAS in patients aged 70 years or older.

Several carotid anatomic and plaque characteristics have been shown to increase the risk of periprocedural stroke during CAS (Table 2), which may be more likely to be present in older patients with carotid disease and thus may help to explain the increased risk of periprocedural embolic stroke in aged patients who undergo CAS [25].

Timing of revascularization in symptomatic patients

The CSTC also performed a meta-analysis of 3 trials (EVA-3S, SPACE, and ICSS) to determine the association of time between symptom onset and risk periprocedural stroke or death in patients undergoing carotid revascularization [44]. The investigators found that the lowest periprocedural stroke or death rates occurred in patients who underwent CEA within 7 days of symptoms, although they found that patients undergoing endarterectomy between 8 and 14 days also had a lower risk of periprocedural events than patients undergoing the operation more than 14 days after symptom onset. Conversely, the investigators found that the risk of periprocedural stroke for patients undergoing CAS was highest in the first 7 days (9.4% risk), and decreased as the interval between symptom onset and stenting increased (8.1% if CAS performed between 8–14 days, 7.3% if performed after 14 days).

Table 2
Carotid plaque and vessel characteristics found to place patients at higher risk for periprocedural stroke during carotid arterial stenting

Plaque characteristics	Anatomic high-risk characteristics
• Soft, lipid-rich plaque • Extensive plaque (>1.5 cm) • Intraplaque hemorrhage • Thin fibrous cap • Heavily calcified plaque • Preocclusive lesion • Bifurcation stenosis • Lesion located at a curve	• Aortoiliac tortuosity • Type III or IV arch anatomy • Bovine anatomy • Arch disease • Proximal or distal internal carotid toruosity

Data from Noiphithak R, Liengudom A. Recent update on carotid endarterectomy versus carotid artery stenting. Cerebrovasc Dis 2017;43:68–75.

CURRENT RECOMMENDATIONS AND FUTURE DIRECTIONS

Numerous guidelines have been published regarding the appropriateness of carotid revascularization (be it CEA or CAS) for patients with carotid stenosis. Not surprisingly, given the ever-increasing volume of data generated from randomized clinical trials and clinical registries, there is some discordance among guidelines in terms of when and which type of revascularization is recommended [45]. The following review of current recommendations for carotid stenosis management are based primarily on the 2017 Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS), which are the most recent to be published [32].

Asymptomatic stenosis

The only recommendations achieving class I status (Table 3) and backed by level I evidence in the ESVS guidelines are for daily low-dose aspirin, statin therapy, and maintenance of long-term blood pressure less than 140/90 mm Hg [32]. Notably, there are no class 1 recommendations promoting carotid revascularization, be it by endarterectomy or stenting, for asymptomatic disease. The only ESVS recommendation for revascularization that achieved class IIa status (based on level B evidence) was for patients with 60% to 99% carotid stenosis to be considered for CEA if (1) the procedure is performed by a surgeon with documented perioperative stroke/death rates of less than 3%, (2) the patient's life expectance exceeds 5 years, and (3) the patients has one or more characteristics on imaging that place them at higher risk for embolic stroke (see Box 1). Carotid stenting, meanwhile, received IIb classification as a potential alternative to CEA if the aforementioned criteria were met, irrespective of the presence or absence of anatomic/physiologic characteristics that would potentially place patients at high risk during endarterectomy.

Table 3
Classes of recommendation and levels of evidence described

Class of recommendation	Class I	Evidence and/or general agreement that given treatment or procedure is beneficial, useful, and effective
	Class II	Conflicting evidence and/or divergence of opinion about the usefulness/efficacy of given treatment or procedure
	Class IIa	Weight of evidence/opinion in favor of usefulness/efficacy
	Class IIb	Usefulness/efficacy less well established by evidence/opinion
	Class III	Evidence of general agreement that treatment or procedure is not useful/effective, and in some cases may be harmful
Level of evidence	Level A	Data derived from multiple randomized clinical trials or meta-analyses
	Level B	Data derived from a single randomized clinical trial or large nonrandomized studies
	Level C	Consensus of opinion of experts and/or small studies, retrospective studies, registries

Symptomatic stenosis

Regarding patients with symptomatic carotid stenosis, the ESVS makes a class 1 recommendation (based on level A evidence) for CEA in patients who report carotid territory symptoms within the past 6 months, and who have 70% to 99% stenosis, as long as the documented procedural death/stroke rate of the surgeon is less than 6% [32]. The ESVS also recommended CEA in patients with 50% to 69% symptomatic stenosis, but only as a class IIa recommendation (albeit based on level A evidence). Importantly, an additional class I recommendation from these most recent guidelines that concerned revascularization in symptomatic patients was that patients aged more than 70 years who had 50% to 99% stenosis should preferentially undergo CEA and not CAS. For younger patients, CAS was recommended with class IIb status as an alternative to CEA. Finally, the ESVS recommended (with class I status) that any symptomatic patient with 50% to 99% stenosis in whom revascularization is deemed appropriate should be performed within 14 days of symptom onset, and by endarterectomy (not stenting) when done within that timeframe.

Ongoing trials

Several clinical trials may serve to further clarify if revascularization has a role in the management of carotid disease in the modern era. CREST-2, which began enrolling patients in December of 2014, is being conducted as 2 parallel multicenter, randomized, observer-blinded endpoint clinical trials: one comparing CAS with BMT and the other comparing CEA to BMT [46]. BMT for this trial includes aggressive antihypertensive and antilipid treatment as well as patient enrollment in a lifestyle management program for promotion of weight loss, smoking cessation, glucose control, and exercise. Adult patients with $\geq$70% stenosis, no ipsilateral stroke, or transient ischemic attack within 180 days of randomization, and no other serious medical problems will be eligible for enrollment. The primary endpoints of the trial with be combined stroke or death within 44 days of randomization or ipsilateral stroke within the first 4 years from randomization. MI is not a component of the primary endpoint in this trial. The ACST-2 trial, meanwhile, will compare CAS and CEA in asymptomatic patients with 70% to 99% stenosis [47]. Early results suggest near-universal compliance with BMT in trial participants, and suggest a 1-month risk of 30-day disabling stroke, fatal MI, or death of 1.0% in those patients undergoing revascularization.

SUMMARY

Indications for revascularization for carotid artery stenosis have become more nuanced since the results of NASCET and ACAS were first released. Revascularization for patients with asymptomatic disease has been approached more wearily, because the risk of stroke in patients who are treated medically is now lower. However, certain imaging characteristics confer a higher risk of stroke in patients with asymptomatic stenosis, and revascularization in patients with these symptoms is generally viewed as acceptable. Symptomatic patients with 70% to 99% stenosis are clearly recommended for revascularization, and patients with 50% to 69% less strongly so. Revascularization within 14 days of onset is increasingly preferred, although when it is possible to intervene within this timeframe, CEA is clearly preferred to CAS. At this time, there is no population in whom CAS is clearly preferred to CEA. The balance of evidence from randomized clinical trials tends to favor endarterectomy over stenting, although ongoing trials may serve to better define patient subgroups in whom CAS is an equal alternative to CEA. As a practical consideration, Medicare only reimburses for CAS procedures that are performed in symptomatic patients with $\geq$70% stenosis and a physiologic and/or anatomic condition that places them at high risk during endarterectomy (see Table 1) [48]. Symptomatic patients with 50% to 69% stenosis and asymptomatic patients with $\geq$80% stenosis may be also be covered if they are at high risk for CEA and if their stenting procedure is performed within the context of a clinical trial. Medicare will only cover procedures if certain approved stenting systems are used, and if the procedure includes an embolic protection device.

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