Trials and Frontiers in Carotid Endarterectomy and Stenting

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Based on the strength of randomized trials from the 1990s, major societal guidelines recommend carotid endarterectomy (CEA) for severe (≥70%), symptomatic carotid stenosis if an operative stroke/death rate of <6% can be maintained (history and major trials in carotid revascularization are summarized in the online-only Data Supplement).[1–4] Though the benefit is less evident, most guidelines also recommend consideration of CEA for 50% to 69% symptomatic stenosis.[2–4]

There are subtle differences in recommendations regarding carotid artery stenting (CAS) in symptomatic patients. Some guidelines stipulate that CEA should be preferred over CAS in patients with severe (≥70%) symptomatic carotid stenosis,[2,5] especially if >70 years old,[4] whereas others position CAS as an alternative.[1,3] Though the risk of operative stroke/death is higher with CAS, major randomized clinical trials (RCTs) report event rates under the recommended 6% cutoff for both treatment modalities.

Regarding asymptomatic disease, CEA is recommended for patients with stenosis ≥60% to 70% in highly selected patients as long as operative stroke/death rates <3% can be maintained.[1] A predicted life expectancy of at least 3 to 5 years has also been suggested.[2] The 3% threshold has been easily met by CEA cohorts in the CREST (Carotid Revascularization Endarterectomy Versus Stenting Trial; 1.4%)[6] and the ACT1 (Asymptomatic Carotid Trial; 1.7%),[7] suggesting that an even lower threshold may be appropriate.

Controversially, some guidelines have recommended that CAS can be considered in highly selected patients with asymptomatic carotid stenosis ≥60% to 70%,[1,4,8] whereas others argue that the evidence remains insufficient.[2] The lack of consensus in the management of asymptomatic carotid stenosis is reflective of an ongoing need for high-quality RCT data to guide practice.

Operative Risk

CEA Operative Stroke Risk and High Risk Designation

Most clinical trials in carotid revascularization have focused on average operative-risk patients, excluding patients with anatomic risk factors, major comorbidities, or advanced age. Many patients have also been excluded from these studies if they had neurological dysfunction or dementia that would limit stroke assessment or other common conditions that carry stroke risk such as atrial fibrillation.[7,9] However, clinicians frequently must make treatment decisions for patients who would have been excluded from these trials because of presumed excessive operative risk, thereby limiting the generalizability of RCT findings.

The high risk designation (Table 1) was adopted by Centers for Medicare and Medicaid Services from CAS trials such as the SAPPHIRE trial (Stenting and Angioplasty With Protection in Patients at High Risk for Endarterectomy), attempting to define a population at increased risk for complications with CEA who might, therefore, be better suited for CAS. A review of the Society for Vascular Surgery's Vascular Registry showed that the high risk classification is successful in identifying a group of CEA patients at increased risk of operative stroke/death/myocardial infarction (MI) in symptomatic (7.3% in high risk versus 4.6% in normal risk; $P<0.01$) and asymptomatic patients (5.0% in high risk versus 2.2% in normal risk; $P<0.001$).[10]

However, it has not been demonstrated that high-risk patients do better with CAS than CEA. Registry and institutional data suggest that in asymptomatic high-risk patients, CEA and CAS have similar stroke/death/MI rates, and in symptomatic high-risk patients, CAS carries higher risk.[11,12]

Apart from high risk designation, reviews of various databases have led to identification of various risk factors that predict poor outcomes after CEA.[13–15] Despite this work, there are no reliable, validated prediction models for determining high operative risk that can currently assist in choosing between revascularization strategies. In general, high anatomic risk patients may be more appropriate for CAS[2] as are patients with severe comorbid cardiac disease, based on excess operative cardiac risk that may be mitigated with CAS.[16] Furthermore, true high-risk patients (such as the largely asymptomatic cohort of high-risk patients studied in SAPPHIRE) may do better with intensive medical

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Table 1. Centers for Medicare and Medicaid Services High Risk for CEA Criteria*

Anatomic high risk
Tandem stenosis >70%
Bilateral carotid stenosis
Contralateral carotid occlusion
Recurrent carotid stenosis
Prior radiation therapy or radical neck dissection
High (above C2) or low (below clavicle) carotid bifurcation
Physiological high risk
Age ≥75 y
NYHA CHF Class III/IV
Left ventricular ejection fraction <30%
Coronary artery disease involving ≥2 vessels
Unstable angina
Recent MI (within 6 wk)
Severe pulmonary disease
Chronic renal insufficiency

CEA indicates carotid endarterectomy; CHF, congestive heart failure; MI, myocardial infarction; and NYHA, New York Heart Association.

*Including other conditions that were used to determine patients at high risk for CEA in prior carotid artery stenting trials and studies.

therapy alone, especially if operative stroke/death rates are anticipated to be higher than recommended safety thresholds (6% for symptomatic patients and 3% for asymptomatic patients).

CAS Operative Stroke Risk

High-Risk Anatomy

To tailor treatment strategy to individual patients, major interest has developed in identifying whether any carotid lesion characteristics place a patient at high risk for operative stroke with CAS. Various lesion-related and procedure-related risk factors have been described, which may increase the CAS-related risk of operative stroke (Table 2; Figure), many of which have been identified on secondary analyses of major CAS trials.[18–20] It is likely that increased prevalence of these high risk features is at least partially responsible for worse CAS outcomes in elderly patients (Table 3). Patients ≥80 years are more likely to have several of the lesion- and procedure-related anatomic characteristics, which make CAS more difficult and are associated with higher stroke risk.[21–24]

To recognize these features and guide treatment choice, preoperative computed tomography angiography of the neck (including the aortic arch) is recommended for patients being considered for CAS. This helps to determine the best means of accessing the lesion, any disadvantageous lesion characteristics, distal internal carotid artery anatomy, and embolic protection device (EPD) selection. Magnetic resonance angiography would be an acceptable alternative, although visualization of the aortic arch is not routinely provided and calcium identification is more limited.

Table 2. Factors Potentially Increasing Risk of Stroke With CAS

Access related
Arch calcification
Arch type II or III
Tandem lesion in CCA or innominate
ICA-CCA angulation ≥60°
Lesion related
Increasing stenosis severity
Circumferential calcification
Ulcerated lesion
Ostial lesion
Lesion length >10–15 mm
Multiple stent use
Sequential lesions
Echolucent plaque (on ultrasound)
Distal ICA
Tortuosity
Diffuse atherosclerosis
Tandem lesion
Thrombus
Small caliber
Operator characteristics
Inexperience
Lack of preprocedure CTA/MRA
Aortic arch injection
Failure to use EPD
Predilation prior to EPD
Failure to choose correct EPD for anatomy

CAS indicates carotid artery stenting; CCA, common carotid artery; CTA, computed tomography angiography; EPD, embolic protection device; ICA, internal carotid artery; and MRA, magnetic resonance angiography.

Embolic Protection

Reviews have consistently suggested that use of EPDs at the time of CAS reduces the risk of operative stroke,[20] though data from randomized trials are lacking. Accordingly, EPD use is mandated in major RCTs (CREST, CREST-2[NCT02089217]) and is required for reimbursement by Centers for Medicare and Medicaid Services.

However, catheter manipulation in a highly calcified aortic arch can lead to cerebral embolization prior to the deployment of an EPD, which may be a major cause of stroke associated with CAS.[25–27] Even if the arch is safely navigated, deployment of a distal EPD first requires passing the device across the lesion in an unprotected fashion, a step which also incurs risk of embolic stroke.

Transcarotid artery revascularization was developed whereby direct surgical exposure of the common carotid artery allows for common carotid artery access and initiation of embolic protection via flow reversal, with blood

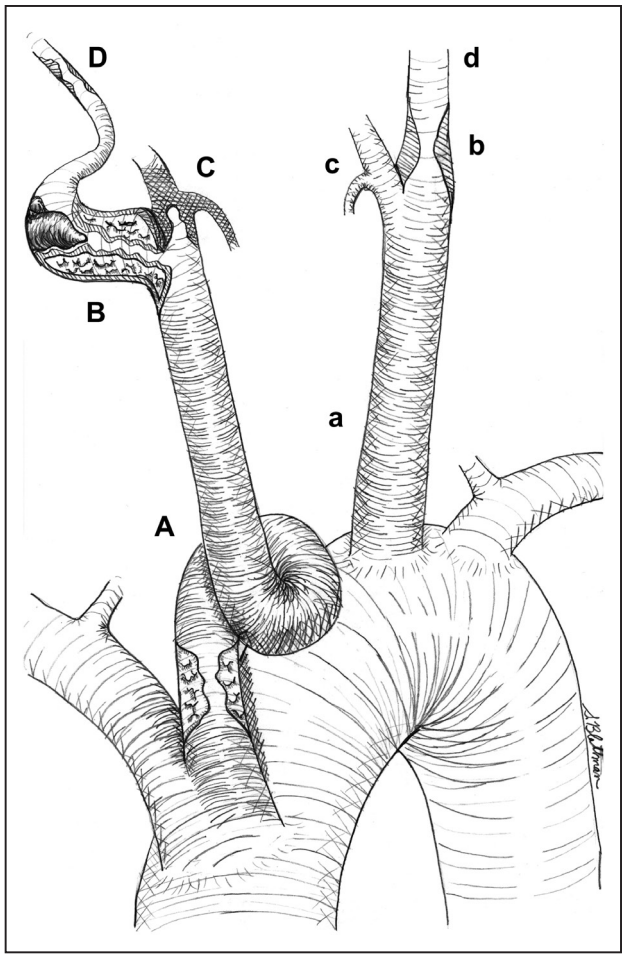

Figure. Favorable and unfavorable anatomy for carotid stenting. **Right** (unfavorable): **A**, Innominate takeoff from ascending aorta, Proximal common carotid artery (CCA) tandem lesion, Tortuous CCA; (**B**) High-grade, calcified internal carotid artery (ICA) stenosis, ICA thrombus, angulated ICA takeoff; (**C**) Occluded external carotid artery (ECA); (**D**) Small diameter distal ICA with disease. **Left** (favorable): **a**, Left CCA takeoff from **top** of aortic arch, CCA free of disease and straight; (**b**) Moderate-grade, smooth ICA stenosis with minimal calcification, straight ICA takeoff; (**c**) Patent ECA; (**d**) Moderate to large diameter distal ICA with no disease. Adapted from Schermerhorn et al[17] with permission. Copyright ©2007, Wolters Kluwer Health/Lippincott Williams & Wilkins.

return via the femoral vein.[28] This technique avoids risks associated with catheterization of the aortic arch and proximal common carotid artery and does not necessitate crossing of the stenosis prior to initiation of embolic protection. In a mixed cohort of symptomatic (25%) and asymptomatic (75%) patients, a single-arm trial of transcarotid artery revascularization was associated with an operative stroke/death rate of 2.8%.[26]

Stent Design

The contribution of stent design to operative stroke risk has been controversial. Some have argued that a closed-cell architecture is more likely to act as a scaffold for unstable plaque and prevent embolization, while others prefer the flexibility of open-cell designs for navigating severely stenotic and tortuous arteries. Analyses of large CAS databases and CAS trials have suggested that closed-cell stents incur lower operative transient ischemic attack (TIA)/stroke rates, compared with open-cell stents.[29–31] As a result, newer carotid stent designs emphasize small free cell areas, in some cases using multilayer or micromesh coverage.

Table 3. High CAS Risk Anatomic Features Associated With Age ≥80 Years

Access related
Aortic arch/supra-aortic vessel calcification
Aortic arch elongation (type II/III arch)
Tandem lesion in CCA or innominate
ICA-CCA tortuosity
Lesion related
Severe stenosis >85%
Heavily calcified stenosis
Ulcerated lesion

CAS indicates carotid artery stenting; CCA, common carotid artery; and ICA, internal carotid artery.

Operator Experience

For CAS, operator experience is critically important. A pooled analysis of early carotid stent trials for symptomatic carotid stenosis showed that operators with low (mean ≤3.2 procedures per year) or intermediate (mean 3.2–5.6 procedures per year) in-trial case volume had 10.1% and 8.4% risk of operative stroke/death, respectively. High-volume operators (>5.6 procedures per year) had the lowest operative stroke/death rate at 5.1%.[32] In CREST, physicians underwent rigorous credentialing with case review and participation in a lead-in phase prior to enrolling patients to mitigate the effect of operator experience.[33]

Furthermore, there is reason to think that CAS outcomes are not as good in the community where operator volume is lower. In a study of >20 000 Medicare patient undergoing CAS, the median annual operator volume was only 3.0 per year.[34] Patients treated by operators with <6 procedures per year were found to have an elevated risk of 30-day mortality (odds ratio, 1.9; [95% confidence interval, 1.3–1.9]) compared with patients treated by operators with ≥24 procedures per year. While an analysis of the CAPTURE 2 (Carotid ACCULINK/ACCUNET Post Approval Trial to Uncover Rare Events) CAS registry has suggested that it may take up to 72 cases for an operator to achieve an operative stroke/death rate <3% in asymptomatic patient,[35] decreasing case volumes may make this goal unrealistic.

MI and Cranial Nerve Injury

In initial studies comparing CEA to CAS, rates of MI were <1% for both procedures, likely because cardiac biomarkers were not measured routinely.[36–38] The high-risk SAPPHIRE trial, which systematically collected cardiac biomarkers, was the exception, reporting MI rates of 5.9% for CEA and 2.4% for CAS.[39] In the average-risk group studied in CREST, MI occurred in 2.3% of patients undergoing CEA and 1.1% undergoing CAS (P=0.03).[16,40] In CREST, the MI end point required biomarker elevation plus either chest pain or electrocardiographic evidence of ischemia (biomarkers were routinely collected, but isolated biomarker elevations were not

considered as MIs). As a result, the higher MI rates seen in CREST may be partially attributable to the detection of some asymptomatic MIs. This has led to considerable controversy regarding the inclusion of MI in the primary composite end point, essentially equating the clinical importance of perioperative myocardial ischemia to stroke or death. Patients who suffered an MI (as defined in CREST) had increased risk of 4-year mortality (hazard ratio [HR], 3.4; [95% confidence interval, 1.7–6.9]), which was comparable to the increased risk of 4-year mortality associated with operative stroke (HR, 2.8; [95% confidence interval, 1.6–4.8]), illustrating the importance of these events.[16,41] However, a subsequent quality of life study showed that, in CREST, operative stroke had a greater and more sustained impact on quality of life than MI.[42] Of major ongoing trials, CREST-2 and the ECST-2 (European Carotid Surgery Trial 2; ISRCTN 97744893) will not include MI as a component of their composite primary end points.

Cranial nerve injury may also have meaningful clinical consequences in patients undergoing CEA. In CREST, the rate of cranial nerve injury for CEA was 4.6%.[43] However, 34% of deficits had resolved at 1-month follow-up and 81% resolved by 1 year. No difference in quality of life associated with cranial nerve injury was detected at 1-year follow-up. Registry studies have confirmed that, in most cases, cranial nerve injury-related symptoms resolve in follow-up.[44]

Developments and Controversies in Symptomatic Carotid Stenosis

Timing and Type of Revascularization After Onset of Symptoms

Data from randomized trials suggests that the attributable risk reduction of stroke/death associated with revascularization is highest within 14 days of symptom onset and diminishes thereafter.[45] As a result, most guidelines recommend revascularization within this 14-day period.[2–4] Revascularization within 48 hours of symptom onset has been associated with higher risk of neurological complications (including hemorrhagic conversion) and is typically avoided.[4]

Interestingly, randomized trials and large database reviews have shown that CAS performed within the first 7 to 14 days after symptom onset is associated with high stroke/death rates, particularly when compared with CEA.[46–48] CEA is therefore preferred over CAS when revascularization is performed within 14 days of symptom onset.[4]

Revascularization After Thrombolysis or Endovascular Intracranial Intervention

With increasing utilization of systemic thrombolysis and endovascular intracranial interventions, the risk of revascularization may be affected. Though limited, current data suggest that CEA can be safely performed within 14 days of thrombolysis but should be avoided within the first 72 hours because of risk of intracranial hemorrhage.[49] It has been recommended that patients only be considered for early CEA after thrombolysis if 50% to 99% ipsilateral internal carotid artery stenosis is present and the following criteria are met: (1) rapid neurological recovery, (2) infarct <1/3 middle cerebral artery territory, (3) previously occluded middle cerebral artery main stem has recanalized, and (4) no parenchymal hemorrhage or brain edema.[4]

There are little data to guide decisions related to revascularization after endovascular intracranial interventions (thrombectomy, intra-arterial thrombolysis), and the practice of concurrent CAS at the time of intracranial intervention is variable.

Role of Dual Antiplatelet Therapy

There are compelling data that dual antiplatelet therapy, when initiated early after symptom onset, can reduce recurrence of neurological events after noncardioembolic TIA/stroke.[50] Specific to carotid disease, it has been shown that initiation of dual antiplatelet therapy in patients with recently symptomatic carotid stenosis leads to decreased transcranial Doppler-detected microembolization (which are associated with TIA/stroke risk)[51] and recurrent neurological events.[52] Early initiation of dual antiplatelet therapy should be considered after symptom onset, though this must be weighed against bleeding risk of any planned revascularization.[4,53]

Developments and Controversies in Asymptomatic Carotid Stenosis

Identifying Asymptomatic Patients With High Long-Term Stroke Risk

The most widely used estimator of long-term stroke risk in asymptomatic patients is severity of stenosis.[1,2,8] Additionally, stenosis progression occurs in ≈5% of patients with asymptomatic carotid stenosis annually and leads many to consider close ultrasound follow-up or revascularization because of perception of high associated risk.[54,55] However, these methods in isolation are imperfect predictors of stroke risk, which has prompted interest in other ways of identifying asymptomatic patients with high long-term stroke risk who might benefit most from revascularization.[56]

The ACSRS study (Asymptomatic Carotid Stenosis and Risk of Stroke) determined predictors of ipsilateral TIA/stroke in asymptomatic patients on medical therapy, incorporating plaque morphology characteristics from ultrasound.[57] The addition of clinical and ultrasound-detected plaque features to stenosis severity improved the ability to predict stroke: the highest risk subgroup was found to have a 5-year stroke rate of 10% to 20%.

The effect of plaque morphology on subsequent stroke risk has also been studied using magnetic resonance imaging. A meta-analysis showed that magnetic resonance imaging–detected intraplaque hemorrhage (HR, 3.7) and lipid-rich necrotic core (HR, 5.7) are both significant predictors of TIA/stroke in patients with asymptomatic carotid disease.[58]

Transcranial Doppler of the middle cerebral artery can detect microembolization from a proximal carotid stenosis. The ACES (Asymptomatic Carotid Emboli Study) prospectively studied patients with ≥70% asymptomatic stenosis. Transcranial Doppler surveillance detected microemboli in

16%, with significant hazard of subsequent ipsilateral TIA/stroke (HR, 2.54).[59]

Transcranial Doppler can also be used to quantify cerebrovascular reserve (CVR), though other methods are also used. Patients with normal CVR will have increased flow in the middle cerebral artery after administration of a vasodilator; patients with impaired CVR will not show this typical response. A meta-analysis of multiple methods for measuring CVR showed a significant association between impaired CVR and subsequent TIA/stroke in asymptomatic patients (odds ratio, 4.7).[60]

These methods are promising and may guide selection of asymptomatic patients who will benefit most from revascularization. In fact, the European Society for Vascular Surgery guidelines recommend consideration for revascularization of asymptomatic carotid stenosis ≥60% only if 1 of these high-risk imaging characteristics is also seen (Table I in the online-only Data Supplement).[4]

Best Therapy for Asymptomatic Patients: A Moving Target

Improving Stroke Risk With Intensive Medical Therapy

In major trials comparing CEA to best medical therapy in asymptomatic patients, statin medications were not widely used. It was only in the later years of ACST (Asymptomatic Carotid Surgery Trial) that lipid-lowering medications were implemented.[61] Even within these trials, rate of any stroke on BMT improved from 3.5% per year in ACAS to 1.4% per year in the latter half of ACST as medical management improved.[62] It should be noted that the gradual implementation of lipid-lowering therapy in ACST did not negate the beneficial effect of CEA, though it did decrease the absolute benefit of revascularization.[61]

Aggressive lipid lowering has become a recent area of interest although this approach has not yet been tested in the setting of carotid artery disease. Injectable PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors (evolocumab, alirocumab) lead to reduction of low-density lipoprotein cholesterol even in patients already on statins. Though these agents are not yet widely available, their use is associated with reduction in cardiovascular events.[63,64]

Improvements in antiplatelet therapy for carotid disease may also be demonstrated in the coming years. New P2Y12 antagonists include clopidogrel, ticagrelor, prasugrel, ticlopidine, and cangrelor. PAR-1 (protease-activated receptor 1) inhibitors, such as vorapaxar, have also been developed. For ticagrelor, a subgroup analysis of the SOCRATES trial (Acute Stroke or Transient Ischemic Attack Treated With Aspirin or Ticagrelor and Patient Outcomes)[65] demonstrated that in patients with potentially symptomatic atherosclerotic disease (including some with internal carotid artery stenosis), ticagrelor treatment was associated with 90-day stroke, MI, or death rate of 6.7% compared with 9.6% in patients on aspirin (P=0.003).[66]

In the context of improvements in medical therapy, reviews of randomized and nonrandomized studies have shown that annual risk of stroke with medical therapy for asymptomatic carotid stenosis has consistently improved since the publication of ACAS.[62,67]

Improving Operative Risks With Revascularization and Intensive Medical Therapy

Operative stroke/death rates have continued to improve for CEA based on randomized trial evidence and clinical registries (Table II in the online-only Data Supplement). From 1991 to 2010, published data have shown a 6% annual reduction in operative stroke/death.[68] These trends coincide with the precipitous drop in cigarette smoking, adoption of routine statin use, and the increasing use of dual antiplatelet therapy, which may be associated with improved operative outcomes and long-term outcomes after revascularization.[69] Accordingly, there have been increasing calls to lower the acceptable stroke/death thresholds set by many guidelines (<6% symptomatic and <3% asymptomatic), especially given improvements in medical therapy.

Complication rates have also improved with CAS (Table II in the online-only Data Supplement). In CREST and ACT1, which mandated EPD use, 30-day stroke/death rates of 2.5% and 2.9% were reported, respectively,[6,7] and are acceptable based on current guidelines.

The successful implementation of intensive medical therapy outside of the trial setting is another area of uncertainty. Current evidence suggests that IMT regimens should include antithrombotic therapy, aggressive hyperlipidemia treatment with high-intensity statins when tolerated (regardless of low-density lipoprotein level), antihypertensive medications, aggressive control of hyperglycemia in diabetics to A1C <7%, smoking cessation, and lifestyle modification (exercise and diet counseling).[8,70] Future trials will yield important information as to how frequently the varied goals of IMT are met, but the generalizability of these regimens remains unclear.

The Need for Additional Trial Data

Ongoing uncertainty regarding indications for carotid revascularization has led to wide international variation in practice patterns, particularly for asymptomatic disease. In the United States, registry-based data suggest that roughly 60% of carotid revascularizations are performed in asymptomatic patients.[71] Internationally, rates of asymptomatic carotid revascularization range from 0% in Denmark to 73% in Italy.[71] This variability is reflective of ongoing uncertainty. The results from major ongoing randomized controlled trials, such as CREST-2 and ECST-2, will guide management in the years to come.

CEA and stenting are among the most studied surgical procedures in history, with >20 000 patients in RCTs. Both forms of revascularization are proven to be safe when performed by experienced practitioners in properly selected patients. Future efforts must focus on determining which patient populations truly benefit from these sophisticated techniques, as every treatment decision carries complex risk implications.

Disclosures

None.

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KEY WORDS: carotid stenosis ■ decision making ■ endarterectomy ■ stents ■ stroke

Trials and Frontiers in Carotid Endarterectomy and Stenting

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SUPPLEMENTAL MATERIAL:

"History and Major Trials in Carotid Revascularization"
Supplemental Tables I & II

Trials and Frontiers in Carotid Endarterectomy and Stenting

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History and Major Trials in Carotid Revascularization

DEVELOPMENT AND ADOPTION OF CAROTID REVASCULARIZATION

The ancient Greeks recognized a connection between the carotid artery and neurologic symptoms, but it wasn't until 1951 that C. Miller Fisher established carotid artery pathology as a common cause of stroke.[1, 2] "It is even conceivable that some day vascular surgery will find a way to bypass the occluded portion of the artery during the period of ominous fleeting symptoms," he wrote, presaging the era of carotid revascularization.[3]

Following Fisher's observations, in short order, the first carotid reconstruction was performed in 1951 by Raul Carerra in Buenos Aires, and the first carotid endarterectomy (CEA) was performed by Michael DeBakey in 1953 (though not reported until 1975).[4] Over the ensuing 30 years, CEA was widely adopted but skepticism regarding its safety began to mount.[5-9] These concerns persisted until the publication of landmark trials in the early and mid-1990s that established the safety and effectiveness of CEA as treatment for carotid artery stenosis and led to its widespread adoption.[10]

In 1977, Klaus Mathias performed the first carotid angioplasty in canines.[11] The first carotid angioplasty in humans was performed by Kerber *et al* in 1980,[12] and the technology developed rapidly thereafter. Appropriation of stents for use in the carotid artery followed, in the 1990s, with the first report from Edward Diethrich describing an 89% clinical success rate in 110 patients. Reports from Sanjay Yadav and Gary Roubin shortly followed.[13, 14] In the early 2000s, the first randomized trial evidence became available[15], leading to FDA approval of a carotid stent system in 2004. CAS volume increased markedly thereafter.[16]

Both methods of revascularization have undergone iterative refinements, such that the procedures, as they are performed today, bear little resemblance to antecedent techniques. The safety of revascularization has improved considerably against a backdrop of improving medical therapy for atherosclerosis, making treatment choice a controversial and complex undertaking.

SYMPTOMATIC CAROTID STENOSIS

In the 1990s, the results from 3 major randomized controlled trials comparing carotid endarterectomy (CEA) to best medical therapy (BMT) in average risk symptomatic patients were reported.[17-19] The data from these 3 trials were pooled,[20, 21] and analysis of >6,000 patients found that CEA patients with ≥ 70% stenosis had a stroke/death absolute risk reduction of 16.0% at 5 years ($P<0.001$) and a NNT of 6 (number needed to treat to prevent 1 event at 5 years). This benefit was evident within 1 year of follow-up and persisted through 8 years. Modest benefit was also seen for patients with 50-69% stenosis, where a stroke/death absolute risk reduction of 4.6% at 5 years ($P=0.04$) and NNT 14.

In these landmark trials, for patients who underwent CEA, the 30-day rate of stroke/death was found to be 7.1%. Results for CEA in more recent RCTs suggest lower operative stroke/death rates can be achieved for average-risk, symptomatic patients: 3.2% in the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST)[22] and 3.3% in the International Carotid Stenting Trial (ICSS).[23]

About a decade later, studies examining whether a similar benefit could be obtained with carotid artery angioplasty and stenting proliferated. The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial was reported in 2004 and suggested that in "high risk" symptomatic patients, CAS may be a viable alternative to CEA,

despite the fact that 70% of patients had asymptomatic disease.[15] Based on the results of SAPPHIRE and industry-supported "high risk" carotid stent registries[24], the Centers for Medicare and Medicaid Services (CMS) adopted the high operative risk categorization (Table 1).

As CAS evolved, more studies were performed comparing CEA to CAS in average risk patients to potentially expand applicability of CAS. The 3 most prominent subsequent trials in symptomatic patients all suggested that CAS was associated with higher rates of operative stroke/death compared to CEA.[23, 25, 26] However, there were significant variations in study design, utilization of stents, deployment of embolic protection devices and interventionist experience.

The Carotid Revascularization Endarterectomy vs. Stent Trial (CREST) utilized a uniform stent platform, mandated embolic protection, and rigorous physician credentialing protocols. The primary outcome was a composite of any operative stroke, myocardial infarction (MI), or death + long-term ipsilateral stroke. For the 2,502 patients studied (both symptomatic and asymptomatic), the occurrence of operative stroke was higher in patients undergoing CAS (2.3% CEA vs 4.1% CAS, P=0.01). However, because MI occurred more frequently after CEA, the primary endpoint at 4-years was no different between groups for all patients (6.8% CEA vs 7.2% CAS, P=0.51) nor for symptomatic patients (8.4% CEA vs 8.6% CAS, P=0.69).[27] At 10 years follow-up, the rate of long-term ipsilateral stroke (excluding the operative period) was similar regardless of treatment modality[28], suggesting that the durability of CEA and CAS are similar and that any differences in adverse outcomes are incurred in the immediate perioperative period.

CREST also comprehensively evaluated advanced age as an important modifier of operative risk in carotid revascularization, showing patients ≥ 70 years old had better outcomes with CEA.[27, 29] The relative benefit of CEA for patients older than 70 years was also reported by the SPACE investigators[26] and confirmed with a pooled analysis of EVA-3S, SPACE, ICSS and the symptomatic CREST cohort.[30]

ASYMPTOMATIC CAROTID STENOSIS

The two major trials that have guided treatment principles in asymptomatic carotid disease to this day are: the Asymptomatic Carotid Atherosclerosis Study (ACAS)[31] and the Asymptomatic Carotid Surgery Trial (ACST).[32] For ACAS, 1,662 patients with asymptomatic carotid stenosis ≥ 60% were randomized to CEA with BMT or BMT alone. Patients undergoing CEA had a lower 5-year risk of operative stroke/death + postoperative *ipsilateral* stroke (5.1% vs 11.0%, P=0.004). This led to the reported 5-year relative risk reduction of 53% associated with CEA but an absolute risk reduction of only 6.0%.

ACST is the largest study to date comparing CEA to BMT. From 1993-2003, 3,120 patients, from 126 centers in 30 countries, with asymptomatic carotid stenosis ≥ 70% were randomized to CEA with BMT or BMT alone.[32] Unlike the prior studies where BMT was aspirin alone, in ACST, BMT consisted of antiplatelet therapy, antihypertensive treatment, and, in the later years of the study, lipid-lowering therapy. Patients undergoing CEA again exhibited decreased rates of operative stroke/death + postoperative *any* stroke at 5 years (6.9% vs 10.9% P=0.0001) and 10 years (13.4% vs 17.9%, P=0.009).

The best trial data available for the evaluation of CAS in asymptomatic patients comes from CREST and the Asymptomatic Carotid Trial I (ACT I).[33] In the asymptomatic subgroup of CREST, the operative stroke/death rate associated with CEA was among the lowest reported at

1.4% and was not significantly different than stroke/death rates associated with CAS (2.5%, P=0.15). Similarly, at 10-years follow-up the rates of operative stroke/death + post-procedure ipsilateral stroke were also no different (CEA 7.9% vs CAS 8.6%, P=0.41).[28] Treatment strategies were not demonstrably different when utilizing study endpoints that included operative myocardial infarction.

ACT I was designed to test noninferiority of CAS to CEA in average-risk patients with asymptomatic carotid stenosis $\geq$ 70%.[33] Patients were enrolled in a 3:1 fashion with 1,089 patients in the CAS arm and 364 in the CEA arm. Notably, all patients were younger than 79 years old. Very low operative stroke/death rates were again observed (1.7% CEA vs 2.9% CAS, P=0.33). Overall 5-year stroke-free survival was not different based on treatment type (94.7% CEA vs 93.1% CAS, P=0.44). Similarly, the primary composite endpoint (which included myocardial infarction) was not different between groups. The authors concluded that CAS is non-inferior to CEA in the treatment of asymptomatic carotid stenosis.

Supplemental Table I: Features potentially conferring high risk of long-term stroke in patients with asymptomatic stenosis

High risk features	Detection method
ACSRS high risk features	
History of contralateral TIA or stroke	History
Severe stenosis (83-99% high risk)	Duplex ultrasound
Presence of discrete white areas without acoustic shadowing	Computerized ultrasound plaque analysis
Large plaque area	
>80 mm^2 – high risk	Computerized ultrasound plaque analysis
40-80 mm^2 – moderate risk	
<40 mm^2 – low risk	
Low grayscale median (GSM)	
Low GSM (<15) – high risk	Computerized ultrasound plaque analysis
Intermediate GSM (15-30) – moderate risk	
High GSM (>30) – low risk	
Large juxtaluminal black (hypoechoic) area	
>8 mm^2 – high risk	Computerized ultrasound plaque analysis
4-8 mm^2 – moderate risk	
<4 mm^2 – low risk	
Plaque type	
Types 1 & 2 – uniformly or mainly echolucent – high risk	Computerized ultrasound plaque analysis
Type 3 – mainly echogenic – moderate risk	
Type 4 – uniformly echogenic – low risk	
Other high risk features	
Progression in stenosis severity	Duplex ultrasound
Ongoing microembolization	Transcranial Doppler ultrasound
Silent embolic infarcts	CT or MRI
Intraplaque hemorrhage	MRI
Reduced cerebral blood flow reserve	Transcranial Doppler ultrasound

ACSRS, Asymptomatic Carotid Stenosis and Risk of Stroke[34]

Supplemental Table II: Improving operative stroke/death rates in major randomized trials

Trial	Publication Year	CEA*	CAS*
Symptomatic			
NASCET	1991, 1998	6.7%	
ECST	2003	7.5%	
EVA-3S	2008	3.9%	9.6%
SPACE	2008	6.6%	7.4%
ICSS	2010	3.4%	7.4%
CREST	2010, 2016	3.2%	6.0%
Asymptomatic			
ACAS	1995	2.3%	
ACST	2004	2.8%	
CREST	2010, 2016	1.4%	2.5%
ACT I	2016	1.7%	2.9%

*30-day any operative stroke/death

NASCET, North American Symptomatic Carotid Endarterectomy Trial[17]
ECST, European Carotid Surgery Trial[18]
EVA-3S, Endarterectomy Versus Angioplasty in patients with Symptomatic Severe carotid Stenosis[25]
SPACE, Stent-Protected Angioplasty versus Carotid Endarterectomy[26]
ICSS, International Carotid Stenting Study[23]
CREST, Carotid Revascularization Endarterectomy versus Stenting Trial[27]
ACAS, Asymptomatic Carotid Atherosclerosis Study[31]
ACST, Asymptomatic Carotid Surgery Trial[32]
ACT I, Asymptomatic Carotid Trial I[33]

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