REVIEW

MARK BAIN, MD
Cerebrovascular Center, Neuroscience Institute, Cleveland Clinic

ASMA M. MOHEET, MD
Cerebrovascular Center, Neuroscience Institute, Cleveland Clinic

PETER RASMUSSEN, MD
Cerebrovascular Center, Neuroscience Institute, Cleveland Clinic

Which patients benefit from carotid stenting? What recent trials show

ABSTRACT

So far, angioplasty with stenting of the carotid arteries does not seem to offer any clear advantage over traditional carotid endarterectomy for patients with symptomatic or asymptomatic stenosis. This paper reviews recent and ongoing studies of carotid revascularization, with conclusions on how these treatments should be used, based on what we know now.

KEY POINTS

In patients with asymptomatic carotid stenosis greater than 60% or symptomatic carotid stenosis greater than 50%, carotid endarterectomy has been proven to be superior to medical therapy alone.

In clinical trials, carotid stenting did not appear to have a clear advantage over endarterectomy in patients at average surgical risk.

Stenting may be most advantageous when used in patients with symptomatic carotid stenosis who would be at high risk of perioperative complications if they were to undergo carotid endarterectomy.

Whether carotid stenting has any advantage over carotid surgery (endarterectomy)—and for which patients—is still a topic of study and debate.

Treatment of carotid atherosclerosis and stenosis is important in preventing stroke and its comorbidities. Today, three main treatments exist: medical management (lipid-lowering, antihypertensive, and antiplatelet therapy), surgery, and, more recently, carotid angioplasty and stenting. The rationale for these treatments is to decrease the risk of cerebral infarction by stabilizing or removing plaque and improving blood flow.

Surgery has proven beneficial in patients with symptomatic carotid stenosis greater than 50% or asymptomatic stenosis greater than 60%, but it is risky in some patients. Stenting has evolved in part from the success of surgery and the need for alternative treatments for patients who are at unacceptable risk of perioperative complications. However, it does not have a clear advantage over surgery in patients at average risk. Further, its use in patients with asymptomatic stenosis of any severity is still controversial.

In this paper we review the major trials of carotid endarterectomy and stenting and summarize what we know today about who should undergo these therapies.

NOT ALL STROKES ARE DUE TO CAROTID ATHEROSCLEROSIS

Depending on the institution's referral pattern and population served, between 80% and 90% of strokes are ischemic (the rest being hemorrhagic).[1] Atherosclerosis of large arteries (typically defined as more than 50% stenosis of

a major brain artery or branch cortical artery[2]) is just one cause of ischemic stroke, but it is an important one. Other identifiable causes of ischemic stroke include cardioembolism and small-artery occlusion (lacunar stroke), and some cases are idiopathic.

Large-artery atherosclerotic disease can damage the brain gradually, with carotid stenosis resulting in hypoperfusion and subsequent cerebral infarction. More commonly, however, the carotid plaque often seen in large-artery atherosclerotic disease can ulcerate and occlude the vessel acutely or generate platelet aggregates that may embolize, resulting in cerebral infarction or transient ischemic attack.

In the Lausanne Stroke Registry,[3] the rate of ischemic stroke in patients with a greater than 50% large-artery stenosis ranged from 27% in 1979 to 17% in 2003, the decline likely being due to therapeutic advances.

SURGERY BEATS MEDICAL THERAPY FOR CAROTID ATHEROSCLEROSIS

Four landmark trials provided substantial evidence that carotid endarterectomy is better than medical management in patients with symptomatic or asymptomatic high-grade stenosis. These trials indirectly paved the way for carotid stenting.

The North American Symptomatic Carotid Endarterectomy Trial (NASCET)

Patients at 50 clinical centers who had had a hemispheric or retinal transient ischemic attack or a nondisabling stroke were randomized to undergo surgery (carotid endarterectomy) or no surgery. All patients received maximal medical management consisting of blood pressure control, lipid management if indicated, and antiplatelet therapy with aspirin. At baseline, 37% of patients were taking 650 mg or more of aspirin per day, and 11% were taking less than 325 mg per day. The patients were stratified into two prespecified groups on the basis of the severity of carotid stenosis: those with narrowing of 30% to 69% and those with narrowing of 70% to 99%.

Results in high-grade stenosis. In August 1991, the investigators published their results in patients with symptomatic high-grade (70%–99%) stenosis.[4] Surgical treatment was more beneficial than medical management alone: the cumulative risk of any ipsilateral stroke at 2 years was 26% in the medical group and 9% in the surgical group, an absolute risk reduction of 17%. The benefit of endarterectomy was still apparent at 8 years of follow-up.[5]

Results in moderate stenosis. In 1998, the investigators published their results in patients with symptomatic moderate (< 70%) stenosis.[5] Surgery was more beneficial than medical therapy in this subgroup as well: at 5 years, the rate of any ipsilateral stroke in patients with 50% to 69% stenosis was 15.7% in those treated surgically and 22.2% in those treated medically ($P = .045$). In patients with less than 50% stenosis, the 5-year stroke rate was not significantly lower with endarterectomy than with medical therapy.

The European Carotid Surgery Trial (ECST)

The ECST,[6] published in 1998, corroborated the NASCET findings. This multicenter, randomized, controlled trial enrolled 3,024 patients with symptoms of at least one transient ischemic attack in the distribution of one or both carotid arteries.

Results. In patients with stenosis of greater than 80% (60% by the NASCET criteria for calculating angiographic stenosis), the frequency of major stroke or death at 3 years was 26.5% in the control group and 14.9% in the surgery group, an absolute difference of 11.6%.

For surgery to be beneficial, the rate of serious complications has to be < 3%, and the expected patient survival ≥ 5 years

The Endarterectomy for Asymptomatic Carotid Artery Stenosis (ACAS) trial

The NASCET and ECST studies made it clear that select groups of patients with symptomatic carotid stenosis benefit from carotid endarterectomy. But what about patients with stenosis but no prior stroke?

The ACAS trial aimed to find out.[7] In this pivotal study, 1,662 patients with asymptomatic carotid artery stenosis greater than 60% were randomized to receive either medical therapy alone or medical plus surgical therapy.

Results were published in 2004. After a median follow-up of 2.7 years, the aggregate 5-year risk of ipsilateral stroke, any perioperative stroke, or death was estimated to be 5.1% in the surgical group and 11.0% in the medi-

cal group, a relative risk reduction of 53%. However, for surgery to be beneficial, the rate of perioperative death and other serious complications had to be less than 3%, and the expected patient survival had to be at least 5 years.

Of note, the benefit of carotid endarterectomy in this study was predominantly in men, with less of a benefit for women and diabetic patients. Furthermore, even though endarterectomy was beneficial in this asymptomatic cohort, the overall benefit in terms of stroke risk reduction was small compared with that in NASCET and ECST, in which patients had symptomatic disease.

The Asymptomatic Carotid Surgery Trial (ACST)

In this European version of ACAS, published in 2004, 3,120 patients with asymptomatic carotid narrowing on ultrasonography were randomized to undergo surgery or medical therapy.

Results. The risk of stroke or death within 30 days of carotid endarterectomy was 3.1%. In patients younger than 75 years who had carotid narrowing of 70% or more, immediate surgery decreased the net 5-year stroke risk from 12% to 6%.[8]

Whether embolic protection devices reduce periprocedural stroke rates remains to be seen

WHO SHOULD NOT UNDERGO CAROTID ENDARTERECTOMY?

From these studies, we can conclude that patients with symptomatic carotid stenosis of 50% or greater and patients with asymptomatic stenosis of 60% or greater benefit from carotid endarterectomy, but only if the perioperative rate of death and other serious complications is less than 3%.[7]

What are the risk factors for complications during this surgery? In 2006, Cremonesi et al,[9] in a consensus paper, defined patients as being at high risk if they had any of the following:

- Contralateral laryngeal nerve palsy
- Radiation therapy to the neck
- Previous carotid endarterectomy with recurrent stenosis
- Lesions high in the cervical internal carotid artery or below the clavicle in the common carotid artery
- Severe tandem lesions
- Age greater than 80 years
- Severe pulmonary disease
- Congestive heart failure (New York Heart Association class 3 or 4) or known severe left ventricular dysfunction
- Open heart surgery needed within 6 weeks
- Myocardial infarction within the past 4 weeks
- Unstable angina
- Contralateral carotid occlusion.

Could endovascular treatment be the answer for these patients at high risk who should not undergo carotid endarterectomy? Indeed, the procedure is being studied extensively and performed more frequently. We summarize the major studies below.

STUDIES OF CAROTID STENTING VS ENDARTERECTOMY

The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS)

This study, published in 2001,[10] was the first randomized, multicenter trial to compare the risks and benefits of endovascular treatment (angioplasty with or without stenting) of carotid and vertebral artery stenosis with those of conventional surgery.

To be included, patients had to have carotid artery stenosis (symptomatic or asymptomatic) that was suitable for either carotid endarterectomy or endovascular treatment. Patients were not grouped on the basis of the severity of their stenosis, but the mean stenosis in randomized patients was 86%.

A total of 504 patients were enrolled, of whom 251 were randomized to undergo endovascular treatment. Most patients in this group underwent angioplasty alone, but 26% also received stents because of suboptimal vessel dilatation or at the discretion of the intervening physician.

The primary end point was any disabling stroke or death. Secondary end points were any ipsilateral stroke lasting longer than 7 days and the combination of death or disabling ipsilateral stroke.

The results showed no significant difference between endovascular treatment and surgery in any of these end points at 3 years. However, the overall rates of procedural stroke and death were nearly double those seen in

NASCET and ECST. The investigators could not determine the reason for this higher risk, but they hypothesized that CAVATAS included patients at higher risk.

The restenosis rate was higher in the endovascular therapy group (14%) than in the surgery group (4%; $P < .001$). On the other hand, the surgery group had a higher rate of minor complications, including cranial nerve palsies and neck hematomas.

Carotid Revascularization With Endarterectomy or Stenting Systems (CARESS)

This prospective, multicenter, phase 2 trial, published in 2003, compared the outcomes of standard carotid endarterectomy vs carotid artery stenting using distal embolic protection devices.[11] All the patients in this study had at least 50% symptomatic stenosis or 75% asymptomatic stenosis.

Results. At 30 days, 7 (2.4%) of 254 patients in the endarterectomy group had had strokes, and one of the 7 patients with stroke died, so the combined rate of stroke or death (the primary end point) was 2.4%. In the stenting group, 3 (2.1%) of 143 patients had strokes and no patients died. Overall, there was no significant difference in the composite of death, stroke, or myocardial infarction (the secondary end point): 3% for carotid endarterectomy and 2% for stenting patients.

The Stenting and Angioplasty With Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial

In this trial,[12] published in 2004, patients had to have either symptomatic carotid disease with 50% stenosis or greater or asymptomatic stenosis of 80% or greater, determined by ultrasonography. Further, all patients had to have at least one comorbid condition that increased their perioperative risk. Up until this point, no trial had strictly defined patients at increased risk for complications after carotid endarterectomy and assessed subsequent outcomes. The risk factors included severe cardiac or pulmonary disease, age greater than 80, postendarterectomy carotid stenosis, previous neck surgery, previous neck radiation, contralateral recurrent laryngeal nerve palsy, and contralateral carotid occlusion.

Patients were randomized to undergo carotid artery stenting with distal protection or carotid endarterectomy.

The primary end points of this study were the cumulative incidence of major cardiovascular events at 1 year; death, stroke, or myocardial infarction within 30 days of intervention; and ipsilateral stroke between 31 days and 1 year. Secondary outcomes measured were the rates of target-vessel recanalization at 1 year, cranial nerve palsy, and surgical site complications.

Results. The rate of stroke or death was similar in both groups. The stenting group had fewer adverse cardiac events (mainly non-Q-wave myocardial infarction) than the surgery group. At 1 year the rate of major ipsilateral stroke was 3.3% in the endarterectomy group vs 0% in the stenting group (the difference was not significant), and the cardiovascular event rates continued to be higher in the endarterectomy group.

The investigators noted that myocardial infarction was included as a primary end point because patients with atherosclerotic vascular disease who undergo either stenting or endarterectomy are at a substantial risk of myocardial infarction, and a Q-wave or a non-Q-wave myocardial infarction in the perioperative period increases the risk of future complications and death. A perioperative non-Q-wave infarction increases the risk of death by a factor of 6 and increases the risk of myocardial infarction by a factor of 27 in the subsequent 6 months.

SAPPHIRE: Stenting was not inferior to surgery in high-risk patients

Overall, this study presents evidence that stenting, using distal embolic protection devices, is not inferior to endarterectomy and has fewer cardiovascular complications in patients who have at least one risk factor.

The Endarterectomy Versus Stenting in Patients With Symptomatic Severe Carotid Stenosis (EVA-3S) study

This recent multicenter, randomized study[13] was designed to determine if stenting is as good as (not inferior to) carotid endarterectomy in patients with symptomatic carotid stenosis of at least 60%. The primary end point was to be the incidence of stroke or death within 30 days after treatment. However, the trial was stopped early after the inclusion of 527 patients for reasons of safety and futility.

Results. The 30-day incidence of any

stroke or death was higher in the stenting group (9.6% vs 3.9%). The relative risk of any stroke or death after stenting as compared with endarterectomy was 2.5. The 30-day incidence of disabling stroke or death was also higher in the stenting group (3.4% vs 1.5%; relative risk 2.2). At 6 months, the incidence of any stroke or death was 6.1% after endarterectomy and 11.7% after stenting ($P = .02$). There was a trend toward more major local complications after stenting and systemic complications after endarterectomy. Cranial-nerve injury was more common after endarterectomy than after stenting (as expected). Overall, death and stroke rates were lower at 1 month and 6 months with endarterectomy than with stenting.

The Stent-Protected Angioplasty Versus Carotid Endarterectomy (SPACE) trial

This randomized, multicenter study,[14] published in 2006, was also designed to compare the safety and efficacy of carotid stenting and endarterectomy. Some 1,200 patients with symptomatic carotid artery stenosis confirmed by ultrasonography were randomly assigned within 180 days of a transient ischemic attack or moderate stroke to undergo carotid artery stenting (n = 605) or carotid endarterectomy (n = 595). The primary end point was ipsilateral ischemic stroke or death 30 days after the procedure. A total of 1,183 patients were included in the analysis.

Results. The rate of the primary end point was 6.84% with stenting and 6.34% with endarterectomy. The study failed to prove the noninferiority of carotid artery stenting compared with carotid endarterectomy for the periprocedural complication rate. Results at 6 to 24 months are awaited.

The Carotid Revascularization Endarterectomy Versus Stenting (CREST) trial

Perhaps the most anxiously awaited results are those of the CREST trial,[15] funded by the National Institutes of Health. This is a prospective, randomized, parallel, two-arm, multicenter clinical trial with blinded end point evaluation. Anticipated enrollment will include 2,500 patients. Patients are eligible for enrollment if they have symptoms of carotid stenosis within 180 days of a stroke or transient ischemic attack with ipsilateral carotid stenosis of at least 50% by angiography (70% by ultrasonography), or if they have asymptomatic carotid stenosis of at least 60% by angiography (70% by ultrasonography).

Patients are being randomized to undergo either carotid artery stenting or carotid endarterectomy. All receive aspirin as antiplatelet therapy, treatment for hypertension, and management of other stroke risk factors. Follow-up will last 4 years, with clinic visits at 1, 6, 12, 18, 24, 30, 36, 42, and 48 months. Primary outcome measures will be rates of death, stroke, or myocardial infarction at 30 days postoperatively, and ipsilateral stroke at 30 days postoperatively.

As of February 2007, 1,506 patients had been enrolled and 1,453 had been randomized at 94 sites in North America.

MEDICAID AND MEDICARE NOW PAY FOR THESE THERAPIES

Medicare now covers carotid stenting, with limitations

An important practical consideration for patients and physicians is whether Medicaid and Medicare will pay for these therapies.

In July 2001, Medicare began to cover percutaneous transluminal angioplasty of the carotid artery with concurrent stent placement, when furnished in accordance with US Food and Drug Administration (FDA) protocols governing Category B (nonexperimental) investigational device exemption clinical trials.[16] Angioplasty of the carotid artery, when provided solely for the purpose of carotid artery dilation concurrent with carotid stent placement, is considered to be a reasonable and necessary service when provided in the context of clinical trials.

In March 2005, Medicare began to provide coverage for percutaneous transluminal angioplasty of the carotid artery concurrent with the placement of an FDA-approved carotid stent with embolic protection for the following groups of patients:

- Those who would be at high risk during carotid endarterectomy and who also have symptomatic carotid artery stenosis of 70% or greater. Coverage is limited to procedures performed using FDA-approved carotid artery stenting systems and embolic protection devices.

- Those who would be at high risk during endarterectomy and who have symptomatic carotid artery stenosis of 50% to 70%, in accordance with the Category B Investigational Device Exemption clinical trials regulation, as a routine cost under the clinical trials policy, or in accordance with the national coverage determination on carotid artery stenting post-approval.
- Those who would be at high risk during carotid endarterectomy and have asymptomatic carotid artery stenosis greater than 80%, in accordance with the Category B Investigational Device Exemption clinical trials regulation, as a routine cost under the clinical trials policy, or in accordance with the national coverage determination on carotid artery stenting postapproval studies.

As noted above, Medicare and Medicaid will only cover carotid stenting if the stent system is FDA-approved, with concomitant use of a distal embolic protection device. However, in view of conflicting data from stenting trials to date, including EVA-3S[13] and SPACE,[14] it remains to be seen if emboli protection devices significantly reduce periprocedural stroke rates. The FDA recommends that if it is not technically possible to use one of these devices, then the procedure should be aborted due to safety issues.

These coverage decisions are an important practical aspect of carotid stenting and they should be familiar to physicians when they see and refer patients with carotid disease.

WHAT CAN WE SAY AT THIS POINT?

Given the multiple recent and ongoing trials of stenting vs endarterectomy in carotid stenosis, debate continues as to what the role of stenting will be in the future. What can we say at this point?

In patients with asymptomatic carotid stenosis of greater than 60% or symptomatic carotid stenosis of greater than 50%, carotid endarterectomy has been proven to be superior to medical therapy alone.

The efficacy and safety of carotid stenting compared with carotid endarterectomy is still uncertain. In the trials reviewed above, carotid stenting did not appear to have a clear advantage over endarterectomy in patients at average surgical risk. Stenting may be most advantageous when used in patients with symptomatic carotid stenosis who would be at high operative risk, as indicated by the SAPPHIRE trial.

In patients with severe but asymptomatic carotid stenosis who are at high operative risk, the addition of carotid angioplasty and stenting to maximum medical therapy remains controversial. The periprocedural complication rate in these patients may actually exceed the rate of stroke in asymptomatic patients with greater than 60% stenosis who do not undergo stenting or surgery. In addition, subgroup analyses of patients with 70% to 99% symptomatic stenosis in various trials show that surgical benefit is greater in men than in women, and it remains to be seen whether there is any benefit in women with moderate stenoses, asymptomatic lesions, or both.[17]

Antihypertensive, antiplatelet, and statin drugs remain the cornerstone of therapy

Further experience and study are needed, and the results of the Carotid Stenting vs Surgery of Severe Carotid Artery Disease and Stroke Prevention in Asymptomatic Patients (ACT I) study (comparing stenting and surgery in asymptomatic carotid stenosis), and the ongoing CREST trial (comparing stenting and surgery in symptomatic and asymptomatic carotid stenosis) are eagerly awaited. Until then, clinicians should continue to weigh individual patient risks and benefits when referring patients for surgical treatment of carotid atherosclerotic disease. Regardless of whether surgery is undertaken, maximal medical therapy with the use of antiplatelet agents, blood pressure control, and statin therapy remains the mainstay of treatment.

REFERENCES

1. **Incidence and Prevalence: 2006 Chart Book on Cardiovascular and Lung Diseases**. Bethesda, MD: National Heart, Lung, and Blood Institute; 2006.
2. **Adams HP Jr, Bendixen BH, Kappelle LJ, et al**. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke 1993; 24:35–41.
3. **Carrera E, Maeder-Ingvar M, Rossetti AO, Devuyst G, Bogousslavsky J; Lausanne Stroke Registry**. Trends in risk factors, patterns and causes in hospitalized strokes over 25 years: The Lausanne Stroke Registry. Cerebrovasc Dis 2007; 24:97–103.
4. **North American Symptomatic Carotid Endarterectomy Trial**

Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. N Engl J Med 1991; 325:445–453.
5. **Barnett HJ, Taylor DW, Eliasziw M, et al**. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. North America Symptomatic Carotid Endarterectomy Trial Collaborators. N Engl J Med 1998; 339:1415–1425.
6. **European Carotid Surgery Trialists' Collaborative Group**. Randomized trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). Lancet 1998; 351:1379–1387.
7. **Halliday A, Mansfield A, Marro J, et al; MRC Asymptomatic Carotid Surgery Collaborative Group**. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomized controlled trial. Lancet 2004; 363:1491–1502.
8. **Executive Committee for the Asymptomatic Carotid Atherosclerosis Study**. Endarterectomy for asymptomatic carotid artery stenosis. JAMA 1995; 273:1421–1428.
9. **Cremonesi A, Setacci C, Bignamini A, et al**. Carotid artery stenting: first consensus document of the ICCS-SPREAD Joint Committee. Stroke 2006; 37:2400–2409.
10. **CAVATAS Investigators**. Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomized trial. Lancet 2001; 357:1729–1737.
11. **CARESS Steering Committee**. Carotid revascularization using endarterectomy or stenting systems (CARESS): phase I clinical trial: J Endovasc Ther 2003; 10:1021–1030.
12. **Yadav JS, Wholey MD, Kuntz RE, et al; Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy Investigators**. Protected carotid-artery stenting versus endarterectomy in high-risk patients, N Engl J Med 2004; 351:1493–1501.
13. **Mas JL, Chatellier G, Beyssen B, et al; EVA-3S Investigators**. Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis. N Engl J Med 2006; 355:1660–1671.
14. **Ringleb PA, Allenberg J, Bruckmann H, et al; SPACE Collaborative Group**. 30 day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomised non-inferiority trial. Lancet 2006; 368:1239–1247.
15. **CREST**. Carotid Revascularization Endarterectomy vs Stent Trial. The Internet Stroke Center. www.strokecenter.org/trials/trialDetail.aspx?tid=80&search_string=crest.
16. **Center for Medicare and Medicaid Services**. Expansion of coverage for percutaneous transluminal angioplasty (PTA). www.cms.hhs.gov/ContractorLearningResources/downloads/JA3811.pdf.
17. **Rothwell PM, Goldstein LB**. Carotid endarterectomy for asymptomatic carotid stenosis: asymptomatic carotid surgery trial. Stroke 2004; 35:2425–2427.

***ADDRESS**: Peter Rasmussen, MD, Cerebrovascular Center, S80, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail rasmusp@ccf.org.*