Carotid Stenting vs Endarterectomy: New Results in Perspective

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Carotid artery stenosis is a major risk factor for stroke, and treatments for this condition to decrease the risk of stroke include medical therapy, carotid endarterectomy (CEA), and, more recently, carotid angioplasty and stenting (CAS). Randomized controlled trials comparing the efficacy of CEA vs medical therapy showed a clear benefit for CEA in patients with symptomatic carotid artery stenosis of greater than 70% and a lesser benefit in patients with 50% to 69% stenosis. Treatments have evolved in the ensuing 20 years, and a new method, CAS, has emerged as a possible alternative to CEA. In early results, CAS proved feasible but did not compare favorably with CEA. Later and larger-scale studies comparing CAS to CEA failed to reach conclusions regarding a clear neurologic outcome advantage of one method over the other. This subject was of sufficient interest that 2 larger-scale randomized controlled trials comparing CAS and CEA, the Carotid Revascularization Endarterectomy vs Stenting Trial and the International Carotid Stenting Study, were undertaken to further explore this issue. This brief review places the new data arising from these studies in the context of prior efforts to address the problem of carotid artery stenosis and explores further opportunities for improvement and patient recommendations in light of these new findings.

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ACAS = Asymptomatic Carotid Atherosclerosis Study; CAS = carotid angioplasty and stenting; CEA = carotid endarterectomy; CREST = Carotid Revascularization Endarterectomy vs. Stenting Trial; DWI = diffusion-weighted magnetic resonance imaging; ECST = European Carotid Surgery Trial; EPD = embolic protection device; EVA-3S = Endarterectomy vs Angioplasty in Patients with Symptomatic Severe Carotid Stenosis; FLAIR = fluid-attenuated inversion recovery; ICSS = International Carotid Stenting Study; MI = myocardial infarction; MT = medical therapy; NASCET = North American Symptomatic Carotid Endarterectomy Trial; RCT = randomized controlled trial; SAPPHIRE = Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy; SF-36 = 36-Item Short-Form Health Survey; SPACE = Stent-protected Percutaneous Angioplasty of the Carotid vs Endarterectomy

The past year has seen the publication of 2 large, widely anticipated, multicenter, randomized controlled trials (RCTs)[1,2] examining the relative merits of carotid angioplasty and stenting (CAS) vs carotid endarterectomy (CEA) as treatments to decrease the risk of stroke in patients with moderate to severe (>50%) carotid artery stenosis. The results may help clinicians and patients make a more informed choice about which of the 2 procedures is more appropriate for treating carotid occlusive disease. This article provides specific background information that helps place these new results in a broader context.

In the United States, 795,000 strokes occur each year, or about 1 stroke every 40 seconds. Of these, 600,000 are new strokes. According to the National Center for Health Statistics, stroke is the third leading cause of death and is a leading cause of long-term disability.[3] The direct and indirect costs associated with stroke for 2010 are projected to total $73.7 billion. The prevalence of stroke in patients 20 years or older is approximately 2.9% across the entire US population, with significant regional, age, sex, and racial differences in prevalence. Most strokes (approximately 83%) are ischemic and thromboembolic. This major health issue has been addressed in a number of ways, including identification of risk factors, modifiable risk factor management, medical therapy (MT), and interventional management.

The primary modifiable risk factors associated with stroke are hypertension, atrial fibrillation, cigarette smoking, diabetes mellitus, dyslipidemia, physical inactivity, and obesity. Evidence that reducing these risk factors decreases the prevalence of stroke was suggested in the Framingham Study, which assessed trends in incidence and severity of stroke over a 50-year period.[4] A significant trend in reduced stroke incidence and a corresponding reduction in risk factors suggested the importance of risk factor reduction in decreasing stroke incidence. To put this in perspective, projecting the risk reduction of approximately 25% observed in the Framingham Study across the entire population would result in about 200,000 fewer strokes per year. Although statistical limitations and regional variations in the incidence of stroke make this an oversimplified projection, it does suggest that providing support to risk factor reduction may provide the greatest reduction in stroke incidence. The pertinence of such findings to patients with established carotid occlusive disease, however, is unclear.

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The prevalence of asymptomatic moderate to severe (≥50%) carotid artery stenosis is estimated at 5% to 9% in those 65 years or older,[5,6] with significantly higher prevalence in men than in women. Given that approximately 12.6% of the US population is in this age group, 1.3 to 2.4 million patients may have this condition, not including additional cases in those aged 40 to 65 years. The prevalence of symptomatic carotid artery stenosis is less well characterized, but the annual prevalence of transient isch-

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TABLE. **Randomized Controlled Trials of Surgical and Interventional Treatment and Medical Therapy in Patients With Specified Carotid Artery Stenosis**[a]

Study	No. of patients	Last enrollment	Carotid artery stenosis (%)[b]	Patient status	Intervention benefit?	*P* value	Annual ARR (%)
NASCET[9]	659	2/1991	70-99	Symptomatic	Yes	<.001	11.3
NASCET[10]	858	12/1996	50-69	Symptomatic	Yes	.045	1.3
ECST[11]	646	1/1991	70-99	Symptomatic	Yes	<.001	4.2
ECST[11]	429	1995	50-69	Symptomatic	Yes	.05[c]	1.1
VA[12]	444	9/1987	50-99	Asymptomatic	Yes	<.001	3.0
ACAS[13]	1662	10/1993	60-99	Asymptomatic	Yes	.004	1.2
ACST[14]	3120	7/2003	60-99	Asymptomatic	Yes	<.001	1.1
CAVATAS[15]	504	7/1997	50-99	Symptomatic	No	.90	0.0
SAPPHIRE[16,17]	334	7/2002	50-99	Both, high risk	Noninferior	.71	0.0
SPACE[18]	1200	2/2006	50-99	Symptomatic	No	.09	0.0
EVA-3S[19]	527	9/2005	60-99	Symptomatic	No	.004	–3.3
ICSS[1]	1713	10/2008	50-99	Symptomatic	No	.006	–1.1
CREST[2]	2502	7/2008	50-99	Both	Equivalent	.51	0.0

[a] ACAS = Asymptomatic Carotid Atherosclerosis Study; ACST = Asymptomatic Carotid Surgery Trial; ARR = absolute risk reduction; CAS = carotid angioplasty and stenting; CAVATAS = Carotid and Vertebral Artery Transluminal Angioplasty Study; CEA = carotid endarterectomy; CREST = Carotid Revascularization Endarterectomy vs Stenting Trial; ECST = European Carotid Surgery Trial; EVA-3S = Endarterectomy vs Angioplasty in Patients with Symptomatic Severe Carotid Stenosis; ICSS = International Carotid Stenting Study; MT = medical therapy; NASCET = North American Symptomatic Carotid Endarterectomy Trial; SAPPHIRE = Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy; SPACE = Stent-protected Percutaneous Angioplasty of the Carotid vs Endarterectomy; VA = Veterans Affairs Cooperative Study.

[b] Methods used for determining the percentage of carotid artery stenosis were not the same in all studies. In ACST, for example, Duplex ultrasonography was the primary method.

[c] For the same end point as used in NASCET; *P*=.43.

emic events is estimated at 4.9 million patients.[7] Nearly 36% of these will have moderate to severe carotid artery stenosis.[8] Given the prevalence of moderate to severe carotid artery stenosis and its contribution to stroke risk, considerable effort has been expended to match such patients with the most effective treatments. Randomized controlled trials of surgical and interventional treatment and MT (Table) have led to guidelines supported by class I evidence, recommending which patients will benefit from a given treatment.

LANDMARK TRIALS COMPARING CEA vs MT

In patients with symptomatic carotid artery stenosis, class I evidence from NASCET (the North American Symptomatic Carotid Endarterectomy Trial) and ECST (the European Carotid Surgery Trial) indicates that patients with greater than 50% stenosis can benefit from a combination of CEA and MT vs MT alone. The incidence of perioperative stroke (within 30 days of surgery) or death was 5.8% to 6.7% for combined CEA and MT vs 2.5% to 3.3% for MT alone.[9,10,20,21] This perioperative outcome disadvantage in patients treated with both CEA and MT was overcome at 3 to 6 months and remained so for the duration of the study. The absolute risk reduction increased with the severity of the carotid artery stenosis and decreased with moderate degrees of stenosis. The 2-year risk of ipsilateral stroke and stroke or death in patients with 70% to 99% carotid artery stenosis was 26.0% and 32.3% in patients treated with MT alone vs 9.0% and 15.8% in patients treated with both CEA and MT. To put this in context, approximately 8 CEAs would be required to decrease the number of strokes by 1 at 2 years after surgery. Patients with moderate stenosis (50%-69%) also benefited from CEA, but the risk reduction for stroke and stroke or death in NASCET (6.5% and 10.0%, respectively) was reduced. For NASCET and this patient group, approximately 20 CEAs would be required to reduce the number of strokes by 1 at 2 years after surgery in comparison with MT alone.[22] The ECST results for 50% to 69% carotid artery stenosis are more complex. When the angiographic results were reanalyzed using the technique for measuring the percentage of carotid artery stenosis in NASCET, the benefit for CEA in prevention of periprocedural death and any stroke was significant (*P*=.05). However, no significant benefit was found for CEA in the primary end point used in NASCET, periprocedural stroke and death and subsequent ipsilateral stroke (*P*=.43).[11]

Class I evidence from the Veterans Affairs Cooperative Study Group, the Asymptomatic Carotid Atherosclerosis Study (ACAS), and the Asymptomatic Carotid Surgery Trial also supports combined CEA and MT vs MT alone in asymptomatic patients with greater than 60% carotid artery stenosis[12-14]; however, the absolute risk reduction was smaller than observed in symptomatic patients with moderate to severe carotid artery stenosis. The risk of stroke or death within 30 days of CEA in these RCTs was from 2.3%

to 3.3% compared with 0.4% to 0.9% for MT during the same period. With projected 5-year follow-up in ACAS, risk for ipsilateral stroke and any perioperative stroke or death in patients with 60% or greater stenosis was reduced by 5.9% (11.0% vs 5.1% for MT and CEA, respectively). An estimated 48 to 83 CEAs would be required to decrease the number of strokes by 1 during a 2-year period. More recently, longer-term follow-up data indicate that the 10-year risk reduction was 4.6%, making the number required to treat with CEA in asymptomatic patients higher still.[23] Some consider this an indication of cost vs benefit and thus consider it controversial to provide surgery to asymptomatic patients with carotid artery stenosis of greater than 60%.[24-26] Nonetheless, the estimated percentage of patients undergoing CEA in the United States for asymptomatic carotid artery stenosis ranges from 50% to 90%.[22,27]

All these RCTs had strict selection criteria for both patients and surgeons, and the outcomes reported may not reflect outcomes in the community at large. The reported risk reduction for stroke in patients undergoing CEA is sensitive to stroke and death outcomes in the perioperative period. In asymptomatic patients, an increase of only 2% in the perioperative stroke and death rate from 3% to 5% would nearly eliminate any stroke risk reduction over 2 years.[22] Such information is rarely available to referring physicians for a variety of reasons, including lack of resources for adequate follow-up, the costs associated with maintaining an accurate database, and absent regulatory requirements for such data.

EARLY RESULTS FOR CAS vs CEA

Patients at increased risk of perioperative mortality due to coexisting cardiovascular, respiratory, or angiographic risk factors were excluded from the RCTs comparing outcomes for combined CEA and MT vs MT alone. Initial endovascular studies compared outcomes in high-risk patients for CEA vs endovascular carotid balloon angioplasty. In one of the first trials, CAVATAS (Carotid and Vertebral Artery Transluminal Angioplasty Study),[15] the 30-day stroke or death rate was 10% in both angioplasty- and CEA-treated patients, sufficiently high that these procedures may have eliminated any benefit compared with MT alone. Of the strokes due to cerebral infarction, 73% were intraprocedural in the endovascular group, with 3 (14%) of 22 occurring before angioplasty and 13 (59%) of 22 occurring immediately or soon after balloon dilatation or stenting. These data suggested that angioplasty resulted in distal propagation of atheromatous or other embolic material. Stents adapted for the carotid artery were introduced into medical practice during this trial (1994) and were used in only 26% of the endovascular cases. Because a subgroup analysis suggested that carotid stents decreased intraprocedural stroke risk, they became a standard primary treatment in endovascular trials owing to concerns about plaque rupture, carotid dissection, and thromboembolism with carotid angioplasty alone. The rate of severe stenosis or occlusion on ultrasonography at 1 year was 20% in the endovascular group and 5% in the CEA treatment group. Longer-term results (median follow-up, 5 years) demonstrated that the rate of nonperioperative stroke was not significantly different between endovascularly and CEA-treated patients (1.4% vs 1.1% per year, respectively),[28] but the authors appropriately indicated that the study was underpowered to detect such a difference. The initial CAVATAS results supported further study and development of endovascular technology, particularly with a view to decreasing intraprocedural stroke and restenosis.

Advancing on the previous results, the SAPPHIRE (Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy) study tested the hypothesis that CAS was noninferior to CEA in high-risk patients.[16] The endovascular proceduralists used a self-expanding, crush-resistant Nitinol stent and an embolic protection device (EPD) with 100-μm pore size in the wire mesh that was deployed distal to the carotid artery stenosis before stent deployment and angioplasty. Most patients (approximately 70%) in both treatment arms had asymptomatic carotid artery stenosis. The 30-day incidence of stroke or death was 3.7% and 5.3% for CAS- and CEA-treated patients, respectively. The authors added another end point, the incidence of myocardial infarction (MI), which was 1.9% for CAS-treated patients and 5.3% for CEA-treated patients. The inclusion of this end point in such studies is controversial[29] and may often have limited bearing on quality of life, as will be discussed. At 1 year, the incidence of stroke or death was 12.8% and 20.1% in CAS- and CEA-treated patients, respectively. The results suggested the noninferiority of CAS to CEA treatment in this high-risk patient group. Considering that approximately 70% of patients were asymptomatic, however, the incidence of stroke or death is higher than that reported previously,[12,13] raising concerns regarding the benefit for either CAS or CEA in high-risk asymptomatic patients. These results demonstrated the feasibility of using carotid stents with EPD. Left open was the question of efficacy compared with CEA in patients with symptomatic or asymptomatic carotid artery stenosis as shown in previous RCTs. A secondary end point assessed was cranial nerve palsy; unsurprisingly, it was lower in the CAS-treated patients.

Subsequently, the SAPPHIRE investigators reported longer-term results, and no difference between CAS and CEA was evident. The prespecified major secondary end point was any periprocedural stroke, death, or MI and ipsi-

lateral stroke or death. At 3 years, the cumulative evidence for that end point was 24.6% for CAS-treated patients and 26.9% for CEA-treated patients (*P*=.71).[17]

TRIALS OF CAROTID STENTING AND SURGERY IN CONVENTIONAL RISK PATIENTS

The EVA-3S (Endarterectomy vs Angioplasty in Patients with Symptomatic Severe Carotid Stenosis) trial was designed to test the hypothesis that CAS was noninferior to CEA in patients with symptomatic carotid artery stenosis of 50% or greater. EVA-3S was stopped prematurely for reasons of safety and futility, when the relative increase in the 30-day risk of stroke or death for CAS vs CEA was 2.5 (9.6% vs 3.9%). However, a variety of stents with or without EPD were used, and the level of experience of the endovascular interventionalists with carotid stenting varied significantly.[30] Most strokes (approximately 70%) in the CAS group occurred on the day of surgery, but it is unclear whether they occurred during the procedure. The incidence of stroke decreased from 25% in the early phase of the study in which EPDs were not used to 7.9% after the use of EPDs was required. Despite the small sample size, these differential results were considered compelling evidence supporting the use of EPDs during CAS. No significant difference was noted in the incidence of MI between CAS- and CEA-treated patients at 30 days (0.8% vs 0.4%, respectively). The EVA-3S investigators later published a follow-up report showing that, with median follow-up of 3.5 years, the cumulative probability of periprocedural stroke or death and subsequent ipsilateral stroke was 11.1% for CAS and 6.2% for CEA (*P*=.03).[19]

The larger multicenter SPACE (Stent-protected Percutaneous Angioplasty of the Carotid vs Endarterectomy) trial again tested the noninferiority hypothesis for CAS vs CEA in symptomatic patients with greater than 50% carotid artery stenosis using NASCET stenosis criteria.[18] To qualify for CAS in SPACE, endovascular interventionalists had to provide 25 consecutive successful angioplasty or stent procedures (not necessarily carotid). A variety of stents with or without prior angioplasty were permitted. Use of an EPD was optional. The incidence of ipsilateral stroke or death at 30 days was not significantly different between CAS- and CEA-treated patients (6.84% vs 6.34%). Of note, no periprocedural MIs were reported for CAS- or CEA-treated patients.

Noninferiority for CAS was not demonstrated, possibly because of the small difference in outcome results and an insufficient sample size. The CEA results obtained in this study compared well with those obtained in NASCET and ECST. An EPD was used in 27% of CAS cases, but subgroup analysis surprisingly suggested no difference in stroke rate between those with vs those without placement of an EPD. This subgroup analysis and its limitations were not explicitly described and are thus open to question. The incidence of stroke or death was higher in patients older than 75 years, and there was a suggestion that this effect was greater in the CAS-treated group.[31] At 2-year follow-up, findings for CAS vs CEA had not changed. During this time interval, the incidence rates of end points for CAS and CEA were indistinguishable.[32] The recurrence of greater than 70% carotid artery stenosis at 2 years was higher in CAS- vs CEA-treated patients (11.1% vs 4.6%) and bears further follow-up and study. This study suggested that, in symptomatic patients with greater than 50% carotid artery stenosis who met the exclusion criteria, there is no reason to prefer CAS over CEA. It also indicated that more highly powered RCTs will be required to address this question.

RECENT LARGE TRIALS COMPARING CAS vs CEA

Two large randomized trials sufficiently powered and funded to address the question of the relative safety of CAS vs CEA in symptomatic and asymptomatic patients with greater than 50% carotid artery stenosis by NASCET criteria have provided the clearest data on this subject to date. An MT arm in this patient population has been problematic to defend given the clear benefit of combined CEA and MT vs MT alone in the RCTs described previously. This is particularly true for patients with symptomatic severe carotid artery stenosis.

In the ICSS (International Carotid Stenting Study), 1713 patients were enrolled and randomized from 50 mostly European academic centers. The interim safety analysis has been reported. Limited experience was required for proceduralists to participate in the study.[1] To be designated as experienced, the interventionalist had to have performed at least 50 stenting procedures with at least 10 carotid artery cases. A variety of stents were permitted and a variety of EPDs were used in 72% of CAS-treated patients, possibly more accurately reflecting practice in the broader medical community. The mean time intervals from the most recent event to treatment were 35 days for CAS and 40 days for CEA. The main safety end point—stroke, death, or procedural MI at 120 days—was 8.5% and 5.2% for CAS and CEA, respectively (hazard ratio, 1.69; *P*=.006).

At 30 days, the incidence of disabling stroke was the same in both groups (1.7%), but the incidence of fatal and nondisabling stroke was significantly higher in CAS-treated patients. Of periprocedural strokes, 74% in CAS-treated patients and 44% in CEA-treated patients occurred on the day of the procedure. Whether most strokes in the CAS-treated patients were intraprocedural could not be ascertained on the basis of this report. The incidence of proce-

dural MI was less than 0.6% in both treatment groups, but 3 of the 8 MIs were fatal. Electrocardiography and biomarkers such as creatine kinase and troponin were not required at set times before and after the procedure, suggesting that the incidence of MI was underestimated in this study. The high proportion of fatal MI, nearly 40%, is probably accounted for by an assessment that includes only extreme presentations of MI.

The 30-day incidence of stroke or death in the CEA-treated group is among the best ever reported for symptomatic patients, and the results for the CAS group are in the same range as those for CEA in NASCET. The aggregate 30-day risk of stroke, death, or MI was 7.4% for CAS and 4.0% for CEA. As in other CAS vs CEA studies, more cranial nerve palsies occurred in the CEA-treated group. The incidence of severe hematoma, another finding with possible implications for morbidity, length of hospital stay, and cost, was significantly higher in CEA-treated patients. The ICSS authors concluded that CEA remains the treatment of choice for symptomatic patients with severe carotid artery stenosis who are suitable candidates for surgery.

CREST (the Carotid Revascularization Endarterectomy vs Stenting Trial) is the largest trial to date comparing outcomes in patients with symptomatic and asymptomatic carotid artery stenosis.[2] The study design was to test for superiority with the null hypothesis as the equivalence of the 2 treatments. The study enrolled 2502 patients at 117 centers in the United States and Canada. A rigorous training and credentialing process for proceduralists preceded randomization.[33] Surgeons and proceduralists had to have minimum acceptable outcome results for inclusion in the study. Exclusion criteria similar to those in NASCET and ACAS were used. The protocol specified use of a single stenting system and, when feasible, the same EPD in CAS-treated patients. The primary end point for the study was any periprocedural stroke, MI, death, or postprocedural ipsilateral stroke up to 4 years after intervention. The inclusion of MI in the aggregate end point differs from the earlier RCTs comparing combined CEA and MT with MT alone, except for ICSS, in which MI was a component of the main safety outcome. Myocardial infarction was rigorously defined by specifically timed enzyme (creatine kinase and troponin) and electrocardiographic studies and was independently adjudicated by a cardiologist blinded to the treatment. Unique among these studies, CREST included an assessment of general health status with the use of the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) at 2 weeks, 1 month, and 1 year after the procedure. An EPD was successfully used in 96% of CAS-treated patients.

Incidence of the primary end point at a mean follow-up of 2.5 years did not differ significantly (7.2% for CAS vs 6.8% for CEA; P=.51). However, the 30-day incidence of stroke or death was 4.4% and 2.3% for CAS- and CEA-treated symptomatic and asymptomatic patients, respectively, a difference that was significant. The incidence of MI was significantly higher in CEA- than in CAS-treated patients (2.3% vs 1.1%). Thus, the increase in stroke incidence in CAS-treated patients may be offset by an increase in MI in CEA-treated patients. Interestingly, the SF-36 data indicate that the impact on quality of life by MI was not significant, whereas the impact of major or minor stroke was significant. As a note of caution, however, end-organ function is not rigorously assessed for either stroke (cognitive testing) or for MI (echocardiographic assessment).

These were combined outcomes for both symptomatic and asymptomatic patients. However, no significant differences (CAS vs CEA) in results were noted when the outcomes were examined by symptomatic status. The 30-day incidence of stroke or death was 2.5% vs 1.4% in asymptomatic patients treated with CAS vs CEA, results that are about equal to those reported in ACAS for CEA-treated patients and superior to MT for CAS-treated patients. The 30-day incidence of stroke or death in symptomatic patients treated with CAS vs CEA was 6.0% vs 3.2%, results that are about equal to those obtained in NASCET for CEA and to MT for the CAS-treated patients. A 4-year Kaplan-Meier curve examining freedom from the primary end point demonstrated no significant difference in the curves for CAS vs CEA treatment out to 4 years (risk reduction, <1% per year), showing that both methods result in durable benefit. The SF-36 subscale data at 1 year indicate that the increased incidence of cranial nerve palsy in CEA-treated patients has no significant impact on quality of life.

These results corroborate and extend those of the ICSS study. From the stroke or death outcome perspective, CEA is superior to CAS in both asymptomatic and symptomatic patients undergoing invasive treatment. Using the primary end point described in the CREST study, however, the null hypothesis must be accepted. Even using the more widely accepted end point of stroke or death, the CREST and ICSS results suggest that a distinct improvement in both CEA and CAS outcomes has taken place since the NASCET and ECST results were published. The outcomes of CEA and CAS are unclear in patients excluded from these trials because of high surgical risk or other risk factors. If SAPPHIRE is taken as any indication, the risk of stroke or death will be higher in such patients in both treatment groups. Are there patients with moderate to severe carotid artery stenosis for whom CAS is the superior method? A notable finding in CREST is the trend indicating that CAS may be superior to CEA in younger patients (<70 years), a result that will require further verification. Nonetheless, these findings suggest that CAS may be the superior treat-

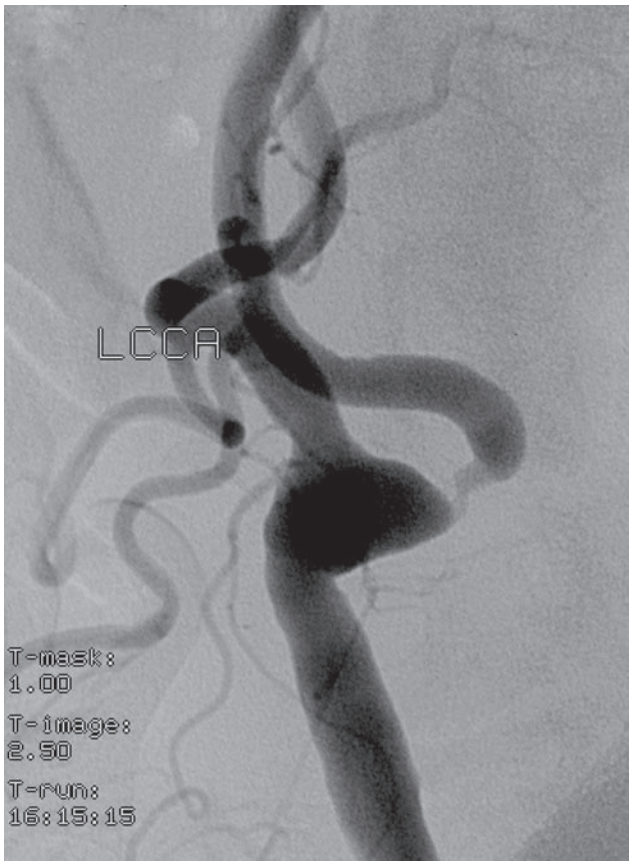

FIGURE. Left common carotid artery (LCCA) angiogram in a 78-year-old man demonstrating significant carotid tortuosity with a 90° angulated ostium of the left internal carotid artery and critical stenosis distal to the bifurcation. Such carotid tortuosity poses significant challenges to the endovascular proceduralist and may contribute to distal embolization during carotid angioplasty and stenting and positioning of a distal endovascular protection device.
From *J Invasive Cardiol*,[41] with permission.

ment for carotid occlusive disease in some patients. A preplanned meta-analysis of the pooled EVA-3S, SPACE, and ICSS trials provides additional support for this age effect on stroke and death outcomes for CAS vs CEA.[34]

MOVING TARGETS AND OPPORTUNITIES FOR FURTHER IMPROVEMENT

Since the initial RCTs demonstrating the benefit of combined CEA and MT vs MT alone, MT has evolved to include more potent antiplatelet agents, specifically clopidogrel, and treatments for dyslipidemia, primarily the statins. This moving target has not been systematically reexamined in an RCT. Growing evidence suggests that, in patients with asymptomatic carotid artery stenosis greater than 50% who are treated with MT, the incidence of stroke is low enough to justify reexamination of combined CEA and MT vs MT alone.[35,36] An RCT examining the relative benefits of combined CEA and MT, combined CAS and MT, or MT alone in this patient population may be warranted. Such a trial, SPACE-2, is already under way in Germany and Austria,[37] and ICSS-2 includes plans to examine outcomes in these treatment groups. In the United States, such a study would cost tens of millions of dollars, but some have suggested that performing 48 to 83 CEAs to decrease the number of strokes by 1 carries a cost that far outweighs the cost such a study would entail. This is particularly relevant because most CEAs performed in the United States are for asymptomatic patients with greater than 50% carotid artery stenosis.

Can CAS outcomes be improved? A clue may lie in the observation that 70% or more of all periprocedural strokes in CAS-treated patients occurred on the day of the procedure. More information is essential on the timing of stroke, especially as it relates to specific elements of the CAS procedure, such as initial catheterization, EPD placement, stent deployment, and EPD removal. Transcranial Doppler ultrasonography allows real-time assessment of when microembolic signals are detected in the insonated portion of the cerebral circulation. One study demonstrated that microembolic signals are detected during all steps of the CAS procedure despite the presence of an EPD.[38]

Whether an EPD provides any benefit remains a matter of debate. The EVA-3S results suggest benefit, whereas the ICSS results suggest possible harm. In a selected group of the ICSS patients, diffusion-weighted magnetic resonance imaging (DWI) was performed before, 1 to 3 days after, and 27 to 33 days after either CEA or CAS with or without an EPD.[39] A new DWI lesion was detected in 50% of patients in the stenting group (n=124) and 17% of patients in the CEA-treated group (n=107), possibly indicative of cerebral injury. Fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging performed at 1 month also demonstrated a difference between the treatment groups, although the percentage of patients with injury in each group was considerably lower with FLAIR imaging than with earlier DWI. Most interesting was the finding that, among patients treated with CAS, the incidence of new DWI lesions was significantly higher in those with an EPD (73%) than in those without (34%). Although advocated by some,[40] the use of DWI lesions as a surrogate marker for cerebral injury may be premature, given the dearth of sensitivity and specificity data for this method. Nonetheless, this finding suggests an opportunity to further improve on EPD technology, using some combination of magnetic resonance imaging and transcranial Doppler ultrasonography.

The increased incidence of embolization with CAS could result from carotid tortuosity (Figure),[41] a problem that may be more common in elderly patients. Carotid tor-

tuosity poses less of a problem for CEA, in which surgeons have proximal and distal control of the carotid artery. Some have advocated proximal protection for CAS, wherein a balloon is inflated in the common and external carotid arteries before traversing the lesion with a catheter.[42] This results in either no flow or retrograde blood flow through the instrumented carotid artery and may decrease distal propagation of embolic material with cannulation and carotid stenting, thus perhaps obviating the need for EPD.

WHAT TO RECOMMEND TO THE PATIENT?

Current RCT results indicate that outcomes are improving for patients requiring treatment for carotid artery stenosis, whether for intervention or MT. The stroke outcome benefits of intervention vs MT alone for patients with a symptomatic carotid artery stenosis of greater than 70% have decreased since the initial RCTs as a result of improvements in MT.[36] Nonetheless, intervention continues to confer an outcome benefit in this patient group. Clearly, a higher stroke risk is associated with CAS than with CEA when patients with symptomatic high-grade carotid occlusion are not differentiated. However, the CREST results suggest that outcomes are not significantly different between CAS and CEA when they are performed at centers with experienced proceduralists and when an aggregate end point of MI and stroke is used. Furthermore, patients younger than 60 years may have an equivalent or better stroke outcome with CAS vs CEA, and those younger than 70 years may have an equivalent or better aggregate outcome with CAS. For patients older than 70 years with symptomatic carotid artery stenosis, CEA remains the best option. However, for those at high risk for surgery, CAS will likely provide a benefit compared with MT. The same considerations apply to those with lower-grade (50%-69%) symptomatic carotid artery stenosis, with the understanding that the outcome benefit of intervention vs MT alone is significantly decreased.

The smaller stroke risk reduction benefit obtained in previous RCTs for patients with asymptomatic carotid occlusive disease undergoing CEA vs MT alone makes the decision of selecting intervention (CAS or CEA) challenging to both the clinician and the patient. The reduction in strokes achieved with current MT (approximately 50% lower incidence than that reported in ACAS) has doubled the number of patients needed to undergo CEA to reduce the number of strokes by 1. That number, already large after the initial ACAS report, is now approaching 200 patients. For CAS, the number can be estimated at approximately 500 patients. Ongoing studies comparing intervention with optimal MT in patients with asymptomatic carotid artery stenosis of greater than 50%, such as SPACE-2, may shed further light on this issue. For now, this decision is best reached after considering all comorbid conditions and anatomic issues for a given patient, with the understanding that stroke risk reduction outcome benefits are likely to be small.

Finally, all such considerations are contingent on minimum acceptable outcomes and procedural experience at a given facility. Referring physicians can increase the likelihood that patients will achieve these outcome benefits by becoming aware of the reported procedural experience and outcomes at the centers to which they refer their patients and placing such information in the context of the results described in this article.

CONCLUSION

The CREST and ICSS results are welcome and powerful additions to the body of literature on the relative merits of CEA and CAS as treatments for the continuing problem of carotid artery stenosis as a cause of stroke. Both studies demonstrate that outcomes for both CEA and CAS have improved significantly compared with results obtained in earlier RCTs, a trend that also holds true for MT. These results are likely to play an important role in future deliberations by the Centers for Medicare & Medicaid Services. We can all look forward to more progress and new data regarding the relative costs and benefits of CAS vs CEA, long-term restenosis rates, and further definition of subgroups that may benefit from specific interventions.

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