

# CAS in Asymptomatic Patients at High Risk for CEA: An Inappropriate and Unproven Option

BY ANTHONY J. COMEROTA, MD

All invasive procedures are associated with risks of adverse events. Stroke is the procedure-related adverse event that is most devastating for patients with asymptomatic carotid disease, the endpoint for which treatment is designed to avoid. A basic question that all physicians should address is, "Has the procedure that I am recommending been shown to benefit the patient with regard to the outcome for which the patient is being treated?" Namely, does carotid artery stenting (CAS) reduce the risk of stroke? The answer to this important question is "No," because CAS has never been shown to reduce stroke risk in any patient category, especially in patients with asymptomatic disease. That being the case, it is important and instructive to evaluate the available information regarding CAS, as well as the evolution of the argument that CAS should be recommended for patients with asymptomatic disease.

## TRIAL DATA

Randomized trials of best medical care versus carotid endarterectomy (CEA) in reasonable-risk patients have demonstrated the significant benefit of CEA in both symptomatic and asymptomatic patients.<sup>1-4</sup> Additionally, these trials have identified the natural history of carotid disease when treated with best medical care, albeit medical care available 15 to 20 years ago.

In the Asymptomatic Carotid Atherosclerosis Study (ACAS), the mean time from randomization to CEA was 12 days.<sup>3</sup> Because 30 days after the procedure is the accepted time frame for defining procedure-related events, 42 days from randomization was the intent-to-treat time frame for "procedure-related events" for both treatment groups. In patients who underwent CEA, the procedure-related stroke/death rate was 1.5%, whereas for patients randomized to best medical care, the stroke/death rate was .4% during the 42 days from ran-

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domization. It is safe to assume that medical care has improved during the past 15 years, with the development of statins, ACE inhibitors, second-generation platelet inhibitors, improved antihypertensives, and other pharmacotherapy. Therefore, comparing current invasive treatment options to best medical care results observed 15 or more years ago unquestionably casts the best medical care group in the worst-case scenario. The 1.5% procedure-related stroke/death rate for CEA in patients with asymptomatic carotid disease is admirably low and a worthy target for any intervention. However, even with a 1.5% procedure-related stroke/death rate, it requires 87 patients to be treated to avoid only one stroke.<sup>5</sup> Additionally, because women did not receive benefit from CEA as part of ACAS, it seems unreasonable to suggest CAS for women with asymptomatic carotid disease by extrapolation of the overall ACAS data.

Octogenarians also deserve special mention. It is now commonplace for CAS enthusiasts to refer to patients  $\geq 80$  years of age as being "high-risk" because they were excluded from the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and ACAS. However, they were excluded from these trials because patients  $\geq 80$  years were less likely to survive the 5-year-minimum projected study period independent of treatment for their carotid disease—not because investigators feared higher procedure-related events in older patients. Interestingly, a paradox has occurred with CAS in this subgroup of patients. CAS has resulted in procedure-related stroke and death rates of 13% to 25%,<sup>6-8</sup> observa-

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tions not noted in patients undergoing CEA.<sup>9</sup> Until data are available indicating otherwise, it is clear that octogenarians should not be offered CAS for any indication unless they are part of a randomized trial.

In general, randomized trials comparing CAS with CEA have failed to show benefit of CAS. On the contrary, the bulk of data actually show that CEA is superior. The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) demonstrated disappointing results of both CAS and CEA.<sup>10</sup> Ipsilateral stroke or death occurred in 10% of patients undergoing CAS and 9.9% of those undergoing CEA. Severe carotid restenosis at 1 year was more common after CAS (18.5%) in comparison to CEA (5.2%,  $P < .001$ ).<sup>11</sup> In those patients with severe recurrent stenosis, ipsilateral symptoms occurred significantly more frequently in CAS patients (7.8%) than CEA patients (0%,  $P < .02$ ). Although stents were used in only 26% of patients undergoing carotid angioplasty, the presence or absence of a stent did not influence the rate of restenosis. It is evident that the patients in CAVATAS did not benefit from either interventional procedure, and these results are no better and likely worse than the natural history of the disease for which the patients were being treated.

A trial randomizing symptomatic patients to CAS or CEA was stopped by the study's Data and Safety Monitoring Board.<sup>12</sup> It became evident that it was unethical to continue in light of the high morbidity rate of CAS. The stroke rate of 12.2% resulting from CAS was significantly greater than the 3.6% observed with CEA ( $P < .02$ ).

Another randomized trial of CAS versus CEA in patients with symptomatic  $\geq 70\%$  carotid stenosis was initiated, which was stopped by the Data and Safety Monitoring Board after 17 patients were randomized because of exorbitantly high complications of CAS (71%) versus none in the CEA group.<sup>13</sup> Enthusiasts argue that the early trials applied outdated techniques and that catheters and delivery systems are now lower-profile, stents are improved, and cerebral protection and pharmacotherapy are enhanced. I believe all of this is true; however, the question remains: have the instruments, techniques, and pharmacotherapy been improved to the point of patient benefit? Is it not the responsibility of the carotid interventionists to show that CAS is better than the natural course of the disease treated with today's best medical care?

#### ARCHeR/SAPPHIRE

Two carotid stenting systems, Acculink/Accunet (Guidant Corporation, Indianapolis, IN) and Precise/AngioGuard (Cordis Corporation, a Johnson & Johnson company, Miami, FL), have been approved by the

FDA for use in the US as a result of the Acculink for Revascularization of Carotids in High-Risk Patients (ARCHeR) and Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) data sets, respectively.<sup>14-16</sup> An evaluation of the data that led to their approval should help physicians put into perspective the relative merits of CAS, understanding that the CAS results in these data sets are better than those that can be expected in the general community because the CAS interventionists were chosen due to their recognized expertise.

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The ARCHeR registry included 581 patients considered at high risk for CEA.<sup>14</sup> Forty-eight percent of patients were asymptomatic. The device failed in 7.9%. The overall 30-day stroke/death rate was 6.6%. Thirty-two percent of patients were treated for recurrent carotid stenosis, which is associated with low procedure-related risk because most are neointimal fibroplasia and have low embolic potential. Sixty-eight percent were treated for primary atherosclerosis of the carotid bifurcation. In the atherosclerotic patients, the 30-day stroke/death rate was 9.5%, and in the dialysis-dependent subset of patients, the 30-day stroke/death rate was 29%. Unfortunately, data regarding the procedure-related event rate in asymptomatic atherosclerotic patients were not separated from the overall group.

The SAPPHIRE trial compared CAS with CEA in patients at high risk for CEA.<sup>15,16</sup> Seventy percent of the patients were asymptomatic. The published results of the randomized cohort demonstrated comparability between the two techniques, with a trend toward better outcomes in the CAS group, predominantly due to less cardiac morbidity.<sup>15</sup> Because of these observations, enthusiasts for CAS argue that the procedure should be offered to patients with asymptomatic disease. However, what is important to patients (and should be important to physicians) is whether patients will receive benefit from their intervention, not whether CAS is comparable to another procedure associated with high morbidity and from which patients receive no benefit.

It is interesting to examine the design and evolution of the SAPPHIRE study, which compared patients at high risk for CEA to either CAS or CEA. However, the majority of patients were treated as part of the SAPPHIRE registry due to physicians' preference, who

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judged that CEA should not be offered.

The evolution of SAPHIRE is interesting but unfortunately flawed. The SAPHIRE Feasibility Study was designed to test the angioplasty and stent device and compare the outcome to historical controls of CEA. Stopping rules for CAS were calculated using event rates of stroke and death that exceeded twice the frequency recorded in CEA trials. The event rate selected for the calculation was 6.7%, taken from the cohort of NASCET patients having 50% to 69% stenosis.<sup>2</sup> This was higher than the 5.8% procedure-related event rate observed in the NASCET patients having 70% to 99% stenosis and much higher than the 1.5% procedure-related event rate observed in ACAS.

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Although the demographics and clinical presentation of patients in the Feasibility Study were not revealed, there is nothing to suggest that they differed from the remaining patients in SAPHIRE, which reported that 70% were asymptomatic and 30% were symptomatic.

The stopping threshold for the Feasibility Study was a procedure-related event rate of 13.4% (twice the risk of CEA in the 50% to 69% stenosis NASCET cohort). The major procedure-related adverse event rate of the Feasibility Study was 6.9%. Therefore, SAPHIRE was continued. However, because 70% of SAPHIRE patients were asymptomatic, the appropriate calculation of the stopping threshold should have been apportioned according to the CEA-related risk reported in ACAS and the overall procedure-related risk from NASCET. When calculated and apportioned appropriately, the 30-day CEA event rate would have been calculated to be 2.9%, and the 6.7% observed event rate of CAS in the Feasibility Study would have exceeded twice the known risk of CEA, and SAPHIRE would not have been continued.

The interventionists performing CAS in SAPHIRE were chosen because of their widely known skills and reputation. Therefore, the SAPHIRE results are the best that can be expected and, in all likelihood, community results with CAS will be substantially worse. Consequently, if CAS is widely performed for asymptomatic disease, it is likely that the stroke/death rate will exceed that observed in SAPHIRE and far exceed that observed with best medical care.

The SAPHIRE results pointed to a reduction in strokes/death/myocardial infarction in CAS patients compared to those undergoing CEA. Often overlooked in the appreciation of these data is the fact that a significantly greater number of CAS patients had previous coronary revascularization (CABG, PCI) compared to the CEA patients. Coronary revascularization is known to reduce the risk of subsequent procedure-related death and myocardial infarction.<sup>17</sup> Additionally, all CAS patients were treated with clopidogrel according to protocol guidelines, which was not the case with CEA patients. Therefore, CAS patients were protected from myocardial ischemia by virtue of previous coronary revascularization and more aggressive pharmacotherapy, a significant bias.

Patients in the SAPHIRE trial were either part of the smaller randomized cohort or were treated as part of the registry due to physician preference. All patients with asymptomatic disease who underwent CAS in SAPHIRE had a 30-day stroke/death rate of 5.4%. This should be compared to the anticipated .4% if treated with best medical care. This resulted in an approximate increase of 1400% in the relative risk of stroke and death during the next month if treated with CAS. In light of this high procedure-related risk, one must ask whether these high-risk patients had high-risk lesions. It appears that is not the case, because <2% of these asymptomatic CAS patients had  $\geq 90\%$  internal carotid artery stenosis, and <20% of CAS patients had  $\geq 80\%$  stenosis as reported by the arteriographic core laboratory. It does not seem reasonable for high-risk patients with <80% carotid stenosis to be offered a procedure associated with the procedure-related stroke/death rate observed with CAS. Even in patients with  $\geq 80\%$  stenosis, a procedure-related stroke/death rate of more than 5% will not show benefit.

When evaluated at 12 months, 28% of registry patients had >50% restenosis. Because the mean percent diameter reduction stenosis before stenting was 66%, can this be considered a worthwhile benefit in light of the procedure-related risk? Most physicians would agree that an intervention that only achieves a 10% to 15% improvement in luminal diameter at 1 year in patients with asymptomatic disease is not worth the 5.4% procedure-related risk of stroke/death or the associated expense of the procedure.

## CONCLUSION

After evaluating the body of data available on CAS, and giving weight to results of randomized trials and the registries evaluated by the FDA that led to device approval, treating patients who have asymptomatic carotid disease with CAS cannot be recommended. The procedure-related event rate is exorbitant in patients  $\geq 80\%$

years and is far from the procedure-related event threshold to show benefit if compared to best medical care. Because CAS has not been shown to prevent stroke, patients  $\geq 80$  years should not be offered the procedure. There are no data suggesting that female patients will benefit, and current results of CAS exceed the morbidity threshold to argue potential benefit. Therefore, it is inappropriate for patients with asymptomatic carotid stenosis to be treated with carotid angioplasty and stenting unless they are part of a randomized trial. ■

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There has traditionally been substantial resistance to the concept of pre-emptive revascularization of severe carotid stenosis in asymptomatic patients. Although the surgical community has embraced carotid endarterectomy (CEA) of asymptomatic carotid disease, the reception has been much less warm in neurological circles. Although the asymptomatic carotid atherosclerosis trial (ACAS) provided clear evidence for the superiority of medical management combined with CEA versus medical management alone in asymptomatic patients with 60% or more stenosis, the benefit was small in absolute terms and was skeptically received.<sup>1</sup>

However, the benefit of CEA in asymptomatic patients was confirmed last year with the publication of the very large asymptomatic carotid stenosis trial (ACST).<sup>2</sup> The ACST trial randomized 3,120 patients to CEA plus best medical treatment versus medical treatment alone. Stenosis  $>60\%$  on ultrasound had to be present. There was a 2.8% perioperative risk of stroke and death in the surgical arm. At 5 years, the risk of stroke or perioperative death was 11.78% in the medical treatment alone arm versus 6.42% in the surgical treatment arm, with the benefit becoming apparent at approximately 2 years after randomization. For the first time, the ACST trial also demonstrated a benefit for women with surgery. It also demonstrated for the first time a reduction in contralateral stroke after CEA in asymptomatic patients, indicating that improvement in collateral circulation to the contralateral hemisphere can have a benefit in terms of stroke prevention.

Physicians opposed to CEA in asymptomatic patients hypothesize that if all of these patients received adequate medical treatment, there would be no need for revascularization. The ACST trial clearly disproves this sentiment: medical treatment was carefully monitored, and there were very high rates of compliance for antiplatelet therapy, antihypertensive therapy, and lipid-lowering therapy, and yet the surgical arm still did better than medical treatment alone. In summary, the evidence for revascularization for asymptomatic carotid stenosis with surgery is fairly convincing.

## CAROTID STENTING WITH EMBOLI PROTECTION

Let us move on to the use of a less-invasive treatment, carotid artery stenting with emboli protection, for the treatment of asymptomatic carotid disease. I will confine my remarks to patients with comorbid conditions at high risk for surgery because to date, although this has been the most carefully studied set, it is important to note that there are ongoing trials in