CAS in Asymptomatic Patients

Is carotid artery stenting justified for patients with asymptomatic carotid artery stenosis?

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The recent randomized trials of carotid endarterectomy (CEA) versus carotid artery stenting (CAS) have certainly provided food for thought. In many other arterial territories, the Achilles' heel of the endovascular option is usually durability rather than procedural risk (for example, endovascular aneurysm repair). It is clear, however, that after a safe CAS procedure, the results may be as durable as CEA, certainly in the intermediate term (2–4 years), in terms of survival free of ipsilateral stroke.[1,2] It is also quite clear that CAS may be associated with an unacceptable procedural hazard. With procedural all-stroke/death rates between 6.8% and 9.6% in recent trials of symptomatic patients, can endovascular treatment of asymptomatic patients in whom there is an exceedingly narrow risk-benefit margin be justified?[3,4]

The question that needs to be addressed is whether or not CAS can be performed with an all-stroke/death rate of ≤ 3% (the upper limit set by the American Heart Association for acceptable procedural risk associated with CEA) in asymptomatic patients: the so-called 3% rule.[5] This article seeks to explore the available literature, focusing on level I evidence when possible, to answer this question.

RATIONALE AND EVIDENCE BASE FOR INTERVENTION IN ASYMPTOMATIC CAROTID STENOSES

In offering intervention to this patient population, the intention is to reduce the risk of ipsilateral ischemic hemispheric stroke by the removal or stabilization of a potential source of emboli and/or the removal or widening of a flow-limiting lesion. The level I evidence supporting this strategy is based on the Veterans Affairs (VA) Study, the Asymptomatic Carotid Atherosclerosis Study (ACAS), and the Asymptomatic Carotid Surgery Trial (ACST).[6-8] In the VA study, men with > 50% carotid stenosis (as indicated by angiography) were randomized to aspirin alone or aspirin plus CEA. In ACAS, patients were randomized between best medical therapy or CEA plus best medical therapy, whereas in ACST, patients were randomized to immediate or deferred CEA.

ABSOLUTE, RELATIVE RISK REDUCTIONS, AND NUMBERS NEEDED TO TREAT BASED ON RCTs

The pooled data from ACAS and ACST (4,779 patients) demonstrated that with a net procedural hazard (stroke and death) of 2.9%, the relative risk reduction (RRR) for patients having a carotid intervention was 31% ($P = .001$), meaning an absolute risk reduction (ARR) of approximately 3% over approximately 3 years. Therefore, the number needed to treat (NNT) is approximately 33 interventions to prevent one stroke with no statistical benefit until approximately 3 years after intervention (indicating that patients should have at least this life expectancy to benefit). This would appear to be quite an undertaking.

ANNUAL STROKE RISK FOR PATIENTS WITH ASYMPTOMATIC CAROTID ARTERY STENOSIS

Data from ACAS and ACST suggest a stroke risk of approximately 2% per year in patients with carotid stenosis ≥ 60%. However, outcome rates from randomized controlled trials (RCTs) lack generalizability,[9] and the REACH registry, which recently detailed cardiovascular event rates in 30,329 patients without carotid disease and 3,164 patients with asymptomatic carotid disease, revealed higher stroke rates despite contemporary best medical therapy in > 70% of included patients. Compared with patients without

carotid disease, those with asymptomatic carotid stenosis had higher age- and sex-adjusted 1-year rates of transient ischemic attack (3.51% vs 1.61%; $P < .0001$), nonfatal stroke (2.65% vs 1.75%; $P = .0009$), fatal stroke (0.49% vs 0.26%; $P = .04$), cardiovascular death (2.29% vs 1.52%; $P = .002$), and composite endpoint of cardiovascular death/myocardial infarction/stroke (6.03% vs 4.29%; $P < .0001$).[10]

IDENTIFYING PATIENTS WITH ASYMPTOMATIC CAROTID STENOSIS AT INCREASED RISK OF STROKE

What is quite clear is that there are subsets of asymptomatic patients who are at increased risk of stroke in whom the ARR is higher and the NNT lower. Risk modifiers include age, gender, previous cerebrovascular symptoms, contralateral events or interventions, the presence of silent infarcts on brain imaging (computed tomography or magnetic resonance), plaque characteristics, severity of stenosis (a surrogate marker of potential embolic load), and medical therapy. For example, in ACAS, there was an RRR of 50% and 9% for patients < 68 years and > 68 years, respectively. In ACST, there was an ARR of 7.8% and 3.3% in patients < 75 and > 75 years, respectively. ACST reveals an absolute 5-year gain of 7.4% ± 1.5% for patients with a stenosis of < 80% and a gain of only 4.6% ± 1.8% for patients with a stenosis of 90% to 99%. The relationship between degree of stenosis and benefit from intervention for asymptomatic patients is, of course, the exact opposite from that of symptomatic patients. ACST demonstrated higher absolute 5-year gain for patients with previous contralateral symptoms, and the REACH registry revealed that stroke was powerfully predicted by previous cerebrovascular ischemic events.

THE 3% RULE: CONTEMPORARY CAS RESULTS FROM RANDOMIZED TRIALS

Of the recent sizeable randomized trials comparing CEA and CAS, only SAPPHIRE and CREST have included asymptomatic patients; CREST is yet to report. SAPPHIRE included only patients who were conventionally considered to be at high risk for CEA and chose as its primary outcome event a composite endpoint that included myocardial infarction. This was novel for trials of carotid intervention that had previously focused only on stroke and death. However, periprocedural or perioperative myocardial infarction is a major safety endpoint that is very relevant to the patient and should be evaluated as part of any cardiovascular trial, including those that evaluate carotid interventions.

In the periprocedural period, the cumulative incidence of death, myocardial infarction, or stroke among patients with asymptomatic carotid artery stenosis was 5.4% among those undergoing CAS as compared with 10.2% among those undergoing CEA ($P = .20$). It is not clear what the isolated stroke/death rates were. The SAPPHIRE investigators argue that because asymptomatic patients in SAPPHIRE had > 80% carotid stenosis, higher procedural risks were acceptable because the stroke rates associated with tighter carotid stenoses were higher in these patients than in those with > 60% stenoses who were included in ACAS and ACST. This contradicts the subgroup analyses of ACAS and ACST, and notably, the reference given to support the investigators' claim dates to 1986, at which time patients would not have been on best medical therapy by contemporary standards.[11] It should also be kept in mind that a number of patients in SAPPHIRE were included on the grounds of medical comorbidity. It is not clear what proportion of patients had chronic obstructive pulmonary disease/ischemic heart disease, etc., compared to those deemed to be at high surgical risk for technical reasons (eg, restenosis after CEA or radiation stenosis). Patients with medical comorbidities have reduced survival rates, and therefore, it is important to ensure as low a procedural hazard as possible for these patients.

REGISTRY DATA

Data from two prospective, multicenter, postmarket surveillance studies in high-surgical-risk patients were recently reported: 2,145 patients from the Emboshield and Xact Postapproval Carotid Stent Trial (EX) (Abbott Vascular, Santa Clara, CA) and 4,175 patients from the Carotid Acculink/Accunet Postapproval Trial to Uncover Rare Events (C2) (Guidant Corporation).[12] Both studies had pre- and postprocedure neurological evaluation and independent adjudication of neurological events. The overall 30-day death and stroke rates were 4.1% (95% confidence interval [CI], 3.3%–5%) for EX and 3.4% (95% CI, 2.9%–4%) for C2. In the population comparable with American Heart Association guidelines (< 80 years), the combined 30-day death and stroke rates were 5.3% (95% CI, 3.6%–7.4%) for symptomatic patients and 2.9% (95% CI, 2.4%–3.4%) for asymptomatic patients, independent of unfavorable risk factors (anatomic or physiologic); in patients > 80 years, this rate was 10.5% (95% CI, 6.3%–16%) and 4.4% (95% CI, 3.3%–5.7%), respectively. In subjects with anatomic features unfavorable for surgery, the 30-day death and stroke rates were 1.7% (95% CI, 0%–8.9%) and 2.7% (95% CI, 1.3%–4.9%) for symptomatic and asymptomatic cohorts, respectively, independent of age.

PROCEDURAL STROKE/DEATH FOR CONTEMPORARY CAS WITHIN RCTs IN SYMPTOMATIC PATIENTS FOCUSING ON SUBGROUPS LIKELY TO BENEFIT

It is accepted that the procedural risks associated with treatment of symptomatic patients is higher than that for the treatment of asymptomatic patients. The updated Pro-

CAS registry of 5,341 patients demonstrated that treating a symptomatic stenosis (as compared with an asymptomatic stenosis) was an independent predictor of stroke/death with an odds ratio of 1.54 (1.1–2.1; $P = .008$). Therefore, it seems sensible to conclude that if symptomatic patients can be treated with a 3% procedural hazard, it is likely that this could be the case for a comparable population of asymptomatic patients.

Subgroup analyses from SPACE, a randomized comparison of CAS and CEA in low-risk symptomatic patients, provide some interesting findings.[13]

- For patients ≤ 62 years of age, the 30-day ipsilateral stroke/death rate was 2.2% for CAS and 8.1% for CEA. For patients 62 to 68 years, the ipsilateral stroke/death rate was 2.8% for CAS versus 4.3% for CEA. Incidentally, in the lead-in phase for the CREST trial, the event rates for CAS in patients under 60 and patients 60 to 69 years (adjusted for gender, protection device, and symptom status) were 1.7% and 1.3%, respectively. These are the patients, given their expected survival, who would be likely to benefit from intervention for an asymptomatic carotid stenosis.
- For patients with a stenosis of 60% to 69%, the ipsilateral stroke and death rates for CAS and CEA were 3.3% and 4%, respectively. It should be remembered that those with lesser degrees of asymptomatic stenosis gained more from intervention in ACAS and ACST-2 than those with higher-grade stenoses.
- For patents with contralateral stenosis in SPACE, the event rates for CAS and CEA were 2.6% versus 12.8%. ACST also demonstrated increased benefit for patients with contralateral carotid occlusion.

NONNEUROLOGICAL COMPLICATIONS

Averaged outcomes for persistent (rather than transient) cranial nerve injury and myocardial infarction (from EVA-3S, CAVATAS, NASCET, and ECST) are as follows: for cranial nerve injury, the rates are 0% and 0.5% for CAS and CEA, respectively, and for myocardial infarction, they are 0.4% and 1% for CAS and CEA, respectively. If the stroke/death rates for CAS in asymptomatic patients are similar to those of CEA, then the relative incidences of nonneurological complications assume importance.

NUMBERS OF ASYMPTOMATIC PATIENTS BEING OFFERED CEA

For much of Europe and North America, asymptomatic patients have always constituted a sizeable proportion of all patients offered carotid revascularization strategies. Since publication of the 5-year results from ACST, the (traditionally conservative) Northern European countries have increased their rates of carotid intervention in younger asymptomatic patients. For example, the UK Carotid Interventions Audit shows an increase in CEA for asymptomatic patients: 8% in 2002, 16% in 2006 to 2008, and approximately 20% to 25% currently.[14]

SUMMARY

Any discussions regarding intervention for an asymptomatic carotid stenosis must hinge on procedural hazards incurred and life expectancy of the patients being considered for intervention. Although results in SAPPHIRE did not meet the 3% cutoff, recent registry data with independent review in a similar population of patients (high surgical risk) indicate acceptable results. Furthermore, in the subsets of asymptomatic patients who are particularly likely to benefit from intervention, CAS outcomes in the same subsets within randomized trials of symptomatic patients (in whom procedural risks are higher) meet the 3% rule.

CONCLUSION

There are many advocates of carotid stenting who would feel comfortable offering CAS for a patient with an asymp-

COMMENTARY BY ISSAM D. MOUSSA, MD

I would like to congratulate the author on this excellent article. It is a clear and thorough review of the data pertaining to CAS in asymptomatic patients, a subset for which there is significant debate and controversy. However, there are some areas in which our opinions on the data differ, perhaps illustrating some of the interpretative disparities currently seen in the global vascular community on the whole. For example, it is difficult to draw meaningful conclusions with regard to patients treated in different clinical trials if their data (eg, carotid stenosis severity) were determined by different imaging modalities, such as duplex ultrasound rather than angiography, or if the clinical trials being compared were not powered to show certain statistical differences. I also believe it is important to point out in any review of past data, particularly those derived from trials conducted early in the history of a procedure, that the evolution of technology, incremental advancements through the collective learning curve, and the enhanced understanding of appropriate patient selection are significant factors in the application of these data to current practices.

tomatic carotid stenosis. Equally, there are many detractors of CAS who would consider the endovascular treatment of asymptomatic carotid stenosis something of an anathema, leading us to this quotation from Bertrand Russell:

> If a man is offered a fact which goes against his instincts, he will scrutinize it closely, and unless the evidence is overwhelming, he will refuse to believe it. If, on the other hand, he is offered something which affords a reason for acting in accordance to his instincts, he will accept it even on the slightest evidence.

The truth is that there is insufficient level I evidence at the current time to countenance a strategy of offering CAS to either high-surgical- or standard-risk populations. This accepted, results extrapolated from randomized trials of symptomatic patients and large-registry outcome data suggest that CAS can be performed safely in asymptomatic patients. The author urges readers to support one of many ongoing trials of carotid intervention in asymptomatic patients, including ACT1, SPACE2, TACIT, and ACST-2. ■

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