Perspectives on Recent CAS Trial Data

Thought leaders provide insights on findings from EVA-3S, SPACE, SAPPHIRE, and the recent registry data, and discuss what can be learned from studies that seem to offer conflicting results.

PANEL

Alain Branchereau, MD, is Professor of Vascular Surgery at the Université de la Méditerranée, in Marseille, France. Dr. Branchereau may be reached at +33 491 38 57 62; abranche@ap-hm.fr.

Sumaira Macdonald, MBChB (Comm.), FRCP, FRCR, PhD, is a Consultant Vascular Radiologist and Honorary Clinical Senior Lecturer at Freeman Hospital, Newcastle upon Tyne, England. Dr. Macdonald may be reached at sumaira.macdonald@nuth.nhs.uk.

Mark H. Wholey, MD, is a Clinical Professor of Radiology at the University of Pittsburgh School of Medicine, UPMC Shadyside Hospital, and Chairman of the Pittsburgh Vascular Institute in Pennsylvania. Dr. Wholey may be reached at (412) 623-2083; wholeymh@upmc.edu.

Jacques Busquet, MD, is Coordinator of Vascular and Endovascular Surgery, Cardio-Vascular Department, Clinique Chirurgicale Val d'Or–Saint Cloud, The Rothschild Foundation Group, in Paris, France. Dr. Busquet may be reached at jbusquet@wanadoo.fr.

Richard Green, MD, is Chairman, Department of Surgery at Lenox Hill Hospital in New York. Dr. Green may be reached at (212) 434-3400; rgreen@lenoxhill.net.

William Gray, MD, is from the Center for Interventional Vascular Therapy, Columbia University Medical Center, Cardiovascular Research Foundation, in New York. Dr. Gray may be reached at wgray@crf.org.

A WORD FROM AN EVA-3S PARTICIPANT

Alain Branchereau, MD, a Principal Investigator for the EVA-3S trial, discusses the protocol of the trial, its physician experience requirements, and the future of CAS.

Endovascular Today: *The EVA-3S trial has received tremendous exposure in the US and has prompted significant debate related to the design of the study. Is it accurate to say that the surgeons in the endarterectomy (CEA) arm were required to have a minimum of 25 cases in the preceding year, but an interventionist could participate in the carotid stenting (CAS) arm with no previous CAS experience if he or she were supervised by a proctor?*

Dr. Branchereau: No, that is not exactly correct. The interventionists had to have performed at least 12 CAS cases prior to entering into the trial. Any interventionist who did not meet these criteria intervened with a proctor, who was in the room, scrubbed, and wearing gloves.

At the beginning of EVA-3S, in November 2000, the required previous operator experience for stenting was usual because, at that time, a very small number of interventionists in Europe or the US had experience with more than 100 cases. There were many people, however, who had extensive experience in CEA.

To join the trial, each center was required to form a team of physicians composed of one neurologist, one vascular surgeon, and one interventionist. The neurologist handled the initial evaluation and patient follow-up, the vascular surgeon had to have performed at least 25 CEAs in the year before enrollment, and the interventionist must have performed at least 12 CAS procedures, or at least 35 stenting procedures in the supra-aortic trunks, five of which were in the carotid artery. The radiologist must have, in the 3 previous years, performed at least 50 angiographies of the carotid arteries yearly. The surgeon must have sent the operative protocols and the hospital discharge forms of each of these 25 procedures to the scientific committee of the trial.

Centers that could fulfill all requirements except those with regard to the interventional physician could still join the EVA-3S study and randomly assign patients, but all stenting procedures had to be performed under the supervision of an experienced tutor until the local interventional physician became self-sufficient (according to the tutor) and performed a sufficient number of procedures according to the predefined criteria. These are the facts written in the protocol.

Endovascular Today: *Under the protocol of the study, was it possible for the interventionist to be performing his first CAS procedure and still be in the study?*

Dr. Branchereau: Yes, it was possible. The interventionist requiring this scenario had to perform at least 10 to 15 cases with a proctor from another center. It was the responsibility of the proctor then to decide if the "interventionist in training" was qualified to enter the trial on his own. *Post hoc* analyses have shown that there was no one-center effect, meaning no center had impacted the results, and that 15.8% of stent placements were performed by experienced physicians (more than 50 previous cases), 45.4% by physicians having performed 50 or fewer, and 38.8% by physicians still in procedural training. The 30-day stroke plus death rates in these three groups were 12.2%, 11%, and 7.1%, respectively (P=.49). It is much more important that we realize in the analysis of the results that the protocol continued for 5 years, and there was no difference between the beginning and end periods, which is why we cannot say that the results are due to a learning curve.

Endovascular Today: *In 2003, the trial started requiring embolic protection. Were you able to determine if that made a difference?*

Dr. Branchereau: Yes, there was a trend, but the difference was not significant. We cannot say that there was a difference between the cases with protection and without protection. The question of the benefit of protection is still pending.

Endovascular Today: *The high major adverse event (MAE) rate in the CAS arm is one remarkable aspect about EVA-3S. The other remarkable aspect was the low stroke rate for CEA. Can you comment on these two issues?*

Dr. Branchereau: It is important to note the stroke rate in the angioplasty arm. It is not surprising if you notice that in most trials, not all lesions are atherosclerotic. SAPPHIRE, for example, includes patients with recurrent stenosis, or post-radiation stenosis, and, like in other registries, asymptomatic and symptomatic patients. If you look at the trials that performed only on symptomatic atherosclerotic patients—like those in EVA-3S and SPACE—you have approximately the same rate of accident. In 2001, the Wallstent trial, sponsored by the Schneider Company before it was acquired by Boston Scientific Corporation (Natick, MA), performed on symptomatic patients and was interrupted due to an excessive risk of stroke in the CAS arm. After randomization of 219 patients, the results showed a 30-day stroke plus death rate of 12% in the CAS arm compared to 4.5% in the surgical arm. These results were only published as an abstract in *Stroke* in 2001. In 1998, the Leicester trial on symptomatic patients conducted by

Ross Naylor, MD, was rapidly abandoned due to an unacceptable stroke rate in the CAS group (5/7). The problem is that symptomatic atherosclerotic stenosis is a much more severe disease than nonatherosclerotic disease and asymptomatic stenosis. The point is that many trials present a mix of cases, but if you only perform angioplasty and stenting in cases of severe symptomatic atherosclerotic stenosis, these lesions are very dangerous, and the rate of accident will be the same as observed in EVA-3S, SPACE, and the Wallstent trial. In addition, if you look at trials such as CAPTURE, the pilot study of CREST, and the registry from Michel Makaroun, MD, et al at the University of Pittsburgh School of Medicine, all observed a higher rate of accident in the elderly patient. Why? The elderly patients have more severe atherosclerotic lesions than others. We know that the rate of accident is significantly higher in this population, and now everyone recommends to not perform CAS in patients older than 75 years because a high-risk lesion will make the procedure risky.

Endovascular Today: *Compared to the SPACE study, your CEA arm had a much lower MAE rate. Can you comment?*

Dr. Branchereau: In France, more than 90% of vascular surgery procedures and most CEAs are performed by vascular surgeons who specialize in vascular surgery. We have had a specific board of vascular surgery for approximately 15 to 20 years. This is one good reason. All vascular surgeons would agree and tell you that the MAE risk is higher if you have a CEA performed by a surgeon operating only on two or three patients a year than if you are operated on by a surgeon who performed 25, 50, or 100 cases a year. It is evidence-based.

Endovascular Today: *Do you know the percentage of general surgeons performing CEA in Germany?*

Dr. Branchereau: No, but I know in Germany, like in Britain and the US, there are a lot of vascular surgery procedures performed by general surgeons. Five or 6 years ago, the US vascular surgeons fought to separate from the American Board of Surgery, but unfortunately, they did not win the battle. I think that at least the results from this trial will help them to continue the fighting. The minimum amount of 25 CEA cases a year was difficult, because in France there are some vascular surgeons doing fewer than 25 cases who could not participate in the trial.

Endovascular Today: *Do you think that many of the surgeons who participated in EVA-3S did more than 25 procedures in the year?*

Dr. Branchereau: Absolutely. For instance, in my group, two vascular surgeons participated in EVA-3S. One was doing approximately 80 cases a year, and the other performed 50. I think this is the case in most other centers. Most of the vascular surgeons who participated were doing 50 cases a year; they were highly skilled. Moreover, in France, a great number of vascular surgeons perform a completion angiogram at the end of the procedure. In my opinion, it may play a role, but it is very difficult to prove.

Endovascular Today: *What do you see as the future of carotid stenting in France?*

Dr. Branchereau: This is a difficult question and a problem we now face. We are embarrassed because the insurance system and the Ministry of Health are very skeptical after this trial. We have some cases, for example, of very high-risk patients or patients with restenosis, or post-radiation stenosis, for which, in my opinion, stenting is a good solution. However, it is true that it represents maybe 300 to 500 cases in France a year.

Stenting will evolve and improve. The improvement in guidewires and embolic protection systems will continue and allow us to decrease the stroke rate. I do not know the future, but currently, CEA remains the gold standard in France. There will be other trials and other data. SPACE and EVA-3S are not in favor of stenting, but we will gather more data and continue the evolution of the technique. If the trial had been done in 1998 and 2001, the results of stenting would have been worse. The Wallstent and the Leicester trials were stopped quickly due to the stroke rate with CAS. The EVA-3S results show that stenting has improved since then. Nevertheless, it is a reality that CAS is less developed in France than in some other European countries due to the limitations issued by the National Health Insurance System.

Endovascular Today: *Do you perform stenting?*

Dr. Branchereau: Yes, in my department, we operate on approximately 150 to 200 carotid lesions a year, and of those, 15 to 20 are CAS procedures.

RAISING CRITICAL QUESTIONS

Sumaira Macdonald, MBChB (Comm.), FRCP, FRCR, PhD, discusses the questions she posed to the EVA-3S and SPACE presenters at VEITH, the difference between failure to show noninferiority and superiority, and critical aspects of future trial design.

Endovascular Today: *After the presentation of the EVA-3S and SPACE trial data at the VEITH Symposium in*

November 2006, you posed questions regarding some of the findings and conclusions. What was the reason for your concern?

Dr. Macdonald: I posed two questions regarding the 30-day results of EVA-3S. The first was a query regarding the trial's requirement for the periprocedural dual antiplatelet regimen. In SAPPHIRE and SPACE, combined aspirin and clopidogrel with appropriate preloading and 28-day post-stenting course were mandatory, just as they are in the ongoing trials, CREST and ICSS. EVA-3S simply recommended this protocol, and yet there is level-1 evidence in support of the importance of this regimen, not only in the setting of coronary intervention (CREDO and PCI CURE trials),[1,2] but also for CAS.[3] The stroke rate is significantly higher when aspirin and heparin are employed in place of a dual antiplatelet regimen.

It is a little strange that the EVA-3S safety committee should overlook this fact and instead choose to mandate the use of cerebral protection when we have, at best, level-3 evidence for routine use of these devices from the available literature. Furthermore, the data on which the committee made its decision are decidedly weak; the absolute numbers of procedural strokes were three in the protected patients (3/58; 5.2%) and two in the unprotected patients (2/15; 13.3%), reaching significance only because of the differences in size of the denominator. Furthermore, a substantial number of events were nonprocedural and could not, therefore, logically be prevented by use of a protection device. There was, of course, no randomized comparison of protected and unprotected stenting.

My second question was aimed at evaluating the level of experience for those performing CAS within EVA-3S. The investigators consistently point out that there were no significant differences in outcome between those centers performing fewer than 21 procedures, 21 to 40, and more than 40 procedures. To try to state that experience makes no difference in outcome for CAS flies in the face of both logic and the literature. CAVATAS clearly showed the influence of experience on outcome for both CEA and CAS (only 26% of patients received stents in this landmark trial). Furthermore, the fact that a center is high-volume does not mean that every interventionist (surgeon, radiologist, or cardiologist) is experienced. It would be more meaningful to compare results of individuals rather than that of centers. CAS is a complex intervention and, like CEA, is unsafe when performed in low volume.

Let us compare "like" with "like." EVA-3S mandated that surgeons performing CEA should have performed 25 of these procedures in the preceding year. We can assume that those operating within the trial had, on the whole, been qualified to do so for at least 1 year and therefore had probably performed more than 25 CEAs. Those performing CAS had to have performed a total of 12 CAS procedures or five CAS procedures plus 35 stenting procedures in the supra-aortic trunks, which is technically an entirely different procedure with much lower risk. Any experienced carotid stenter will point out that the learning curve for CAS is probably well in excess of 40 cases and may even be more than a couple hundred,[4] especially for surgeons performing CAS, as they are traditionally less comfortable with catheter/guidewire techniques.

I asked why 12 patients were "crossed over intraoperatively to CEA" from CAS within the trial. This seems a little high. The possible reasons for this are controversial. As a vascular/interventional radiologist, I could not "cross a patient over intraoperatively," as I do not know how to perform CEA and neither does an interventional cardiologist. The inference is that, first, in 12 cases, the decision to stent was inappropriate (therefore, that the operators were inexperienced in patient selection for the technique); a learning curve involves more than technical ability. Second, that the operators involved in these "cross-overs" were vascular surgeons. The trial had several operators listed as VSI, or vascular surgeon interventionist.

Endovascular Today: *Did you feel your questions were adequately addressed by the presenters?*

Dr. Macdonald: Unfortunately, my second question was not answered as the speaker stated that he did not understand it. In response to my first question, it was pointed out that there was no significant difference in outcomes for those patients on dual and single antiplatelet regimen. Quite clearly, this is a nonrandomized comparison of patients treated with and without "standard of care" antiplatelets and represents a tiny subset analysis.

Endovascular Today: *How would you describe the response to either or both of these studies in the UK to date?*

Dr. Macdonald: Physicians and health care providers in the UK value and are heavily influenced by evidence-based medicine. Within the National Health Service, we are fortunate because reimbursement and litigation issues are less relevant than in other health care settings.

Accepting this, CEA is an operation that is very much enjoyed by vascular surgeons, and in the UK the procedure is performed by vascular surgeons and occasional-

ly neurosurgeons. CAS is performed largely by interventional radiologists, some interventional neuroradiologists, two vascular surgeons, to my knowledge, and a small but growing number of interventional cardiologists. There is, of course, the potential for personal agendas to influence opinion and practice. I have heard a senior vascular surgeon describe SPACE as the death knell for CAS. If we wish to be controversial about it, we could describe the situation as a boxing match between an enthusiast in one corner and a Luddite in the other. Reason rests somewhere between the two extremes. Most stroke physicians and neurologists with an interest in stroke prevention are candid about the results of SPACE and EVA-3S, both of which were prematurely stopped, thereby leading to a potential overestimate of procedural risk for CAS, that is, data analysis occurring at a random high and are willing to continue to randomize within ICSS. Certainly, this is the case for those few centers with relatively high CAS throughput. For centers intending to start a CAS regimen, there is on the whole more apprehension than was previously the case before publication of the 30-day results of EVA-3S and SPACE.

Endovascular Today: *Have the data slowed the trend toward stenting of carotid artery stenosis in favor of CEA? In your opinion, why or why not?*

Dr. Macdonald: With the caveat of novice centers starting a carotid stenting program, the data have not slowed carotid stenting in the UK, and those with a good grasp of randomized trials see the value of supporting trials to completion. Those who are considered to be at high risk for CEA—and there is no consensus on "high risk"—will continue to be offered CAS if there are experienced interventionists available. Outside this indication, patients will be randomized within ICSS. With the exception of a tiny minority of centers, very few symptomatic low-operative-risk patients receive stents outside of trials, and very few asymptomatic patients are stented in our relatively conservative environment.

Endovascular Today: *What conclusions do you feel can be drawn from each of these trials?*

Dr. Macdonald: Regarding EVA-3S, would it not be ethically very difficult to offer CAS to a low-operative-risk symptomatic patient in France? However, I think EVA-3S proves that CAS should be performed by physicians who are not just technically experienced but who are also adept at the evaluation of anatomic suitability for CAS. In EVA-3S, interventionists used five different stents and seven different cerebral protection devices, and experience with only two procedures was required for any new device used. By comparison, in CREST, 1,472 patients were enrolled in a lead-in phase that required training programs of up to 20 procedures per investigator using a single stent and protection system. Quite simply, CAS should be performed by properly trained and experienced people—this is clearly not rocket science.

Regarding SPACE, I would first like to quote Professor Nick Cheshire, who stated at Controversies and Updates in Vascular Surgery in January 2007 that, "failing to show noninferiority of CAS is not the same as proving superiority of CEA." I think we should be mindful of this fact.

We must also bear in mind that this trial was prematurely stopped for reasons of futility and lack of funding. This trial, designed as a noninferiority trial, mandated a preset value of delta (the maximum acceptable difference in outcomes between the two treatments offered). The upper limit for the margin of noninferiority was preset at +2.5. The trial was originally powered for 1,900 patients, but at around 1,100, patients it became clear to the statisticians and data-monitoring committee that the trial would have only a 50% chance of showing noninferiority for CAS at the original target of 1,900 patients, but would have an 80% chance of demonstrating noninferiority at 2,500 patients. Without funding to support ongoing recruitment, the trial was stopped. In SPACE, although there was no significant difference between CAS or CEA for either analysis, there was a slight trend toward CEA. Clearly, a trend is a very soft outcome measure in the context of a randomized trial and should be interpreted with caution. Because the upper confidence interval limit for the primary outcome was more than 2.5, the study failed to show noninferiority for CAS. This does not mean that superiority for CEA was shown.

For superiority to be shown, the 95% confidence interval for the treatment effect should lie not only entirely above delta (+2.5 in this instance) but also above zero. In switching from noninferiority to superiority constructs, the intention to treat analysis assumes greater importance, within a noninferiority trial, both intention-to-treat and per-protocol analyses should be given equal weighting. From any perspective, in SPACE, both intention-to-treat and per-protocol confidence intervals crossed zero (ie, the superiority of CEA was not shown).

To quote Professor Ross Naylor, of Leicester Royal Infirmary, "In other words, surgeons will conclude that carotid angioplasty and stenting was inferior to carotid endarterectomy, although interventionists will conclude

that there was no significant difference."[5]

Last, Andreas Kastrup, of Göttingen, Germany, in addressing the audience at the International Symposium on Complications After Endovascular Repair of Aneurysms and Carotid Artery Stenosis in December 2006, indicated that in SPACE, the stroke rate was lower in the CAS limb than in the CEA limb before routine cerebral protection was employed. He added, "This will never be published." There is a learning curve also for the safe use of cerebral protection systems, and it remains possible that interventionists who were accustomed to unprotected CAS exposed SPACE trial patients to their learning curve for cerebral protection.

Endovascular Today: *What are your feelings concerning the SAPPHIRE trial? What would you consider to be its strengths, and in which areas did it fall short?*

Dr. Macdonald: Concerning SAPPHIRE, the primary outcome was combined stroke, death, and myocardial infarction (MI). Outcomes for symptomatic high-operative risk patients were significantly better for CAS than CEA, resulting largely from the differences in MI between treatment limbs. There were no significant differences between stroke and death. Some have criticized the "creative" use of this composite endpoint on the basis that traditionally, trials of CEA against best medical therapy have not included MI, but pragmatically, MI is important to the patient. Although the stroke/death outcomes for CAS for symptomatic patients were within the American Heart Association (AHA) Guidelines (≤6% all stroke/death), the outcomes for CAS in the asymptomatic population (the majority) were higher than the cut-off given by the AHA for asymptomatic patients (ie, stroke/death should be ≤3%). In SAPPHIRE, the 30-day stroke/death rate for asymptomatic patients, although lower in the CAS limb than in the CEA limb, was 5.8%. We must remember that the risk of stroke in medically treated asymptomatic patients is around 2% per annum, and arguably, we are doing more harm than good when intervening in high-risk asymptomatic patients either by CAS or CEA.

On another quite separate note, regarding patients thought to be at high surgical risk due to significant coronary artery disease, it remains entirely possible, but unsubstantiated, that percutaneous coronary intervention could have been performed by interventional cardiologists involved in SAPPHIRE, at the same sitting, immediately preceding CAS. While this might seem unfair in the setting of a trial that includes MI in a composite endpoint, in reality, it is perhaps an advantage of endovascular management of carotid artery disease—that the coronaries can be stented "on the way up."

SAPPHIRE's main strength was that it was the first to show definitively that CAS is less cardiopathic than CEA. Although this had been considered to be the case anecdotally, it had not previously been demonstrated in a purely clinical setting. Trial weaknesses include the fact that it was also prematurely stopped (largely due to increasing resistance from referring clinicians and patients to randomize), the involvement of industry in the design of this commercially sponsored trial, and the fact that 400 patients were excluded from the trial because they were considered too high-risk, surgically.

Endovascular Today: *How can future trials address lessons learned in previous studies?*

Dr. Macdonald: I think we should support trials that are funded by independent national funding bodies. For example, the recently launched Asymptomatic Carotid Surgery Trial 2 (ACST-2), comparing CAS and CEA for asymptomatic patients with significant carotid disease is funded by Health Technologies Assessment, CREST is funded by the National Institutes of Health and National Institute of Neurological Disorders and Stroke, and ICSS is funded by the Medical Research Council. We should strive to support such trials to completion.

Second, we owe it to the patients recruited in future trials to include only experienced operators/interventionists, even if this means relatively slow recruitment and stringent proctoring and credentialing programs. Recall that 40% of interested centers were rejected by the technical management committee of ACAS on the basis of limited experience, and that those centers with poor outcomes within the trial were prevented from recruiting additional patients. When EVA-3S was launched in 2000, there were only four centers in France capable of offering CAS, and because recruitment was painfully slow, other less-experienced centers were subsequently allowed to recruit, as stated by Patrice Bergeron, MD, at the International Symposium on Complications After Endovascular Repair of Aneurysms and Carotid Artery Stenosis in Leuven, Belgium, December 2006.

Third, if the need arises to reinterpret the results of a noninferiority trial as a superiority trial or vice versa, then the caveats and limitations of so doing are made transparent to the readership of any journal in which these trials are published and that the methodology and limitations of any trial that could have profound implications for a technique such as CAS be fully divulged.

Endovascular Today: *What expectations do you have from trials that are currently underway, such as ICSS and CREST?*

Dr. Macdonald: ICSS, (or CAVATAS-2), an international trial comparing CAS and CEA for low-risk symptomatic patients has recruited more than 1,100 patients as of January 2007, and has a target of 1,500. The safety committee has seen no cause for concern, and we can expect this trial to run to completion. CREST, including asymptomatic patients, similarly has posed no problems for their safety committee. It is unlikely that the results of these trials will, in isolation, sway public opinion worldwide, but their results will add to a bank of level-1 evidence and, by combining the results of all randomized trials involving CAS, allow meaningful subset analyses that may point to particular strengths and weaknesses of CAS with respect to patient, lesion, and clinical variables.

1. Mehta SR, Yusuf S, Peters RJ, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet. 2001;18:527-533.
2. Steinhubl SR, Berger PB, Mann JT III, et al for the CREDO Investigators. Clopidogrel for the reduction of events during observation, early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. JAMA. 2002;288:2411-2420.
3. McKevitt FM, Randall MS, Cleveland TJ, et al. The benefits of combined anti-platelet treatment in carotid artery stenting. Eur J Vasc Endovasc Surg. 2005;29:522-527.
4. Verzini F, Cao P, De Rango P, et al. Appropriateness of learning curve for carotid artery stenting: an analysis of periprocedural complications. J Vasc Surg. 2006;44:1205-1211.
5. Naylor AR. SPACE: not the final frontier. Lancet. 2006;368:1215-1216.

IMPROVING TRIAL DESIGN

Mark H. Wholey, MD, explains why patient selection and operator experience remain critical to CAS studies and the future of the procedure.

Endovascular Today: *What are your thoughts on the EVA-3S trial?*

Dr. Wholey: It is an interesting French trial with a major bias in favor of CEA. The major limitation to the trial was that France has been very resistant to minimally invasive CAS as a replacement for surgery. As a result, the surgeons performing the stenting had very minimal and limited training, which created a trial comparing experienced surgeons performing CEA with inexperienced operators performing CAS.

We know that with CAS, there are two critical ways to avoid stroke: patient selection and operator experience. The trial never had a chance because it included operators who had performed a minimum of three carotid stent placements in their lifetime. You cannot have someone who has done three or five carotid stenting procedures enter into a randomized trial against experienced surgeons. Quite frankly, I do not discuss the trial. I was startled that EVA-3S was accepted by peer-review in the *NEJM*. I do not think they had experienced reviewers, and it never should have been accepted.

Endovascular Today: *How do you view the SPACE trial?*

Dr. Wholey: The SPACE trial is a different situation. I thought the SPACE trial was good. It was randomized on 1,200 symptomatic patients, which is not a small number. I think one of the reasons that that trial was terminated prematurely was financing. They claimed that CAS did not meet noninferiority compared to surgery, but the bottom line is that it was an equivalence trial, and at the time that the trial was discontinued, the MAE rate for surgery was 6.34%, and stenting was 6.84%. Basically, in the symptomatic patients, both arms were statistically equivalent. To the best of my knowledge, I think those investigators were well-qualified.

Endovascular Today: *What are your thoughts on the SAPPHIRE trial?*

Dr. Wholey: I think the SAPPHIRE trial was a landmark trial; it was the first randomized trial that had any significance comparing high-risk CAS and CEA patients. The stenting arm, in all parameters, showed to be equivalent or better than surgery.

The subsets in SAPPHIRE were the most impressive. The diabetic subset had an impressive statistical difference in favor of CAS. Although there were only 85 patients in that subset, it was clear that stenting was so superior in all parameters—periprocedural strokes, MIs, and bleeding event rates. If you look at the endpoints, they were all clearly more established in the CAS arm than the CEA arm.

Endovascular Today: *What criticisms of SAPPHIRE did you observe?*

Dr. Wholey: I think there was a lot of resistance to the trial at this year's VEITH meeting based on several issues, the primary argument being that the inclusion criteria were not high-risk. However, I think they were very high-risk criteria. The patients had class 3 congestive failure, ejection fractions of 20% to 30%, and contralateral occlusions. Surgeons have a 14% stroke rate in the NASCET trial for contralateral occlusions. This tells me that these were high-risk patients. I think that chapter can be closed: carotid stenting in the high-risk asymptomatic patients is as good as surgery.

Another criticism of SAPPHIRE is that it was underpowered. I think the randomized component of it was especially good. The registry showed 7% periprocedural stroke, death, or MI. Non–Q-wave MIs were a predictor

of MI for the future. The endpoints were good, but surgeons could not handle MI as an endpoint. If you look at the SAPPHIRE randomized trial, there were no major strokes. I think it was a well-run trial, and I believe the data are accurate.

Endovascular Today: *Do you think the lack of major strokes in SAPPHIRE was because of the experience of the operators?*

Dr. Wholey: I think SAPPHIRE had experienced operators, but CABERNET had *very* experienced operators. The MAE rate was 3.4% all procedural stroke, death, and MI. There is no question that if you want to include octogenarians and symptomatic patients within the trial, the number of investigational sites should be limited. For example, in CAPTURE, 144 sites were chosen for the enrollment of 3,500 patients. Obviously this number of sites resulted in operators with minimal experience. This could account for the 16.7% stroke rate in the octogenarians and 11% in the nonoctogenarian symptomatic patients.

If we want to eliminate strokes, we should do a trial of the 10 most-respected hospitals and investigators in the country. You do 400 patients, all comers: octogenarians, symptomatics, and asymptomatics. Octogenarians should not be a separate subset. We should establish which patients are too high risk for stenting. We have designated patients too high risk for surgery, but we need that designation for stenting. Then we would not have 16% procedural morbidity; we would have 5% in the symptomatic and 3% in the asymptomatic.

Endovascular Today: *Why was the CEA major adverse event rate so high in SAPPHIRE?*

Dr. Wholey: That rate was high because they included MI as an endpoint, with 7% incidence of non–Q-wave MIs. That is why the 30-day event rate was 7% stenting and 12% for surgery, and the 7% difference was made up of the MIs. The stroke rates for surgery and stenting were very similar, except in the diabetic subset where stenting was clearly superior.

Endovascular Today: *How would you suggest determining which patients are too high-risk for stenting?*

Dr. Wholey: We would say "This asymptomatic patient with a 95% lesion is too high-risk for stenting. Why? Because the patient has a type 3 or 4 aortic arch, and we were 20 minutes in the diagnostic study just getting the catheters in the complex innominate, or the complex carotid, or the bovine arch." Therefore, if it takes you 20 minutes to do the diagnostic procedure with much difficulty, you should not do the stenting. Also, octogenarians should be staged with the diagnosis done one day and stenting performed the next day.

In another scenario, you have a symptomatic patient with an ulcerated lesion, and on Volcano intravascular ultrasound (Volcano Therapeutics, Inc., Laguna Hills, CA) virtual histology you note vulnerable plaque and thrombotically active plaque, or a thin fibrous cap that could rupture when stented or ballooned. On lesion analysis of plaque characteristics via Volcano virtual histology, you can determine that the patient is not a candidate for stenting.

Endovascular Today: *What effect will the trials have on the future of CAS?*

Dr. Wholey: In the beginning, we thought we could stent everyone. These trials, in a certain sense, are more harmful than good because if we continue with an event rate of 10% in octogenarians, and 12% in CREST, CMS will not allow reimbursement. This will result in CAS becoming a niche procedure. That is not satisfactory.

Endovascular Today: *What would be an ideal CAS trial design?*

Dr. Wholey: I am convinced that we need to do a trial of ultra-experienced operators who know what patients not to stent, who know they can stent the easy patients in 20 or 30 minutes, and they know patient selection. They will not stent the patients who are risk predictors because we know from our data in Pittsburgh that patients with lesions 2 cm long or greater are definitely at higher risk than every other factor. That was our predictor. It is imperative that we draw up predictors that say, "You are too high risk for stenting."

We must also include octogenarians and symptomatic patients. I say that age should not be a risk factor if the aortic arch and the lesions are satisfactory; I think we could stent those patients. We are collecting data from five high-volume experienced centers: Lenox Hill, UPMC Shadyside, Hoag Memorial Hospital, Leipzig Heart Center, and Dortmund, Germany. We have looked at that collective data in both octogenarians and nonoctogenarians, and the all-stroke and death rates varied from 1.3% to 3.6%. There was little difference between octogenarians and nonoctogenarians in those experienced centers.

Endovascular Today: *What are your thoughts on CREST?*

Dr. Wholey: I think CREST is a solid trial. We desperately need CREST because that is the only way CMS is going to listen. CREST is a long way from finishing, and

unfortunately, CREST has a 12% octogenarian stroke rate. They pulled octogenarians from the lead-in phase of the trial, which is not good!

Endovascular Today: *What is the difference between CREST and SAPPHIRE?*

Dr. Wholey: CREST is a much lower-risk trial than SAPPHIRE, and its criteria for entry are similar to the NASCET enrollment. CREST has several enrollment criteria exclusions that did not exist for SAPPHIRE. For example, CREST would not enroll patients with either ejection fractions less than 30% or recent MI.

If there are other trials running when CREST is running, CREST may not finish. CREST is gaining momentum and is doing well—they have 1,500 patients enrolled. When they started enrolling the asymptomatic patients, it helped the trial. We need CREST because it will give us an indication of whether we can do low-risk symptomatic and asymptomatic patients with a 5% to 6% periprocedural event rate in the symptomatic group and 3% in the asymptomatic population.

Endovascular Today: *When can we expect data from CREST to affect procedure?*

Dr. Wholey: It will be a couple of years, minimum. With our regulatory policy, once CREST completes, it will take an additional year to compile the 1-year data. It is a 2,400 patient trial, so it will be at least another 2 years. It will then require submission, FDA panel review, and ultimately a CMS approval process. Unfortunately, we are terribly over-regulated by the FDA, CMS, IRB, and considering that CAS represents a high-risk procedure, there is always the threat of malpractice. We are not getting the choice of devices that are available in Europe. We have distal protection devices in this country, but we do not have flow reversal or proximal flow control, and we should have both of these. We do not have a choice of stents and, if a promising one is introduced, it is 3 or 4 years before it is available for clinical application. The entire process moves very slowly.

Endovascular Today: *How does the protocol for ACT differ from the other trials?*

Dr. Wholey: ACT is a low-risk, asymptomatic-only trial with 3:1 randomization, which means that one patient is randomized for every three who are stented, and it is enrolling quite slowly—at least here in Pittsburgh—and it is totally dependent on the Xact stent and the Emboshield filter (Abbott Vascular, Santa Clara, CA). We are bound to that system. ACT-1 basically competes with CREST, yet they are ongoing because the companies want approval for a low-risk reimbursement. I have not yet seen any preliminary data yet.

Endovascular Today: *What is the best way to compare these trials?*

Dr. Wholey: Variations in the enrollment criteria existed among the trials. ARCHeR, for example, did not include contralateral strokes and death at 1 year, but SAPPHIRE was somewhat more inclusive and did include all strokes and MI at 1 year. There were variations in the endpoints of the trial. Again, although these were not overwhelming, they may have had an influence on the overall outcomes. The 30-day endpoints were quite similar, but the 1-year endpoints were different. Questions to ask are, "What was the periprocedural stroke and death rate? What was the major stroke event rate?" Certainly minor strokes are important, but most minor strokes will return to some degree of normal functionality. Unfortunately, major strokes are disabling and rarely ever return to baseline.

Endovascular Today: *How do you perceive the surgeon's perspective regarding CAS?*

Dr. Wholey: Surgeons who extensively perform CEA do a very good job, so they are fairly satisfied. Surgeons are not going to participate in randomized trials unless they can also do stenting. However, surgeons who are not involved in endovascular stenting have no incentive to enroll because they are getting good results with surgery, and they will not enroll their patients with stenting when they look at the data. The data show them that stenting is no better than surgery and may be worse in the symptomatic patient. Furthermore, those of us who support CAS would like better data from the symptomatic and the octogenarian patients.

Endovascular Today: *What does the future hold for CAS?*

Dr. Wholey: We have to be patient in the learning process of carotid stenting. We must remember that the first aortocoronary bypass procedures were not that smooth either. The technology is evolving, and the filters, recovery systems, flow reversal, and operator skills will improve with time. I think it is a matter of time before we work out the problems with octogenarians, but we have to be patient; it is a new procedure, in only its second generation. It will take time before the experienced operators lay out the criteria and then even more time to get regulatory approval.

I think there is a lull in CAS because those of us who have done more than 1,000 cases are tired of talking about it, and we are tired of the continual battles with

CMS and the FDA, as well as sending patients home with critical lesions that are preocclusive but who unfortunately do not meet the entry criteria for the category B IDE trials. Consequently, these patients are being discharged with a stroke warrant. It is not that we are losing interest so much as saying that we are becoming somewhat disenchanted with the overall process.

Endovascular Today: *What can operators do to improve their CAS results?*

Dr. Wholey: If these trials keep producing the data that they do with symptomatics and octogenarians, it is more harmful than good. Opening these trials to 100 sites and 4,000 to 5,000 patients is not a good idea. Initially, you would like 10 high-volume, experienced operators to participate in a 500-patient trial that includes all levels—symptomatic, asymptomatic and octogenarians—and come in with a 6% or better all-stroke event rate. I think we can show that the best operators can achieve these good numbers, which will help us conclude that others can do the same after responsible credentialing. Inexperienced operators should be willing to spend more time in the training process. The problem may be that single operators are not yet good enough in the early stages of CAS; maybe it takes dual operators. We have to tighten up the whole process to include training and credentialing.

EUROPEAN PERSPECTIVES

Jacques Busquet, MD, a French vascular surgeon, weighs in on the real-world aspect of the EVA-3S trial's results and the importance of continued development of CAS procedures.

Endovascular Today: *Have the EVA-3S results had a profound effect on the use of CAS in France?*

Dr. Busquet: As you know, the results of the EVA-3S study were published in October 2006 in the prestigious and famous *New England Journal of Medicine* (*NEJM.* 2006;355:1660-1671). In France, there are two points of view among physicians regarding this study. First, if you are not a CAS and angioplasty specialist and you read the *NEJM* article, you recognize that there are still some significant problems concerning the technique and risks regarding this procedure. Second, if you are a very good CAS specialist, you admit that the CAS arm of the study was not well-developed, which is a problem with the study. However, this study will probably not affect the use of CAS in France.

There is a general qualification of CAS in France, but the procedure is not reimbursed. Therefore, this technique is only practiced in public centers or in an official CAS trial. In trials, the company sponsoring the trial is supposed to supply the materials, and the procedure is reimbursed either by the study or the hospital. This effectively limits the acceptance of CAS.

I first began performing CAS with Edward Diethrich, MD, in the early 90s. I am now working at a prestigious, private institution in Paris, but I am not allowed to do this sort of case on my patients because of the legal environment. Even if I found a patient willing to pay for the CAS procedure, if the case resulted in a poor outcome and lawsuit, the suing party would be able to demonstrate that this is a risky and experimental technique simply based on the government's decision not to reimburse the procedure.

Endovascular Today: *What do thought leaders in France think of the trial's results?*

Dr. Busquet: The data from EVA-3S are understood based on which side of the debate you stand. Most vascular surgeons—and especially professors—would say that this study demonstrates that surgery is superior to CAS. Furthermore, they would say that this study represents the real world and that CAS and stenting is a risky procedure. Most surgeons are not surprised by EVA-3S's trial data because they believe that surgery is better. The *NEJM* is read by every doctor, and the negative CAS results pose a problem for its continued development. CAS is a difficult technique even for very experienced interventionists. I hope that the next studies' designs will be more favorable, and I regret these poor results.

Endovascular Today: *EVA-3S's surgical results are among the best surgical results ever published. Do you think that those results were real-world results?*

Dr. Busquet: The selected centers in France had very experienced surgeons, the technique is well-established, and the results were extraordinarily good. The surgical requirements for the trial were 25 CEAs in the previous year, which amounts to one every 2 weeks. That was the minimum requirement; most participating surgeons had far more experience than the minimum requirement. The selected centers had good surgeons, staff, follow-up, and technique.

On the other hand, the requirement for the CAS arm of the trial was only 12 CAS procedures or five supra-aortic trunk angioplasties. Furthermore, if a participating physician did not meet this CAS requirement, he could proceed if he was supervised by an experienced supervisor. Even though these supervisors were very good, they were not familiar with the patient or the

center, which is very important. Therefore, in this CAS arm, many inexperienced interventionists did work on the patients, which was a weakness of the study. Half of the cases were done in five centers, and the other half were in 25 centers; in fact, the problem was in the small centers. Some centers performed CAS having only one past experience doing that procedure. Therefore, there is a real difference of results among the centers, especially in the CAS group.

Endovascular Today: *The average enrollment per center was 1.7 patients. How does that affect the study?*

Dr. Busquet: There were some inexperienced centers, which had no learning curve, and many people have stressed the learning curve in the importance of this technique. Too many centers did not have sufficient experience.

Endovascular Today: *In light of the deficiencies in the design of this study, how should physicians value its results?*

Dr. Busquet: We are democratic people, and we must consider that this article was accepted and published in the *NEJM*. We must act with it and consider that these people tried their best. Personally, I think the results reflect badly on CAS, and I am sure that some healthcare regulators in France, Europe, and the US will use this article against the development of CAS. Therefore, we must be patient and remember that there are a lot of waves in the ocean, some are high and some are low. I am in favor of CAS and its continued development, but we have to work very hard to get the full results regarding CAS, and I am sure we will get better results in the future. In France, this study could very well represent the real world. This is a concern for industry because the companies obviously want to sell products, and interventionists will require a great deal of training. This is a technique that is impossible to put in some hands without training to overcome the learning curve.

Endovascular Today: *How can these be deemed real-world results if the study is comparing surgeons who are highly skilled performing CEA against interventionists who may be performing their first CAS case?*

Dr. Busquet: Yes, this is what we have extracted from the study. I do not think the surgeons intentionally pushed for such a bad result. We must consider that this article is negative for those of us who want to develop the CAS technique, but we must recognize that CAS is still a very difficult technique. I believe it is important to avoid using these results to create a lot of politics. This is a published article; we have to consider it, we have to be careful, and we have to be trained because the learning curve is so important.

Endovascular Today: *What can we learn from the results?*

Dr. Busquet: In fact, this bad result must lead us to a new consideration of anatomic pathology of the plaque, security of the stenting, embolic protection, and stent design. I think that this bad result will help us to progress in a positive way. From the results, we can learn that training is very important, stroke is a significant perioperative risk, and it is a bigger risk when you are a beginner. The technique is still under development, the companies are doing well with developing new stents, and we will probably concentrate in the training, technique, and stent and accessory design to be as good as possible.

HEALTHY DISCUSSION

Richard Green, MD, discusses how these trial data have caused the endovascular community to debate the safety of CAS and proper trial design—and how that is a good thing.

Endovascular Today: *Were the training requirements of SAPPHIRE more rigorous than EVA-3S? If so, why?*

Dr. Green: The SAPPHIRE investigators, while early in their experience, were still more experienced than the majority of the EVA-3S group. The sponsors determine the training requirements for CAS studies in the US. The FDA signs off on that protocol. The current status in the US is that of perhaps 20 to 30 trial sites with extensive experience and everyone else. Although the CAPTURE data indicate no difference in outcome based upon operator experience, I find it hard to believe that a handful of cases are equivalent to hundreds of cases. I do not believe that either SAPPHIRE or EVA-3S demonstrated real-world use of CAS.

Endovascular Today: *In the CEA arm of the study, EVA-3S reported one of the lowest rates of adverse events ever recorded. Do you have any thoughts on why its adverse event rate was so low?*

Dr. Green: Carotid surgery is getting safer. This is a procedure that can be done under regional anesthesia and has the advantage of distal control of the ICA before any manipulation of a potentially unstable plaque. I think the MAE rate for CEA reported in EVA-3S is real world, and it is corroborated by similar results looking at administrative databases in the states of California and Maryland.

Endovascular Today: *What is the overall significance of EVA-3S?*

Dr. Green: Data from several sources now indicate that outcomes after CAS are related to a number of factors that are different than the factors influencing outcomes after CEA. The results of EVA-3S, if confirmed, would suggest that the symptomatic patient is at higher risk for CAS. These data in no way prove that, but they should raise our suspicion and prompt further investigation. I would hope that future studies require operators past their learning curves and utilize the best technology available. In other words, let us test the hypothesis by using high-volume operators and give them the option of a variety of protection systems and stent designs to optimize the result in each patient.

Endovascular Today: *What can the EVA-3S and SPACE trials teach us?*

Dr. Green: Trials designed poorly, even if prospective and randomized, do not provide definitive answers to difficult questions.

Endovascular Today: *What are your thoughts on the decision to publish these data by* Lancet *and the* New England Journal of Medicine*?*

Dr. Green: Both studies have certainly generated lots of discussion, and that is good as long as we insist on corroborating data before changing practice patterns.

Endovascular Today: *Why was the CEA MAE rate so high in SAPPHIRE? How does that MAE rate compare to other studies of CEA?*

Dr. Green: SAPPHIRE was the first CEA trial to look at and include MI as a primary endpoint. We have to remember that these patients were at extremely high risk for operation largely because of cardiac disease. I do not believe that the high MAE rates were a reflection of the surgeons, as many of them participated in ACAS (Asymptomatic Carotid Artery Stenosis) and had superb outcomes.

Endovascular Today: *Why were the CEA results better in EVA-3S (MAE: 3.9%) than in SAPPHIRE (MAE: 12.6%)?*

Dr. Green: The patients in EVA-3S and SAPPHIRE differed in the degree of operative risk. The former was a low-risk trial, the latter a high-risk trial. EVA-3S attempted to be a real-world trial and failed because of the lack of expertise in the CAS group. SAPPHIRE was never intended to be a real-world trial; it was conceived to show noninferiority of a new technique in a population known to be at extremely high risk for the conventional therapy.

CAPTURE IN THE CONTEXT OF SPACE AND EVA-3S

William A. Gray, MD, discusses what lessons can be learned from large-population, high-enrollment, postapproval registries.

Endovascular Today: *What is the CAPTURE registry? Why was it started?*

Dr. Gray: The CAPTURE registry was a condition of approval that the FDA mandated when Guidant (now Abbott) received its approval for the Accunet and Acculink stent systems. It is a typical postmarket surveillance trial, and there were several goals. One goal was to survey for rare and unanticipated device-related events. The pivotal trials that led to device approval (in this case, ARCHeR) would not have identified these rare events, which occur with a less than 1% incidence. The second goal was to examine the transfer of the technology from the trial setting into the community; this registry was a measure of how well physicians can be selected and trained to do the procedure. Lastly, the original CAPTURE registry was meant to be a 1,500-patient registry but was extended at the request of Guidant/Abbott and approved by the FDA for an extension to allow for data gathering and further analysis of carotid stenting in the community at large.

Before the CAPTURE dataset became available, we really had very small data cohorts; 300 to 500 patient pivotal trials really do not allow for any significant subset analysis, but this 3,500 patient registry has allowed for that. The enrollment is now well over 3,500 patients, but we were able to look at the data and analyze these 3,500.

Endovascular Today: *Of those 3,500 patients, is there an argument that these are cherry-picked patients, or are physicians required to submit all of their patient data to the registry?*

Dr. Gray: Basically the sites and investigators who were performing carotid stenting and involved in the CAPTURE registry were asked to enroll all their patients undergoing carotid stenting with this embolic protection stent system. That does not mean that all patients in the US were in CAPTURE; actually, based on estimates of the US activity of CAS, it represents only a fraction of the total. To the extent that the physicians were contributing and participating from a research perspective, they were encouraged to enroll all of their patients. I should also say that it was encouraged that patients be enrolled according to the IFU so that enrolled patients should have followed FDA approval language, which means they should have been high-surgical-risk for a CEA due to either pre-

specified, asymptomatic with stenosis >80%, symptomatic with stenosis >50%, and so on.

Endovascular Today: *So the CAPTURE registry also includes the subset of patients that was not covered by the CMS reimbursement?*

Dr. Gray: That is correct, and this is one of the reasons the CAPTURE demographics become somewhat self-fulfilling from the symptomatic cohort standpoint. We only had 14% symptomatic patients in this study, largely because symptomatic patients were treated on-label and were not required to be in the study, but the CAPTURE registry and other postmarket surveillance registries have provided some of those asymptomatic patients continued access to this therapy in the face of a CMS noncoverage decision in this group.

Endovascular Today: *There are different definitions for the major adverse events when dealing with carotid studies; does the inclusion of any stroke or MI also impact those results?*

Dr. Gray: That is a great question. Clearly the inclusion of MI and all stroke (not just ipsilateral but contralateral) affects the outcomes. You will see in subsequent publications that there is actually a 1% rate of contralateral stroke or nonipsilateral stroke, which occurs in this and most other surveys. In other trials that do not include all-stroke and only ipsilateral stroke, they are missing some of the strokes that occur in carotid stenting and will, by comparison, have better outcomes. The issue comparing outcomes across trials is a complex one given the differences in populations studied, that is, inclusion and exclusion criteria, definitions used for adverse outcomes, primary endpoint definitions (the aforementioned stroke example is a good one), and event adjudication through the clinical events committee process. I am coming to the conclusion that the best way to compare outcomes across trials is by using major stroke and death, which are not subjective measures.

Endovascular Today: *Is there an argument to be made that those strokes were wholly unrelated to the procedure taking place?*

Dr. Gray: That argument is probably not valid; the nonipsilateral stroke should be included in order to assess the risk of the entire procedure. Interestingly, if one looks at the overall procedure, it appears that the periprocedural risk of contralateral stroke is the same, roughly 1%, regardless of whether the patient is over 80 years of age, symptomatic or asymptomatic, or the operator's expertise—all of those features that you would think predict the rate of nonipsilateral stroke actually do not. There is something happening from a procedural standpoint that we need to learn more about, but it clearly does make a difference. Obviously, MI will contribute to the total number of events at 30 days, but more importantly, the process of adjudication—which is having a clinical events committee looking at events—seems to increase the total number of events at 30 days because we are forced to define events more clearly.

Endovascular Today: *In order to compare apples to apples, can we compare SAPPHIRE with the EVA-3S and SPACE studies?*

Dr. Gray: No, because they compare differing patient cohorts. EVA-3S, SPACE, and SAPPHIRE were all randomized. SAPPHIRE is a high-surgical-risk trial in which only about 25% of the patients were symptomatic; the patients in EVA-3S and SPACE were all symptomatic and were not defined as high-surgical-risk patients. EVA-3S and SPACE are reasonably comparable to each other because they seem to study the same patient population: symptomatic, reasonable surgical risk; but they are not comparable with each other in terms of operator expertise, which was poor for the stenting arm of the EVA-3S.

Endovascular Today: *Why was there such a large divergence of adverse events between the CAS and CEA arms in the EVA-3S study?*

Dr. Gray: EVA-3S had the lowest rate of complications with CEA ever reported in a symptomatic patient population; it also had one of the highest rates of complications ever reported in the stenting arm of a carotid trial. There are several reasons why we believe that occurred. First, operator experience was quite limited in the EVA-3S stent arm, whereas the experience level in the surgical arm was quite good—enrolling surgeons had to have performed 25 or more CEAs per year. In the CAS arm, operators could have done as few as five carotid stents or as many as 12, with no reports as to whether they used embolic protection, the particular technique, or the outcomes. There was no central organization within that trial that vetted operators for the CAS arm. It was possible to be an EVA-3S CAS investigator, having never done a carotid stent, and performing your first randomized case being proctored by a physician who had done five carotid stents, who may or may not have used embolic protection before. The results of that first case are included in the pivotal data. This obviously represents a learning curve function reminiscent of the original Wallstent trial, which had very similar results at 1 year with a 12% complication rate in the stent arm and a 4% to 5% com-

plication rate in the surgical arm, largely the result of a lack of trained operators, by today's standards. The inclusion of nontrained or poorly trained operators is a major criticism of EVA-3S.

Endovascular Today: *CAPTURE showed that there was little difference between the results obtained by operators at all levels of experience. What accounts for the similarity of outcomes in CAPTURE versus what we are seeing with EVA-3S?*

Dr. Gray: There are selection criteria for operators that were followed in CAPTURE: participants had to be peripheral interventionists of good standing who had previously performed a certain number of cerebral angiograms and rapid-exchange procedures, and had experience with .014-inch-based systems. There was no indication that a selection of operators like that occurred with EVA-3S. There was no mention of mandated training in EVA-3S, just the proctorship. In CAPTURE, operators with no prior experience underwent a 2-day intensive training course that included wet lab models and simulation training, and they were offered proctors for their first several cases. There was a careful rollout of selected operators for this technology, with training geared toward previous operator experience.

Endovascular Today: *Outside of any training or experience required in some of the studies versus EVA-3S, what other factors would account for the differences between the CAS and CEA arms?*

Dr. Gray: There was initially a nonmandated use of embolic protection, so of the first 80 patients, only a portion received embolic protection. The Data and Safety Monitoring Board got together after analyzing the data and, realizing that the outcomes for nonembolic protected patients were poor, mandated embolic protection, but not before there were four or five events related to nonprotected procedures (highly unusual in itself), which raised the overall rate of complications in the stent arm. Second, there was no standard equipment use mandated in the EVA-3S study; there were seven embolic protection devices and five different stents listed in the manuscript. That amount of variation in equipment in a population of operators with limited experience probably led to some complications. Lastly, the overall number of randomized cases performed per site per year was 1.7 in EVA-3S. The poor rate of enrollment per site speaks to the issue of low-volume operators, who probably have poorer outcomes in general, especially when initially poorly trained.

Endovascular Today: *The conclusion of SPACE was that CAS failed to demonstrate noninferiority to CEA. Many people might read that to mean that it demonstrated inferiority. What in fact happened in the study?*

Dr. Gray: The trial did not enroll enough patients to demonstrate noninferiority. Just because something is not noninferior does not mean it is superior or inferior. It means that it has not been proven to be noninferior, but that doesn't mean that it cannot be.

Endovascular Today: *Why was it unable to enroll enough patients?*

Dr. Gray: There was an interval analysis performed that was prespecified in the SPACE trial that occurred at 1,200 patients, which was meant to look at safety and outcomes. The Data and Safety Monitoring Board decided that, at the current rate of complications and the current difference between the two arms, more than double the number already enrolled would be needed. The null hypothesis that needed to be rejected was that CAS is not noninferior to CEA, that that there is actually some difference between the two therapies. At 1,200 patients, they found that they would need another 2,500 patients for a total of approximately 3,500. At that point, the trial sponsors withdrew support. So, after they decided to pull the plug on the trial, which may have made sense from an economic standpoint, we are unfortunately left with these results. If you look at the results, with almost 600 patients in each arm, there was a nonstatistically significant difference of four events in 30 days: 37 in the surgery arm and 41 in the stent arm. It is also important to note that in SPACE, there was no mandate for embolic protection, and only 27% of patients actually received embolic protection. Despite of some of these issues, I do not view SPACE as a negative trial for CAS. Stenting actually had very comparable outcomes to CEA even without the standard use of embolic protection.

Endovascular Today: *Do you believe that the treatment of patients in the US will change as a result of these studies?*

Dr. Gray: Honestly, if we thought that SPACE or EVA-3S were representative of outcomes in CAS, then we would have to stop trials like CREST, or at least the symptomatic arm of CREST; it would be unethical to continue to randomize patients if we believed that there was a difference between the therapies. However, I think the conduct, execution, and design of EVA-3S was so poor that it makes it difficult to analyze the results in a meaningful way, so we continue to randomize patients with normal surgical risks in the US in hopes of answering these important questions. SPACE and EVA-3S clearly did not give us the definitive answers. ■