

The CAS Roundtable

Interventional experts Barry T. Katzen, MD; Lee R. Guterman, PhD, MD; and Jay S. Yadav, MD, discuss recent trial data, learning curves, and today's device options for treating carotid artery stenosis.



Barry T. Katzen

Recent data have been published calling into question the efficacy of carotid artery stenting (CAS) versus carotid endarterectomy (CEA) (ie, EVA-3S and SPACE). What do these data tell us?



Lee R. Guterman

Dr. Katzen: Each trial gives us different information. On the surface, the EVA-3S trial seems to show that there is no benefit from CAS and that, in fact, CAS may be more dangerous than CEA. I believe, however, that the trial is so significantly flawed that it is erroneous to draw such a conclusion. One of the things that we have learned in the past decade is that CAS is definitely an operator-dependent procedure, as is CEA. This particular trial benchmarked established technicians and technology against evolving technicians and technology. As opposed to some of the other trials that are ongoing in the US, there was very little site certification and site accreditation, and the minimum amount of cases was far lower than the CREST trial. Personally, I think it would be very difficult to draw the conclusions that the authors of the EVA-3S trial have published.

The SPACE trial, which was published in *The Lancet*, was halted prematurely. When a trial is terminated prematurely because of lack of funding or lack of statistical validity, essentially the trial really has no data. The SPACE trial was not terminated because one side or the other met the primary endpoint, it was terminated because the two arms were so close that they did not have the funding or the inclination to go on to increase the number of patients. On the surface, the results of the SPACE trial look identical in both arms. Therefore, someone who is in favor of stenting could use the data to show that CAS is equal to CEA, although there would be no statistical validity to back such a statement.

Dr. Guterman: There is a steep learning curve as a physician acquires the skills needed to perform angioplasty and stenting for the cervical carotid bifurcation disease. This is especially true as you layer on the use of distal or

proximal protection devices. Yet, if there are significant obstacles to gaining the skills for new carotid interventionists, how could the lead-in data for more than 500 patients in the CREST study report the opposite message? Lead-in phase patients followed in the CREST registry had very low overall morbidity and mortality, even though many of the stent procedures were performed by less-experienced physicians. I believe the CREST study, when completed, will provide the most comprehensive and complete dataset available based on the study design and the participants.

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-Dr. Katzen

Dr. Yadav: The SPACE trial actually demonstrated equivalence of CEA and CAS in symptomatic patients, even without the mandatory use of embolic protection device. These results have been misrepresented, including by the authors themselves. EVA-3S demonstrated superiority of CEA, but is deeply flawed. The interventionists essentially learned intervention during the trial and were not qualified to do carotid stenting; most were typically vascular surgeons with no previous interventional experience. Embolic protection device use was not mandated until later in the trial, and a variety of stents and embolic protection devices could be used and mixed and matched per the investigators whims.

How would you characterize the learning curve for CAS? What level of experience should an interventionist achieve to be considered as having mastered the curve?

Dr. Yadav: To be considered an experienced interventionist, one should have performed at least 200 cases. On top of that baseline interventional experience, they should have performed 25 cerebral angiograms and 25 CAS procedures. I would consider this the minimum.

Dr. Katzen: We have some conflicting data to support different positions in this area. One of the things learned through the CREST trial, as documented by the Interventional Management Committee, was that there is a learning curve that probably was on the order of 20 to 25 cases. On the other hand, the CAPTURE data, which are not adjudicated data, seem to show that the level of training or experience may not influence outcomes. I think most of us believe that in a highly scrutinized environment, there is a definite learning curve associated with CAS, and that it is probably somewhere between 15 and 25 cases with embolic protection. Obviously, even with that, all of us are learning with every case we perform.

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-Dr. Yadav

Dr. Guterman: The learning curve obstacles can be defined as arch access, guide placement, distal or proximal protection device delivery and deployment, and lesion manipulation by angioplasty and stenting. New operators have significant problems with arch access and guide placement secondary to tortuous takeoff of the left carotid from the arch and aberrant anatomy. Once a catheter is in place in the common carotid, delivering the guide sheath can be challenging, especially when the external carotid origin is stenotic and the external carotid artery cannot be used as a for distal wire stabilization. Crossing the lesion can be challenging, and placement of the filter into a safe landing zone requires experience, especially when hairpin turns exist distal to the lesion. Angioplasty and stent placement can be difficult if the lesion extends into a curved portion of the internal carotid artery. Filter capture can also present obstacles when the cells of the stent compromise the lumen of the treated vessel and prevent capture sheath delivery and filter capture. I feel that a firm foundation in cerebral angiography helps prevent access and guide placement problems.

How does patient anatomy affect device selection? Are some devices better suited for certain anatomies?

Dr. Katzen: There is no question that each device has advantages and disadvantages. I believe that the state of the art is finally reaching the point that we have multiple devices available to us. Regrettably, because of the regulatory environment in the US, we are not always able to choose to use a certain device based on a certain anat-

omy. That being said, it certainly appears from work being done in Europe, and also internally in clinical trials, that there may be differences between open- and closed-cell devices, possibly even clinical differences. We know that they behave differently.

One fundamental question is whether CAS is a one-size-fits-all type of procedure (ie, can one type of stent be used for all lesions?). I think it is unlikely that this is the case. It is more likely that we will continue to analyze which stents might be more suited to particular lesions, and try to achieve better analysis of such data. There are preliminary data from Alberto Cremonesi, MD, and Marc Bosiers, MD, suggesting that closed-cell design may have significant advantages over open-cell design. The other important issues that need to be taken into account are trackability and deliverability.

Regarding patient anatomy, it is important to note that for many years we have been focusing on which patients are at high risk for surgery to include them in stent trials. However, we probably need to be looking more carefully at understanding better which patients are at high risk for stenting. More detailed evaluation of morphology is going to help with that transition.

Dr. Guterman: Arch access can also govern the choice of devices. In patients with arches that present challenging angles relative to the take off of the left common carotid, I find a SIM2 (Cook Medical, Bloomington, IN) shape to be very helpful for the initial cannulation of the left common ostium. The SIM2 insert for the 6-F and 7-F guide sheath can be too rigid to function well in acute angles formed between the aortic arch and the common carotid artery. In these cases, I have used the Envoy 6-F guide catheter (Cordis Corporation, a Johnson & Johnson company, Miami, FL) in a SIM2 shape. Presently, only the monorail carotid Wallstent (Boston Scientific Corporation, Natick, MA), with a diameter of 8 mm or less, will fit in this guide catheter. Therefore, to use this system the common carotid artery must be less than 8 mm. Shortly, the NexStent (Boston Scientific Corporation) will be approved and this monorail stent will be able to fit through a 6-F guide catheter as well.

Calcified lesions that extend into tortuous anatomy can be the most difficult to stent. Stiffer constructs will straighten the vessel in the region of the stenosis, resulting in distal kinking. Nitinol stents with open-cell design approximate the curves well, but stent struts can bulge into the lumen of the parent vessel in areas of tight radius of curvature. These struts often cannot be seen with fluoroscopy due to the poor fluoroscopic visualization of nitinol devices.

Dr. Yadav: Open-cell designs allow better conformation of the stent to the vessel and reduce kinking of the

distal artery. Closed-cell has been touted as reducing the risk of stroke, but there is no evidence for this in any of the multicenter, independently adjudicated trials. Wall apposition with closed-cell designs is poor, and restenosis appears to be higher. Both approaches are useful, and it is a matter of operator experience and preference, just as in the coronaries.

How does plaque morphology affect decision-making regarding treatment and device selection?

Dr. Katzen: At this point, at our institution, we have tended to not take into account plaque morphology (with the exception of dense calcification) regarding specific device selection. However, when a patient is ulcerated, we do not think that patient is excluded from CAS. Similarly, when looking at hypoechoic versus hyperechoic plaque, we have not brought those factors into play in terms of patient selection at this point.

Dr. Guterman: In lesions that are heavily calcified within 1 cm to 2 cm of the bifurcation, I like to use the predilatation balloon not only to improve lumen diameter prior to stenting, but also to test the carotid bulb and sinus. The predilatation helps determine the sensitivity of the carotid bulb reflex and the magnitude of the hypotension and/or bradycardia that can occur. This bulb challenge helps guide my choice of postdilatation balloon diameter.

Dr. Yadav: Again, there has been a tremendous amount of unsupported speculation and guesswork. There are no systematic studies that answer these questions. It is illogical to propose using one device for the symptomatic, ulcerated plaque where there is great concern about embolization and a different device for the supposedly less-risky plaque. Should you not use what you believe is the best device all the time?

I do use a different technique in the elderly symptomatic patients who have been demonstrated in multiple studies to have higher stroke rates. I put in a second filter through the stent before I postdilute the stent to provide maximal protection at this critical step. I do not do this all time, however, because of the technical challenge of this approach.

What are the current standards for symptomatic patients versus asymptomatic patients with regard to when to intervene?

Dr. Guterman: For asymptomatic patients, the margins that govern treatment outcomes are narrow. Therefore, careful patient selection is critical. Although ACAS suggests treating patients with >60% stenosis, I prefer patients with stenosis that approaches 75% to

80%, confirmed using ultrasound systolic and diastolic velocities and an additional confirmatory test, such as CTA or MRA. The NASCET trial did follow patient with an asymptomatic lesion contralateral to the symptomatic lesion. There is some evidence to support an increase in stroke risk as a function of increasing stenosis in asymptomatic patients. Therefore, I consider treating asymptomatic lesions if they approach 80%. For symptomatic patients (males >50%; females >70% stenosis), revascularization is indicated and can significantly reduce stroke risk.

“... I prefer patients with stenosis that approaches 75% to 80% and confirmed using ultrasound systolic and diastolic velocities...”
-Dr. Guterman

Dr. Katzen: At Baptist Cardiac & Vascular Institute, we have a fairly conservative approach to asymptomatic patients regarding any type of invasive therapy. We have noticed great benefits to modern and maximum medical therapy, and therefore tend to push medical therapy until lesions get to be $\geq 80\%$. That being said, generally speaking, in asymptomatic patients we do not recommend treatment unless they get to $\geq 80\%$, which in our lab is a very high bar. It is a diastolic velocity of >137 cm/s, or something that looks like a near occlusion on MRA or CTA. In symptomatic patients, I am much more inclined to treat patients with lesser degrees of severity of illness (approximately $\geq 60\%$ stenosis).

Dr. Yadav: Symptomatic patients with $\geq 50\%$ stenosis who are at high surgical risk should have stenting with embolic protection; if they are older than 80 years, an experienced operator and some technique modification is necessary. Asymptomatic patients with $\geq 80\%$ stenosis who are at high surgical risk should have stenting with embolic protection.

There is no clear evidence for cognitive decline in asymptomatic patients after CAS. The only good randomized data was from CAVATAS, and it demonstrated no difference in cognitive function between CAS and CEA.

The CREST and TACIT trials are ongoing. What have they shown?

Dr. Katzen: CREST, in particular, has provided a lot of useful information. First, from the lead-in data, we have learned a lot about the relative safety of CAS, and we have learned that, in carefully selected hands, CAS can

be performed with an acceptable rate of safety. However, for the CREST trial, there was a very high bar; participants had to have performed 25 carotid angioplasty and stenting procedures, and once those had been accomplished, it was necessary to move on to a lead-in phase with an additional 10 cases, the outcomes of which were reviewed by the interventional management committee. Many of the operators who had events or questionable outcomes were sent back for an additional 10 cases before they were able to enter the randomization part of the trial.

Analysis of CREST lead-in patients showed an increased risk in octogenarians, which led to exclusion of those patients in the lead-in phase. Octogenarians are not excluded from the randomized part of the trial.

Another point that CREST has shown us—through silence, so to speak—is that the trial is still going on, unlike the EVA-3S trial, which I take to mean that there has been no significant difference between the two arms such that there was no safety endpoint reached that would require the trial to be stopped. The fact that CREST is ongoing makes me very optimistic about the outcomes for CAS.

Dr. Yadav: I believe these trials will show equivalence of CEA and CAS in low-risk patients. More interesting are technique and device refinements to treat the symptomatic elderly patients who do poorly with either CAS or CEA, and who represent a large number of patients.

Dr. Katzen: TACIT is another trial that we are very excited about, but it has yet to get underway. John Rundback, MD, and Matt Thompson, MD, are the principal investigators, and I am the study chair; we are currently actively looking for funding. We strongly believe that there is an important need for a trial that compares maximum medical therapy to any type of invasive therapy.

I think an interesting observation that came out of a very small study conducted by Dr. Rodney Raabe was the possible cognitive decline in asymptomatic patients. This is very critical to the future of understanding the role of carotid circulation on cerebral function. It is one of the reasons that we have included it as part of the TACIT trial plan; we think it deserves to have a pivotal trial. At this point, it is a very intriguing and tantalizing benefit, but much more study and proof is necessary.

What is your position regarding proximal occlusion versus distal protection versus no protection?

Dr. Yadav: With competent operators, protection clearly decreases the risk of stroke, as shown in the AngioGuard (Cordis Corporation) feasibility studies in Europe and the US. Due to ease of use and data, filters

remain the device of choice. Proximal protection has a role in acute stroke, thrombotic lesions, and unusual distal anatomy, but their size and risk of stroke during insertion need to be considered.

Dr. Katzen: I do not believe in using no protection at all. On the other hand, we know that using filters for embolic protection results in a stroke rate that, while reduced compared to no protection, is still significant. I think that proximal occlusion, although it looks very attractive, may have some pitfalls and certainly deserves further study.

We are very excited about being part of the EMPIRE trial, which is the reversal of flow trial for embolic protection using not only proximal occlusion, but also positively setting up reversal of flow. We will not know of any statistical significance until these studies are completed.

Dr. Guterman: I try to use distal protection in all cases of carotid angioplasty and stenting. The filter landing zone distal to the lesion can be tortuous and/or irregular, resulting in difficult delivery or retrieval. In some cases, the lesion is incorporated into the tortuous segment, resulting in difficulties navigating the distal protection device through the lesion. Devices that use a lead wire and catheter have helped solve this issue in some cases. Proximal protection may be an invaluable tool in cases in which tortuous anatomy or lesion characteristics preclude the positioning of distal protection safely. Distal protection devices with a lower crossing profile and increased flexibility are being tested and, as the technology improves, we may see devices that can be placed easily in the internal carotid distal to the carotid stenosis. ■

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Jay S. Yadav, MD, is the inventor of the AngioGuard emboli-protection device used in the SAPHIRE trial and was a shareholder in AngioGuard, Inc., at the time of its purchase by Johnson & Johnson in 1999. He has disclosed that he receives recurring payments from Johnson & Johnson as a former shareholder of AngioGuard, Inc. He does not own any shares of stock in Johnson & Johnson. Dr. Yadav may be reached at jyadav@cardiomems.com.