The Journey of Carotid Stenting in Contemporary Stroke Prevention

Lessons learned during the development of carotid artery stenting and a look at where we go from here.

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As the concepts and technology that drive carotid artery stenting (CAS) as an option for treating extracranial carotid occlusive disease have matured, the understanding of CAS's value to our patients has followed a roller coaster pattern in recent years. The safety of CAS has improved dramatically during the past 10 years, with recent studies achieving perioperative stroke/death rates that are within recommended guidelines for carotid repair.[1-6] However, it is challenging to interpret what the available data and the existing clinical practice patterns mean. The results of CREST have left many questions unanswered, and this will be especially evident once the subanalysis is published.

During the time that CAS has developed, our approach to endovascular repair in every vascular bed has become significantly more sophisticated, and we are using and transferring those skills to all our work. The overall level of endovascular skill for all specialties is better now than it was 10 years ago, and we have become a lot smarter about managing carotid disease in the interim. In my opinion, trends are emerging from the research, clinical experience, and development in this area that show a trajectory toward establishing a major role for carotid stenting in the management of carotid occlusive disease and the prevention of stroke.

DEVELOPMENTAL PATHWAY

Anyone in the active practice of carotid endarterectomy (CEA) will attest that during the removal of carotid bifurcation plaque, one often finds friable, seemingly antibiological material that defies proper description and will cure any onlooker of interest in fast food. In addition, carotid bifurcation stenosis causes problems through embolization, a process during which the moonscape flow surface of the heterogeneous lesion becomes unstable. Given these factors as a starting point, it makes little sense a priori that CAS would be effective in preventing stroke because it modifies the plaque in situ. This helps to explain some of the heartfelt resistance that many endarterectomists have had for CAS.

However, let's look beyond this initial impression for a moment. If the carotid stenosis were not attached to the brain, it would be ideal for successful endovascular intervention. The lesions are almost always focal, with healthier artery proximally and distally. The lesions are stenoses, not occlusions, and it is almost always possible to dilate them with standard balloon technology. Perhaps to render the lesion harmless to the patient, the stent must only modify the morphology of the flow surface. In fact, it appears that the scaffolding provided by the carotid stent is enough to maintain an adequate lumen and, at the same time, prevent the carotid lesion from becoming unstable. This is borne out by the long-term follow-up after EVA-3S, SPACE, SAPPHIRE, and CREST, which all show the same level of stroke protection after both CAS and CEA once the patient is beyond the first 30 days.[1,7-9]

The important difference between CAS and CEA in all randomized trials so far is the perioperative risk of stroke. In the CREST trial, the risk of major stroke and the risk of death were not significantly different between CAS and CEA, but there were more minor strokes with CAS. Our challenge is to make the perioperative period safer if CAS is going to be of value to our

patients in preventing stroke. One would hope that we were paying attention and honing our skills during the past decade as CAS has been developing and that we have learned something along the way: which patients, arches, and lesions can be safely considered for CAS. This is exactly what we are experiencing, and there is mounting evidence that CAS has become safer.

When perioperative morbidity rates for CAS from the early 2000s are compared with those from the end of the decade, we see that the stroke/death rates have decreased from the high single digits (eg, 8% in ARCHER) to the low single digits (3% or less range for PROTECT, EPIC, EMPIRE, and ARMOUR trials).[2-5,10] The CREST trial also showed a steady improvement in periprocedural results for CAS. Although these data are not yet published, it is impressive to see how much the perioperative results for CAS have improved over time as the available devices, inclusion criteria for the study, and participating investigators were held constant. Information about the change in results of CAS over the course of the CREST trial is available at the US Food and Drug Administration Web site and was presented during the administration's panel on CAS on January 26, 2011.[11]

Each of the sophisticated endovascular procedures in our repertoire is the product of a gradual building process with incremental improvements in technology, technique, and clinical skill, creating a feedback loop that leads to better results. No one expected endovascular repair of aortic aneurysm or recanalization and reconstruction of a superficial femoral artery occlusion to be a finished product on day one. In contradistinction, CAS was presented as a finished product and a replacement for CEA. Whether this was hubris, a miscalculation based on previous successes, a misunderstanding of how confounding carotid disease can be, a demand from the regulatory system (that expected a complete CAS system to be tested before any approval could be achieved), youthful enthusiasm, or all of these, is not clear.

However, if CAS were being rolled out today, it would be done differently. It would likely be introduced in the same manner as other endovascular procedures have been presented—as a partial solution that will likely grow into the new role with improvements over time. What if the regulatory apparatus, the market for medical devices, the research institutions, the physicians, and the patients had insisted that endovascular aneurysm repair had to solve all of the potential problems up front, including difficult neck anatomy and endoleak, to become a viable treatment? It would never have gotten off the ground.

Take yourself back to Y2K. The dawn of the new millennium was a rapid development phase for many of the things that we rely on now in various aspects of daily life: the dissemination of web-based information and business opportunities, digital communication, an Internet-based economy, the emergence of Google, the ability to move capital rapidly from place to place, and the realization that everyone would have a cell phone, to name just a few. This was also a time frame during which the pace of development in the endovascular field was on an amazing slope of progress. Multiple vascular beds were being treated with new techniques and new attitudes at once. Most of our current procedures have developed significantly during the past 10 years. Clopidogrel was new, and there were no drug-eluting coronary stents yet available. The top-selling endovascular aneurysm repair grafts of the time have gone by the wayside. The possibility that carotid disease could be solved using stent implantation evoked opinion from all and emotion from most. This was the era in which the CREST trial began to enroll.

In 2001, the first major randomized trial comparing CAS and CEA, the CAVATAS trial, was published.[12] Neither CAS nor CEA performed well; the stroke and death rates were > 10% in each group. Among those undergoing intervention, all received angioplasty but only one-quarter received a stent. So, without a scaffold being used in most of the patients and without any method of cerebral protection, the stroke and death rate was 10%. At the time, in my vascular surgeon's mind's eye, I imagined that the rate of complications should have been 50% because I had the experience of handling nasty plaque material for many years. This was the first indication that it would be a matter of time, technology, and case selection before carotid intervention would become a worthwhile approach. Since then, a lot of toil and trouble have gone into the development of CAS.

WHAT HAVE WE LEARNED?

Developments in the endovascular arena during recent years have facilitated the field of CAS, including a trained workforce, the broader availability of endovascular skills and techniques, a wider experience with carotid and cerebral arteriography, improvements in noninvasive duplex and axial imaging, a better understanding of vulnerable plaque, and the general appreciation of endovascular techniques and what they can do in all vascular beds. At the same time, we are chastened by some of the things that we learned the hard way with CAS. For example, CAS is not a direct replacement for CEA. In the same way that there are many factors

that make a patient a better or worse candidate for CEA, there are other factors that influence the suitability of patients for CAS. CEA will be performed for many years to come and will continue to be the best solution for a large proportion of patients with carotid bifurcation stenosis.

We also know that there is a learning curve in terms of the number of procedures performed by each operator, as well as in terms of patient selection. Trial results have been profoundly influenced by the experience and abilities of the practicing clinicians, and this is grossly evident in the randomized trials of CAS and CEA. We know that octogenarians should be managed carefully. Furthermore, we have learned about the clinically unapparent but nevertheless worrisome lesions that can be detected by diffusion-weighted magnetic resonance imaging of the brain after all forms of carotid reconstruction and that these lesions must be better understood and managed. Some type of cerebral protection is required to make CAS viable, and proximal occlusion is tolerated in most patients.

We have learned new facets of arch anatomy and cerebral physiology. Carotid lesions are more dynamic structures than previously thought and are capable of significant remodeling. We now know at least some of the factors that make a patient high risk for CAS. Events after CAS are more frequent, more often minor, and more often delayed in comparison to CEA. We must make the first 30 days as safe as possible to offer value to our patients with CAS.

What can we show for our collective efforts? We have randomized trials, recommendations for training, and the widespread practice of CAS in communities around the world. There are multiple databases, including one maintained by the Centers for Medicare & Medicaid Services. Most sophisticated hospitals have specific criteria to obtain privileges to perform CAS. We now have multiple options for cerebral protection during CAS. We have seen improving results: CAS has been performed with incredibly low risk considering conformance of both the symptomatic and asymptomatic arms of the CREST trial to American Heart Association guidelines (3% stroke and death rate for asymptomatic patients, 6% for symptomatic patients). We have multiple stents and cerebral protection devices with at least some form of approval in many countries. There are also some wounded feelings left over from interspecialty conflict, and there is exasperation among many clinicians at the slow pace of the regulatory progress.

We also have the CREST trial, of which we should be proud. CREST was a valiant, multispecialty effort in which patients, physicians, industry, and the National Institutes of Health pursued a level of investigation and clinical science that was courageous, especially at the time it was initiated. The CREST trial was the only one among the major randomized trials that included both symptomatic and asymptomatic patients and required a high level of expertise for those performing both procedures. Ten plus years later, the results show that this endeavor has never been as simple as we all hoped. A more definitive answer is not to be had immediately, especially in light of the results for separate endpoints (ie, more minor strokes after CAS and more myocardial infarctions after CEA). Information will be made available in subsequent publications that should help us to understand which subgroups are better treated with CEA and which are better treated with CAS. By virtue of when it was planned, CREST had a lot of criteria for what makes a good CEA candidate but minimal criteria for what makes a good CAS candidate.

WHERE DO WE GO FROM HERE?

I am one of the foolish people who imagined that the role of stents in managing carotid bifurcation stenosis would be more settled by this point. We still have our work cut out for us. A well-done procedure presupposes a well-trained workforce. The quality of the endovascular skills and the number of people who possess them, from a number of fields, is dramatically better now than it was 10 years ago. However, as CAS goes through fits and starts, we will have to be resourceful in managing the staffing for these cases in an effort to maintain the proficiency of practitioners who have gone before and improve the experience of those who hope to gain proficiency.

An absolute stroke rate of 1% appears to be due to arch manipulation. What if you could take the arch out of the equation whenever there was significant tortuosity or disease by performing direct cervical access? Some strokes occur in the hours or days after the CAS procedure, presumably with embolization through the open cells of the carotid stent. What if different stent designs could be used to prevent these episodes of delayed perioperative embolization? We know that patients with recent symptoms have a higher risk of stroke after CAS. What if proximal occlusion could be used for cerebral protection in these patients? What if various stent designs and methods of cerebral protection could be customized to the needs of each individual patient taking into account the presentation, the lesion, and the anatomy to design an optimal treatment plan? The results of contemporary medical management of critical but asymptomatic carotid stenosis without mechanical repair has not yet been established, so the added value

of carotid repair cannot be fully understood in this group. Optimal management of asymptomatic stenosis is a major issue on the horizon for all clinicians that must be addressed during the next few years and will certainly influence the practice of CAS.

CONCLUSION

Trends emerging from research and clinical experience suggest a major role for CAS in the management of carotid occlusive disease. However, further development will be required. CAS and CEA will likely be complementary for the foreseeable future. We need to keep calm and keep working. Although there are issues that are yet to be fully understood, carotid stents are of value to our patients. ■

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