Applying CREST to Clinical Practice

With further collaboration among specialties and careful consideration of the available data, CAS performed by experienced operators may become accepted as frontline therapy in properly selected patients.

BY CHRIS METZGER, MD

Stroke is a devastating clinical problem affecting a large number of patients. It is the third leading cause of death and the leading cause of disability in the United States.[1] It is estimated that there are approximately 165,000 strokes per year in the United States alone,[1] and up to 30% of ischemic strokes are caused by obstructive carotid atherosclerosis.[2] Carotid endarterectomy (CEA) has been established as being superior to medical therapy alone for the prevention of stroke in patients with obstructive carotid stenosis in carefully selected patients performed by experienced operators.[3-5] However, many patients with carotid atherosclerosis are at increased risk for CEA and were not included in these trials demonstrating the benefit of CEA over medical therapy.

Carotid artery stenting (CAS) has been studied extensively during the last 10+ years as a potential carotid revascularization strategy for patients at risk for CEA. With increasing operator experience and proper case selection, and with improved outcomes noted in carotid stent trials, CAS is now worthy of consideration as frontline therapy for carotid revascularization in patients with carotid artery disease, whether or not they are at increased risk for CEA. CAS has theoretical advantages as a less invasive form of revascularization applicable to a wider spectrum of patients. However, to be accepted as front line therapy for a majority of patients, it must be validated in carefully controlled, randomized comparison trials.

The recently published CREST trial[6] provides invaluable insight into the comparisons of CAS with endarterectomy in patients who are "standard risk" for CEA. Before CREST there was a paucity of carefully controlled randomized clinical trials of CEA versus CAS. Several European trials (EVA-3S, ICSS, and SPACE) also included standard-risk patients.[7-9] These three studies enrolled symptomatic patients. The validity of these studies had been widely challenged because of a significant difference in the expe-

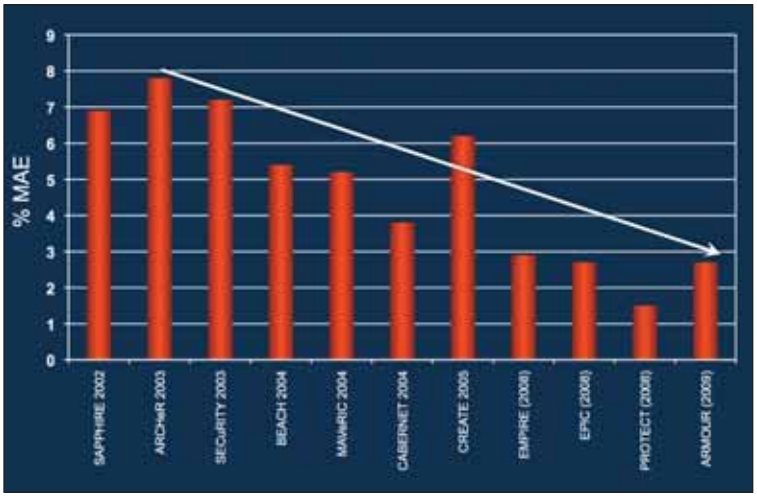

Figure 1. What was happening in CAS during CREST? Eleven US Food and Drug Administration approval trials with improving outcomes (all approved as safe and effective). MAE, major adverse events. Figure courtesy of Dr. William A. Gray.

rience level, with less experienced carotid stent operators compared directly versus experienced surgeons in the CEA arm. In addition, the use of embolic protection and technique have not been mandated to the level seen in North American trials. Their applicability to clinical practice in the United States by experienced operators and careful technique is less certain. The SAPPHIRE trial was a landmark North American trial comparing CAS to CEA with experienced operators in both arms, and this study demonstrated noninferiority of CAS compared to CEA in patients at high risk for CEA. CREST represents the only contemporary North American randomized trial in standard-risk patients comparing CAS and CEA and the only published randomized North American trial to date that includes asymptomatic patients in this comparison.

The ACT 1 trial is an ongoing landmark North American randomized trial comparing CEA to CAS by experienced operators in each arm for patients that are asymptomatic and are at standard risk for carotid endarterectomy. This trial should provide further important information on this group of patients.

HISTORICAL PERSPECTIVE

Before discussing the CREST trial and applying it to clinical practice, it is important to view CREST in the context of the history of carotid stenting and the data provided on CAS before, during, and after the CREST trial. Applying the CREST data to clinical practice will depend in part on decisions made by CMS regarding reimbursement of carotid stenting in standard risk patients. The CREST results will also need to be placed in context of other studies and individualized to each patient when applying these results.

CEA has been viewed as the gold standard for carotid revascularization. As previously mentioned, it has been established to be superior to medical therapy in carefully selected patients by experienced operators when compared to medical therapy for the prevention of stroke.[3-5] However, before we look at CAS and compare this to the gold standard of CEA, it is important to remember the limitations of the CEA data.

First, the studies that established endarterectomy as superior to medical therapy were performed in carefully selected patients at experienced centers. The mortality of CEA performed at lower-volume centers is 2 to 5 times that of those seen in the CEA trials.[10] There were a large number of anatomic and physiologic exclusion criteria, and only a very small percentage of patients with carotid disease were enrolled in the trials. The results of ACAS and NASCET were used to help establish the American Heart Association (AHA) guidelines for performance in carotid revascularization. The results of CEA are worse in

Event	30 days, N=145
Death, Stroke and MI*	1. 4%
All Stroke and Death*	1.4%
Major Stroke and Death*	0.0%
Death	0.0%
All Stroke	1.4%
Major Stroke	0.0%
Minor Stroke	1.4%
MI	0.0%
	31-365 days, N=106
Ipsilateral Stroke	0.0%

Figure 2. ACT 1 outcomes: lead-in patients (adjudicated by CEC). Figure presented by Drs. Ken Rosenfield and Jon Matsumara, Co-Principal Investigators; VIVA, September 2007.

patients who met exclusion criteria for these studies, even if performed by experienced operators. For patients who have physiologic or anatomic increased risk for endarterectomy, there is often a 7% to 20% rate of stroke, death, or myocardial infarction (MI) at 30 days.[11-14] In a review of 10-year outcomes of CEA performed in CEA restenosis patients at the Cleveland Clinic and Mayo Clinic, the stroke and death rate approached 10%.[15] Many of these surgical series lacked consistent, independent neurologic assessment, and it has been clearly shown that adding an independent neurologic assessment increases the reported stroke rate approximately threefold.[16]

CAS was introduced and studied initially only in patients at high risk for carotid endarterectomy. These studies were performed early in the operator's learning curve with first-generation equipment, and before some of the "lessons learned" in terms of case selection. Furthermore, all of these studies had independent neurologic assessment and most had objective measures for myocardial ischemia. These were performed in an era of high scrutiny. These initial CAS trials in high-risk patients could not be directly compared to CEA trials because this was not an "apples-to-apples" comparison. Nonetheless, CAS in the early days compared very favorably to the weighted historical control of CEA in similar patients.[17] Important benefits of carotid stenting were recognized early. This included a very low target lesion revascularization (TLR) rate after carotid stenting, with 2-year TLR rates of 2.5% in the ARCHER trial[17] and 2% at 3 years in the SAPPHIRE trial.[18] The majority of strokes seen were minor strokes, with minimal clinical impact seen in follow-up of these patients. More than half of the patients with minor strokes had a normal

NIH Stroke Scale at 30-day follow-up,[17] and all patients with minor strokes had an NIH Stroke Scale of 0 or 1 at 1-year follow-up.[17] Stenting consistently was effective at preventing ipsilateral strokes, with > 3% ipsilateral stroke seen to 3- to 4-year follow-up in multiple, carefully followed trials.[6,10-17] The procedural success rate was high at ≥ 98%, and even early trials had a low rate of major stroke of ≤ 1.5%.[18]

OVERVIEW OF CREST

CREST enrolled 2,502 patients from 117 North American centers from 2003 to 2008.[6] There were experienced operators in each arm, the carotid stenting technique and the use of embolic protection were mandated, and there was independent, blinded neurologic assessment for stroke outcomes and blinded cardiology assessment of cardiac events (Figure 1). With this careful, randomized comparison, CEA and CAS were equivalent with regard to the primary endpoint of a composite endpoint of stroke, MI, or deaths from any cause during the periprocedural period and ipsilateral stroke within 4 years of randomization. CREST also showed that there was no difference between the two strategies with regard to major strokes. Both treatments were equally effective at preventing strokes with a ≤ 2.4% stroke rate in either arm at 4-year follow-up. Furthermore, both had very low TLR rates, which were similar.

There were more minor strokes seen in the carotid stent arm and more MIs in the CEA, both reaching statistical significance. As discussed, the meaningful clinical impact of minor strokes in follow-up was negligible, and similarly, small MIs are likely to have minimal meaningful impact at follow-up. CREST again demonstrated a significant increased risk of cranial nerve injury in the CEA arm (4.8% in CEA, 0.3% in CAS arm), almost identical to the rates seen in the randomized SAPPHIRE trial.[18] CREST did suggest a potential advantage of CAS in younger patients and a potential benefit of CEA in elderly patients.

HOW CREST FITS IN WITH OTHER CONTEMPORARY CAS TRIALS

First, CREST corroborates the noninferiority of CAS compared to CEA by experienced operators in standard-risk patients that was seen in the high-risk patients in the SAPPHIRE randomized trial, the only other carefully controlled, randomized comparison trial between the two strategies with experienced operators in both arms. It corroborates the durability of carotid stenting with equal or better rates of TLR and equivalence in stroke prevention over prolonged follow-up. It confirms the advantage of CAS over CEA with regard to lower rates of MI and cranial nerve injury sustained after the revascularization procedure.

Over the prolonged enrollment period of CREST, carotid stent trials have consistently shown improved outcomes in carefully controlled trials. The last four FDA on-label approval trials have all shown a ≤ 3% rate of stroke, death, and MI at 30 days in high-risk CEA patients.[19-22] In the highest-risk subgroups of symptomatic and octogenarian patients, the proximal protection devices have a very low event rate.[22] The ACT 1 lead-in data in asymptomatic patients < 80 years of age performed by experienced operators have an extremely low event rate of 1.4% minor stroke rate, with no strokes at 1-year follow-up in an adjudicated cohort. There were no major strokes seen in the ACT I lead-in data (Figure 2).[23] The CREST data evolved over an 8-year enrollment period, with the results concordant with the improving results over this time period (Figure 3).

The favorable results noted in CREST were seen at a time where several of the operators were relatively early in their learning curve and were performed with first-generation carotid stent and embolic protection systems. With the evolution of CAS, experience has led to better case selection, likely seen toward the end of the CREST trial and demonstrated with the low event rates seen in other recent carotid stent trials. The CREST results are also consistent with the improving results of CAS over the same time period shown in the real world carotid stent post-marketing surveillance registries. The SAPPHIRE WW trial[24] has careful independent neurologic assess-

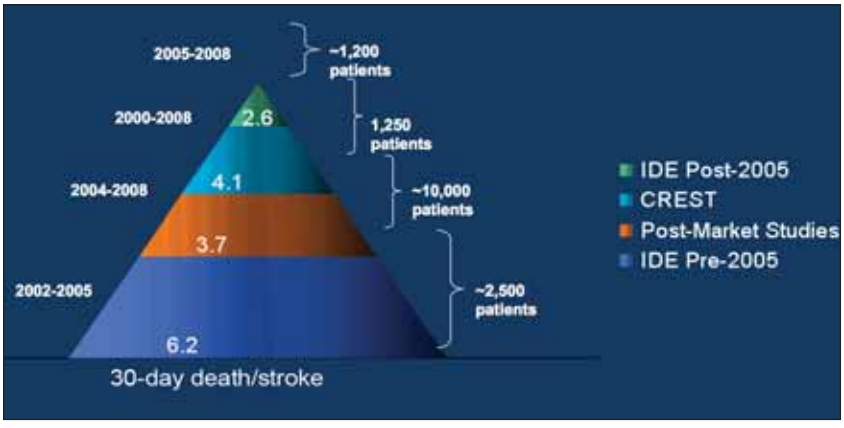

Figure 3. CREST results fit well into the progression of CAS outcome improvement in past decade. Figure courtesy of Dr. William A. Gray.

ment and mandated cardiac enzymes, and demonstrates favorably low event rates of stroke, death, or MI at 30 days in a high-risk CEA patient cohort, consistent with the AHA published guidelines[25] and at least consistent with CEA results in a weighted, historical control group. Similar favorable results are also seen in the EXACT/CAPTURE II study in a large number of patients.[26]

APPLYING CREST AND LESSONS LEARNED TO 2010 CLINICAL PRACTICE

Provided that CMS decisions and insurance reimbursement allow for clinical determination of the optimal form of carotid revascularization, what do CREST and other contemporary carotid stent trials tell us to help select patients for CAS? First, I believe that CREST and other data clearly show that operator experience and careful patient selection are paramount to low-risk CAS. Consistently, it has been shown that outcomes with CAS (and CEA) are significantly better with experienced operators. For CAS, with a very sensitive "end organ" and excellent alternatives of endarterectomy and medical therapy, it is imperative that the procedure be performed after proper training. Based on AHA guidelines and consensus opinion, this would involve only operators who have had formal carotid stent training after significant experience with endovascular procedures in other areas. At an absolute minimum, it is suggested that operators should have a minimum of 50 to 100 other endovascular procedures in addition to significant experience with 0.014-inch wire technology, rapid-exchange equipment, and embolic protection systems.

Operators must understand the carotid and cerebral anatomy and its relationship to neurologic function. All CAS operators should be appropriately trained by experienced operators, with a minimum of 50 to 100 carotid and cerebral angiographies and a minimum of 25 proctored carotid stenting procedures completed before performing CAS independently. In addition, the operator's institution must have a support network including trained endovascular staff, sophisticated equipment including digital subtraction, road mapping, etc., and readily available independent neurologic assessment. A collaborative working relationship amongst the surgical, medical, and neurologic communities is imperative.

CREST and other data also suggest the need for meticulous CAS technique. This includes a mandated use of embolic protection devices in combination with a single approved carotid stent strategy. Further techniques such as minimal manipulation in the aortic arch, minimal contrast utilization, predilatation performed in a majority of patients, and careful pre- and postcerebral angiography are important for low-event carotid stenting. The poor results seen for CAS in the EVA-3S trial are testimony that experience in other disciplines does not necessarily translate directly into CAS in the initial portion of an operator's learning curve.

CREST also would suggest that younger age may offer a slight advantage of CAS over CEA; this was also seen in the SPACE trial,[9] where carotid stenting had a very low event rate for patients aged < 68 years. This is further corroborated by the excellent early results of the ACT 1 lead-in data, performed in patients aged < 80 years by experienced operators.

In elderly patients, a very careful risk/benefit assessment is indicated. CREST would suggest a potential benefit of CEA over CAS in these patients. However, there are contemporary data to suggest that CAS can be performed safely in octogenarians. This selection must be individualized and is best performed by experienced operators carefully selecting appropriate patients, with consideration for the use of proximal embolic protection if feasible.[20,27,28]

Based on CREST and contemporary data, it is very possible that a new paradigm should exist whereby we first ask what a patient's "carotid artery stent risk" is rather than his CEA risk. If the patient is acceptably low risk for CAS, is carefully selected, and the procedure is performed by an experienced operator with close follow-up, carotid stenting may be considered a potential viable front line revascularization for this patient. Operator experience, careful technique, and case selection cannot be overemphasized. At no point should we take a patient who is at high risk for carotid stenting but low risk for endarterectomy and perform stenting. One must always consider the relatively benign course of asymptomatic carotid disease and weigh the risks and benefits of CAS and consider the excellent alternatives of CEA and/or medical therapy in these patients.

CONCLUSION

The CREST trial provides important information regarding CAS and CEA in standard-risk patients. These data, in combination with the previous SAPPHIRE randomized trial, ongoing real world carotid stent registry trials and contemporary on-label trials together suggest that CAS in selective patients by experienced operators is not only a good alternative for patients at high risk for CEA but potentially an equally efficacious therapy for patients at standard risk for CEA. The ACT 1 trial will provide additional important information for this patient group in another well-performed randomized trial. Hopefully, this information will lead to a more collaborative, collegial effort amongst the specialties involved in treating patients with carotid artery disease, industry, and

insurers such that we can provide maximal benefit to our patients with carotid artery disease. ■

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