Impact of the CREST Trial

A historical perspective of this trial and a look at some of the tough questions that still remain.

BY GARY S. ROUBIN, MD, PHD

When is the right time to subject a new interventional technique to a rigorous, prospective, randomized comparison to an accepted therapy? There is no easy answer to this. Was carotid stenting (indications and technique) too much of a rapidly moving target from 1999 to 2009 to allow a fair comparison to surgery? The upcoming CREST trial results may provide the answer. As of this time, I have no knowledge of the outcomes in this trial, which is the largest of all prospective randomized trials studying carotid revascularization. It has been more than 10 years since our small group began this saga, and it speaks to the rigor and integrity of CREST that the principal investigators remain blinded to the outcome. In the coming months, the CREST Executive Committee will meet to take a first look at this very large data set, and a manuscript that will provide outcome results to the medical community will be available in February 2010.

It has been a long and difficult road, and I must pay special tribute to the late Robert Hobson, MD, who led the CREST trial for many years. Among the many contributions during his career, Bob is notable for his assertion that "even large multicenter case series (registries) represent a large collection of anecdotes." Tribute must also be paid to Tom Brott, MD, the principal investigator for Neurology, who was also present from the outset and has more than adequately led CREST since Bob's passing. Again, to quote from another CREST stalwart, George Howard, PhD, principal investigator for Data Management and Statistics at the University of Alabama at Birmingham: "Tom has no dog in the hunt."

All of us have devoted thousands of hours to the trial, beginning with meetings with the National Institute of Neurological Disorders and Stroke division of the National Institutes of Health (NIH) and the US Food and Drug Administration (FDA), as well as industry and investigator meetings. The protocol was formulated based on our experience during the 1990s, when the prevailing thought was that the issue was an "either/or" question concerning carotid endarterectomy (CEA) versus stenting. In 2009, we all acknowledge that patient selection for either of these revascularization methods is critical to safety and efficacy. In 2000, we had access to a single first-generation stent and an embolic protection device, and we opted to go with the tools available at the time. On many occasions, we discussed expanding our toolbox, but the myriad of FDA and industry administrative issues seemed daunting.

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The fact that the CREST recruitment timeline encompassed an 8-year period during which there was a steep collective learning curve, with respect to indications for stenting, cannot be overemphasized. Early on, within the interventional community, surgical rejection or perceived high CEA risk was an a priori indication for stenting, with poor or no appreciation for anatomical or clinical features that denoted high stent risk. During the course of the CREST trial, the complication rates in the FDA/industry, high-CEA-risk registry studies have progressively fallen from 5%–10% to 2%–5%. This is precisely because operators became smarter about whom to stent and whom not to stent and how to do it better.

CREST, by protocol, did not include high-CEA-risk patients, and although a diligent and detailed attempt was made to define the carotid stent cohort, the criteria that would allow us to also exclude high stent risk in 1999 were not nearly as refined as they are today (Table 1).

OPERATOR CREDENTIALING

From the outset, CREST focused on operator credentialing and training for stent operators. I have no doubt that the credentialing of CREST operators was more rigorous than any similar stent trial to date. However, there was a great deal of pressure to boost recruitment by increasing the number of sites, and this in turn put pressure on the Interventional Management Committee to credential operators at sites that were perceived to be potentially good recruitment sites. The details of this arduous exercise that involved 137 conference calls and evaluating 427 applicants from over 100 sites will be presented in publication form (presently under review). Finally, 224 operators at 122 sites were credentialed for participation in the randomized study. Seventy-seven of these operators did not have their work reviewed directly but were "grandfathered" into the trial on the recommendation of the industry sponsor and their performance in ongoing FDA industry registry studies.

So what can be concluded about the quality of CREST stent operators? In my estimation, they represent a broad spectrum (some low, but mostly mid to high level) of operators from a large number of medical centers with a mixed experience with carotid stenting. Unlike the ACAS trial, these operators were not handpicked to ensure the best outcome possible.

From the perspective of an operator who has performed thousands of cases, most of the CREST operators were on the upslope of the learning curve during the course of the study. The positive aspect of this is that CREST outcomes will be representative of the community during the time course of the study (from 2000–2008).

UNDERSTANDING CREST OUTCOMES

CREST outcome data will differ from what has been seen in previous randomized studies comparing endarterectomy and medical therapy. First, both CEA and stenting cohorts were subjected to the best contemporary medical management. For the first time, the primary endpoint, in addition to 30-day stroke/death and ipsilateral stroke over follow-up, will include perioperative myocardial infarction. In addition, CEA will be subjected to critical neurological monitoring at 24 hours after the procedure, including completion of the NIH Stroke Scale by an independent neurologist. These two factors will allow CREST to judge stenting and CEA using identical comparators and will be a major contribution of the trial. In contrast to prior CEA trials, there was no upper age limit in CREST. The combined primary endpoint will include amaurosis fugax as a comparable stroke event. Alternatively, serious cranial injuries (even those with permanent consequences) will not be considered in the primary analysis. Hopefully, these events have been captured by the Clinical Events Committee and should be examined in a secondary analysis.

The primary endpoint analysis in CREST will be based on intention to treat. Sound scientific methodology underpins this approach. However, there is merit in understanding precisely what the complication rates were for the interventions that were actually performed. This aspect of the trial is important to understand. When the CREST protocol was written, the standard practice was referral to surgery based on carotid duplex analysis.

TABLE 1. THE STRENGTHS AND LIMITATIONS OF THE CREST TRIAL

STRENGTHS

- Largest prospective, randomized carotid revascularization trial ever conducted
- Most rigorous prospective data on neurological and cardiovascular complications from CEA and stenting ever collected
- Most rigorous operator training and credentialing ever undertaken in such a trial
- Large number of operators and study sites will make results applicable to the community
- Quality-of-life and cost data will facilitate state-of-the-art cost-efficiency analysis
- All patients were subjected to a protocol-driven best medical therapy regimen

LIMITATIONS

- Indications and exclusions for stenting were based on early experience (1994–1999)
- Utilized a single, first-generation stent and embolic protection device
- Most operators proceeded stenting patients during variable points on their learning curve of experience
- Stenting results may better represent 2000 to 2008 outcomes than 2010 to 2018 outcomes

Because precise anatomical assessment is not as important for CEA, other imaging studies were not required for patients in whom duplex criteria suggested severe stenosis. Less-severe lesions required angiography before entry into the trial. Toward the end of the trial, as magnetic resonance angiography and computed tomographic angiography technology developed, these imaging modalities were permitted to assess lesion severity in addition to duplex measurements.

Today, we understand the critical importance of suitable anatomy before proceeding with carotid stenting. However, there are unfortunate, unintended consequences for the CREST protocol. Patients randomized to stenting on the basis of duplex should have been crossed over to CEA if angiographic anatomy was unsuitable. Crossovers are a problem for statisticians and were discouraged in CREST. A patient of mine in CREST who was randomized to stenting was shown on subsequent angiography to have unsuitable anatomy for stenting and was crossed over to elective CEA the next day. The patient died postoperatively and will be analyzed as a stent death.

A large concern is that we have no way of knowing how many patients were not considered stent candidates but underwent stenting per protocol assignment and had a complication. The potential problem is compounded by the learning curve issues evident for stent operators during the study. It would be helpful to look at complication rates in the stenting cohort over time, but unfortunately, such analysis will be confounded by new waves of potentially "green" or inexperienced operators being constantly injected into the study during its course.

Late restenosis data will be based on duplex velocity analysis. There was no protocol-driven angiographic follow-up for either stent or CEA patients in CREST. Because the relationship between duplex velocities and angiographic outcomes in stent patients requires much further study, comparisons based on duplex velocities should be made with caution. Preliminary data from other studies suggest velocity measurements after stenting need to be recalibrated to reflect angiographic findings.

APPLICATION TO CLINICAL PRACTICE

How should the results of CREST be applied to clinical practice? It should be emphasized that the rigor of CREST data management and the broad spectrum of both CEA and stent operators are representative of the medical community and should allow us to apply the results to the entire community. CEA results should be representative of a stable, established surgical procedure that has changed very little during the last decade. The same cannot be said for carotid stenting, but it will provide an important set of baseline outcome data against which future studies can be judged.

Further, carotid stenting should not be practiced in the future the way it was practiced during the time course of CREST or as dictated by the CREST protocol. We now have imaging modalities, noninvasive and invasive, that allow us to select appropriate candidates for stenting. All other patients should be treated with CEA or medical therapy. Devices and techniques have evolved markedly, and we appreciate that one device is not suitable for all situations. There has been a fundamental improvement in embolic filter device profile, trackability, efficacy, and safety since the CREST instigation. In addition, the way we perform the procedure has fundamentally changed to minimize lesion dilatation (angioplasty) and manipulation. Most thoughtful observers would agree that stenting outcomes should only improve, and there is evidence from registry studies that prove that this is the case.

Ultimately, both CEA and stenting are only as safe and effective as the operators who perform the procedures. The CREST results should be used to underpin rigorous objective performance and outcome criteria that should be applied to all operators and medical centers.

ULTIMATE CONTRIBUTION OF CREST

As a busy, practicing cardiologist and clinical investigator who spent many years randomizing patients in the early NIH percutaneous transluminal coronary angioplasty versus surgery trials (EAST and BARI), I have a unique perspective on the manner in which rigorous, prospective, randomized trials can benefit and guide a new interventional technique. EAST and BARI were trials that were done when the "intervention" in "percutaneous coronary intervention" was only a primitive balloon. There were no coronary stents available at the time these trials were undertaken. Yet the outcomes from these trials underpinned the subsequent development of a major medical intervention. I predict the same will be true for the CREST trial and carotid stenting.

In addition to the intention-to-treat and primary endpoint analysis, secondary analyses will provide a wealth of information about carotid revascularization. We will be able to investigate the outcomes in the actual-treatment-received groups, the rate of crossover from one therapy to another, the influence of this on outcomes, the influence of myocardial infarction on periprocedural survival after carotid revascularization, the incidence of cranial nerve injuries, influence on length of stay and quality of life, the anatomic predictors of stroke and death in patients undergoing stenting, and the relationship of credentialing methodology and lead-in results to operator and site out-

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comes in the randomized study and a comprehensive quality-of-life and cost/benefit analysis.

The ultimate contribution of CREST may well amount to the organized manner in which carotid stenting was launched in more than 120 medical centers in North America. CREST legitimized a revascularization method that, at the time of the CREST launch, was still received by many detractors as an "untested and potentially dangerous procedure with scant data on long-term outcomes and efficacy." For an endovascular procedure with a steep learning curve, operators needed to have access to patients and actually perform the procedure to develop the skill set to make stenting an effective option. CREST created an environment in which this could occur with operator training and outcome assessment, and it accordingly achieved this objective.

So after tens of thousands of hours of investigator time and tens of millions of taxpayer dollars, did we start CREST 5 or 10 years too early? The Data Safety and Monitoring Committee of the National Institute of Neurological Disorders and Stroke has closely reviewed all outcomes from the outset and has not expressed safety concerns during the randomized trial, and we will have the answer to this question in the coming months. ■

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