# CREST: Addressing Frequently Asked Questions

CREST Principal Investigator Thomas G. Brott, MD, and Project Director Alice Sheffet, PhD, address a few of the common questions regarding the landmark carotid revascularization trial.

**Can you briefly explain the original rationale for including myocardial infarction (MI) as a component of the primary endpoint of CREST?**

Previous randomized clinical trials (RCT) of carotid endarterectomy (CEA) suggested that MI is not rare during the periprocedural period. In NASCET, the rate was 0.8% (symptomatic patients), and in ACAS, the rate was 0.5% (asymptomatic patients). In addition, during the planning of CREST in the late 1990s, we were aware of the emerging literature indicating the association of perioperative MI with subsequent cardiac events and mortality. Accordingly, because there was reason to believe that carotid artery stenting (CAS) and CEA might differ with regard to MI, we agreed that it needed to be ascertained as an endpoint.

Why was it part of the primary endpoint? At that time, there were no data available on the long-term cardiovascular (or neurological) consequences of periprocedural stroke. Thus, we did not have evidence then to establish which event was more important to the patient, MI or stroke.

**Was this decision ultimately validated by the results of CREST?**

Yes. First, occurrence of MI during the periprocedural period did differ, with about twice as many MIs occurring among the CEA patients. Second, MI was important because any MI was associated with an increase in mortality during follow-up, consistent with previous studies. That finding is complicated, however, because any periprocedural stroke was also associated with an increase in mortality during follow-up, and we were not able to establish cause and effect for either MI or stroke. Third, we learned more about the consequences of MI and stroke for the surviving patient. Periprocedural stroke had a significant impact on quality of life at 1 year, but MI did not.

The bottom line is that both MI and stroke are important complications of CAS and CEA. Both need to be minimized.

**Did the addition of asymptomatic patients halfway through CREST affect the strength of the conclusions from CREST?**

The potential lower power associated with anticipated lower event rates in the asymptomatic patients was of concern to the study investigators, to the Data Safety and Monitoring Board, and to the US Food and Drug Administration (FDA). However, the anticipated lower event rate was offset by the higher number of events associated with extended, longer than originally anticipated, follow-up (of up to 4 years; mean, 2.5 years). Accordingly, the absence of an interaction with symptomatic status and the primary endpoint meant that the primary CREST results held for both symptomatic and asymptomatic patients.

Importantly, we believe the inclusion of asymptomatic patients actually increased the impact of the CREST results. In 2005, at the time we made the change, use of CAS in asymptomatic patients had been limited primarily to patients considered high risk for CEA. CREST offered the opportunity to obtain rigorous RCT data on conventional-risk patients. Then and now, 75% or more patients undergoing CAS or CEA in the United States are asymptomatic. Inclusion of asymptomatic patients thus provided greater generalizability for the CREST results.

**Briefly explain the rationale for the CREST dataset being subjected to two separate analyses—National Institutes of Health (NIH) and PMA—if they were prespecified and whether the results were consistent or discordant.**

CREST is an atypical NIH-funded RCT in that it had two sets of planned analyses that were prespecified in the original protocol. The primary analysis, from the perspective of the investigators and NIH, was a superiority analysis in the intent-to-treat cohort comparing the safety and efficacy of CAS to CEA over 4 years of patient follow-up. Because this comparison required the use of a carotid stent system that did not have device approval by the FDA, a regulatory component of the protocol was necessary. The regulatory analysis was an equivalency analysis to assess if CAS was "as good or better" than the standard treatment of CEA at 1 year of follow-up for each patient. The shorter time horizon of the FDA analysis may have related to the statutory requirement that the FDA process not be unnecessarily burdensome, although this was not explicitly stated. While the equivalency approach was prespecified, the per-protocol cohort was not, being defined by the FDA after completion of enrollment and follow-up, although before unblinding of the investigators and Abbott Vascular (Santa Clara, CA).

The results of the NIH and FDA analyses were concordant. Discordancy was possible, but the CREST biostatistical team led by George Howard, DrPH, used a simulation approach to determine the risk. The odds for discordant results in the primary endpoint were less than one chance in a thousand.

**What are your thoughts as to why the CREST results and conclusions seem to be at odds with the major European trials in CAS (EVA-3S, SPACE, ICSS)?**

These comparisons are not easy. Many of your readers may not appreciate the following: SPACE did not establish a difference between CAS and CEA. EVA-3S did show a significant advantage for CEA in the short term but did not show a significant advantage for CEA in the longer term, the time frame of CREST. ICSS did show a significant short-term advantage for CEA at 120 days but has not yet reported results in the time frame of CREST.

Nonetheless, stroke occurred in excess during the periprocedural period in these trials, as most recently reported in the investigators' meta-analysis. Why? First, the level of training required for the interventionists in CREST was exceptional. To be considered for credentialing, each interventionist had to submit up to 20 cases or more to the CREST Interventional Committee for analysis. Completion of a CREST training program followed. Before randomization, each interventionist had to perform CAS with the Acculink and Accunet carotid stent system (Abbott Vascular) in up to 20 patients, and have excellent results. This CREST lead-in phase enrolled 1,565 patients, almost three times as many patients than enrolled in EVA-3S, approximately 25% more patients than enrolled in SPACE, and < 10% fewer patients than enrolled in ICSS. None of those trials included a credentialing phase, and the requirements for interventionists were modest.

Second, as alluded to previously, the primary endpoints were different. Only CREST went out to 4 years of follow-up. The CREST investigators agreed that differences between CAS and CEA beyond the first 30 days could be important, reflecting potential differences in clinical and anatomic durability. Also, MI was a component of the primary endpoint in CREST alone, for the reasons stated. If MI had not been included, the periprocedural differences between CAS and CEA in CREST would have been concordant with the short-term results of the European trials. However, the rates for periprocedural stroke and death for CAS were lower in CREST than in any of the European trials. These rates are within the requirements of current guideline statements, for both symptomatic and asymptomatic patients.

Third, in CREST, CAS was performed with embolic protection in 96.1% of patients. The CREST investigators are aware of the lack of RCT evidence showing the benefit of embolic protection. We are also aware of a magnetic resonance imaging substudy from ICSS showing a higher rate of diffusion-weighted imaging lesions in patients undergoing CAS with embolic protection. However, the CREST senior interventionists point to the low rates of periprocedural stroke in CREST as the best evidence, the lowest rates yet reported in a large RCT. That is, when provided in the setting of careful training and credentialing, embolic protection adds benefit to CAS. We agree.

**Why were differences in outcomes per specialty found in the lead-in phase, but not in the randomized phase?**

As stated previously, the CREST lead-in phase was a rigorous credentialing, training program for CAS. Because it preceded entry into the randomized phase, we anticipated learning and improvement on the part of the individual interventionist—in general and in use of the CREST devices. Accordingly, one may have predicted that learning and improvement might be greater for stenters with less experience with endovascular techniques and CAS. That learning and improvement—catch-up if you will—may have occurred. Endovascular techniques have long been part of the skill set for interventional cardiologists. Not so for vascular surgeons. As mentioned, the lead-in phase was substantial, with 1,565 patients undergoing CAS. The results showed that vascular surgeon stenters had a complication rate that was significantly higher than the comparator, cardiologist stenters. In the randomized phase, 2,502 cases later, that difference was no longer present (nor were the results for any specialty group outliers compared to cardiology). We suggest that this

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change to relative equivalence of CAS results by specialty was due in part to CREST training and credentialing. A more important explanation may be the evolution of endovascular techniques within the medical specialties. During the last decade, vascular surgeons and the other specialists represented in CREST have gained greater opportunities for endovascular training (from residency through fellowship) and have gained opportunities for endovascular practice throughout the United States.

**What role did industry play in the sponsorship and guidance of CREST?**

CREST was funded by NIH/NINDS in 1999. The award did not include funding for CAS devices. In 2000, Guidant Corporation (acquired by Abbott Vascular in May 2006) agreed to partner with CREST and provide devices for the CREST lead-in and the CREST randomized phase. Guidant submitted an application for an investigational device exemption (IDE) to the FDA and received approval in June 2000. Until 2003, Guidant was the IDE sponsor, maintaining regulatory and reporting responsibility to the FDA. They provided device training and enabled interventionists to perform CAS procedures with the Acculink and Accunet carotid stent system. Guidant provided the devices at premarket value/price to the US sites and at no cost to the VA sites and Canadian centers.

CREST leadership directed trial activities while Guidant maintained FDA regulatory responsibility. In 2003, the IDE was transferred to CREST, centralizing site management. To support the IDE, Guidant/Abbott Vascular provided financial support to CREST, and continues to do so. From 2000 through 2010, they financed CREST's entire site-monitoring program. In addition, Abbott Vascular provided staff for on-site monitoring from 2010 to 2011 at 32 CREST domestic and Canadian clinical sites before the FDA audits. Abbott Vascular submitted the PMA for the RX Acculink and the RX Accunet devices using CREST data and received marketing approval for an expanded label in May 2011. Overall, Guidant/Abbott has financed approximately 15% of the total cost of CREST. ■

*Alice Sheffet, PhD, is CREST Project Director and Assistant Professor, Department of Surgery at UMDNJ-New Jersey Medical School in Newark, New Jersey. She has disclosed that she has no financial interests related to this article. Dr. Sheffet may be reached at (973) 972-7718; sheffeaj@umdnj.edu.*

*Thomas G. Brott, MD, is Principal Investigator of the CREST trial and Eugene and Marcia Applebaum Professor of the Neurosciences and Dean for Research at the Mayo Clinic in Jacksonville, Florida. He has disclosed that he has no financial interests related to this article.*