CREST-2

Guiding Treatments for Asymptomatic Carotid Disease

Examining stenting and endarterectomy in the context of intensive medical management.

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In 2010, a grant proposal to evaluate the best approach for managing patients with high-grade primary carotid atherosclerotic stenosis was first submitted for funding to the National Institute of Neurological Disorders and Stroke (NINDS) of the National Institutes of Health (NIH). In this conception, CREST-2 was to be a single randomized trial with two treatment arms: best revascularization (either carotid endarterectomy [CEA] or carotid artery stenting [CAS]) and intensive medical management versus intensive medical management alone.

Based on feedback obtained during the review process, a revised proposal was submitted in early November 2011. In this revised approach, CREST-2 was fundamentally redesigned to be two parallel, randomized trials. One trial would randomize patients with at least 70% stenosis of the cervical internal carotid artery to either the combination of CEA and intensive medical management or intensive medical management alone. Another trial would randomize patients with at least 70% stenosis of the cervical internal carotid artery to either the combination of CAS and intensive medical management or intensive medical management alone. A single, three-arm trial of CEA, CAS, and medical management was not seen as appropriate because some patients are more suited for CEA, and others are more suited for CAS. Thus, a single, three-arm trial could be subject to bias toward one revascularization procedure or another, depending on patient selection.

The coprincipal investigators of CREST-2 consider it vital that the study has a rapid initiation phase and that the recruitment phase not be protracted. The intent is to minimize protocol amendments and case report form modifications and to use all other standard means of maximizing administrative efficiency and recruitment efforts.

The key asset for CREST-2 is the infrastructure, network, expertise, and goodwill built over the past decade through the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) team. When CREST was operating at peak efficiency, the trial was accruing nearly one patient per day. However, this rate was achieved only after overcoming numerous challenges.[1] The institutional experience with centers in CREST will serve as an important advantage in CREST-2 in terms of rapid initiation. In fact, the network of CREST centers was seen as such a crucial element to the success of CREST-2 that it influenced the name of the trial. CREST-2 is not a trial of CEA versus CAS, yet the "CREST" acronym remains in recognition that CREST-2 is the second trial to be conducted by the CREST team.

We recognize that some centers with a large referral base for patients with symptomatic carotid stenosis may have a relatively less robust referral base for patients with asymptomatic stenosis. Further, several new centers have emerged over the years with a major focus on the treatment of carotid disease that did not get an opportunity to participate in CREST. So, while many CREST centers will form the core of CREST-2, several additional centers will be able to join the trial.

WHY CREST-2 NOW?

The results of CREST were published in 2010 and provide the foundation for CREST-2.[2] CREST is a randomized trial comparing CEA to CAS in patients with symptomatic (n = 1,321) and asymptomatic (n = 1,181) carotid artery stenosis. While results based on a mean follow-up of 4 years have been reported, follow-up out to 10 years continues.[2,3] At 4 years, no significant difference was found for symptomatic and asymptomatic patients in the estimated rates of the primary endpoint (the composite of periprocedural stroke, myocardial infarction [MI], or death and ipsilateral stroke, thereafter). For asymptomatic patients, the CREST results provided the following positive information.

CEA and CAS Continue to Improve

In CREST, rates for the primary composite periprocedural endpoint of any stroke, MI, or death were very low for both groups. The rate was 4.5% for CEA and 5.2% for CAS. For the more limited composite endpoint of any stroke or death in the first 30 days, rates were even lower; in fact, these rates were the lowest yet achieved in any large, randomized trial of treatment for carotid artery disease. For CEA, the rate was 2.3%, and for CAS, the rate was 4.4%. Importantly, these low rates were accomplished across a broad spectrum of academic and community clinical centers (n = 117) located in the United States and Canada.

A relatively recently introduced therapy such as CAS can be anticipated to demonstrate a noticeable improvement in the outcomes and complication profile. Favorable secular trends in the safety of CAS have been seen in the Nationwide Inpatient Sample.[4] This may explain the low risk of CAS documented in CREST. The simultaneous improvement in outcomes after CEA, when compared to previous randomized trials of the procedure, was a bit less anticipated, because of a history with CEA training and technique that now extends over more than 50 years.[5,6] This is strong evidence that safety for both revascularization procedures continues to improve and has not yet plateaued.

Medical Treatments Are Also Improving

Several physicians have recently argued that asymptomatic carotid stenosis is a benign disease—if treated medically with contemporary pharmacologic treatments (ie, 21st-century guideline-driven, intensively monitored treatments for hypertension, hyperlipidemia, diabetes, smoking cessation, etc.). Perhaps the most pertinent evidence for an improvement in medical therapy comes from two randomized trials comparing treatments for intracranial arterial stenosis. Between

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1999 and 2003, the Warfarin Aspirin Symptomatic Intracranial Disease (WASID) trial randomized 567 patients with symptomatic high-grade intracranial atherosclerotic stenosis to aspirin or warfarin and managed risk factors using standard approaches prevalent during that time period.[7] This study reported a 30-day rate of stroke or death of 10.7% and a 1-year rate of the primary endpoint (ischemic stroke, brain hemorrhage, or death from vascular causes other than stroke) of 25.7%. Only a decade later (between 2008 and 2011), the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) study randomized 451 similar patients to intracranial stenting or medical therapy.[8] Unlike WASID, medical therapy implemented in this trial was much more aggressive, guideline-driven, and intensely monitored. For the medical patients in SAMMPRIS, the stroke and death outcome (5.8%) and the stroke, MI, and death composite primary outcome (12.2%) were both low, about half of what had been achieved in WASID.

Which Treatment Is Best for Asymptomatic Patients: Medical Management or Revascularization?

The Centers for Medicare & Medicaid Services (CMS) asked this question in January 2012 as part of a Medical Evidence Development and Coverage Advisory Committee (MEDCAC) public hearing.[9] A multidisciplinary panel heard presentations from physician-leaders with expertise in CEA, CAS, and medical stroke prevention, as well as leaders from a wide array of medical specialty societies. The speakers provided a detailed summary of the evidence supporting available treatments and their own perspective on patient needs. The panel then questioned the designated speakers. Finally, panel members voted individually on a series of questions relevant to managing patients with asymptomatic carotid stenosis that were posed by CMS. Members scored responses on a scale of 1 (low confidence) to 5 (high confidence). To the question "How confident are you that there is adequate evidence to determine if persons in the Medicare population who are asymptomatic for carotid atherosclerosis can be identified

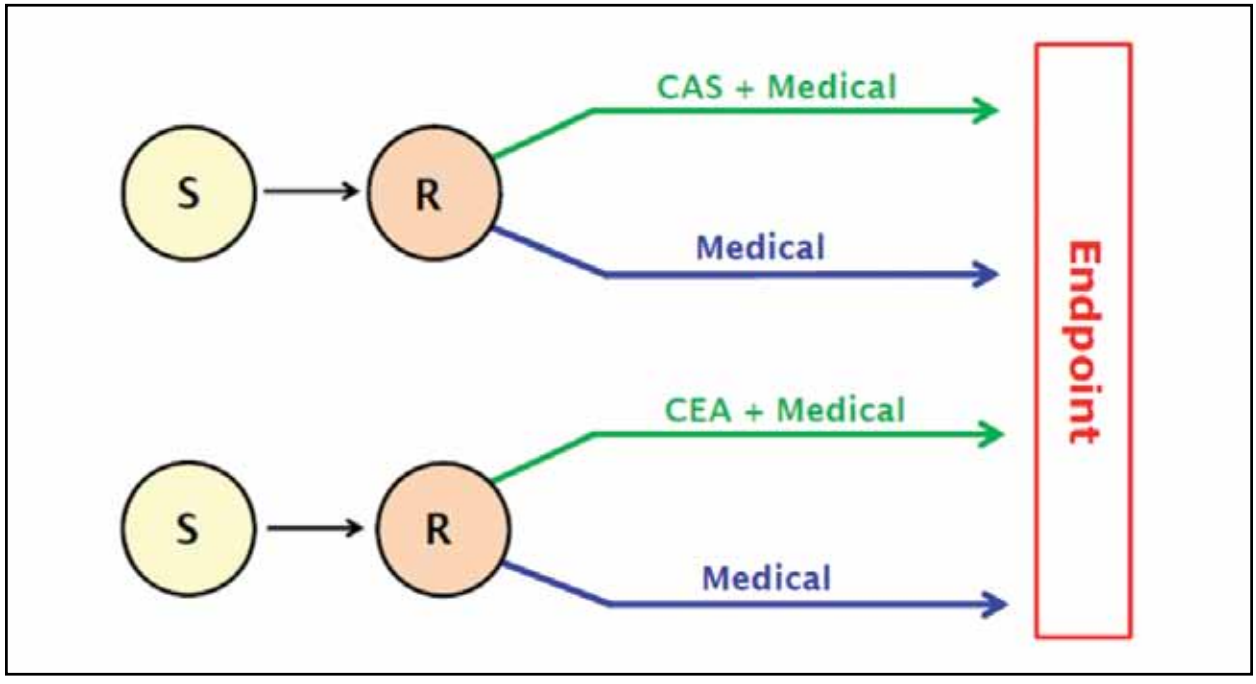

Figure 1. CREST-2 parallel study design. Endpoint = stroke and death in first 30 days and ipsilateral stroke thereafter up to 4 years. S, screening; R, randomization.

as being at high risk for stroke in either cerebral hemisphere?" the mean score was 3 (range, 1 to 4). To the question, "For persons with asymptomatic carotid atherosclerosis and carotid narrowing (≥ 60% by angiography or ≥ 70% by ultrasound) who are not generally considered at high risk for adverse events from CEA, how confident are you that there is adequate evidence to determine whether or not either CAS or CEA is the favored treatment strategy, as compared to best medical therapy alone, to decrease stroke or death in the Medicare population?" the mean score was 2 (range, 1 to 5). To the question, "For persons with asymptomatic carotid atherosclerosis who are not generally considered at high risk for stroke in either cerebral hemisphere, how confident are you that there is adequate evidence to determine whether or not CAS or CEA or best medical therapy alone is the favored treatment strategy to decrease stroke or death in the Medicare population?" the mean score was 2.89 (range, 1 to 5). Thus, the panel showed its ambivalence toward CAS, and revascularization in general, as compared to best medical therapy in older adults.

The Best Rationale for CREST-2

Are both CEA and CAS procedures effective, or is neither necessary? Because CREST did not include a medical arm, and medical therapy was last tested in this patient population 2 decades ago, the question cannot be answered based on reliable level 1 data. The answers mentioned previously provide the rationale for CREST-2. The CREST-2 trial is timely. The multispecialty CREST clinical trial network provides a unique opportunity to perform this trial. CREST successfully randomized 2,502 patients to compare CEA to CAS.[10] It successfully credentialed and trained operators so that these procedures were delivered with unprecedented safety and clinical durability.[11] The 1,181 asymptomatic patients in this trial were enrolled expeditiously over a short period of 3 years. Thus, CREST-2 is uniquely positioned to test the merits of revascularization in the context of intensive medical management.

THE DESIGN OF CREST-2

It is important to note that some aspects of the CREST-2 protocol will continue to evolve over the upcoming months before enrollment commences. Before CREST began and during the course of the trial, the CREST team received invaluable guidance from staff at the NINDS, CMS, and the Food and Drug Administration. Similarly, for the CREST-2 protocol, input from those agencies is ongoing. In addition, CREST was funded under an R01 investigator-initiated grant mechanism that provided primary design responsibility to the principal investigator and the CREST investiga-

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tor leadership. Under the U01 funding mechanism, new for large clinical trials at NINDS, the director and staff at NINDS will have a greater role in the design and execution of CREST-2. Finally, the CREST-2 investigators have had ongoing discussions with investigators of the second European Carotid Surgery Trial (ECST-2). Both groups see major benefit in cooperation, and so harmonization of these two protocols would be ideal, if feasible.

MAJOR FEATURES OF CREST-2

The primary objectives of the trial are (1) to determine if intensive medical therapy alone is different from CAS plus intensive medical therapy and (2) to determine if intensive medical therapy is different from CEA plus intensive medical therapy. The primary endpoint will be any stroke or death during the periprocedural period and ipsilateral stroke thereafter, out to 4 years of follow-up. Eligibility criteria include asymptomatic status for 180 days from the time of the baseline assessment, carotid stenosis ≥ 70% as determined by duplex ultrasound, and one confirmatory study (magnetic resonance or CT angiography).

Patients will be randomized to only one of two trials within CREST-2, either CAS plus medical management compared to medical management alone or CEA plus medical management compared to medical management alone (Figure 1). Medical therapy in this trial will be modeled after the intensive medical therapy regimen successfully employed in SAMMPRIS. The sample size will be such as to provide approximately 85% power to test the primary objective.

CONCLUSION

In summary, the evidence base for treatment of patients with asymptomatic carotid stenosis may no longer apply for decision making today. The results of the Asymptomatic Carotid Atherosclerosis Study (ACAS) were published in 1995.[4] Most of the patients enrolled in the Asymptomatic Carotid Surgery Trial (ACST) were randomized in the 1990s.[12] Outcomes following CEA, CAS, and medical treatment for these patients have all improved in the past 2 decades. Therefore, the time has come to test whether contemporary intensive medical therapy is an acceptable alternative to contemporary CEA or CAS. CREST-2 has the investigators, study teams, asymptomatic patients, and robust study design that will be needed to provide these answers. ■

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