A Summary of the CREST Trial

This trial was designed to meet the need for a sufficient comparison of CAS and CEA for patients with carotid atherosclerosis.

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The Carotid Revascularization Endarterectomy Versus Stent Trial (CREST) was designed in the late 1990s and was started in 2000.1,2 At the time, there had been no adequate, randomized comparisons of carotid endarterectomy (CEA) and protected carotid artery stenting (CAS). Endarterectomy had been well established to be superior to medical therapy in stroke prevention in the symptomatic but otherwise medically well patient with a > 50% stenosis of the carotid bulb.3 Asymptomatic stenosis treatment remained controversial despite the results of the Asymptomatic Carotid Atherosclerosis Study (ACAS).4 Until then, the only large trial of carotid endovascular therapy, Carotid and Vertebral Transluminal Angioplasty Study (CAVATAS), had been completed and the results presented in abstract form in 1999.5 That study showed no statistically significant difference in stroke or death rates between balloon angioplasty without embolic protection devices and endarterectomy, even out to 8 years of follow-up; there were, however, numerically more strokes in the angioplasty arm.

Some other trials of CAS were conducted, but they were small, poorly run, or never completed.6,7 Protected stenting (ie, stenting with the use of an embolic protection device) using a dedicated, specially designed stent stent had therefore not been validated outside of registries.8-11 The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial, which was designed to compare the safety and efficacy of protected CAS versus CEA in high-surgical-risk patients, had just begun enrolling patients.12 The reason for the CREST trial was self-evident: compare protected CAS versus CEA in low-surgical-risk, symptomatic patients.

STUDY DESIGN

CREST was sponsored by both the National Institutes of Health (NIH) and Guidant (now Abbott Vascular [Santa Clara, CA]). Guidant supplied the devices for all of the United States and Canadian centers, comprising a small portion of the funding (15%) as well as support personnel until 2003.13 The NIH provided the bulk of the funding for the study, which was a prospective, randomized, parallel, two-arm, multicenter trial with blinded endpoint assessment. It was designed as a 2,500-patient trial to compare the relative efficacy of CAS versus CEA to determine superiority. There was equal randomization between CEA and protected CAS using the RX Accunet embolic protection device (Abbott Vascular) (“whenever feasible”) and the RX Acculink carotid stent system (Abbott Vascular) in standard-surgical-risk, symptomatic patients with a carotid bifurcation stenosis ≥ 50% on angiography, ≥ 70% on ultrasonography, or ≥ 70% on computed tomographic angiography or magnetic resonance angiography if the stenosis on ultrasonography was 50% to 69%.1

For a number of reasons, in 2005, the study was changed to include asymptomatic patients with a stenosis ≥ 60% by angiography, ≥ 70% on ultrasonography, or ≥ 80% on computed tomographic angiography or magnetic resonance angiography if the stenosis on ultrasonography was 50% to 69%. The study also included a vetting of interventionists with an additional lead-in/credentialing phase averaging roughly 20 patients per interventionist.13,14 In addition to the exclusion of high-surgical-risk patients, the study excluded patients who had contraindications to CAS such as severe tortuosity, extensive or diffuse atherosclerotic disease involving the aortic arch and proximal common carotid artery, an intraluminal filling defect, ipsilateral intracranial or extracranial arterial stenosis greater in severity than the lesion to be treated, and occlusion or “string sign” > 1 cm of the ipsilateral common or internal carotid artery. The use of 325-mg aspirin in the CEA arm and dual-antiplatelet therapy (325 mg of aspirin plus 75 mg of clopidogrel, or 250 mg of ticlopidine, 1–2 tablets daily) in
the CAS arm were mandated by the protocol for at least 30 days, with aspirin in all patients thereafter.

**STUDY ENDPOINTS**

The study’s primary endpoint consisted of the composite of any stroke, myocardial infarction (MI), or death during the periprocedural period (ie, within 30 days of the procedure) plus ipsilateral stroke within 4 years of randomization. Neurological evaluations were performed by neurologists, or “neuroscientists/physicians certified in the use of the” NIH Stroke Scale, at baseline preprocedure, 18 to 54 hours after the procedure, 1 month, and every 6 months thereafter. Stroke was defined as “an acute neurologic event with focal symptoms and signs, lasting for 24 hours or more, that were consistent with focal cerebral ischemia.” Stroke was further defined as “major” if the NIH Stroke Scale score was 9 or higher 90 days after the procedure. MI was defined by a creatine kinase myocardial band or troponin level that was ≥ 2 times the upper limit of normal associated with either chest pain, symptoms consistent with ischemia, or electrocardiographic evidence of ischemia (new ST depression or elevation ≥ 1 mm in two or more contiguous leads).

The study included angiographic, carotid duplex ultrasound, and electrocardiographic core laboratories, and carotid stenosis measurements used the NASCET (North American Symptomatic Carotid Endarterectomy Trial) method (a more specific but less sensitive approach than other methods). CREST had several prespecified secondary endpoints including differential efficacy of both procedures in men and women, comparison of periprocedural morbidity and mortality and > 30-day morbidity and mortality, an assessment of the morphology of the treated segment at 6 months and 1 year for the two procedures, a comparison of measures of health-related quality of life and cost effectiveness, and the identification of subgroups at differential risk for CAS and CEA. The study used an intention-to-treat analysis because there was a small amount of crossover after randomization; 5.7% randomized to CAS underwent CEA, and 1% randomized to CEA underwent CAS.

**OPERATOR SELECTION**

As previously mentioned, CREST rigorously vetted surgeons and interventionists. The vetting of the latter set a new standard; only 225 (52%) of 429 interventionists who applied to be in the trial were finally approved for randomization. Those who were refused outright had a median case experience of 12 (range, 1–56). Only 70 operators were judged to have sufficient experience with the procedure and study devices (range of device experience, 7–81) to be allowed to randomize patients without lead-in cases. Two hundred and forty two met the criteria for the lead-in phase; this group submitted a median of 29 cases (range, 3–63) to be considered. Of this group, 160 (66%) were approved for randomization after completing an average of nine (range, 1–35) lead-in cases.

**RESULTS**

Randomization was completed in July 2008 after 2,522 patients were enrolled (1,271 CAS and 1,251 CEA) with a median follow-up of 2.5 years. The study results were presented in February of 2010 at the International Stroke Conference and published online ahead of print in May 2010 and printed July 1, 2010 in the *New England Journal of Medicine*. Approximately 5.4% of the CAS patients and 8.8% of the CEA patients were lost to follow-up or withdrew consent, and the data from one center (nice CAS and 11 CEA patients) were excluded due to data fabrication. The patients were very well matched in terms of demographics other than a slightly higher preponderance of patients with dyslipidemia in the CEA group (85.8% vs 82.9%, *P* = .05) and more patients smoking in the CAS group during follow-up (21.8% vs 13.8%; *P* = .03). The median time to treatment from randomization was similar (median 6 days for CAS and 7 days for CEA). The majority of the CEA procedures were performed under general anesthesia (90%), and most had a patch (62.4%) or shunt (56.7%). The overwhelming majority of CAS procedures were performed with embolic protection (96.1%), and most had predilation before stenting (67.7%). There was a surprisingly high rate (12.1%) of patients not taking dual-antiplatelet agents at 4 weeks and a similarly high rate of no aspirin use among CEA patients (8.9%).

There was no difference in the primary study endpoint of any periprocedural stroke, MI, death, or postprocedural ipsilateral stroke within 30 days (CAS 5.2 ± 0.6 vs CEA 4.5 ± 0.6; hazard ratio [HR], 1.18 [0.82–1.68]; *P* = .38) plus ipsilateral up to 4 years, mean 2.5 years (CAS 7.2 ± 0.8 vs CEA 6.8 ± 0.8; HR, 1.11 [0.81–1.51]; *P* = .51). For the individual endpoint of periprocedural death (CAS 0.7 ± 0.2 vs CEA 0.3 ± 0.2; *P* = .18), there was no difference, but for any periprocedural stroke (CAS 4.1 ± 0.6 vs CEA 2.3 ± 0.4; HR, 1.79 [1.14–2.82]; *P* = .01) or MI (CAS 1.1 ± 0.3 vs CEA 2.3 ± 0.4; HR, 0.5 [0.26–0.94]; *P* = .03), there were significant differences. There was no statistical difference in major ipsilateral stroke incidence in the perioperative period (CAS 0.9 ± 0.3 vs CEA 0.3 ± 0.2; *P* = .09) or during the remainder of the study (CAS 1.4 ± 0.3 vs CEA 0.8 ± 0.3; *P* = .28). After the periprocedural period, the incidence of ipsilateral stroke was similar (CEA 2.4% vs CAS 2%; *P* = .85), as was the risk of fatal stroke (CAS, N = 7; CEA, N = 6).

There was no difference in the primary endpoint dur-
ing the perioperative period among symptomatic patients (CAS 6.7% vs CEA 5.4%; HR, 1.26 [0.81–1.96]) or asymptomatic patients (CAS 3.5% vs CEA 3.6%; HR, 1.02 [0.65–1.86]). There was no interaction between sex and symptomatic status and treatment effect, although there was an interaction between age and efficacy (P = .02). The crossover point for age was at approximately 70 years, with greater efficacy with CAS in younger patients and greater efficacy with CEA for older patients. The risk of cranial nerve injury was significantly higher in the CEA group (0.3% vs 4.7%). In a post hoc analysis, there was an effect of minor or major stroke on physical health as measured by the SF-36 physical component scale, but the effect of perioperative MI was “less certain.”

**DISCUSSION**

The CREST trial, the first trial to compare protected CAS versus CEA in standard-surgical-risk symptomatic and asymptomatic patients, has shown that both procedures are equivalent in major perioperative morbidity and mortality as well as long-term stroke prevention. While there was a difference in the risk of perioperative stroke with an increased risk in the endovascular group, most of these strokes were minor. Conversely, there was a higher risk of MI in the surgical group.

Beyond the perioperative period, the efficacy of the procedures in stroke prevention is equivalent, however. Importantly, the 30-day outcomes for both procedures met the accepted thresholds for clinical benefit compared to medical therapy, that is, < 6% for symptomatic (6% stroke/death with CREST CAS and 3.2% for CREST CEA) and < 3% for asymptomatic patients (in CREST, the rate of 30-day stroke/death with CAS was 2.3% for ACAS-eligible patients). These results contradict the results of the recent randomized European trials that have compared CAS and CEA, all of which showed inferiority or failed to show superiority. There are many possible reasons for these differences, but technical factors (operator experience, use of a single stent system, and the use of embolic protection devices) may be the most likely contributing factors.

Unlike the results of previous CEA trials, there was no effect of sex on procedural effectiveness, and there was not any differential benefit based on symptomatic status. There was a significant benefit to CAS in younger patients and vice versa. There are several issues that have not yet been addressed by the published results, including the comparative long-term patency or need for repeat revascularization with each procedure has yet to be determined. Moreover, newer embolic protection devices and stents have become available and could be associated with lower stroke rates, thus indicating the potential to further improve on CREST’s CAS outcomes.

**CONCLUSION**

The CREST trial has shown that protected CAS and CEA are both good options for patients and their advising physicians in the treatment of low-surgical-risk patients with bifurcation carotid atherosclerosis.

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