What Can We Learn From CREST?

Highlighting the data and take-home points of this landmark carotid revascularization trial.

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The Carotid Revascularization Endarterectomy Versus Stent Trial (CREST) was initiated under the support of the National Institutes of Health and the National Institute of Neurological Disorder and Stroke to compare the efficacy of carotid artery stenting (CAS) to carotid endarterectomy (CEA) for the revascularization of extracranial stenoses of the internal carotid artery in patients with standard surgical risk. CREST was the largest study of its kind and was adequately powered to uncover significant differences in the results of both procedures. This prospective, randomized, parallel, two-arm, multicenter trial included 2,502 patients and examined the composite primary endpoint of myocardial infarction (MI), stroke, or death during the periprocedural period plus any ipsilateral stroke within 4 years after randomization.

Both symptomatic and asymptomatic patients were enrolled. Patients with symptomatic stenoses were included if the stenosis severity was > 50% angiographically (based on NASCET [North American Symptomatic Carotid Endarterectomy Trial] criteria) or > 70% measured by ultrasound, computed tomography angiography (CTA), or magnetic resonance angiography (MRA). Patients with asymptomatic stenoses were included if the stenosis severity exceeded 60% by angiography, 70% by ultrasonography, or 80% by CTA or MRA.[1] The primary endpoint occurred in 7.2% ± 0.8% of patients treated with stenting and in 6.8% ± 0.8% who underwent surgical revascularization (P = .51). The mean follow-up period was 2.5 years.[2]

There was no significant difference in the composite secondary endpoint defined as periprocedural (30 day) death, stroke, or MI (5.2% ± 0.6% for CAS vs 4.5% ± 0.6% for CEA; P = .38). Likewise, there was no significant difference in overall mortality (0.7% vs 0.3%; P = .18). However, whereas strokes were more frequent after CAS (4.1% vs. 2.3%; P = .01), MI was more common in patients treated surgically (2.3% vs 1.1%; P = .03). There was a trend toward a higher incidence of major ipsilateral stroke at 30 days in the CAS group (CAS 0.9% ± 0.3% vs CEA 0.3% ± 0.2%; P = .09). However, there was no difference in major ipsilateral stroke at long-term follow-up (CAS 1.4% ± 0.3% vs CEA 0.8% ± 0.3%; P = .28).

Does It Matter Whether Patients Are Symptomatic or Asymptomatic?

Following international definitions, a stenosis was defined as symptomatic if it had caused any neurological symptoms within 180 days of enrollment and randomization. There was no difference between CAS and CEA in the primary endpoint for patients with symptomatic stenoses (6.7% ± 1.0% vs 5.4% ± 0.9%; P = .30).[3] The combined stroke and death rate in symptomatic patients, however, was higher in the endovascular group (6.0% ± 0.9% vs 3.2% ± 0.7%; P = .02). Importantly, there was no difference in asymptomatic subjects (2.5% ± 0.6% vs 1.4% ± 0.5%; P = .15). The rate of MI was lower after CAS compared to surgery in symptomatic patients (1.0% ± 0.4% vs 2.3 ± 0.6%; P = .08) as well as in asymptomatic patients (1.2% ± 0.3% vs 2.2% ± 0.6%; P = .20). CREST was the first trial to show stroke and death rates for both procedures within a range recommended in the current American Heart Association guidelines for the prevention of stroke (< 6% in symptomatic and < 3% in asymptomatic patients).[4]

A subgroup analysis, which excluded patients older than 80 years of age, was performed to allow better comparison of CREST to previous clinical trials that generally excluded octogenarians. The 30-day stroke and death rate for the symptomatic cohort younger than 80 years was 5.6% ± 1.0% for CAS and 2.6% ± 0.7% for CEA. The corresponding rates in patients with asymptomatic stenoses were 2.4% ± 0.7% for CAS and 1.5% ± 0.5% for CEA.[3]

Are Octogenarians at High Risk for Carotid Intervention?

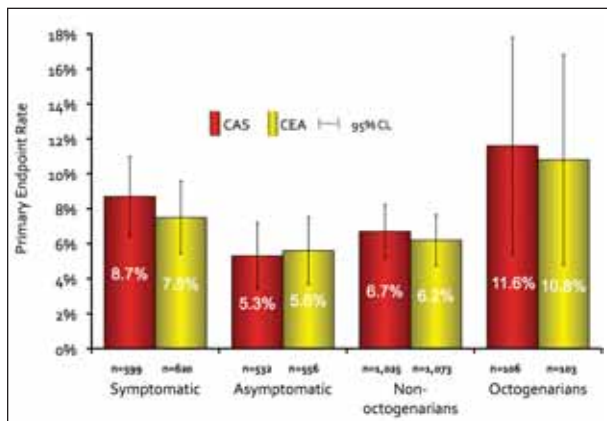In 2004, Hobson et al presented a subgroup analysis of the CREST lead-in phase analyzing the association of age

Figure 1. Primary composite endpoint of CAS and CEA by symptomatic or octogenarian status.

Figure 2. Association of minor stroke and MI with long-term mortality.

and periprocedural stroke and death.[5] In total, 749 patients randomized to CAS were divided into four groups according to age. The rate of complications was higher with increasing age. The stroke and death rate by age category was 1.7% (n = 2 of 120) in those younger than 60 years, 1.3% (n = 3 of 229) in those 60 to 69 years old, 5.3% (n = 16 of 301) in those 70 to 79 years old, and 12.1% (n = 12 of 99) in octogenarians. In octogenarians, the stenoses were more severe (73.5% vs 71.5%), with more residual stenoses after stenting (12.6% vs 11.5%).

Higher complication rates in elderly patients appear to be a consistent finding, as this has been reported in a number of previous studies. Age and comorbidities may be less important reasons than the more frequently associated unfavorable anatomy due to carotid tortuosity[5] and hostile arch related to an unfavorable takeoff of cranial vessels, as well as more pronounced atherosclerotic disease. Therefore, technical challenges could have a more pronounced impact on outcomes in elderly patients in the lead-in phase because difficult anatomy may be compounded by more limited operator experience and familiarity with the equipment used in the trial (RX Accunet for distal protection and RX Acculink stents [Abbott Vascular, Santa Clara, CA]).

Importantly, adverse events were more common in octogenarians regardless of the revascularization mode, and unlike some previous studies, there was no difference in the primary endpoint between CAS and CEA in octogenarians (Figure 1). Invariably, strokes are the result of distal embolization caused by catheter manipulation within the aortic arch, wiring of the lesion, and stenting. Our distal protection devices offer only limited protection due to larger pore sizes than a significant amount of the embolic debris and suboptimal filter-to-vessel wall apposition, particularly in tortuous vessels more frequently encountered in octogenarians. In elderly patients with tortuous carotid arteries,
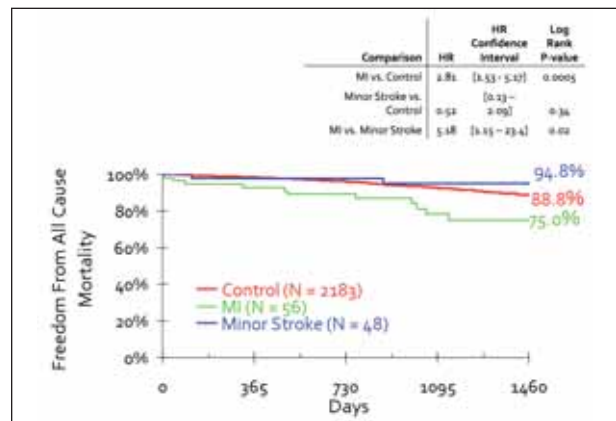
proximal protection may have advantages in periprocedural stroke prevention.

Does Sex Have an Influence on CAS and CEA Outcomes?

The influence of sex on an increased perioperative risk of stroke and death during carotid revascularization has been well described for CEA. The Asymptomatic Carotid Atherosclerosis Study (ACAS) was the first study showing a nonsignificant trend toward increased stroke and death risk in women (P = .12).[6] The European Carotid Surgery Trial (ECST) found an increased periprocedural risk for women with symptomatic stenoses (11.1% vs 6.4%; P = .002).[7] Schulz and Rothwell postulated that this effect may be caused by the female carotid anatomy.[8] Women's internal carotid arteries can be up to 40% smaller in diameter than men's, making CEA technically more challenging.

In 2009, Howard et al presented an analysis of the lead-in phase of CREST comparing the results of 1,564 patients undergoing CAS by sex (26.5% of all stenoses were symptomatic).[9] There was no significant difference in the periprocedural stroke and death rate for women (4.5%; n = 26 of 579) compared to men (4.2%; n = 41 of 985). Taking symptomatic status into account, the difference between symptomatic and asymptomatic women (5.6% vs 4.1%) was smaller than it was for men (5.9% vs. 3.5%). After adjustment for demographic factors (age or race), vessel characteristics (reference diameter, lesion length, percent stenosis, or symptomatic status), or cardiovascular risk factors (hypertension, hyperlipidemia, diabetes, or smoking), the differences driven by gender were not significant.

In 2011, Howard et al presented the results of CREST comparing CAS and CEA according to gender. The composite primary endpoint of MI, stroke, or death during the periprocedural period or ipsilateral stroke within 4 years did
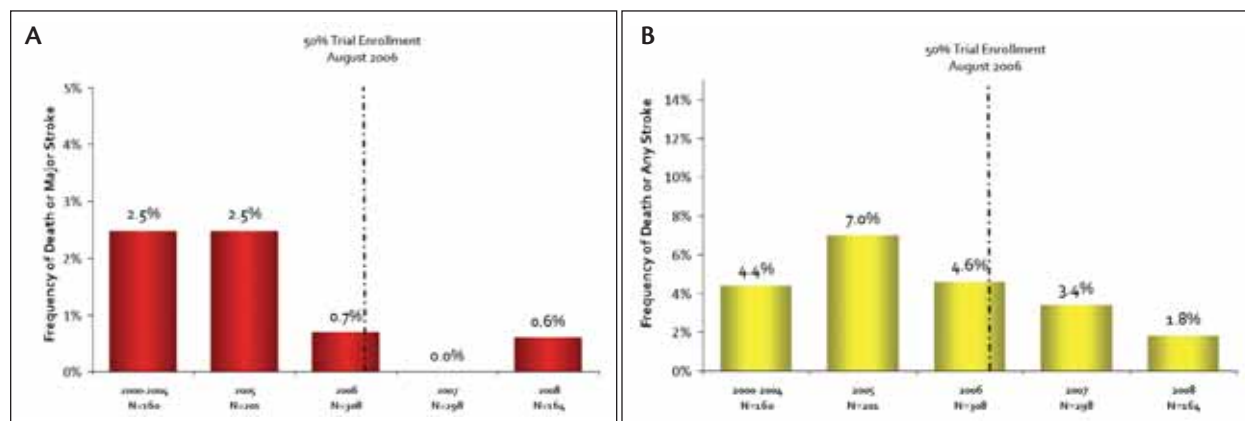
Figure 3. The effect of interventionists' learning curves during CREST. Death or major stroke rates for CAS over the period of CREST enrollment (A). Death or any stroke rates for CAS over the period of CREST enrollment (B).

not differ significantly by sex ($P_{interaction}$ = .34). The primary endpoint occurred in 6.2% of men treated with CAS compared to 6.8% treated with CEA (hazard ratio [HR], 0.99; 95% confidence interval [CI], 0.57–1.41; P = .94).[10] The rates for women were 8.9% in the stenting group versus 6.7% in the surgical group (HR, 1.35; 95% CI, 0.82–2.23; P = .24). Regarding periprocedural events only, the rate of complications was 4.3% in the male CAS group compared with 4.9% in the male surgical group (HR, 0.9; 95% CI, 0.57–1.41; P = .64). Among women, the rate in the CAS group was 6.8% compared with 3.8% in the CEA group (HR, 1.84; 95% CI, 1.01–3.37; P = .064).

What Is the Role of MI After Carotid Revascularization?

Periprocedural MI was one component of the composite primary endpoint. Cardiac biomarkers and electrocardiography were performed before and 6 to 8 hours postprocedure. The level of cardiac biomarkers was followed, and serial electrocardiography was performed in case of pathological postprocedural elevation of biomarkers, chest pain lasting for more than 15 minutes, or if other symptoms suggested myocardial ischemia. MI occurred in 14 patients undergoing CAS (1.1%) and 28 patients treated with CEA (2.3%; HR, 0.5; 95% CI, 0.26–0.94; P = .032).[11]

In addition, an increase in cardiac biomarkers only was seen in eight CAS patients (0.6%) and 12 in CEA patients (0.97%; HR, 0.66; 95% CI, 0.27–1.61; P = .36). Importantly, mortality was higher in subjects with a periprocedural MI than in those without after 4 years of follow-up (HR, 3.4; 95% CI, 1.67–6.92; P < .001). Similar results were found in patients in whom only increased biomarkers were detected (HR, 3.57; 95% CI, 1.46–8.68; P = .005). Multivariable analysis showed that the only independent predictor of periprocedural myocardial infarction was a history of previous cardio-

vascular disease (P = .02). Baseline creatinine clearance of < 30 mL/min and a history of cardiovascular disease were predictors for the composite endpoint of MI and isolated biomarker release. The inclusion of periprocedural MI or biomarker release in the primary endpoint for trials examining a procedure's efficacy in stroke prevention has been debated with controversy. However, the impact of periprocedural MI on long-term mortality appears to be more important than that of periprocedural minor strokes and therefore should not be discounted (Figure 2).[12]

QUALITY OF LIFE AFTER CAROTID REVASCULARIZATION

Overall, CREST demonstrated fewer strokes in the endarterectomy group and a lower risk of MI in the stenting group. Although there was no difference in major strokes (0.9% for CAS vs 0.6% for CEA; P = .52), the incidence of minor strokes was significantly higher in the CAS group (4.1% vs 2.3%; P = .01). How does this translate into quality-of-life (QOL) measures? QOL studies suggest that the effect of a minor stroke is more severe than that of MI at 1-year follow-up.[2] However, many deficits related to minor strokes after CAS diminish or completely resolve. For example, in the Acculink Carotid Stent System for Revascularization "of Carotids in High-Risk Patients (ARCHER) trial, most deficits were no longer apparent after months of follow-up.[13] Cranial nerve injury, a complication seen primarily after CEA, was not included in the QOL analysis. The appearance of cranial nerve palsies with CAS was 0% compared with 5.3% in the endarterectomy cohort (n = 62 of 1,176; P < .0001), of which 3.6% persisted for 1 month (n = 42 of 1,176; P < .0001) and 2.1% for at least 6 months (n = 25 of 1,176; P < .0001).[12]

As demonstrated in the ECST trial, the overall risk of permanent cranial nerve injury was 0.5%, and 5.1% of the

patients experienced at least a temporary motor nerve palsy (36 hypoglossal, 31 mandibular branch of the facial nerve, 17 recurrent laryngeal nerve, and one accessory nerve palsy).[14]

Most health care providers who have followed patients with cranial nerve palsies as a result of carotid surgery would probably agree that these deficits affecting sensation, appearance, swallowing, and speech are not minor and can significantly affect QOL. Given these important neurological deficits, similar to those reported with minor strokes, patients with cranial nerve palsies should be taken into account when assessing the impact of procedure-related adverse neurological events on QOL. Finally, local access complications may affect postprocedural QOL. In the endovascular group, 1.1% had access-site complications requiring further treatment compared with 3.7% in the surgical group ($P < .001$). Although two patients treated with CAS needed a surgical intervention due to postinterventional hematoma, the corresponding number of reoperations needed among CEA patients was 17.

What Is the Importance of Operator Experience?

In CREST, the majority of deaths and major strokes appeared within the first half of patient enrollment. This underlines the importance of experience and the impact of the interventionists' learning curves on patient outcomes (Figure 3) and confirms findings of a number of previous studies suggesting better outcomes with more experience.

What Is the Role of Medical Management?

One limitation of this largest trial comparing CAS and CEA to date is the poor knowledge of patients' medications. This information may have been useful for the analysis of cerebrovascular and cardiovascular events. All patients were required to continue aspirin therapy, but no data were available regarding the use of dual-antiplatelet, statin (except in patients with hyperlipidemia), or ß-blocker therapy, all of which may affect the periprocedural rate of MI or long-term risk of cerebrovascular and major adverse cardiac events.

To allow better comparison between CAS and CEA, all subjects participating in future trials should be treated with the best medical treatment, and their medication should be documented. Importantly, very little data are available on stroke risk in patients with optimal medical therapy. Given the significant but relatively small benefit seen with surgical revascularization in asymptomatic patients in an era when statins, angiotensin-converting enzyme inhibitors, and thienopyridines were not routinely used, optimally, any mode of revascularization, even in the absence of symptoms, should occur with optimal medical management and be compared with a control arm of patients treated with medical management only.
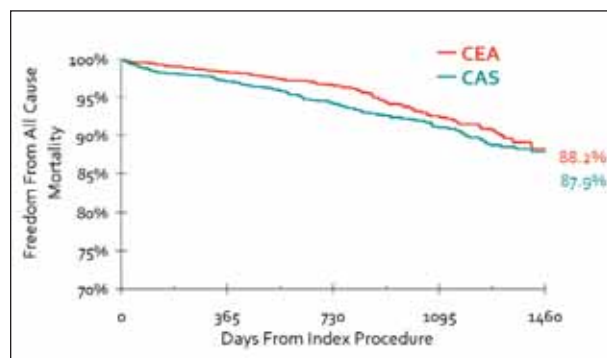

Figure 4. Similar mortality rates after CAS and CEA up to 4 years.

LESSONS LEARNED FROM CREST

The most important lesson to be learned from CREST is that CAS was noninferior to CEA in the treatment of extracranial stenoses of the internal carotid artery in patients at standard risk for surgery. The risk of major stroke or death did not differ significantly between both groups regardless of whether patients were symptomatic or asymptomatic. Although in the endovascular group, the rate of minor strokes was higher than in the group treated with surgery, CEA was associated with a higher rate of periprocedural MI, cranial nerve palsies, and vascular access complications. The composite primary endpoint of periprocedural MI, stroke, or death and ipsilateral stroke within 4 years within randomization was well balanced between both groups (Figure 4). Therefore, the long-term results are equivalent.

The following observations merit attention. First, the observed composite major event rates of stroke and death are low, equal to, or lower than the expected event rates seen in historical controls and equal to those recommended by the American Heart Association whether CAS or CEA was used. Second, although periprocedural events were more common in octogenarians regardless of revascularization mode, there was no difference in event rates between revascularization modes. Third, sex did not have a significant impact on long-term outcomes. Fourth, although minor strokes appear to have a differing impact on patients' QOL than MI (in patients who survive the infarctions), other adverse events such as the neurological deficits caused by cranial nerve injuries or access-related complications need to be taken into account when analyzing patients' QOL. Finally, operator experience clearly affects outcomes.

FUTURE PERSPECTIVES

Despite a 40-year history, the benefits of carotid surgery have only become evident during the past 2 decades. As with any medical technology, CAS is constantly undergoing modifications aiming to improve procedural safety. In the

past 2 decades, this has resulted in a steady decline in adverse events. Similar to surgery, it is unlikely that a standard procedural technique and equipment are best suited for all patients because the anatomy is highly variable. Although interventionists taking part in CREST were limited to the use of only one stent system (RX Acculink) and one distal filter system (RX Accunet) for embolic protection, there were no restrictions in surgical techniques in the CEA group. Meanwhile, newer embolic protection devices and stents have become available, which could be associated with lower stroke rates, thus potentially improving outcomes for CAS. In future trials, interventionists should be allowed to tailor the approach, technique, and equipment according to the patients' anatomy.

Further, the impact of optimal medical management on stroke risk in patients with carotid disease is worth reinvestigating. To allow better comparison between CAS and CEA, all subjects participating in future trials should be treated with best medical treatment, and their medication should be documented. Importantly, very little data are available on stroke risk in patients with optimal medical therapy. Given the significant but relatively small benefit seen with surgical revascularization in asymptomatic patients in an era when statins, angiotensin-converting enzyme inhibitors, and thienopyridines were not routinely used, optimally, any mode of revascularization in the absence of symptoms should occur with optimal medical management and be compared with a control arm of patients treated with medical management only.

Finally, although major stroke rates are low after both types of revascularization, events continue to occur. Therefore, both surgeons and interventionists must continue their quest to eliminate the risk of stroke whether caused by carotid disease itself or by its revascularization. ■

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