Minor Stroke Versus CNI in CREST

Cranial nerve injury should be included in a 30-day neurological outcomes composite endpoint in carotid revascularization.

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CREST (Carotid Revascularization Endarterectomy Versus Stenting Trial) is a prospective, multicenter, randomized, controlled trial that compared surgical carotid endarterectomy (CEA) to endovascular carotid artery stenting (CAS) with primary endpoints of periprocedural stroke, myocardial infarction (MI), or death, or postprocedural ipsilateral stroke up to 4 years in standard-risk patients.[1,2] CREST results indicate that stenting may be equivalent to CEA with respect to the primary endpoints. Overall, the trial demonstrated fewer strokes in the CEA group with a lower risk of MI associated with CAS. The number of minor strokes in the CAS group was significantly higher, and quality-of-life (QOL) studies suggest that the impact of minor stroke is greater than that of MI in patients. However, cranial nerve injury (CNI) is a complication seen primarily after CEA. Debate exists whether CNI affects QOL to the same degree as minor stroke. The authors contend that CNI is of relevance to QOL and should be included in a 30-day neurological outcomes composite endpoint for this and future carotid revascularization trials.

CREST STUDY BACKGROUND AND DESIGN

By 2000, the safety of CAS demonstrated in case series justified comparison to CEA in standard or standard-risk patients (patients who do not fit into anatomic or functional high risk for surgery categories) to determine the optimum surgical approach for these lesions. Both anatomical and functional criteria were considered.

Against this background, CREST was initiated.[1] The trial involved 117 sites (108 in the United States and nine in Canada) comparing CEA and CAS outcomes in the treatment of symptomatic and asymptomatic carotid artery disease (asymptomatic patients were eligible for inclusion in CREST in 2005). The team at each center included a neurologist, an interventionist, a vascular surgeon or neurosurgeon, and a research coordinator.

> " . . . cranial nerve palsies (seen primarily with CEA) may affect QOL in ways similar to minor stroke."

In CREST, the primary endpoint was composite occurrence of stroke, MI, or death from any cause during the 30-day periprocedural period or any postprocedural ipsilateral stroke within 4 years of randomization.[1,2] A recurrent or new stroke was defined as an acute neurological ischemic event of at least 24-hour duration with focal signs and symptoms, and the diagnosis of a stroke was adjudicated by at least two neurologists blinded to treatment. A major stroke was defined as a stroke-causing symptom or a National Institutes of Health Stroke Scale (NIHSS) score of 9 or higher 90 days after the procedure. A minor stroke was defined as stroke symptoms associated with an NIHSS score of 8 or lower. An MI was defined as the combination of elevation of cardiac enzymes (creatinine kinase-MB or troponin level) to a value of two or more times the upper limit of normal at the laboratory at the individual clinical center, plus chest pain or equivalent symptoms consistent with ischemia or electrocardiography evidence of ischemia, including new ST-segment depression or elevation > 1 mm in two or more leads. The diagnosis of MI was determined by two cardiologists blinded to treatment. Secondary aims of the study included the impact of symptomatic status, sex, and age on the treatment effect. Restenosis rates, QOL, and cost were also evaluated. CNI was evaluated in the secondary analysis and was not included in the QOL analysis.

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RESULTS

The CREST results included 2,502 patients, 1,262 assigned to CAS and 1,240 to CEA. The combined primary endpoint demonstrated equivalence between CAS and CEA (7.2% vs 6.8%; *P* = .51 for stroke, death, MI, or long-term [4 year] ipsilateral stroke event). Periprocedural endpoints were likewise statistically equivalent (5.2% for CAS vs 4.5% for CEA; *P* = .38). Moreover, CAS and CEA demonstrated countervailing and complementary risks in subset analysis. Although the rates of major stroke for CAS and CEA were approximately equal (0.9% vs 0.6%; *P* = .52), the rate of minor stroke for CAS exceeded that for CEA (total 4.1% vs total 2.3%; *P* = .01). CAS was superior to CEA with respect to the incidence of periprocedural MI (1.1% vs 2.3%; *P* = .03). In addition, cranial nerve palsies were less frequent during the periprocedural period with CAS (0.3% vs 4.7% with CEA; hazard ratio, 0.07; 95% confidence interval, 0.02–0.18). There was no differential treatment effect with regard to the primary endpoint according to symptomatic status.

The QOL analyses among survivors at 1 year suggested that stroke had a greater adverse effect on a variety of categories than did MI. As mentioned, CNI was not included in the QOL analysis.

DISCUSSION

In 2004, Cunningham et al[3] reported the incidence and outcomes of patients who sustained CNI in the European Carotid Surgery Trial (ECST). Among the 1,739 patients who underwent CEA in ECST, 106 (6.1%) were found to have one or more cranial nerve palsies, Horner syndrome, and/or injuries to cutaneous sensory nerves of the cervical plexus. Eighty-eight patients (5.1%) had a motor CNI (36 hypoglossal, 31 marginal mandibular branch of the facial nerve, 17 recurrent laryngeal nerve, and one accessory nerve) or Horner syndrome.[3] One-third of the deficits had resolved at the time of the hospital discharge; 3.7% persisted beyond discharge. Ninety-two percent had resolved during the 4-month follow-up period, meaning that 8% were permanent, for an overall risk of permanent CNI of 0.5%. CNI, as expected, can affect QOL in very relevant ways, including swallowing difficulty, hoarseness, and disfigurement. For these reasons, it is reasonable and important to include patients with CNI into a composite endpoint describing 30-day neurological outcomes. Moreover, safety endpoints for CEA should include the incidence of CNI.

Similarly to the experience with CNI after CEA, the RX Acculink carotid stent system (Abbott Vascular, Santa Clara, CA) for the Revascularization of Carotids in High-Risk patients (ARCHER) trial has shown that most minor strokes after CAS resolve completely within several months.[4] Although the authors are in no way trying to minimize the importance of all strokes after carotid artery procedures, CREST demonstrated the lowest rate of major stroke of any carotid trial thus far. To truly evaluate the outcome of CEA versus CAS on QOL, all outcomes and complications need to be addressed and evaluated for both procedures. In our opinion, it is unfair to criticize a minor stroke risk of 4.1% with CAS and say that is too high, yet disregard a 4.7% risk of CNI with CEA and say that is expected if the impact of both minor stroke and CNI on QOL might be similar and if these data are to be used to help guide patient treatment.

The results of CREST confirm the findings of the Stent-Supported Percutaneous Angioplasty of the Carotid Artery Versus Endarterectomy (SPACE) trial[5,6] that rigorous training requirements and experience can make a difference, even with first-generation technology, as was the case with CREST, in which the protocol for CAS specified the use of the RX Acculink stent and, whenever feasible, the RX Accunet embolic-protection device (Abbott Vascular).[1] CAS is a relatively new technique in comparison to CEA. Each trial gives us different information, and no single trial holds all the answers. We will learn much from CREST, as we have from the other well-designed trials that preceded it. The CREST results suggest overall equivalence between CEA and CAS for the primary endpoint of the study.

CREST does have some limitations. The study had a prolonged enrollment period during which stenting technology and operator experience improved greatly. With improved technology, such as proximal embolic protection devices, and with improvements in operator technique, it is possible that the stroke rate with CAS in current practice may be less than that seen in CREST. However, one may argue that the rigorous training and requirements for operators participating in CREST may make CAS appear safer than it actually is in a standard population of practitioners with average experience.

CONCLUSION

CREST results indicate the equivalence of stenting to CEA with the lowest rate of major stroke and death in any trial so far. The trial demonstrated fewer strokes in the CEA group with a lower risk of MI with CAS. QOL studies suggest, however, that stroke, even minor, may have a more adverse effect on long-term outcome than MI, whereas cranial nerve palsies (seen primarily with CEA) may affect QOL in ways similar to minor stroke. As

such, these data should be included in the 30-day neurological outcome data. Moreover, the ARCHER trial has shown that most minor strokes after CAS resolve completely within several months. Analyses of these outcomes are greatly anticipated. The CREST results suggest that both CEA and CAS are associated with low perioperative complication rates and excellent longer-term results at experienced centers. ■

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