# Minor Stroke Versus CNI in CREST

Cranial nerve injuries are not the equivalent of strokes, but what is their bearing on CREST?

**BY FRANK J. VEITH, MD**

In the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST),[1] the higher incidence of cranial nerve injuries (CNIs) after carotid endarterectomy (CEA) than after carotid stenting (CAS) raises the question: Should CNIs be regarded as the equivalent of strokes in evaluating invasive treatments for carotid bifurcation stenosis (CS)? They definitely should not be for several reasons.

The goal of any treatment for CS is to prevent stroke and death. Thus, stroke and death rates after any such treatments should be the primary endpoint to determine success and failure of the treatment. So-called "composite endpoints" that include other complications of treatment such as myocardial infarctions (MIs) or CNIs are artificial and misleading, although clearly of interest and importance. Because CREST used a composite of death, stroke, and MI as its primary endpoint, the conclusion that CAS and CEA are equivalent is not exactly correct.

CAS and CEA do not have equal outcomes because stroke and death were more frequent after CAS than after CEA.[1,2] Only when the greater number of MIs in the CEA arm (which could have been due to the less intensive antiplatelet therapy CEA patients received) was added to the composite endpoint were the adverse event rates of the two procedures apparently equivalent.[1]

Yet, the consequences of a minor or nonfatal stroke are far more substantial than a minor or nonfatal MI. Even if measurable neurological defects after a stroke resolve fully, unmeasurable changes in mood and intellect may persist and impact negatively on quality of life (QOL). In CREST, the strokes and MIs that occurred were not equivalent, and this was reflected in the more-impaired QOL that was observed in patients who had had strokes than those who had had MIs.

The same reasoning can be applied to the equivalence of CNIs and strokes. Certainly some strokes and CNIs can be devastating, particularly if the latter are permanent and involve swallowing or speech. However, in CREST, almost all of the CNIs, like most of the strokes, were temporary and minor with no permanent measurable long-term neurological deficits. Importantly, the CNIs, unlike the strokes, did not produce brain cell death and the subsequent consequences of unmeasurable alterations in mood and unquantifiable deficits in memory and intelligence—which are known to occur after even minor strokes that have neurological defects that appear to resolve.

> "Importantly, the CNIs, unlike the strokes, did not produce brain cell death and the subsequent consequences . . . "

Thus, although the minor CNIs that occurred in CREST are an important complication of CEA and should be considered in the interpretation of the trial, in no way can they be considered the equivalent of minor strokes with only transient measurable defects. The brain is a remarkable organ and, in many cases, has the capacity to recover from the measurable effects of a cerebral infarct. However, such "minor" strokes should never be considered an acceptable consequence of any therapy designed to prevent strokes. This is particularly true for the asymptomatic CS patients who comprised 47% of the patients in the CREST trial.[1]

In light of the recently observed falling stroke rates in asymptomatic patients who are not treated by either CEA or CAS, it is likely that most of the asymptomatic CS patients in CREST would have been as well served by treatment with intensive medical therapy (with statins, antihypertensives, antiplatelet agents, and other drugs) as they were by either CAS or CEA.[3,4] Trials comparing CAS and CEA to current medical therapy in asymptomatic patients are sorely needed.

Just as even minor strokes with apparent recovery are an important negative consequence of any treatment designed to prevent strokes, so too are brain defects seen on diffusion-

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weighted magnetic resonance images. Even though these may be silent on neurological examinations, they may be associated with other unmeasurable defects in mood or intellect. It is, therefore, important in considering CREST to be aware of findings from other recent trials that have examined such parameters. One such trial is the International Carotid Stenting Study (ICSS), which found significantly more defects on diffusion-weighted magnetic resonance imaging studies as well as strokes after CAS than after CEA.[5] Although ICSS has its flaws, as do all randomized trials, this important European trial also compared CEA and CAS as treatment for CS, and did so entirely in symptomatic patients.[5] Its results must be considered in evaluating the CAS versus CEA question.

## CONCLUSION

CREST is an important trial that was designed and conducted in exemplary fashion. It produced important findings, among which are that both CEA and CAS can be performed with acceptably low mortality and morbidity rates. With current improvements in CAS (better embolic protection, better stents, better patient selection, etc.), it is likely that the procedure may be performed with even better outcomes than in CREST. Nevertheless, all vascular specialists should avoid the temptation to over-interpret CREST and consider it in a vacuum as the "definitive" or "final" trial.

CREST, like all trials, has its flaws, among which is implying that strokes are equivalent to MIs in its use of a composite endpoint. For similar reasons, it is not justified to equate strokes and CNIs. More trials are needed in symptomatic patients with improved CAS techniques and in asymptomatic patients comparing CAS and CEA to best medical treatment. Better methods are also needed to select asymptomatic CS patients who are at high risk of having a stroke so they can clearly and cost effectively benefit from CAS or CEA. Only then will we know which treatment—CAS, CEA, or best medical therapy—is best for each specific group of patients with CS. ■

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