Emerging Therapy Critique

The International Carotid Stenting Study and the North American Carotid Revascularization Endarterectomy Versus Stenting Trial

Fueling the Debate About Carotid Artery Stenting

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Recently, 2 multicenter studies pitting carotid endarterectomy (CEA, the defending champion) against carotid artery stenting (CAS, the challenger) have been reported.\(^1\)\(^2\) These 2 studies have reported somewhat differing results, raising the question of whether 1 trial has the “right message” or is the “truth” somewhat more nuanced?

The International Carotid Stenting Study (ICSS) was the first of the randomized CAS versus CEA trials that completed recruitment and was not stopped prematurely.\(^1\) The study enrolled patients with ipsilateral carotid territory symptoms within the previous 12 months and with at least 50% internal carotid artery stenosis. A total of 1713 patients were recruited from 50 academic centers. Surgeons were required to have performed at least 50 CEA operations and interventionalists were required to have done at least 50 stenting procedures with at least 10 in the internal carotid artery.

The North American Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) originally included only symptomatic patients with at least 50% stenosis on angiography or 70% by ultrasound.\(^2\) In 2005, asymptomatic patients with at least 60% stenosis by angiography or 70% by ultrasound also became eligible. A total of 2502 patients were enrolled (including 1181 asymptomatic subjects) from 108 centers. Both surgeons and interventionalists were required to be certified as meeting performance benchmarks. Less experienced interventionalists were required to participate in a lead-in phase before joining the main study.

In ICSS, the risk of stroke, death, and myocardial infarction (MI) in the CAS group (8.5%) was significantly higher than in the surgical arm (5.2%, \(P=0.006\)) with a major difference in the occurrence of minor strokes.\(^3\) The finding that CEA is safer than CAS is also supported by the results of an MRI substudy, which showed significantly more new diffusion-weighted imaging lesions in CAS than in CEA patients.\(^3\) MI did not play a major role in ICSS and was confined to single cases with no significant difference but more fatal events in the CAS group.

The CREST trial showed no significant difference between both arms concerning the combined end point stroke, death, and MI.\(^2\) The rate of strokes in CREST is still significantly higher after CAS, but the 30-day rate of any stroke was 4.1% instead of 7.7% in ICSS. CREST is the trial with the lowest perioperative and peri-interventional complication rates meeting the quality criteria for symptomatic and asymptomatic stenoses. In contrast to ICSS results, the rate of periprocedural MI was significantly higher after CEA (CEA 2.3%, CAS 1.1%; \(P=0.03\)). Common interpretation of CREST is that endovascular and surgical therapy represent 2 means of treatment that can be done with reasonable complication rates. Many interventionalists hope that equivalence in the combined end point will contribute to establish CAS as an alternative to CEA for conventional risk patients.

What are the differences between ICSS and CREST and which conclusion is valid for daily practice and management of patients with carotid stenoses? The Table provides an overview of select end points of several multicenter carotid revascularization trials.

In terms of MI, it can be seen that the rate of MI in the CEA arm is higher in CREST (2.3%) than in other studies such as ICSS (0.5%) and Endarterectomy Versus Angioplasty in Patients With Symptomatic Severe Carotid Stenosis (EVA-3S)\(^5\) (0.8%). The CREST trial policy of routine cardiac enzyme measurement may partially explain the elevated rate of MI in the surgical arm of CREST. Because MI was included in the primary end point of CREST, but not the other studies, it will be important to assess the impact of these cardiac events on patient outcomes. A myocardial event with overt clinical symptoms and electrocardiographic changes may have more significance than an event with an elevated troponin and electrocardiographic changes.

Second, there is the issue of practitioner credentialing. Study centers in CREST had to undergo a vigorous credentialing process.\(^6\) Consequent monitoring of cases was started in a lead-in phase until quality criteria were fulfilled by surgeons as well as interventionalists of different professional groups. Minimum requirement for ICSS interventional centers was only 10 CAS cases with the consequence of potential asymmetry in the experience between interventional therapy and more established surgery.
Conducting a clinical trial with an evolving technology is difficult and none of the studies completed to date is perfect. The European CAS trials were started at a time when neither training of interventionalists nor technique and quality criteria of the CAS procedure were sufficiently standardized. An interventionalist who had just done 10 cases cannot be regarded as a specialist and randomization of patients to this therapist may carry increased risks. Do we need a randomized trial to demonstrate that carotid stenting done by less experienced interventionalists is inferior to surgery with well-established techniques and quality criteria?

Although the CREST investigators were aware of these problems and tried to establish quality standards first before they started the trial, CREST has its own problems. First, the inclusion of lower-risk asymptomatic patients to a pool of symptomatic patients combines 2 very different populations in terms of physiology and short-term stroke risk. Combining asymptomatic and symptomatic patients also reduces periprocedural events and serves to obscure potentially real differences between the 2 groups. In fact, if one looks at the traditional end point of periprocedural stroke/death in symptomatic patients only, CEA was superior to CAS (3.2% versus 6.0%, \( P=0.02 \)). Some clinicians will be persuaded by this fact to justify the preference for CEA in symptomatic patients.

Another problem with CREST goes back to credentialing. Four hundred twenty-seven interventionalists applied for preference for CEA in symptomatic patients. Of these, only 52% (224) were approved.6 Although the CREST investigators were aware of these problems and tried to establish quality standards first before they started the trial, CREST has its own problems. First, the inclusion of lower-risk asymptomatic patients to a pool of symptomatic patients combines 2 very different populations in terms of physiology and short-term stroke risk. Combining asymptomatic and symptomatic patients also reduces periprocedural events and serves to obscure potentially real differences between the 2 groups. In fact, if one looks at the traditional end point of periprocedural stroke/death in symptomatic patients only, CEA was superior to CAS (3.2% versus 6.0%, \( P=0.02 \)). Some clinicians will be persuaded by this fact to justify the preference for CEA in symptomatic patients.

In terms of the future, the equivalence between both arms in CREST justifies further studies with CAS. The study is an important step and shows the way interventionalists have to go toward standardization. Regarding periprocedural strokes, CAS still needs major improvements to achieve the high standards of vascular surgery. Improved distal protection devices and the value of proximal protection and transradial approaches need to be evaluated.7 For CEA, greater use of adjunctive medications such as statins and local anesthesia could reduce the perioperative MI rate.8

Finally, CREST included asymptomatic cases and could be used as justification for widespread stenting of patients with incidental findings. We have to keep in mind that medical therapy has improved significantly since the completion of previous landmark studies and many asymptomatic carotid stenoses are quite benign under medical therapy alone.9,10 Revascularization should be confined to patients more likely to survive at least 5 years and with an increased stroke risk (patients <75 years, males, evidence of microemboli).11,12 To avoid overtreatment of asymptomatic carotid stenosis, further studies such as Stent-protected Percutaneous Angioplasty of the Carotid vs Endarterectomy (SPACE) II that include a treatment arm featuring aggressive medical therapy are essential.

### Disclosures
S.C. is a consultant for Abbott Vascular and Astra Zeneca.

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