Carotid Revascularization Strategies

The Need for More Data

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We believe that ACT I can contribute important information for clinicians. First, we should recognize that the vast majority of carotid revascularization procedures performed in the United States are in asymptomatic patients and high-quality data are needed on the outcomes of these patients. In a recent analysis of CEA and CAS performance in Medicare recipients, the proportion of asymptomatic subjects was 87.3% for CEA and 87.5% for CAS. Although CREST enrolled 2502 patients, the study had insufficient power to compare the subgroup of 1181 asymptomatic randomized patients. Conversely, ACT I will enroll 1658 patients and has been designed with 80% power to detect a 3% difference between the groups.

CREST initially began as a study comparing CEA and CAS in patients with symptomatic stenosis of 50% to 99%. In 2005, CREST allowed the enrollment of asymptomatic subjects but at the study’s conclusion, it was underpowered to examine outcomes in the asymptomatic subgroup. Furthermore, there was a concerning trend with regard to stroke outcomes in asymptomatic patients in CREST. The rate of periprocedure stroke/death and subsequent ipsilateral stroke was 4.5% in the CAS group and 2.7% in the CEA group (P = 0.07). One wonders if this would have been statistically significant with a few hundred more patients. ACT I, with a target sample size of 1658, may shed light on this issue and also has the potential for allowing a pooled analysis of the ACT I and CREST asymptomatic patients. An additional randomized controlled trial is critical to provide an independent result in a separate cohort to compare with data obtained in CREST. There are several other reasons for neurologists, surgeons, and interventionalists to support the completion of ACT I. First, CREST generated important observations with respect to elderly patients and women. There was an interaction with age and the relative merits of CAS versus CEA. For the stroke end point, CAS results were better than CEA in younger patients and worse in older subjects with the inflection point at 64 years. Second, CREST identified that women undergoing CAS had a higher periprocedure complication rate than men. Given the importance of these subgroups, it is critical that a second randomized controlled trial be completed to determine whether these are durable findings, especially as interventionalists gain more experience with CAS.

On the subject of experience, there has been the suggestion from registries and CREST that complication rates after CAS have been decreasing over the past decade. One study found that interventionalists who perform a minimum of 72 CAS procedures had the best results. With increased experience in recent years, will ACT I show improved results compared with CREST in asymptomatic patients? Will the concerning trend mentioned be replicated?

Received November 17, 2011; accepted November 22, 2011.

The opinions in this editorial are not necessarily those of the editors or of the American Heart Association.

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Stroke 2012;43:00-00.

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Over the past decade, >1 million carotid revascularization procedures have been performed. During this time period, the frequency of carotid endarterectomy (CEA) has slightly declined, whereas carotid artery stenting (CAS) has increased. Somewhat surprisingly, in this timeframe, only 2 large (enrolling >1000 patients) randomized controlled trials have been initiated in North America to assess the merits of carotid revascularization approaches. Is this paucity of high-quality data due to limited funding, the influence of competing interests, or are there simply not that many burning questions left?

The first of the major randomized controlled trials is the Carotid Revascularization Endarterectomy versus Stent Trial (CREST). The principal results of CREST, which enrolled approximately equal numbers of symptomatic and asymptomatic patients, were published in 2010. For the primary end point of periprocedure stroke, myocardial infarction, death, or subsequent ipsilateral stroke, there was not a significant difference between the 2 treatments (6.8% CEA versus 7.2% CAS, P = 0.51). However, the components of the primary end point differed in the 2 groups with periprocedure stroke more common with CAS and periprocedure myocardial infarction more frequent after CEA.

Where does this leave the second of the large randomized controlled trials, the Asymptomatic Carotid Trial I (ACT I)? Are there any major issues that remain to be resolved? Briefly, ACT I is a noninferiority study that aims to compare CEA and CAS in asymptomatic, standard-risk patients aged <80 years with 70% to 99% stenosis by duplex ultrasound. The study’s primary end point is periprocedure stroke, myocardial infarction, or death plus subsequent ipsilateral stroke up to 12 months. The study has a 3:1 (CAS to CEA) randomization scheme. The noninferiority margin of the study is 3.0%. ACT I differs from CREST by focusing on asymptomatic patients and also in excluding patients >80 years and rigorously controlling vascular risk factors in both groups. Over 1300 patients have been enrolled thus far.

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Stroke 2012;43:00-00.

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Stroke is available at http://stroke.ahajournals.org
DOI: 10.1161/STROKEAHA.111.641514
Some clinicians will contend that ACT I does not address the “elephant in the room,” which is whether either procedure is superior to medical therapy alone in asymptomatic patients. We agree that this is an important issue. Comparisons of carotid revascularization with medical therapy have been launched in Europe and are in the planning stages in North America. We support such studies, but also encourage all clinicians to complete ACT I to better define the role of CEA and CAS in the treatment of asymptomatic stenosis and help properly plan and power future randomized trials.

Our patients deserve the best information to judge the merits of the various revascularization strategies. With >1 million carotid procedures in the United States in the past decade alone (and counting), the healthcare system needs further clarity as well.

Acknowledgments
We thank Dr Kenneth Rosenfield for review of the article.

Disclosures
The authors are members of the executive committee of the ACT I trial and have been compensated by Abbott Vascular for this function.

References

Key Words: carotid endarterectomy ■ carotid stenting ■ carotid stenosis ■ clinical trials
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*Stroke*. published online February 2, 2012;
*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/early/2012/02/02/STROKEAHA.111.641514.citation

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