Carotid Artery Stenting
Meeting the Recruitment Challenge of a Clinical Trial

Robert W. Hobson II, MD; Thomas G. Brott, MD; Gary S. Roubin, MD, PhD; Frank L. Silver, MD; Henry J.M. Barnett, MD

Clinical efficacy of carotid endarterectomy (CEA), when combined with best medical care and compared with optimal medical management alone, was established in rigorous clinical trials for symptomatic and asymptomatic extracranial carotid occlusive disease. Enrollment was slow for each, and so reporting of results occurred years after the first randomizations. Nonetheless, increases in the numbers of CEA centers in the US and Canada occurred soon after these results became available. These increases indicated that physicians were exercising restraint while the trials were in progress and then increased referrals for and performance of CEA in response to the positive results.

Carotid artery stenting (CAS) has been recommended as a less invasive but potentially equally effective treatment for carotid disease. Physicians and patients are eager for information comparing CEA and CAS. Data derived from previous and current attempts at randomized clinical trials and registries (P.L. Whitlow et al, personal communication, 2003) have raised the question of comparability of CEA and CAS, particularly in high-risk patients. None of these trials was powered to compare efficacy of CEA and CAS in symptomatic patients, in which the evidence for CEA is the strongest. Fortunately, larger clinical trials are currently underway in North America and Europe. Recruitment into these trials will also be slow and the data may not be available for next 2 to 3 years.

As was recommended previously for CEA, caution should be exercised in the use of CAS, pending reports from these rigorous randomized comparisons of CEA to CAS. We ask that specialists in Cardiology, Neurology, Internal–Family Medicine, Vascular and Neurosurgery, Interventional Radiology, and Interventional Neuroradiology, join us to ensure that larger randomized clinical trials such as CREST are not placed in jeopardy by early approval of interventional devices. For example, a recent Food and Drug Administration Advisory Panel recommended approval of a CAS stent and protection system for use in patients at higher risk, despite the size limitations of the pivotal randomized trial (SAPPHIRE: 96 symptomatic and 219 asymptomatic patients) and despite the absence of comparative data for medical treatment alone. The availability of an approved device “on the shelf” must not result in use of CAS in patients for whom adequate safety and efficacy data are not available.

In CREST, a multidisciplinary group has worked toward the goal of comparing efficacy between CEA and CAS in patients with symptomatic carotid stenoses. Recruitment of trial participants has been slow but compares favorably with data on the number of participants recruited per center per year in other clinical trials (Table), including the recently published data from the ACST (Asymptomatic Carotid Surgery Trial) investigators. These rates demonstrate the challenges of patient enrollment into trials of treatments in which opinions of physicians, and patients, may be strongly held. In the NASCET trial, Canadian centers were particularly effective contributors to this process. Fourteen percent of the NASCET centers were located in Canada, and yet these investigators randomized 40% of the randomized participants. For CREST to be successful, more Canadian sites must join CREST and again assist with the recruitment of patients with extracranial carotid occlusive disease.

Specialists in the United States must also redouble their efforts to achieve adequate recruitment into CREST and other trials comparing CEA and CAS to sustain support from the National Institute of Neurological Disorders and Stroke, National Institutes of Health, and the greater medical community. Carotid Revascularization Endarterectomy versus Stent Trial (CREST) sites currently headed by Principal Investigators in Neurology, Interventional Radiology/Neuroradiology, Vascular, and Neurosurgery are recruiting at rates approaching 0.60 participants per center per month, whereas centers headed by Principal Investigators in Cardiology are recruiting at the rate of 0.25 participants per center per month. Given the pivotal role that cardiologists have made to the development of carotid stenting, it is now imperative that they take a greater responsibility in recruitment of patients. The CREST Executive Committee is reaching out to these practitioners to stimulate recruitment efforts. CREST will complete expansion of its clinical sites over the next 18 to 24 months.
months, from the current 57 centers to 80 to 100 centers, with at least 8 in Canada. The CREST randomization goal is 1200 to 1600 symptomatic patients.

The Executive Committee has examined Medicare Provider Analysis and Review (MEDPAR) data\(^7\) on the number of carotid endarterectomies performed at each medical center in the United States. In 2002, Medicare billing for CEA was documented in 89 860 patients as compared with billings for CAS in 3909 patients. Although it has been estimated that \(\approx 140,000\) CEAs are performed annually in the United States,\(^8\) MEDPAR data included Medicare billing only and probably underestimated the total number of patients undergoing CEA or CAS. Assuming that two-thirds of the endarterectomies are performed for asymptomatic carotid stenosis, we estimate that \(\approx 45,000\) patients with symptomatic disease are being treated annually with CEA rather than being considered for CREST. If CREST is to accomplish its goal of completing its recruitment, all specialists must cooperate to evaluate this patient population for its suitability to be included in the trial. This will require substantial interest and support from the surgical community, and cardiology groups will need to collaborate with neurology as well as other surgical and interventional colleagues to accomplish this goal.

In North America, CREST may be our last opportunity to compare the efficacy of CEA and CAS in conventional risk patients. We are asking that all interested practitioners in every center act as an enthusiastic team throughout the trial. Experience has taught that this collegial approach produces the best recruitment records and the most complete data with minimal loss to follow-up. If we fail to achieve a study of adequate size, we will not produce convincing evidence of the value of carotid stenting in stroke prevention. The question as to whether stenting is either equal to or superior to endarterectomy will not be answered. Uncertainty will forever cast a long shadow over the use of what may in fact be a worthy therapy.

### Average Number of Patients Recruited Per Center Per Year

<table>
<thead>
<tr>
<th>Study</th>
<th>Average No. of Patients Recruited Per Center Per Year</th>
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<tbody>
<tr>
<td>NASCET(^1,2)</td>
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<td>ACAS(^6)</td>
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<td>WALLSTENT(^7)</td>
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<td>SAPPHIRE(^4)</td>
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</tr>
<tr>
<td>CREST(^13)</td>
<td>6.4</td>
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</tbody>
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### References

15. Public Advisory Committee of the FDA. Circulatory System Device Panel meeting. April 21, 2004, Gaithersburg, MD.

**Key Words:** carotid endarterectomy ■ carotid stenosis ■ randomized controlled trials ■ stents
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