The CARESS Trial

This groundbreaking study sponsored by the International Society for Endovascular Specialists (ISES) involving collaboration among industry, the FDA, and CMS, is the first to address a broad range of symptomatic and asymptomatic carotid lesions.

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Cerebrovascular disease, including carotid artery stenosis, affects 750,000 people annually in the US. Stroke continues to be the third leading cause of death in North America, with nearly 168,000 deaths in the US each year.

During the last decade, angioplasty/stenting has been investigated for the treatment of carotid occlusive disease compared with carotid endarterectomy (CEA), which is the standard of care. Recent enhancements in stent technology and the introduction of cerebral protection devices to prevent embolization have proven more effective.

In current clinical practice, patients who are deemed to be at high risk for surgery or who are poor candidates for CEA are often referred for carotid stenting. Most patients with carotid stenosis are not at high risk and, to date, there have been no prospective clinical trials that have been based on the broad category of standard-risk patients commonly treated in clinical practice.

THE NEED

The optimal design of a clinical trial to compare two different treatments is a prospective, randomized trial, providing level-1 evidence of efficacy. A number of factors, including the healthcare delivery system, reimbursement, and patient referral patterns, may result in randomized trial recruitment of patients who are atypical of those encountered in broad clinical practice. In addition, in the context of rapidly evolving technology, there is a risk that in the time required to complete a well-designed randomized trial of a single carotid stenting system, the procedure and technology used in the trial will be outdated and replaced by new technology before the trial is complete.

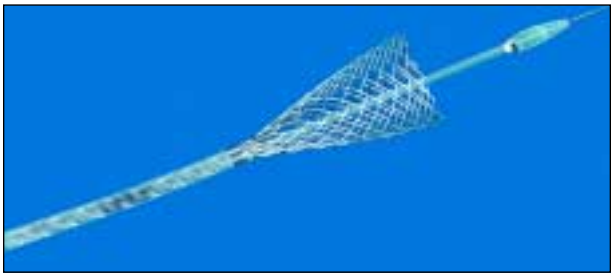

Figure 1. Boston Scientific Corporation's (Natick, MA) Monorail Wallstent device.

At the present time, there are no FDA-approved carotid stenting systems available for widespread clinical use. Because most current clinical trials of carotid stenting have focused on narrow-indication, high-risk patient populations with carotid artery disease, they are unlikely to shed light on the overall question of whether carotid stenting with distal cerebral protection is comparable to the clinical standard of care—CEA—for most patients with carotid stenosis who are at risk for stroke.

THE CARESS TRIAL

Recognizing the need for a proof-of-principle trial, the International Society of Endovascular Specialists (ISES) sponsored the CArotid Revascularization using Endarterectomy or Stenting Systems (CARESS) trial. CARESS compares the safety, efficacy, and equivalence of carotid stenting under cerebral protection to CEA for broad-risk indications reflective of the majority of patients in clinical practice. This trial was developed through early collaboration between ISES, the FDA, CMS, industry, the National Institutes of Health, and the New England Research Institutes, Inc.

CARESS is a multicenter, prospective, nonrandomized clinical trial designed as an equivalence cohort study to determine whether the stroke/death rate after carotid stenting with cerebral protection is comparable to CEA, the standard of care for patients with symptomatic and asymptomatic carotid stenosis. Additionally, recognizing the National Institutes of Health sponsorship of Carotid

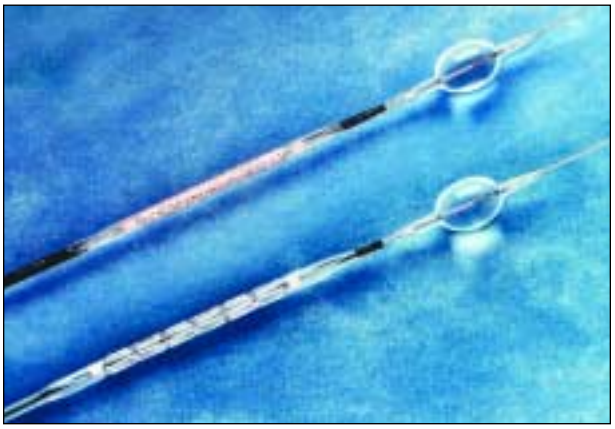

Figure 2. Medtronic Vascular's (Medtronic Vascular, Santa Rosa, CA) GuardWire Plus embolic protection system.

Revascularization: Endarterectomy or Stent Trial (CREST), any patient eligible for CREST was excluded from the CARESS study. Also, by designing a protocol utilizing the full spectrum of risk (ie, symptomatic and asymptomatic), CARESS addresses the increasing concerns of government agencies regarding off-label use of medical devices.

The CARESS phase I trial was designed to provide a reliable estimate for the 30-day primary endpoint (death and/or stroke from any cause) in the CEA arm of the study for future use in power calculations for a broader phase II clinical trial comparing CEA to carotid stenting systems (CSS). Phase I involved patients with symptomatic (≥50%) and asymptomatic (≥75%) carotid stenoses treated with CEA or with CSS using the Monorail Wallstent (Figure 1) with embolic protection (GuardWire Plus) (Figure 2).

An enrollment goal of 450 subjects (300 CEA, 150 CSS) provided both sufficient precision in determining the 30-day event rates in the CEA arm and enough CSS cases to ensure comparable patients in each treatment cohort. The primary endpoint included death and/or stroke from any cause within 30 days of the procedure. The secondary endpoint included any-cause death and/or stroke and documented MI within 30 days of the procedure (Table 1).

Fourteen US clinical centers participated in the phase I trial, and 397 enrolled patients underwent treatment: 254 with CEA and 143 with CSS. Baseline demographics and lesion characteristics did not differ between the two groups. The majority of patients (68%) had asymptomatic carotid stenosis; more than 90% of patients had >75% stenosis (Figure 3).

There was no difference between the groups in the primary endpoint: both had a 2% 30-day all-cause mortality and nonfatal stroke rate (*P*=.8502). In addition, there was no significant difference in the secondary endpoint (30-day all-cause mortality, nonfatal stroke, and MI): 3% for CEA and 2% for CSS (*P*=.5998). This study demonstrated equivalence of CEA and CSS in the 30-day outcomes. The low (2%) stroke/death rate in each arm, which was achieved in a wide spectrum of patients, is consistent with the overall 1.8% stroke/death rate reported from multiple studies of carotid stenting with cerebral protection and the 1% to 2% range of stroke/death rates for CEA in broad clinical practice.

The CARESS phase I trial achieved a low (2%) stroke/death rate in both symptomatic and asymptomatic patients, with independent postoperative neurological assessment, suggesting that both procedures have similar clinical benefit for patients. Although the phase I study sample size was sufficient to estimate this primary endpoint, the study was not designed to address any treatment arm differences. Long-term assessment of neurologi-

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TABLE 1. RESULTS: PRIMARY/SECONDARY ENDPOINTS

	Primary Endpoint		Secondary Endpoint	
	CEA	CSS	CEA	CSS
No. at risk	254	143	254	143
No. of events	6	3	8	3
No. censored	35	9	35	9
KM estimate	.0230	.0214	.0309	0.0214
Standard error	.0093	.0122	.0108	0.0122
P value	.8741		.5494	

Two percent event rate for both CEA and CSS; no statistically significant difference between groups.
Information adapted from: CARESS Steering Committee: Carotid Revascularization Using Endarterectomy or Stenting Systems (CARESS): Results of Phase I Study. J Endovasc Therapy. *2003;10:1021-1030.*

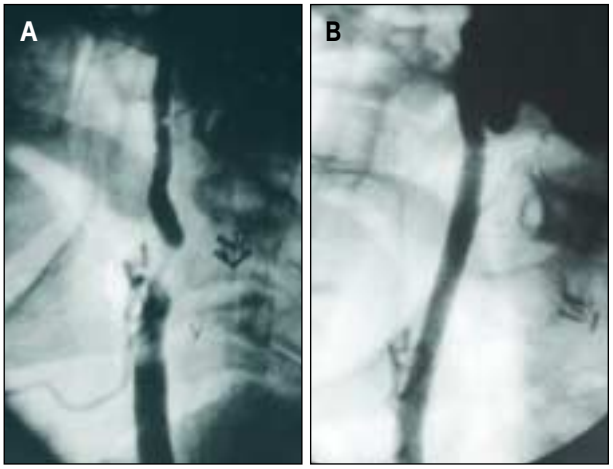

Figure 3. A CARESS case prior to (A) and after (B) stent deployment in a high-grade lesion.

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cal outcome and confirmation of carotid patency by ultrasound imaging are needed to confirm the equivalence of CSS to CEA.

CONCLUSION

In summary, the CARESS phase I study achieved excellent protocol compliance, timely enrollment, and acceptable data quality using concurrent CEA controls recruited on a 2:1 basis (CEA to CSS). The 2% 30-day primary endpoint rate in both arms of the study was sufficient to derive sample sizes for the phase II pivotal study, which will assess the equivalence of the procedures in nonrandom but concurrently assigned reverse ratios of 2,000 CSS patients to 1,000 CEA patients. Unlike the phase I trial, the phase II study will offer at least two, and up to six different CSSs, which will be randomly selected at each clinical center. The phase II protocol is approved by the FDA, supported by CMS, and is pending funding. Because large trials, such as the phase II, are generally not viable for any one manufacturer, there is an opportunity for several manufacturers to participate in a cost-efficient manner while still obtaining adequate data on a single stenting system for a pre-market application submission. For further information, please refer to the December 2003 edition of the *Journal of Endovascular Therapy*. ■

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