



September 26, 2007

Mr. James Swink  
Center for Devices and Radiological Health  
Food and Drug Administration  
9200 Corporate Blvd.  
Mail Stop: HFZ-450  
Rockville, MD 20850

RE: October 11, 2007 Circulatory Device Panel Meeting Regarding  
Clinical Trial Designs for Carotid Artery Stenting in Patients not at  
High Risk

Dear Mr. Swink:

On behalf of the 2,300 members of the Society for Vascular Surgery (SVS), we offer the following written comments for consideration at the October 11, 2007 meeting of the Circulatory Device Panel Meeting regarding current and future clinical trial designs for carotid artery stenting in patients not at high risk for adverse events from surgical revascularization.

Stroke is the third highest cause of death in the United States. There are 700,000 new strokes and approximately 150,000 stroke-related deaths each year. Although some stroke victims recover fully and resume normal life activities, many others suffer severe and unrecoverable brain injury that terminates their independent existence. Approximately one-third of all strokes result from carotid bifurcation atherosclerosis. Individuals with severe asymptomatic carotid artery stenosis face a natural history stroke risk of approximately 12% over five years, while patients with severe stenosis plus lateralizing transient neurologic deficits have a vastly more ominous outlook. Therefore, SVS first recommendation is that all future study designs recognize the marked difference in natural history between asymptomatic and symptomatic individuals with research protocols that separate and control for these two disparate groups prospectively.

SVS is invested in and supportive of the new minimally invasive CAS therapy, as evidenced by original research and peer-reviewed publications on CAS by vascular surgeons and SVS members. Nevertheless, CAS must evolve in the setting of one proven effective therapy, carotid endarterectomy (CEA), and the possibility that medical therapy for this disorder may be improving. It is important to note that CEA was not always safe and effective, but with investigative focus plus simultaneous improvements in patient selection, surgical technique and perioperative care, CEA now

has broad population (symptomatic plus asymptomatic) peri-procedural stroke/death rates in the 1.5-3.5% range.<sup>1,2</sup> Using this history of CEA as a lesson, SVS supports evidence-based deployment of CAS technology, and the question is how best to develop the evidence. CAS currently holds a broad-label FDA approval in high-surgical-risk patients, but CMS coverage is restricted. SVS second suggestion, therefore, is that as a general goal, CAS studies going forward in standard-surgical-risk patients would be designed to suffice for both FDA approval and CMS coverage.

Must all CAS studies be RCTs? SVS acknowledges the undeniable importance of randomized controlled trials. Well designed RCTs provide the most powerful level 1 evidence for clinical efficacy compared to existing therapy. CREST and ACT1 currently represent active RCTs that address CAS efficacy in standard risk patients. SVS recommends that alternative study designs approved by FDA should avoid interfering with recruitment for these and any other new CAS-related RCTs. Protocols written for alternative research designs may be written such that RCT eligibility constitutes an exclusion criterion for the non-RCT studies.

Despite our strong support for RCTs, SVS notes that there are disadvantages associated with RCT design, and other trial methodologies should be considered to provide valid scientific answers to questions that will never be addressed by RCTs. RCTs are slow to recruit, and populations are shaped and focused by rigid inclusion and exclusion criteria. The expense and manpower requirements of RCTs limit the number and size of studies that can be undertaken. The criticism that RCT results bear little relationship to “real-world” outcomes is an overstatement, but there is concern that outcomes across the Medicare population may vary from RCT results where providers are highly experienced and subjects may be carefully chosen. As our third recommendation, SVS urges the FDA to approach alternative study designs with special care to avoid devaluation of ongoing RCTs in respect of the patients, investigators and sponsors of these important resource-intensive studies.

In future study designs for CAS in standard surgical risk carotid disease patients, SVS recommends that strong consideration be given to the use of specialty-society based CAS registries in study designs. The SVS Vascular Registry (SVS VR) for CAS and CEA is a sophisticated web-based data collection tool that provides real-time collection with sufficient detail to allow completely risk-adjusted data analysis. The SVS VR is straightforward in use. SVS VR has been endorsed by other specialty societies, has a broad-based steering committee, uses a fully independent and well-respected data engine (New England Research Institute), and is reasonably inexpensive. SVS realizes that at least one other specialty-society based registry has CAS and CEA data collection ability, and it may be that multiple data engines could be used in parallel for real-world studies of CAS compared to CEA in standard risk patients. Thus, as a final recommendation, SVS suggests strong consideration be given to use of existing, highly functional CAS/CEA registries in upcoming studies. This concept will be developed in more detail at the October 11<sup>th</sup> FDA Panel meeting.

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SVS appreciates the opportunity to submit these comments and looks forward to working with the Circulatory Device Panel and the FDA to implement these recommendations. Please feel free to contact Pam Phillips, Director of Health Policy and Government Relations at 703-573-7894 or PPhillips@vascularsociety.org, if we can provide further information.

Yours truly,

*Robert M. Zwolak, M.D.*

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Chair, Health Policy Committee

Society for Vascular Surgery

1. Matsen SL, Chang DC, Perler BA, Roseborough GS, Williams GM. Trends in the in-hospital stroke rate following carotid endarterectomy in California and Maryland. *J Vasc Surg.* Sep 2006;44(3):488-495.
2. Stoner MC, Abbott WM, Wong DR, et al. Defining the high-risk patient for carotid endarterectomy: an analysis of the prospective National Surgical Quality Improvement Program database. *J Vasc Surg.* Feb 2006;43(2):285-295; discussion 295-286.