



**Public Comments to the FDA Circulatory System  
Devices Panel**

**On**

**Clinical Trial Design Issues For Carotid Artery Stents  
Intended To Reopen Stenotic Carotid Arteries In The Neck**

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## **INTRODUCTION**

I am Christopher White, MD, FACC, FSCAI and I am representing the American College of Cardiology and the Society for Cardiovascular Angiography and Interventions. I am also the Chairman of the Department of Cardiology at the Ochsner Clinic Foundation, in New Orleans. And I recently completed my term of service on the Circulatory Systems Device Panel. We appreciate this opportunity to present recommendations to the panel, look forward to this discussion and would be pleased to receive comments or questions from the panel.

The ACC is a 34,000 member non-profit professional medical society and teaching institution whose purpose is to advocate for quality cardiovascular care through education, research promotion, development and application of standards and guidelines- and to influence health care policy. The College represents more than 90 percent of the cardiologists practicing in the United States.

The Society for Cardiovascular Angiography and Interventions (SCAI) is a professional association representing over 3,800 invasive and interventional cardiologists. SCAI promotes excellence in cardiac catheterization, angiography, and interventional cardiology through physician education and representation, and quality initiatives to enhance patient care.

## **STUDY DESIGN**

I believe the question the FDA is asking the panel is what is the appropriate study design(s) needed for approval of carotid artery stenting (CAS) (with emboli protection) in asymptomatic and symptomatic average surgical risk patients. Maybe phrased another way, is a study design other than a randomized trial sufficient to support this approval.

1. For peripheral vascular devices, the FDA has accepted the use of performance goals and objective performance criteria (OPC) in non-randomized trial designs for the major peripheral vascular beds: high surgical risk carotid stent registries, iliac, renal and SFA stenting.
2. The FDA established a precedent for endovascular procedures as alternatives for open surgery in approving AAA stent-grafts (Gore, Medtronic, and Guidant devices) as safe and effective based upon concurrent control, non-randomized trial designs.

## **RISK-BASED DIFFERENCES**

Are average or low surgical risk carotid disease patients unique in some way? There is no apparent reason to require randomized trials in average surgical risk patients with obstructive carotid artery disease. They do not represent unique issues or subsets of the population that would require a randomized control trial can produce data needed to determine safety and efficacy.

1. In contrast to other peripheral vascular beds, there are published expert consensus criteria (by medicine/neurology and surgery) based upon randomized control trial data for

threshold 30-day complication rates (asymptomatic  $\leq 3\%$  and symptomatic  $\leq 6\%$ ) for carotid endarterectomy (CEA).

2. One example, based upon the precedents set for single arm registry trials with the use of OPC's, a viable option for CAS approval in asymptomatic average surgical risk patients would be to conduct a trial using enrollment criteria similar to the Asymptomatic Carotid Atherosclerosis Study (ACAS)

3. ACAS was the basis for the 3%-rule, the 30-day acceptable target for CEA complications, in asymptomatic average risk patients. If a CAS non-randomized study, matching the patient population from ACAS produced a 30-day stroke and death rate statistically within the boundaries of the ACAS data ( $\leq 3\%$ ), then CAS should be considered safe and effective and approved therapy in this population of patients.

### **ALTERNATIVE STUDY DESIGNS**

A non-randomized concurrent control trial for average surgical risk patients with obstructive carotid artery disease is more rigorous than an uncontrolled single arm registry trial. Similar to the AAA stent-graft trials, the non-randomized control group provides a comparison to standard of care therapy.

1. There are statistical adjustments that can be made if some key patient or lesion characteristics were not balanced between the two groups.
2. This trial design also assures equal application of event definitions, adjudication of events, data collection, etc. The main risk with this design is the potential for a significant imbalance of one or more patient characteristics between the two groups. However, again this is a risk the company assumes if they use this design, as they have done with AAA stent-grafts.

### **ADDITIONAL CHALLENGES**

It is important that the study design question is not confused with other challenges that have been raised about requirements for approval of average surgical risk CAS. That is, current day best medical therapy (BMT) comparison and three arm randomized trials comparing CEA, CAS and BMT.

1. While there may be benefit medically of refreshing the BMT and CEA data, this is beyond the scope needed for approval of a device.
2. Nor should a possible CMS requirement for randomized data to assess reimbursement be automatically carried over by FDA for a device approval. FDA is interested in safety and efficacy while CMS is interested in necessary and reasonable.

### **POTENTIAL EFFECTS ON RANDOMIZED CONTROLLED TRIALS**

An argument can be made that less restrictive, non-randomized trial designs could potentially cannibalize patients and prevent current ongoing randomized trials (CREST, ACT-1) from finishing.

1. To protect the randomized trials, the non-randomized trials would exclude any patient who was a candidate to enter a randomized controlled trial. This strategy was employed in the CARESS Phase One cohort controlled trial.
2. The rapidity of enrollment in non-randomized trials would have the benefit of completing a trial with a single generation of equipment and a stable level of operator experience. The evolution of equipment and expertise over time makes some of these  $\geq 5$  year duration randomized trials difficult to interpret.
3. Randomized patients may not be representative of patients in our clinical practices, just as ACAS and NASCET are not representative of everyday CEA patients treated in our hospitals today. Non-randomized trials would be relevant to “real-world” patients. Randomized trials represent highly selected patient populations, which can answer specific questions. Less restrictive trials generate data that is useful and perhaps applicable to wider population of patients.
4. Non-randomized trials are less expensive, and would encourage more trials to be conducted ultimately contributing to more clinical data collected.

### **CONCLUSION**

We hope the panel will carefully consider these recommendations and we would be pleased to work with the FDA to improve the treatment of patients with carotid stenosis.