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September 26, 2007

Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, MD 20850

Re: Trial Designs for Carotid Artery Stenting

Dear Sir/Madam:

On behalf of the American Heart Association (AHA), including the American Stroke Association (ASA) and over 22.5 million AHA and ASA volunteers and supporters, we appreciate the opportunity to submit comments to the Food and Drug Administration (FDA) on clinical trial designs for carotid artery stenting in patients not at high risk for adverse events from surgical revascularization.

Since 1924, the American Heart Association has dedicated itself to reducing disability and death from cardiovascular disease and stroke–the #1 and #3 leading causes of death in the United States – through research, education, community-based programs, and advocacy. AHA is also a leader in analysis of available data documenting the absolute and relative risks of procedures and therapies. As part of this effort, the Association produces evidence-based clinical guidelines and scientific statements designed to raise awareness of and advise physicians and other providers regarding the prevention, treatment, and management of cardiovascular disease and stroke. AHA and ASA are committed to achieving a reduction in cardiovascular disease, stroke, and associated risk by 25% by 2010.

AHA appreciates the Agency's decision to examine clinical trial designs for carotid artery stenting. In recent years, carotid artery stenting has become an increasingly common treatment for carotid artery stenosis, particularly in patients at high risk for carotid endarterectomy (CEA) surgery. And while several systems have been approved by FDA for patients at high risk for CEA – and Medicare currently covers carotid artery stenting in a few high risk patient populations–there is no FDA-approved carotid artery stenting system for patients at conventional risk.

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In order for the FDA, payors, and health care providers to evaluate the use of carotid artery stenting in conventional risk patients and determine if stenting improves outcomes or is the appropriate treatment for this patient population, we must have sufficient clinical data from well-designed trials. In general, AHA advocates for the use of randomized clinical trials – the gold standard in studies – as the preferred method to obtain scientific evidence, especially for important clinical questions such as this. However, we acknowledge that there may be situations where it is difficult to obtain data through the use of a randomized clinical trial, and in these situations it may be appropriate to consider alternative methods of data collection. Nevertheless, regardless of the study design, there are certain elements that must be considered in any study or clinical trial. We expand upon these comments below.

Existing Trials of Carotid Artery Stenting

AHA is aware of several ongoing clinical trials involving low or conventional risk cohorts of patients that are being enrolled into randomized controlled clinical trials comparing carotid artery stenting vs. carotid endarterectomy. Most notably, the CREST (Carotid Revascularization Endarterectomy vs. Stenting Trial), is a Phase III study being funded by the National Institutes of Health which is enrolling conventional risk NASCET (North American Symptomatic Carotid Endarterectomy Trial) eligible patients with a >50% carotid artery symptomatic stenosis, and asymptomatic patients with a >60% stenosis. This is an "equivalency trial", which has currently enrolled >2000 patients (combined symptomatic and asymptomatic), with a total anticipated enrollment of 2500 patients, and should be completed within the next 12-18 months. A second randomized controlled clinical trial involving recruitment of only asymptomatic patients with carotid artery stenosis, the ACT (Asymptomatic Carotid Stenosis Stenting vs. Endarterectomy Trial), sponsored by Abbott Vascular, Inc., is also in progress. This trial has enrolled >400 patients out of a total enrollment of 1700 patients, to directly compare outcome measures between carotid artery stenting vs. endarterectomy. A third study in progress in Europe is comparing carotid artery stenting vs. "best medical treatment of asymptomatic high grade carotid artery stenosis >80%," over a 2 year time period, sponsored by Vienna General Hospital, Austria, and is seeking to enroll 300 patients. The primary hypothesis is that due to the low frequency of neurological complications (approximately 2% a year) in asymptomatic patients, the preferred treatment modality is currently unknown. Modern best medical treatment may manage to stabilize the atherosclerotic plaque, while carotid stenting has the potential of resolving the carotid stenosis.

All of these trials, which are controlled and randomized between either carotid artery stenting, carotid artery surgery, and/or best medical therapy, are likely to provide important information about the efficacy of carotid artery stenting in patients considered for carotid artery revascularization.

Randomized Controlled Trials and Alternative Trial Designs

AHA wishes to reaffirm its position regarding the seminal importance of randomized controlled trials. A well-designed randomized controlled trial will provide the most powerful level 1 evidence for clinical efficacy compared to existing therapy. The criticism that randomized controlled trial results bear little relationship to "real-world" outcomes is an overstatement, but there is concern that outcomes across the Medicare population may vary from randomized

controlled trial results where providers are highly experienced and subjects may be carefully chosen. In this regard, CREST and ACT-1 constitute the active randomized controlled trials of which we are aware that address the question of carotid artery stenting efficacy in customary risk patients. The former includes both symptomatic and asymptomatic patients, while the latter is limited to asymptomatic subjects. It is our position that alternative study designs approved by the FDA should avoid interfering with recruitment for these, or any other carotid artery stent-related randomized controlled trial. We urge the Agency to approach alternative study designs with special care to avoid devaluation of ongoing randomized controlled trials in consideration of the patients, investigators and sponsors of these important resource-intensive studies.

Thus, having issued these words of support for randomized controlled trials, AHA realizes there are some disadvantages to the randomized controlled trial design and therefore opportunities for other trial methodologies to provide valid scientific evidence. While conventional trials with patient-level randomization have substantial scientific advantages, we recognize that performing such a trial for carotid procedures is a particular challenge. Randomized controlled trials are traditionally slow to recruit, and populations are shaped and focused by rigid inclusion and exclusion criteria. The expense and manpower requirements of randomized controlled trials limit the number and size of studies that can be undertaken. Among the difficulties encountered in the conduct of randomized controlled trials are recruitment of a representative group of patients and centers, a learning curve associated with use of various procedures and devices, rapid evolution of technology, and changing natural history of disease (e.g., due to improvements in medical therapy of risk factors.) Accordingly, we believe it is reasonable to consider alternative research designs that offer timely and scientifically credible results. This could include cohort studies paired with randomized controlled trials (with appropriate propensity or risk adjustment), comparisons with historic controls, merging patient-level results from multiple trials, or other methods acknowledgeably less rigorous than randomized trials. In addition, alternative randomized trial designs should be used to speed decisions, including adaptive designs (to the extent they can be shown to improve trial efficiency) or Bayesian techniques (with acknowledgement of the potential bias in their use in Phase III trials).

Desired Elements of a Carotid Artery Stenting Trial

Previous randomized trials have included patients considered to be at high risk for carotid endarterectomy. Anatomical and comorbid factors that characterize high surgical risk patients as defined by FDA and CMS formed the basis for FDA panel approval of carotid artery stenting, and subsequent full CMS reimbursement for symptomatic high risk patients, as well as reimbursement for asymptomatic high risk patients for patients enrolled in post-market surveillance registry trials. AHA recognizes the importance of distinguishing between patients with these previously defined high risk parameters and the large group of patients who do not have such characteristics. Patients who do not have any of the anatomic or comorbid characteristics of the high surgical risk groups are considered to be at “low or conventional” risk for carotid endarterectomy and constitute the subject of this letter. The conventional risk cohort would include symptomatic and asymptomatic subjects with atherosclerotic extracranial internal carotid stenosis, determined to be $\geq$70% and $\leq$99% stenosis by duplex ultrasound or by angiography, with or without involvement of the contiguous common artery. Specific cohorts that could be studied include both those under and over 80 years of age, who are considered

eligible and reasonable risk for carotid endarterectomy. In order to be considered for randomization between two therapies, the patient must be deemed eligible for both, with clinical equipoise based on available evidence

The outcome measures are a critical component of any trial. Study endpoints necessarily will depend on the specific trial design and population under investigation. In general, however, AHA recommends that the clinical trials evaluating carotid artery stenting in low surgical risk subjects with carotid artery stenoses consider the following endpoints: total stroke, ipsilateral stroke, myocardial infarction, and all-cause mortality. The length of study follow-up and timing in which endpoints are determined will also vary by study. Important time-points for most study designs will be 30-days and one-year. Longer follow-up times would be appropriate in trials that include a medical management arm. In such studies, two-year follow-up for those involving symptomatic carotid artery stenoses, and five-year follow-up for those involving asymptomatic disease is prudent, as has been done in prior studies of carotid endarterectomy.

Concluding Remarks

In conclusion, we appreciate the Agency's decision to examine clinical trial design for carotid artery stenting in patients not at high risk for surgical revascularization. Ideally, randomized control trials will provide the highest level of evidence and we encourage enrollment in the CREST and ACT-1 trials. However, we support consideration of alternative trial designs to gather additional evidence regarding the efficacy of carotid artery stenting in a timely and cost efficient manner.

If you have any questions or need any additional information, please do not hesitate to contact Susan Bishop, MA, Regulatory Relations Manager, at 202-785-7908 or via email at susan.k.bishop@heart.org.

Sincerely,

Daniel W. Jones, MD
President, AHA

Mark A. Creager, MD
Member, AHA Board of Directors