

## **Trial Design Issues Associated with Evaluation of Distal Protection Devices in Diseased Saphenous Vein Grafts**

### **I. Introduction**

Coronary artery bypass surgery (CABG) is an important treatment option for patients with significant ischemic heart disease. The surgical option, however, is not a permanent fix because there is 1) continued progression of atherosclerosis in the native coronary arteries and 2) progressive attrition of saphenous vein graft patency. Advancement of disease in native coronary arteries occurs in approximately 4% of patients annually during the first 10 years post-CABG.<sup>1</sup> Saphenous vein graft (SVG) attrition is approximately 7% during the first week even with aspirin therapy, 15 – 20% during the first year, 1% to 2% from 1 to 6 years, and 4% per year from 6 to 10 years after surgery.<sup>2-6</sup> Although it is clear that arterial grafts are superior, the limited number of arterial anastomoses that are possible mandates continued heavy use of venous conduits.

Deterioration of native vessel and graft lumens after surgery has resulted in an increasing need for repeat revascularization procedures. Surgical reoperation is associated with a higher mortality and morbidity than the initial procedure. Hence, percutaneous treatment of symptomatic vein graft disease is often a preferred initial treatment strategy. Unlike native coronary artery disease due to fibrous or calcified plaques, vein graft narrowings often contain thrombotic and degenerative material that is easily disrupted by catheter-based therapies. The dislodgement of material downstream during a SVG procedure is associated with a relatively high incidence of death and myocardial infarction when compared to percutaneous treatment of other lesion subsets. It has been hypothesized that distal protection may significantly reduce complication rates by collection of dislodged material that would otherwise embolize downstream during the interventional procedure.

The Agency acknowledges that development of safe and effective distal protection devices for use in diseased saphenous vein grafts is currently an important research area in interventional cardiology. To this end the Division of Cardiovascular and Respiratory Devices (DCRD) is seeking input on several issues regarding study design in this area. A series of questions has been formulated to help guide the discussion.

Please note that in several of the questions that follow, a composite endpoint of Major Adverse Cardiac Events (MACE) is used. MACE is defined by death, Q wave or non-Q wave myocardial infarction, emergent bypass surgery, or repeat percutaneous target vessel revascularization.

## **II. Questions**

### **Control Group**

1. A wide range of procedure success and complication rates has been reported in the SVG literature.<sup>7-29</sup> Part of the variability can be explained by assessment of graft age, lesion length, and thrombus burden. Risk is known to increase with older grafts, longer lesions, and grafts with a large thrombus burden. Other key factors that lead to a high probability of distal embolization of material with resulting myocardial infarction, death, or emergent CABG remain incompletely understood.
  - a. Given our current understanding of vein graft disease, please discuss the need for a randomized trial design when evaluating a new distal protection device for SVG use. When is a randomized trial necessary to ensure comparison to an appropriate control group?
  - b. Please discuss whether adequate trials can be designed with historical controls or objective performance criteria for assessment of this technology.
  - c. If a randomized trial is warranted, please discuss whether the control arm should incorporate use of an approved distal protection device. If so, please discuss use of an equivalence hypothesis, rather than a superiority hypothesis, for this study.

### **Study Endpoints**

2. Please discuss use of the 30-day MACE rate as the primary endpoint in a SVG distal protection device trial. Please discuss whether use of this composite endpoint adequately captures important clinical events. Please discuss whether an in-hospital or 14 day MACE rate would be acceptable as a primary endpoint. Please discuss any alternatives to MACE that would be important to consider.
3. Please discuss what secondary endpoints should be emphasized in a SVG distal protection device trial. For example, should a pathological description of the type and amount of debris removed by the device be included?

### **Study Protocol Issues**

4. Please comment on appropriate entry criteria for a SVG trial that is intended to evaluate a new distal protection device. Please discuss any special patient populations that should be excluded or studied separately.

5. Please comment on use of adjunctive antithrombotic medications. Please discuss, for example, whether Glycoprotein IIb/IIIa drug use should be left to operator discretion or be prospectively outlined in the protocol.

### **III. References**

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