Carotid stenting in high-risk patients: Design and rationale of the SAPPHIRE trial

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Carotid endarterectomy (CEA) was first proposed as a treatment for preventing stroke by C. Miller Fisher in the 1950s, and CEA was first performed in 1954 by Debakey in the United States and by Eastcott in England. Forty years were to pass, however, before there was any evidence that CEA was beneficial. The publication of the North American Symptomatic Carotid Endarterectomy Trial (NASCET) in 1991 provided the first definitive proof of the utility of endarterectomy in preventing stroke. Carotid artery stenting was first performed in 1994, and with the completion of the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial in 2002, we had clear evidence that in selected patient groups protected carotid stenting was superior to CEA.

RATIONALE FOR SAPPHIRE'S HIGH-RISK FOCUS

The SAPPHIRE trial focused on patients at potentially increased surgical risk for several reasons. At the time of the trial's design, clinical equipoise did not exist, particularly in the surgical and neurologic communities, for the randomization of low-surgical-risk patients to an interventional treatment.[1,2] Although patients with the types of comorbid conditions included in the SAPPHIRE trial were frequently excluded from the previous major randomized trials of CEA, they do frequently require and undergo CEA. Indeed, they appear to represent the majority of patients undergoing CEA, and concerns have been raised about the generalizability of the CEA trial results in view of the degree of patient selection.[3]

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In a large study of more than 100,000 Medicare patients undergoing CEA, Wennberg et al[4] found that perioperative mortality at hospitals that had participated in NASCET and the Asymptomatic Carotid Atherosclerosis Study (ACAS) was 1.4%. Because mortality was 0.6% in NASCET and only 0 to 1% in ACAS, the authors concluded that the trials were not representative of the patients being routinely treated with CEA. In a recent review of Medicare patients in Ohio undergoing CEA, 1 in 6 was over 80 years of age and would have been excluded from both NASCET and ACAS.[5] In the Cleveland Clinic prospective surgical registry of more than 3,000 CEA cases, the rate of perioperative death, stroke, or myocardial infarction (MI) was 7.4% for patients in the high-risk group compared with 2.9% for those in the low-risk group.[2] The authors concluded that the "initial clinical evaluation of carotid stenting might best be undertaken in such a high-risk population, one that comprises patients for whom standard therapy is associated with a high rate of complications."[2]

STUDY DESIGN AND ENROLLMENT CRITERIA

The SAPPHIRE trial was a randomized study comparing carotid stenting with the AngioGuard embolic protection device to CEA in patients at increased risk for carotid surgery. The trial was conducted at 29 US centers, all of which were carefully screened by the executive committee, and surgeons and interventionalists were required to submit experience and results. For surgeons the median annual number of endarterectomies was 30 (range, 15 to 100). The mean stroke, death, or MI complication rate was less than 3%. For interventionalists the median total number of carotid stent procedures performed was 64 (range, 20 to 700) and the mean stroke, death, or MI complication rate was 4%.

To be enrolled, patients had to have 50% or greater stenosis by ultrasonography if they were

TABLE 1
Comorbidity criteria for SAPPHIRE trial enrollment

Congestive heart failure (NYHA class III or IV)
Left ventricular ejection fraction < 30%
Need for open heart surgery within 6 weeks
Recent myocardial infarction
Unstable angina
Severe pulmonary disease
Contralateral carotid occlusion
Contralateral laryngeal nerve palsy
Radiation therapy of the neck
Radical neck surgery
Previous endarterectomy with recurrent stenosis
High cervical ICA lesions or CCA lesions below the clavicle
Severe tandem lesions
Age > 80 years

NYHA = New York Heart Association; ICA = internal carotid artery; CCA = common carotid artery

symptomatic or 80% or greater stenosis if they were asymptomatic, as well as meet one or more comorbidity criteria, listed in **Table 1**, that placed them at increased risk for surgery.

All patients were seen by a team made up of a neurologist, a surgeon, and an interventionalist. Randomization required consensus of the entire team. If the surgeon felt that he or she could not operate, and the interventionalist felt that intervention was possible, the patient was entered into a stent registry. Conversely, if the interventionalist did not feel that he or she could perform the intervention, and the surgeon felt that surgery was possible, the patient was entered into a surgical registry.

Patients were randomized on the basis of ultrasonography, and the surgical patients did not undergo angiography.

The primary end points are a composite of death, any stroke, or MI 30 days after the procedure, as well as ipsilateral stroke or death 1 year after the procedure. There are multiple secondary end points, including restenosis rates, technical procedural success, quality of life, and economic outcomes.

ENROLLMENT DATA AND PATIENT CHARACTERISTICS

A total of 723 patients were enrolled in the trial. The registry arm was completed in February 2002 with 409 patients entered in the stent registry and 7 patients entered in the surgical registry. The randomized arm was stopped in June 2002 with a total of 307 patients entered (156 randomized to stenting and 151 randomized to CEA).

In the randomized trial, the mean patient age was 72, and one third of patients were symptomatic. There was a high prevalence of coronary artery disease, previous bypass surgery, and previous endarterectomy. The patients entered into the stent registry had a higher incidence f radiation treatment, previous endarterectomy, high or low lesions, and presence of more than one high-risk criterion as compared with the patients entered into the randomized study.

Publication of clinical outcomes of the SAPPHIRE trial will be forthcoming.

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