Limitations to the Value of the SAPPHIRE Trial

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The SAPPHIRE trial has become the "jewel in the crown" of those who are in favor of carotid angioplasty and stenting (CAS). They say that scientific proof now exists to show that this treatment should now be offered to all high-risk patients with carotid artery stenosis. Because the trial was passed by the US Food and Drug Administration (FDA) and published in the New England Journal of Medicine it must be OK; therefore, no other trials are needed—let us just go ahead and treat everyone with carotid stenosis using CAS. This view of course exaggerates the facts and instead diminishes one's faith in the FDA and the New England Journal of Medicine.This trial should be shown to every undergraduate as an example of how not to do a trial.

First and foremost, a trial should not be biased toward either treatment being assessed. A good starting point is to have neutral financing and the total involvement of participants who are uncertain which is the best treatment. The essential ingredient for the organizers of such a trial is that they must be uncertain about the efficacy of the new intervention as opposed to the competing treatment and have no vested interest in the outcome. Level I trials, which this purports to be, should have unbiased randomization with a low false-positive or -negative rate. In this trial, there had to be a "consensus" before patients were randomized; fair enough, but what criteria were used to include or exclude a patient? What do we then find? Four hundred nine patients were placed in a CAS registry and 7 in a surgical registry, and 307 were finally randomized. Repeated attempts at trying to find out why 409 patients were left out of a so-called randomized trial bring forth the answer "because the surgeons felt they were inoperable or too difficult to operate on." Really, who are these surgeons? Most of those I have spoken to have great difficulty in finding anyone who could not be operated on except for very high lesions or patients with a string sign. We do not know, as no details have been given, which is unacceptable. Next, we have the inclusion criteria that state that in order to enter, all patients must be high risk. High risk for what? Probably high risk for myocardial infarction. "High risk" was defined as patients with at least one of the following: contralateral carotid occlusion, radiation therapy to the neck, previous CEA with recurrent stenosis, difficult surgical access, contralateral laryngeal nerve palsy, severe tandem lesions, heart failure, CABG or open heart surgery within 6 weeks, myocardial infarction 1 day to 4 weeks prior to treatment, unstable angina or angina at low workloads, severe (?) pulmonary disease, or age > 80 years. Many of the patients I normally operate on fall into this so-called high-risk category. All of them can be operated on using a variety of well-known strategies such as local anesthesia, and they would not be regarded as high risk by many outside this trial.

The outcome of a trial will depend on the end points chosen. The end points chosen here were biased against CEA. The usual hard end points of a carotid treatment trial are stroke and death. In this trial, myocardial infarction was included as an end point for a group of patients who are known to be prone to this complication because of general anesthesia. Just to bias things further, the infarction could be clinically silent and only detectable by biochemical tests. If myocardial infarction is omitted, there is no difference between CAS and CEA at 30 days.

This brings up another point. The risk, at 30 days, of stroke and death after CEA was 6.1%. One has to ask how experienced the surgeons were when an international randomized trial of several thousand patients (ACST) published recently showed a 30-day stroke and death rate of half of this figure at 3.1% with appropriate neurologic monitoring. The answer is that 50% of the surgeons in the SAPPHIRE trial did less than 30 CEAs a year and were therefore relatively inexperienced—another bias toward CAS.

Almost 70% of the patients in this trial were asymptomatic. We know for these patients that the 30-day death and stroke rate should be no more than 3%. Patients in this trial have therefore been needlessly exposed to an excess 3.1% stroke and death rate that they would not have had if they had been left alone. This means that in this trial, around six patients died or had a stroke for no reason at all. On this basis, one has to doubt the conclusion that CAS is equivalent to surgery for the treatment of so-called high-risk patients. If this is the result in the hands of experts, one can only feel sorry for the great majority of patients when CAS is used on them by the relatively inexperienced practitioner.

As Perler said, "Extrapolating and misrepresenting trial data for marketing purposes is dangerous." This trial is flawed in so many ways that the results are of practically no use to the practicing doctor. The ideal trial should have few exclusions, treat either symptomatic or asymptomatic patients separately, and be run by totally neutral investigators without a vested interest and neutral funding. The end points should be hard and not biased toward either treatment. Investigators should have a track record and be experienced. Only then will we have the data we need to offer our patients the best treatment be it CAS or CEA. For all of these reasons, the SAPPHIRE trial is of very little value in offering guidance in the treatment of our patients and should not be quoted as a landmark study.