Randomized trials in coronary bypass surgery

THOMAS KILLIP, M.D., AND THOMAS J. RYAN, M.D.

CORONARY artery bypass grafting is an effective treatment for increasing myocardial blood flow in selected patients with coronary artery disease. After this procedure, symptoms improve, coronary blood flow to the affected area is increased, and exercise tolerance is enhanced.1 In patients who have received maximal drug therapy and yet remain intolerably symptomatic, bypass surgery clearly adds a brilliant therapeutic advantage, at least for a few years.

More than a year has elapsed since the initial results of the Coronary Artery Surgery Study (CASS) randomized trial were published in Circulation.2,3 providing ample time for the medical community to assimilate the data collected from the 6 year follow-up of the 780 patients with proven coronary artery disease who were randomly assigned to either continued medical therapy or coronary bypass surgery on entry to the study that began recruitment in August 1975. Extensive follow-up data from the two other large randomized trials are now available, so that it should be possible to identify quite precisely what unanswered questions remain regarding the effectiveness of the operation. Does coronary artery bypass prolong life over the long term? Does it affect the rate of subsequent myocardial infarction? Are there clearly defined subsets among patients with chronic stable ischemic heart disease who may uniquely benefit from operation?

When the primary end point of all-cause mortality in CASS was examined for the entire population equally and randomly assigned to surgical or medical therapy, cumulative survival after 6 years was 92% and 90%, respectively. These data permit the conclusion that there is no statistically significant survival advantage in embarking on prompt bypass surgery for patients with coronary disease similar to those in the CASS randomized population, although it is recognized that important differences in outcome in carefully defined subgroups may be hidden in analysis of the population as a whole. Such a conclusion is consonant with the findings of the Veterans Administration Cooperative Study.4 Of course, in discussing VA data, we are referring to patients without left main disease and to the results from all the participating sites. It has been suggested by some that the VA data should be presented only after eliminating participating clinics that randomized few patients and had high operative mortality. However, such an ex post facto adjustment breaks the integrity of a randomized trial and is scientifically invalid. One could reasonably ask why not eliminate the centers with the highest medical mortality, thus generating a bias favoring the medical outcome.

The final report of the European Coronary Surgery Study (ECSS), published 1 year before the CASS results, had different conclusions.5,6 In a randomized trial of 767 patients, there was a highly significant advantage in survival rate for patients randomized to surgical therapy after 5 years of follow-up (surgery 92.4%, medical 83.6%; p = .00025). Retrospective stratification of patients in the ECSS showed that the greatest advantage in survival occurred in patients with three-vessel coronary disease and those patients with two-vessel disease in whom the proximal portion of the left anterior descending coronary artery was involved. However, presence of proximal left anterior descending disease was not a predictor of prognosis when lumen reduction of 75% rather than 50% was used as a criterion for significant disease. Within the ECSS population, a number of prognostic variables were independent predictors of outcome and included the presence of peripheral arterial disease, marked ST segment depression on an exercise electrocardiogram, abnormal resting electrocardiogram, and increasing age. For all of these high-risk subgroups, surgical therapy resulted in a significantly better outcome than with continued medical therapy.

The VA trial demonstrated a significant advantage in favor of surgery in patients with left main coronary artery disease,7 a finding that was strongly supported by ECSS results. However, after 5 years of follow-up, a statistically significant difference was not achieved. In the VA trial survival was improved significantly in a high-risk tercile selected on the basis of New York Heart Association classification, history of myocardial
infarction, history of hypertension and resting ST segment abnormality on the electrocardiogram.

By study design, the CASS randomized cohort was prospectively stratified according to the number of vessels diseased as well as to ventricular function. A definite trend favoring surgical therapy was found in this study in patients with three-vessel disease and reduced ejection fraction. Because the number of patients in this subgroup followed a full 5 years was comparatively small, the statistical power of observation was low and the results were interpreted cautiously. That continued follow-up of this important subgroup might show an advantage in favor of surgery was suggested by the improved survival for the medically assigned patients in CASS who had normal ventricular function compared with the medically assigned patients who had impaired ventricular function after 5 years (95% vs 84%; p = .0001). Survival for patients in the surgical group who had impaired ventricular function compared with those with normal ventricular function was not significantly different. Recent analysis with an additional 14 months of follow-up presented at an NHLBI workshop showed a statistically significant survival advantage in favor of surgical assignment (p < .01) for those patients with three-vessel disease and impaired ventricular function. Noteworthy is the observation that the survival curves for the medically and surgically assigned patients with three-vessel disease and normal ventricular function are identical over 5 years. It is quite certain that this subgroup with three-vessel disease and normal ventricular function will not show an advantage for surgical therapy with continued follow-up.

A unique aspect of the CASS trial is the follow-up data on 1315 additional patients who qualified for randomization but who chose not to be randomized.9 Referred to as "randomizable" patients, these individuals received either medical treatment or coronary bypass surgery based on the recommendation of their treating physicians and were not part of the randomized assignment. The survival curves of the medically treated randomizable patients were superimposable on the medically assigned randomized survival curves in all analyses that were performed. Similarly, survival curves of the randomizable patients who underwent bypass surgery were superimposable on the survival curves of the surgically assigned randomized patients. The point thus seems well made that the randomized patients in CASS are not a special subset of those eligible for randomization but are truly representative of all those who were potentially randomizable.

Neither the VA nor the CASS trials have shown a significant difference in mortality when all patients are grouped according to their original therapeutic assignments. Furthermore, the VA and CASS investigators observed no advantage between medical or surgical therapy in single-vessel disease. The excellent prognosis in patients with single-vessel disease has been confirmed by other studies.9 10 Similarly, in none of the three trials is there an improved survival for surgical therapy when the data from all patients with two-vessel disease are analyzed. It is apparent, therefore, that discussion of a possible survival advantage bestowed by bypass surgery should be focused on patients with three-vessel disease, and of course on those with hemodynamically critical left main obstruction.

All three studies have addressed the question of whether bypass surgery protects patients with coronary artery disease against the major hazard of myocardial infarction. The unanimous answer appears to be no.11 12 All have reported essentially similar infarction rates over several years of follow-up of patients assigned to medical or surgical therapy, with the appearance of new Q waves on the electrocardiogram used as the diagnostic criterion. The conclusion that bypass surgery does not protect from the subsequent risk of myocardial infarction is well supported from the data.

Results from the randomized trials do not directly answer questions about the duration of effectiveness of the procedure. However, recent reports from the VA trial provide important information.13 Throughout the follow-up in the VA study, there has been a trend favoring surgery, albeit not achieving statistical significance when patients with left main disease are eliminated from analysis. This difference reached its maximum after 7 years of follow-up. However, between 7 and 11 years after surgery, the rate of surgical mortality has accelerated and, at 11 years, the two survival curves have converged. This pattern has been observed both with and without including patients with left main disease. Since few internal mammary artery anastomoses were performed in the VA study, these observations suggest that the venous conduits may be failing after about 7 years.

Data from the Montreal Heart Institute also indicate accelerated deterioration of venous grafts 5 to 7 years after surgery. The mean graft closure rate was 1% between 1 and 6 years after surgery but increased threefold or fourfold during the following 5 to 6 years.14 These observations were recorded before recent results suggested improved graft patency in pa-

*Detre KM: Unpublished data from Veterans Administration Coronary Bypass Trial. Personal communication.
patients treated with antiplatelet-aggregation agents.\textsuperscript{15} The advantages of the internal mammary artery for bypass have been reviewed by others.\textsuperscript{16}

The effects of bypass on atherosclerotic disease in the native vessels have been studied by several groups.\textsuperscript{17, 18} Occlusive disease appears to progress rapidly in the proximal portion of the anastomosed coronary artery in many subjects. When repeat coronary arteriography is performed within a year, approximately 55\% of the proximal segments show progression of disease, a rate of progression fivefold greater than that in nonoperated vessels.

Recently Cashin et al.\textsuperscript{19} reported rapid progression of coronary obstruction after bypass grafting in coronary arteries with no or minimal (less than 30\% diameter reduction) atherosclerotic lesions. These observations on progression of disease in the native circulation after bypass surgery strongly emphasize, in our view, that indications for surgery in the individual patient should be scrutinized most carefully. Recurrent ischemia may persist if revascularization has been inadequate. Inappropriate bypass grafting to patent vessels may accelerate the rate of occlusion.

Although the primary aim of all three randomized trials has been the same — to determine whether assignment to medical or surgical therapy offers a significant advantage for long-term survival — there are both explicit and implicit differences among the trials. Recruitment periods of the three studies overlapped. The VA enrolled patients from 1972 to 1974, the ECSS from 1973 to 1976, and CASS from 1975 to 1979. The average age was similar in the three studies, 49 to 53 years. Only men were enrolled in the VA and ECSS studies, and 10\% of the CASS population were women. The angiographic definition of coronary artery disease was a 50\% diameter reduction in both the VA and ECSS, whereas CASS used a 70\% diameter reduction. This difference in angiographic severity of disease appears to have had little influence on the CASS findings, since reanalysis with a 50\% narrowing criterion did not change the study results. No study enrolled patients with unstable angina, although more than half of those in the VA trial had angina at rest. Subjects were required to have “severe” (most likely class III and probably some class IV) angina in the VA trial. In the ECSS, a retrospective analysis revealed 57\% of the patients had class I or II angina and 42\% had class III.\textsuperscript{20} CASS enrolled patients who had mild-to-moderate angina (less than class II) and was the only study to include patients without angina. Patients who were asymptomatic after a myocardial infarction represented 20\% of the CASS population.

Criteria for extent of abnormality in ventricular function varied in the three studies. About 70\% of the VA subjects had some impairment of ventricular function and 26\% had ejection fractions less than 0.45. The protocol for the ECSS required normal ventricular function and ejection fraction. However, since ejection fraction was estimated rather than measured in the early cases,\textsuperscript{*} it is quite likely that some patients had abnormal ventricular function. In CASS, 20\% of the patients had ejection fractions between 0.35 and 0.50.

Analysis of differences and similarities among the three trials is a task of great importance. It is highly unlikely that any further randomized trials of coronary bypass surgery will be performed. A task force representing the principal investigators from each study is working to examine the three trials in detail to strengthen common conclusions.

Despite some obvious differences in study populations, the time frame of the investigation, differing medical and surgical mortality, number of grafts anastomosed, and some likely differences in medical management after randomization, certain conclusions seem warranted from the large body of data available:

1. Effective coronary bypass surgery improves survival in patients with hemodynamically significant left main disease.

2. Bypass surgery does not protect from the risk of subsequent myocardial infarction.

3. Bypass surgery appears to offer a survival advantage in high-risk patients with three-vessel disease and reduced ventricular function. Other criteria for high risk, such as those identified by the VA third tertile and ECSS subgroups, may also identify patients for whom surgical therapy improves survival.

4. Graft patency is not permanently ensured but deteriorates with time.

5. Accelerated changes in the bypassed vessels may develop postoperatively. Normal or minimally diseased coronary arteries may be especially susceptible.

6. Bypass surgery can be safely postponed in the patient with coronary artery disease who is functioning well despite ischemic symptoms until such time as symptoms are unresponsive to medical therapy or unless clinical factors suggesting a high risk are identified, such as left main disease or three-vessel disease with reduced left ventricular function.

References


2. CASS Principal Investigators and their associates: Coronary Artery

*Varauskas E: Personal communication.
8. CASS Principal Investigators and Their Associates: Coronary Artery Surgery Study (CASS): a randomized trial of coronary artery bypass surgery. Comparability of entry characteristics and survival in randomized patients and nonrandomized patients meeting randomization criteria. J Am Coll Cardiol 3: 114, 1984