Editorial Comment

Coronary Artery Surgery Study Revisited
Limitation of the Intent-to-Treat Principle

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In the two recent 10-year follow-up Coronary Artery Surgery Study (CASS) reports\(^1-2\) in this issue of *Circulation*, different analyses have been used: intent-to-treat analysis—ignoring a major amount of crossover to surgery—and examining the effect only while on the assigned treatment. The justification is presumed to be that with death and myocardial infarction as end points it is more prudent to adhere to the intent-to-treat principle, assessing the preventive aspect, whereas to evaluate the efficacy of a treatment in relieving symptoms or improving quality of life, the censored analysis examining the actual treatment employed is more relevant.

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Thus, we have two approaches, neither of which is entirely satisfactory, given the circumstances. With both groups (surgical and medical therapies) receiving medical treatment and a 40% crossover to surgery by medical-therapy patients based on clinical condition and accepted indications for surgery, it is difficult to sort out with confidence the impacts of the two therapies under consideration. The frequency of crossover surgery can be regarded as an outcome if it can be accepted that this indicates a failure of medical therapy. However, no criteria for these were specified in the design of CASS, so it is difficult to judge whether the option for surgery represents a real need or the application of conventional wisdom and hence a self-fulfilling prophesy.

The management of patients with coronary disease has changed dramatically during the past several decades. Because absence or abolition of symptoms is no guarantee against coronary attacks and sudden death, the goals are now to prevent attacks and prolong life even when symptoms are absent. Medical therapy has now improved so that it is seldom impossible to relieve angina. The use of \(\beta\)-blockers, calcium antagonists, long-acting nitrates, and aspirin and intervention against coronary risk factors have enabled physicians to treat patients for longer periods without resorting to revascularization.

Along with these improvements in medical options there have been advances in revascularization procedures, now including coronary angioplasty. Also, improved myocardial preservation techniques have made coronary artery bypass graft (CABG) surgery a reasonable, safe procedure, and the increasing use of internal mammary artery grafts and supplementary platelet-active drugs have extended long-term graft patency. Revascularization for patients whose symptoms cannot be controlled by antianginal therapy or who cannot tolerate the medications required seems justified. Surgery in patients with easily controlled mild angina or asymptomatic myocardial infarction is justified only if it can be shown to reduce the likelihood of future coronary attacks and to prolong life, without undue surgical risk.

The role of CABG surgery in mild angina must be viewed from the perspective of the natural history of the disease.\(^3\) Without modern treatment the prognosis for patients with either myocardial infarction or angina pectoris is poor. Framingham Study data collected over three decades, beginning when treatment of both angina and myocardial infarction was rather primitive, indicate that angina carries a risk of cardiovascular sequelae 1.6–3.0-fold that of the general population, so that risks of myocardial infarction, cardiac failure, and sudden death are substantial.\(^4\) Within 10 years of angina, 30% of women and 40% of men die, a mortality rate 1.6–1.9-fold that of the general population of the same age. Following an initial myocardial infarction, one third will have a recurrent infarction within 10 years; 30% and 40%, respectively, of men and women will develop angina, 16% and 24% will suffer stroke, 27% and 31% will develop cardiac failure, and 20% and 10% will die suddenly. About 60% will not survive for longer than 10 years. These risks are 2.4–5.8-fold those of the general population.\(^4\)

Recent trials of medically treated patients with angiographically demonstrated coronary disease have indicated a much improved survival rate compared with this "natural history" of untreated disease.\(^5\) The annual mortality rate in those assigned to medical treatment in the three major trials comparing medical and surgical treatment was 1.6% in CASS,\(^6\) 3.2% in the European Coronary Surgery Study,\(^7\) and 4.2%
in the Veterans Administration Coronary Artery Bypass Surgery Cooperative Study.\(^8\) The variation in the mortality rates reported in these trials can be attributed not only to progressive improvement in medical therapy but also to varied criteria for excluding high-risk patients in each trial.\(^5\)

Characteristics of medically treated patients indicating high risk have been identified, including congestive heart failure, severe multivessel disease, impaired left ventricular function, and an ischemic exercise response.\(^9\) It appears that those at highest risk may be those most likely to benefit from CABG surgery.

Consideration of the trials has evolved into a concept of the proper indication for CABG surgery. The Veterans Administration Cooperative Study\(^8\) did not indicate any significant differences overall in survival of surgically over medically treated patients in relation to their original therapeutic assignment. However, two subsets were purported to have a survival advantage with surgery: those with left main-stem coronary artery disease and those with NYHA functional class III or IV angina, a history of prior myocardial infarction, a history of hypertension, or resting ST segment abnormalities. The European Coronary Surgery Study\(^7\) found a significant survival advantage at 5 years of follow-up for patients randomized to surgical treatment. The greatest benefit was noted in those with either left main, three-vessel, or two-vessel coronary artery disease (including proximal left anterior descending). None of the studies showed an advantage of surgery over medical therapy in reducing the risk of subsequent myocardial infarction, but all found CABG surgery superior to medical therapy in relieving angina and improving exercise tolerance.\(^10\)

It is interesting that neither surgery nor antianginal medical therapy has been rigorously tested in a placebo-controlled trial of enhanced survival. Hence, if there is no difference between surgical and medical treatment, we cannot determine whether this means both are better, no different, or worse than doing nothing. We can only take comfort in an external standard of comparison, such as the Framingham Study data,\(^11\) which appears to indicate that both are, on average, better than doing nothing. However, comparison with the natural history of disease determined by observational epidemiological studies is speculative because trials generally involve a select group of participants and epidemiological studies do not.

The report of the 10-year follow-up of survival and myocardial infarction in the randomized CASS reported in this issue of Circulation\(^1\) is an extension of previously reported findings\(^6\) and based on a longer follow-up. The previous report of the CASS trial did not find any significant differences in the 8-year survival of patients randomly assigned to either medical or surgical treatment. Improved 7-year survival was reported in a subset of patients with three-vessel coronary artery disease and decreased ejection fraction (0.35–0.49) who received surgery.\(^12\) The current 10-year follow-up report does not credibly strengthen this conclusion. After 10 years there is now a 40% crossover to surgery in the medical group, very likely because of deterioration in their condition. Because both groups in the trial received medical treatment and 40% of the medical group received surgery, the summary finding of no difference in survival or infarction rate may well be due to the fact that at 10 years there was actually little difference in treatment of the subgroups. Without taking into account the 40% crossover to surgery there is no difference in survival or coronary events between patients receiving medical or surgical treatment using intent-to-treat analysis. The question is whether this analysis is appropriate under these conditions.

Analysis by the intent-to-treat principle in this study\(^1\) could deprive us of some clinically important information. The conclusion that an initial strategy of medical treatment should be used for patients with mild angina and normal left ventricular function seems justified. However, the study was not designed to test this specific hypothesis. Examination of the outcome in the medical group depending on whether or not they had had surgery was rejected on the grounds that this would be biased against medical therapy because only survivors would be eligible for surgery. However, this bias is evidently small because of the low overall mortality in this select group of patients. The much stronger bias is that medical patients who underwent surgery presumably had more ominous clinical findings. Assuming that they would be expected to have a worse prognosis, it is interesting to note that the investigators find that removing them from the analysis does not change the conclusions.

In a 10-year follow-up of quality of life of CASS patients by Rogers et al, reporting in this issue of Circulation,\(^2\) a similar survival and quality of life was observed in medically and surgically treated patients. They found that when the 40% of patients who underwent late CABG surgery were excluded from analysis, it appeared that patients treated surgically continued to have improvement in symptoms compared with those continuing on medical treatment, even at 10 years, whereas symptoms did not improve in patients continuing on medical therapy. This advantage is relevant only if those who went to late surgery from medical treatment had an acceptable surgical mortality. It is also possible that some of those kept on medical treatment despite symptoms were considered too ill to tolerate surgery. It is asserted that quality of life equalization in the two groups at 10 years could be due to the beneficial effect of late CABG surgery in those initially treated only medically. It should be emphasized, however, that this benefit is unfortunately transient, as inferred from analysis of the surgically treated subgroup at 1 and 5 years.

One wonders how much crossover can be tolerated in any trial while adhering to the intent-to-treat principle. The Coronary Drug Project\(^13\) showed that
analysis by adherence to treatment can be misleading. Also, in this project adherence to treatment was not at the patient's discretion but rather was determined by his or her physician depending on the clinical condition of the patient. However, the huge crossover bias in this study seems to outweigh any possible bias of "on-treatment" analysis, especially because those crossing over to surgery were likely to have deteriorated clinically. The authors note that patients who crossed over had ejection fractions similar to those of patients who did not, but this was based on baseline data, not interim findings.

It is probably true that patients with mild angina and normal ventricular function survive as well on medical as on surgical treatment, providing they have an option for later surgery. However, this trial does not constitute a fair test of the efficacy of medical therapy compared with surgical therapy. It is doubtful that anyone would accept the findings if this were a comparison of two drugs in which subjects were allowed to switch over to one of the two drugs depending on their clinical condition during the trial, with 40% exercising this option. Thus, considering that both medical and surgical groups received medical treatment, the conclusion appears to be that the addition of surgery to medical treatment appears to be beneficial only if the ejection fraction was initially under 0.50, (but not too low) in coronary patients less than 60 years old who are willing to be studied, are not in heart failure, and do not have left main coronary artery disease, compared with medical treatment of patients with the option for surgical treatment should their clinical condition deteriorate. In comparing the two treatments it is noteworthy that 35 of 390 surgical patients (9%) required repeat CABG surgery and 156 (40%) required medical treatment for recurrent angina.

In considering medical options there is too little information about the efficacy of risk factor management. Avoidance of cigarette smoking deserves a high priority as it has been shown to substantially reduce risk. It is probably the single most effective risk factor intervention after a myocardial infarction. It lowers the risks of fatal reinfarction, sudden death, and total mortality by 20-50%, and it also reduces the risk of nonfatal reinfarction, particularly in the first 5 years. Five-year follow-up in the CASS registry showed a higher occurrence of coronary deaths in those who continued to smoke compared to those who quit. Thus, continued smoking can cancel much of the benefits of surgery. The Coronary Drug Project data suggest that control of blood lipids with nicotinic acid is worthwhile. Weight control can improve all the ingredients of the cardiovascular risk profile as well as exercise tolerance. Diets emphasizing fish would seem to have merit. Since surgery does not halt progression of atherosclerosis, drug therapy to improve the total cholesterol:HDL cholesterol ratio is indicated. Such therapy has been shown to slow progression and even sometimes to cause some regression of atherosclerosis.

Considering the constraints under which the study was required to operate—no placebo group, an option for surgery on clinical deterioration, medical therapy for both groups—the CASS investigators have done their best to interpret the results. A number of impressions may be derived and questions asked. Could it be that there is no need to agonize about a choice between medical and surgical therapy? No urgency, perhaps, to resort to early surgery in patients who are symptom-free on treatment or medically well controlled? Or, possibly, no need to be driven by coronary artery pathology to resort to surgery?

The decision to revascularize in a given patient is complex because it must take into account not only the coronary pathology but left ventricular function, evidence of myocardial ischemia, age, sex, concomitant medical conditions, and the experience of the team performing the revascularization. The lifestyle of the patient is of major importance in the decision. The choice of one type of therapy—medical or surgical—over the other cannot be made with great confidence based on trials to date. The studies do appear to indicate that there is little penalty in withholding surgery in patients with mild symptoms and normal left ventricular function.

References


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