Does coronary bypass surgery improve long-term survival?

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■ The question posed by the title implies comparison of coronary bypass surgery with some alternative therapeutic approach. At present, there are three principal alternatives: no treatment, medical therapy, and percutaneous transluminal coronary angioplasty. Admitting that definitive data on long-term survival are lacking, the clinician is faced with a choice based on incomplete knowledge—a common dilemma in clinical practice. This discussion is restricted to symptomatic coronary artery disease.

□ INDEX TERM: AORTOCORONARY BYPASS; CORONARY DISEASE □ CLEVE CLIN J MED 1989; 56:561–568

LONG-TERM prognosis for patients receiving no treatment for arteriographically demonstrated coronary disease has not been studied. One might refer to studies performed in the 1960–1970 period and assume that the limited therapeutic approach at that time did not alter prognosis. Although this is probably true, some would argue that those early prognostic studies are not applicable to more recent history because the nature of the disease may have changed. Because of ethical considerations, study of untreated symptomatic coronary disease will not be done. Beta-adrenergic blockade therapy and use of calcium channel blockers have altered the treatment of coronary disease. Unfortunately, no satisfactory study has addressed *long-term* survival with either medication, and it is unlikely that such an investigation will be initiated in the future. In my opinion, these treatments have largely symptomatic rather than prognostic benefit in the treatment of chronic manifestations of obstructive coronary disease. A recent therapeutic approach has been radical manipulation of diet and the use of more effective drugs to modify serum lipids. The effect of these measures on survival is unknown. Not only has the long-term benefit of medical treatment not been studied, but also medical treatment has not been standardized in trials of medical-surgical treatment.

One of the difficulties in most randomized clinical trials of coronary disease is that the patient entry period is long and follow-up requires five or more additional years. Assuming a year for planning and another year for analysis, writing, and publication, eight or more years may pass. During that interval, the accepted technique of one or both treatments may have changed, perhaps decreasing the relevance of the findings. Changes in technique may affect the immediate results primarily (e.g., cardioplegia in bypass surgery or steerable catheters in percutaneous transluminal coronary angiography [PTCA]) or the long-term results (e.g., internal thoracic [mammary] artery grafting and measures used to prevent restenosis after PTCA). Differences in quality of medical treatment and skill in performance of invasive procedures may affect both immediate and long-term results.

An inconvenience in therapeutic trials is the fact that patients may change to the alternative treatment

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(crossover). This noncompliance with originally assigned treatment creates problems in evaluation. Peto et al[1] suggested that all patients be retained for statistical analysis in the therapeutic group to which they were originally assigned, but stated that a large number of crossovers destroys a clinical trial. They advised analyzing adherent and nonadherent patients in each therapeutic group and reporting results separately. Several trials of medical-surgical treatment of coronary disease have followed their advice about retention of patients in groups originally assigned, but the investigators claimed that the "philosophy of treatment" or "intention to treat" was being studied rather than treatment itself.[2,3]

Some patients assigned to surgery died before the scheduled operative date or died after they had rejected the assignment. Naturally, surgeons object strongly to ascription of deaths to surgery if no operation has been performed. On the other hand, many medical patients crossover to surgery even at an early date in a trial; late crossovers are usually due to poorly controlled symptoms. The latter are more likely to occur in patients whose prognosis is considered to be poor. With one exception,[4] separate reporting of compliant and noncompliant patients has not been done.

The duration of follow-up is important in studying a chronic disease. It has been shown that vein graft patency is high (80%–85%) at five years but decreases progressively after that time and is about 50%–60% at 10 years.[5–8] About 95% of internal thoracic artery grafts are patent at 10 years.[6–8] Therefore, survival curves should be extended to 10 years to allow for failure of vein grafts. The duration of follow-up desirable for PTCA cannot be determined because of the paucity of long-term studies and their relatively short duration compared to those of bypass surgery. In the case of PTCA-surgical comparisons, the 10-year minimum for surgical cases would be the determining factor.

BRIEF HISTORY

Favaloro's introduction of coronary bypass surgery in 1968[9] was hailed as a major advance. Skeptics thought that similar symptomatic results might be achieved by a sham operation. Most recognized that angina usually was relieved by operation, but some thought that relief resulted from periarterial neurectomy due to operative manipulation. Evidence of prolonged patency of vein grafts and postoperative improvement in stress tests convinced most that revascularization of the myocardium was responsible for relief of angina. Soon, cardiac surgeons were busy with severely symptomatic patients, and the usually satisfactory relief of angina and low operative mortality resulted in rapid expansion of indications for therapy. Uncontrolled studies indicated that long-term survival was high for surgical patients.

In an early study, Vismara et al[10] compared the incidence of sudden death (within six hours of the onset of acute symptoms) in medically and surgically treated patients with multivessel disease, drawn from the same time period (1970–1973). Baseline characteristics of the two groups were similar. Sudden death was significantly more frequent in the medical group. Hammermeister et al[11] studied disease of two arteries in a group of surgically treated patients, matching each case with a medically treated patient having similar baseline variables. Surgical patients had significantly higher survival.

CLINICAL TRIALS

VA Cooperative Study

Although small randomized studies had been initiated simultaneously, the Veterans Administration reported the first large multicenter randomized prospective clinical trial comparing medical treatment and bypass surgery for patients with angina pectoris due to coronary atherosclerosis.[12] A group of 686 men with stable angina pectoris and either abnormal electrocardiograms or positive stress tests was selected, but 90 patients were studied separately because of the presence of left main coronary artery disease. All had at least 50% narrowing of one or more main coronary arteries. The remaining patients were randomly assigned, 310 to medical therapy and 286 to surgery, and 268 of the latter actually underwent operation. Unfortunately, the quality of surgical treatment was low: operative mortality was 6%, the perioperative myocardial infarction rate was 18%, and graft patency was 69%. All these measures of quality affect both early and late survival. These and many other problems cast doubt on the value of the trial.[13] At 36 months, survival was 87% for the medically treated group and 88% for the surgically treated group. Later, five-year survival was reported to be 80% for medical treatment and 82% for surgical treatment. Eleven-year survival was 58% for both groups. It is curious that surgical survival was higher for single-artery disease (70% *v* 65%) and three-artery disease (56% *v* 50%) at 11 years, but it was much lower for two-artery disease (55% *v* 69%). The serious prognostic implications of severe left main artery disease were recognized, and surgical results compared to historical control suggested surgical benefit. The VA group, in a separate study, confirmed this conclusion.[14]

Gradually during the 1970–1975 period, it became accepted practice in the United States that patients with severe angina should be treated surgically, barring some contraindication. Superior control of symptoms by bypass operation was admitted even by those who doubted any prognostic benefit. This recognition influenced patient selection for the next two clinical trials, both of which excluded patients with severe angina pectoris.

European Coronary Artery Study Group

The second large randomized multicenter trial was initiated by the European Coronary Artery Study Group with enrollment of patients starting in September 1973.[2] As in the VA study, 50% narrowing of the coronary lumen was the minimum required, but unlike the VA trial, multivessel disease was also required. Only patients whose estimated or calculated ejection fractions were at least 50% were included. Patients with severe angina that could not be controlled by medical therapy were excluded, although precise classification of angina was not required. A medical group (373 patients) was compared with a group randomly assigned to surgery (395 patients), although 27 of the latter did not undergo operation. Analysis was made by policy of treatment rather than treatment received, so that all patients remained in the group to which they were assigned initially. Operative mortality was 3.3% for those assigned to surgery—a figure much lower than that of the VA trial but higher than that of many surgical centers not included in the study. Perioperative myocardial infarction and graft patency were not reported.

At two years, survival was significantly higher for the surgical group having three-artery disease. A subsequent report showed persistence of survival benefit for surgical cases at five years for this subset, and this benefit accounted for most of the improved survival observed for the whole group (94% surgical, 84% medical).[15] Survival of patients with three-artery disease was significantly different for medical (82%) and surgical (94%) treatment. Extension of the follow-up to 10–12 years showed a survival advantage for surgical patients.[4] The gap between medical and surgical survival rates was greatest at five years (83% *v* 92%, respectively) and decreased at 10 years (70% *v* 76%), but the difference was still significant. Thirty-seven percent of the medical group had crossed over to surgery during the follow-up period. A unique feature of the European trial is that information was provided on survival according to treatment received as well as policy of treatment. Survival rates were 62% for 237 patients who continued with medical treatment and 86% for crossovers to surgery. Difficulties in assessing the meaning of this difference will be discussed below.

Coronary Artery Surgery Study

The European trial was more restrictive in some ways than the subsequently instituted Coronary Artery Surgery Study (CASS) randomized trial. Patients with disease of single arteries were excluded in the European study because a low mortality rate was anticipated and therefore meaningful analysis could be simplified by the exclusion. The other important restriction was exclusion of two of the three groups in the CASS: the group with mild angina pectoris and low ejection fractions (<0.50) and the group that had myocardial infarction without subsequent angina. Exclusion of the latter group is particularly important because many cardiologists and surgeons have considered such patients candidates for medical treatment. In the CASS, only patients with mild or no angina pectoris were admissible to the study; the symptomatic status was less restrictive in the European study. Narrowing of the coronary lumen by 70% of the normal diameter was required in the CASS and narrowing to 50% was required in the European trial. Finally, left main artery lesions of 70% or greater constituted an exclusion criterion in the CASS. In essence, the CASS attempted to answer more clinical questions with a single trial than did the European group.

The CASS created a large registry of patients who had coronary arteriography for suspected coronary artery disease.[16] Out of this registry, a relatively small subset of 2,099 patients met criteria for inclusion in a prospective randomized trial and 780 agreed to participate. Patients with severe left main coronary artery disease were excluded. All patients had at least 70% narrowing of one of the three main coronary arteries excluding the left main. Eighteen selection or exclusion criteria were outlined, but briefly, all patients had either mild angina pectoris Canadian grades I or II or previous myocardial infarction without subsequent angina. The anginal group was divided into a large subset with ejection fractions of at least 0.50 (Group A—66%) and a smaller subset with lower ejection fractions (Group B—14%). The subset of patients who were asymptomatic following myocardial infarction constituted Group C (21%). Operative mortality was 1.4% for the randomized group, and the perioperative infarction rate was 6.4%. Survival rates were 95% and 96% at five years for medical and surgical treatment, respectively, in Group A, and identical (89%) for Group C. Group B medical and surgical survival rates

were 85% and 96%, respectively—not a statistically significant difference for this relatively small group. Later, seven-year survival rates of Group B patients were reported to be 70% for medical patients and 84% for the surgical subset.[17] Improved survival of surgical patients was due to the low survival of medical patients in the subset that had three-artery disease (65% medical and 88% surgical survival rates). Survival of surgical patients with low ejection fractions and one- or two-vessel disease was actually lower than that of three-vessel disease.

Recently, limited preliminary information has become available on ten-year follow-up of the CASS randomized patients.[18] Medical and surgical survival rates were 78% and 81%, respectively. Improved survival was noted for patients with proximal anterior descending artery disease and those with three-artery disease and low ejection fractions.

The CASS also studied survival of patients who met the criteria for the trial but refused to participate.[19] Although the baseline characteristics of the randomized and these "randomizable" patients showed considerable differences, survival rates of the whole groups and a number of subsets were similar. This similarity was interpreted as confirmation of the results of the randomized trial.

A peculiarity of the CASS trial was that five-year survival of medical patients with two-artery disease was slightly higher than that of patients with disease of a single vessel (94% *v* 93%).[3] Group A must have contained the most patients with single-vessel disease, but survival of medical patients was slightly higher (95% *v* 94%) than that of patients with one- or two-artery disease. Allowing for the vagaries associated with multiple analyses in a single study, it is curious that survival of Group A patients was essentially the same as that of patients in the CASS registry who had no significant coronary disease.[20,21]

The disparity of five-year survival of patients in the CASS trial and in the European trial was considered to be most likely due to possible differences in severity of angina pectoris.[3] The European group retrospectively reviewed the condition of patients on entry and found that 42% had angina Canadian grade III.[22] However, a CASS registry study showed that severity of angina pectoris was not an independent prognostic variable.[20]

Actually, patients in the European study are more readily compared to patients in the CASS trial who had two- or three-artery disease and ejection fractions of at least 0.50. These had five-year medical survival rates of 97% and 94%, respectively, for 99 and 90 patients. The European group reported five-year medical survival rates of 87.5% and 84.8% for two- and three-artery disease, respectively. Our survival rates for patients in Group A with two- and three-artery disease were similar to the European figures.[23] It is difficult to reconcile these differences in survival on the basis of published information.

Comparison and analysis

The surprisingly high five-year survival of medically treated patients in the CASS and the lower survival reported by the European group stimulated my colleagues and me to review our experience in concurrent observational studies.[23,24] Slight modifications of the 18 CASS criteria for patient selection were used to select similar patients from the same time period (1975–1979), and 408 medical patients and 390 surgical patients were studied. Follow-up was almost complete. Although selection of patients was based on the CASS criteria, five-year survival rates resembled those of the European trial much more closely than those of the CASS. Survival of medically treated patients at five years was 89% and that for surgically treated patients was 95%—a statistically significant difference. Survival of 179 patients who had internal thoracic (mammary) artery grafts was 99%. Survival was also better for surgically treated patients than for medically treated patients in all subsets of patients who had internal thoracic artery grafts as part of their operative procedures, and the differences were statistically significant for some subsets. The small size of many subsets compromised the possibility of demonstrating the statistical significance in comparisons.

The possibility that failure of vein grafts due to the development of atherosclerosis might affect long-term survival was studied in a 10-year actuarial extension of our previous studies.[25] Survival rates were 77% for the medical group and 83% for surgical patients—a statistically significant difference. The subset of 179 patients having internal thoracic artery grafts had a 91% survival rate. All subsets except Group C showed higher survival for the surgical group, and the improvement was statistically significant for the majority. During the time period of patient selection, internal thoracic artery grafts were used in patients considered to be relatively low-risk operative candidates, so improved survival might be expected. However, statistical correction for differences in baseline variables showed persistence of survival benefit for the internal thoracic artery subset. Analysis of surgical patients who had only saphenous vein grafts showed that 10-year survival was the same as that of the medical group, 31% of whom actually had undergone operation at some subsequent date. An early survival advantage

was evident for the internal thoracic artery group, and the difference from the group having only vein grafts widened throughout the course of the study. The results are consistent with the development of atherosclerosis and occlusion in vein grafts. As in the European study, survival was much higher in medically treated patients who crossed over to bypass surgery than in the group that remained with the original choice of treatment.

One of the problems of subset analysis in all studies is that numbers of patients may be so small that demonstration of statistical difference is impaired. Survival rates of most subsets of patients who had internal thoracic artery grafts was significantly higher than for similar medically treated patients, and the remaining subsets also had higher survival rates (8%–21%) that were not statistically significant. In each instance, the number of patients who had internal thoracic artery grafts was small. Only a very large study or individual studies directed at specific subsets would answer the question of statistical (and clinical) significance. No significant improvement in survival was shown for CASS Group C (myocardial infarction without subsequent angina). Numbers of Group C patients were relatively small in our observational study because many cardiologists thought that surgery was not indicated for such patients. If this group had not been included in the CASS, the overall results might have been different. Inclusion of single-artery disease in the CASS tended to raise survival rates.

In summary, randomized prospective trials are best compared if the selection criteria are similar, if not identical. Unfortunately, the CASS and European trials are dissimilar and comparisons are difficult on the basis of published data. Still, the five-year survival of CASS patients with ejection fractions of at least 0.50 seems quite high and the European results are within the range of clinical expectation. Our study, using CASS selection criteria, showed survival results close to those of the European study at five years. At 10 years, our survival rates for both medically and surgically treated patients are somewhat higher than those in the European study. An observational study is difficult to compare directly with a randomized prospective trial, but the results should be roughly similar if the patient selection criteria were uniform. Certainly if the results of a trial are to be applicable to clinical practice, a careful observational study should be more comparable to a prospective trial than would be ordinary clinical experience without strict adherence to selection of patients.

On the basis of the European trial and our observational study, I believe that in these relatively low-risk patients a survival advantage has been demonstrated for early bypass surgery compared with medical treatment with or without subsequent operation. In the future, attention must be paid to surgical technique because internal thoracic artery grafting provides a distinct prognostic benefit.

Bypass surgery for acute myocardial infarction has been applied most extensively in Des Moines and Spokane.[26,27] In-hospital mortality has been impressively low, less than predicted for standard medical treatment, although there were no control patients receiving alternative treatments. The Spokane group reported long-term actuarial survival, some patients having been followed up for as long as 10 years. Ten-year survival was 91.8% for patients who had undergone operation within six hours after the onset of symptoms—a remarkable finding.

Unfortunately, emergency bypass operations are wasteful of the time of the surgeon's team. A randomized trial would be difficult to implement in these days of enthusiasm for thrombolysis. Routine thrombolytic therapy instituted within a few hours after the onset of symptoms followed by random assignment to medical treatment or bypass surgery might be a scheme for a clinical trial. Surgery could be immediate or delayed after randomization. The apparent lack of benefit of early angioplasty after thrombolysis applies to six-week survival only.[28] Late survival is related more to the extent of ventricular damage, the number of arteries severely narrowed or obstructed, progression of the coronary disease, and patency of grafts than to initial symptomatic presentation.

PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY

Before patient entry had been completed in the CASS trial, Grüntzig introduced a new therapeutic procedure (PTCA) that was to be applied widely for the treatment of symptomatic coronary artery disease.[29] Originally used for the treatment of disease of single arteries, it soon was applied to multivessel disease. Most cardiologists thought that severely symptomatic patients were best treated by invasive techniques (PTCA or bypass surgery); if the anatomy was favorable for angioplasty, some cardiologists gave the patient the choice of the two invasive techniques with the implication that results were equal. Was the implication based on data or hope?

The two advantages of PTCA in comparison with bypass surgery are that it is less invasive and less expensive. Only brief hospitalization is expected for PTCA, and

the patient may return immediately to normal physical activity in successful cases. Incisional pain is avoided. The primary success rate is 90% or more for selected patients, and the rates of myocardial infarction and death following the procedure are in the same range as those of bypass surgery. The economic advantage of PTCA is that the primary procedure costs about one-third as much as bypass surgery.

The disadvantages of PTCA must be balanced against these considerable advantages. Many candidates for bypass surgery are not good candidates for PTCA. Lesions are often multiple in a single vessel, and some lesions may be difficult to reach. Heavily calcified lesions and total occlusions do not respond well to PTCA. Most angioplasty operators avoid left main artery lesions. Severe narrowing in multiple vessels is treated in stages on different days by some operators. When complications arise during treatment, emergency operation may be required, and elective operation usually is indicated if an artery cannot be dilated.

One of the principal problems associated with PTCA is the high percentage of restenosis or occlusion, especially during the first six months after the initial procedure. If symptoms indicate restenosis during the first few days, repeat PTCA or bypass surgery is indicated on an urgent basis. Recurrent symptoms are common; restenosis occurred in 39% of one large carefully studied group of patients.[30] Some PTCA operators advise routine arteriography six months after the primary procedure.

Repeat PTCA or bypass surgery is usually advised for restenosis or occlusion. A second or third restenosis may occur. New lesions in the left main coronary artery have been reported following PTCA, and these are thought to be secondary to trauma resulting from manipulation of the catheter. These complications add to the risk as well as the cost of treatment.

The advantage of bypass surgery is implied in its name—lesions are bypassed so that progression of stenosis or occlusion of a treated vessel is only of academic interest if the graft remains open. The artery dilated by PTCA remains diseased and is susceptible to progressive narrowing or occlusion without the protection of a distal source of blood flow that is provided by a graft. Of course, some grafts fail, but early patency is high, and the patency rate is acceptable at five years.[5] In the case of internal thoracic artery grafts, patency is high at 10 years.[5,6]

The CASS group reviewed 21,478 registry patients for suitability for PTCA on the basis of a relatively simple computer program.[31] More than 25% of the whole group had no significant coronary artery disease. The 796 patients selected represented 3.7% of the whole group. The mean follow-up period for medically treated patients was 17 months. Bypass surgery had been performed in 47% within 90 days of catheterization and all surgically treated patients were considered to be in the medically treated group until the day of operation. Only 48 (6%) had disease of two arteries, none had three-artery involvement, and 29 (4%) had left main artery disease, now usually considered a contraindication to PTCA. Four-year medical survival rates of patients with anterior descending, circumflex, and right coronary artery single-vessel disease were 99%, 95%, and 89%, respectively, but bypass operation had been performed in 60%, 48%, and 21% of the three groups, respectively. All medically treated patients with disease of two arteries survived, but 31 (65%) had bypass surgery.

It was concluded that this study could serve as a useful standard against which the results of PTCA might be compared. Changes in arteriographic criteria for PTCA have impaired the relevance of this study to current practice, and the high percentage of bypass surgery for single-vessel disease of the anterior descending and right coronary arteries in the CASS leads to decreased confidence in survival results. Isolated circumflex artery disease was treated surgically least frequently and had the highest mortality of any single-artery disease. If one accepts the survival rates of medically treated subsets of patients in this study as standards against which to measure the effectiveness of PTCA, no survival advantage at four years could be demonstrated in an angioplasty series of reasonable size except, perhaps, for disease of the proximal circumflex artery. This fact emphasizes the need for randomized trials.

Some five-year survival studies have been done in patients who underwent PTCA, but none with concurrent controls having medical treatment or bypass surgery. Grüntzig et al[32] called for a randomized prospective trial in 1979, but only recently have such trials comparing PTCA and bypass surgery been initiated. It will be more than five years before these trials will be reported. A joint committee of the American College of Cardiology and the American Heart Association called for "... long-term follow-up of large numbers of patients treated by these two competing interventions with matched cohorts ...," in addition to the randomized trials.[33] No such studies have been reported except for that of Kramer et al[34] in which PTCA and bypass surgery for anterior descending artery disease were compared in a concurrent observational study. Total five-year survival was significantly higher (98% *v* 95%) for the surgical group than the medical, but cardiac survival was similar.

Event rates favored surgical patients. Because five-year survival is high for medically treated patients with single-artery disease, it probably will require a follow-up of seven or eight years to show significant differences in cardiac mortality. It is likely that a shorter follow-up period will clarify survival in multivessel disease.

Finci et al[35] compared the results of PTCA for multivessel disease with those of grafting both internal mammary arteries; both groups of 80 patients were drawn from the same entry period. Mean follow-up was one year, so long-term survival is unknown. Functional improvement was superior in the surgically treated group. Extension of the follow-up period should provide useful survival information.

No attempt will be made here to evaluate the clinical use of laser therapy in coronary artery disease. It should be regarded as an experimental procedure at this time, although it has theoretical advantages.

CONCLUSIONS

To return to the question posed in the title, it is my opinion that survival is improved by bypass surgery in comparison with medical treatment, even in patients with single-artery disease and in low-risk patients with ejection fractions of at least 0.50. Internal thoracic artery grafting has a conspicuous prognostic advantage over the saphenous vein technique.

No decision can be made relative to PTCA–bypass surgery comparison because of the lack of adequate long-term studies. In the absence of these data, one might still guess. Barring the early discovery of safe drug therapy that effectively delays the appearance of restenosis after PTCA and the development of atherosclerosis in the saphenous vein grafts, I think that bypass grafting will prove prognostically superior to PTCA for both single-artery disease (followed up eight or more years) and multivessel disease (followed up five or six years). If such drug therapy is developed, it would also be expected to decrease the rate of progression or induce regression of lesions in native arteries. In that case, trials comparing the new medical therapy and invasive techniques would be required. If the new medical therapy proved uniformly effective, invasive procedures might be reserved for emergencies and for symptomatic relief.

Realistically, a monumental improvement in medical treatment is not likely to appear soon. Therefore, bypass surgery will continue to be done on a large scale and, in a subset of surgical candidates, PTCA will be performed. This latter treatment group is likely to shrink in size as more prognostic data are accumulated, but it will not disappear.

Laser therapy is still an investigative procedure.

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