Survival of Medically Treated Patients in the Coronary Artery Surgery Study (CASS) Registry

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SUMMARY  The objective of this study was to evaluate the impact on survival of the anatomic extent of obstructive coronary artery disease and of two measures of left ventricular (LV) performance. This study is based on 20,088 patients without previous coronary artery bypass graft surgery who were enrolled in the registry of the National Heart, Lung, and Blood Institute Coronary Artery Surgery Study from 1975 to 1979. The cumulative 4-year survival of medically managed patients was analyzed to determine the survival of specific subsets of patients with obstructive coronary disease. The vital status of 99.8% of the patients was known. The 4-year survival of medically treated patients with no significant obstructive disease was 97%, in contrast to 92%, 84% and 68% in patients with one-, two- and three-vessel disease, respectively. The presence of left main coronary artery disease decreased survival significantly. The 4-year survival decreased from 70% to 60% in patients with three-vessel disease when significant obstruction of the left main coronary artery was also present. Patients with significant coronary artery disease who had an ejection fraction of 50–100%, 35–49%, and 0–34% had a 4-year survival of 92%, 83% and 58%, respectively. The systolic contraction pattern was assessed in five selected segments and given a score of 1–6, with a score of 1 for normal function, increasing to 6 if an aneurysm was present. In a patient with normal LV contraction in all five segments of the LV ventricular angiogram, the LV score would equal 5. Patients with an LV score of 5–11, 12–16 and 17–30 had 4-year survivals of 90%, 71% and 53%, respectively. Patients with good LV function (a score of 5–11) had a 4-year survival of 94%, 91% and 79% for one-, two- and three-vessel disease, respectively. Patients with poor left ventricular function (score of 17–30) had a 4-year survival rate of 67%, 61% and 42% in one-, two- and three-vessel disease, respectively. Thus, LV function is a more important predictor of survival than the number of diseased vessels.

THE CUMULATIVE survival of patients with coronary artery disease who receive medical management, as reported in studies since Herrick and Nuzum's clinical description of 1918, is extremely variable. Before the development of coronary angiography, the extent of coronary artery disease could not be reliably determined. Therefore, it is not surprising that the 5-year survival rates reported ranged from 15% to 75%.1-11 The poor survival rates of medically treated patients reported in earlier studies has influenced the increasing frequency with which surgical management is recommended for patients with coronary artery disease. It is important to obtain as precise a classification of patients with coronary artery disease as possible when considering therapy on the basis of long-term survival. The frequent use of the bypass surgery to treat coronary artery disease makes it difficult to study the natural history of patients with obstructive coronary artery disease in this country. Many patients suspected clinically of having coronary artery disease have been studied by angiography in the National Heart, Lung, and Blood Institute Coronary Artery Surgery Study (CASS).12 A detailed analysis of the coronary arterio-

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Received July 6, 1981; revision accepted February 10, 1982.
maximal narrowing of the luminal diameter, was recorded for each of 27 coronary artery segments. The criterion for clinically significant one-, two- or three-vessel coronary artery obstruction was either 70% or more reduction in the internal diameter of the right or left anterior descending or left circumflex coronary artery or 50% or more reduction in the internal diameter of the left main coronary artery.

The ejection fraction was calculated from left ventricular (LV) angiograms and provided a good global measure of LV function. Not all patients had determinations of ejection fraction, primarily because of technical and logistic reasons. By evaluation of the segmental LV performance pattern, calculated as an LV score, LV function could be determined in 97% of the patients. This LV score provides a quantitative assessment of the segmental abnormalities of the left ventricle.12

With the use of a 30° right anterior oblique view of the LV angiogram, the ventriculogram was divided into five segments: anterobasal, anterolateral, apical, diaphragmatic and posterolateral. The systolic contraction pattern of each of the five segments was numerically scored: 1 = normal, 2 = moderate hypokinesis, 3 = severe hypokinesis, 4 = akinesis, 5 = dyskinesis and 6 = aneurysm present. The LV score is the sum of the points of these five segments. Thus, in a patient with normal systolic contraction in all five segments of the LV angiogram, the LV score would be 5 (fig. 1).

The decision for surgical or medical therapy in registry patients, was made by the study physicians in conjunction with the referring physicians and the patient. Although some patients with significant coronary disease were treated medically because they were anatomically or hemodynamically unsuitable for surgery, 93% of all patients in this study had at least one operable vessel. The proportion of each subgroup treated medically varied from site to site. Since patients were not randomized in this registry study, the decision to treat a patient medically or surgically was determined by prevailing clinical opinion. Considering the expected differences of such opinions between institutions and the variability of patient populations, the data presented in this study are viewed as being representative of clinical practice in the United States and Canada during this period.

Patients who were chosen for surgical therapy were initially regarded as medically treated. Many patients who were initially treated medically later had coronary bypass graft surgery. Most often, subsequent therapy was performed because of the failure of medical therapy to provide adequate control of the patient's angina. At the time of coronary bypass surgery, patients were withdrawn from further analysis. Exposure time was calculated from the time of enrollment in the CASS registry; early deaths before scheduled surgery were considered a failure of medical therapy.

Survival curves were calculated by the life-table method and were compared by log-rank statistics.13 For 99.8% of these patients, the vital status was known.

Results

In this group of patients with significant disease who were referred for coronary angiography, 5804 patients were found not to have significant obstruction of the coronary arteries. The 4-year survival of patients with no significant obstructive coronary disease was 97%. The anatomic extent of disease in the coronary vessels was directly related to survival. The 4-year survival rates were 92%, 84% and 68% for patients with one-, two- and three-vessel disease, respectively (fig. 2). Patients with at least one operable vessel did not differ significantly with regard to survival from patients with inoperable vessels; therefore, these groups were considered together for this study. In patients with two-vessel disease, the presence of left main coronary artery disease did not significantly (p = 0.89) alter the 4-year survival — 80% compared with 84% (fig. 3). However, in patients with three-vessel disease, the presence of an obstructed left main coronary artery decreased the 4-year survival to 60%, compared with 70% in patients with three-vessel disease without left main coronary artery disease (p < 0.001). The LV ejection fraction had a major effect on survival. Patients who had at least one-vessel disease, without 50% or more left main coronary artery obstruction and an ejection fraction of 50–100%, 35–49% and less than 35%, had a 4-year survival of 92%, 83% and 58%, respectively (p < 0.0001) (fig. 4). Within the one-, two- and three-vessel disease subgroups, ejection fraction was a very important predictor of survival. For each ejection fraction category, survival decreased according to the number of vessels obstructed (p < 0.001) (fig. 4).

A good correlation was also found between LV performance based on the LV score and cumulative survival. This is expected, since the LV ejection fraction and the LV score are correlated (r = −0.74). Patients with an LV score of 5–11, 12–16 and 17–30 had different 4-year survivals — 90%, 71% and 53%, respectively (p < 0.0001) (fig. 5). Analysis of survival was
also made on the basis of both extent of obstruction and LV function. Within the three subgroups of LV function, survival decreased according to the number of vessels diseased (p < 0.001). The effects of the extent of vessels diseased in the subgroups of patients with good LV function (LV score 5–11), moderate impairment of LV function (LV score 12–16) and poor LV function (LV score 17–30) are listed in figure 5. Patients with good LV function had a 4-year survival of 94%, 91% and 79% for one-, two- and three-vessel disease, respectively. The 4-year survival rates of the patients with one- and two-vessel disease and poor ventricular performance were 67% and 61%, respectively. The 4-year survival of patients with three-vessel disease and poor ventricular performance was 42%. This is significantly lower than that for the one- and two-vessel disease groups with poor ventricular performance (p = 0.001).

The percentage of patients being treated medically at a fixed time after angiographic study is presented in figure 6.
figure 6. The percentage of patients being treated medically was higher among those with less severe angina ($p < 0.0001$) and those with fewer vessels diseased. There was more surgery for patients with proximal vessels diseased when the analysis was restricted to CASS patients with three-vessel disease. The same findings (not presented) hold true for patients with one- and two-vessel disease. Among patients with three-vessel disease, a higher proportion of patients were treated medically when they had poor LV function compared with patients who had three-vessel disease and better LV function. The number of patients receiving a coronary bypass graft operation was influenced by angina class, extent of coronary disease, number of proximal obstructions greater than 70%, and LV performance. Figure 6 shows the rate and time until surgery for patients on the basis of these four important variables.

Figure 7 shows the percentage of patients who received coronary artery bypass surgery within 6 months of their enrollment in CASS. This figure reinforces in more detail the findings of figure 6. The percentage treated surgically increased as the number of vessels diseased increased; the percentage also increased with a better ventricular performance for a fixed number of vessels diseased. Among the CASS participants, most patients with left main coronary artery obstruction of 50% or more received surgery within 6 months.

Discussion

In the CASS registry, both the extent of obstructive coronary disease and the status of LV function were evaluated in a standardized manner with routine quality control of the angiographic readings. The 99.8% follow-up of this large group of patients has made possible an evaluation of the relationship between both the number of obstructed major coronary arteries and LV performance and the subsequent survival of medically treated patients in a number of subgroups.

The cumulative survival of medically treated patients in the CASS group is better than that reported in most earlier studies, particularly in patients with three-vessel disease. The survival of medically treated patients in the Duke University data bank is similar to that in CASS experience.

Many factors may have influenced the difference. One major factor may be the use of different techniques of statistical analysis. Another major difference between this study and some earlier reported studies is the medical treatment provided. In this study, β-blocking drugs were prescribed frequently for medically treated patients. The earlier studies may also
have included more patients with advanced congestive failure and ventricular aneurysm. Still another difference between our study and others is the availability of ventricular performance data on most patients. The CASS registry has permitted the delineation of subgroups of patients within the one-, two- and three-vessel stratification disease categories on the basis of LV performance.

LV contraction patterns have an important influence on subsequent survival, particularly in patients with more extensive anatomic involvement of their coronary vessels.\(^\text{15}\) Again, this study shows that ventricular performance may be a more important predictor of subsequent survival than the number of diseased vessels.

The 4-year cumulative survival of medically treated patients in the CASS registry is lower than that reported for the medically assigned patients in the Veterans Administration coronary artery surgery study\(^\text{16}\): one-vessel, 91% vs 96%; two-vessel, 83% vs 87%; and three-vessel, 68% vs 74%\(^\text{16}\).

The European Coronary Artery Surgery Study enrolled only patients who had at least two-vessel disease and good LV function. The 4-year survival of the CASS patients with good ventricular function shows close correlation with the 4-year cumulative survival of patients in the European study assigned to medical therapy. The comparison between CASS and the European Randomized Study for patients with two-vessel and three-vessel disease is, respectively, 94% vs 93% and 82% vs 84%\(^\text{14}\).

It is difficult, under the best of circumstances, to use medical survival in a registry such as CASS for medical-surgical comparisons. In patients with three-vessel disease, the 4-year survival is 42–79%, depending on the performance of the left ventricle. Thus, to have reasonable validity in such comparisons, one must have comparable data on both medically and surgically treated patients. This means that the same clinicians should record data at the same time period for both medically and surgically treated cases. It is rare that two published papers in the literature contain sufficient data to allow a sophisticated adjustment to another data set. In addition, such data from two sources are recorded by different clinicians, so the comparability of the data is suspect. An additional complicating factor is surgery occurring at variable intervals among those who were initially treated therapeutically by medical treatment alone. The decision for surgery depends differentially on many characteristics. For example, with
Figure 6. Percentage of patients treated without coronary artery bypass surgery is presented by time. CHCLAS = Canadian Heart Association functional classification; LV = left ventricular.

Figure 7. Percentage of patients receiving coronary artery bypass surgery within 6 months of angiographic study. Percentage is presented for patients with one-, two-, and three-vessel disease, including left main coronary artery disease (LMCA) and patients with 50% or more LMCA disease.

A given number of vessels diseased, the surgical cases include a higher proportion of patients who have good ventricular performance than in the overall CASS registry. Mathematical adjustment in response to this factor depends on fine subdivision for its validity or on assumptions about a mathematical model. All of this again implies that data such as those presented here may not profitably be used for medical/surgical survival comparisons when surgical survival curves from another data base are used.

The high cumulative survival of patients with good ventricular function and two-vessel disease may explain why the European Randomized Study of Coronary Artery Surgery failed to show a significant difference in survival between medically and surgically treated patients with two-vessel disease, since this study randomized only patients with good LV performance.

The survival of these medically treated patients cannot be used for direct comparison with the survival of patients with comparable disease treated surgically,
since not all medically treated patients were surgical candidates. Also, many patients who received medical treatment initially were subsequently treated surgically. Nevertheless, the poor cumulative survival of medically treated patients with two- and three-vessel disease and poor ventricular function may suggest earlier consideration of surgical treatment for these patients. However, patients with evidence of ventricular dysfunction have been reported to have a higher operative mortality. The operative risk of coronary bypass surgery at the 15 CASS clinical units and the factors that influence it have been reported. The operative mortality for all coronary artery bypass graft surgery was 2.3%. In patients with a history of congestive heart failure, the operative mortality was 4.7%, and in patients with pulmonary rales at baseline it was 7.5%.

The results of the CASS show better or similar cumulative survival of medically treated patients with one-, two- and three-vessel disease than previously reported. In addition, LV performance has an important influence on subsequent survival. Even when the probability of survival is already high, such as in the patients with only one or two obstructed coronary arteries, the effect of poor ventricular performance is significant. When the severity of the arterial disease increases, the impact of LV performance is even greater.

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Circulation. 1982;66:562-568
doi: 10.1161/01.CIR.66.3.562

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