JACC Vol. 3, No. 3
March 1984:772–9

COOPERATIVE STUDIES

Prognostic Importance of a Clinical Profile and Exercise Test in Medically Treated Patients With Coronary Artery Disease

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To identify predictors of mortality in medically treated patients with symptomatic coronary artery disease, 30 variables were analyzed in 4,083 patients. Regression analysis demonstrated that seven variables were independent predictors of survival. A high risk subgroup (annual mortality rate above 5%) was identified, consisting of patients wi.h either a congestive heart failure score of 3 to 4 or 1 mm or greater ST segment depression and final exercise stage of 1 or less. When all 30 variables were analyzed conjointly, the left ventricular contraction pattern ($p < 0.0001$) and the number of diseased coronary vessels ($p < 0.003$) proved to be the most important predictors of survival. In a subgroup of 572 patients with three vessel coronary disease and preserved left ventricular function, the probability of survival at 4 years ranged from 53% for patients only able to achieve stage ½ of exercise to 100% for patients able to exercise into stage 5 ($p < 0.004$). Thus, in patients with defined coronary pathoanatomy, clinical and exercise variables primarily relating to the functional state of the left ventricle are helpful in assessing prognosis.

Identification of patients with coronary artery disease who are at greater risk of dying has been a major objective for the use of noninvasive testing. Once identified, such patients are considered premier candidates for coronary angiography and likely prospects for coronary bypass surgery. This approach has created a great demand for accurate prognostic studies. The majority of studies relating to the prognosis in patients with coronary disease have relied on cardiac catheterization data which have established the number of coronary vessels with a defined degree of obstruction and left ventricular function as the main determinants of survival (1–7). While a number of studies have shown that exercise testing can identify patients with extensive coronary artery disease (8–10) and poorer prognosis (11–13), many have been limited by the small numbers of patients studied (14–16) and the lack of complete catheterization (14) and exercise (13,16) data on all patients.

The goals of our study were to identify the important noninvasive and invasive predictors of survival in patients referred to the catheterization laboratory who were able to undergo exercise testing and were subsequently managed with medical treatment. A second objective was to determine whether readily available variables obtained by the clinical history, physical examination and exercise test would yield independent prognostic information in subsets of patients with defined coronary pathoanatomy and left ventricular function. To overcome the limitations inherent in small samples, we analyzed data available from the National Collaborative Coronary Artery Surgery Study (CASS).

Methods

Study group. The Coronary Artery Surgery Study (CASS) registry contains 24,959 patients with suspected or proven coronary artery disease who were referred to the 15 cooperating centers for cardiac catheterization. Although exercise testing was not mandatory for registry patients, it was encouraged, and the results were recorded when available. This study is based on an analysis of 4,083 (16%) registry

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0735-1097/84/$3.00

patients with no previous cardiac surgery, who were able to undergo a graded treadmill exercise test using the standard or modified Bruce protocol (17) at one of the participating institutions within 1 month of the catheterization. No exercise test was performed in the early convalescent period after myocardial infarction.

Study protocol. The following information was collected prospectively on each patient and recorded on standardized forms: a clinical profile, data from physical examination and laboratory studies, exercise test results, chest X-ray findings, precise angiographic characterization of the coronary arteries and left ventricle, electrocardiographic findings and information on surgical procedures (if applicable). All patients were followed up at yearly intervals for a minimum of 3 years to ascertain health status. Overall the follow-up was 99% complete.

Selective coronary arteriograms were obtained in multiple projections with either the brachial or femoral artery technique. Clinically important coronary artery disease was defined as 70% or greater narrowing of the diameter in either the left anterior descending, left circumflex or right coronary artery or their major branches or 50% or greater stenosis of the left main segment. Left ventriculography was performed using a single plane adaptation of the area-length method, and the ejection fraction was determined from the right anterior oblique projection (18). In addition, a left ventricular contraction score was calculated on the basis of a subjective grading of the left ventricular angiogram as described previously (19). In brief, the left ventricular silhouette in the right anterior oblique projection was divided into five segments, and each segment was assigned a score: 1 = normal, 2 = mild hypokinesia, 3 = moderate hypokinesia, 4 = akinesia, 5 = dyskinesia and 6 = aneurysm. The left ventricular score, which is the sum score of the five segmental scores, could range from 5 to 30.

Data analyzed. The noninvasive and invasive data analyzed in this study consisted of 18 clinical or historical variables, 7 variables obtained from the exercise test and 5 obtained from the cardiac catheterization as delineated in Table 1 and described previously in detail (19). The variables were selected because they were considered related to survival on the basis of clinical judgment or previous publications. One clinical variable, the congestive heart failure score, was derived arbitrarily by assigning a score of 1 for each of the following characteristics: a history of congestive heart failure, use of diuretics, therapy with digitalis and the presence of rales on physical examination.

Statistical methods and definitions. Univariate analysis of categorical variables was performed using the chi-square test. Quantitative variables were analyzed by using the Student's *t* test. Differences were considered significant at probability (p) values of 0.05 or less. The multivariate relation of the clinical, exercise and angiographic variables to survival was examined with a stepwise linear regression analysis. This method determines independent variables, ranking them in order of potency, and eliminates variables that do not add further independent statistical information. Cumulative survival curves from the time of enrollment into the Coronary Artery Surgery Study registry were calculated with the life-table method and compared by log-rank statistics (20). A Cox proportional hazards model was used (21) for determination of the role of additional variables in the survival analysis.

Definition of relative risk. The relative risk was computed for the variables predictive of survival. It is the ratio of the mortality for the group of patients with a characteristic to the mortality for the group of patients without the characteristic, and therefore is an index of the association of a characteristic to mortality. A relative risk ratio greater than 1 indicates that the particular characteristic is associated with increased mortality.

Definitions of medical treatment: Methods 1 and 2. Because the patients were not randomized in this registry study, the decision to treat a patient medically or surgically was determined by the referring physician and the patient. Coronary bypass surgery was performed in 1,474 patients (36%). Hence, we used two separate definitions of medically-treated patients when analyzing our results. By the first definition, all patients were initially considered as medically treated; those subsequently undergoing coronary bypass surgery were withdrawn from further analysis at the time of surgery (Method 1). By the second definition, all patients undergoing bypass surgery within a site-specific time frame were excluded from the analysis (Method 2). This time frame encompassed 95% of the patients operated on at a particular site within the first year.

Results

Predictors of survival by univariate analysis: relation to ventricular function. During follow-up, 212 patients (5%) died. Eight-two percent of the deaths were reported to be either sudden (< 1 hour) or cardiac-related. Results of the initial univariate screening indicated that 12 variables were important predictors of survival (Table 2). Many of the variables with the highest risk ratios were primarily related to the functional status of the left ventricle such as the presence of prior myocardial infarction, a history of congestive heart failure, cardiac enlargement, digitalis therapy, a low final exercise stage achieved and a high left ventricular score.

Predictors of survival by regression analysis: cardiac enlargement and congestive heart failure. Because many of the variables univariately predictive of survival were likely to have overlapping prognostic significance, a multivariate stepwise Cox regression analysis was employed. Patients were then stratified according to the variables selected by the Cox model, and survival curves were plotted in an at-

Table 1. Baseline Variables Analyzed

Clinical Variables		Exercise Test	Cardiac Catheterization
Gender	Family history of coronary disease	Limiting symptom	Number of stenotic coronary vessels
Age	History of hypertension	Angina	Left ventricular score
Chest pain	Previous myocardial infarction	Ventricular arrhythmias	Left ventricular ejection fraction
Description (definite angina, probable angina, nonischemic chest pain, none)	Risk factor index	Peak heart rate	Left main coronary disease
Severity	Previous cardiac arrest	Peak systolic blood pressure	Left ventricular end-diastolic pressure
Congestive heart failure	Baseline ST segment on rest electrocardiogram	ST segment response	
Documented history	Drug therapy	Final exercise stage	
Functional impairment (none, mild, moderate, severe)	Digitalis		
Rales by examination	Diuretic drugs		
Cardiac enlargement	Beta-adrenergic blockade		
Score			

tempt to define risk categories. Analyses using the clinical data followed by the addition of the exercise variables were performed first, and last, the catheterization data were added to the Cox analysis. This approach was chosen because it duplicates the sequence used in clinical practice. The most important clinical variables identified were the presence of cardiac enlargement and the congestive heart failure score. When the latter variable was stratified (Fig. 1), 4 year survival rates by Method 1 were 90% for patients with no or mild congestive heart failure (score 0 to 2), compared with 62% for patients with moderate heart failure (score 3) and 18% for patients with severe heart failure (score 4). When the clinical and exercise variables were analyzed conjointly (Method 1, Table 3; Method 2, Table 4), the final exercise stage achieved and the ST segment response during the exercise test emerged as the most important exercise determinants of survival. Combination and stratification of these two readily available exercise variables (Method 1, Fig. 2; Method 2, Fig. 3) demonstrated that the probability of survival at 5 years ranged from 72% for those patients exhibiting 1 mm or greater ST segment depression who were able to achieve only stage 1 or less of exercise to 95% for patients with less than 1 mm of ST depression who were able to exercise to stage 3 or greater.

Predictors of survival by conjoint analysis: left ventricular score. When all the clinical, exercise test and catheterization variables were analyzed conjointly (Method 1, Table 3; Method 2, Table 4), the left ventricular score ($p < 0.0001$) emerged as the most important variable related to survival followed by the number of stenosed coronary vessels ($p < 0.003$). Additionally, three clinical (gender, diuretic and digitalis therapy) and two exercise test (peak heart rate and final exercise stage) variables yielded independent prognostic information when examined in conjunction with the catheterization data.

Independent predictors of survival. To identify which clinical or exercise variables were the independent predictors of survival in subsets of patients with defined anatomy, we subdivided the group into low (5 to 9) and high (≥ 10) left ventricular scores and repeated separate Cox analyses according to the number of coronary vessels diseased in each of these groups. In the 3,040 patients with relatively preserved left ventricular function (scores 5 to 9), the following variables provided independent prognostic information: congestive heart failure score and peak heart rate during exercise testing in patients with one vessel coronary artery disease, congestive heart failure score in patients with two vessel disease and the final exercise stage in patients with three vessel disease. The final exercise stage was then stratified in the subgroup of 572 patients with three vessel coronary disease and preserved left ventricular function (left ventricular scores 5 to 9). The 4 year survival rate for the entire subgroup was 82%, but ranged from 53% for the 56 patients only able to exercise into stage ½ to 100% for the 10 patients able to achieve stage 5 or more ($p < 0.004$, Fig. 4). The precise location of the coronary artery narrowings had some effect on the exercise performance in patients with three vessel coronary artery disease. Proximal stenoses of all three coronary vessels were present in 11% of patients able to achieve final stage 5 or more, 22% of patients achieving final stages 2 to 4 and 33% of patients only able to exercise into stage 1 or less ($p < 0.008$). In the patients with poorer left ventricular function (left ventricular scores ≥ 10), the following variables were significant predictors

Table 2. Univariate Predictors of Survival

Characteristic	Survivors (n = 3,871)	Nonsurvivors (n = 212)	Relative Risk
Age (yr)			
< 40	356 (9%)	14 (7%)	0.8
40 to 60	2,884 (75%)	127 (60%)	0.4
> 60	631 (16%)	71 (33%)	2.5
Gender			
Male	2,973 (77%)	186 (88%)	2.0
Female	898 (23%)	26 (12%)	0.5
Prior myocardial infarction			
Present	1,498 (39%)	122 (58%)	2.4
Absent	2,080 (54%)	68 (32%)	0.4
Unknown	293 (7%)	22 (10%)	
History of congestive heart failure			
Present	247 (6%)	60 (28%)	5.0
Absent	3,624 (94%)	152 (72%)	0.2
Cardiac enlargement			
None	3,469 (90%)	156 (74%)	0.3
Slight	328 (9%)	25(12%)	1.4
Moderate	67 (2%)	27 (13%)	7.3
Severe	5 (<1%)	4 (22%)	8.8
Unknown	2 (<1%)	0 (0%)	
Digitalis therapy			
Yes	402 (10%)	70 (33%)	3.8
No	3,469 (90%)	142 (67%)	0.3
Congestive heart failure score			
0	2,784 (72%)	102 (48%)	0.4
1	809 (21%)	43 (20%)	1.0
2	190 (5%)	22 (10%)	2.0
3	83 (2%)	34 (16%)	7.3
4	5 (1%)	11 (5%)	13.8
Final exercise stage			
0–½	294 (8%)	34 (16%)	2.0
1	639 (17%)	48 (23%)	1.4
2	1,074 (28%)	67 (32%)	1.2
3	1,266 (33%)	47 (22%)	0.7
4–7	598 (14%)	16 (7%)	0.5
ST segment depression (mm)			
< 1	2,197 (57%)	100 (47%)	0.7
1–2	897 (23%)	55 (26%)	1.2
> 2	681 (18%)	49 (23%)	1.4
Unknown	96 (2%)	8 (4%)	
Peak heart rate (beats/min)			
< 130	1,461 (38%)	96 (45%)	1.4
≥ 130	2,406 (62%)	116 (55%)	0.7
Unknown	4 (<1%)	0 (0%)	
Left ventricular score			
5 to 9	2,948 (76%)	92 (43%)	0.3
10 to 14	646 (17%)	55 (26%)	1.6
> 15	168 (4%)	54 (26%)	6.0
Unknown	109 (3%)	11 (5%)	
Number of stenosed coronary vessels			
0	1,326 (34%)	32 (15%)	0.3
1	868 (22%)	47 (22%)	1.0
2	798 (21%)	56 (26%)	1.4
3	879 (23%)	77 (36%)	2.0

JACC Vol. 3, No. 3
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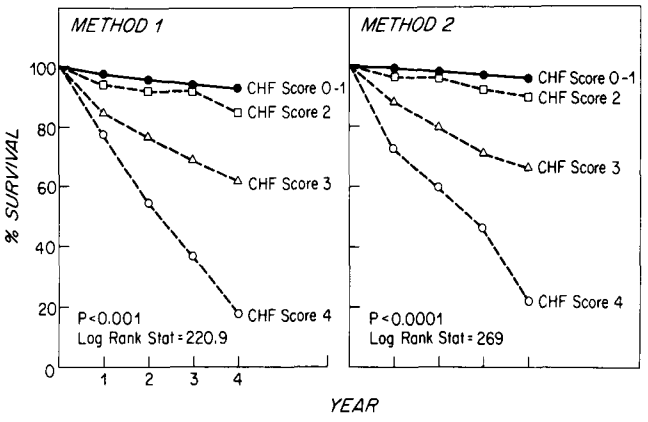


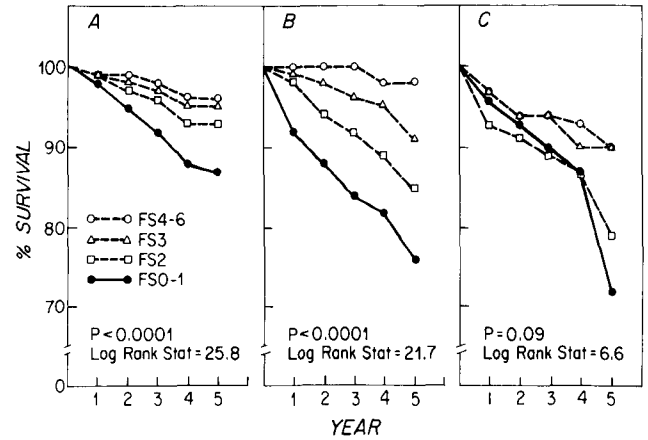
Figure 1. Cumulative survival rates related to the congestive heart failure (CHF) score by Methods 1 and 2. The total score was calculated by assigning 1 point for each of the following characteristics: a history of congestive heart failure, use of diuretic drugs, digitalis therapy and the presence of rales on examination. The log-rank statistic, with its corresponding p value, tests for statistically different survival patterns among the individual groups.

of survival: congestive heart failure score in patients with one and three vessel coronary disease, and ST segment response in patients with two vessel coronary disease.

Discussion

Comparison with previous studies. Previous studies (1–7,11–16) have correlated certain characteristics of patients with coronary artery disease with survival. Many of these studies (1–7) have analyzed only the data obtained

Figure 2. Cumulative survival rates using Method 1 based on the final exercise stage (FS) achieved for the patients with less than 1 mm (**A**), 1 to 2 mm (**B**) and greater than 2 mm (**C**) ST segment depression during exercise testing. A high risk subgroup (n = 492, annual mortality rate above 5%) comprised patients with 1 mm or greater ST depression and a final exercise stage of 1 or less, whereas a low risk subgroup (n = 1,302, annual mortality rate less than 1%) consisted of patients with less than 1 mm ST depression and a final exercise stage of 3 or higher.



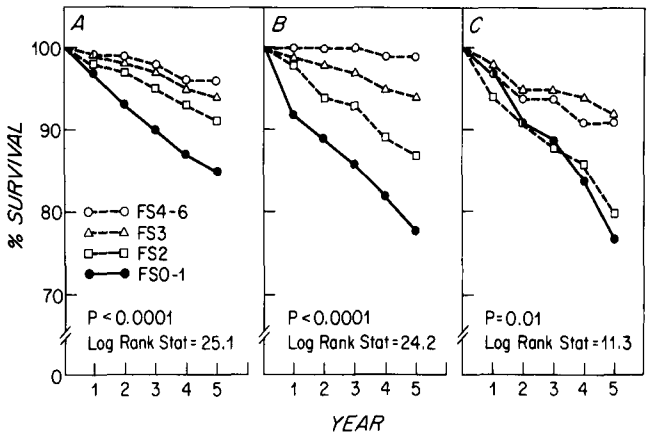


Figure 3. Same analysis as in Figure 2 using Method 2.

from cardiac catheterization. Only one previous study (13) performed a complete analysis of all the available clinical, exercise test and angiographic variables in a large study group, but it was limited by the restriction of exercise data to 46% of patients. The present study attempted to identify the variables predictive of survival using clinical, exercise and angiographic variables, and also tried to determine whether any of the clinical and exercise variables were useful in assessing prognosis in patients whose coronary artery anatomy and left ventricular function had been defined.

Our study utilized data available from a large number of patients enrolled in the Coronary Artery Surgery Study who were symptomatically able to undergo exercise testing and who were followed up prospectively. Because all patients were referred for cardiac catheterization and had undergone exercise testing, our results might not be applicable to other symptomatic patients not undergoing catheterization or exercise testing, or to the asymptomatic individual.

Analysis of data. Because many patients (36% of the total group) underwent coronary bypass operations after enrollment, the data were analyzed using two methods of dealing with the surgically treated patients. The outcome variables and survival rates were similar using either method of analysis.

Twelve variables were identified initially by univariate analysis as predictors of survival in the total group of patients. Because several variables yielded redundant prognostic information, a stepwise multivariate analysis was performed that takes into account the effects of one variable on another. By using only the clinical and exercise test variables initially, we hoped to identify those patients at higher risk of dying who would be good candidates for cardiac catheterization and possibly coronary bypass surgery.

Clinical predictors of survival. The presence of congestive heart failure at rest was the most potent clinical predictor of survival when the clinical and exercise test variables were analyzed. Two other significant clinical variables, the presence of a prior myocardial infarction and

Table 3. Predictors of Survival by Multivariate Analysis (Method 1)

Covariates	Coefficient	95% Confidence Intervals	Chi-square	p Value
Clinical and exercise variables				
Congestive heart failure score	0.51	0.35, 0.67	40.27	0.00001
Gender	−1.27	−1.83, −0.71	21.36	0.00001
Final exercise stage	−0.30	−0.44 −0.16	16.01	0.0001
Cardiac enlargement	0.36	0.12, 0.60	8.60	0.0034
Age	0.03	0.01, 0.05	7.90	0.0049
Prior myocardial infarction	0.46	0.10, 0.82	6.66	0.0099
ST segment response	0.21	0.01, 0.41	4.09	0.0431
Clinical exercise and angiographic variables				
Left ventricular score	0.10	0.05, 0.15	16.72	0.0001
Number of vessels diseased	0.22	0.07, 0.37	8.92	0.0028
Gender	−0.90	−1.55, −0.25	7.63	0.0057
Diuretic therapy	−0.54	−0.12, −0.96	6.51	0.0107
Peak heart rate	−0.009	−0.001, −0.017	4.74	0.0295
Digitalis therapy	−0.51	−0.03, −0.99	4.40	0.0360
Final exercise stage	−0.18	−0.01, −0.35	4.09	0.0432

cardiac enlargement, are also related to ventricular dysfunction. These results confirm two other large studies involving multivariate analysis of clinical data (13,22). Hammermeister et al. (13) identified the clinical variables: cardiac enlargement, use of diuretics, S_3 gallop and congestive heart failure as predictive of survival among 47 variables analyzed from the Seattle Heart Watch Study. Harris and coworkers (22) found that class 4 heart failure, cardiac enlargement and a history of myocardial infarction were 3 of the 12 clinical variables (from a total of 57 analyzed) independently predictive of survival.

Exercise test predictors of survival: duration of exercise and the ST segment response. These two variables emerged as the most important exercise test variables. By combining and quantifying them, an extremely low risk subgroup comprising 32% of our group could be identified with an annual mortality rate of 1% or less: those patients showing less than 1 mm of ST segment depression who could exercise into stage 3 or greater of the Bruce protocol. In contrast, the 492 patients (12%) who had at least 1 mm ST segment depression and who could only exercise into stage 1 had an annual mortality rate of 5% or more. Using these two readily obtainable exercise variables, almost one half of our group could be stratified in a lower and higher risk subset. Hammermeister et al. (13) also identified the exercise duration and the hemodynamic response (blood pressure and heart rate) as the most important exercise predictors of survival. One important difference between their

Table 4. Predictors of Survival by Multivariate Analysis (Method 2)

Covariates	Coefficient	95% Confidence Intervals	Chi-square	p Value
Clinical and exercise variables				
Congestive heart failure score	0.44	0.29, 0.58	151.02	0.00001
Prior myocardial infarction	0.56	0.25, 0.88	37.04	0.00001
Final exercise stage	−0.27	−0.40, −0.14	29.86	0.00001
Gender	−1.21	−1.68, −0.74	29.80	0.00001
Age	0.04	0.02, 0.06	15.03	0.00001
Cardiac enlargement	0.37	0.15, 0.59	10.53	0.0012
History of heart failure	−0.39	−0.67, −0.12	7.77	0.0053
ST segment response	0.08	0.01, 0.14	5.64	0.0175
Clinical, exercise and angiographic variables				
Left ventricular score	0.10	0.05, 0.14	201.01	0.00001
Number of vessels diseased	0.38	0.22, 0.54	51.56	0.00001
Congestive heart failure score	0.34	0.19, 0.49	33.83	0.00001
Final exercise stage	−0.24	−0.38, −0.10	15.69	0.0001
Cardiac enlargement	0.31	0.08, 0.55	6.36	0.0117
Gender	−0.55	−1.02, −0.07	5.19	0.0227

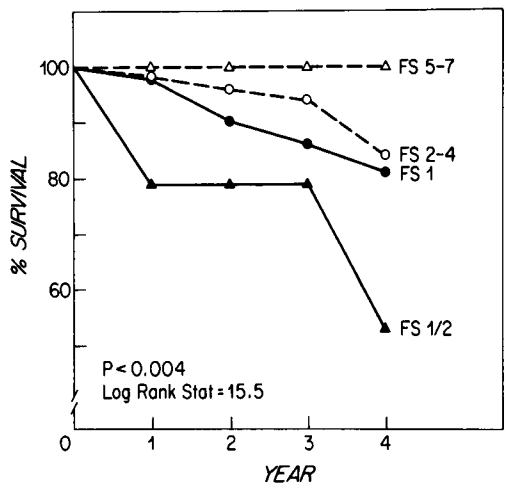


Figure 4. Cumulative survival rates according to the final exercise stage (FS) achieved by the 572 patients with three vessel coronary artery disease and left ventricular scores 5 to 9.

study and ours is that their study failed to demonstrate that the ST segment response was an independent predictor of survival. This difference may have been the result of a qualitative analysis of the ST segment response employed by the Seattle Heart Watch (13) in contrast to the quantification of the ST segment response used in our study.

Podrid and coworkers (14) analyzed the prognostic significance of 2 mm or greater ST segment depression during exercise testing in 142 patients and found that the annual mortality rate of these patients was only 1.4%. Survival of patients varied from 0.5 to 2% per year depending on exercise capacity. In our study, the annual mortality rate of the 730 patients with 2 mm or greater ST depression was 3.6% and ranged from 5.6% for those patients achieving stage 1 or less of exercise to 2.0% for those patients achieving stage 3 of exercise. It is likely that the differences in mortality in the two studies were related to differences in the two groups. Only 13% of the patients in the study by Podrid et al. underwent catheterization.

Angiographic versus noninvasive predictors of survival. When all the variables were analyzed by the final stepwise survival model, the left ventricular contraction pattern was the most important predictor of survival followed by the number of diseased coronary vessels, confirming the results of previous investigations (1–7). Our study, in addition, demonstrated that three clinical variables (gender, diuretic and digitalis therapy) and two exercise variables (peak heart rate and final exercise stage) provided independent prognostic information. These findings suggest that the prognosis of patients with coronary disease may depend more on the functional state of the left ventricle than on the number of diseased coronary vessels. Although the invasively determined left ventricular score emerged as the most important variable, information about the exercise capacity that characterizes the left ventricular function during exercise may further define prognosis. In a subset of patients with three vessel coronary disease and preserved left ventricular function at rest, the final exercise stage was an additional predictor of survival. A recent investigation (23) also demonstrated that exercise capacity was important in defining the prognosis of such patients with three vessel coronary disease. Those patients able to achieve a bicycle work load of 100 watts or more had an annual mortality rate of 4% compared with 9% ($p = 0.04$ at 1 year) for patients unable to achieve that final work load (23).

Conclusions. The results of our study indicate that the presence of several noninvasively determined characteristics is associated with poorer survival rates in patients referred for cardiac catheterization. Most of the important predictors were related to the functional state of the left ventricle. A low risk subgroup of patients can be identified by either the absence of congestive heart failure or the ability to exercise into stage 3 of exercise without ST segment depression. Moreover, even when the catheterization data have been obtained, several clinical and exercise variables contribute information to further define prognosis and therefore should be considered in the recommendation of medical or surgical therapy in an individual patient.

APPENDIX

Physicians and Operating Clinical Sites of the Coronary Artery Surgery Study (CASS)

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