Survival in Medically Treated Coronary Artery Disease

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SUMMARY **In 1214 symptomatic medically treated patients with coronary artery disease, 57 noninvasive baseline clinical characteristics and 24 catheterization descriptors were analyzed by a multivariable analysis technique to determine the characteristics that were independent predictors of survival and, in particular, to determine whether noninvasive characteristics contributed prognostic information in addition to catheterization findings. When the noninvasive characteristics were analyzed, 31 characteristics were significant ($p < 0.05$) univariate predictors of survival, but only 12 contained significant independent prognostic information. Five- and 7-year survival rates in 197 patients who had none of the independently significant noninvasive characteristics were both 90%. Nineteen variables were significant when the catheterization descriptors were analyzed individually. Only seven were independently significant when they were analyzed jointly. When all 81 baseline characteristics were analyzed jointly, seven noninvasive characteristics (history of peripheral vascular disease, New York Heart Association class IV heart failure, nonspecific intraventricular conduction defect, progressive chest pain, nocturnal pain, premature ventricular complexes on the resting ECG, and left bundle branch block) and six invasive characteristics (left-main stenosis, arteriovenous oxygen difference, number of diseased vessels, abnormal left ventricular contraction, left ventricular end-diastolic pressure and anterior asynergy) were independently significant. Different survival rates may occur in subsets that are uniform with respect to only one or two important characteristics (e.g., coronary anatomy and ventricular function) because of differences in other important baseline characteristics. Both noninvasive and invasive characteristics must be taken into account to define prognosis in coronary disease fully.**

EARLY STUDIES of patients with clinically diagnosed coronary artery disease identified clinical characteristics such as age, sex, previous myocardial infarction, ECG abnormalities and heart failure as important predictors of survival.[1-5] With the use of coronary angiography, the extent of coronary disease[6-9] and the quality of left ventricular (LV) function[10, 11] were shown to be accurate predictors of survival. Although noninvasive descriptors still receive some attention,[9-12] until recently the relationship between noninvasive and invasive descriptors in predicting survival has not been extensively examined.

Patients with coronary disease are usually classified by the number of diseased vessels and the quality of LV function. Survival within these categories is considered a manifestation of the natural history of the disease.[13] While such a classification produces a clinically useful stratification of the survival rates, the outcomes in each category vary significantly. For example, 2-year survival rates have varied from approximately 93%[14] to approximately 83%[12] in patients with three-vessel disease and a normal left ventricle.

One explanation for the variation in survivals is that clinical characteristics and hemodynamic parameters that are not taken into account in a classification based on angiographic and ventriculographic findings do contain significant independent predictive information. Because increasing severity or prevalence of noninvasive or hemodynamic abnormalities is usually associated with increasing severity of coronary disease, it is difficult to ascertain their independent prognostic significance. When their effect is analyzed individually in multiple subsets that control the number of diseased vessels and the quality of ventricular function, sample sizes become too small to derive meaningful conclusions.[9, 12-15] An alternative approach is to use multivariable analysis techniques. An early study that used discriminant analysis[9] identified heart size, dyspnea on exertion and resting heart rate as independent predictors of survival but did not take into account ventriculographic findings. Recently, Hammermeister et al.,[17] using a complex strategy based on a combination of univariate and multivariable analysis methods, identified independent predictors of survival among 46 baseline characteristics.

In this study we examined 57 noninvasively acquired clinical characteristics and 24 catheterization descriptors in 1214 medically treated patients with significant coronary disease to determine: 1) which noninvasive characteristics were significant independent predictors of survival; 2) which catheterization descriptors were significant independent predictors of survival, and 3) which, if any, clinical characteristics contributed independent predictive information in combination with the catheterization findings.

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Methods

Patient Population

Between November 1969 and January 1978, significant coronary disease (defined as ≥ 75% obstruction of one or more major coronary arteries[16]) was diagnosed by cardiac catheterization in 2123 patients at Duke University Medical Center. This number does not include patients who had prior revascularization procedures, congenital heart disease, hypertrophic cardiomyopathy, or valvular heart disease other than mitral insufficiency thought to be secondary to ischemic heart disease. All but 130 patients were catheterized because of recurrent chest pain suspected of being ischemic in origin. The patients without chest pain were a heterogeneous group and were catheterized for a variety of reasons, including complications of acute myocardial infarction, severe heart failure, intractable arrhythmias, previous myocardial infarction and abnormal resting or exercise ECGs; they were excluded from this study because they did not have ischemic pain. Of the 1993 patients with chest pain and significant coronary disease, 779 were treated surgically. The 1214 patients who were treated medically constituted the population for this study. One hundred twenty-seven (10%) of these patients subsequently underwent surgery after 6 months or more of medical therapy. The crossover patients had a higher prevalence of normal left ventricular function and a lower prevalence of New York Heart Association (NYHA) class IV heart failure than the noncrossover patients.

The manner in which the decision was made to treat a patient medically or surgically has been discussed previously.[15] It was an individual decision made by the physician in conjunction with his patient. All physicians had access to the clinical information system described below and frequently used it to review the clinical outcome of medically and surgically treated patients of interest. Except in patients with left-main coronary disease, intractable angina was the main indication for surgical therapy. Most of the medically treated patients were anatomically and hemodynamically suitable for surgery but did not undergo operation because they had an adequate symptomatic response to medical therapy. However, some patients were treated medically because they were considered unsuitable for surgery.

Information System

The computerized information system used in this study has been outlined previously.[18] In summary, a clinical, noninvasive data set comprising descriptors of demographics, history, physical examination, chest x-ray and ECG was collected prospectively on each patient at the time of catheterization. The noninvasive clinical descriptors and the invasive hemodynamic, angiographic and ventriculographic descriptors obtained by catheterization and the details of the selected therapy constituted the baseline data set on each patient. Follow-up information was collected 6 and 12 months after catheterization and annually thereafter.

Data Set

The data set analyzed in this study consisted of 57 noninvasive clinical characteristics and 24 catheterization parameters (table 1). The 81 characteristics were derived from 89 descriptors that have been collected since November 1969.[15] Some descriptors, including right-heart hemodynamic parameters, ejection fraction and treadmill test results, were omitted because the information had not been collected on every patient. Ejection fractions were obtained in 27% of patients prior to 1974 and in 91% of patients since then. Exercise tests were obtained in 61% of the patients. The diagnostic and prognostic significance of the exercise test in this subset of patients has been reported previously.[19] For the 81 characteristics that were analyzed, the information was complete in all but 11 patients.

Clinical (Noninvasive) Data

Clinical information was gathered by a cardiology fellow on standardized forms and was verified by a staff cardiologist. The historical characteristics included descriptors of chest pain, heart failure, previous myocardial infarction, risk factors and coexisting diseases. Chest pain was characterized according to its frequency, time of occurrence, severity, type and course in the 6 weeks preceding catheterization. Pain frequency was recorded as the number of episodes per week; pain severity was classified according to NYHA criteria;[20] a patient was considered to be functional class IV if there were any episodes of rest pain in the 6 weeks preceding catheterization. The pain type was characterized as nonanginal, atypical or typical and the pain course was characterized as improving, stable or progressive. Progressive chest pain was defined as a clinical increase in severity or frequency in the 6 weeks preceding catheterization. Progressive pain was described as unstable angina if it necessitated admission to a coronary care unit to rule out myocardial infarction and continued despite therapy. Chest pain accompanied by reversible ST-segment elevation was identified as variant angina.

Congestive heart failure was defined as evidence of salt and water retention (i.e., history of edema or proxysmal nocturnal dyspnea or previous physician documentation of rales, pulmonary congestion or ventricular gallop). Dyspnea alone was not considered evidence of congestive heart failure. The severity of heart failure at the time of catheterization was classified according to NYHA criteria. The presence of cardiomegaly on the chest x-ray was determined from the cardiothoracic ratio, although the actual ratio was not recorded. The physical examination and ECG characteristics that were collected and stored are listed in table 1.

TABLE 1. *Noninvasive and Invasive Baseline Characteristics*

Sex	Physical examination	Hemodynamics
Age	Xanthoma	LV end-diastolic pressure
Duration of IHD	Abnormal precordial impulse	Aortic systolic pressure
Chest pain	Rales	Aortic diastolic pressure
Type (typical angina, atypical angina, nonanginal)	Atrial gallop	Arteriovenous oxygen difference
Course of pain (improving, stable, progressing, unstable)	Ventricular gallop	Cardiac index
Severity of pain (NYHA class I-IV)	Systolic ejection murmur	Coronary anatomy
Variant angina	Early systolic murmur	Number of vessels with significant stenosis
Nocturnal angina	Midsystolic murmur	Significant left main coronary stenosis (subtotal, total)
Frequency of pain	Late systolic murmur	Significant left anterior descending stenosis (subtotal, total)
Hx myocardial infarction	Holosystolic murmur	Significant left circumflex stenosis (subtotal, total)
Hx arrhythmias	Peripheral pulses absent	Significant right coronary artery stenosis (subtotal, total)
Hx congestive heart failure	Pulse bruits	Left ventriculogram
Severity of heart failure (NYHA class I-IV)	Cardiomegaly, chest x-ray	Abnormal contraction
Hx hypertension	Electrocardiogram	Diffusely abnormal contraction
Hx diabetes	Normal sinus rhythm	Asynergy, apical
Hx obesity	0.04 sec Q-waves	Asynergy, anterior
Hx smoking	Left ventricular hypertrophy	Asynergy, inferior
Hx hyperlipidemia	Left bundle branch block	Aneurysm
Family hx IHD	Right bundle branch block	Mitral insufficiency (grade 1-4)
Hx cerebrovascular disease	Nonspecific intraventricular conduction defect	
Hx peripheral vascular disease	Left axis deviation	
Hx menopause	Right axis deviation	
	Resting ST-T wave changes	
	Resting PVCs	

Abbreviations: IHD = ischemic heart disease; Hx = history of; NYHA class = New York Heart Association functional class; PVC = premature ventricular complex; LV = left ventricular.

Catheterization Data

At catheterization, hemodynamic measurements were routinely performed before cineangiography. To define prognostically abnormal levels of arteriovenous oxygen difference (AVOD) and left ventricular end-diastolic pressure (LVEDP), survival rates were plotted against small increments in each descriptor and the level above which survival declined was selected as the upper limit of normal. These levels were 5.0 vol% for AVOD and 17 mm Hg for LVEDP.

Selective coronary cineangiograms were obtained in multiple left anterior oblique (LAO) and right anterior oblique (RAO) views. Biplane left ventriculography was performed in simultaneous shallow RAO and steep LAO projections. Angiograms were interpreted by at least two of three experienced angiographers in conference. An accuracy of 79% in relation to autopsy findings has been reported,[21] and 86% agreement between two observers in 340 coronary segments has been recorded (unpublished data). Significant ($\geq$ 75%) stenoses were classified as either total or subtotal according to the presence or absence of 100% occlusion. The LV contraction pattern was interpreted as normal or abnormal where normal indicated the absence of asynergy and abnormal indicated the presence of one or more localized areas of asynergy. Abnormal ventriculograms were also characterized as diffusely abnormal if there were multiple areas of asynergy producing a diffusely abnormal contraction pattern with an estimated ejection fraction of less than 25%.

Follow-up

Follow-up information was obtained at each interval by a staff cardiologist during a clinic visit or by a research associate by telephone. All patients had been followed for at least 12 months, 786 had been followed for 3 years, 489 for 5 years and 210 for 7 years. Overall, the follow-up was 99% complete. At each interval, functional status was ascertained and interval hospitalizations were documented. The patient's physician was contacted for further information when a patient died or if there was any possibility that a hospitalization was related to an ischemic event. The physician was asked to confirm his diagnosis for each event and, if relevant, to provide discharge summaries and documentation. Evidence of enzyme and electrocardiographic changes was obtained for fatal and nonfatal infarcts, as was a description of the cause and circumstances of all deaths. If a patient died outside hospital without recent physician contact, as much information as possible about the the circumstances of the death was gathered from a close relative.

Data Analysis

Cumulative survival rates from the time of catheterization were calculated by standard life-table methods.[22] Patients who were treated medically at first and then underwent surgery were included in the life-table calculations until the time of surgery, when they were withdrawn alive. Survival rates were not calculated when fewer than 15 patients remained to be followed during an interval.

Breslow's formulation[23] of the Cox proportional hazards model[24] was used to analyze the relationship between baseline characteristics and survival in the 1214 patients. The Cox model was selected as the most appropriate method of analysis because it can handle both discrete and continuous patient variables, it uses censored data from patients who have not died but have been followed for varying intervals, and it analyzes the overall survival curve of the population in question rather than survival at one time point.

Each characteristic was analyzed individually with the Cox model to derive an unadjusted (univariate) chi-square statistic that was a measure of the relationship between that characteristic and survival without adjusting for the effects of any other characteristics. To determine which characteristics contained independent prognostic information, variables were analyzed jointly with the Cox model according to a strategy similar to the one proposed by Peduzzi et al.[25] (see Appendix for details). With this strategy, an essentially unlimited number of variables could be considered in the model building process to identify independent predictors of survival. The independent significance of a variable, that is, its relationship with survival after adjusting for the effects of other characteristics, was expressed by an adjusted chi-square statistic that was calculated by dividing the square of the Cox regression parameter estimate by its estimated variance.

Analyses were performed on the 57 clinical characteristics, the 24 catheterization parameters, and all 81 variables.

Results

Two hundred fifty-nine of the 1214 patients died during follow-up. The life-table survival curve of the total group is shown in figure 1. Fourteen noncardiovascular deaths were excluded from this and subsequent analyses by withdrawing (censoring) the patients at the time of death. The 1-, 5- and 7-year survival rates of the total population were 91%, 72% and 65%, respectively.

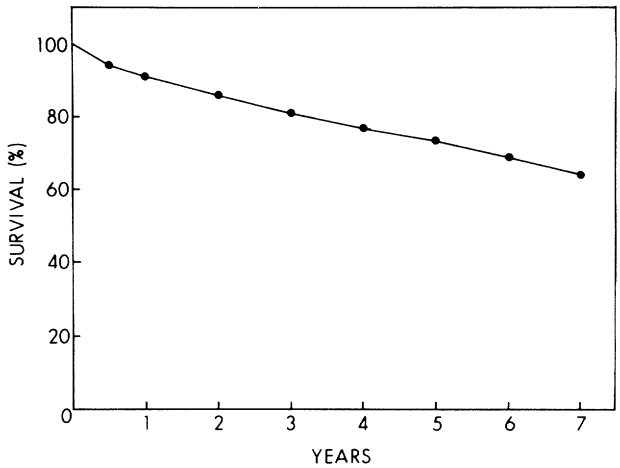

FIGURE 1. *Cumulative survival rate of 1214 medically treated patients with significant coronary disease catheterized because of chest pain. Fourteen noncardiovascular deaths were not included.*

Analysis of Clinical (Noninvasive) Characteristics

Thirty-one of the 57 noninvasive characteristics were significant ($p < 0.05$) univariate predictors of survival (table 2). These included descriptors of the history, physical examination, ECG and chest x-ray. Twelve characteristics were identified as significant independent predictors of survival when the noninvasive characteristics were analyzed jointly (table 3). The 3-year survival rate of 92 patients with NYHA class IV heart failure, left bundle branch block or nonspecific intraventricular conduction defect — the noninvasive characteristics individually associated with the highest

TABLE 2. *Univariately Significant Noninvasive Predictors of Survival*

NYHA class IV heart failure	Chest pain frequency	Stable chest pain
History of heart failure	Age	NYHA class II chest pain
Cardiomegaly on chest x-ray	Q-waves on ECG	Holosystolic murmur
Ventricular gallop	Rales	Atrial gallop
Nonspecific intraventricular conduction defect on ECG	Typical angina	NYHA class I heart failure*
Duration of symptoms	Nocturnal chest pain	NYHA class IV chest pain*
Resting ST-T wave changes	NYHA class III heart failure	Left ventricular hypertrophy on ECG*
Abnormal precordial impulse	Pulse bruit	Absent peripheral pulses*
Left bundle branch block	History of peripheral vascular disease	Abnormal ECG rhythm*
History of myocardial infarction	PVCs on resting ECG	
Progressive chest pain	Atypical angina	

Variables are listed in descending order of unadjusted chi-square statistics.
*Unadjusted $p < 0.05$. For all other variables, unadjusted $p < 0.01$.
Abbreviations: NYHA class = New York Heart Association functional class; PVC = premature ventricular complex.

TABLE 3. *Independently Significant Noninvasive Predictors of Survival*

Characteristic	Adjusted *p*
NYHA class IV heart failure	<0.01
Progressive chest pain	<0.01
Nonspecific intraventricular conduction defect	<0.01
Resting ST-T wave changes	<0.01
Cardiomegaly on chest x-ray	<0.01
Left bundle branch block	<0.01
History of peripheral vascular disease	<0.01
PVCs on resting ECG	<0.01
Duration of symptoms	<0.01
Sex	<0.05
History of myocardial infarction	<0.05
Chest pain frequency	<0.05

Variables are listed in descending order of adjusted chi-square statistics.
NYHA class = New York Heart Association functional class; PVC = premature ventricular complex.

risk — was 37%. Patients who had none of the high-risk characteristics but whose symptoms had persisted for longer than 10 years (102 patients) or who had cardiomegaly on the chest x-ray (164 patients), a history of peripheral vascular disease (50 patients) or premature ventricular complexes (PVCs) on the resting ECG (43 patients) were at intermediate risk, with 3-year survival rates of 65%, 72%, 66% and 60%, respectively.

One hundred ninety-seven patients had none of the high- or intermediate-risk characteristics and experienced fewer than 15 episodes per week of chest pain at the time of catheterization and did not have resting ECG ST-T-wave changes, a history of previous myocardial infarction or progressive chest pain. The 3-, 5- and 7-year survival rates of these low-risk patients was 95%, 90% and 90%, respectively. The association between sex and survival was most apparent in this low-risk subgroup. There were no deaths among the 18 females in the group. However, six patients with significant left main stenosis were in the low-risk subgroup, of whom two died.

Analysis of Catheterization Parameters

Anatomy

Nineteen of the 24 catheterization characteristics were significant univariate predictors of survival (table 4). Seven characteristics were identified as independent predictors when the catheterization parameters were analyzed jointly (table 5). Significant left-main stenosis and the number of diseased vessels were among the most important of the independent catheterization parameters. The survival curves of patients with single-vessel disease (307 patients), two-vessel disease (309 patients), three-vessel disease (521 patients) and left-main disease (77 patients) are shown in figure 2. The respective 5-year survival rates for these categories were 92%, 85%, 64% and 37%.

Ventricular Function

Two descriptors of the overall LV contraction pattern and one descriptor of the site of asynergy contained independent prognostic information. Combination of the two descriptors of overall LV contraction classified ventricular function into three levels (fig. 3). There were 504 patients with a normal contraction pattern (5-year survival = 89%), 558 with moderately abnormal contraction characterized by an abnormal but not diffusely abnormal contraction pattern (5-year survival = 70%), and 152 with severely abnormal contraction characterized by a diffusely abnormal contraction pattern (5-year survival = 38%). Survival in patients with moderate LV dysfunction could be further stratified by the presence or absence of anterior asynergy. Five-year survival rates were 76% in 292 patients in whom it was absent, and 62% in 266 patients in whom it was present.

The relationship between survival and the three levels of LV contraction pattern in one-, two- and three-vessel disease is illustrated in figure 4. In single-vessel disease, 5-year survival rates were 97% in 188 patients with normal LV contraction and 83% in 112 patients with moderate LV dysfunction. Only seven

TABLE 4. *Univariately Significant Catheterization Predictors of Survival*

Diffusely abnormal LV contraction	Mitral insufficiency	Inferior LV asynergy
LV end-diastolic pressure	Anterior LV asynergy	Significant right coronary stenosis
Significant left-main stenosis	Apical LV asynergy	Total right coronary occlusion
Subtotal left-main stenosis	Cardiac index	Total left circumflex occlusion
Arteriovenous oxygen difference	Total left anterior descending occlusion	LV aneurysm*
Number of diseased vessels	Significant left circumflex stenosis	
Abnormal LV contraction	Significant left anterior descending stenosis	

Variables are listed in descending order of unadjusted chi-square statistics.
*Unadjusted $p < 0.05$. For all other variables, unadjusted $p < 0.01$.
Abbreviation: LV = left ventricular.

TABLE 5. *Independently Significant Catheterization Predictors of Survival*

Characteristic	Adjusted *p*
Significant left-main stenosis	<0.01
Arteriovenous oxygen difference	<0.01
Number of diseased vessels	<0.01
Diffusely abnormal LV contraction	<0.01
LV end-diastolic pressure	<0.01
Abnormal LV contraction	<0.05
Anterior LV asynergy	<0.05

Variables are listed in descending order of adjusted chi-square statistics.
Abbreviation: LV = left ventricular.

patients with single-vessel disease had severe LV dysfunction. In two-vessel disease, 5-year survival rates were 92% in 157 patients with normal LV function and 87% in 128 patients with moderate LV dysfunction. Twenty-four patients with two-vessel disease and severe LV dysfunction had a 2-year survival rate of 66%. In three-vessel disease, the 5-year survival rates were 82% in 137 patients with normal LV function, 63% in 283 patients with moderate LV dysfunction and 43% in 101 patients with severe LV dysfunction. Of the 77 patients with left-main disease, 22 with normal LV function had a 2-year survival rate of 80%, 35 with moderate LV dysfunction had a 2-year survival rate of 53% and in the 20 patients with severe LV dysfunction 75% were dead within 3 years.

Hemodynamics

Two hemodynamic parameters, AVOD and LVEDP, contributed significant prognostic information over and above the descriptors of coronary anatomy and LV contraction. The association between abnormal hemodynamic parameters (AVOD > 5 vol% or LVEDP > 17 mm Hg) and decreased survival was most apparent in patients with three-vessel disease (fig. 5). In patients with three-vessel disease and moderate LV dysfunction, the survival rate from years 1–5 was, on the average, 12% higher in those with normal hemodynamic parameters than in those with abnormal hemodynamic parameters.

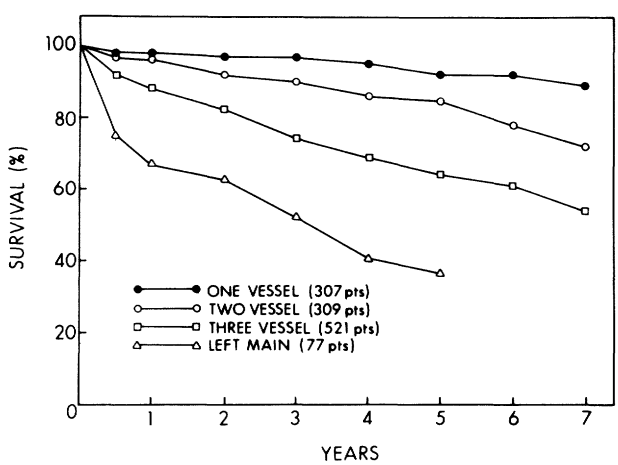

FIGURE 2. *Cumulative survival rates in patients with one-, two-, three-vessel and left-main coronary disease.*

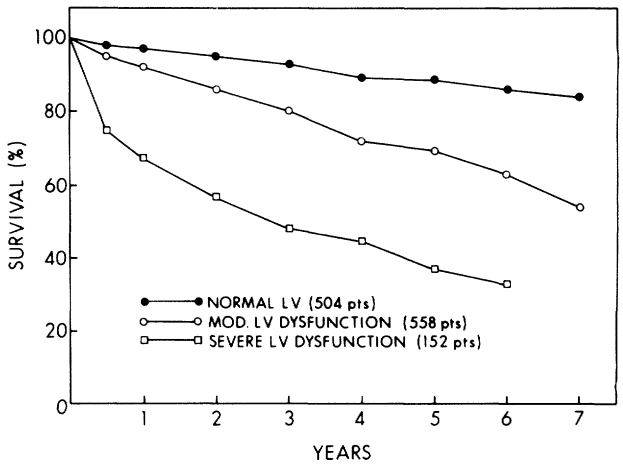

FIGURE 3. *Cumulative survival rates related to the overall left ventricular (LV) contraction pattern. Moderate LV dysfunction is an abnormal but not diffusely abnormal contraction pattern. Severe LV dysfunction is a diffusely abnormal LV contraction pattern.*

Analysis of Combined Noninvasive and Invasive Characteristics

When all 81 baseline characteristics were subjected to joint multivariable analysis with the Cox survival

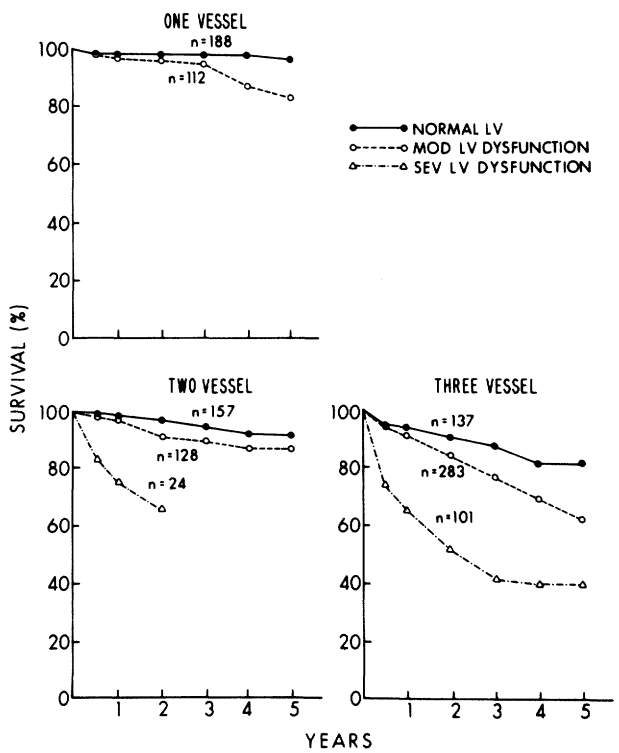

FIGURE 4. *Cumulative survival rates related to the number of significantly stenosed vessels and left ventricular (LV) contraction pattern.*

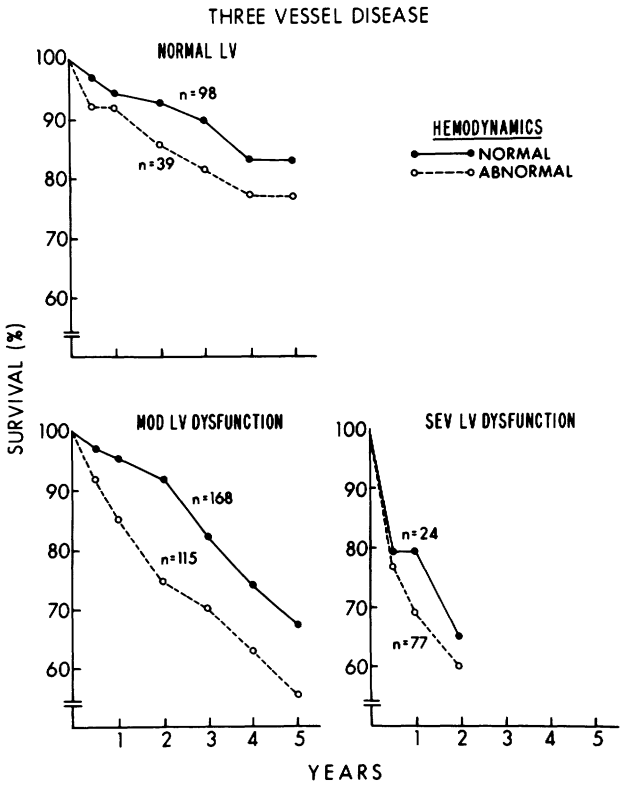

FIGURE 5. *Cumulative survival rates related to hemodynamic parameters and left ventricular (LV) contraction pattern in patients with three-vessel disease. Normal hemodynamics = arteriovenous oxygen difference ≤ 5 vol% and LV end-diastolic pressure ≤ 17 mm Hg. Abnormal hemodynamics = arteriovenous oxygen difference > 5 vol% or LV end-diastolic pressure > 17 mmHg.*

TABLE 6. *Independently Significant Predictors of Survival after Joint Analysis of 81 Noninvasive and Invasive Baseline Characteristics*

Characteristic	Adjusted *p*
Significant left-main stenosis	<0.01
History of peripheral vascular disease	<0.01
NYHA class IV failure	<0.01
Arteriovenous oxygen difference	<0.01
Number of diseased vessels	<0.01
Abnormal LV contraction	<0.01
PVCs on resting ECG	<0.01
Nonspecific intraventricular conduction defect	<0.01
LV end-diastolic pressure	<0.01
Anterior LV asynergy	<0.01
Progressive chest pain	<0.05
Nocturnal chest pain	<0.05
Left bundle branch block	<0.05

Variables are listed in descending order of adjusted chi-square statistics.

Abbreviations: NYHA class = New York Heart Association functional class; LV = left ventricular; PVC = premature ventricular complex.

model, 13 characteristics (seven noninvasive and six invasive) were identified as independent predictors of survival (table 6). The noninvasive characteristics that were independently significant in combination with the catheterization findings were: a history of peripheral vascular disease, NYHA class IV heart failure, PVCs on the resting ECG, nonspecific intraventricular conduction defect, progressive chest pain, nocturnal chest pain and left bundle branch block.

Forty-six patients had a history of peripheral vascular disease in the absence of NYHA class IV heart failure, PVCs, nonspecific intraventricular conduction defect and left bundle branch block. Fourteen of the 49 died, resulting in a 67% 3-year survival rate. The prevalences of three-vessel disease, left-main disease, abnormal ventricular contraction and abnormal hemodynamic parameters in patients with a history of peripheral vascular disease were similar to those in the total population. There was some interaction between progressive chest pain and history of peripheral vascular disease. Twenty-six of the 46 patients had progressive chest pain, and 10 died.

NYHA class IV heart failure, PVCs on the resting ECG, nonspecific intraventricular conduction defect and left bundle branch block identified small subsets of patients with advanced coronary disease and severely impaired LV function who had a worse survival than could be predicted from the catheterization findings. Of 135 patients with one or more of these abnormalities, 95 had three-vessel or left-main disease and 93 had severe LV dysfunction or abnormal hemodynamics. Of 35 patients with NYHA class IV heart failure, 29 had three-vessel or left-main disease, 30 had severe LV dysfunction or abnormal hemodynamics and 28 died within 3 years.

Of the two independently significant chest pain descriptors, the relationship between progressive chest pain and survival was more clinically significant. It was present in 461 patients and was more common in patients with left-main (57%) and three-vessel disease (44%) than in patients with two-vessel (34%) and single-vessel (28%) disease. The association between progressive chest pain and decreased survival was apparent at almost all levels of vessel involvement and ventricular function. This consistent effect is illustrated in figure 6 for patients with one-, two- and three-vessel disease and normal or moderately impaired LV function. In patients with three-vessel disease and severely impaired LV contraction, the 3-year survival rate was 39% in 49 patients with progressive chest pain, compared with 64% in 52 patients with nonprogressive chest pain. The combination of progressive chest pain with either NYHA class IV heart failure or nonspecific intraventricular conduction was particularly lethal, with 27 deaths among 32 patients with one of these combinations.

The combined effect that progressive chest pain and abnormal hemodynamic parameters had on survival in a subset of patients with defined coronary anatomy and ventricular contraction pattern is demonstrated in figure 7. The 2-year survival rate of patients with

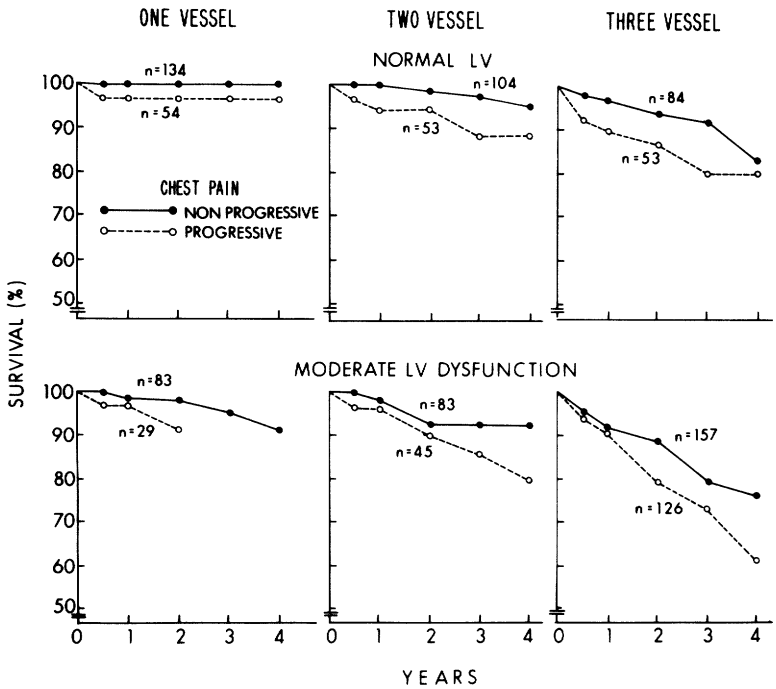

FIGURE 6. *Cumulative survival rates related to progressive and nonprogressive chest pain in patients with one-, two- and three-vessel disease and normal and moderately impaired left ventricular (LV) function.*

three-vessel disease and moderately abnormal LV contraction varied from 68% in 58 patients with progressive chest pain and abnormal hemodynamic parameters to 93% in 100 patients with nonprogressive chest pain and normal hemodynamic parameters.

Discussion

The prognostic significance of 81 baseline characteristics has been determined in 1214 medically treated patients with significant coronary artery disease. Using a single multivariable analysis technique, the relationship between each characteristic and overall survival was examined in the total group of patients with and without adjustment for the effect of other characteristics. This approach avoided the problems associated with attempting to determine the significance of numerous characteristics within multiple subsets. With 1214 patients in the total group, we could illustrate the effect of many important characteristics within common clinical subsets.

Fifty characteristics were significant univariate predictors of survival. However, there was considerable overlap in the prognostic information contained in many of the baseline characteristics, and when characteristics were examined after adjusting for the effects of other characteristics, relatively few in each group contained significant independent prognostic information.

The independently significant noninvasive characteristics identified in this study corresponded closely to those identified in studies in uncatheterized patients who have clinically diagnosed coronary disease.[1-5] Using various combinations of the noninvasive characteristics in this study we could stratify survival over a range varying from a 3-year survival rate of 37% to a 7-year survival rate of 90%. With the addition of descriptors of exercise test performance and radionuclide angiography to the noninvasive data set for future studies, prediction of survival by noninvasive characteristics may be even further refined.

Analysis of catheterization parameters confirmed the well-established prognostic importance of ventricular function and coronary anatomy.[6-15] Descriptors of both overall and localized ventricular contraction abnormalities contributed independent information and were among the most important characteristics.

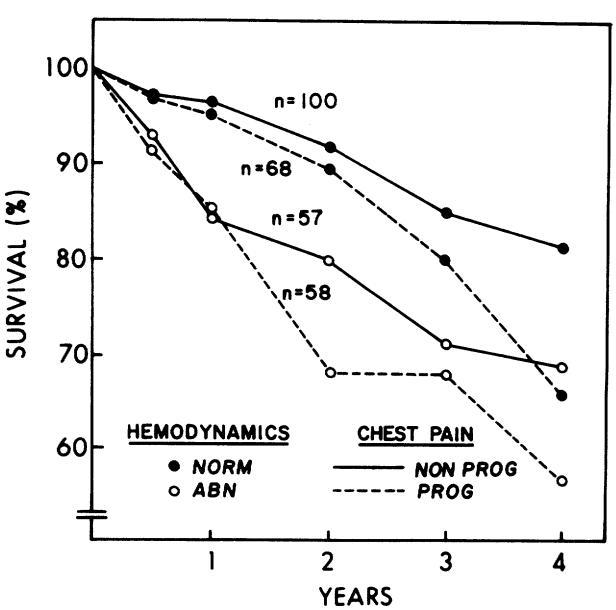

FIGURE 7. *Cumulative survival rates related to progressive (PROG) and nonprogressive (NONPROG) chest pain and normal (NORM) and abnormal (ABN) hemodynamic parameters in patients with three-vessel disease and moderate left ventricular (LV) dysfunction.*

LVEDP and AVOD have previously been identified as being individually associated with survival.[12, 15] However, their independence of coronary anatomy and LV contraction pattern and of each other had not been firmly established. In this study, complete characterization of LV function for prognostic purposes required descriptors of the overall contraction pattern, the sites of asynergy, the end-diastolic pressure and the AVOD.

Ejection fraction data were not analyzed in this study because they were complete in only a subset of patients with shorter follow-up than the total group. The ejection fraction is an important prognostic characteristic,[17] and fewer important descriptors might have been required to fully characterize LV function if ejection fractions had been available. The fact that left-main coronary disease was the most important prognostic variable reflects both the severity of the lesion itself and the degree of impaired LV function that existed in this medically treated subset.

From the analysis of all 81 baseline characteristics together, we conclude that neither noninvasive nor invasive characteristics alone were sufficient to define prognosis completely. For example, when noninvasive characteristics alone were used to predict survival, six patients with left-main coronary disease were included in the low-risk subgroup. On the other hand, noninvasive predictors added significant prognostic information to the catheterization findings. Of these, the risk associated with a history of peripheral vascular disease appeared to be independent of baseline ventricular function, suggesting that the combination of coronary disease and peripheral vascular disease was a marker of rapidly advancing arteriosclerosis.

Clinically, progressive chest pain was the most important of the independently significant clinical characteristics. Approximately one-third of the patients were suffering from progressive chest pain and, although its prevalence was related to the severity of the coronary disease, it was present in a significant proportion of patients at all levels of anatomic involvement and ventricular function. The effect of progressive chest pain on survival was consistently apparent across different degrees of disease severity and in particular, it was associated with a decreased survival in patients with normal ventricular contraction.

The definition of progressive chest pain in this study is similar to the definitions of unstable angina used by some authors.[26-30] Angina of recent onset was not automatically classified as progressive unless it actually increased in severity or frequency over a short period. Previous studies have not clearly demonstrated that chest pain characteristics are independently predictive of survival[6, 10, 11, 12, 17] Difficulty in defining a homogeneous population may be part of the explanation, but usually the effects of chest pain have been examined in small subsets and the problems associated with small patient numbers and interpretation of multiple statistical analyses with varying results have been encountered.

A small subset of patients with progressive chest pain had unstable angina, but unstable angina was not identified as an independently significant characteristic. This result indicates that when the other prognostic characteristics were considered, unstable angina did not contribute a significant risk greater than that associated with progressive chest pain. Thus in unstable angina, although there is an increased risk attributable to progressive chest pain as suggested by Alison et al.,[31] coronary anatomy and ventricular function are the main determinants of survival. The definition of unstable angina in the National Heart, Lung, and Blood Institute (NHLBI) randomized trial[32, 33] was similar to the definition of unstable angina in this study. Since patients unsuitable for surgery or with left-main coronary disease were excluded from the NHLBI trial, it is not surprising that the mortality among medically treated patients was lower than that recorded in early studies[27, 28] of uncatheterized, unselected patients with unstable angina.

Of the six independently significant noninvasive characteristics that did not remain significant in combination with the catheterization parameters, ST-T-wave changes, a history of previous myocardial infarction and cardiomegaly on the chest x-ray were related to ventricular function, which was more accurately described by ventriculographic and hemodynamic descriptors. The duration of symptoms, another independent clinical characteristic that failed to remain significant, has previously been shown to be associated with the extent of anatomical involvement.[12]

In a recent multiple variable analysis, Hammermeister et al.[17] similarly identified both noninvasive and invasive descriptors as independent predictors of survival. These investigators also found extent of coronary disease and ventricular function to be the significant invasive predictors. Ventricular arrhythmia on the resting ECG was independently significant in both studies. Their results differ from ours in regard to other noninvasive predictors. Hammermeister et al. identified only age in addition to ventricular arrhythmias as an independent descriptor; we identified six other clinical characteristics, including two related to pain pattern, as significant. The outcome of the two populations was different. There were 70 cardiovascular deaths among the 746 patients studied by Hammermeister et al., compared with 245 deaths among 1214 patients in the present study. There are at least four explanations for these differences. First, 39% of the patients in Hammermeister's study had no vessels with $\geq$ 70% stenosis and only 12% had significant three-vessel disease as defined in the present study. In another series of our own patients with only 50% stenosis, the survival was almost 100%.[16] Second, follow-up in the present study may have been longer, though this is not clear from the data in the Hammermeister paper. Third, the Seattle group included fewer descriptors of chest pain in their analysis. Fourth, the methods of analysis were different.

The stepwise analysis strategy used in the present study permitted a large number of characteristics to be analyzed jointly, with each characteristic being a candidate for inclusion in the final model regardless of its univariate significance. For example, sex was not a significant univariate predictor of survival but was selected in the final combination of clinical

characteristics, indicating that it contributed significant prognostic information after adjustment for the effect of the other independent characteristics. In the strategies applied to Cox model analysis of multiple characteristics by the Seattle group,[17, 34] the number of variables in the final analysis was limited by excluding those that were not significant in various intermediate stages of univariate and multivariable analysis. In the strategy applied to survival in coronary disease,[17] a discriminant analysis that can consider survival at only one time point was used for variable screening, and the Cox model was only applied at the final step. In both strategies, a variable that might have been significant in the final analysis may have been excluded because it was not significant at an intermediate stage. In fact, the number of vessels with ≥ 70% stenosis was eliminated by early discriminant analysis in one study[17] and when reintroduced into the final analysis, it was significant. There may have been other unrecognized, potentially significant characteristics that were also eliminated at an earlier stage.

The fact that in this study, 13 characteristics contained significant independent prognostic information indicates that the natural history of coronary artery disease can not be defined without reference to multiple baseline characteristics. The main determinant of the spectrum of prognostic characteristics in a population sample is the process by which patients are selected. Since the selection process varies from institution to institution, it is not surprising that there is a wide variation in reported survivals in coronary disease. Subsetting with respect to coronary anatomy and ventricular function controls the effect of two important prognostic factors, but still permits variation in important clinical and hemodynamic characteristics. The effect that variation in both progressive chest pain and hemodynamic parameters can have has been illustrated in this study. In one subset with defined coronary anatomy and LV function, 2-year survival varied from 93% in patients with normal hemodynamics and nonprogressive chest pain to 68% in patients with abnormal hemodynamics and progressive chest pain, an order of magnitude that is similar to the range of reported survival in patients with similar coronary anatomy and ventricular function.[12, 14]

An important implication of these results is that patients with different pain patterns cannot be compared, although they may have identical coronary anatomy and ventricular function. Thus, patients with uniformly stable or unstable angina cannot be readily compared with each other or with patients in the present study unless allowance is made for the heterogeneity of our patients with respect to pain pattern.

Differences in the prevalence of important prognostic characteristics may explain the higher survival rates in medically treated patients in the Veterans Administration (VA) Cooperative Study[14] compared with patients with equivalent coronary anatomy and ventricular function in the present study. Patients with unstable angina or congestive heart failure were excluded from the VA study. Patients with inoperable lesions were also excluded from the VA study but were included in this study, and in addition, 50% stenosis was considered significant in the VA study but only ≥ 75% stenosis was considered significant in the present study. The consistently lower survival rates reported from the Cleveland Clinic[7, 8, 10, 12] for patients with apparently equivalent catheterization findings are not so readily explainable.

These considerations emphasize the dangers in comparing the effect of treatment interventions within subsets based on a small number of prognostic characteristics; for example, the number of diseased vessels and ventricular function. Because multiple characteristics contribute to the final outcome, baseline comparability of the treatment and control groups cannot be ensured. In nonrandomized[35] and randomized trials,[36] treatment comparisons ought to include adjustment for differences in clinical and catheterization baseline characteristics.

Appendix

Strategy for Variable Selection

The stepwise strategy for selection of independently significant variables was similar to that of Peduzzi et al.[25] First, the characteristic with the largest single degree of freedom global chi-square statistic (Cox's equation 18) was selected for the model and the maximum likelihood estimate (MLE) of its regression parameter was computed. Then, adjusted single degree of freedom chi-square statistics (denoted by Q statistics) were calculated for each of the other characteristics. The Q statistics were similar to Cox's equation 18 but used only the derivatives of the log likelihood function taken with respect to each candidate parameter and evaluated at the MLE for the parameters already in the model and at zero for variables not yet selected. The characteristic with the largest Q statistic was the next one included in the model. After a variable was selected and new MLEs were computed for each variable in the model, chi-square statistics based on the square of the MLE divided by its estimated variance (denoted by MLE chi square) were calculated. Variables that had an MLE chi square not significant at the 5% level were dropped from the model. The stepwise selection process continued until no remaining variable had a Q statistic significant at the 10% level. The Q statistic computed for any variable before entry into the model agreed closely with its MLE chi square calculated immediately after entry. Our computer program for performing these Cox model analyses is an SAS (Statistical Analysis System) procedure.

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