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ORIGINAL ARTICLES

Variables Predictive of Survival in Patients with Coronary Disease

Selection by Univariate and Multivariate Analyses from the Clinical, Electrocardiographic, Exercise, Arteriographic, and Quantitative Angiographic Evaluations

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SUMMARY **A progression of univariate followed by multivariate analyses was applied to 46 variables selected from the clinical examination, exercise test, coronary arteriography, and quantitative angiographic assessment of left ventricular function in patients with coronary disease to determine those variables most predictive of survival. For the 733 medically treated patients, the final Cox's regression analysis showed that the left ventricular ejection fraction was most predictive of survival, followed by age, number of vessels with stenosis(es) ≥70%, and ventricular arrhythmia on the resting electrocardiogram. For the 1870 surgically treated patients, ventricular arrhythmia on the resting electrocardiogram was most predictive of survival followed by ejection fraction, heart murmur, left main coronary artery stenosis ≥50%, and use of diuretic agents.**

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IDENTIFICATION OF VARIABLES PREDICTIVE OF SURVIVAL or mortality in patients with coronary disease is important not only to identify patients at high risk for special attention, but also to assist in design and assessment of clinical trials (particularly nonrandomized) of therapeutic interventions such as coronary artery surgery and β-blocking agents. Many studies have been published identifying variables predictive of survival from the clinical examination, the resting electrocardiogram, the exercise electrocardiogram, the coronary arteriogram, and qualitative assessment of left ventricular function. These have been recently reviewed in detail.[1] One of these studies includes a multivariate analysis of coronary arteriographic variables together with variables from the clinical examination.[2] It is clear that left ventricular function assessed by angiography is an important predictor of survival.[3] However, we are not aware of studies reporting variables predictive of survival selected by multivariate statistical techniques from the clinical, arteriographic, and quantitative angiographic assessment of the coronary disease patient. It is the purpose of this report to identify the most important variables predictive of survival from the commonly performed examinations available to the modern cardiologist, including the clinical examination, resting electrocardiogram, maximal treadmill exercise stress test, coronary arteriogram, and quantitative analysis of the left ventricular angiogram. In the following companion paper, these variables are used to identify similar medically and surgically treated cohorts for comparisons of survival.

Methods

Seattle Heart Watch

Seattle Heart Watch is a cooperative, communitywide registry whose major goal is to identify people at risk of sudden cardiac death. Patients who underwent coronary arteriography for suspected coronary disease were entered into the angiography registry of Seattle Heart Watch from all of the laboratories performing coronary arteriography in Seattle (three private and two university teaching hospitals).[4] This report is based on an analysis of 746

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medically treated patients who underwent coronary arteriography and left ventricular angiography for suspected coronary disease between January 1, 1971 and December 31, 1974 (average follow-up 42 months; range 30–78 months); and 1870 patients who underwent direct myocardial revascularization between January 1, 1969 and December 31, 1974, (average follow-up 44 months; range 30–98 months). The surgical cohort represents 94% (1870 of 1985) of patients undergoing direct myocardial revascularization in Seattle during this time. However, entry into the medical cohort was limited to approximately 40% of available patients due to insufficient funding for data technicians at all contributing hospitals. Table 1 shows the distribution of the two cohorts by age, sex, and coronary disease. Follow-up with respect to cardiovascular death, myocardial infarction, or hospitalization related to coronary disease was done by mailing questionnaires at 6-month intervals. Review of hospital records, death certificates, and any other relevant information was used to classify follow-up events. In the event of a death, a panel of three cardiologists provided independent classifications of the cause of death — cardiac (sudden or non-sudden), noncardiac, or procedural (includes operative mortality in surgical cohort). In the medical cohort, 70 of the 85 deaths (82%) were from cardiac causes, and in the surgical cohort, 151 of the 173 deaths (87%) were from cardiac causes (including cardiac-related procedural deaths in both groups).

TABLE 1. *Demographic Data*

	Medically treated patients Number	(%)	Surgically treated patients Number	(%)
Age (years)				
≤ 40	90	(12)	104	(6)
41–50	222	(30)	503	(27)
51–60	316	(43)	894	(49)
≥ 61	102	(14)	335	(18)
	730		1,836	
Sex				
Male	584	(80)	1,651	(88)
Female	149	(20)	219	(12)
	733		1,870	
Coronary vessels ≥ 70% stenosis				
0	283	(39)	17*	(1)
1	213	(29)	502	(27)
2	149	(20)	718	(38)
3	88	(12)	633	(34)
	733		1,870	

*Patients who had 50-69% stenoses in one or more major coronary artery(ies) and were felt to be surgical candidates.

Data Collection

Upon entry into the angiography registry, more than 300 items from the history, physical examination, resting electrocardiogram, chest roentgenogram, exercise electrocardiogram, and cardiac catheterization were coded on standardized forms. The treadmill maximal exercise stress test was performed according to the Bruce protocol.[5] Left ventricular volumes were calculated at the two university laboratories from the left ventricular angiograms as described by Dodge et al.[6] or as modified by Kennedy et al.[7] for the single-plane cineangiogram.

Forty-six variables were selected for further analysis based on their possible relevance to survival as judged from previous publications and clinical experience. Some of the variables are defined as follows: unstable angina — angina at rest or nocturnal angina; myocardial infarction — documented by ECG or enzyme changes; risk factor index — number of the four following risk factors in any patient: smoking, hypertension, diabetes, and positive family history of coronary disease; resting ST-segment depression — horizontal or downsloping ST-segment depression ≥0.5 mm; resting ST-segment elevation — ST-segment elevation ≥0.5 mm; left ventricular ischemia — electrocardiographic T wave abnormalities; functional aerobic impairment — percent decrement from predicted maximal oxygen consumption based on age, sex, and activity status;[5] exertional hypotension — blood pressure during exertion lower than resting blood pressure before exercise testing; exertional ST-segment depression — horizontal or downsloping ST-segment depression ≥1 mm during or after exercise; exertional ST-segment elevation — ST-segment-elevation ≥1 mm during or after exercise; feasibility index — number of vessels with proximal stenosis(es) ≥70% minus the number of graftable distal vessels. Left ventricular contraction grade was based on a subjective grading of the left ventricular angiogram as described by Hamilton et al.[8] Brief definitions are as follows: I = normal, II = hypokinesis or akinesis involving less than 25% of the ventricular circumference, III = hypokinesis or akinesis involving 25–75% of the ventricular circumference, IV = dyskinesis, V = diffuse hypokinesis or akinesis involving more than 75% of the ventricular circumference.

Data Analyses

The goal of the analyses was to determine which variables were independently predictive of survival and from which predictive models could be developed. This was done in a stepwise manner, beginning first with the identification of 46 variables of potential predictive value, based on previous studies and clinical experience. These 46 variables were then screened using univariate statistical methods followed by multivariate screening, in which variables identified as univariately predictive of survival were entered into stepwise, linear, discriminant analyses based on survival at 2 years.[9] The interval of 2 years was selected because discriminant analysis requires all patients to be followed for a minimum, fixed period of time; most

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patients in this study had been followed 2 years or more. Finally, variables identified as multivariately discriminating between survivors and nonsurvivors at 2 years were then entered into Cox's regression model for survival analysis[10] to determine variables predictive of survival over the entire follow-up period. A stepwise algorithm was used to select the most important covariates.

Two techniques of univariate screening were used. First, the significance of the difference of means of continuous variables (*t* test) or distribution of dichotomous variables (chi square test or Fisher's exact text) between survivors and nonsurvivors in both the medical and surgical cohorts was calculated. Second, mortality rates were calculated for subgroups of the medical and surgical cohorts defined by specified values or categories of each variable. Bonferroni's inequality was used to construct simultaneous 95% confidence intervals for these exponential rates.[11] A variable was defined as univariately predictive of survival if the 95% simultaneous confidence intervals for any of the categories of that variable did not overlap.

The stepwise, discriminant analyses used cardiac death within 2 years as the event of interest and were performed initially in blocks using those variables which were univariately predictive of survival. The blocks of variables were defined to relate to increasing complexity of patient evaluation: first, the routine clinical evaluation including history, physical examination, chest roentgenogram, and resting electrocardiogram (18 variables); then the exercise stress test (8 variables); and finally, the cardiac catheterization (9 variables). The final stepwise, discriminant analysis included all variables which were at least marginally predictive of survival within each block ($F \geq 2.7$). Because exercise testing was performed on only 38% of the surgical cohort and 75% of the medical cohort, the final stepwise, discriminant analyses were performed both with and without the exercise stress test variables.

The variables which were least marginally predictive of survival at 2 years in the final stepwise, discriminant analysis were entered into another stepwise selection method using Cox's regression model for survival analysis. This is both an analogue of multiple linear regression analysis and an exponential model designed for survival data which uses the variable amounts of follow-up available. The stepwise selection method for Cox's model used maximum likelihood principles, choosing the variable in each step which maximized the likelihood function and terminating when the increase in likelihood caused by the addition of another variable to the model was not significant at $\alpha = 0.05$ (based on $\chi^2_1 = -2$ log likelihood ratio).

Finally, to illustrate the effect of these variables on survival, 3-year survival probabilities ($\hat{P}_r$) were calculated using the Cox model according to the equation

$$\hat{P}_r = \hat{F}_o(t)e^{\beta_1(X_1 - \bar{X}_1) + \beta_2(X_2 - \bar{X}_2) + \ldots \beta_p(X_p - \bar{X}_p)} \quad (1)$$

where $F_o(t)$ is the probability of survival to time t with all variables set equal to their mean and β is a measure of the predictive value of the independent variables. Further discussion of the use of this model is given by Breslow.[12, 13]

Results

The results of the two types of univariate screening, given in table 2, indicate that 35 of the 46 variables were univariately predictive of survival for the medical cohort or the surgical cohort or both. The remaining 11 variables which were not predictive of survival by these univariate tests are: unstable angina, risk factor index, resting ST-segment elevation, left ventricular ischemia, exertional hypotension, chest pain during exercise testing, exertional ST-segment depression, exertional ST-segment elevation, feasibility index, stroke volume, and cardiac output; these variables were excluded from further analysis. The 35 variables univariately predictive of survival were then divided into three groups: those from the clinical examination, those from the exercise test, and those from cardiac catheterization. Further screening was performed using stepwise, discriminant analysis. The results of these discriminant analyses are given in table 3.

For the 18 variables from the clinical examination which were univariately predictive of survival (table 2), a stepwise, discriminant analysis indicated that nine variables for the medical cohort and five for the surgical cohort were potentially predictive of survival ($F \geq 2.7$, table 3). Cardiac enlargement, ventricular arrhythmia, age, and use of diuretics demonstrated the strongest relationships with 2-year cardiac mortality in the medical cohort. In the surgical cohort, ventricular arrhythmia and congestive heart failure demonstrated the strongest relationship with 2-year cardiac mortality.

Of the eight exercise test variables univariately predictive of survival (table 2), four were selected by the stepwise, discriminant analysis (table 3). In the medical cohort, the maximum pressure-rate product was by far the most important variable. In the surgical cohort, only two variables were selected from the preoperative exercise test — maximal change in heart rate and total duration of exercise. Neither demonstrated a very strong relationship with 2-year cardiac mortality.

From the nine variables obtained at cardiac catheterization which were univariately predictive of survival (table 2), four were selected by the stepwise, discriminant analysis (table 3). In the medical cohort, a strong relationship was demonstrated between end-systolic volume and cardiac death within 2 years. In fact, the relationship was so strong ($F = 63.9$), that no other variables added a significant contribution to prediction of cardiac death within 2 years. In the surgical cohort, ejection fraction, presence of stenosis greater than 50% in the left main coronary artery, and left ventricular contraction grade were the most important variables.

The variables selected in each category by stepwise, discriminant analyses (table 3) were then

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TABLE 2. *Univariate Analyses for Variables Predictive of Survival**

Source Variable	Significantly different between survivors and nonsurvivors: Medical	Significantly different between survivors and nonsurvivors: Surgical	Mortality rates (deaths/1000 man-years)	Medical	Surgical
Clinical examination					
Age	Yes	Yes			
Sex	Yes	No	Male	54	
			Female	21	
Angina	Yes	No	Present	58	
			Absent	14	
Myocardial infarction	Yes	No	Present	72	
			Absent	33	
Congestive heart failure	Yes	Yes	Present	196	99
			Absent	35	35
Functional class	Yes	Yes	I	20	
			II	32	
			III	91	
			IV	152	
Use of digitalis preparation	Yes	Yes	Yes	136	74
			No	35	36
Use of diuretic	Yes	Yes	Yes	128	68
			No	31	35
Use of antiarrhythmic agent	Yes	No	Yes	113	
			No	41	
Relative weight	Yes	No			
Diastolic pressure	Yes	No			
S_3 gallop	Yes	Yes	Present	228	
			Absent	38	
Heart murmur	Yes	Yes	Present	95	64
			Absent	38	35
Cardiac enlargement	Yes	Yes	Present	204	88
			Absent	34	38
Ventricular arrhythmia	Yes	Yes	Present	141	127
			Absent	40	35
Resting ST-segment depression	Yes	Yes			
LVH	Yes	No	Present	145	
			Absent	30	
Prolonged QRS	Yes	Yes	Present	172	
			Absent	42	
Exercise test					
Exercise duration (seconds)	Yes	Yes	$\leq$ 180	106	
			181-360	41	
			$\geq$ 361	22	
Functional aerobic impairment (%)	Yes	Yes			
Maximum exercise heart rate	Yes	No			
Maximum exercise systolic pressure (mm Hg)	Yes	No	$\leq$ 130	143	
			131-160	37	
			$\geq$ 161	24	
Maximum exercise PRP	Yes	No	$\leq$ 26,700	62	
			26,800-39,800	16	
			$\geq$ 39,900	0	
Maximal increment in exercise heart rate	Yes	No			
Maximal increment in exercise systolic pressure (mm Hg)	Yes	No	$\leq$ 32	72	
			33-96	23	
			$\geq$ 97	0	
Exertional arrhythmia	Yes	No	Present	80	
			Absent	32	
Cardiac catheterization					
Number of stenotic vessels ($\geq$ 70%)	Yes	Yes	1	30	25
			2	96	33
			3	161	60
Collateral vessels	Yes	No	Present	76	
			Absent	22	
Left main stenosis $\geq$ 50%	Yes	Yes	Present	165	100
			Absent	44	34
LVEDP (mm Hg)	Yes	Yes	$\leq$ 12	28	
			13-18	65	
			$\geq$ 19	118	
Mitral regurgitation	Yes	Yes	Present	349	
			Absent	44	

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TABLE 2. (*Continued*)

Source Variable	Significantly different between survivors and nonsurvivors: Medical	Surgical		Mortality rates (deaths/1000 man-years): Medical	Surgical
Left ventricular contraction grade	Yes	Yes	1	16	
			2	21	
			3	60	
			4	113	
			5	214	
End-diastolic volume (ml/m²)	Yes	Yes	≤ 90	30	32
			91-110	68	42
			≥ 111	178	126
End-systolic volume (ml/m²)	Yes	Yes	≤ 34	23	29
			35-44	58	33
			≥ 45	132	84
Ejection fraction	Yes	Yes	≤ 30	272	144
			31-50	85	54
			≥ 51	22	30

*Mortality rates are given only when significantly different (nonoverlapping 95% confidence intervals) between subgroups.
Abbreviations: LVH = left ventricular hypertrophy on resting ECG; PRP = pressure rate product; LVEDP = left ventricular end-diastolic pressure.

simultaneously entered into a final stepwise, discriminant analysis. The results, excluding the exercise test variables, are shown in table 4. For medically treated patients, end-systolic volume, ventricular arrhythmia on the resting electrocardiogram, and age were the most predictive variables. In the surgical cohort, congestive heart failure, ejection fraction, percent stenosis of left main coronary artery, and ventricular arrhythmia were most predictive; but four additional variables demonstrated relationships to death within 2

TABLE 3. *Results of Preliminary Stepwise, Discriminant Analysis Selecting Variables Predictive of Death Within 2 Years*

Source of variables Variable	Medical cohort: Increase in R^2	F (1, ∞)	Surgical cohort: Increase in R^2	F (1, ∞)
History, physical examination, ECG, X-ray	N = 499		N = 777	
Cardiac enlargement	0.053	27.6		
Ventricular arrhythmia	0.030	16.2	0.021	17.0
Age	0.021	11.4	0.008	6.3
Use of diuretic	0.018	10.1		
S_3 gallop	0.011	6.4		
Congestive heart failure	0.007	4.1	0.012	9.6
Resting ST-segment depression	0.006	3.7		
Sex	0.006	3.5		
Heart murmur	0.006	3.5	0.005	3.7
Use of antiarrhythmic drugs			0.008	6.7
Maximal treadmill exercise test	N = 417		N = 513	
Maximal pressure rate product	0.048	20.9		
Maximum systolic pressure	0.013	5.8		
Maximal increment in heart rate	0.010	4.6	0.007	3.7
Total duration of exercise			0.009	4.7
Arteriography-Angiography	N = 381		N = 593	
End-systolic volume	0.144	63.9		
Ejection fraction			0.013	7.7
Left main coronary artery stenosis ≥ 50%			0.010	5.9
Contraction grade			0.007	4.3

Abbreviation: N = number of patients used in each stepwise, discriminant analysis (known values for all variables).

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TABLE 4. *Final Stepwise, Discriminant Analysis Selecting Variables Predictive of Survival from Among All Variables Previously Screened Excluding Exercise Test Variables*

Variable	Medical: Increase in R^2 (N = 439)	Medical: F (1, ∞)	Surgical: Increase in R^2 (N = 664)	Surgical: F (1, ∞)
End-systolic volume	0.118	58.2		
Ventricular arrhythmia	0.030	15.1	0.007	5.02
Age	0.017	8.7		
Congestive heart failure			0.021	14.3
Ejection fraction			0.014	9.5
% Stenosis in left main coronary artery			0.010	7.1
Use of antiarrhythmic drugs			0.005	3.8
Murmur			0.006	3.8
Use of diuretics			0.004	2.7
LV contraction grade			0.004	2.8
Total R^2	0.165		0.071	

Abbreviation: N = number of patients used in each stepwise, discriminant analysis.

years which were of borderline significance and, therefore, were included in further analyses. The exercise variables were excluded from this analysis and the subsequent Cox's regression analysis because these data were available in only 38% of the surgical cohort and 75% of the medical cohort. When this stepwise, discriminant analysis included the exercise variables, increase in heart rate with maximal exertion was predictive of cardiac death within 2 years (F = 13.2, increase in R^2 = 0.036) in the 311 medically treated patients in whom these data were available. No exercise variables were predictive of cardiac death within 2 years in the 335 surgically treated patients with these data available.

TABLE 5. *Stepwise Selection of Covariates Using Cox's Regression Model for Survival Analysis*

Cohort	Step	Variable entered	χ_1^2
Medical		N = 550	
	1	Ejection fraction	48.54
	2	Age	17.16
	3	Number of vessels with stenosis(es) ≥ 70%	7.36
	4	Ventricular arrhythmia	4.46
Surgical		N = 913	
	1	Ventricular arrhythmia	19.4
	2	Ejection fraction	13.22
	3	Heart murmur	10.96
	4	Left main coronary artery stenosis	7.94
	5	Use of diuretics	5.38

Abbreviation: N = number of patients used in each Cox's regression analysis.

TABLE 6. *Predicted 3-Year Survival Probabilities for Discrete Values of Age, Ejection Fraction and Number of Stenotic Vessels, and Presence or Absence of Ventricular Arrhythmia*

Medically Treated Patients

		Number of stenotic vessels (≥ 70%): 1	2	3
Ejection fraction = 0.60				
Age	Ventricular arrhythmia			
40	−	0.97	0.95	0.93
40	+	0.96	0.94	0.91
50	−	0.96	0.94	0.90
50	+	0.95	0.92	0.88
60	−	0.94	0.91	0.87
60	+	0.92	0.89	0.84
Ejection fraction = 0.45				
Age	Ventricular arrhythmia			
40	−	0.94	0.90	0.86
40	+	0.92	0.88	0.82
50	−	0.91	0.87	0.81
50	+	0.89	0.83	0.76
60	−	0.88	0.82	0.75
60	+	0.85	0.78	0.68
Ejection fraction = 0.30				
Age	Ventricular arrhythmia			
40	−	0.87	0.81	0.72
40	+	0.83	0.76	0.66
50	−	0.82	0.74	0.64
50	+	0.78	0.68	0.56
60	−	0.76	0.66	0.54
60	+	0.71	0.59	0.45

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For the subsequent analyses, the decision was made to reintroduce the variable indicating the number of coronary vessels with at least a 70% stenosis. This decision was based on the fact that this variable is usually considered one of the most important predictors of mortality in coronary disease patients, even though it did not demonstrate a relationship with 2-year mortality as strong as other variables in the preceding discriminant analysis. This subjective judgment of the possible importance of this variable, despite the initial screening out by the discriminant analyses, turned out to be correct, since the number of vessels with ≥70% stenosis was one of four variables finally selected by Cox's regression analysis as most predictive of survival in the medical cohort.

The results of the final variable selection procedure using Cox's survival regression model[9] are given in table 5. Although end-systolic volume had previously demonstrated a very strong relationship with survival in the medical cohort, it was not selected as being significant in the Cox's regression analysis because ejection fraction demonstrated a stronger relationship when all follow-up data were used. Ejection fraction and end-systolic volume are highly correlated, so that once the variable having the strongest relationship with survival is selected, the amount of additional information contributed by the other is not statistically significant.

Table 6 shows estimated 3-year-survival probabilities calculated according to equation (1) for medically treated patients with coronary disease for three discrete values of ejection fraction and age, number of vessels with stenosis ≥70%, and presence or absence of ventricular arrhythmia. These variables define more than 18-fold differences in 3-year probability of death, from 0.03 for a 40-year-old patient with ejection fraction of 0.60, single-vessel disease, and no ventricular arrhythmia on resting electrocardiogram, to 0.55 for a 60-year-old patient with ejection fraction of 0.30, three-vessel disease, and ventricular arrhythmia on resting electrocardiogram.

Table 7 shows similar estimated 3-year survival probabilities for surgically treated patients calculated for three discrete values of ejection fraction and the dichotomous variables: ventricular arrhythmia on resting electrocardiogram, diuretic usage, heart murmur, and left main coronary artery stenosis ≥50%. These variables define a similar 18-fold spread in 3-year probability of death, from 0.04 in a patient with an ejection fraction of 0.60 and the other four variables absent, to 0.74 in a patient with an ejection fraction of 0.30 and the other four variables present.

Discussion

This study was designed to identify variables predictive of survival from the clinical tools commonly used by the cardiologist in the evaluation of the symptomatic patient with coronary disease. In medically treated patients, ejection fraction was most predictive

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TABLE 7. *Predicted 3-Year Survival Probabilities for Discrete Values of Ejection Fraction and Presence or Absence of Ventricular Arrhythmia, Heart Murmur, Use of Diuretic Agent, and Left Main Coronary Artery Stenosis (≥ 50%)*

		Surgically Treated Patients			
		Left main stenosis < 50%		Left main stenosis ≥ 50%	
		Heart murmur absent	Heart murmur present	Heart murmur absent	Heart murmur present
Ejection fraction = 0.60					
Ventricular arrhythmia	Use of diuretic				
−	−	0.96	0.94	0.93	0.87
−	+	0.94	0.89	0.87	0.78
+	−	0.93	0.87	0.85	0.75
+	+	0.87	0.78	0.75	0.60
Ejection fraction = 0.45					
Ventricular arrhythmia	Use of diuretic				
−	−	0.94	0.90	0.89	0.80
−	+	0.90	0.83	0.80	0.67
+	−	0.88	0.80	0.77	0.63
+	+	0.80	0.67	0.63	0.43
Ejection fraction = 0.30					
Ventricular arrhythmia	Use of diuretic				
−	−	0.91	0.84	0.82	0.70
−	+	0.84	0.73	0.70	0.53
+	−	0.82	0.70	0.66	0.47
+	+	0.70	0.52	0.48	0.26

of survival, followed by age and extent of coronary disease. In surgically treated patients, any ventricular arrhythmia on the resting electrocardiogram was the most significant variable followed by several variables related to left ventricular function.

Patient Population

The results of any analysis of this type are influenced by the type of patients studied. All patients included here presented themselves to a cardiologist and had coronary arteriography, almost always for evaluation and treatment of chest pain. Patients were selected by their physicians for medical or surgical therapy on the basis of clinical criteria then in common use. Our previous analysis showed that the medically treated cohort differed from the surgically treated cohort in a number of important variables.[4]

Exercise Test Data

When the exercise variables are examined, the hemodynamic response to exercise and duration of exercise are clearly predictive of survival, while exertional ST-segment depression does not contribute additional information predictive of survival when considered together with these other exercise variables in patients with known coronary disease. Similar findings have been reported by Bruce et al. in another group of Seattle Heart Watch patients.[14] The hemodynamic response to exercise (blood pressure and pulse) is probably in large part a reflection of the functional status of the left ventricle,[14] again confirming the finding of this report that left ventricular function is the most important predictor of survival in coronary disease patients. However, in patients undergoing catheterization with arteriography and quantitative angiography, the exercise test variables do not appear to contribute greatly to prediction of prognosis in addition to the clinical and catheterization variables. It is not surprising that direct analysis of left ventricular function by invasive means should provide better prediction of survival than the indirect parameters of the exercise test. These observations in no way negate the prognostic usefulness of the exercise test, particularly in patients not undergoing cardiac catheterization, and underscore the importance of observing blood pressure and pulse changes during exercise. The restriction of exercise data to 46% (1193 of 2603) of the population studied may limit the applicability of these findings and led us to eliminate the exercise variables from the final stepwise, discriminant analysis (table 4) and Cox's regression analyses (table 5).

Selection of Variables

We used a progression of statistical techniques to select, from a pool of over 300 variables (many of which were redundant or obviously unimportant), a small, manageable number of variables which would give all or nearly all of the prognostic information available to us for the purpose of creating matched pairs of medically and surgically treated patients with similar survival expectations and for use in Cox's regression analysis in testing for the effect of treatment on survival (see the following paper). The order of the progression we chose was: 1) selection based on clinical judgment and previous studies (46 variables), 2) two univariate tests — mortality rates and differences in means or distributions between survivors and nonsurvivors (35 variables), 3) stepwise, discriminant analyses performed on groups of variables according to source (clinical examination, exercise test, or cardiac catheterizations; 18 variables), 4) a stepwise, discriminant analysis performed on all the statistically significant variables from the previous step (10 variables), and 5) Cox's regression analysis (seven variables). It was not feasible to enter all possible variables at steps 4 or 5 because the computer programs could not handle large numbers of variables simultaneously and because of the expense of multiple runs of these complex programs adding one variable at a time. We do not imply that the seven variables finally selected (table 5) are necessarily unique solutions to the question; another progression or technique of statistical analyses might result in a somewhat different list of variables, particularly for those variables at the low range of statistical significance. However, ejection fraction, ventricular arrhythmia, and age (or other closely related variables, such as end-systolic volume) appear to be so relevant to survival that any sound multivariate technique would select them.

Other Studies

We are aware of only one other report of multivariate analyses relating both clinical and catheterization variables to survival.[2] Although quantitative angiographic estimates of left ventricular function were not available in this report, heart size on the plain chest film and a history of congestive heart failure symptoms were two of the first three predictive variables on discriminant function analysis. These data indicating the prognostic importance of left ventricular function are compatible with ours.

Other univariate and multivariate studies not involving angiographic or arteriographic data have recently been reviewed by Moss.[1] A univariate study from the Cleveland Clinic documents the prognostic importance of qualitative assessment of left ventricular function in medically treated patients,[3] while the study of Solignac et al. indicates the significance of left ventricular function in late postoperative survival.[15]

Clinical Significance of Findings

The prime importance of variables related to left ventricular function as predictors of survival suggests several corollaries relevant to the current controversy

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about the effect of coronary surgery on survival. First, since left ventricular function measured at rest is the most important predictor of survival in the medical cohort, and since poor left ventricular function is associated with high operative and early medical mortality, and since left ventricular function at rest is not improved by revascularization,[16] one would not anticipate significantly improved survival from surgical therapy in patients with severe left ventricular dysfunction (e.g., ejection fraction <0.30). The similar overall poor survival of medical and surgical patients with severe left ventricular dysfunction[4, 17] seems to corroborate this point.

Second, patients with normal left ventricular function will have good early survival (several years) regardless of the extent of their coronary disease (with the possible exception of patients with severe left main coronary artery stenosis). Thus, short term studies[4, 18] comparing survival of medically and surgically treated patients cannot be expected to show differences in survival. Follow-ups of 5 years or more may be necessary to obtain definitive answers. However, if myocardial revascularization prevents myocardial infarction or development of left ventricular dysfunction, then this group of patients ultimately has the most to gain from surgery.

Finally, as appears to be the case, short-term studies (2–3 years) would be most likely to show significant effects on survival by revascularization in patients with moderate impairment of survival and left ventricular function. In our previous report of nonrandomized patients analyzed by extent of coronary disease and ejection fraction, the subgroup with two-vessel disease and moderate impairment of left ventricular function (ejection fraction = 0.31–0.50) showed the most significant difference in survival between medical and surgical therapy.[4] Similarly, the VA Cooperative Study on Stable Angina shows a trend toward improved survival in surgically treated patients with three-vessel disease and abnormal left ventricular function (patients with heart failure or severe impairment of left ventricular function were excluded).[19]

The number of significantly diseased coronary vessels was a predictive variable in the medical cohort, but not the surgical cohort. Since the surgical cohort had a larger number of vessels with stenosis(es) ≥70% per patient (2.07) than the medical cohort (1.72), the absence of this variable as a predictor of survival in the surgical cohort suggests that it has been successfully altered by surgery.

The presence or absence of ventricular arrhythmia on the resting electrocardiogram was a significant predictor in both the medical cohort and the surgical cohort. It is encouraging to note that the prognostic significance of this variable was in addition to variables relevant to left ventricular function or extent of coronary disease. Thus, suppression of ventricular arrhythmias by antiarrhythmic drugs has a possible potential for altering survival and underscores the need for controlled trials on the effect of antiarrhythmic therapy on late survival. We had available only a crude assessment of ventricular arrhythmia (presence or absence on resting electrocardiogram). More sophisticated detection by ambulatory monitoring or exercise testing would probably enhance the prognostic significance of this variable.

Three of the five variables predictive of survival in the surgical cohort probably relate to left ventricular function either directly or indirectly: ejection fraction, heart murmur, and use of diuretics. The relationship with ejection fraction and use of diuretics to left ventricular function is relatively clear. While the presence of a heart murmur in the general population probably does not relate to left ventricular function, in patients with coronary artery disease it usually means mitral regurgitation secondary to papillary muscle dysfunction. This condition is frequently associated with extensive myocardial damage. Nevertheless, heart murmur predicts survival independent of ejection fraction, suggesting that the presence of mitral regurgitation is an ominous finding regardless of ejection fraction.

An important use of this data is in the identification of cohorts of patients with similar baseline survival characteristics or in the multivariate correction of differences in survival characteristics of two cohorts of patients. In the following report, we use these variables to analyze the effect of surgical revascularization on survival in nonrandomized cohorts of medically and surgically treated coronary disease patients.

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Evidence from a Nonrandomized Study that Coronary Surgery Prolongs Survival in Patients with Two-Vessel Coronary Disease

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SUMMARY **Within the larger Seattle Heart Watch arteriography registry, surgically treated patients nonrandomly selected for direct myocardial revascularization were matched to medically treated patients such that each of the 287 pairs was identical in seven variables (ejection fraction, ventricular arrhythmia on resting electrocardiogram, age, heart murmur, stenosis of left main coronary artery ≥50%, number of vessels with stenosis ≥70%, and use of diuretics) previously demonstrated to be independently predictive of survival. Actuarial survival analyses based on cardiovascular deaths (average follow-up 3.5 years) indicate improved survival for the entire surgical matched pair cohort ($p = 0.008$) and for the surgically treated subgroup with two-vessel disease ($p = 0.0002$) when compared to the medical cohort. These results were confirmed by examination of the entire arteriography registry (n = 1524) in which these seven variables were known, using Cox's model for survival analysis. This multivariate, statistical technique indicated that the surgical mode of therapy was significantly predictive of improved survival in surgically treated patients for the entire registry ($p = 0.008$) and for the subgroup with two-vessel disease ($p = 0.0005$).**

WHILE DIRECT MYOCARDIAL REVASCULARIZATION often provides symptomatic relief for patients with chronic angina, the effect of surgery on survival is controversial.[1, 2] We have reported on survival analyses of nonrandomized medically and surgically treated patients who had been classified and compared according to ejection fraction and number of stenotic (≥70%) vessels.[3] Although we noted better survival in surgically treated patients with normal or moderately abnormal ejection fraction and two-vessel disease, differences remained in survival-related variables between the two cohorts which may have accounted for some of the differences in survival. In this report we will detail further survival analyses and attempt to correct for the differences between the two cohorts caused by the nonrandom selection for surgery. The results suggest that surgical therapy provides improved survival over medical therapy in patients with two-vessel disease.

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Methods

We have used two approaches in our analyses: a univariate, matched pair technique and a complex, multivariate analysis, the Cox's regression model for survival data.[4]