NATURAL HISTORY OF CORONARY ARTERY DISEASE*

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WITH recent advances in surgery of the coronary arteries the identification of patients likely to benefit from such treatment becomes crucial. In order to advise patients regarding revascularization procedures it is essential to understand the natural history of ischemic heart disease from the standpoint of the individual and the likelihood that he will ultimately derive benefit. The physician must know which factors are of prognostic import in order to approach intelligently the question of clinical management when diverse therapeutic possibilities exist. Coronary arteriography with all its limitations[1] provides essential information regarding the feasibility of surgery, offers a standard upon which to gauge severity of disease, and promises valuable prognostic indices beyond available clinical measures.[2]

We analyzed data from 301 patients studied for ischemic heart disease by means of coronary arteriography from July 1965 through June 1970. Prior to July 1970 saphenous-vein bypass grafts and other forms of surgical therapy intended for the relief of angina pectoris were not performed routinely at the University of Alabama Medical Center.

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These patients have been observed up to four years since initial evaluation. In this report we describe the mortality of the disease as related to clinical and laboratory observations at the time of arteriography in order to isolate the factors which can be used for predicting subsequent mortality.

Methods

The experimental population included all individuals referred for evaluation of ischemic heart disease who underwent coronary arteriography at the Medical Center from July 1965 through June 1970. During this period selective coronary arteriograms using the technique of Sones and Shirey[3] were performed on 437 patients. Associated cardiovascular disease such as myocardiopathy or significant valvular disease, noncardiovascular disease severely impairing prognosis, or technically unsatisfactory arteriographic studies constituted exclusions from the study. Of the 304 remaining patients, two could not be located for follow-up information and one patient died during the immediate postcatheterization period. Fifty-five patients subsequent to arteriography underwent cardiovascular surgical procedures and are omitted from these analyses.

The data on the remaining 246 patients used for this study were obtained from the history, physical examination, and laboratory procedures completed during the admission work-up prior to coronary arteriography. Historical variables were coded by two of the investigators (A.O. and C.P.R.) using predetermined definitions.

Clinical History and Physical Examination

Definite angina pectoris was defined as retrosternal discomfort precipitated by exertion and relieved by rest, assuming all other chest pain, atypical in location or primarly brought on by nonexertional stress, as questionable. In subsequent discussion only such chest pain classified as definite angina pectoris will be referred to as angina pectoris. Unstable angina was defined as definite or questionable angina either occurring at rest, lasting 15 minutes or more during a single episode, or having onset three months or less prior to admission. A history of myocardial infarction was based on length of hospitalization, type of pain, elevation of enzymes, and electrocardiographic changes. Paroxysmal noc-

turnal dyspnea (PND), orthopnea, and dyspnea on exertion (DOE) were also recorded. Patients were grouped by smoking habits into non-smokers, ex-smokers, those smoking less than 20 cigarettes per day, and those smoking 20 or more cigarettes per day. Other historical variables included history of hypertension or diabetes and current drug therapy. The supine systolic and fifth-phase diastolic blood pressure recorded from the right arm was used.

Other Clinical Measurements

Laboratory variables included plasma cholesterol, triglyceride, and glucose; only cholesterol determinations were used for the present analyses. Electrocardiograms were classified according to the Minnesota Code,[4] with the addition of a code for "true" posterior infarction. Heart rate was also determined from the resting electrocardiogram. Exercise electrocardiograms were performed on patients to a 90% predicted maximal heart rate or clinical indication for stopping, using the stages of the Bruce test,[5] although a few early tests were completed using a different methodology.[6] A positive exercise response consisted of at least 1.0 mm. horizontal down-sloping ST segment depression of 0.08 seconds duration or 2.0 mm. of ST elevation during or after exercise. Heart size was calculated from PA and lateral chest roentgenograms and expressed as volume per square meter of body surface area.[7]

Scoring of Coronary Arteriograms

All coronary arteriograms were reviewed by a single observer (W.B.J.) without knowledge of the clinical history. Each of the three major vessels was subdivided into proximal and distal halves and graded separately on a numerical basis: 1=no significant obstruction; 2=less than 50% obstruction; 3=50% to 75% obstruction; 4=more than 75% obstruction; 5=complete occlusion. The main left segment was also evaluated. The maximal score for each of the seven arterial segments was used to categorize the arteriogram. For most analyses a composite score consisting of no-vessel, one-vessel, two-vessel, and three-vessel disease was computed. For this score we arbitrarily considered a vessel diseased if the maximal obstruction in any vessel was 50% or more. Obstruction of the main left was regarded as equivalent to disease of the anterior descending and circumflex arteries.

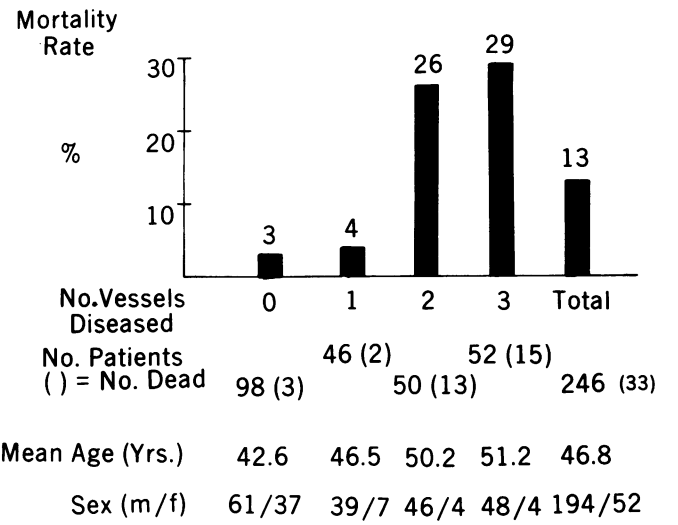


Fig. 1. Mortality by selected characteristics and number of vessels diseased.

Follow-up

The referring physician of each patient was contacted to determine the cardiovascular status of each individual and to request permission for follow-up examination at the Heart Evaluation Clinic of the Medical Center. Those patients who had moved or had changed physicians were contacted by letter or telephone to obtain follow-up information.

For patients who died during the period of follow-up a summary of the terminal episode was obtained from the physician if possible; if not, from the family; death certificates were obtained and the underlying cause of death noted.

Computation Methods

Discriminant function analysis[8] was used to develop a linear prediction equation of living versus dead as a function of selected variables and to test for the independent contribution of each with an appropriate significance test (Snedecor's F test). Selection of important variables was made by a modification, "Max R^2 method,"[9] of the standard "stepwise regression" procedure. Estimates of survival curves were obtained

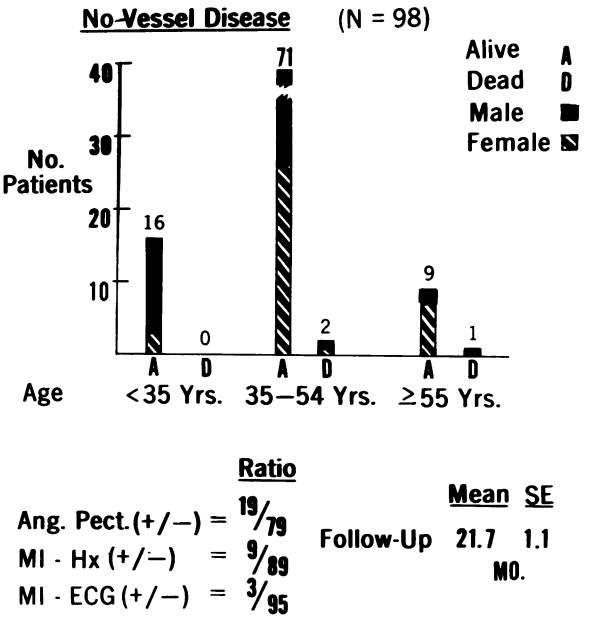
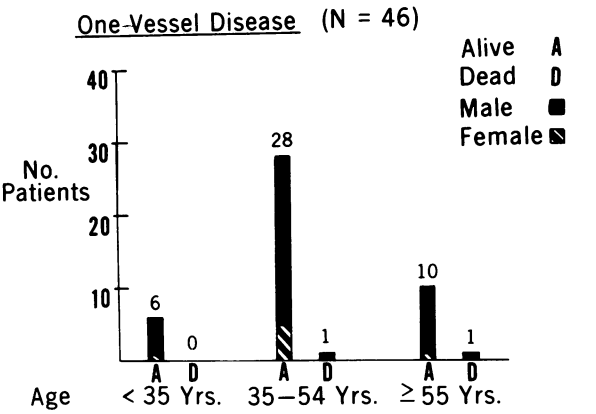


Fig. 2. Distribution of selected population characteristics in no-vessel disease (N = 98).

by the Bohmer "product-limit" procedure as described by Kaplan and Meier[10] and summarized by Burdette and Gehan.[11] Relative risk is the ratio of the rate for those individuals with a selected trait to the rate for those without the trait. Mortality rates are described in terms of the total period of follow-up.

Results

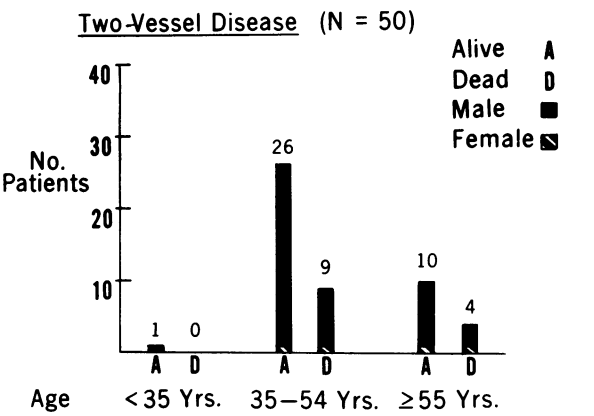
Age at time of the arteriogram ranged from 18 to 72 years with a mean age of 46.8 years for the total group of 246 patients (Figure 1). Seventy-nine per cent, 194 of the patients, were men. With rare exceptions all patients evaluated had chest pain, thought by the referring physician or the patient to be angina pectoris. A few patients were evaluated because of recent electrocardiographic changes. Fifty-six per cent of the men and 31% of the women were classified as definitely having angina pectoris by the criteria described. Of 172 patients presenting with either definite or questionable angina pectoris, 12% had onset of symptoms within three months prior to admission for the coronary arteriogram. Thirty-eight per cent of the patients had a definite history



	Ratio
Ang. Pect. (+/−)	29/17
MI - Hx (+/−)	24/22
MI - ECG (+/−)	16/30

	Mean	SE
Follow-Up	19.9 MO.	1.4

Fig. 3. Distribution of selected population characteristics in one-vessel disease (N = 46).



	Ratio
Ang. Pect. (+/−)	35/15
MI - Hx (+/−)	27/23
MI - ECG (+/−)	19/31

	Mean	SE
Follow-Up	22.7 MO.	1.9

Fig. 4. Distribution of selected population characteristics in two-vessel disease (N = 50).

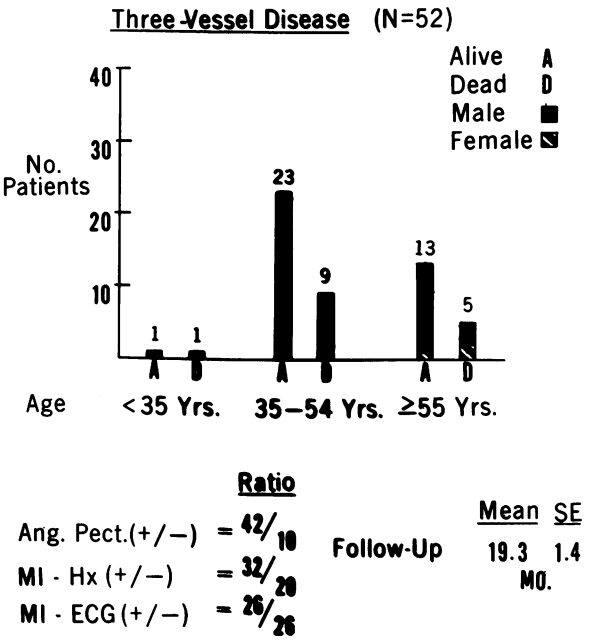


Fig. 5. Distribution of selected population characteristics in three-vesssel disease (N = 52).

of myocardial infarction and 26% had electrocardiographic evidence of myocardial infarction. The prevalence of angina pectoris and a history of electrocardiographic evidence of infarction all increased directly with the number of significantly diseased vessels. Of the 246 patients studied, 40% had no significant anatomical disease, i.e., a lesion obstructing 50% or more of a major vessel; 19% had one vessel diseased; 20% two vessels diseased; and 21% three vessels diseased.

The composition of the group with no significant disease, comprising 98 persons, is shown in Figure 2. A history accepted as definite angina pectoris occurred in 19 patients (20%), and significant Q waves were found on the resting electrocardiograms in three patients (3%) of this group. With mean follow-up of 22 months there were only three deaths in this group of 98 patients. One death was attributed to pancreatic neoplasm, another to cerebral hemorrhage, and the third to congestive heart failure in a black male with suspect myocardiopathy. The prevalence of angina pectoris as defined and significant Q waves increased markedly in 46 patients with one-vessel disease to 63% and

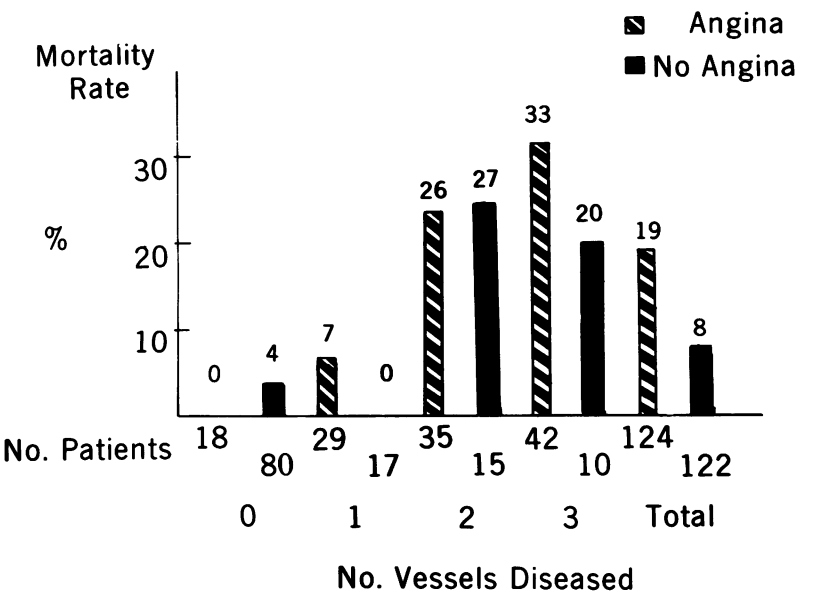


Fig. 6. Mortality by presence of angina and number of vessels diseased.

35% respectively (Figure 3). Two deaths occurred in this group of 46 patients with mean follow-up of 20 months, a mortality rate of 4% during the entire period of observation. Both deaths in the one-vessel disease group were attributed to ischemic heart disease; it is of note that both patients had total obstruction of a proximal arterial segment. Figures 4 and 5 illustrate the distribution of selected population characteristics in those with multiple-vessel disease. The proportion with definite angina pectoris ranged from 70% to 80% and with electrocardiographic evidence of myocardial infarction from 31% to 50%. Of the 28 deaths which occurred in the group of 102 patients with at least two-vessel disease only one, carcinoma of the maxillary sinus, was not attributed to cardiovascular disease. Eighty-five per cent of the deaths occurred in patients with multiple-vessel disease, representing only 41% of the total population. The over-all mortality rate with mean follow-up of 21 months for patients with at least two-vessel disease was 27%.

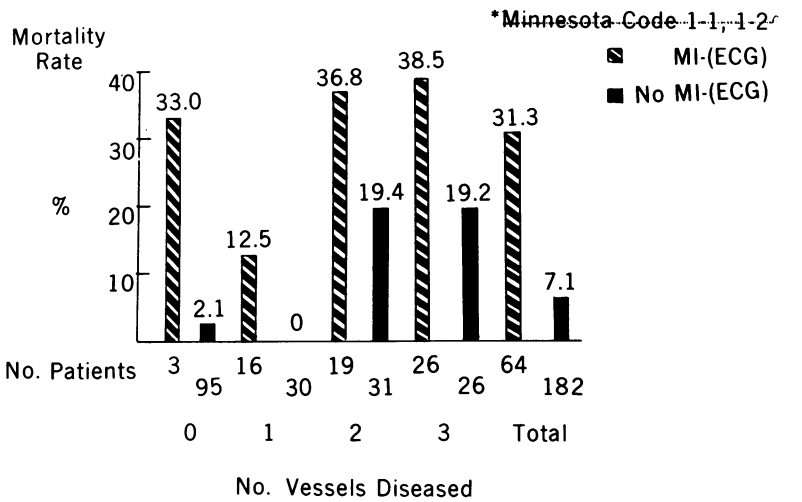


Fig. 7. Mortality by presence of MI (ECG) and number of vessels diseased (Minnesota code 1-1, 1-2).

Variables Studied and Mortality

Risk factors. Mean cholesterol (243.5 ± 7.1 mg.%)* systolic blood pressure (131.8 ± 2.0 mm. Hg), and the prevalence of smoking ≥ 20 cigarettes per day (0.40 ± 0.05) in the group with multiple-vessel disease were higher than those with less severe disease (224.6 ± 3.6 mg.%), (129.5 ± 1.7 mm. Hg), and (0.32 ± 0.04) respectively. Yet none of these major risk factors contributed independently to estimation of survival. Only hypertension (systolic ≥ 160 mm. Hg or diastolic ≥ 95 mm. Hg) or a history of hypertension conferred an increased relative risk of death, 1.5, in patients with multiple-vessel disease.

Angina pectoris. Those patients with a history accepted as definite angina pectoris had a mortality rate of 19% as compared to 8% for patients without angina pectoris, a relative risk of 2.4. It is apparent from Figure 6 that the risk of death in patients with angina pectoris increased with the number of vessels significantly obstructed. Yet no consistent difference was apparent in those with at least two-vessel disease; the relative risk with angina was 1.0 for those with two-vessel disease and 1.7 for those with three-vessel disease.

Variants of definite and questionable angina pectoris were also con-

*Mean ± standard error.

TABLE I. MORTALITY BY SYMPTOMS OF CONGESTIVE HEART FAILURE AND NUMBER OF VESSELS DISEASED

Number vessels diseased	*Symptoms CHF*			*No symptoms CHF*		
	Dead	*Alive*	*Mortality rate (%)*	*Dead*	*Alive*	*Mortality rate (%)*
0	1	8	11.1	2	87	2.2
1	1	5	16.7	1	39	2.5
2	9	5	64.3	4	32	11.1
3	7	9	43.8	8	28	22.2
Total	18	27	40.0	15	186	8.1

sidered in 102 patients with multiple-vessel disease. Absence of recorded symptoms were regarded as a negative response. Of 10 patients with recent onset of angina two died (20%), as compared with a 28% mortality for those without recent onset of angina, a relative risk of 0.7. The relative risk for 29 patients with angina at rest was 1.2 and for 28 patients with angina lasting 15 minutes or more, 1.7. The relative risk of nocturnal angina in 25 patients did not exceed one.

Myocardial infarction. Electrocardiographic evidence of myocardial infarction was associated with an increased mortality for each subgroup including those with two- and three-vessel disease (Figure 7). The relative risk for those with more severe coronary artery disease was twice that of patients without abnormal electrocardiograms. A history of myocardial infarction offered no additional information concerning prognosis.

Congestive heart failure. For this study symptoms of congestive heart failure (pulmonary venous hypertension) were defined as DOE accompanied by either PND or orthopnea. The increment in mortality rates with number of diseased vessels was much more evident in the group with congestive heart failure. Less than half of the patients with two or more vessels significantly obstructed and symptoms of congestive heart failure survived the period of follow-up (Table I). Whether a patient was taking digitalis appeared to have little effect on the mortality rates.

The distribution of heart size varied by severity of coronary disease and status of patients at time of follow-up (Table II). Arbitrarily using 396 cc./M^2 as an optimal dividing point, the proportion of patients exceeding this limit progressed from 43% for those patients with no

TABLE II. MORTALITY BY HEART SIZE AND NUMBER OF VESSELS DISEASED

Number vessels diseased	Heart volume ≥ 396 cc./M^2 Dead	Alive	Mortality rate (%)	Heart volume < 396 cc./M^2 Dead	Alive	Mortality rate (%)
0	2	34	5.5	0	47	0.0
1	1	20	4.8	0	22	0.0
2	11	16	40.7	1	14	6.7
3	13	21	38.2	2	7	22.2
Total	27	91	22.9	3	90	3.2

significant disease to 79% of patients with three-vessel disease. This value approximates the 60th percentile for heart volume in a random sample of the 50- to 59-year-old Birmingham population.[12] Of 27 deaths in patients with multiple-vessel disease only three deaths occurred among those with heart volume less than 396 cc./M^2. The mortality rate for patients with disease of two or more vessels and high heart volume approximated 39%, a relative risk of more than three compared to individuals with similar coronary disease but smaller heart volumes.

Electrocardiographic variables. Several electrocardiographic variables in addition to abnormal Q waves were distributed differently between survivors and nonsurvivors with multiple-vessel disease. The mean heart rate for patients dying during the period of follow-up exceeded that of the survivors at time of coronary arteriograms. The mean heart rate for nonsurvivors with at least two-vessel disease was 82.4 ± 2.6 beats per minute compared to 74.0 ± 1.4 beats per minute for survivors. Combined ST-T wave changes (Minnesota Code IV irrespective of digitalis) conferred almost two times the risk of mortality among those with two- and three-vessel disease. The number of patients with increased R-wave amplitude was too small to permit analysis.

The exercise electrocardiogram provided additional information; only the ST-segment response was evaluated at this time. An inordinately high proportion of patients subsequently dying did not have exercise tests at the time of evaluation, presumably because of severe angina or cardiac failure; therefore the greatest number of deaths occurred in those unable to exercise.

Irrespective of digitalis, left ventricular hypertrophy, etc., only two of the 14 nonsurvivors tested in the two- and three-vessel disease group

TABLE III. DISCRIMINANT FUNCTION ANALYSIS
†R = 0.61 R^2 = 0.37 N = 210

Variable	*P value**	*Standard B value*
Heart size	< 0.0001	0.265
Ant. descend. art., dist.	< 0.0013	0.203
DOE & (PND/Orthopnea)	< 0.0062	0.173
Heart rate	< 0.0225	0.130
Main left art.	< 0.0432	0.115
Circumflex art., dist.	< 0.0835	0.103
Right art., prox.	< 0.0929	0.103

*Two-sided.
†This is the square root of the coefficient of determination; it measures strength of association, but should not be interpreted as a multiple correlation coefficient.

had negative (actually borderline) exercise electrocardiograms. Of the 92 patients with no significant coronary artery disease tested only six patients had positive exercise tests, of whom two also had angina pectoris. Another 15 patients had "positive" tests which could be attributed to other factors: abnormal resting electrocardiogram (10 patients), digitalis (three patients), and left ventricular hypertrophy (two patients).

Multiple factors and mortality. Many of the factors studied were highly interrelated and also correlated with the severity of coronary artery disease. We considered the important variables in this group simultaneously by means of discriminant function analysis to predict status (alive or dead) at the time of follow-up. In this manner we selected the best independent predictors in the diseased group of subsequent mortality while at the same time adjusting for age and other confounding influences. Statistically this method also improved estimation of significance by using actual values of continuous variables rather than arbitrary levels. Multivariate analysis of these data was complicated by incomplete data on some of the patients studied; unfortunately exercise tests could not be included for this reason. The final analysis included 210 patients with complete data.

Seven factors contributed significantly to the prediction of mortality in this group of patients (Table III). Overall, the coefficient of determination was highly significant ($p < 0.0001$), with a value of 0.37. Thirty-seven per cent of the variance in mortality could be predicted with this set of variables. Heart size and obstruction of the anterior descending and main left artery and symptoms of congestive heart fail-

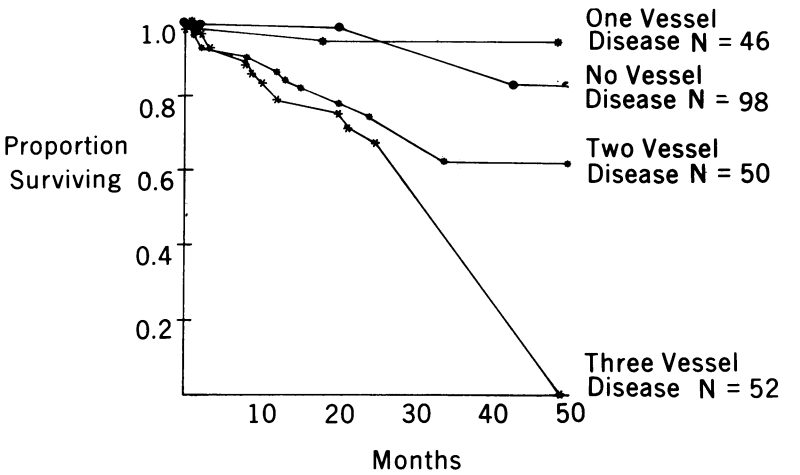


Fig. 8. Estimated survival curves following arteriogram by number of vessels diseased.

ure stand out as the critical variables in the set of predictive factors evaluated. In this combination of predictive factors, data from the coronary arteriogram accounted for 40% of the variability in predicting survival. Multiple-vessel disease involving the anterior descending vessel seemed especially important.

Survival curves. Figure 8 illustrates the estimated survival of the patients grouped by the number of diseased vessels. The terminal portion of the curves was unduly influenced by the small numbers of patients at later periods of follow-up. As expected, the slopes of the survival curves for those with less than two-vessel disease are relatively flat. Survival curves for the two- and three-vessel disease groups parallel each other with approximately 65% to 75% survival at two years. Until this point in time the slope of these curves appear constant. Twenty-eight deaths occurred in these disease groups among 102 men with mean follow-up of about 20 months, yielding better than one in four chances of dying within two years as depicted by the survival curves. It should be noted that the terminal point on the three-vessel disease curve is zero since the person in that group with the longest follow-up died giving (theoretically) no likelihood of survival beyond that point for any member of the group.

Discussion

Study of a group of patients before the era of coronary vein bypass operations disclosed several factors critically influencing the natural history of ischemic heart disease. With selected clinical features and coronary arteriograms it was possible to delineate a subgroup of patients with significant coronary artery disease yet having an excellent prognosis. The need for surgical therapy in these individuals must be questioned. On the other hand, signs and symptoms of cardiac failure in patients with multiple-vessel disease portend an especially unfavorable prognosis.

We found seven factors which stand out as independent predictors of mortality during the period of observation: heart size, disease ($\geq$ 50% obstruction) of the distal anterior descending artery, DOE accompanied by PND or orthopnea, resting heart rate, disease of the main left, distal circumflex, and proximal right coronary artery. This constellation of variables most likely represents two basic determinants of prognosis: presence of cardiac failure (pulmonary venous hypertension), not necessarily overt, and multiple-vessel disease of the coronary arteries. Studies in men evaluated at time of myocardial infarction by Norris and his co-workers have revealed four major factors predicting three-year survival: age, heart size, degree of pulmonary congestion, and previous ischemia.[13] Other long-term follow-up studies of patients with angina pectoris or myocardial infarction have also noted that congestive heart failure, cardiac enlargement, hypertension, and electrocardiographic abnormalities have altered survival time.[14, 15]

As estimated from our survival curves, approximately 95% of patients with less than two-vessel disease survived two years, whereas only 70% of those with multiple-vessel disease survived as long. These findings reaffirm the importance of coronary arteriography in identifying patients with ischemic heart disease at high risk of dying within several years of their arteriogram. None of the deaths in the group without significant disease as evaluated by the arteriogram could be directly attributed to ischemic heart disease. The mortality rate (27%) over the duration of follow-up for patients with multiple-vessel disease exceeded sixfold that of patients with less severe disease. In nonhospital populations the mortality rate for a confirmed infarction group after the first six months was relatively constant at about 4% to 5% per year, as

opposed to a constant rate of approximately 3% per year after the diagnosis of angina pectoris.[16, 17]

Undoubtedly a more critical scoring system of the coronary arteriogram would enhance prediction of mortality. Yet technical difficulties of arterial assessment in different views coupled with variation in the cardiac cycle precluded more precise definition in this study. A variable indeterminable in the present study, progression of lesions with time, may also be meaningful. The importance of collateral circulation has not been resolved, although several studies have noted minimal effects on prognosis.[18, 19] We did not evaluate collateral circulation.

Freisinger and his co-workers, using a somewhat different scoring technique, found prognosis predominantly a function of arteriographic changes rather than any clinical parameters.[2] It is of interest that the proportion of patients with minimal disease and severe disease alive at two years postcoronary arteriography in their study correspond closely to our findings.

Many of the clinical measures varied directly with the severity of coronary artery disease, such as prevalence of angina pectoris as defined, history of myocardial infarction, heart size, heart rate, electrocardiographic changes, and major risk factors, such as cholesterol and systolic blood pressure.

Age in the rather homogenous group studied had little effect on survival. Neither angina pectoris nor its variants, nocturnal angina and unstable angina, independently affected long-term prognosis. Although ST segment changes, Q-wave abnormalities, and hypertension by history or examination separately produced a twofold greater risk of mortality in our patients with multiple-vessel disease, these factors were not independently associated with mortality in the discriminant function analysis. Frank[16] has reported that men with ischemic heart disease and elevated blood pressure or specified abnormalities in their electrocardiogram were at higher risk of dying than men without these abnormalities under observation for 30 months. Cholesterol related only to severity of coronary artery disease but not to mortality. Other investigators have not considered cholesterol a potent factor in survival of men with manifest ischemic heart disease although there may be a relation in women.[6, 20] Hyperlipidemia has been implicated in the progression of coronary artery lesions.[21] The possibilities exist that blood pressure and cholesterol determinations in a hospital-based population may be mis-

leading or that the influence of the anatomical status of the coronary arteries as a predictor overwhelms the influence of these risk factors. Data on cigarette smoking showed no marked relation to mortality but was based on medical records with incomplete recording in a number of instances.

This selected group of patients characterized by coronary arteriograms provided an opportunity to observe the course of ischemic heart disease without surgical intervention. Our follow-up evaluation of patients with single-vessel disease disclosed that the mortality rate resembled those without significant disease of the vasculature more closely than patients with multiple-vessel disease. Although the mean period of observation is relatively short, surgery must be questioned seriously in this group with significant ischemic heart disease but a uniformly good prognosis. However, patients with two or more diseased vessels, especially with involvement of the anterior descending, complicated by even moderate increases in heart size and with other signs or symptoms of cardiac failure are at very high risk of death with medical therapy. The mortality rate over a two-year period for patients with these characteristics most likely varies between 30% and 50%. The prime question remains: Of these patients so identified and suitable for revascularization procedures, how many can expect increased longevity as a result of surgical therapy?

Acknowledgments

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