JACC Vol. 3, No. 3
March 1984:659–67

CLINICAL STUDIES

Clinical and Angiographic Factors Associated With Progression of Coronary Artery Disease

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To characterize the clinical and angiographic factors associated with progression of coronary atherosclerosis, 313 consecutive medically treated patients who had had two coronary arteriograms 3 to 119 months (mean 39 ± 25) apart were studied. One hundred eighty-one patients underwent recatheterization for stable angina, 52 for unstable angina and 80 for various other reasons. In addition to the conventional angiographic features present at the first angiographic study (number of diseased vessels 1.5 ± 0.8, ejection fraction 59 ± 11%), an extent score was defined based on the number of coronary segments with 5 to 75% narrowings from a 15 segment coding system.

Multivariate logistic regression identified four independent predictors of progression of coronary artery disease: the interval between studies ($p < 0.0001$), unstable angina ($p < 0.0001$), a high extent score ($p = 0.0001$) and young age ($p = 0.0026$). In a subset of 74 patients aged 50 years or younger with, at the time of the first evaluation, an extent score of 4 or more, the probability of progression between 2 and 4 years and after 4 years was, respectively, 80 and 90% compared with 50% for the other patients. Risk stratification for progression of coronary artery disease can thus be obtained.

Attempts to identify progressive coronary artery disease in a general population of patients with coronary artery disease have given conflicting results (1). Previous studies (2–20) have included in their definition of progression of disease the whole spectrum of lumen reduction, including coronary artery occlusion. However, whereas occlusion is considered an abrupt process, coronary atherosclerosis is generally seen as a chronic and progressive disease. Therefore, the pathophysiologic significance of occlusion and progression may differ (21).

The purpose of the present investigation was to examine the clinical, electrocardiographic and angiographic factors associated with progression, without occlusion, of coronary artery disease in a large series of medically treated patients undergoing a repeat coronary angiography. A multivariate logistic regression model was used to identify the independent predictors of progression of disease.

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It has been suggested (6,12,15,16,20) that progression of coronary artery disease occurs mainly at sites of preexisting lesions. To account for this pathophysiologic concept, an extent score was defined as the number of moderately stenosed segments in a 15 segment coding system. This score accurately predicted subsequent progression by univariate and multivariate analysis and allowed a risk stratification at the time of the first catheterization.

Methods

Patients. From January 1, 1970 to May 1, 1982, 413 patients at our institution underwent two coronary arteriographic studies performed at least 3 months apart and without interim coronary bypass surgery or angioplasty. Fifty-one patients with initially normal coronary arteries or without at least one 50% or greater diameter stenosis were excluded. Forty-nine others were excluded because of poor quality of the angiograms, lack of left ventriculography or an unacceptable change in view angulations between the two angiograms. Data on 313 patients with at least one 50% or greater stenosis at the first catheterization were considered. Of these 313 patients, 35 had one or more 50 to 69%

0735-1097/84/$3.00

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stenosis; 278 patients had either one coronary artery narrowed by 70% or more or the left main coronary artery narrowed by 50% or more.

Forty of these patients underwent recatheterization on an elective basis as a part of another research project that was approved by the Ethics Committee of our institution. The other 273 patients underwent recatheterization for various clinical reasons (Table 1). In 52 patients recatheterization was performed while they were in the coronary care unit for an episode of unstable angina; the study was performed after stabilization of the clinical and electrocardiographic manifestations of unstable angina a mean of 8 ± 4 days after admission, making it unlikely that ongoing ischemia had affected the evaluation of segmental wall motion.

Clinical data. Age at the time of the first angiographic study, sex and family history of coronary artery disease were registered. The diagnosis of previous or interim myocardial infarction was documented (22) by the presence of at least two of the following three criteria: chest pain of 30 minutes or more duration, appearance of new Q waves or of evolving ST segment changes on the electrocardiogram; and elevation of serum creatine kinase or oxalic transaminase, or both, to at least twice the upper limit of normal. Smoking status, cholesterol level, hypertension and functional angina class according to the classification of the Canadian Cardiovascular Society (23) were recorded at both the first and second studies. The electrocardiograms were analyzed according to the Minnesota Code (24). All these data were available for all patients except for the cholesterol levels missing in 24 patients.

Assessment of coronary artery disease. Selective coronary arteriography was performed by techniques previously described (25) with the systematic addition of craniocaudal projections beginning in 1973 (26). The percent diameter narrowing was assessed in 15 coronary artery segments (27) (Fig. 1) by a consensus of three observers unaware of the clinical diagnosis (28). Segments distal to a site of occlusion were coded as tiny or congenitally nonexistent. Both films were simultaneously projected and visualized for purpose of comparison. Progression was defined as: 1) a 20% or greater increase in stenosis in a segment narrowed 50% or more, or 2) a 30% or more increase in stenosis in a segment with less than 50% initial obstruction (5,29). Occlusion, defined by the appearance of a new complete obstruction in a segment previously patent, was considered separately and not counted as progression. Revascularization of an occluded artery was observed in three patients and regression from an initial less than 100% occlusion in nine others.

Table 1. Indications for Recatheterization

	No. Patients (%)
Persistent stable angina	160 (51.1%)
Hospitalization for unstable angina	52 (16.6%)
Research protocol	40 (12.8%)
New atypical symptoms	2 (6.4%)
Delayed surgery	1 (0.3%)
Recent myocardial infarction	15 (4.8%)
Multiple reasons	25 (8.0%)

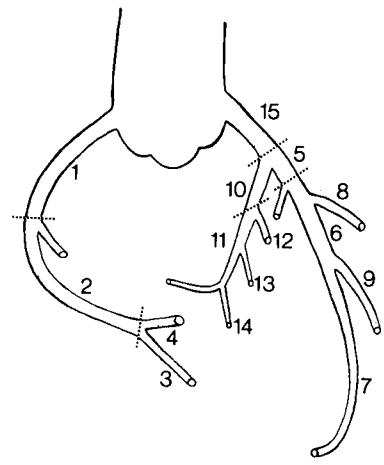


Figure 1. Division of the coronary tree. The following segments were analyzed: 1) proximal right coronary artery; 2) distal right coronary artery; 3) right posterior descending artery; 4) crux area and posterolateral branches; 5) proximal (preseptal) left anterior descending artery; 6) mid left anterior descending artery; 7) distal left anterior descending artery; 8) first diagonal artery; 9) second diagonal artery; 10) proximal left circumflex artery; 11) distal left circumflex artery; 12) first obtuse marginal branch; 13) second obtuse marginal branch; 14) third obtuse marginal branch; and 15) left main coronary artery.

From the raw data, several indexes of extent or severity of coronary artery disease were computed. The number of initially diseased vessels was defined according to Coronary Artery Surgery Study (CASS) criteria (23). The Friesinger score (30) quantifies the severity of the obstruction in classes (< 50, 50 to 90, > 90 and 100%) for each of the three main coronary vessels and also accounts for multiple 50 to 90% narrowings of the same vessel. In the Gensini scoring system (31), the grading factor is related to both the importance of the myocardial perfusion and to the degree of stenosis. We also counted the number of segments with severe (80 to 99%) stenoses. Finally, we defined an extent score calculated as the number of segments showing stenoses of 5 to 75% at the first evaluation. This score is not related to a hemodynamic concept, but defines the number of mild to moderate coronary artery lesions with a potential for progression that could be clinically important.

Left ventriculography was performed in the 30° right anterior oblique projection and analyzed by dividing the left ventricular contour in five segments (23). Ejection fraction was calculated for all patients by the area-length method (32).

Analysis of the data. Univariate comparisons between the group of patients with and the group without progression of disease were performed by the chi-square test and the *t* test. To identify the best set of independent predictors of progression, the data were fit by a multivariate logistic model (33): $p = \{1 + \exp(-a - b_1x_1 - b_2x_2 \ldots b_nx_n)\}^{-1}$, where p is the probability of progression and $x_1, x_2 \ldots x_n$ the n variables retained in a stepwise manner. The maximal likelihood method was used for the calculation of a, b_1, $b_2 \ldots b_n$ (34). At each step, the additional contribution of the next selected variable was assessed by a likelihood ratio test. Goodness of fit of the model was finally checked by Hosmer's statistic (35). Variables were considered significant when the probability (p) value was less than 0.05.

Results

Characteristics of the study group (Tables 2 and 3). The study group consisted mainly of young patients (mean age 47.7 years) with good left ventricular function (mean ejection fraction 59%). Although the whole spectrum of severity of coronary artery disease was present, only 13.6% of these patients had three vessel disease.

Table 2. Characteristics of 313 Patients at the Time of the First Coronary Angiogram

Age (yr)*	47.7 ± 7.8
Sex	
Male	263 (84%)
Female	50 (16%)
Smokers	236 (75%)
Angina class†	
0	23 (7%)
1 to 2	146 (47%)
3	50 (16%)
4	51 (16%)
No exertional angina	43 (14%)
Previous myocardial infarction	149 (48%)
Q wave on electrocardiogram	
Anterior	44 (14%)
Inferior	66 (21%)
Both	6 (2%)
Vessels with ≥70% stenosis	
0	35 (11%)
1	126 (40%)
2	110 (35%)
3	42 (14%)
Extent score*‡	3.42 ± 1.96
Friesinger score*	7.30 ± 2.89
Gensini score*	36.1 ± 31.6
Ejection fraction*	59.0 ± 11.4
Use of nitroglycerin during the catheterization	132 (42%)

*Mean ± standard deviation; †Canadian Cardiovascular Society definition; ‡defined by counting the number of 5 to 75% narrowed segments from a 15 segment coding system.

Table 3. Characteristics of 313 Patients at the Time of the Second Angiogram

Interval between studies (mo)*	38.7 ± 24.6
Smokers	179 (57%)
Angina class†	
0	18 (6%)
1 to 2	91 (29%)
3	80 (26%)
4	88 (28%)
No exertional angina	36 (11%)
Angina at rest	124 (40%)
Progression in angina functional class	123 (39%)
Myocardial infarction between studies	65 (21%)
New Q wave on electrocardiogram	38 (12%)
Vessels with ≥70% stenosis	
0	21 (7%)
1	91 (29%)
2	113 (36%)
3	88 (28%)
Extent score‡	3.07 ± 1.84
Friesinger score*	8.73 ± 3.07
Gensini score*	51.7 ± 37.4
Ejection fraction*	55.1 ± 13.8
Use of nitroglycerin during the catheterization	138 (44%)
Patients with progression	139 (44%)
Patients with occlusion	98 (31%)

*Mean ± standard deviation; †Canadian Cardiovascular Society definition; ‡defined by counting the number of 5 to 75% narrowed segments from a 15 segment coding system.

On the first angiogram, 3,903 segments could be analyzed (12.4 per patient); 225 segments showed progression of disease on the repeat angiogram. The distribution of progression among the various segments is shown in Table 4. Progression in at least one segment was present in 139 patients (44% of the series).

Univariate analysis (Tables 5 to 7). Of the clinical and electrocardiographic baseline characteristics, only young age predicted subsequent progression of disease; the classic "risk factors" did not.

The angiographic severity of coronary artery disease did not differ in the group with and in the group without progression of disease when analyzed by the number of diseased vessels, the number of severe (80 to 99%) stenoses or the Friesinger score, but did by the Gensini score (32 ± 27 versus 39 ± 34, $p < 0.05$). The extent score was higher in the group with than in the group without progression (3.91 ± 2.11 versus 3.04 ± 1.78, $p < 0.001$).

Many interim events and chacteristics at the time of the second angiogram were associated with progression of disease: they included the time interval between the two studies ($p < 0.001$), new onset of congestive heart failure ($p = 0.01$), occurrence of a new myocardial infarction ($p =$

Table 4. Progression by Segments

	No. Patients
Left main coronary artery	11
Proximal (preseptal) left anterior descending artery	24
Mid left anterior descending artery	17
Distal left anterior descending artery	7
First diagonal artery	6
Second diagonal artery	3
Proximal left circumflex artery	19
Distal left circumflex artery	27
First obtuse marginal artery branch	30
Second obtuse marginal artery branch	9
Third obtuse marginal artery branch	1
Proximal right coronary artery	38
Distal right coronary artery	20
Right posterior descending artery	2
Crux area and posterolateral branches	11

Two hundred twenty-five progressions were recorded among 139 patients with at least one progression.

0.05), appearance of a new Q wave on the electrocardiogram ($p < 0.01$) or of a new akinetic area in the left ventricular angiogram ($p = 0.01$), progression in angina functional class ($p < 0.05$), appearance of angina at rest ($p < 0.001$) and presence of unstable angina ($p < 0.001$) at the time of the second angiogram. New occlusion and decrease in ejection fraction were slightly more frequent in the group with progression but this trend was not statistically significant. Finally, the use of nitroglycerin during the procedure of the second catheterization was more frequent in the group with progression ($p < 0.01$).

Multivariate logistic regression (Table 8). Among the 12 variables found significant by univariate analysis, the stepwise process selected four independent predictors of progression. These were the time interval between the studies ($p < 0.0001$), the presence of unstable angina at the time of the second angiogram ($p < 0.0001$), the initial extent score ($p = 0.0001$) and age ($p = 0.0026$).

The coefficients (bi) from Equation 1 are given in Table 8. The probability of progression for an individual patient can be calculated by substituting the variables by their actual values. For example, consider the odds of progression in a 58 year old man being evaluated for stable angina, who was catheterized 2 years previously with an extent score of 2 at that time.

From the coefficient of Table 8 we compute: $\exp(-a - b_1x_1 - b_2x_2 - b_3x_3 - b_4x_4) = \exp\{-(0.872) - (0.0267)(24) - (0.882)(-1) - (0.269)(2) - (-0.514)(58)\} = \exp(1.812) = 6.12$; the probability of progression in this patient is:

$$\frac{1}{1 + 6.12} = 0.14.$$

To evaluate the fit of the logistic model to the observed cases of progression, the probability of progression was computed in this way for each patient and the total group was divided into classes defined by fixed cutpoints of the calculated probability. This operation is summarized in Figure 2. The computation of Hosmer's statistic ($\chi^2 = 10.65$, $dF = 8$, $p = 0.22$, NS) confirmed the good reliability of the predicted probability of progression.

Table 5. Clinical Predictors of Progression of Disease

Variables	Progression (n = 139 patients)	No Progression (n = 174 patients)	p Value
Age (yr)	46.7 ± 7.5*	48.5 ± 7.8*	0.05
Duration of the disease (mo)	28 ± 38*	33 ± 38*	NS
Cholesterol levels† (mg/dl)	237 ± 38*	239 ± 53*	NS
Interval between studies (mo)	47 ± 25*	32 ± 22*	< 0.001
	No. (%)	No. (%)	
Previous myocardial infarction	68 (49)	81 (46)	NS
Positive family history	77 (55)	97 (55)	NS
Hypertension	41 (29)	50 (28)	NS
Smokers	108 (78)	129 (74)	NS
Congestive heart failure			
1st catheterization	1 (1)	1 (1)	NS
2nd catheterization	18 (13)	6 (3)	0.01
Angina at rest			
1st catheterization	47 (34)	46 (26)	NS
2nd catheterization	70 (50)	54 (31)	< 0.001
Progression of angina functional class	64 (46)	59 (34)	< 0.05
Interim myocardial infarction	36 (26)	29 (17)	0.05
Unstable angina at 2nd catheterization	40 (29)	12 (7)	< 0.001

*Mean ± standard deviation; †data available for 289 patients. NS = not significant; p = probability.

Table 6. Electrocardiographic Predictors of Progression of Disease

	Progression (n = 139 patients) No. (%)	No Progression (n = 174 patients) No. (%)	p Value
First electrocardiogram			
Abnormal Q wave	54 (39)	65 (37)	NS
ST depression at rest	5 (4)	10 (6)	NS
Bundle branch block	13 (9)	21 (12)	NS
Left ventricular hypertrophy	10 (7)	9 (5)	NS
Second electrocardiogram			
New abnormal Q wave	25 (18)	13 (7)	< 0.01
New ST depression at rest	18 (13)	19 (11)	NS
New bundle branch block	8 (6)	5 (3)	NS
New pattern of left ventricular hypertrophy	7 (5)	6 (3)	NS

NS = not significant; p = probability.

Prediction of progression of disease with variables present at the time of the first evaluation. Two characteristics present at baseline, extent score and age were significantly associated with subsequent progression by multivariate analysis. They were combined to try to identify patients at high risk of progression. The high risk group was defined by an extent score of 4 or geater and an age of 50 or greater and included 74 patients. When compared with the 239 other patients (lower risk group), the less than 2 year chance of progression of the high risk group was roughly the same (8 of 26 versus 20 of 99, NS) (Fig. 3). However, this difference in progression became very significant after 2 years: between 2 and 4 years, progression had occurred in 20 of 26 patients in the high risk group compared with 31 of 61 patients in the lower risk group ($p < 0.025$). After 4 years, progression was registered in 20 of 22 patients in the former group, and in 40 of 79 patients in the latter group ($p < 0.001$).

Discussion

The present study attempts to characterize the clinical, electrocardiographic and angiographic factors associated with progression, without occlusion of coronary artery disease. A large number of patients recatheterized for a variety of clinical reasons 3 to 119 months after a first angiogram is included. Two baseline characteristics, age and extent of coronary artery disease, and two interim events, the time interval between the two studies and unstable angina, were independent predictors of progresssion of coronary artery disease.

Time interval between studies. Some previous studies (2,19,20) have failed to demonstrate any relation between time and progression of coronary artery disease. In the present investigation, the probability of progression of disease increased with time; this effect was important between 3 and 24 months, and was less pronounced after 2 years both in the high risk and lower risk groups of patients (Fig. 3). In a retrospective study such as this, the reasons for the significant correlation between progression and time are difficult to determine but may include patient selection, factors related to the detectability of progression or the chances of progresssion. Even if the last possibility is true, it is not possible to ascertain whether progression occurred incrementally (1) or as a continuous process: serial ($\geq$ 3) angiograms would be required to answer this question.

Clinical predictors of progression. The large data bases of the CASS (23) and Veterans Administration (36) studies have demonstrated a poor relation between angina symptoms and the severity of coronary artery disease. Is the relation between the clinical evolution and anatomic pro-

Table 7. Angiographic Predictors of Progression

	Progression (n = 139 patients)	No Progression (n = 174 patients)	p Value
No. of diseased vessels	1.43 ± 0.87*	1.56 ± 0.86*	NS
Friesinger score	7.0 ± 2.6*	7.5 ± 3.0*	NS
Gensini score	32 ± 27*	39 ± 34*	< 0.05
No. of severe (80 to 99%) stenoses	0.66 ± 0.84*	0.83 ± 0.91*	NS
Extent score	3.91 ± 2.11*	3.05 ± 1.78*	< 0.001
Ejection fraction	58 ± 11*	59 ± 11*	NS
Change in ejection fraction	−5 ± 12*	−3 ± 10*	NS
	No. (%)	No. (%)	
Use of nitroglycerin			
1st catheterization	73 (52)	93 (53)	NS
2nd catheterization	73 (52)	65 (37)	< 0.01
New akinesia	32 (23)	21 (12)	0.01
New occlusion	49 (35)	49 (28)	NS

*Mean ± standard deviation. NS = not significant; p = probability.

Table 8. Summary of Stepwise Logistic Regression Analysis

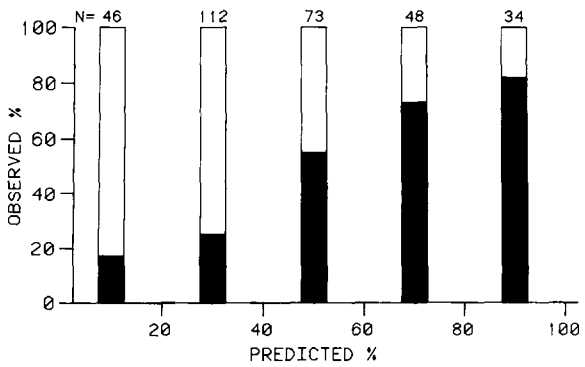
Variables Entered	χ^2	p Value	bi	Odds Ratio	95% Confidence Limits for Odds Ratio	Difference Associated With Odds Ratio
Interval between studies (mo)	24.36	< 0.0001	0.0267	2.22	(1.59 to 3.11)	60 versus 30 mo
Unstable angina†‡	24.07	< 0.0001	0.882	5.83	(2.73 to 12.43)	Presence versus absence
Extent score*	16.16	0.0001	0.269	1.71	(1.30 to 2.24)	Extent score = 4 versus
Age (yr)*	9.06	0.0026	−0.0514	1.67	(1.19 to 2.34)	50 versus 60 yr
Constant a			0.872			

*At first catheterization; †at second catheterization; ‡scored (−1) when absent and (+1) when present.

gression any better? Some studies (3,5,16) have suggested a good correlation, while others (2,4,6) have not. In the present investigation, a correlation is clearly found: by univariate analysis, progression could be predicted by a worsening in angina functional class ($p < 0.05$), angina at rest ($p < 0.001$), interim myocardial infarction ($p = 0.05$) and unstable angina ($p < 0.001$) at the time of the second catheterization. On the other hand, recatheterization because of stable angina, delayed surgery or as part of a research protocol did not correlate with progression of disease. By multivariate analysis, unstable angina remained strongly predictive of progression.

Unstable angina. The finding that this clinical syndrome was strongly associated with progression of coronary artery disease confirms our previous report (29) that progression of disease was more prevalent in 33 patients with unstable angina than in 33 patients with stable angina matched for age and severity of coronary artery disease. This observation has important pathophysiologic and therapeutic implications.

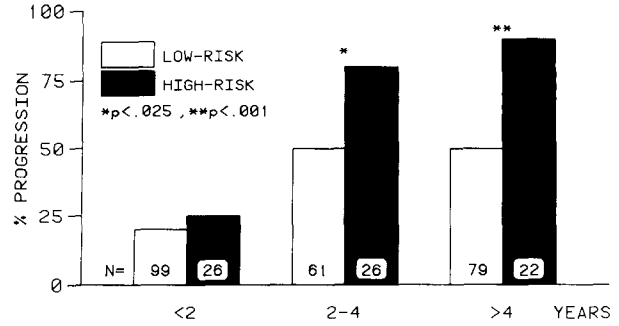
Figure 2. Predicted versus observed probabilities (%) of progression of disease. To evaluate the fit of the estimated logistic function to the observed cases of progression, the total sample was divided into classes defined by fixed (0.2, 0.4 . . .) cutpoints of the predicted probability of progression (X axis). In each class, patients with progression were counted and reported for the group size (indicated at **top of bars**), providing an observed rate of progression (**dark bars**). The figure shows that this observed probability of progression was in good accordance with the predicted one.



Extent score. In the present study, neither the number of diseased vessels nor the Friesinger score was a significant predictor of progression disease. The Gensini score was significantly higher in the group without progression, but the difference was not significant by multivariate anlysis.

These results are not surprising considering that the various scoring systems are designed to evaluate the hemodynamic consequences of stenoses by considering their severity and the number of diseased vessels. Therapeutic decisions are often based on such indexes of severity. However, these systems may not be adequate to evaluate progression of the disease by angiographic criteria. Thus, the highest scores in the Friesinger and Gensini systems are found when stenoses are greater than 90%. Our definition asking for a 20% increase in severity when the narrowing is 50% or more would preclude any detection of progression with initial stenoses 80% or more. The scoring systems are also based on the number of diseased vessels rather than on the extent of coronary atherosclerosis; in the Friesinger system a mark of 1 is added if multiple stenoses are found in the same vessel, whereas the Gensini system considers the quality of collateral vessels and the ability of the vessel to accept and sustain a bypass graft. To optimize detection of

Figure 3. Progression of disease in low risk and high risk groups. The groups are defined by the two baseline characteristics associated by multivariate analysis to subsequent progression. The high risk group includes the 74 patients with an extent score of 4 or more and an age of 50 years or less. The 239 other patients constitute the low risk group. The size of each group at the various time intervals is indicated at the **bottom of each bar**.



progression, we calculated an extent score based on the number of coronary artery segments narrowed by 5 to 75% from a 15 segment coding system. This extent score conceptually differs from the aforementioned indexes of hemodynamic severity and merely reflects the extent of atherosclerotic angiographic involvement. This extent score was a powerful predictor of progression by both univariate and multivariate analysis.

A previous study (6) showed that abnormal segments were more prone than normal segments to progression of disease; however, the segments are clustered by patients and do not constitute independent observations (37). In our study, the analysis was carried out by patient and the extent score identified a subset of high risk patients. We can only express hypotheses about the significance of the extent score; clearly, however, it indicates more extensive and more active disease. Whether the pathophysiology is related to a hyperreactivity of the vascular wall or to a more systemic disease such as platelet or prostaglandin abnormalities is unknown. Pathophysiologic studies in the subgroup of young patients with a high extent score will be necessary to define the relevance of the extent score to the mechanisms of progression of coronary artery disease.

Age. Progression of disease was more frequent in younger patients both by univariate and multivariate analysis. This observation was previously suggested in our (12) and other (2,9) institutions. Thus, while coronary artery disease and multivessel disease are more frequent in older patients (38), younger patients are more prone to disease progression.

Risk factors and progression. The risk factors—smoking status, hypertension and serum cholesterol level—did not predict subsequent progression. This relation is in accord with previous studies performed in our (5) and other (4,6,8,9,19) institutions; other studies (2,10,13,14,17,18,39) have given conflicting results. A definite assessment of the role of the risk factors in progression of coronary artery disease would require a cohort studied by serial measurements of these factors as time-dependent covariates.

Coronary artery disease appears to be a multistage process (40): risk factors for progression would thus not necessarily be risk factors for initiation of the disease. The contrasting role of age in predicting the presence and severity of coronary artery disease and in predicting progression of disease is in accord with this concept. Also smoking status, while strongly predictive of myocardial infarction, is only weakly related to angina pectoris (41).

Progression and changes in left ventricular wall motion. Previous reports have identified myocardial infarction (2–4, 6,9,17,19), a decrease in ejection fraction (4,11) and new akinesia (5,9,16) as reliable markers of progression of coronary artery disease. In the present study, interim myocardial infarction ($p = 0.05$), onset of congestive heart failure ($p = 0.01$) and new akinesia ($p = 0.01$) were more frequent among patients with progression of disease. However, none of these differences remained significant by multivariate analysis.

Markis et al. (11) previously reported a strong association between left ventricular damage and interim coronary occlusion. The rather weak relation between progression of disease and new myocardial damage in the present investigation may be related to our definition of progression, which excluded new occlusion.

Limitations of this study. Repeat appraisal of the native coronary circulation in this study was performed on a research basis in only a minority (40 of 313) of patients. For the remaining patients, the physician's request for repeat catheterization was made for various clinical reasons. Obviously, the restudy was limited to survivors who were not treated surgically, and our patients are thus not representative of the entire natural history of coronary artery disease. Progression can be influenced by many factors and some possible correlates of progression were unavailable on a retrospective basis such as the educational and socioeconomic status, the psychologic type and some biologic features such as the lipid profile and high density lipoprotein cholesterol. The data for cholesterol levels were available for 289 patients and did not correlate with progression of disease.

We carefully excluded all pairs of films with a poor contrast or an unacceptable discrepancy between the viewing incidences. Nevertheless, a perfect matching of the angle of the views is only achievable in a prospective study. Such a study should also standardize the use of nitroglycerin because this drug can magnify the degree of a stenosis (42): in our study, nitroglycerin use at the time of the second angiogram was related to progression of disease by univariate analysis. However, it was not retained as an independent factor of progression by the logistic regression model. Therefore, the significance of the four factors identified by the multivariate analysis cannot be attributed to an imbalance regarding the use of this drug.

Finally, the visual comparison of coronary angiograms and the definition of progression of coronary artery disease may be questioned (43). Whereas the interobserver (19,28,44–46) and intraobserver (45) variability in the analysis of one coronary angiogram have been extensively studied, we are aware of only one study (47) on the reproducibility of the criteria used to assess progression of disease. Therefore, a conservative definition (5,29) of progression was selected, which was in accord with the known precision of the reading procedure (28,47).

In this study, occlusion was not considered progression although it constitutes one of the forms of progression of ischemic heart disease. However, occlusion and progression represent two different pathophysiologic phenomena, one more acute and usually caused by thrombosis, the other more chronic and representing true progression of atherosclerosis. This decision could have influenced the results in both groups, with and without progression. In some patients,

progression is followed, and thus hidden, by an occlusion at the same site. In our study, occlusion was more frequent in the group of patients whose disease progressed but the difference was not significant. Other patients with occlusion followed by incomplete repermeabilization of the thrombus could be considered patients with progression. However, neither the occurrence of new myocardial infarction, new Q waves, new akinesia or change in ejection fraction were significant by multivariate analysis, suggesting that the overall results of this study represent a true appraisal of the factors involved in progression.

Clinical implications. The model described in this study provides the first quantitative approach to predict coronary artery disease progression. Its internal reliability as assessed by the goodness of fit statistic (Fig. 2) was good. Its transferability (48) to other groups of patients remains to be established and only the clinical and angiographic follow-up of a prospective cohort could definitively establish the factors associated with progression. However, if confirmed in a new series of patients, our model could have important practical implications.

The calculation of the probability of progression of disease could help the clinician to judge if a repeat catheterization is indicated when a procedure is delayed or when the anginal syndrome persists, despite optimal medical treatment. The chances of progression could then be evaluated by the baseline characteristics and the interim events. Also, the high risk group of young patients with a high extent score should be submitted to closer follow-up and, perhaps, to a repeat angiogram. Pathophysiologic studies in this subset of patients may be indicated as well as therapeutic interventions aimed at slowing down the process of atherogenesis.

We thank Diane Asselin-Roy and Ginette Bleau for their secretarial work.

References

1. Petch MC. The progression of coronary artery disease. Br Med J 1981;283:1073–4.
2. Bemis CE, Gorlin R, Kemp HG, Herman MV. Progression of coronary artery disease. A clinical angiographic study. Circulation 1973;48:455–63.
3. Dyrda I, Petitclerc R, Saltiel J, Bourassa MG. Clinical indices of angiographic progression in coronary artery disease (abstr). Circulation 1973;48(suppl IV):IV-58.
4. Buda AJ, Macdonald IL, Kwok KL, Orr SA. Coronary disease progression and its effect on left ventricular function. Chest 1982;82:285–90.
5. Bourassa MG, Ryan TJ, Goulet C, et al. Early progression of coronary disease in patients assigned to medical therapy (abstr). Circulation 1981;64(suppl IV):IV-83.
6. Bruschke AVG, Wijers THS, Kolsters W, Landman J. The anatomic evolution of coronary artery disease demonstrated by coronary arteriography in 256 nonoperated patients. Circulation 1981;63:527–36.
7. Gohlke H, Sturzenhofecker P, Gornandt L, Haakshorst W, Roskamm H. Progression und Regression der koronaren Herzerkrankung im chronishen Infarkstadium bei Patienten unter 40. Schweiz Med Wochenschr 1980;110:1663–5.
8. Kimbiris D, Segal BL. Coronary disease progression in patients with and without saphenous vein bypass surgery. Am Heart J 1981;102:811–8.
9. Kramer JR, Kitazume H, Proudfit WL, Matsuda Y, Williams GW, Sones FM Jr. Progression and regression of coronary atherosclerosis: relation to risk factors. Am Heart J 1983;105:134–44.
10. Sanmarco ME, Selvester RH, Brooks SH, Blankenhorn DH. Risk factors reduction and changes in coronary arteriography (abstr). Circulation 1976;53(suppl II):II-140.
11. Markis JE, Joffee CD, Roberts BH, et al. Evolution of left ventricular dysfunction in coronary artery disease. Serial cineangiographic studies without surgery. Circulation 1980;62:141–8.
12. Marchandise B, Bourassa MG, Chaitman BR, Lespérance J. Angiographic evaluation of the natural history of normal coronary arteries and mild coronary atherosclerosis. Am J Cardiol 1978;41:216–20.
13. Ben-Zvi J, Hildner FJ, Javier RP. Progression of coronary artery disease. Cinearteriographic and clinical observations in medically and surgically treated patients. Am J Cardiol 1974;34:295–301.
14. Raichlen JS, Achuff SC, Bulkley BH, Pearson TA. Risk factors and angiographic progression of coronary artery disease (abstr). Circulation 1982;66(suppl II):II-283.
15. Palac RT, Hwang MH, Meadows WR, et al. Progression of coronary artery disease in medically and surgically treated patients 5 years after randomization. Circulation 1981;64(suppl II):II-17–21.
16. Passoni F, D'Urbano M, Aiazzi L, et al. L'evoluzione naturale della coronaropatia aterosclerotica. Minn Med 1982;73:55–60.
17. Rosch J, Rahimtoola SH. Progression of angiographically determined coronary stenosis. Cardiovasc Clin 1977;8:55–70.
18. Roskamm H, Sturzenhofecker P, Gornandt L, Gohlke H, Haakshortst W. Progression and regression of coronary artery disease in postinfarction patients less than 40 years of age. Cleve Clin Q 1980;47:192–4.
19. Shub C, Vlietstra RE, Smith HC, Fulton RE, Elveback LR. The unpredictable progression of symptomatic coronary artery disease. A serial clinical angiographic analysis. Mayo Clin Proc 1981;56:155–60.
20. Gensini GG, Kelly AE. Incidence and progression of coronary artery disease. An angiographic correlation in 1263 patients. Arch Intern Med 1972;129:814–27.
21. Selzer A, Pasternak RC. Role of coronary arteriography in the evaluation of patients with coronary artery disease. Am J Med 1981;70:747–51.
22. Bloor CM, Roeske WR, O'Rourke RA. Clinical pathologic correlates in acute myocardial infarction. Adv Cardiol 1978;23:14–24.
23. Principal Investigators of CASS and Their Associates. The National Heart, Lung and Blood Institute Coronary Artery Surgery Study (CASS). Circulation 1981;63(suppl I):I-1–81.
24. Rose GA, Blackburn H. Electrocardiographic grading codes. Circulation 1973;47(suppl I):I-39–42.
25. Bourassa MG, Lespérance J, Campeau L. Selective coronary arteriography by the percutaneous femoral artery approach. Am J Roentgenol 1969;107:377–83.
26. Lespérance J, Saltiel J, Bourassa MG. Angulated views in the sagittal plane for improved accuracy of cinecoronary angiography. Am J Roentgenol 1974;121:565–74.
27. Bourassa MG, Lespérance J, Corbara F, Saltiel J, Campeau L. Progression of obstructive coronary artery disease 5 to 7 years after aorto-coronary bypass surgery. Circulation 1979;58(suppl I):I-100–6.
28. Sanmarco ME, Brooks SH, Blankenhorn DH. Reproducibility of a consensus panel in the interpretation of coronary angiograms. Am Heart J 1978;96:430–7.
29. Moise A, Théroux P, Taeymans Y, et al. Unstable angina and progression of coronary atherosclerosis. N Engl J Med 1983;309:685–9.
30. Humphries JON, Kuller L, Ross RS, Friesinger GC, Page EE. Natural history of ischemic heart disease in relation to arteriographic findings. A twelve year study of 224 patients. Circulation 1974;49:489–97.

31. Gensini GG. Coronary Arteriography. Mount Kisco, NY: Futura, 1975:272.

32. Sandler H, Dodge HT. The use of single plane angiocardiograms for the calculation of left ventricular volume in man. Am Heart J 1968;75:325–34.

33. Cox DR. The Analysis of Binary Data. London: Methuen, 1970:91.

34. Engelman L. PLR stepwise logistic regression. In: Dixon WJ, Brown MR, eds. BMDP Statistical Software. Berkeley: University of California Press, 1981:330.

35. Lemeshow S, Hosmer DW. A review of goodness of fit statistics for use in the development of logistic regression models. Am J Epidemiol 1982;115:92–106.

36. Hultgren HN, Peduzzi PN. Does severity of angina relate prognosis? (abstr). Circulation 1982;66(suppl II):II-370.

37. Miller RG, Efron B, Brown BW, Moses LE. Biostatistics Casebook. New York: John Wiley & Sons 1980:123.

38. Fisher LD, Kennedy JW, Chaitman BR, et al. Diagnostic quantification of CASS (Coronary Artery Surgery Study) clinical and exercise test results in determining presence and extent of coronary artery disease: a multivariate approach. Circulation 1981;63:987–1000.

39. Nash DT, Gensini G, Esente P. Effect of lipid-lowering therapy on the progression of coronary atherosclerosis assessed by scheduled repetitive coronary arteriography. Int J Cardiol 1982;2:43–55.

40. Vlietstra RE, Kronmal RA, Frye RL, Seth AK, Tristani FE, Killip T, III. Factors affecting the extent and severity of coronary artery disease in patients enrolled in the Coronary Artery Surgery Study. Arteriosclerosis 1982;2:208–15.

41. Kannel W. Cigarettes, coronary occlusions, and myocardial infarction. JAMA 1981;246:871–2.

42. Feldman RL, Pepine CJ, Curry RC, Conti CR. Case againsts routine use of glyceryl dinitrate before coronary angiography. Br Heart J 1978;40:992–7.

43. Brown BG, Bolson EL, Dodge HT. Arteriographic assessment of coronary atherosclerosis. Review of current methods, their limitations, and clinical applications. Arteriosclerosis 1982;2:2–15.

44. De Rouen TA, Murray JA, Owen W. Variability in the analysis of coronary arteriograms. Circulation 1977;55:324–8.

45. Detre KM, Wright E, Murphy ML, Takaro T. Observer agreement in evaluating coronary angiograms. Circulation 1975;52:979–86.

46. Zir L, Miller SW, Dinsmore RE, Gilbert JP, Harthorne JW. Interobserver variability in coronary angiography. Circulation 1976;53:627–32.

47. Detre KM, Kelsey SLF, Passamani ER, et al. Reliability of assessing change with sequential coronary angiography. Am Heart J 1982;104:816–23.

48. McNeil BJ, Hanley JA. Statistical approaches to clinical predictions. N Engl J Med 1981;304:1292–4.