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Importance of Clinical Measures of Ischemia in the Prognosis of Patients With Documented Coronary Artery Disease

ROBERT M. CALIFF, MD, DANIEL B. MARK, MD, MPH, FRANK E. HARRELL, JR., PHD, MARK A. HLATKY, MD, FACC, KERRY L. LEE, PH, ROBERT A. ROSATI, MD, FACC, DAVID B. PRYOR, MD, FACC

Durham, North Carolina

To examine the value of clinical measures of ischemia for stratifying prognosis, 5,886 consecutive patients who had symptomatic significant (≥75% stenosis) coronary artery disease were studied. Using the Cox regression model in a randomly selected half of the patients, the prognostically independent clinical variables were weighted and arranged into a simple angina score: angina score = angina course × (1 + daily angina frequency) + ST-T changes, where angina course was equal to 3 if unstable or variant angina was present, 2 if the patient's angina was progressive with nocturnal episodes, 1 if it was progressive without nocturnal symptoms and 0 if it was stable; 6 points were added for the presence of "ischemic" ST-T changes. This angina score was then validated in an independent patient sample.

The score was a more powerful predictor of prognosis than was any individual anginal descriptor. Furthermore, the angina score added significant independent prognostic information to the patient's age, sex, coronary anatomy and left ventricular function. Patients with three vessel disease and a normal ventricle (n = 1,233) had a 2 year infarction-free survival rate of 90% with an angina score of 0 and a 68% survival rate with an angina score ≥9. With an ejection fraction <50% and three vessel disease (n = 1,116), the corresponding infarction-free survival figures were 76 and 56%. Thus, a careful summarization of clinical markers of ischemia in the form of an angina score can provide a powerful prognostic tool and may aid clinicians in identifying high risk patients who are candidates for aggressive therapeutic interventions.

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Before the advent of coronary angiography, clinicians relied on the severity of a patient's symptoms and abnormalities on the electrocardiogram (ECG) at rest to gauge the severity of coronary artery disease and the necessity of beginning or altering therapy (1). Many studies using cardiac catheterization have now documented that coronary disease may progress to an advanced stage in the absence of symptoms (2). Furthermore, left ventricular function and the extent of anatomic disease have been shown to be of greater prognostic importance than the severity of symptoms (3–5). For these reasons, many clinicians have increasingly relied on the findings at cardiac catheterization to determine therapeutic alternatives and have de-emphasized the patient's symptomatic status and other simple clinical observations (6).

From a series of questions about the quality, severity, frequency and course of the angina and an examination of the rest ECG, the experienced physician forms an overall clinical impression of the tempo of a patient's coronary disease. Most previous studies of prognosis in coronary disease have focused on individual aspects of angina rather than on combining important characteristics of angina into a summary measure similar to the physician's overall impression. This approach tends to weaken the apparent prognostic value of anginal symptoms relative to other variables such as coronary anatomy.

The present study had two goals: The first goal was to determine how to group anginal characteristics into a clinically meaningful index (angina score) with maximal prognostic value. The second goal was to examine the extent to which such an angina score provides prognostic information

From the Division of Cardiology, Department of Medicine and the Division of Biometry, Department of Community and Family Medicine, Duke University Medical Center, Durham, North Carolina. This work was supported by Research Grants HS-03834, HS-04873 and HS-05635 from the National Center for Health Services Research, Bethesda, Maryland; Research Grant HL-17670 from the National Heart, Lung, and Blood Institute, Bethesda; Training Grant LM-07003 and Grant LM-03373 from the National Library of Medicine, Bethesda and a grant from the Andrew W. Mellon Foundation, New York, New York.

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Address for reprints: Robert M. Califf, MD, Box 31123, Duke University Medical Center, Durham, North Carolina 27710.

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independent of coronary anatomy and left ventricular function.

Methods

Baseline data collection and follow-up. Since 1971, information on all patients undergoing cardiac catheterization at Duke University Medical Center has been collected prospectively (7). A complete medical history, physical examination, chest radiograph and standard 12 lead ECG have been obtained in all patients. Catheterization variables describing coronary anatomy and ventricular function have also been collected on all patients (3).

Follow-up information concerning death and nonfatal infarction was obtained prospectively by mailed questionnaire or telephone interview at 6 months, 1 year and yearly intervals thereafter, as described previously (3). Follow-up was 98% complete at all follow-up intervals. The criteria used to diagnose follow-up myocardial infarction have been published (8).

Definitions. Definitions of angina used in this study have been published previously (3,9). Unstable angina was defined as severe angina at rest requiring admission to the cardiac care unit to exclude an acute myocardial infarction during the same admission as that of the cardiac catheterization. Angina was classified as progressive if symptoms had increased in frequency, severity or duration in the 6 weeks before cardiac catheterization but the criteria for unstable angina were not met. Typical angina was defined as discomfort thought by the cardiologist to be characteristic of myocardial ischemia that usually, but not necessarily, fulfilled the classic triad of substernal pain, relief by nitroglycerin and *provocation by exertion*. *Nocturnal angina* was defined as chest discomfort that had awakened the patient within the 6 weeks before catheterization. Variant angina was rest angina accompanied by documented reversible ST segment elevation and no resulting myocardial infarction (10). Angina frequency was estimated from the patient's report of the average number of episodes experienced per day during the 6 weeks before catheterization. If there had been a recent change in the anginal pattern, then the average number of episodes in the 1 to 2 weeks before catheterization was used. New onset angina was defined as angina of <3 months' duration (9). Each patient was assigned to the appropriate New York Heart Association classification (11). The duration of coronary disease symptoms was defined as the time inverval between the first manifestation of coronary disease reported by the patient (either angina or myocardial infarction) and the patient's cardiac catheterization. ST-T wave changes suggestive of ischemia on the last 12 lead rest ECG taken before catheterization were considered present if there was either ≥1 mm of ST depression or T wave inversion in leads with a dominant R wave in the absence of bundle branch block or a paced rhythm.

Study patients. The study group consisted of 5,886 consecutive patients undergoing cardiac catheterization between November 1, 1969 and December 31, 1984 who had symptomatic significant coronary artery disease (≥75% luminal diameter narrowing of at least one major coronary vessel). Patients who had significant primary valvular or congenital heart disease or a cardiomyopathy were excluded. The group was 81% male with a median age of 54 years (10th to 90th percentiles, 41 to 66). Seventy-one percent had typical angina, 2% had nonanginal symptoms and the remainder had atypical angina. Unstable angina was present in 14%, progressive (but not unstable) symptoms in 42% and stable angina in 44%. Thirty-two percent of patients described nocturnal episodes of angina (one-third of this group had stable angina and two-thirds had progressive or unstable angina). The median duration of symptoms was 22 months and 17% of the study patients had had angina <3 months at the time of catheterization. Variant angina was present in 2%. Seventeen percent of patients were in New York Heart Association functional class I and 69% were in ≥class III. The median daily angina frequency was <1 episode (10th to 90th percentiles, 0 to 2). "Ischemic" ST-T changes were present on the rest ECG in 20% of patients, and 40% had evidence of an old Q wave myocardial infarction.

At cardiac catheterization, 47% of the study group had three vessel or left main coronary artery disease, 30% had two vessel disease and 23% had one vessel disease. The median ejection fraction was 54% (10th to 90th percentiles, 31 to 68%).

Cardiac catheterization. Coronary angiography was performed in multiple right anterior oblique and left anterior oblique projections, as previously described (3). Significant coronary artery disease was defined as ≥75% luminal diameter narrowing of a major coronary artery. The coronary angiographic methods used in this study have been validated in a previous angiographic-pathologic study (12). The left ventricular ejection fraction was calculated using the modified area-length method (13).

Statistical methods. Cumulative survival rates were calculated from the day of cardiac catheterization using the Kaplan-Meier method (14). Survival rates for subgroups were not calculated beyond the point at which <20 patients remained at risk. Infarction-free survival was the primary study end point. A secondary analysis was performed using cardiovascular survival as the end point. All patients were considered to be initially treated nonsurgically. The follow-up time of patients undergoing coronary bypass graft surgery (2,768 patients, 47%) was included up to the date of their operation; these patients were then withdrawn (that is, censored) from the survival calculations.

The angina score was derived in four steps: First, the patients were randomly classified into two groups: 1) a training sample of 2,946 patients used for developing the

angina score, and 2) a validation sample of 2,940 patients for evaluating the final score (15). Second, the likelihood ratio chi-square statistic with the Cox proportional hazards regression model was used to measure the strength of association between individual anginal characteristics and infarction-free survival (16,17). Third, a subset of angina variables that contained all the available independent prognostic information was identified using the Cox model. A combination of statistical modeling and clinical intuition was used to select the final angina score variables. The regression model coefficients were rounded and used to assign a weight to each independent anginal characteristic. Finally, the prognostic power of the new angina score was examined in the independent validation sample of 2,940 patients.

Results

Grouping of anginal characteristics into an angina score. The relation of individual anginal characteristics with infarction-free survival in the 2,946 training sample patients is shown in Table 1. The characteristics most strongly associated with the risk of nonfatal myocardial infarction or death were the frequency of anginal episodes, the presence of unstable angina and "ischemic" ST-T wave abnormalities on the ECG. The risk of a cardiac event increased as symptom tempo went from stable angina (lowest risk) to progressive angina without nocturnal episodes, to progressive angina with nocturnal episodes and to unstable angina or variant angina (highest risk). These separate variables and their Cox model regression coefficients were then used to form a summary measure of the patient's angina course, which ranged from 0 to 3 (Table 2). Once the angina course was classified in this fashion, neither the New York Heart Association functional class nor the presence of new onset angina (<3 months) added any additional prognostic information.

Angina frequency (rounded to 0 to 5 episodes/day) added significant information to the angina course (chi-square = 15). Furthermore, the prognostic information added by knowing the frequency of episodes of angina was dependent on the patient's overall angina course (expressed in the Cox model as the product of course [0 to 3] and frequency [0 to 5]). When the course was stable (angina course = 0), there was no additional prognostic information in the daily pain frequency. When the pain was progressive or unstable, however, the cardiac event rate increased with increasing angina frequency (up to a maximum of 5 episodes/day).

The presence of typical angina was a significant prognostic factor that was independent of the angina course and daily frequency (chi-square = 18). The relation of typical angina to prognosis, however, was mediated completely through its relation with the amount of coronary disease present. Thus, 57% of patients with one vessel disease, 67% with two vessel disease and 78% with three vessel disease had typical angina. Once the amount of coronary disease present was taken into account, typical angina provided no additional prognostic information. Similarly, the duration of coronary disease symptoms was related to prognosis independently of the angina course and frequency (chi-square = 11), but its prognostic information was completely subsumed by the coronary anatomy. For this reason, neither typical angina nor the duration of symptoms was retained in the angina score.

The final independent prognostic component of the angina score was the presence of ST-T wave abnormalities at rest (coded as present or absent). Cox model analysis showed that the presence of such changes added six points to the angina score relative to their absence. Thus, the final angina score had three components:

Score = course (0 to 3 points) + course × daily pain frequency (up to 5) + ST-T abnormalities (6 points),

which reduced to:

Score = course × (1 + frequency) + ST-T abnormalities,

Table 1. Association of Individual Anginal Characteristics With Infarction-Free Survival in 2,946 Training Sample Patients

Anginal Characteristic	Univariate χ^2
Frequency of anginal discomfort	24
Unstable angina	21
Typical angina	18
Duration of coronary disease symptoms	17
Progressive angina with nocturnal episodes (but not unstable)	13
Variant angina	11
Progressive (but not unstable) angina	9
New onset (<3 months) angina	6
New York Heart Association class	6
"Ischemic" ECG ST-T changes	32

Table 2. Patient's Anginal Course (0 to 3) Based on Separate Variables and Their Cox Model Regression Coefficients in 2,946 Training Sample Patients

Variable	β	Weight*	χ^2†
Unstable angina	0.90	3	28
Variant angina	0.80	3	6
Progressive angina with nocturnal episodes but without variant or unstable angina	0.64	2	24
Progressive without variant or unstable angina and without nocturnal episodes	0.28	1	4

The reference category is stable angina, which is assigned a weight of 0. *Weights are derived from regression coefficients; †χ^2 values are adjusted for other variables in the model. β = Cox model regression coefficient.

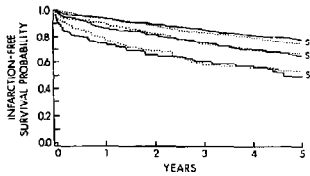

Figure 1. Validation of new angina score in 5,886 patients. Kaplan-Meier infarction-free survival probability (Y axis) is plotted against follow-up time in years (X axis). Infarction-free survival estimates for each of three groups of the angina score are shown for the training sample of patients (n = 2,946) (**solid lines**) and for the validation sample of patients (n = 2,940) (**dashed lines**).

and ranged from 0 (that is, the patients with stable angina and no ST-T wave changes at rest) to a maximal possible 24 (that is, the patient with unstable angina, five or more episodes of pain a day and ST-T wave changes at rest). Neither the score variables nor the score weights were substantially changed when the analysis was repeated with the surgical patients excluded.

Validation of angina score. Validation of the final angina score was accomplished by comparing the Kaplan-Meier estimates of infarction-free survival observed in the 2,946 training sample patients that had been used to develop the score with the corresponding estimates from the 2,940 patients in the independent validation sample. To facilitate comparisons between training and validation samples, the angina score was arbitrarily divided into three levels (Fig. 1). Observed infarction-free survival for each level of the angina score was very close in the two patient samples, indicating that the prognostic stratification provided by the score was reproducible.

Prognostic stratification. Figure 2 shows the relation of the score with prognosis for up to 10 years of follow-up in the total study group. During the first year of follow-up, the cardiac event rate (death or nonfatal myocardial infarction) was 6% in the patients with an angina score of 0 to 2 (Group 1), 12% in those with a score of 3 to 8 (Group 2) and 24% in those with a score ≥9 (Group 3). After the first year, the annual event rate in Group 1 averaged 4%, compared with 5% in Group 2 and Group 3. Additional analyses showed that the effect of the angina score on prognosis was observed mainly during the first year of follow-up and that, by about 3 years, the score did not further stratify prognosis.

Figure 2. Infarction-free survival probability (Y axis) versus 10 year follow-up (X axis) for three angina score groups: Group 1 (score = 0 to 2); Group 2 (score = 3 to 8); Group 3 (score ≥9).

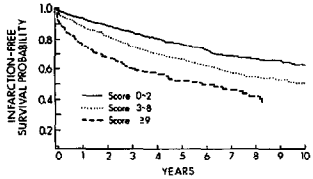

Table 3. Cox Model Analysis of Angina Score and Cardiac Catheterization Variables

Characteristic	χ^2 Infarction-Free Survival*	χ^2 Survival*
Ejection fraction	154	245
Number of diseased vessels	63	68
Left main stenosis	34	73
Angina score	71	40
Age	5	14
Sex	1	2

*χ^2 values are adjusted for other variables in the model

Added value after catheterization. To test the prognostic value of the angina score once the results of cardiac catheterization were known, the score was entered into a Cox model along with variables for left ventricular ejection fraction, number of diseased vessels and amount of left main coronary stenosis, as well as age and sex (Table 3). For both total cardiac events and cardiovascular death, the ejection fraction was the most important prognostic factor. Importantly, in both cases the angina score contributed substantial independent prognostic information to the results of cardiac catheterization. These results were unchanged when the analysis was repeated with the surgically treated patients excluded. Patients with one vessel disease and an ejection fraction ≥50% (n = 981) had a 2 year infarction-free survival of 95% with an angina score of 0 and 90% with an angina score ≥9. The corresponding figures for the patients with one vessel disease and an abnormal left ventricle (n = 394) were 93 and 89%, respectively. Patients with three vessel disease (without significant left main disease) and a normal left ventricle (n = 1,233) had a 2 year infarction-free survival of 90% with an angina score of 0 and 68% with an angina score ≥9. With an ejection fraction <50% and three vessel disease (n = 1,116), the corresponding infarction-free survival figures were 76 and 56%, respectively.

Table 4 documents that combining the different clinical descriptors of ischemia into a weighted score leads to better prognostic predictions than is obtained by using each characteristic individually. No single characteristic of angina contained as much prognostic information as the angina score, although unstable angina (for total events and cardiovascular death) and variant angina (for total events only) were highly significant when considered individually.

Table 4. Prognostic Value of Angina Score Compared With Angina Score Components

Characteristic	χ^2 Infarction-Free Survival*	χ^2 Survival*
Angina score	71	40
Unstable angina	37	31
Variant angina	24	3
Progressive angina with nocturnal episodes	10	5
Progressive angina, no nocturnal episodes	0	0
ST-T wave changes	11	5

*All χ^2 values are adjusted for ejection fraction, number of diseased vessels, amount of left main coronary stenosis, age and sex.

To underscore the clinical importance of the characteristics in the angina score, Cox model predicted survival and infarction-free survival rates for four hypothetical patients of the same age and sex treated with nonsurgical therapy were generated (Table 5). All four patients are 60 year old men with three vessel coronary disease, a left ventricular ejection fraction of 60% and no left main coronary artery stenosis. Patient A has stable angina occurring once a week, no nocturnal angina and a normal rest ECG (angina score = $0 \times (1 + 0) + 0 = 0$). Patient B has stable angina (no change in frequency or severity for at least 6 weeks) that occurs once a day, as well as rest ST depression on the ECG (angina score = $0 \times (1 + 1) + 6 = 6$). Patient C has progressive angina occurring twice daily that occasionally awakens him at night, rest ST depression on the ECG and no prolonged episodes of angina requiring coronary care unit admission (angina score = $2 \times (1 + 2) + 6 = 12$). Patient D has unstable angina requiring coronary care unit admission, four episodes of angina a day and rest ST segment depression on the ECG (angina score = $3 \times (1 + 4) + 6 = 21$). The expected survival rates are quite different for these patients, and the event-free rates are even more disparate despite identical coronary anatomy and left ventricular ejection fraction.

Discussion

Importance of the angina score. This study demonstrates that a simple clinical angina score that summarizes the qualitative and quantitative features of anginal discomfort adds independent prognostic information to the results of cardiac catheterization. The angina score highlights the concept that the patient's symptoms are an independent dimension of coronary disease that affects prognosis above and beyond any effect of the findings at coronary angiography. Furthermore, the prognostic importance of the new angina score significantly exceeds the importance of any single feature of anginal symptoms (Table 4), thus demonstrating the potential value of clinical indexes that simulate the "gestalt" impression of the experienced physician.

Although it is well known that unstable angina places patients at high risk of subsequent cardiac events (3,8,18,19), the importance of other gradations in the overall spectrum of coronary disease symptoms has not been previously demonstrated. Unstable angina, progressive angina and the frequency of anginal episodes reflect the "tempo" or dynamic character of the anginal pattern. Many previous studies have characterized the severity of angina by using the New York Heart Association (NYHA) or the related Canadian Cardiovascular Society class (20,21). Our results (Table 1) and those of the Seattle Heart Watch angiographic registry and the Coronary Artery Surgery Study (CASS) registry have shown that these classification systems do have some prognostic value when considered by themselves (5,22). In agreement with our findings, however, neither the Seattle

Table 5. Cox Model Predicted Survival and Infarction-Free Survival for Four 60 Year Old Men With Three-Vessel Coronary Disease and Ejection Fraction of 60%

	Patient A	Patient B	Patient C	Patient D
Course	Stable	Stable	Progressive with nocturnal episodes	Unstable
Daily angina frequency	0	1	2	4
ST-T changes	No	Yes	Yes	Yes
Angina score	0	6	12	21
Survival				
1 Year	0.96	0.95	0.93	0.88
3 Years	0.91	0.88	0.85	0.78
5 Years	0.86	0.83	0.76	0.72
Infarction-free survival				
1 Year	0.94	0.90	0.84	0.78
3 Years	0.84	0.79	0.72	0.58
5 Years	0.75	0.71	0.63	0.54

Heart Watch registry nor the CASS registry found angina class to be an independent predictor of prognosis in medically treated patients. One explanation for this is that, although the NYHA class is a reasonable measure of current symptom severity, it provides no information about how rapidly symptoms are advancing. In our data, the rate of symptom progression was prognostically much more important than the severity of current symptoms (Table 1). Adding the duration of symptoms or the presence of typical angina does not alleviate this problem; our data show that both of these factors provide no prognostic information that is independent of the amount of coronary disease present. In our study, the tempo and frequency of angina provided important prognostic information even when the coronary anatomy and left ventricular function were known (Table 3).

The angina score emphasizes that the various anginal syndromes fit into an orderly spectrum of prognosis, with unstable angina and variant angina at the high risk end of the spectrum and stable angina at the low risk end. Validation of the angina score in an independent population of patients demonstrates the correctness of this scale. The presence of new onset angina (<3 months), which was shown in a previous study from this laboratory to be prognostically important, was not independent of other more powerful prognostic anginal characteristics (9).

The final component of the angina score, "ischemic" ST-T wave changes, was found to be an adverse prognostic factor in several previous studies (3,5,23). The electrophysiologic basis for ST-T changes at rest and the mechanism for their impact on cardiac event rates remain speculative. It is possible that analysis of specific types of ST-T changes, such as deep symmetric T wave inversion, might further subdivide risk.

The subjective nature of symptoms is a major concern with respect to their use in assessing prognosis. Compared with these "soft" variables, more objective measures, such as treadmill exercise testing, thallium scintigraphy or radionuclide angiography, seem attractive. These tests can be obtained only periodically. however, whereas the patient's symptomatic status is available inexpensively at all times. Furthermore, although subjective characteristics are difficult to quantify, their independent association with prognosis shown in this study provides a strong argument in favor of the continued need to consider them.

Because several clinical variables may measure different aspects of the same pathophysiologic process, maximal information can be extracted when these related variables are combined into a clinical index (15). When taken out of their proper clinical context, the apparent prognostic value of individual components may be considerably diluted because characteristics that describe similar pathophysiology "compete" with each other in standard stepwise multivariable models, yielding smaller statistical values for each of them. Combining characteris ics into an index that more closely simulates the clinical thought process leads to a more realistic appraisal of the prognostic value of these descriptors.

Prognostic value of angina score over time. In our study the prognostic value of the score diminished progressively during follow-up. Thus, symptoms provided information primarily about short-term, rather than long-term, prognosis. This finding confirms the clinician's tacit understanding that a patient's course must be gauged by periodic reevaluation. Perhaps serial measurements of the angina score at regular intervals would greatly improve our ability to predict the risk of a cardiac event prospectively. Support for this approach comes from the Veterans Administration Cooperative Surgery Study, which found that their angina questionnaire was useful in stratifying short-term prognosis when applied at several points in follow-up (24).

Medical therapy. One important limitation of this study is that the angina score does not take into account the patient's antianginal therapy. When we tested the prognostic importance of knowing that the patient was receiving a beta-receptor blocker or a long acting nitrate, these variables did not add to our score. We did not, however, attempt a detailed evaluation of the intensity of therapy, such as the dose or the presence of limiting side effects. The angina questionnaire used in the Veterans Administration Cooperative Surgery Study included a subsection that assigned points for nitrates and beta-receptor blockers, but no attempt was made to determine how much prognostic information was provided by medical therapy that was independent of the severity of angina (24). Thus, it is uncertain how much our angina score would be improved by adding data about prescribed medications.

Conclusions. We have shown that a careful clinical evaluation of the anginal history and rest ECG can be of great importance in predicting a patient's risk of future cardiac events. This information can be incorporated into a simple but powerful clinical angina score that remains a significant prognostic factor even after coronary anatomy and left ventricular function are known. Greater attention to the subjective aspects of coronary artery disease may aid clinicians in targeting effective and aggressive therapeutic interventions to periods of increased risk.

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