PATHOPHYSIOLOGY AND NATURAL HISTORY
CORONARY ARTERY DISEASE

The prognosis for patients with new-onset angina who have undergone cardiac catheterization

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ABSTRACT We investigated the prognostic significance of new-onset angina in patients in whom coronary anatomic characteristics were known. New onset angina was defined as angina of less than 3 months duration. Consecutive patients (n = 1727) with significant coronary artery disease (diagnosed at cardiac catheterization) and who had not had a prior myocardial infarction or congestive heart failure were studied. In patients with new-onset angina (n = 329) there was a higher incidence of single-vessel disease (43% vs 27%) and a lower incidence of triple-vessel (23% vs 35%) and left main artery (5% vs 10%) disease compared with patients with chronic angina (n = 1398). Patients were classified by the presence or absence of preinfarction angina (severe and prolonged angina at rest requiring hospitalization to rule out myocardial infarction). In patients treated without surgery and who did not have preinfarction angina, survival at 1 year was 97% for patients with new-onset angina and 98% for those with chronic angina (p = .27). Among patients not treated surgically who did not have preinfarction angina, at 1 year 16% with new-onset angina and 7% with chronic angina had suffered a cardiac event (nonfatal myocardial infarction or death, p = .006). In patients treated surgically who did not have preinfarction angina, survival at 1 year was 96% both for those with new-onset angina and those with chronic angina (p = .99). The risk of an event in patients treated surgically at 1 year was not statistically different in patients with new-onset angina and those with chronic angina (12% vs 11%, p = .27). Survival and event-free rates were lower in patients with preinfarction angina than in patients who did not have it. The nonsurgically and surgically treated patients with new-onset preinfarction angina remained at higher risk of an event than patients with preinfarction angina and a history of chronic angina. In conclusion, in patients who underwent cardiac catheterization there were no significant differences in survival rates between those with new-onset angina and those with chronic angina. However, patients with new-onset angina were at increased risk of a cardiac event, despite less severe anatomic disease.


GIVEN THE MARKED variability in the natural history of coronary heart disease, clinicians have relied on the identification of prognostic factors to help guide therapeutic decisions. The severity of the symptoms, the location of coronary lesions, and left ventricular function are among the factors that are considered in the identification of patients at increased risk of a myocardial infarction or death.1,2 Controversy has arisen concerning the importance of the recent onset of angina pectoris as an indicator of high risk.3,4 In some studies a prodrome of chest pain that precedes sudden cardiovascular death or acute myocardial infarction has been identified.5,6 The apparent inconsistency is that all patients with stable angina, most of whom have a relatively good prognosis, at one time had recent-onset angina.

The natural history and prognostic significance of new-onset angina have not been adequately characterized. Many investigators have included angina of recent onset in the definition of unstable angina.7 Within this context, the particular group with new-onset angina has been reported to be at higher risk of infarction than the remainder of patients classified as having unstable angina.8 However, results of a recent study indicate that there is a high incidence of single-vessel disease in patients with recent-onset angina.9 To our knowledge, no previous study has considered the prog-
nostic significance of new-onset angina in patients in whom coronary anatomic characteristics were known. This investigation was designed to determine whether new-onset angina, at the time of cardiac catheterization, is independently associated with an adverse prognosis when patient history, results of physical examination, coronary anatomic characteristics, and ventricular function are known.

Methods

Patients. At Duke University Medical Center between November 1969 and April 1982, 3419 consecutive patients without histories of previous myocardial infarction or of congestive heart failure underwent cardiac catheterization for suspected ischemic heart disease in the presence of possible anginal symptoms. Patients who had undergone prior revascularization procedures or had congenital heart disease, hypertrophic cardiomyopathy, or valvular heart disease other than mitral insufficiency thought to be secondary to ischemic heart disease were not included. Of the remaining patients, the study population was limited to the 1727 patients who had significant coronary artery disease, defined as 75% or greater luminal diameter narrowing of one or more major coronary arteries. Patient subgroups were formed based on the presence or absence of two characteristics: preinfarction angina and surgical therapy within 6 weeks after cardiac catheterization. Comparisons of outcomes in new-onset and chronic angina patients were made within each subgroup. Table I lists the number of patients in each group.

Information system and definitions. The computerized information system, data set, method of cardiac catheterization, and follow-up system have been described in detail previously. New-onset angina was defined as discomfort of less than 3 months duration that was thought to be related to ischemic heart disease. Chest discomfort of 3 months or longer duration was referred to as chronic angina. The documentation of the duration of anginal symptoms and all other patient descriptors was done prospectively at the time of cardiac catheterization. During the follow-up period, a myocardial infarction was defined as the characteristic clinical history in association with one of the following criteria: (1) appearance of a new 0.04 sec Q wave on the electrocardiogram (ECG), (2) a typical evolutionary pattern of ST-T wave changes accompanied by a transient elevation of total creatine kinase (CK) level or, if CK was not measured, appropriately timed elevations in serum lactic dehydrogenase (LDH) levels, or (3) if ECGs could not be obtained, or changes were uninterpretable (e.g., because of left bundle branch block), a transient elevation of CK (or of SGOT or LDH if CK was not measured) accompanied by positive isoenzyme changes (appearance of an MB band of CK or reversal of the LDH1:LDH2 ratio). The diagnosis of perioperative myocardial infarction was made only if new 0.04 sec Q waves persisted until the time of discharge from the hospital. The method of verification of ability to recognize infarcts during follow-up has been described. For the purpose of this study, the term "event" refers to cardiovascular death or myocardial infarction.

Definitions of terms used in our angina classification system have been published previously. Progressive angina was chest discomfort that was believed to represent angina, the episodes of which increased in frequency or duration during the 6 weeks before cardiac catheterization. Preinfarction angina was severe angina at rest that required admission to the cardiac care unit to rule out myocardial infarction and that occurred while the patient was in the hospital to undergo cardiac catheterization. Prinzmetal's angina was discomfort at rest that was associated with ST segment elevation on the ECG or with documented chest discomfort, ECG changes, and coronary vasoconstriction at cardiac catheterization. Anginal frequency was estimated from the patients' reports of the number of episodes per week over the 6 weeks before catheterization.

Statistical analysis. Patients were grouped by the presence of new-onset (n = 329) or chronic (n = 1398) angina. Baseline data describing the clinical presentation and catheterization results, particularly the anatomic location of lesions, were compared for patients with new-onset angina and those with chronic angina. Since a large proportion of new-onset angina patients were also classified as having preinfarction angina, in the analysis of patient outcomes the patients were further grouped according to the presence or absence of preinfarction angina. This classification was felt to be clinically justified as well, since patients with preinfarction angina are known to have a relatively poorer prognosis. For both nonsurgical and surgical therapies of coronary artery disease, cumulative survival probabilities were calculated by standard life table methods. The cumulative probability of remaining free of both death and nonfatal infarction (event-free probability) was calculated by the method used to calculate survival probability, with death or nonfatal infarction considered to be the terminating event.

The statistical significance of differences in survival or event probabilities was analyzed by Breslow's formulation of the Cox proportional hazards model. The statistics generated with this model apply to the entire survival or event-free curve rather than to survival or event-free probabilities at a specific point in time.

Figures were generated that illustrated survival or event-free curves adjusted by the Cox model. The mean values for the significant baseline parameters for a given patient population were entered into the derived Cox model to generate survival or event-free probabilities. This adjustment yielded a more valid comparison of the prognoses for new-onset and chronic angina patients because differences in baseline (especially coronary anatomic) characteristics were controlled by a first-order approximation.

Results

Baseline characteristics. The clinical and hemodynamic baseline data for the 1727 patients with significant coronary disease are listed in table 2. Patients with new-onset angina were more likely to be men and to have preinfarction or Prinzmetal's angina, but were...
TABLE 2
Baseline characteristics of patients with significant coronary artery disease

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>New-onset angina (n = 329)</th>
<th>Chronic angina (n = 1398)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Discrete characteristics (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>85</td>
<td>77</td>
</tr>
<tr>
<td>Characteristics of angina</td>
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<td>Typical</td>
<td>67</td>
<td>67</td>
</tr>
<tr>
<td>Nocturnal</td>
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<td>40</td>
</tr>
<tr>
<td>Progressive</td>
<td>48</td>
<td>51</td>
</tr>
<tr>
<td>Prinzmetal's a</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Preinfarction</td>
<td>19</td>
<td>6</td>
</tr>
<tr>
<td>ST-T wave changes</td>
<td>45</td>
<td>37</td>
</tr>
<tr>
<td>Peripheral vascular disease a</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Cerebrovascular disease a</td>
<td>0.3</td>
<td>3</td>
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<tr>
<td><strong>Risk factors</strong></td>
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<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>75</td>
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<tr>
<td>Diabetes</td>
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<tr>
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<td>Hyperlipidemia</td>
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<td>24</td>
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<td>Positive family history</td>
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<td>52</td>
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<td><strong>Continuous characteristics (median)</strong></td>
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<td></td>
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<tr>
<td>Age (yr) a</td>
<td>49</td>
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</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>59</td>
<td>60</td>
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<tr>
<td>LVEDP (torr)</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
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<td>235</td>
</tr>
<tr>
<td>Systolic BP (torr)</td>
<td>120</td>
<td>128</td>
</tr>
</tbody>
</table>

LVEDP = left ventricular end-diastolic pressure; BP = blood pressure.

*p < .05 for difference between groups; *p < .01 for difference between groups.

less likely to have peripheral or cerebrovascular disease. New-onset angina patients were also younger. No differences between groups were found with regard to ejection fraction or left ventricular end-diastolic pressure. When patients with preinfarction angina were excluded, the magnitude of other differences remained unchanged.

Table 3 lists the distribution of the number of coronary arteries diseased among the patients studied. More patients with new-onset angina had single-vessel coronary artery disease (43%) compared with patients with chronic angina (27%). Correspondingly, among those patients with chronic angina, three-vessel disease was more common (35% vs 23%) and left main coronary disease was twice as prevalent (10% vs 5%).

An alternative method of determining the relationship of duration of anginal symptoms to the extent of coronary disease is illustrated in figure 1. This figure plots the proportion of one-, two-, and three-vessel and left main coronary artery disease against the duration of anginal symptoms for patients with significant dis-

ease. The prevalence of single-vessel disease declines with duration of symptoms from 43% in patients who have had symptoms for less than 3 months to 17% in patients who have had symptoms for more than 8 years. The opposite trend is present for three-vessel and left main coronary artery disease patients.

The number of patients with single-vessel disease is shown in table 4, which also shows the involvement of the left anterior descending (LAD) coronary artery in patients with new-onset and chronic angina. Although

FIGURE 1. The frequencies of one-, two-, and three-vessel and left main coronary artery disease plotted against the duration of anginal symptoms at the time of coronary catheterization. Patients with prior myocardial infarction or a history of congestive heart failure are excluded.
single-vessel disease was more common among patients with new-onset angina, the prevalence of LAD disease among those with single-vessel disease was not significantly different between patients with new-onset and chronic angina (59% vs 57%). Moreover, among patients with single-vessel disease, the prevalence of proximal as opposed to distal LAD lesions was not significantly different between new-onset and chronic angina patients (26% vs 27%).

Survival in patients without preinfarction angina. The adjusted probability of survival of patients not treated surgically and with no preinfarction angina is illustrated in figure 2. No significant difference between survival rates for patients with new-onset angina and with chronic angina (p = .27) was found. After 1 year of follow-up the survival rate was 97% for patients with new-onset angina and 98% for those with chronic angina. At 3 years 94% with new-onset angina and 93% with chronic angina were alive.

The adjusted probability of survival in surgically treated patients is shown in figure 3. Again, no difference in this value was found between patients with new-onset angina and those with chronic angina (p = .99). Survival in surgically treated patients was greater than 90% throughout the follow-up period. The overall operative mortality for this group, which includes patients who underwent emergency operations due to instability that developed between the times of cardiac catheterization and surgery and those who underwent ventricular surgery, was 4.6% during the period of the study. During the latter half of the study (January 1976 to April 1982) the operative mortality for those undergoing nonemergency bypass grafting was 2.8% (2.5% in patients without left main coronary artery disease and 2.0% for all patients with normal left ventricular contractile pattern at cardiac catheterization).

Event-free probabilities in patients without preinfarction angina. The adjusted event-free probability curves for the patients who were not treated surgically are shown in figure 4. Patients with new-onset angina were at increased risk of a cardiac event compared with patients with chronic angina. This difference was not significant by univariate analysis (p = .13). However, after adjusting for other characteristics (primarily the less severe anatomic disease of patients with new-onset angina) with the Cox multivariable model, the difference was significant (p = .006). Moreover, patients with new-onset angina as compared with those with chronic angina had a relative risk of 1.8 for a cardiac event when all other baseline characteristics

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were equal (as estimated by the regression model). At 1 year 16% of patients with new-onset angina and 7% of those with chronic angina had either died of cardiovascular disease or had had a myocardial infarction. By 3 years 25% with new-onset angina and 15% with chronic angina had suffered a cardiac event.

The adjusted event-free probability curves for the surgically treated patients are shown in figure 5. These patients were at a relative risk of 1.3 for a cardiac event if new-onset angina was present. This relative risk was not statistically significant, even after adjusting for the extent of coronary disease (p = .27). At 1 year 12% of patients with new-onset angina and 11% of those with chronic angina had suffered an event. Overall, the perioperative infarction rate in these patients has been 6.7% since 1969. For patients who underwent elective bypass grafting between January 1976 and April 1982 the perioperative infarction rate dropped to 5%.

Survival in patients with preinfarction angina. Figures 6 and 7 illustrate the adjusted probabilities of survival for patients with preinfarction angina treated with and without surgery. The curves only extend to 3 years because of the small number of patients. The survival rate of patients with preinfarction angina is lower than that of patients without preinfarction angina (figures 2 and 3). However, within the group of patients with preinfarction angina no significant difference exists between survival rates for patients with new-onset and those with chronic angina. The lower probability of survival for surgically treated patients with preinfarction angina compared with patients without preinfarction angina in part reflects the high operative mortality in our early experience with these patients (8% overall operative mortality) and the large proportion of pa-
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FIGURE 7. Cumulative survival probabilities (adjusted) for surgically treated patients with preinfarction angina who underwent catheterization for chest pain (40 had new-onset and 42 had chronic angina).

FIGURE 8. Cumulative event-free probabilities (adjusted) for patients not treated surgically for coronary artery disease. These patients had preinfarction angina, and underwent catheterization for chest pain (24 patients had new-onset and 38 had chronic angina).

FIGURE 9. Cumulative event-free probabilities (adjusted) for surgically treated patients with preinfarction angina who underwent catheterization for chest pain (40 patients had new-onset and 42 had chronic angina).

Patients with abnormal left ventricular contraction. Since April 1982, 48 patients meeting the criteria for preinfarction angina have undergone surgical treatment and only one operative death has resulted.

Event-free probabilities in patients with preinfarction angina. Figures 8 and 9 illustrate the adjusted event-free rates for patients with preinfarction angina. In this small group of patients the adjusted difference in event-free rates in the nonsurgically treated patients is not statistically significant (p = .16) and the difference for surgically treated patients is only marginally significant (p = .04). The perioperative infarction rate in this group has been 5% since 1969 and 4% since 1976.

Relative importance of descriptors of angina. The descriptors of angina that have prognostic importance in our population of patients who were not treated surgically and who had not had a previous myocardial infarction are preinfarction, progressive, nocturnal, new-onset, Prinzmetal’s, and frequent angina and ST-T abnormalities on resting ECG. Each provides independent information concerning the probability of the occurrence of a cardiac event. Thus, the amount of risk is related to the particular combination of anginal characteristics. One year event rates for some representative combinations are given in table 5. For example, if
only the presence of new-onset angina is used as an indicator of risk (whether or not the other characteristics were present) patients with new-onset angina would be at 19% risk at 1 year of having a nonfatal myocardial infarction or suffering cardiac death. With the use of other characteristics in combination the risk can be further stratified so that nonsurgically treated patients with new-onset angina, resting ST-T wave abnormalities, and nocturnal angina are at 32% risk of a cardiac event at 1 year. Alternatively, patients with none of these characteristics have only at 5% risk of a cardiac event.

**Discussion**

Physicians are often faced with the problem of evaluating a patient with new-onset chest pain. Since angina of recent onset has been included under the rubric of unstable angina, the tendency in recent years has been to perform cardiac catheterization early. Surprisingly little is known about the coronary anatomy and natural history of these patients.

In this study of patients undergoing cardiac catheterization, patients with new-onset angina differed from patients with chronic angina in several regards. The larger proportion of men in the new-onset angina group may simply reflect referral practices. That is, physicians may have a tendency to refer men for cardiac catheterization early in their clinical course, since symptoms are more difficult to interpret in women. The larger proportion of patients with Prinzmetal’s and preinfarction angina in the new-onset angina group may be due to the fact that angina at rest with ST segment changes is a dramatic clinical event that may lead to earlier catheterization. The lower frequency of peripheral and cerebrovascular disease in the new-onset angina patients is consistent with the fact that they were younger and their coronary atherosclerosis was less severe compared with that in patients with chronic angina. The finding of similar left ventricular function in all the patients in this study was expected since these patients were selected based on the absence of a previous infarction.

The differences in coronary anatomic characteristics in the new-onset and chronic angina patients demonstrate that the severity of atherosclerosis is related to the duration of symptoms. The relationship, however, is not strong enough to predict with accuracy the extent of coronary disease in an individual patient. Nevertheless, in terms of overall strategy the relationship may be useful. For example, the physician using cardiac catheterization early in the clinical course is likely to find a large proportion of patients with single-vessel disease, many of whom will be candidates for percutaneous coronary angioplasty. Victor et al. found that 52% of patients with unstable angina of less than 90 days duration had single-vessel disease. Proudfit et al. also found a high incidence of single-vessel disease in patients with new-onset angina.

A predisposition for disease of the LAD was reported for patients with new-onset angina by Victor et al. However, among all patients in our study with single-vessel disease, regardless of the duration of symptoms, the LAD was most frequently involved. Similar results have been found in our analysis of all patients with single-vessel disease undergoing cardiac catheterization at Duke Medical Center. Thus, patients with new-onset angina have no special predisposition for disease of the LAD. This finding either represents a biologic predisposition of the LAD for development of atherosclerosis or a tendency for patients to become symptomatic when this artery is involved.

No differences in survival were observed between patients with new-onset and those with chronic angina. The low mortality was expected in both groups, since patients with a prior myocardial infarction were excluded from the study. The survival figures in our study should not be interpreted as representative of the expected survival for patients in the community: our patients were a select group referred for cardiac catheterization. Patients with the most malignant course may have died suddenly before receiving medical attention and patients with mild symptoms may not have been referred. The major advantage of this study, however, is that the relative importance of the duration of symptoms can be assessed in a group of patients who have been characterized. Thus, the influence of other descriptors of the symptoms, risk factors, and coronary anatomy can be controlled.

A detailed analysis of other prognostic factors has not been reported in this study since the prognostic factors in patients with new-onset angina are not differ-
ent from those in patients with chronic angina. In our patient population and in populations cited in other reports, the state of left ventricular function and the presence or absence of left main coronary artery stenosis are the predominant determinants of survival. In the group of patients with good left ventricular function the coronary anatomic characteristics, the tempo and type of anginal symptoms, and the presence of peripheral vascular disease are most closely related to survival and occurrence of nonfatal infarction. In patients with single-vessel coronary disease the presence of a lesion in the LAD before the first septal perforator is associated with decreased survival, although the magnitude of the effect is not great.

Comparison of the nonsurgical and surgical results in a study such as ours would be inappropriate. The surgically treated patients in this study were selected predominantly due to the greater severity of their symptoms and of their anatomic coronary disease. Numerous other more subtle baseline differences may exist between the surgically and nonsurgically treated patients. Since the purpose of this paper was limited to an investigation of the prognostic significance of new-onset angina, no attempt was made to accomplish the intricate statistical adjustments necessary to interpret the effect of surgery on prognosis in this group of patients.

Furthermore, the absolute survival rates and event-free rates for this series cannot be extrapolated with precision to patients treated in 1983. Cardiac mortality and total event rates for our patients who are not surgically treated have been dropping steadily over time. Similar trends have been reported by others and have been observed in our own surgically treated patients, especially those with preinfarction angina.

Patients with new-onset angina were found to be at significantly higher risk of a cardiac event compared with patients with chronic angina. In this population of patients without previous infarction the major difference was in the risk of nonfatal infarction. We have previously reported that good left ventricular function, lack of previous infarction, LAD stenosis, and young age were the most powerful indicators of whether or not a future cardiac event may be fatal.

The difference in event-free rates was not apparent until adjustment was made for the differences in coronary anatomic characteristics. However, when one realizes that new-onset angina patients had much less severe coronary damage, the differences appear more impressive. A better understanding of the results obtained with the Cox model can be gained by viewing figure 4, in which the event-free rates adjusted for anatomic characteristics for nonsurgically treated patients are illustrated. Short and Stowers reported similar results in a group of patients who did not undergo cardiac catheterization. These findings confirm the impression of many clinicians that the period of initial onset of angina may be a particularly dangerous one.

Among surgically treated patients without preinfarction angina, no statistically significant difference in event-free rates was found. We could not determine whether the lack of a difference was due to the surgical therapy or to patient selection. However, in surgically treated patients with preinfarction angina a marginally significant difference was detected. In all patient groups the trend was in the same direction: increased risk with new-onset angina.

Thus, clinicians should regard new-onset angina as but one important clinical parameter deserving close attention and follow-up. When medical therapy is instituted, consideration should be given to the overall anginal pattern (frequency, duration, severity, ECG changes) since patients with more severe angina patterns are at higher risk of a cardiac event. Many patients with new-onset angina will be candidates for percutaneous coronary angioplasty. However, the role of angioplasty in the prevention of nonfatal infarction has not yet been delineated. Similarly, coronary artery bypass grafting has not been shown to reduce the incidence of nonfatal infarction in patients with unstable angina.

The prognosis for patients with preinfarction angina was poorer than that for patients in other classifications, whether or not the angina was of recent onset. Our criteria for the diagnosis of preinfarction angina required that the patients had been admitted to the cardiac care unit to rule out myocardial infarction during the same hospital stay in which they underwent catheterization. In addition, the patient must have had prolonged angina at rest. These criteria delineate a select group of high-risk patients (9% of the total population), even though their identification is dependent on the subjective judgement of the physician. Fifty-four percent of these patients had nocturnal angina, 68% had resting ST-T wave abnormalities on the ECG, and the average frequency of their episodes of angina was two episodes per day. In previous studies the characteristics of a high-risk group have been delineated and have been termed the "intermediate" syndrome.

Patients with this syndrome have prolonged angina at rest with ST-T wave abnormalities.

In summary, in a well-characterized group of patients new-onset angina was associated with less severe coronary anatomic abnormality than was chronic.

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angina. No particular predisposition for disease of the LAD was found in patients with new-onset angina and they were not at increased risk of death. However, a trend toward a higher risk of cardiac event was found among patients with new-onset angina. This difference was statistically significant among patients not treated surgically who did not have preinfarction angina and among surgically treated patients with preinfarction angina. Although the differences were not significant, similar trends were found in patients not treated surgically who had preinfarction angina and in surgically treated patients without preinfarction angina. Other characteristics of the angina pattern also were found to increase the ability to stratify prognoses.

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