PATHOPHYSIOLOGY AND NATURAL HISTORY
CORONARY ARTERY DISEASE

Long-term prognosis of patients with variant angina

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ABSTRACT The long-term prognosis of variant angina and the factors influencing it were assessed in 217 consecutive patients hospitalized in our coronary care unit and followed for a mean of 65 months (range 2 to 123). Cardiac death occurred in 30 patients and an additional 54 experienced a nonfatal myocardial infarction. Survival at 1 and 5 years was 95% and 89%, respectively; survival without infarction was 83% and 69%. Coronary disease and the degree of disease activity were strong predictors of survival by Cox analysis. Survival at 1 year was 99%, and that at 5 years was 95% and 94%, respectively, for patients with one-vessel disease (n = 81) and for those without stenoses of 70% or greater (n = 87). Survival at 1 and 5 years was only 87% and 77% for those with multivessel disease (n = 40). The Cox analysis selected left ventricular function, initial treatment, extent score, duration of angina at rest, and disease activity as multivariate predictors of survival without infarction. Coronary disease was a strong predictor (p < .0001) of survival without infarction by univariate analysis. Treatment with nifedipine, diltiazem, or verapamil improved survival without infarction compared with other medical treatment (p = .002). Myocardial infarction occurred most commonly soon after diagnosis in patients with a short history of angina at rest. Late coronary events were almost never preceded by resting angina. Circulation 76, No. 5, 990–997, 1987.

CORONARY ARTERY SPASM accounts for the clinical manifestations of variant angina but probably does not play a major role in most patients with other coronary syndromes. Therefore, the long-term outcome of patients with variant angina and the factors influencing their prognosis may differ from those for other patients with coronary disease.

The follow-up of four large series of patients with variant angina has been reported.1–4 In one of these studies we described 169 such patients followed for a mean of 15 months.2 Angina disappeared spontaneously in many patients after 1 year, particularly those with coexisting organic stenoses.5 The purpose of this report is to describe the prognosis, and the factors influencing prognosis, in a larger series of 217 patients followed prospectively for a mean of 65 months.

Methods

Patients. The diagnosis of variant angina was made in patients meeting all the following criteria: (1) burning or squeezing retrosternal chest pain at rest, (2) relief of the pain by nitroglycerin in less than 5 min, (3) ST segment elevation of at least 2 mm not present on the baseline electrocardiogram but documented during pain and disappearing with relief of pain, and (4) no subsequent evidence of myocardial necrosis. Between April 1976 and April 1986, 217 patients meeting these criteria were hospitalized at the Montreal Heart Institute.

The mean age of the patients was 51 years (range 24 to 71); 165 were men and 52 were women. ST segment elevation was noted at the anterior electrocardiographic leads in 112 patients and at the inferior leads in 105 patients. In 161 cases transient ST elevation was detected during resting angina and in the remaining 56 it was documented only after administration of ergonovine.

Patient management. Patients were hospitalized in the coronary care unit, where they underwent continuous electrocardiographic monitoring for at least 3 days. A complete electrocardiogram was recorded during episodes of angina at rest when possible. Coronary arteriography was performed by a percutaneous transfemoral approach by use of preformed catheters with routine filming of sagitally angulated views of the left coronary artery. Patients were not routinely given nitroglycerin before angiography, but if coronary stenoses were present, the involved vessels were restudied in multiple views after administration of nitroglycerin. Coronary arteriography was not performed in nine patients who either had associated life-threatening noncardiac illness (two patients) or developed myocardial

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infarction soon after admission to the hospital (seven patients). In all but 16 of the patients who underwent coronary arteriography, a left ventricular angiogram was filmed in the 30 degree right anterior oblique view.

In 87 patients no organic stenoses of 70% or more of the luminal diameter were seen at coronary arteriography; 81 patients had one-vessel disease (≥70% reduction in diameter) and 40 had multivessel involvement. The left ventriculogram was normal in 142 patients and revealed segmental wall abnormalities in 50 patients. Ergonovine testing was usually not done during coronary arteriography. After arteriography an ergonovine test was performed in the coronary care unit according to a defined protocol in patients with suspected but unproven variant angina.

Coronary artery bypass surgery, with or without plexectomy, was performed as initial treatment in 21 patients and was done during the follow-up period in 11 others. Initial treatment was coronary angioplasty in six patients. Drug treatment was applied initially to 186 patients. During the first part of the study period, from 1976 to 1978, perhexiline maleate was the only calcium antagonist drug available to us; therefore, 40 patients were initially treated with this drug, with long-acting nitrates, or with β-blockers. The remaining 146 patients received nifedipine, diltiazem, verapamil, or combinations of these drugs. Long-acting oral or topical nitrates were added if symptoms persisted on treatment. Four patients who sustained a myocardial infarction soon after the diagnosis was made received no therapy. The usual doses for drugs begun in hospital were 100 to 400 mg twice daily for perhexiline maleate, 20 mg four times daily for nifedipine, 120 mg three times daily for diltiazem, 160 mg three times daily for verapamil, 30 mg four times daily for isosorbide dinitrate, and 2 inches four times daily for nitroglycerin ointment.

After discharge, each patient returned to a special hospital clinic at 1 month, 3 months, and every 3 months thereafter. At each visit a standardized questionnaire, physical examination, and electrocardiogram were recorded. Calcium antagonists were eventually discontinued in 84 of the 158 patients treated with these drugs, occasionally because of side effects but usually because no angina had occurred for at least 6 months.

Myocardial infarction was diagnosed in patients who developed signs of definite or probable infarction (Minnesota code criteria) or who experienced myocardial ischemic pain lasting longer than 30 min followed by confirmatory cardiac enzyme or isoenzyme abnormalities. During the study 14 patients (6%) were lost to follow-up. Five patients who died from noncardiac causes were included in the analysis until their deaths.

**Data analysis.** Table 1 lists the variables that were studied and their subsets. "Extant score" is defined as the number of segments in a 15-segment coding system with 5% to 75% diameter stenoses. In a series of patients who underwent two coronary arteriograms at our institute and were analyzed retrospectively, a high extent score at the first study correlated with coronary disease progression and new total occlusions. Progression of coronary disease was associated with a higher prevalence of unstable angina at the time of the second angiogram and a higher incidence of subsequent mortality and infarction.

As an index of disease activity, we classified patients into three groups: those in whom attacks were rare and could only be documented by ergonovine provocation and those with and without serious arrhythmias during attacks, since such arrhythmias may be an indicator of more severe ischemia and a poorer prognosis. Serious arrhythmias were defined as ventricular fibrillation, ventricular tachycardia, ventricular couplets or bigeminy, second- or third-degree atrioventricular block, or asystole.

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Clinical and angiographic variables&lt;sup&gt;a&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td>Variables</td>
<td>Subsets</td>
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<tr>
<td>Coronary artery disease</td>
<td>No stenosis ≥70%</td>
</tr>
<tr>
<td></td>
<td>One-vessel disease</td>
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<tr>
<td></td>
<td>Multivessel disease</td>
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<tr>
<td>Left ventricular function</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>Abnormal</td>
</tr>
<tr>
<td>Extent score</td>
<td>≤4</td>
</tr>
<tr>
<td></td>
<td>&gt;4</td>
</tr>
<tr>
<td>Disease activity</td>
<td>Arrhythmias during attacks</td>
</tr>
<tr>
<td></td>
<td>No arrhythmias during attacks</td>
</tr>
<tr>
<td></td>
<td>Provoked attacks only</td>
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<tr>
<td>Initial treatment</td>
<td>Nifedipine, diltiazem, verapamil</td>
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<td></td>
<td>Other medical treatment</td>
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<tr>
<td></td>
<td>Bypass surgery ± plexectomy</td>
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<td></td>
<td>PTCA</td>
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<td>Age (yr)</td>
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<td></td>
<td>40–59</td>
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<td></td>
<td>60–79</td>
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<td>Gender</td>
<td>male</td>
</tr>
<tr>
<td></td>
<td>female</td>
</tr>
<tr>
<td>Duration of rest angina</td>
<td>&lt;1 mo</td>
</tr>
<tr>
<td></td>
<td>1 to 3 mo</td>
</tr>
<tr>
<td></td>
<td>&gt;3 mo</td>
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<tr>
<td>Site of ST elevation</td>
<td>anterior</td>
</tr>
<tr>
<td></td>
<td>inferior</td>
</tr>
</tbody>
</table>

<sup>a</sup>The total for each variable is not 217 because of nine patients without coronary arteriograms, 25 without left ventriculograms, 14 patients in whom an extent score could not be calculated, and four patients who developed myocardial infarction before treatment was begun. The classification of disease activity is based on our previous study, which showed that arrhythmias during attacks were an indicator of more severe ischemia.

For the entire population, curves for both survival and survival without myocardial infarction were constructed by means of the standard life table analysis. The relationships between clinical and angiographic variables and end points were first assessed by univariate analysis with use of the chi-square test for categorical data and the two-sample t test for continuous variables. A Cox regression model for survival analysis was then done to determine which variables were multivariate predictors of end point events. Patients with missing values were eliminated from the analyses. Curves for different subgroups were compared with a generalized Wilcoxon (Breslow) test; two-tailed p values are given for these comparisons. A BMDP program was used for these analyses.

**Results**

During a mean follow-up period of 65 months (range 2 to 123), 30 of the 217 patients died from cardiac causes and 54 others developed myocardial infarction. One-half of the 30 deaths were sudden and 15 were in-hospital complications of myocardial infarction. Nine of the 30 deaths and 22 of the 54 myocardial infarctions occurred during the first 3 months, includ-
Extent of Initial treatment ventricular Left activity Coronary artery disease

Survival. The clinical and angiographic variables that correlated with survival are listed in Table 2. By univariate analysis coronary artery disease (number of diseased vessels), left ventricular function, and degree of disease activity were statistically significant predictors of survival. The Cox regression model selected coronary artery disease (p = .001), degree of disease activity (p = .005), and left ventricular function (p = .09) as multivariate predictors of survival.

Cardiac death occurred in 25 of the 208 patients (12%) who underwent coronary arteriography: six of 87 (7%) with no stenosis of 70% or more, six of 81 (7%) with single-vessel disease, and 13 of 40 (33%) with multivessel disease. Survival at 1 and 5 years, respectively, was 99% and 94% for patients with no stenoses of 70% or more, 99% and 95% for patients with single-vessel disease, and only 87% and 77% for those with multivessel disease. Patients with normal left ventricular function had survival rates of 99% and 95% at 1 and 5 years, compared with 96% and 83% in those with abnormal left ventricular function. The classification of disease activity correlated with survival: only three cardiac deaths (5%) occurred in the 56 patients with attacks documented only with ergonovine testing, 12 (12%) occurred in the 102 with documented spontaneous episodes of ST elevation without arrhythmias, and 15 (25%) occurred in the 59 patients with arrhythmias during spontaneous attacks. Figure 2 illustrates the survival curves for these variables.

Survival without myocardial infarction. Survival without myocardial infarction is probably the most clin-
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TABLE 3
Variables predictive of survival without infarction

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis</th>
<th>Cox model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>χ²</td>
<td>p value</td>
</tr>
<tr>
<td>Left ventricular function</td>
<td>15.71</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Initial treatment</td>
<td>12.22</td>
<td>.0005</td>
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<tr>
<td>Extent score</td>
<td>9.45</td>
<td>.002</td>
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<tr>
<td>Duration of resting angina</td>
<td>8.8</td>
<td>.003</td>
</tr>
<tr>
<td>Disease activity</td>
<td>5.74</td>
<td>.016</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>14.68</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Gender</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

A highly useful outcome variable to assess in patients with variant angina. Left ventricular function, extent score, coronary artery disease (number of involved vessels), initial treatment, disease activity, and duration of resting angina before hospitalization were all strong predictors of survival without infarction by univariate analysis, as shown in table 3. Thus, death or myocardial infarction were unlikely to occur in patients with normal ventricular function and no stenoses of 70% or greater or those with single-vessel disease, a low extent score, attacks documented only after ergonovine, and resting angina of at least 3 months duration.

Five variables were selected as predictors by Cox analysis: left ventricular function, initial treatment, extent score, duration of resting angina, and disease activity. Coronary artery disease was not selected because the prognostic information contained in this variable overlaps with left ventricular function and extent score; the correlation coefficient between left ventricular function and coronary artery disease was .34 (p < .0001).

Survival without infarction at 1 and 5 years was 91% and 81% with normal, and 74% and 48% with abnormal left ventricular function, as illustrated in figure 3. Survival without infarction at 1 and 5 years was 93% and 83% in patients with no stenoses of 70% or more, 86% and 74% in patients with single-vessel disease, and 65% and 44% in patients with multivessel disease. In patients with an extent score greater than 4, survival without infarction at 1 and 5 years was 81% and 57%, compared with 88% and 79% in those with an extent score of 4 or less (p = .017). Survival without infarction at 1 and 5 years was 96% and 79% in patients with a history of resting angina of greater than 3 months, 86% and 75% for those with a history of 1 to 3 months, and 73% and 60% for those with a history of less than 1 month (p = .0006).

In patients treated initially with nifedipine, diltiazem, or verapamil, survival without infarction at 1 and 5 years was 90% and 74%, compared with 65% and 55% in patients who initially received other medical treatment, as illustrated in figure 3. The difference between these two groups appeared within the first 3 months and persisted relatively unchanged throughout the rest of the follow-up period.

Myocardial infarction. As listed in table 4, the variables that correlated with the occurrence of myocardial infarction by univariate analysis were left ventricular function, duration of resting angina, coronary artery disease, extent score, and initial treatment. The Cox analysis selected all of these variables except coronary artery disease.

Myocardial infarction occurred in 23 of 142 patients (16%) with normal and 23 of 50 patients (46%) with abnormal left ventricular function (p < .0001). Fifteen of 87 patients without stenoses of 70% or greater (17%), 17 of 81 (21%) with single-vessel disease, and 17 of 40 (43%) with multivessel disease developed infarction (p = .006).

Although only 49% (106 of 217) of the study patients had had resting angina for less than 1 month before hospitalization, 38 of the 54 myocardial infarctions (70%) occurred in this group (p = .0004). The mean time from admission to infarction was 12 ± 17 months in these 38 patients compared with 37 ± 31 months in the remaining 16 (p = .009).

Evolution of symptoms. At the last or most recent follow-up visit only 56 patients still had angina, including exertional angina only. Only 80 patients were still taking antianginal medication. These drugs had most often been discontinued because angina had disappeared; in a few cases they had been stopped due to side effects.

Discussion

This study defines the long-term prognosis and the factors that influence prognosis in patients with variant angina. These findings extend those of our previous report; mean follow-up was 65 compared with 15 months and more patients are included. Overall survival was 95% at 1 year and 89% at 5 years. However, nonfatal myocardial infarction occurred in 25% of the population, most commonly within 3 months of diagnosis. Thus, survival without myocardial infarction was 83% at 1 year and 69% at 5 years. Outcome was slightly better in most subgroups than in our previous report, and the major predictors of long-term prognosis were similar to those found in other patients with coronary disease.

Comparison with other studies. The follow-up of three other large series of patients with variant angina has been reported. Severi et al. described 138
patients from Pisa followed for 2 to 8 years during the 1970s. Most were treated with verapamil and long-acting nitrates. A pattern similar to our study was observed: five deaths and 28 nonfatal infarctions occurred during the first month but only seven cardiac deaths and four infarctions occurred thereafter. These results cannot be accurately compared with ours because Severi et al. considered a diameter stenosis of 50% or more as significant, because 31 of their 138 patients did not undergo coronary arteriography, and because only nine of the 107 who did undergo arteriography had no lesions of 50% or more diameter stenosis.

Mark et al.3 described 109 patients from the Duke computerized data base diagnosed between 1972 and 1982 and followed for a minimum of 6 months. In the 62 patients initially treated medically, 12 deaths and 14 nonfatal infarctions occurred; survival at 1 and 5 years was 88% and 77%, respectively. Calcium-channel blockers were unavailable when most of these patients were diagnosed and nearly half of them underwent a revascularization procedure, making it difficult to compare their results to the present study.

Recently Nakamura et al.4 reported a series of 349 patients with variant angina collected from eight centers in Japan. Only 101 of these patients had organic coronary stenoses of 75% or more; only 21 of these 101 had multivessel disease. During a mean follow-up period of 3.4 years, sudden death occurred in only 2% of this series, and another 5% suffered myocardial infarction. The authors attributed this comparatively good prognosis to the low prevalence of organic coronary lesions in their population and to the fact that 98% were treated with calcium blockers. Reports of smaller series from the United States21, 22 are compatible with the results of these larger studies.

Influence of organic stenoses. In the reports mentioned above1, 3, 4 and in our population, the number of coronary arteries with significant organic stenoses exerted a strong influence on prognosis. A minority of the patients in our study had multivessel disease and those that did had a prognosis much worse than that of the rest of the population. Their 5 year survival was 77%, comparable to the 4 year survival rates of 84% and 68%
for the medically treated patients with two- and three-vessel disease from the Coronary Artery Surgery Study registry. However, 43% (17 of 40) also experienced nonfatal myocardial infarction. By 5 years death or nonfatal infarction had occurred in 56%, compared with 28% of those with two-vessel and 46% of those with three-vessel disease without variant angina in the Duke database.24

In our study survival at 1 and 5 years was nearly identical in patients with single-vessel disease and those with no stenoses of 70% or more. In addition, nonfatal myocardial infarction rates were similar: 15 of 87 (17%) with no stenoses of 70% or more and 17 of 81 (21%) with single-vessel disease. These findings differ in several respects from what is found in patients without variant angina. For example, in the Duke database25 688 patients with one-vessel disease had a 5 year survival rate ranging from 92% to 96%, according to the site of the lesion, which is comparable to the 94% 5 year survival rate seen in our patients with single-vessel disease and variant angina. However, 1516 patients without significant stenoses had a 5 year survival rate above 99%, significantly better than either patients with single-vessel disease or our patients with variant angina without stenoses of 70% or more. Myocardial infarction was a very rare event in Duke patients without significant stenoses but occurred in about 15% of their patients with single-vessel disease by 5 years.

In summary, the presence of variant angina decreases survival and increases the risk of infarction in patients without significant coronary stenoses. In patients with coexisting organic stenoses it appears to increase the risk of infarction but does not drastically alter 5 year mortality. These conclusions are tentative because they are based on comparisons between studies that are likely to have different patient selection and treatment biases.

**Left ventricular function.** In patients with coronary disease who undergo arteriography, left ventricular function is a strong predictor of prognosis.23-26 Although most patients with variant angina have normal ventricular function, this variable emerged from the Cox analysis as the most powerful predictor for both survival without infarction (table 3) and infarction (table 4). Left ventricular dysfunction does not cause myocardial infarction and is an uncommon cause of death in variant angina in the absence of interim infarction. However, a strong correlation between ventricular function and coronary disease was present in this study and clinically left ventricular dysfunction may be viewed as a marker of more severe or extensive coronary disease.

**Disease activity.** As a rough index of disease activity, we classified patients into three groups: those in whom attacks were rare and could only be documented by ergonovine provocation, and those with and without serious arrhythmias during attacks, since such arrhythmias may be an indicator of more severe ischemia and a poorer prognosis.17 The Cox analysis selected disease activity as a multivariate predictor for both survival and survival without infarction. Patients with arrhythmias during attacks had a mortality rate twice as high, 25% vs 12%, as did those without. This finding was not present in our previous report, which included fewer patients and shorter follow-up,2 but is not surprising in light of another study that included patients who had been resuscitated from episodes of sudden death17 in whom ventricular arrhythmias during attacks predicted subsequent sudden death. Elimination of all episodes of ST elevation in patients with life-threatening arrhythmias during attacks should improve their survival.

Patients in whom no spontaneous episodes were detected, in whom the diagnosis was made only by ergonovine provocation, had an excellent prognosis. The low prevalence of multivessel disease in this group partly explains this finding. However, it is tempting to speculate that patients with less frequent attacks are less likely to experience death or infarction. The observation that both spontaneous attacks5 and these complications tend to decrease markedly in the months after diagnosis supports this possibility. An alternate explanation, that some patients in this group may have had a “false positive” response to ergonovine and no spontaneous coronary spasm, is difficult to substantiate in the absence of a test that disproves the diagnosis.

**Cause of infarction.** Among the variables selected by the Cox analysis as predictors of nonfatal infarction were extent score and the duration of the resting angina before hospitalization. Extent score, calculated as the number of coronary segments in a 15 segment coding system containing 5% to 75% stenoses, tends to reflect the diffuseness of coronary disease, as opposed to the number of diseased vessels, which tends to reflect severity. In patients who underwent serial arteriography at our institution, extent score was the strongest variable available at the time of the first study that predicted progression of coronary disease13; extent score and the presence of a stenosis of 80% or more predicted total occlusion.14

A high extent score increases the number of sites at which coronary occlusion can potentially occur, increasing the risk of infarction. Interestingly, in this study myocardial infarction was nearly as common in patients with no stenoses of 70% or more as in patients...
with single-vessel disease. Thus, spasm superimposed on a mild lesion may increase the risk of infarction to that with a more severe lesion. In contrast, in patients without variant angina who had quantitative arteriographic measurements before and after infarction, stenosis severity was the best predictor of which lesions would cause subsequent infarction.27

Myocardial infarction occurred most frequently soon after diagnosis in patients with less than 1 month of angina before admission. Why some patients with variant angina progress to infarction soon after the appearance of symptoms while others have continuing resting angina for months or years without complications is unknown. Myocardial infarction is associated with thrombotic coronary occlusion28 and patients with unstable angina, who have a high short-term risk of infarction, have complex coronary lesions with irregular, often ulcerated surfaces, usually with superimposed thrombi.29 Perhaps lesion morphology determines which patients progress to infarction, with the risk being increased by the transient interruptions in coronary flow caused by spasm.

**Effect of treatment.** Initial treatment was selected as a strong independent predictor of survival without infarction (table 3), but was not a predictor of survival alone (table 2). Too few patients underwent bypass surgery or coronary angioplasty to assess the value of these procedures. Patients treated with nifedipine, dilatazem, or verapamil had a better outcome than patients who received other medical therapy (p = .002). These calcium antagonists exerted their beneficial effects within the first 3 months after diagnosis (figure 3), presumably during the most active phase of the disease.

A limitation of our conclusion with respect to treatment is that patients were not randomly allocated to treatment groups. Patients seen during the first 2 years of our study did not receive nifedipine, dilatazem, or verapamil, but almost all of those seen thereafter were treated with one of these drugs. No other changes in therapy occurred over this interval, except for the introduction of coronary angioplasty, which was applied in only six of these cases. Nevertheless, unrecognized factors may have contributed to the large differences observed between the two treatment groups. A randomized, placebo-controlled trial to prove that calcium antagonists reduce the incidence of myocardial infarction in variant angina is not feasible.

Angina disappeared and antianginal treatment was discontinued during follow-up in most of the study patients.5 Myocardial infarctions and deaths were almost never preceded by episodes of angina at rest after the first year, suggesting that these late events were more often caused by progressive coronary disease than by coronary spasm.

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