Factors influencing the long-term prognosis of treated patients with variant angina

DAVID D. WATERS, M.D., D. DOUGLAS MILLER, M.D., JADWIGA SZLACHCIC, M.D., ALAIN BOUCHARD, M.D., MARGOT MÉTHÉ, R.N., JOHN KREEFT, M.D., AND PIERRE THÉROUX, M.D.

ABSTRACT To determine the prognosis of variant angina and the factors influencing it, 169 consecutive patients hospitalized in our coronary unit were followed for a mean of 15.3 months (range 1 to 68). Survival at 1, 2, and 3 years was 95%, 90%, and 87%, respectively; survival without myocardial infarction was 80%, 78%, and 75%. Twenty of the 22 myocardial infarctions and eight of the 14 deaths occurred within the first 3 months. Mantel-Haenszel log-rank analysis demonstrated that coronary disease, ventricular function, and the degree of disease activity were significant interdependent variables that influenced both survival and survival without infarction. At 1, 2, and 3 years, survival for patients with multivessel disease was 81%, 76%, and 66%; for patients with one-vessel disease, 97%, 92%, and 92%; and for patients without stenoses $\geq$ 70%, 98% at each year ($p = .0003$). Survival without infarction at 1 year was 88% in patients with no stenoses $\geq$ 70% and 82% in patients with single-vessel disease; it did not change thereafter in either group, but was 62%, 58%, and 50% at 1, 2, and 3 years in patients with multivessel disease ($p = .001$). Treatment did not influence survival in any subgroup (only 14 patients died overall) or survival without infarction in patients with multivessel disease. However, in patients without multivessel disease, treatment with nifedipine, diltiazem, and verapamil improved survival without infarction compared to treatment with perhexiline maleate or long-acting nitrates alone (92% vs 67% at 1, 2, and 3 years; $p < .005$). Thus in addition to preventing angina, nifedipine, diltiazem, and verapamil appear to reduce complications in patients with variant angina without multivessel disease.
Circulation 68, No. 2, 258–265, 1983.

PROGNOSIS has been well defined in most subgroups of patients with coronary artery disease. However, the natural history of variant angina is unclear because the syndrome is characterized by frequent spontaneous exacerbations and remissions and because, except for the series described by Maseri et al.[1] and Severi et al.,[2] most reports involve small numbers of patients, heterogenous treatment, or different selection criteria.[3–14]

During a recent 5 year period, 169 patients with variant angina were hospitalized at our institution. All but seven underwent coronary arteriography and all survivors were seen at regular intervals after discharge at our variant angina clinic. The purpose of this article is to describe the prognosis of these patients and to define the factors that influence prognosis.

From the Department of Medicine, Montreal Heart Institute, and the University of Montreal Medical School, Montreal.

Supported in part by grants from Alcan Co., Montreal, the Jean-Louis Lévesque Foundation, Montreal, and the Montreal Heart Institute Research Fund.

Received Nov. 30, 1982; revision accepted April 14, 1983.

Address for correspondence: David D. Waters, M.D., Montreal Heart Institute, 5000 East Belanger St., Montreal H1T 1C8, Quebec, Canada.

Presented in part at the American Heart Association Scientific Sessions, Dallas, November 1982.

Methods

Patients. The diagnosis of variant angina was made in patients meeting all of 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 (ECG) but documented during pain and disappearing with relief of pain, and (4) no subsequent evidence of myocardial necrosis. Between March 1976 and August 1981, 169 patients meeting these criteria were hospitalized at the Montreal Heart Institute.

The mean age of the patients was 51 years (range 24 to 71); 117 were men and 52 were women. Thirty patients had previously had a myocardial infarction, 11 had undergone coronary artery bypass surgery,[15] and six had had percutaneous transluminal coronary angioplasty.[16] Effort angina was present in 89.[17] ST segment elevation was noted at the anterior electrocardiographic leads in 96 patients and at the inferior leads in 73. Attacks were documented in 47 patients during hospitalization only after ergonovine administration; spontaneous attacks were detected in hospital in the other 122 patients.

Patient management. Patients were hospitalized in the coronary care unit, where they underwent continuous electrocardiographic monitoring for at least 3 days. A complete ECG was recorded during episodes of angina at rest when possible. Coro-

nary arteriography was performed by a percutaneous transfemoral approach with preformed catheters,[18] and routine filming of sagittally 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 nitroglycerin administration. Coronary arteriography was not performed in seven patients who either had associated life-threatening noncardiac illness or developed myocardial infarction soon after admission to hospital. In all but eight of the patients who underwent coronary arteriography, a left ventricular angiogram was filmed in the 30 degree right anterior oblique view.

In 63 patients no fixed coronary stenosis ≥ 70% of the luminal diameter was seen at coronary arteriography; 59 patients had one-vessel disease ≥ 70% and 40 had multivessel involvement. Results of left ventriculography were normal in 114 patients and revealed a segmental wall motion abnormality in 40, hypokinesis in 16, akinesis in 20, and dyskinesis in four. Coronary artery spasm developed spontaneously during arteriography in 31 of the 162 patients. Ergonovine testing was rarely done during coronary arteriography. After arteriography an ergonovine test was performed in the coronary care unit according to a defined protocol[19] in patients with suspected but unproven variant angina. Patients with documented variant angina did not undergo ergonovine testing for diagnostic purposes; however, to assess the effect of treatment with calcium antagonist drugs, some of these patients underwent testing before and during treatment according to a research study protocol.[20, 21]

Coronary artery bypass surgery, with or without plexectomy,[13, 22, 23] was performed as initial treatment in 11 patients and was done during the follow-up period in seven others. Drug treatment was applied initially to the other 158 patients. During the first part of the study period, perhexiline maleate was the only calcium antagonist drug available to us; therefore, 45 patients were initially treated with this drug[24] (n = 29) or with long-acting nitrates alone (n = 16). The remaining 113 patients were initially treated with nifedipine (n = 38), diltiazem (n = 32), or verapamil (n = 17) or with combinations of these drugs (nifedipine and diltiazem, n = 25; nifedipine and verapamil, n = 1). Long-acting oral or topical nitrates were added if symptoms persisted on treatment. The usual drug doses 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 ECG were recorded. Calcium antagonists were eventually discontinued in 45 patients, because of serious side effects from perhexiline maleate in eight[24] and because no angina had occurred during several months of treatment in 37 others.[25]

Data analysis. Myocardial infarction was diagnosed in patients who developed symptoms of definite or probable infarction (Minnesota code criteria[26, 27]) or who experienced myocardial ischemic pain lasting longer than 30 min followed by confirmatory cardiac enzyme or isoenzyme abnormalities. During the study, four patients were unavailable for follow-up; another patient who died from a noncardiac cause (suicide) was also considered to be unavailable for follow-up.

For the entire population, curves for both survival and survival without myocardial infarction were constructed by means of the standard life-table analysis.[28] The influence of clinical and angiographic variables on prognosis was assessed with a Mantel-Haenszel log-rank analysis.[29] A multivariate analysis was performed to determine whether the variables that significantly correlated with outcome were independent or interdependent. Table 1 lists the variables that were studied and their subsets. 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 worse prognosis.[30] Serious arrhythmias were defined as ventricular fibrillation, ventricular tachycardia, ventricular couplets or bigeminy, second or third degree atrioventricular block, and asystole.[30]

Results

During a mean follow-up period of 15.3 months (range 1 to 68), 14 of the 169 patients died and 22 others developed myocardial infarction. Twenty of the 22 myocardial infarctions and eight of the 14 deaths occurred during the first 3 months, including seven deaths and 12 infarctions within 1 month. Six of the 14 deaths were sudden and eight were in-hospital complications of myocardial infarction. Figure 1 illustrates the curves for survival and survival without myocardi-

TABLE 1
Clinical and angiographic variables[A]

Variables	Subsets	Patient/ subsets
Coronary artery disease	No stenosis ≥ 70%	63
	One-vessel disease	59
	Multivessel disease	40
Disease activity	Arrhythmias during attacks	57
	No arrhythmias during attacks	65
	Provoked attacks only	47
Left ventricular function	Normal	114
	Abnormal	40
Initial treatment	Nifedipine, diltiazem, verapamil	113
	Other medical treatment	45
	Bypass surgery ± plexectomy	11
Age	20–39 yr	20
	40–59 yr	108
	60–79 yr	41
Duration of rest angina	< 1 mo	46
	1 to 3 mo	72
	> 3 mo	47
Site of ST elevation	Anterior	96
	Inferior	73

[A]The total for each variable is not 169 because of seven patients without coronary arteriography, 15 without left ventriculography, and four in whom the duration of rest angina could not be accurately determined. The classification of disease activity is based on our previous study, which showed that arrhythmias during attacks were an indicator of more severe ischemia.[30]

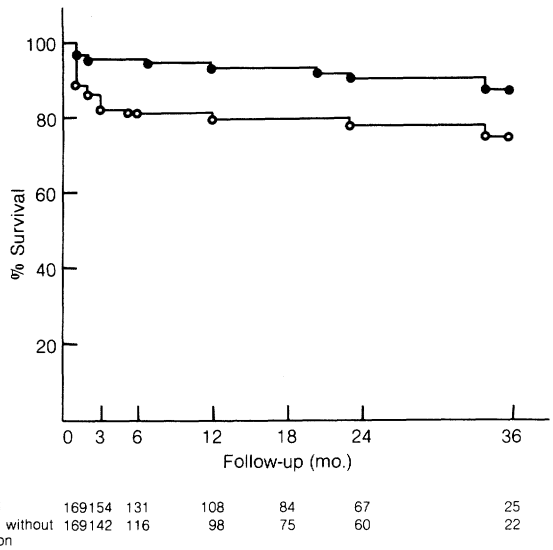

FIGURE 1. Survival and survival without myocardial infarction for the entire patient population. The number of patients completing each follow-up interval without an end-point event are listed. Eight of the 14 deaths and 20 of the 22 myocardial infarctions occurred within the first 3 months.

al infarction for the entire group. At 1, 2, and 3 years, overall survival was 95%, 90%, and 87%, respectively. Survival without infarction at 1, 2, and 3 years was 80%, 78%, and 75%, respectively.

Survival. The clinical and angiographic factors that correlated with survival and survival without infarction and the statistical significances of the observed differences are listed in table 2. The strongest predictor of survival was coronary artery disease. Thirteen deaths occurred in the 162 patients who had coronary arteriography: one in the 63 with no stenoses ≥ 70% (1.6%), three in the 59 with single-vessel disease (5.1%), and nine in the 40 with multivessel disease (22.5%). Left ventricular function and the degree of disease activity also correlated with survival by univariate analysis, but a multivariate analysis indicated that these two variables correlated significantly with coronary artery disease and were thus not independent predictors of survival.

TABLE 2
Predictors of survival and survival without infarction[A]

Variable	Survival		Survival without infarction	
	χ^2	p value	χ^2	p value
Coronary artery disease	14.7	.0003	13.4	.001
Disease activity	5.7	.03	9.6	.004
Left ventricular function	3.0	.04	5.6	.02
Initial treatment	0.89	NS	9.7	.008
Age	2.9	NS	1.0	NS
Duration of rest angina	0.81	NS	2.2	NS
Site of ST elevation	0.17	NS	1.5	NS

[A]Mantel-Haenszel log-rank analysis. Degrees of freedom = 2 for all variables except left ventricular function and site of ST elevation, in which degrees of freedom = 1. One-tailed p values are listed for coronary artery disease, disease activity, and left ventricular function; two-tailed p value for treatment. NS = $p > .1$.

Survival curves are illustrated for each of these three variables in figure 2. At 1, 2, and 3 years, survival for patients with multivessel disease was 81%, 76%, and 66%, respectively; for patients with one-vessel disease, 97%, 92%, and 92%, respectively; and for patients without stenoses ≥ 70%, 98% at each year. The degree of disease activity correlated with survival because no deaths occurred in the subset of 47 patients in whom attacks could be documented only by provocative testing; only four of these 47 had multivessel disease, 19 had single-vessel involvement, and 24 had no stenoses ≥ 70%. Survival was similar in patients with and without arrhythmias during attacks. Patients with normal left ventricular function had survival rates of 97%, 95%, and 91% at 1, 2, and 3 years compared with 88%, 84%, and 84% in those with abnormal left ventricular function.

Survival without myocardial infarction. Coronary artery disease, the degree of disease activity, and left ventricular function also correlated with the other end point studied, survival without myocardial infarction (table 2). Again, coronary artery disease was the strongest predictor statistically. Multivariate analysis indicated that disease activity and left ventricular function were dependent on coronary artery disease and were thus not independent predictors of survival.

Curves for survival without infarction are illustrated for each of these three variables in figure 3. Survival without infarction at 1 year was 88% in patients with no stenoses ≥ 70% and 82% in patients with single-vessel disease; it did not change thereafter in either group, but was 62%, 58%, and 50% at 1, 2, and 3 years in patients with multivessel disease. Myocardial infarction occurred in only two of the 47 patients whose attacks could be documented only by provocative testing. Survival without infarction at 1 year was 87% with normal and 71% with abnormal ventricular function.

The risk of myocardial infarction with survival for at least 1 month thereafter was 6/63 (9.5%) for patients without stenoses ≥ 70%, 7/59 (11.9%) for patients with one-vessel disease, and 8/40 (20%) for those with multivessel disease (one tail, $p < .05$). As noted previously, all but two of the myocardial infarctions occurred within the first 3 months of follow-up.

Effect of treatment. Treatment did not influence over-

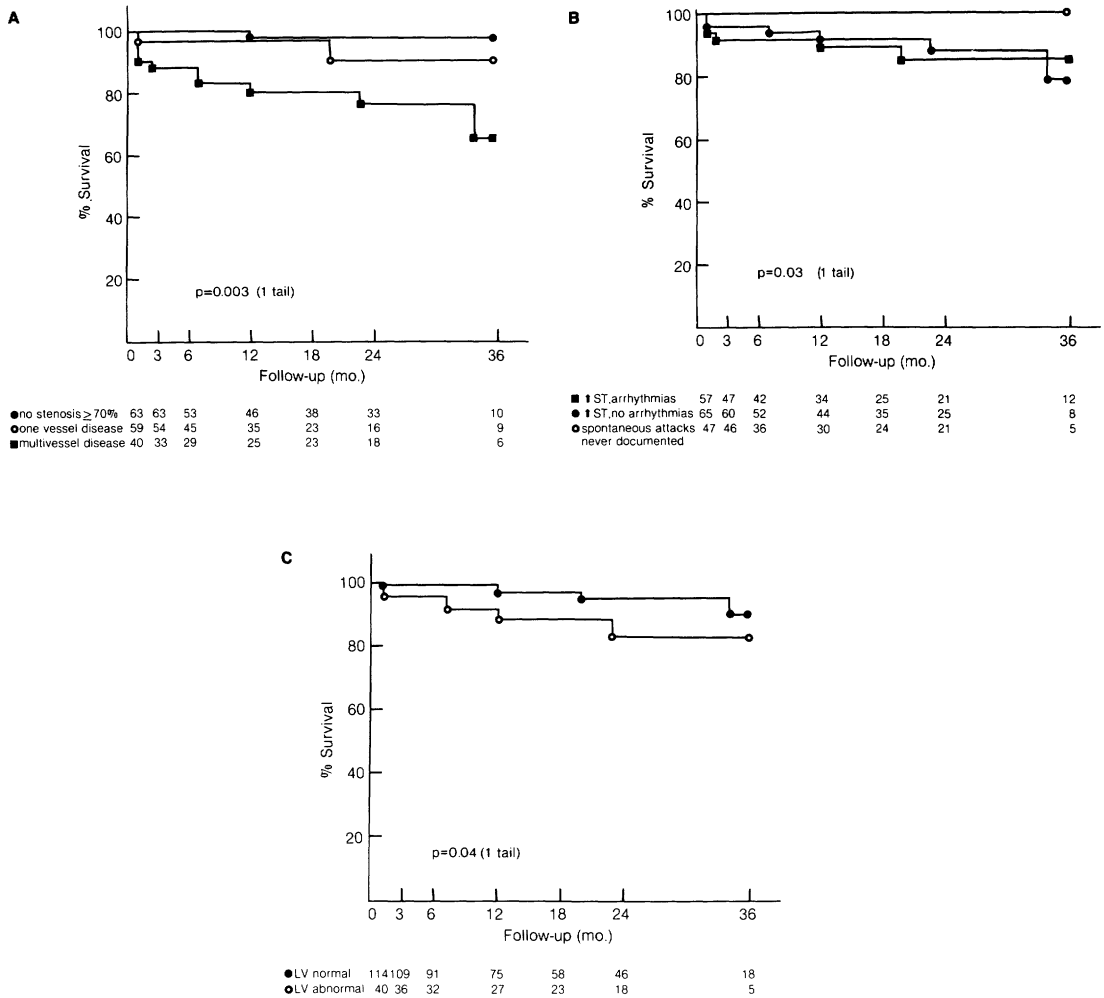

FIGURE 2. Three variables were predictive of survival by univariate analysis: coronary artery disease *(A)*, class of disease activity *(B)*, and left ventricular function *(C)*. The number of patients in each subgroup completing each follow-up interval without an end-point event are listed. ↑ ST, arrhythmias and ↑ ST, no arrhythmias = patients with and without arrhythmias during spontaneous variant angina attacks; spontaneous attacks never documented = patients with attacks in hospital only with ergonovine provocation; LV = left ventriculogram.

all survival but significantly affected survival without infarction (figure 4). The number of patients treated initially with bypass surgery was too small to assess. Survival without infarction at 1 year was 87% in patients treated with nifedipine, diltiazem, and verapamil, compared with 61% in patients treated with perhexiline maleate or nitrates alone. In patients with multivessel disease, treatment did not influence survival without infarction (χ^2 = .17, p = NS). In patients without stenoses ≥ 70%, survival without infarction at 1, 2, and 3 years was 93% with nifedipine, diltiazem, and verapamil, compared with 77% with perhexiline maleate or nitrates alone. Although the risk ratio between the two groups is greater than 3:1, this difference does not attain statistical significance (χ^2 = 2.85; two tail, p = .09). In patients with one-vessel involvement, survival without infarction at 1, 2, and 3 years was 90% with nifedipine, diltiazem, and verapamil compared with 50% with other medical treatment (χ^2 = 9.11, p < .005). Similarly, when all patients without multivessel disease are combined, the difference between the two groups at 1, 2, and 3 years is 92% vs 67% (p < .005). The other variables did not account for these differences.

Discussion

This study defines prognosis and the factors influencing prognosis for patients with variant angina. Survival at 1, 2, and 3 years for all patients was 95%, 90%, and 87%; however, by 1 year 20% of the group had suffered a myocardial infarction or death. Twenty of the 22 infarctions occurred within the first 3 months and none occurred after the first year. In a comparably sized series of variant angina patients, Maseri et al.[1] and Severi et al.[2] observed a similar pattern: five of their 138 patients died and 28 others developed myo-

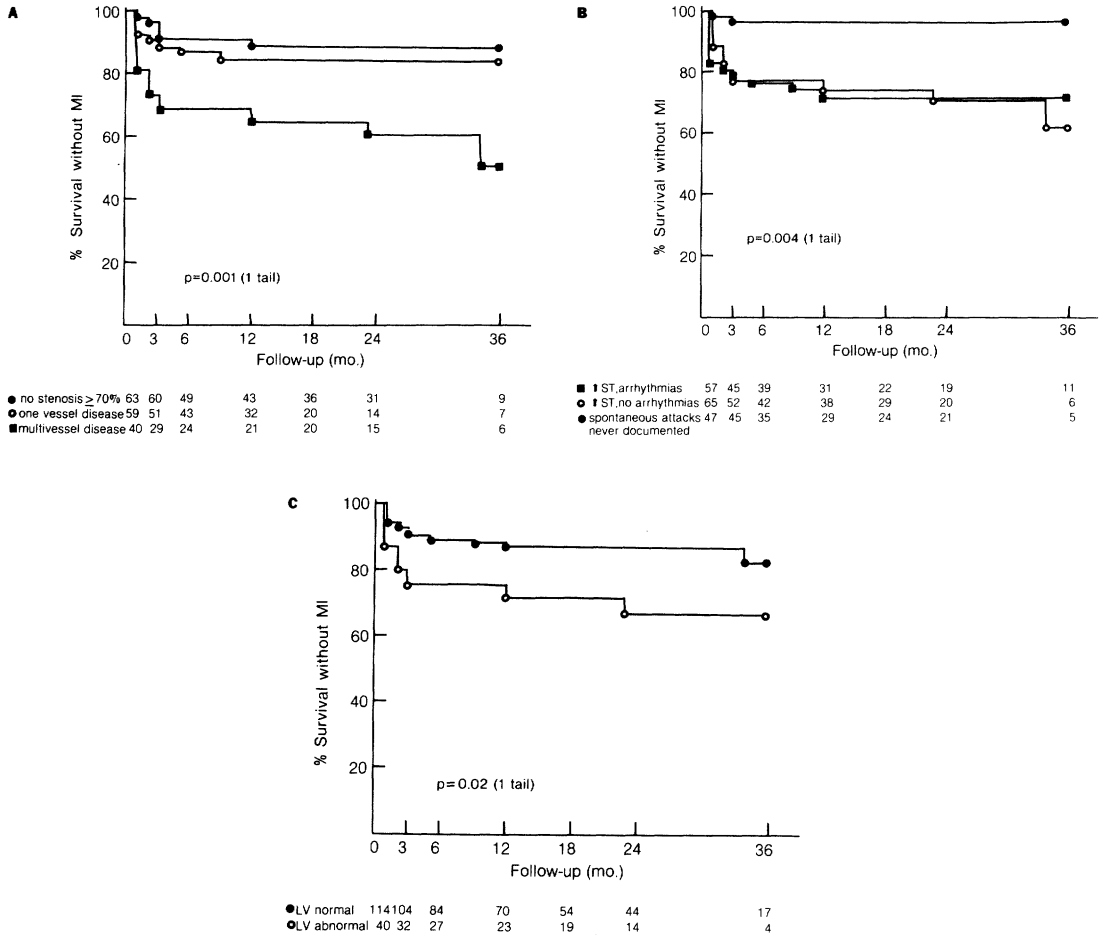

FIGURE 3. Coronary artery disease *(A)*, class of disease activity *(B)*, and left ventricular function *(C)* were predictive of survival without myocardial infarction by univariate analysis. Abbreviations are as in figure 2.

cardial infarction during the first month, but thereafter only seven cardiac deaths and four infarctions occurred during a follow-up of at least 2 years.

In most subsets of patients undergoing coronary arteriography, particularly those with stable angina, the subsequent risk for infarction or death remains relatively unchanged from year to year.[31, 32] The huge decrease after 3 months in the risk of infarction for variant angina patients suggests that some factors active early in the disease later disappear or that the population is composed of two subgroups with markedly different outcomes, with the smaller subgroup invariably progressing to infarction.

The extent and severity of organic coronary stenoses influence survival after myocardial infarction[33] and in stable[31] and unstable[34] angina. This variable was also the strongest predictor of survival and survival without infarction in this study. The outcome for patients with one-vessel disease was similar to that for patients with no stenoses ≥ 70% and markedly better than that in patients with multivessel disease, both for death and myocardial infarction. These results cannot be accurately compared with those of the study of Severi et al.[2] because they considered a stenosis ≥ 50% as significant, because 31 of their 138 patients did not undergo coronary arteriography, and because only nine of the 107 with arteriography had no lesions ≥ 50%. Nevertheless, their patients with multivessel disease had a higher incidence of both death and myocardial infarction than their combined group with one-vessel disease or no significant stenoses.

Left ventricular function is an independent predictor of prognosis in medically treated patients with coronary disease[35]; however, its influence is most marked when severe dysfunction is present,[35] an uncommon finding in variant angina. In the study of Severi et al.,[2] the combined incidence of death and myocardial infarction was significantly greater in the 24 patients with diffuse hypokinesis, akinesis, or aneurysm compared with the 75 with localized hypokinesis or normal left ventriculograms. In our study, left ventricular function correlated weakly with both survival and survival without infarction, but this association was not independent of coronary artery disease.

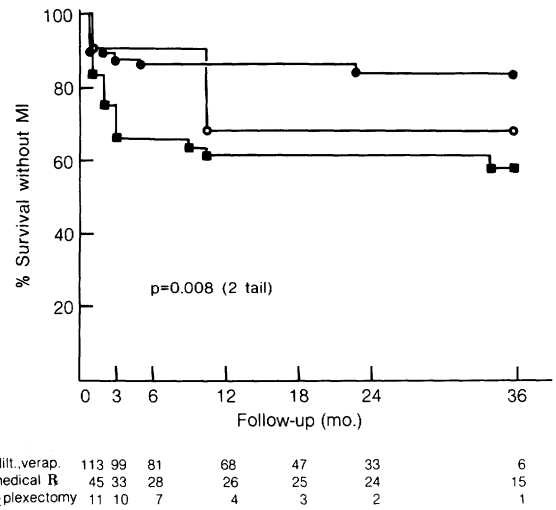

FIGURE 4. Curves for survival without myocardial infarction with patients subdivided according to initial treatment: nifedipine, diltiazem, or verapamil; other medical treatment, consisting of perhexiline maleate (29 patients) or long-acting nitrates alone (16 patients); and coronary bypass surgery (CABS) with or without plexectomy. Excluding the group with bypass surgery and comparing the remaining two groups changes the p value only minimally.

Abrupt changes in the frequency of attacks and spontaneous remissions occur commonly in patients with variant angina. Disease activity is difficult to assess because electrocardiographic monitoring covers only brief periods and because coronary spasm often causes asymptomatic myocardial ischemia or angina without objective evidence of ischemia. Therefore, as an index of disease activity, we classified patients into three groups: those in whom attacks were rare and could not be documented in hospital except with ergonovine provocation, and those with and without serious arrhythmias during attacks. Previous studies suggest that the occurrence of arrhythmias during variant angina episodes may be an indicator of more severe ischemia[30, 36] and a worse prognosis.[30] In this study, patients with and without arrhythmias during attacks had similar curves both for survival and survival without infarction. The third group, those with attacks documented only with provocative testing, had a much better outcome: no deaths and only two myocardial infarctions occurred in these 47 patients. The low prevalence of multivessel disease in this group (4/47) helps to explain their better prognosis.

Effect of treatment. Does treatment with calcium antagonists reduce the risk of myocardial infarction and death in variant angina? Variant angina episodes decrease markedly or disappear completely in most patients treated with these drugs.[37] However, such clinical improvement does not remove the risk for myocardial infarction and death; in fact, variant angina attacks decrease in number or disappear entirely during treatment in most patients who develop these complications.[38]

In the study of Severi et al.,[2] nearly all patients were treated with verapamil; their good long-term prognosis despite a high prevalence of organic coronary disease contrasts with the poor prognosis noted in reports[5, 7–9] in which calcium antagonists were not used. One possible explanation for this difference is that calcium antagonists reduce the incidence of myocardial infarction and death.

In this study, treatment with nifedipine, diltiazem, and verapamil did not improve survival alone but significantly improved survival without infarction compared to treatment with perhexiline maleate or nitrates alone ($p = .008$). Multivariate analysis demonstrated that this difference did not occur in patients with multivessel disease. In patients without stenoses $\geq 70\%$ a greater than threefold difference was present but did not attain statistical significance (death or myocardial infarction occurred in only seven of the 63 patients without stenoses $\geq 70\%$). In patients with one-vessel disease the difference between the two treatment groups at 1, 2, and 3 years was 90% vs 50% ($p < .005$); in all patients without multivessel disease, the difference was 92% vs 67% ($p < .005$).

These findings should not be accepted as definitive because of limitations in our study. Patients were not randomly assigned to the treatment groups. Those who received perhexiline maleate or long-acting nitrates alone were treated during the first 2 years of the study; thereafter all medically treated patients received nifedipine, diltiazem, or verapamil. Thus the differences in prognosis between the two groups could theoretically have been caused by inapparent changes in the patient population or an overall improvement in patient management. On the other hand, larger numbers might show that treatment affects survival as well as survival without infarction; only 14 of our patients died and only six of these deaths were sudden. Effective treatment would logically be expected to prevent sudden deaths caused by arrhythmias during attacks. Conclusive proof that the newer calcium antagonists reduce complications compared with nitrates alone or no treatment would require a large randomized study.

Nevertheless, the available data suggest that all patients with newly diagnosed variant angina without multivessel disease should initially be treated with nifedipine, diltiazem, or verapamil, not only to prevent angina but also to reduce the risk of complications. The clinical efficacy of these three drugs seems approximately equal.[21, 37] Because complications usually

occur within the first 3 months after diagnosis and because symptoms often disappear spontaneously,[25, 39] lifelong treatment may not be required.

Our patients with multivessel disease had the most complications and their prognosis was not improved by the newer calcium antagonist drugs. In our opinion, coronary bypass surgery should be considered for this group. The number of patients in this study who underwent bypass surgery is too small to assess. The results of bypass surgery in variant angina are generally much worse than in stable or unstable angina,[40] but some centers report excellent results when severe organic stenoses are present.[41] Calcium antagonists should probably be administered postoperatively.[42]

References

1. Maseri A, Severi S, De Nes M, L'Abbate A, Chierchia S, Marzilli M, Ballestra AM, Parodi O, Biagini A, Distante A: "Variant" angina: one aspect of a continuous spectrum of vasospastic myocardial ischemia. Pathogenetic mechanisms, estimated incidence and clinical and coronary arteriographic findings in 138 patients. Am J Cardiol **42:** 1019, 1978
2. Severi S, Davies G, Maseri A, Marzullo P, L'Abbate A: Long-term prognosis of "variant" angina with medical treatment. Am J Cardiol **46:** 226, 1980
3. Prinzmetal M, Kennamer R, Merliss R, Wada T, Bor N: Angina pectoris. I. A variant form of angina pectoris. Am J Med **27:** 375, 1959
4. Prinzmetal M, Ekmekci A, Kennamer R, Kwoczynski JK, Shubin H, Toyoshima H: Variant form of angina pectoris. Previously undelineated syndrome. JAMA **174:** 1794, 1960
5. Silverman ME, Flamm MD Jr: Variant angina pectoris. Anatomic findings and prognostic implications. Ann Intern Med **75:** 339, 1971
6. MacAlpin RN, Kattus AA, Alvaro AB: Angina pectoris at rest with preservation of exercise capacity: Prinzmetal's variant angina. Circulation **47:** 946, 1973
7. Shubrooks SJ Jr, Bete JM, Hutter AM Jr, Block PC, Buckley MJ, Daggett WM, Mundth ED: Variant angina pectoris: clinical and anatomic spectrum and results of coronary bypass surgery. Am J Cardiol **36:** 142, 1975
8. Weiner L, Kasparian H, Duca PR, Walinsky P, Gottlieb RS, Hanckel F, Brest AN: Spectrum of coronary arterial spasm. Clinical, angiographic and myocardial metabolic experience in 29 cases. Am J Cardiol **38:** 945, 1976
9. Selzer A, Langston M, Ruggeroli C, Cohn K: Clinical syndrome of variant angina with normal coronary arteriogram. N Engl J Med **295:** 1343, 1976
10. Johnson AD, Stroud HA, Ross J Jr: Variant angina pectoris. Clinical presentations, coronary angiographic patterns and the results of medical and surgical management in 42 consecutive patients. Chest **73:** 786, 1978
11. Heupler FA Jr: Syndrome of symptomatic coronary arterial spasm with nearly normal coronary arteriograms. Am J Cardiol **45:** 873, 1980
12. Cipriano PR, Koch FH, Rosenthal SJ, Schroeder JS: Clinical course of patients following the demonstration of coronary artery spasm by angiography. Am Heart J **101:** 127, 1981
13. Bertrand ME, Lablanche JM, Tilmant PY: Treatment of Prinzmetal's variant angina: role of medical treatment with nifedipine and surgical coronary revascularization combined with plexectomy. Am J Cardiol **47:** 174, 1981
14. Huckell VF, McLaughlin PR, Morch JE, Wigle ED, Adelman AG: Prinzmetal's angina with documented coronary arterial spasm: treatment and follow-up. Br Heart J **45:** 649, 1981
15. Waters DD, Théroux P, Crittin J, Dauwe F, Mizgala HF: Previously undiagnosed variant angina as a cause of chest pain after coronary artery bypass surgery. Circulation **61:** 1159, 1980
16. David PR, Waters DD, Scholl JM, Crépeau J, Szlachcic J, Lespérance J, Hudon G, Bourassa MG: Percutaneous transluminal coronary angioplasty in patients with variant angina. Circulation **66:** 695, 1982
17. Waters DD, Szlachcic J, Bourassa MG, Scholl JM, Théroux P: Exercise testing in patients with variant angina: results, correlation with clinical and angiographic features and prognostic significance. Circulation **65:** 265, 1982
18. Bourassa MG, Lespérance J, Campeau L: Selective coronary angiography using a percutaneous femoral technique. Can Med Assoc J **102:** 170, 1970
19. Waters DD, Théroux P, Szlachcic J, Dauwe F, Crittin J, Bonan R, Mizgala HF: Ergonovine testing in a coronary care unit. Am J Cardiol **46:** 922, 1980
20. Théroux P, Waters DD, Affaki GS, Crittin J, Bonan R, Mizgala HF: Provocative testing with ergonovine to evaluate the efficacy of treatment with calcium antagonists in variant angina. Circulation **60:** 504, 1979
21. Waters DD, Théroux P, Szlachcic J, Dauwe F: Provocative testing with ergonovine to assess the efficacy of treatment with nifedipine, diltiazem and verapamil in variant angina. Am J Cardiol **48:** 123, 1981
22. Grondin CM, Limet R: Sympathetic denervation in association with coronary artery grafting in patients with Prinzmetal's angina. Ann Thor Surg **23:** 111, 1977
23. Bertrand ME, Lablanche JM, Rousseau MF, Warembourg HH, Stankowtak C, Soots G: Surgical treatment of variant angina: use of plexectomy with aortocoronary bypass. Circulation **61:** 877, 1980
24. Mizgala HF, Crittin J, Waters DD, Théroux P: Results of immediate and long-term treatment of variant angina with perhexiline maleate. Circulation **60** (suppl II): II-181, 1979 (abst)
25. Waters DD, Szlachcic J, Théroux P, Dauwe F, Mizgala HF: Ergonovine testing to detect spontaneous remissions of variant angina during long-term treatment with calcium antagonist drugs. Am J Cardiol **47:** 179, 1981
26. Blackburn H, Keys A, Simonson E, Rautaharju P, Punsar S: The electrocardiogram in population studies: a classification system. Circulation **21:** 1160, 1960
27. Rose GA, Blackburn H: Cardiovascular survey methods. Geneva, 1968, World Health Organization Monograph, vol 56
28. Kalbfleisch JD, Prentice RL: The statistical analysis of failure time data. New York, 1980, John Wiley & Sons
29. Mantel N, Haenszel W: Statistical aspects of the analysis of data from retrospective studies of disease. JNCI **22:** 719, 1959
30. Miller DD, Waters DD, Szlachcic J, Théroux P: Clinical characteristics associated with sudden death in patients with variant angina. Circulation **66:** 588, 1982
31. Reaves TJ, Oberman A, Jones WB, Sheffield LT: Natural history of angina pectoris. Am J Cardiol **33:** 423, 1974
32. Harris PJ, Lee KL, Harrell FE, Behar VS, Rosati RA: Outcome in medically treated coronary artery disease. Ischemic events: nonfatal infarction and death. Circulation **62:** 718, 1980
33. Sanz G, Castaner A, Betriu A, Magrina J, Roig E, Coll S, Paré JC, Navarro-Lopez F: Determinants of prognosis in survivors of myocardial infarction: a prospective clinical angiographic study. N Engl J Med **306:** 1065, 1982
34. Alison HW, Russell RO, Mantle JA, Kouchoukos NT, Moraski RE, Rackley CE: Coronary anatomy and arteriography in patients with unstable angina pectoris. Am J Cardiol **41:** 204, 1978
35. Hammermeister KE, DeRouen TA, Dodge HT: Variables predictive of survival in patients with coronary disease: selection by univariate and multivariate analyses from the clinical, electrocardiographic, exercise, arteriographic and quantitative angiographic evaluations. Circulation **59:** 421, 1979
36. Kerin NZ, Rubenfire M, Maini M, Wajszczuk WJ, Pamatmat A, Cascade PN: Arrhythmias in variant angina pectoris: relationship of arrhythmias to ST-segment elevation and R-wave changes. Circulation **60:** 1343, 1979
37. Kimura E, Kishida H: Treatment of variant angina with drugs: a survey of 11 cardiology institutes in Japan. Circulation **63:** 844, 1981
38. Waters DD, Szlachcic J, Miller D, Théroux P: Clinical characteristics of patients with variant angina complicated by myocardial

infarction or death within one month. Am J Cardiol **49:** 658, 1982
39. Bouchard A, Waters DD, Théroux P: Is remission the most frequent of variant angina? J Am Coll Cardiol (in press)
40. Raizner AE, Chahine RA: The treatment of Prinzmetal's variant angina with coronary bypass surgery. *In* Hurst JW, editor: The heart: update II. New York, 1980, McGraw-Hill Book Co., Inc., p 85
41. Yiannakas J, Heupler F: Bypass surgery for patients with Prinzmetal variant angina and severe coronary obstructions. Circulation **64** (suppl IV): IV-90, 1981 (abst)
42. Buxton AE, Goldberg S, Harken AH, Hirshfeld JW Jr, Kastor JA: Coronary artery spasm immediately following coronary artery bypass surgery: recognition and management. N Engl J Med **304:** 1249, 1981