JACC Vol. 8, No. 1
July 1986:40–9

Relative Value of Clinical Variables, Bicycle Ergometry, Rest Radionuclide Ventriculography and 24 Hour Ambulatory Electrocardiographic Monitoring at Discharge to Predict 1 Year Survival After Myocardial Infarction

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The relative value of predischarge clinical variables, bicycle ergometry, radionuclide ventriculography and 24 hour ambulatory electrocardiographic monitoring for predicting survival during the first year in 351 hospital survivors of acute myocardial infarction was assessed. Discriminant function analysis showed that in patients eligible for stress testing the extent of blood pressure increase during exercise slightly improved the predictive accuracy beyond that of simple clinical variables (history of previous myocardial infarction, persistent heart failure after the acute phase of infarction and use of digitalis at discharge), whereas radionuclide ventriculography and 24 hour electrocardiographic monitoring did not. The predictive value for mortality was 12% with clinical variables alone and 15% with the stress test added.

Radionuclide ventriculography and 24 hour electrocardiographic monitoring were slightly additive to clinical information in the whole group of patients independent of the eligibility for stress testing (predictive value for mortality 24% with clinical variables alone and 26% with radionuclide ejection fraction and 24 hour electrocardiographic monitoring added).

It is concluded that the appropriate use of simple clinical variables and stress testing is sufficient for risk stratification in postinfarction patients, whereas radionuclide ventriculography and 24 hour electrocardiographic monitoring should be limited to patients not eligible for stress testing.

(J Am Coll Cardiol 1986;8:40–9)

Left ventricular function is a major prognostic determinant of survival in the first year after acute myocardial infarction (1–5), although residual myocardial ischemia (6,7) and ventricular arrhythmias (2,8,9) have also been associated with reduced survival. On the basis of these observations different algorithms have been proposed to assess the risk for individual patients early after acute myocardial infarction, including clinical variables and multiple noninvasive or invasive tests (5,10,11). Stress testing (3,5,7,12–15), radionuclide ventriculography (5,16,17) and 24 hour ambulatory electrocardiographic monitoring (2,8,9,18–20) are commonly performed early after myocardial infarction and all have been shown to provide some prognostic information. However, as far as we know, their relative merit in predicting late survival independent of easily obtainable clinical information has not been established, because most reported data have concentrated on one testing method rather than comparing them all.

We have shown in previous studies on postinfarction patients that radionuclide ventriculography and bicycle ergometry provide similar prognostic information (5) and that bicycle ergometry slightly improves the prediction of survival during the first year after myocardial infarction beyond that of routine clinical variables (15). The aim of the present study was to determine whether the results from more expensive tests, such as radionuclide ventriculography and 24 hour ambulatory electrocardiographic monitoring, provide a further improvement of the prognostic judgment compared with the appropriate use of simple clinical variables and inexpensive, widely available and practical forms of stress testing.

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Manuscript received June 25, 1985; revised manuscript received February 4, 1986, accepted February 7, 1986.

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0735-1097/86/$3.50

Methods

Patients. The records of 706 consecutive patients admitted to the coronary care unit of the Thoraxcenter between March 1981 and December 1983 with documented acute myocardial infarction were reviewed. This population includes 26% of patients referred from other hospitals for complications. The diagnosis of acute myocardial infarction was based on at least two of the following criteria: 1) Typical prolonged chest pain at least 45 minutes in duration. 2) In transmural acute myocardial infarction, dynamic electrocardiographic changes such as evolving Q waves longer than 0.04 second with ST-T changes or, in non-Q wave infarctions, ST-T changes persisting for at least 24 hours. 3) Increase of total serum creatine kinase level with a peak level of more than 100 IU/liter (twice the upper limit of normal values in our laboratory). Previous myocardial infarction was diagnosed by a typical history or diagnostic Q wave abnormalities, or both.

Hospital mortality occurred in 104 patients (14%). Coronary artery bypass grafting before hospital discharge was performed in 51 patients, percutaneous transluminal coronary angioplasty for postinfarction angina was performed in 16 cases and cardiac surgery for mitral insufficiency or ventricular septal defect was performed in 9 patients.

Multiple tests. In hospital survivors, symptom-limited bicycle ergometry, rest radionuclide ventriculography and 24 hour ambulatory electrocardiographic monitoring were performed in, respectively, 407, 520 and 389 patients an average of 14 days after myocardial infarction, before hospital discharge. Radionuclide ventriculography and stress testing were performed as previously described (5). Stress testing was symptom limited and medication was not discontinued at the time of the test. Drug therapy included a beta-receptor blocker in 209 patients (52%) and digitalis in 66 (16%). One hundred ninety-one patients were judged not eligible for stress testing, because of angina in 55, heart failure in 47, a noncardiac limitation in 71 and logistic problems in 18. Twenty-four hour ambulatory electrocardiographic recordings were centrally analyzed (21) using a modified Medilog system (MR14).

Patient subsets (Table 1). Six of the surviving patients were lost to follow-up, while 594 patients were followed up for 1 year by regular outpatient visits or, in a few cases, by telephone contact with their general practitioner. Cardiac death was the primary end point of this study but other events, such as nonfatal reinfarction, coronary artery bypass surgery and percutaneous transluminal coronary angioplasty, were also recorded.

Prediction of survival was performed first in the 594 patients who survived hospital stay, including those who underwent revascularization procedures before hospital discharge. Two patients who died of noncardiac causes were excluded from the analysis. Because of the influence that cardiac surgery or percutaneous transluminal coronary angioplasty could have had on the first year course of events, the analysis was repeated after excluding the 76 patients who underwent one or both of these procedures. Depending on the diagnostic tests performed, different subgroups of patients were analyzed: 449 patients were studied with radionuclide ventriculography and stress testing unless contraindicated, while 351 had a complete evaluation including radionuclide angiography, 24 hour ambulatory electrocardiographic monitoring and bicycle ergometry, unless contraindicated.

Statistical analysis. Univariate analysis with the unpaired Student's *t* test for continuous variables and chi-square or Fisher's exact test for discrete variables were applied when appropriate. Data are expressed as mean and standard deviation unless otherwise specified. To compare

Table 1. One Year Survival in 706 Consecutive Patients Admitted to the Coronary Care Unit of the Thoraxcenter With a Proven Diagnosis of Acute Myocardial Infarction

	No. of Patients		No. of Deaths at 1 Year (%)	
Total population	706		176 (25)	
Hospital death	104	706	104 (14)	176
Discharged alive, with 1 year follow-up	596		72 (12)*	
Lost to follow-up	6		—	
Cardiac surgery or PTCA before discharge	76	596 hospital survivors with 1 year follow-up	2 (3)	72*
Discharged on medical therapy	520		70 (13)*	
With RV and XT	355	449 with RV	24 (7)	49
With RV and contraindication for XT	94		25 (26)	
With RV, XT and 24 h ECG	293	351 with RV + 24 h ECG	19 (6)	32
With RV, 24 h ECG and contraindication for XT	58		13 (22)	

*Including two noncardiac deaths. PTCA = percutaneous transluminal coronary angioplasty; RV = radionuclide ventriculography; 24 h ECG = 24 hour ambulatory electrocardiographic monitoring; XT = exercise test (bicycle ergometry).

the predictive value for mortality of different continuous variables, we used receiver-operator characteristic curves as in previous reports from our group (5,15).

The BMDP statistical package for stepwise discriminant analysis (P7M) was used to generate classification functions for different classes of information: clinical variables only and clinical variables combined stepwise with stress testing, radionuclide ventriculography and 24 hour ambulatory electrocardiographic monitoring, to assess whether the combination of the different tests provides additive predictive value beyond clinical data alone.

The clinical variables consisted of age, sex, history of previous myocardial infarction, history of previous angina more than 4 weeks before the index myocardial infarction, anterior location of index myocardial infarction, the worst Killip functional class while in the coronary care unit, presence of angina pectoris during hospital stay, persistence of congestive heart failure after the stay in the coronary care unit, sustained ventricular tachycardia or fibrillation more than 72 hours after myocardial infarction, cardiothoracic ratio at discharge greater than 50% and use of digoxin, diuretic drugs and beta-blockers at discharge.

The stress test variables included percent of predicted work capacity, maximal work load, occurrence of angina during the test, heart rate at peak work load, extent of systolic blood pressure rise, ST depression, ST elevation and any ventricular arrhythmia.

Left ventricular ejection fraction was the only variable included from radionuclide ventriculography.

Variables from 24 hour ambulatory electrocardiographic monitoring in the stepwise analysis included: more than five multiform premature ventricular complexes during any minute of the recording, and the presence of any ventricular couplet or ventricular tachycardia (runs of three or more ventricular complexes with a rate $\geq$ 100/min) during the 24 hour recording period.

The end point of the study was cardiac mortality during the first year after myocardial infarction. In a first pass, stepup analysis was done using an F value of 1.0, which entered in the discriminant function all variables remotely related to the outcome. In the second pass, a stepdown analysis was performed on the selected subgroup of variables using an F value of 4.0 or more. The discriminant functions resulting from the stepdown analysis were then used to predict the classification of the same group of patients for a range of threshold levels of the discriminant function.

Results

Prediction of survival by univariate analysis in all 596 hospital survivors (Tables 2 and 3). During the 1 year follow-up period there were 70 cardiac-related deaths: 37 sudden, 18 from reinfarction, 13 from heart failure and 2 perioperative. There were two noncardiac deaths, which were excluded from analysis. Death occurred within 3 months of the index infarction in 30 cases, between 3 and 6 months in 14 cases and between 6 and 12 months in 26 cases.

All clinical variables reflecting impaired left ventricular function were associated with poor survival. In addition, late ventricular tachycardia or fibrillation was significantly associated with late mortality. Early postinfarction angina was not followed by a higher mortality than that in patients

Table 2. Differences in Clinical Variables Before Discharge Between Late Survivors and Nonsurvivors Among 594 Hospital Survivors

Clinical Variables	Survivors	Nonsurvivors	p Value
No. of patients	524	70	—
Male (%)	79	74	NS
Age (yr)	57 ± 10	62 ± 12	0.0005
Previous angina (%)	36	53	0.01
Previous AMI (%)	26	60	0.0005
Anterior AMI (%)	34	38	NS
Killip class >II (%)	7	28	0.0005
Peak CK (IU/liter)	564 ± 481	590 ± 554	NS
Post-AMI angina (%)	25	27	NS
Late heart failure (%)	13	47	0.0005
Late VT or VF (%)	3	14	0.0005
CTR >50% (%)	20	57	0.0005
Digitalis at discharge (%)	18	56	0.0005
Diuretic therapy at discharge (%)	34	66	0.0005
Beta-blockers at discharge (%)	54	33	0.001
Cardiac surgery or PTCA (%)	12	3	0.01

The data of two patients who died of noncardiac causes are excluded. AMI = acute myocardial infarction; CK = serum creatine kinase; CTR = cardiothoracic ratio; NS = not significant; VF = ventricular fibrillation; VT = sustained ventricular tachycardia; other abbreviations as in Table 1.

Table 3. Differences in Predischarge Bicycle Ergometry, Radionuclide Ventriculography and 24 Hour Ambulatory Electrocardiographic Monitoring Between Late Survivors and Nonsurvivors in 594 Hospital Survivors

	Survivors	Nonsurvivors	p Value
Radionuclide ventriculography			
No. of patients	461	52	—
Ejection fraction (%)	47 ± 14	32 ± 15	0.0005
Bicycle ergometry			
No. of patients	374	29	—
Reason for interrupting the test (%)			
Fatigue	71	62	NS
Angina	6	7	NS
Dyspnea	18	17	NS
Pressure drop	2	13	0.001
Maximal work load (W)	114 ± 33	100 ± 23	0.02
Percent working capacity	79 ± 17	66 ± 15	0.0005
Angina (%)	20	20	NS
Heart rate at rest (beats/min)	82 ± 16	89 ± 18	0.01
Peak heart rate (beats/min)	130 ± 22	133 ± 27	NS
SBP at rest (mm Hg)	121 ± 15	121 ± 20	NS
Peak SBP (mm Hg)	163 ± 28	141 ± 25	0.0005
SBP rise (mm Hg)	42 ± 23	21 ± 19	0.0005
ST depression (%)*	46	53	NS
Work load at ST depression (W)	92 ± 31	82 ± 33	NS
ST elevation (%)*	44	53	NS
Ventricular ectopic activity (%)	22	34	NS
24 h ECG monitoring			
No. of patients	349	39	—
Multiform PVCs >5/min (%)	24	33	NS
Ventricular couplets (%)	31	58	0.001
Ventricular tachycardia (%)	13	38	0.0005

*ST depression or elevation ≥ 1 mm. The data of two patients who died of noncardiac causes during follow-up are excluded. PVCs = premature ventricular complexes; SBP = systolic blood pressure; other abbreviations as in Tables 1 and 2.

without angina; in contrast, a history of stable preinfarction angina was associated with a poor prognosis.

Radionuclide ejection fraction was significantly lower in nonsurvivors, consistent with the clinical findings.

An insufficient maximal work load and an insufficient blood pressure rise during the stress test were predictive of mortality, whereas markers of ischemia, such as angina and ST depression during exercise, were not predictive. Ventricular ectopic activity was more frequent in nonsurvivors, but not significantly so.

Finally, 24 hour ambulatory electrocardiographic monitoring was also predictive because the incidence of repetitive ventricular complexes was higher in nonsurvivors.

Prediction of survival from clinical variables, radionuclide ventriculography and bicycle ergometry in 449 patients treated medically (Tables 4 and 5). Radionuclide ventriculography was performed on 449 of the 520 patients treated medically (Table 1). Three hundred fifty-five patients were eligible for stress testing, whereas 94 were ineligible. Mortality was highest in patients ineligible for the exercise test (n = 25; 26%) and was 7% (n = 24) in patients who were judged eligible for the test. Baseline characteristics of the patients who were and were not eligible for stress testing are reported in Table 4. These data indicate that patients not eligible for testing were older, had more severe left ventricular dysfunction and a higher incidence of early postinfarction angina than did patients who completed the test.

The predictive value of clinical variables, stress testing and radionuclide ejection fraction by univariate analysis was comparable with that found in the whole group of 596 patients described in the previous section (Tables 2 and 3). Ejection fraction was lower in nonsurvivors than in survivors (31 ± 14 versus 47 ± 15%, respectively; $p < 0.0005$). The distribution of radionuclide ejection fraction values in the 449 patients is shown in Figure 1. Among stress test results, the contraindication for the test and the extent of blood pressure increase were the best predictors of prognosis.

The predictive value of radionuclide ejection fraction and stress testing (combined with the contraindication for the test and blood pressure increase) were comparable (Fig. 2), because the sensitivity and the specificity of the two tests largely overlap during the whole range of measurements. The cutoff points with the highest sensitivity and specificity

Table 6. Univariate Predictors of Mortality in 351 Patients With Complete Evaluation

	All Patients			Patients Eligible for Stress Testing			Patients Not Eligible for Stress Testing		
	Survivors	Nonsurv.	p Value	Survivors	Nonsurv.	p Value	Survivors	Nonsurv.	p Value
No. of patients	319	32		274	19		45	13	
Clinical variables									
Age (yr)*	56 ± 10	58 ± 12	NS	54 ± 10	52 ± 11	NS	65 ± 9	67 ± 8	NS
Males (%)	84	84	NS	86	95	NS	73	69	NS
Previous AMI (%)	22	53	0.001	20	47	0.001	29	62	0.02
Previous angina (%)	33	56	0.001	31	37	NS	40	85	0.005
Anterior AMI (%)	37	43	NS	36	53	NS	37	31	NS
Killip class >II (%)	6	25	0.001	5	11	NS	9	46	0.002
Post-AMI angina (%)	17	25	NS	14	21	NS	33	31	NS
Late heart failure (%)	14	50	0.001	12	42	0.001	24	62	0.001
Late VT or VF (%)	4	16	0.005	4	11	NS	4	23	0.05
CTR >50% (%)	20	50	0.001	24	26	NS	24	85	0.001
Digitalis at discharge (%)	16	59	0.001	13	53	0.001	27	69	0.001
Diuretic therapy at discharge (%)	34	72	0.001	32	63	0.01	44	85	0.02
Beta-blockers at discharge (%)	56	37	0.05	60	42	NS	29	31	NS
Radionuclide EF (%)*	47 ± 14	33 ± 16	0.001	48 ± 14	35 ± 18	0.001	45 ± 15	30 ± 12	0.002
24 h ECG monitoring									
Multiform PVCs >5/min (%)	24	34	NS	23	21	NS	29	54	NS
Ventricular couplets (%)	32	59	0.005	31	47	NS	33	77	0.005
Ventricular tachycardia (%)	12	37	0.001	13	21	NS	15	62	0.001

*Mean ± SD. Nonsurv. = nonsurvivors; other abbreviations as in previous tables.

rate) were identified with a blood pressure increase of 30 mm Hg or more and an intermediate risk group included 89 patients with a mortality rate of 12% who had a blood pressure rise of less than 30 mm Hg.

The discriminant function analysis (Table 8) applied to clinical variables only in the entire group of 351 patients resulted in three independent variables predictive of mortality at the 0.05 level of significance: use of digitalis at discharge, history of a previous myocardial infarction and persistence of heart failure after the acute phase of infarction. By adding the results of radionuclide ventriculography and of 24 hour ambulatory electrocardiographic monitoring, ejection fraction and the presence of ventricular tachycardia improved the predictive accuracy compared with that of clinical variables alone.

When a similar stepwise analysis was repeated in the group of patients eligible for the stress test, stress test results (the extent of blood pressure rise) slightly improved the prediction over that of clinical variables alone, but in this subset of patients ejection fraction and the results of 24 hour ambulatory electrocardiographic monitoring did not provide any additional information beyond that provided by the combination of clinical and stress test results.

Discussion

Left ventricular dysfunction, ventricular arrhythmias and residual myocardial ischemia are all important determinants of survival during the first year after myocardial infarction (1,2,6) when considered separately. Consequently, multiple

Table 7. Univariate Predictors of Survival in 293 Patients With Complete Evaluation: Stress Test Results

	Survivors	Nonsurvivors	p Value
No. of patients	274	19	—
Maximal work load (W)	115 ± 32	103 ± 23	NS
Working capacity (%)	79 ± 17	66 ± 14	0.002
Angina (%)	15	11	NS
Heart rate at rest (beats/min)	81 ± 16	93 ± 19	0.002
Peak heart rate (beats/min)	130 ± 22	139 ± 25	0.05
SBP at rest (mm Hg)	121 ± 15	120 ± 18	NS
Peak SBP (mm Hg)	161 ± 26	143 ± 27	0.002
SBP rise (mm Hg)	40 ± 22	24 ± 20	0.002
ST depression (%)	44	47	NS
Any ventricular arrhythmia (%)	22	26	NS

Abbreviations as in previous tables.

Table 8. Prediction of Mortality by Discriminant Function Analysis in 351 Patients With Complete Evaluation

	All Patients		Patients Eligible for Stress Test		
	Clinical Variables	Clinical Variables + EF + 24 h ECG	Clinical Variables	Clinical Variables + Stress Test	Clinical Variables + Stress Test + EF + 24 h ECG
Nonsurvivors (n)	32	32	19	19	19
Survivors (n)	319	319	274	274	274
Clinical variables (F value)					
Discharged on digitalis	20.5	26.4	19.1	15.8	15.8
History of previous AMI	14.1	12.7	7.5	5.8	5.8
Late heart failure	5.5	—	—	—	—
Radionuclide ventriculography (F value)					
Ejection fraction	—	5.2	—	—	—
24 h ECG monitoring (F value)					
Ventricular tachycardia	—	7.5	—	—	—
Stress testing (F value)					
SBP rise	—	—	—	5.0	5.0
Predictive accuracy (%)					
Sensitivity (%)	59	72	63	63	63
Specificity (%)	81	80	67	75	75
Predictive value positive (%)	24	26	12	15	15
Predictive value negative (%)	95	97	96	98	98
Total correct classification (%)	79	79	67	75	75
High risk group (%)	23	25	35	27	27
Risk ratio	5.0	7.7	3.2	4.5	4.5

Abbreviations as in Tables 1 and 2.

tests have been applied to postinfarction patients to improve the prediction of clinical outcome obtainable with clinical variables only (10,11). The questions now are: which of these tests is the most predictive and do we need them all in every patient? Indeed, the present study confirms that clinical variables, stress testing, radionuclide angiography and 24 hour ambulatory electrocardiographic monitoring are all useful in predicting late survival. When clinical information and these tests indicate left ventricular dysfunction and show complex ventricular arrhythmias, late survival is reduced (Table 6).

Surprisingly, early postinfarction angina and ST depression during the exercise test were not predictive of impaired survival. This is largely explained by the fact that 76 patients with more severe early postinfarction angina underwent coronary artery bypass or percutaneous transluminal coro-

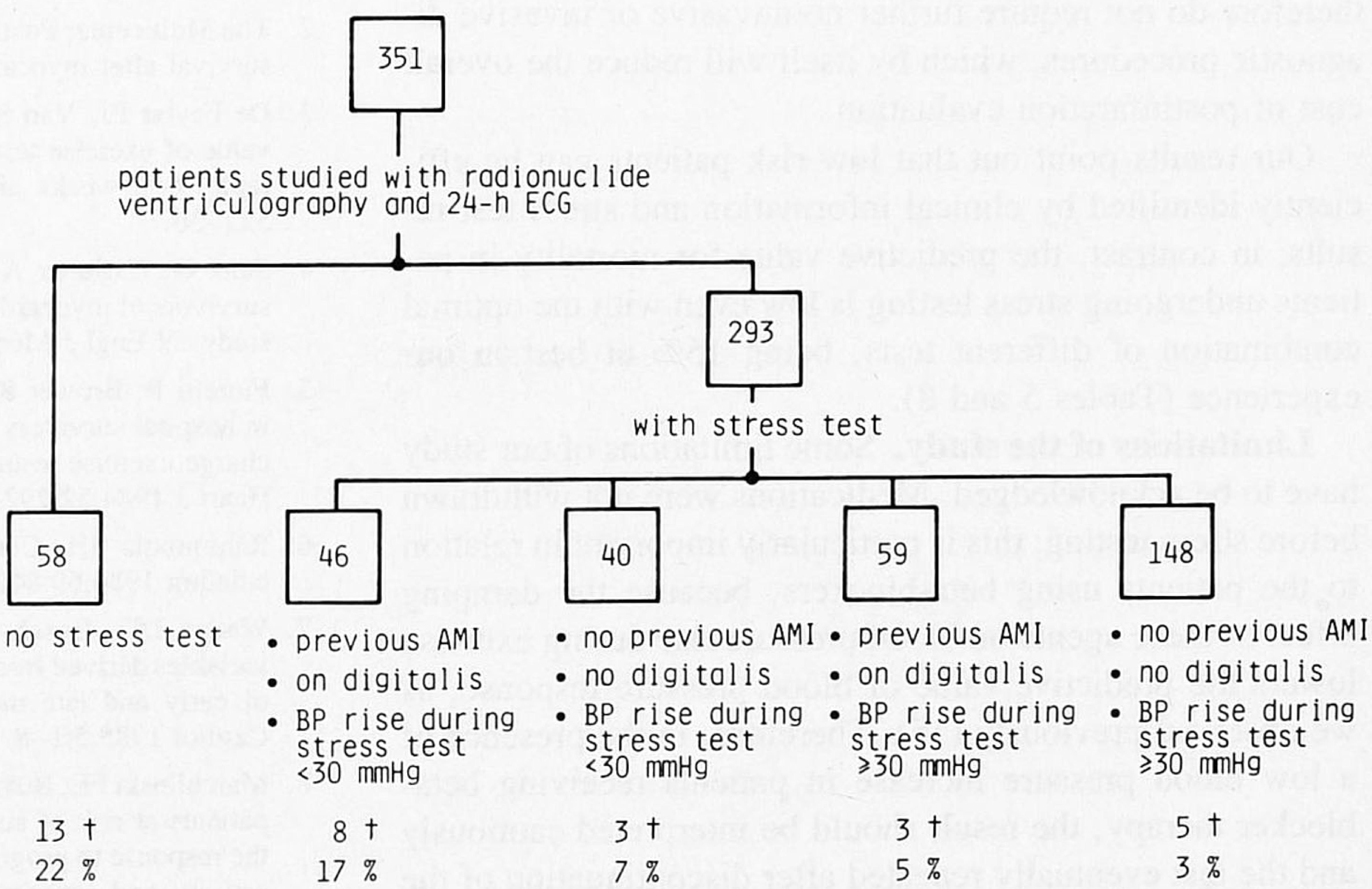

Figure 5. One year mortality after hospital discharge following acute myocardial infarction in subsets of patients based on clinical and exercise test results. AMI = acute myocardial infarction; BP = blood pressure; ECG = electrocardiogram.

nary angioplasty before hospital discharge (22,23) and, therefore, had to be excluded. However, other studies (24,25) have also failed to show ST depression during stress testing to have much prognostic relevance, even when patients undergoing revascularization were excluded (24).

Clinical variables versus multiple tests. Also consistent with previous studies (2,26), stress testing, radionuclide ventriculography and 24 hour ambulatory electrocardiographic monitoring do provide additional prognostic information to that provided by clinical data (Table 8). However, when multivariate analysis was restricted to those patients who completed a stress test, only the extent of blood pressure rise during exercise improved the prediction based on clinical data alone, whereas radionuclide ejection fraction and results of 24 hour ambulatory electrocardiographic monitoring were not additive. The failure of the ejection fraction determination to provide supplemental information is probably related to the better left ventricular function of the patients selected for stress testing compared with that of patients who were not eligible for stress testing (Table 4). Complex ventricular arrhythmias also added little new prognostic information in this group of patients. This finding also is consistent with the observations of many other investigators (1,27) who found that the prognostic relevance of complex ventricular arrhythmias is secondary to the assessment of ejection fraction.

Taken together, our results show that a large percentage of patients at low risk of mortality can be identified with easily obtainable and low cost techniques (Fig. 5). These findings are similar to those recently published by Krone et al. (12), who found a 1% mortality rate during the first year after acute myocardial infarction in patients with no signs of pulmonary congestion and a systolic blood pressure of 110 mm Hg or more during exercise. Such patients, who represent a substantial percentage of postinfarction patients, therefore do not require further noninvasive or invasive diagnostic procedures, which by itself will reduce the overall cost of postinfarction evaluation.

Our results point out that low risk patients can be efficiently identified by clinical information and stress test results; in contrast, the predictive value for mortality in patients undergoing stress testing is low even with the optimal combination of different tests, being 15% at best in our experience (Tables 5 and 8).

Limitations of the study. Some limitations of our study have to be acknowledged. Medications were not withdrawn before stress testing; this is particularly important in relation to the patients using beta-blockers, because the damping effect of these agents on blood pressure rise during exercise lowers the predictive value of blood pressure response, as we observed previously (15). Therefore, in the presence of a low blood pressure increase in patients receiving beta-blocker therapy, the result should be interpreted cautiously and the test eventually repeated after discontinuation of the beta-blocking agent. Furthermore, our results might have been influenced by the exclusion of some patients from analysis because of incomplete evaluation or early revascularization procedures.

Conclusions. We recommend a careful clinical assessment during hospitalization of patients with acute infarction. A history of previous myocardial infarction or requirement of digitalis on discharge by itself categorizes a high risk profile. A symptom-limited stress test should nevertheless be carried out at discharge as a routine procedure. Additional tests, such as radionuclide angiography and 24 hour ambulatory electrocardiographic monitoring, should be carried out only in patients with contraindications for stress testing or in those who complete the test and have an equivocal risk profile. In the low risk group it is unlikely that, unless indicated by symptoms, any particular medical treatment or any procedure of revascularization can significantly improve prognosis during the first year, although this should be prospectively verified. Long-term follow-up is required to determine whether the benign clinical course is maintained in these low risk patients. On the other hand, in the higher risk group, the appropriate treatment will also depend on the results of coronary arteriography. This procedure can be recommended with conviction on the basis of the predictive value of the noninvasive tests.

We gratefully acknowledge A. Peterse and S. Schenderling for the interpretation of 24 hour ambulatory electrocardiographic monitoring data and H. de Wolf for assisting in the preparation of the database.

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JACC Vol. 8, No. 1
July 1986:40–9

Relative Value of Clinical Variables, Bicycle Ergometry, Rest Radionuclide Ventriculography and 24 Hour Ambulatory Electrocardiographic Monitoring at Discharge to Predict 1 Year Survival After Myocardial Infarction

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The relative value of predischarge clinical variables, bicycle ergometry, radionuclide ventriculography and 24 hour ambulatory electrocardiographic monitoring for predicting survival during the first year in 351 hospital survivors of acute myocardial infarction was assessed. Discriminant function analysis showed that in patients eligible for stress testing the extent of blood pressure increase during exercise slightly improved the predictive accuracy beyond that of simple clinical variables (history of previous myocardial infarction, persistent heart failure after the acute phase of infarction and use of digitalis at discharge), whereas radionuclide ventriculography and 24 hour electrocardiographic monitoring did not. The predictive value for mortality was 12% with clinical variables alone and 15% with the stress test added.

Radionuclide ventriculography and 24 hour electrocardiographic monitoring were slightly additive to clinical information in the whole group of patients independent of the eligibility for stress testing (predictive value for mortality 24% with clinical variables alone and 26% with radionuclide ejection fraction and 24 hour electrocardiographic monitoring added).

It is concluded that the appropriate use of simple clinical variables and stress testing is sufficient for risk stratification in postinfarction patients, whereas radionuclide ventriculography and 24 hour electrocardiographic monitoring should be limited to patients not eligible for stress testing.

(J Am Coll Cardiol 1986;8:40–9)

Left ventricular function is a major prognostic determinant of survival in the first year after acute myocardial infarction (1–5), although residual myocardial ischemia (6,7) and ventricular arrhythmias (2,8,9) have also been associated with reduced survival. On the basis of these observations different algorithms have been proposed to assess the risk for individual patients early after acute myocardial infarction, including clinical variables and multiple noninvasive or invasive tests (5,10,11). Stress testing (3,5,7,12–15), radionuclide ventriculography (5,16,17) and 24 hour ambulatory electrocardiographic monitoring (2,8,9,18–20) are commonly performed early after myocardial infarction and all have been shown to provide some prognostic information. However, as far as we know, their relative merit in predicting late survival independent of easily obtainable clinical information has not been established, because most reported data have concentrated on one testing method rather than comparing them all.

We have shown in previous studies on postinfarction patients that radionuclide ventriculography and bicycle ergometry provide similar prognostic information (5) and that bicycle ergometry slightly improves the prediction of survival during the first year after myocardial infarction beyond that of routine clinical variables (15). The aim of the present study was to determine whether the results from more expensive tests, such as radionuclide ventriculography and 24 hour ambulatory electrocardiographic monitoring, provide a further improvement of the prognostic judgment compared with the appropriate use of simple clinical variables and inexpensive, widely available and practical forms of stress testing.

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Manuscript received June 25, 1985; revised manuscript received February 4, 1986, accepted February 7, 1986.

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0735-1097/86/$3.50

Methods

Patients. The records of 706 consecutive patients admitted to the coronary care unit of the Thoraxcenter between March 1981 and December 1983 with documented acute myocardial infarction were reviewed. This population includes 26% of patients referred from other hospitals for complications. The diagnosis of acute myocardial infarction was based on at least two of the following criteria: 1) Typical prolonged chest pain at least 45 minutes in duration. 2) In transmural acute myocardial infarction, dynamic electrocardiographic changes such as evolving Q waves longer than 0.04 second with ST-T changes or, in non-Q wave infarctions, ST-T changes persisting for at least 24 hours. 3) Increase of total serum creatine kinase level with a peak level of more than 100 IU/liter (twice the upper limit of normal values in our laboratory). Previous myocardial infarction was diagnosed by a typical history or diagnostic Q wave abnormalities, or both.

Hospital mortality occurred in 104 patients (14%). Coronary artery bypass grafting before hospital discharge was performed in 51 patients, percutaneous transluminal coronary angioplasty for postinfarction angina was performed in 16 cases and cardiac surgery for mitral insufficiency or ventricular septal defect was performed in 9 patients.

Multiple tests. In hospital survivors, symptom-limited bicycle ergometry, rest radionuclide ventriculography and 24 hour ambulatory electrocardiographic monitoring were performed in, respectively, 407, 520 and 389 patients an average of 14 days after myocardial infarction, before hospital discharge. Radionuclide ventriculography and stress testing were performed as previously described (5). Stress testing was symptom limited and medication was not discontinued at the time of the test. Drug therapy included a beta-receptor blocker in 209 patients (52%) and digitalis in 66 (16%). One hundred ninety-one patients were judged not eligible for stress testing, because of angina in 55, heart failure in 47, a noncardiac limitation in 71 and logistic problems in 18. Twenty-four hour ambulatory electrocardiographic recordings were centrally analyzed (21) using a modified Medilog system (MR14).

Patient subsets (Table 1). Six of the surviving patients were lost to follow-up, while 594 patients were followed up for 1 year by regular outpatient visits or, in a few cases, by telephone contact with their general practitioner. Cardiac death was the primary end point of this study but other events, such as nonfatal reinfarction, coronary artery bypass surgery and percutaneous transluminal coronary angioplasty, were also recorded.

Prediction of survival was performed first in the 594 patients who survived hospital stay, including those who underwent revascularization procedures before hospital discharge. Two patients who died of noncardiac causes were excluded from the analysis. Because of the influence that cardiac surgery or percutaneous transluminal coronary angioplasty could have had on the first year course of events, the analysis was repeated after excluding the 76 patients who underwent one or both of these procedures. Depending on the diagnostic tests performed, different subgroups of patients were analyzed: 449 patients were studied with radionuclide ventriculography and stress testing unless contraindicated, while 351 had a complete evaluation including radionuclide angiography, 24 hour ambulatory electrocardiographic monitoring and bicycle ergometry, unless contraindicated.

Statistical analysis. Univariate analysis with the unpaired Student's t test for continuous variables and chi-square or Fisher's exact test for discrete variables were applied when appropriate. Data are expressed as mean and standard deviation unless otherwise specified. To compare

Table 1. One Year Survival in 706 Consecutive Patients Admitted to the Coronary Care Unit of the Thoraxcenter With a Proven Diagnosis of Acute Myocardial Infarction

	No. of Patients		No. of Deaths at 1 Year (%)	
Total population	706		176 (25)	
Hospital death	104	706	104 (14)	176
Discharged alive, with 1 year follow-up	596		72 (12)*	
Lost to follow-up	6		—	
Cardiac surgery or PTCA before discharge	76	596 hospital survivors with 1 year follow-up	2 (3)	72*
Discharged on medical therapy	520		70 (13)*	
With RV and XT	355	449 with RV	24 (7)	49
With RV and contraindication for XT	94		25 (26)	
With RV, XT and 24 h ECG	293	351 with RV + 24 h ECG	19 (6)	32
With RV, 24 h ECG and contraindication for XT	58		13 (22)	

*Including two noncardiac deaths. PTCA = percutaneous transluminal coronary angioplasty; RV = radionuclide ventriculography; 24 h ECG = 24 hour ambulatory electrocardiographic monitoring; XT = exercise test (bicycle ergometry).

the predictive value for mortality of different continuous variables, we used receiver-operator characteristic curves as in previous reports from our group (5,15).

The BMDP statistical package for stepwise discriminant analysis (P7M) was used to generate classification functions for different classes of information: clinical variables only and clinical variables combined stepwise with stress testing, radionuclide ventriculography and 24 hour ambulatory electrocardiographic monitoring, to assess whether the combination of the different tests provides additive predictive value beyond clinical data alone.

The clinical variables consisted of age, sex, history of previous myocardial infarction, history of previous angina more than 4 weeks before the index myocardial infarction, anterior location of index myocardial infarction, the worst Killip functional class while in the coronary care unit, presence of angina pectoris during hospital stay, persistence of congestive heart failure after the stay in the coronary care unit, sustained ventricular tachycardia or fibrillation more than 72 hours after myocardial infarction, cardiothoracic ratio at discharge greater than 50% and use of digoxin, diuretic drugs and beta-blockers at discharge.

The stress test variables included percent of predicted work capacity, maximal work load, occurrence of angina during the test, heart rate at peak work load, extent of systolic blood pressure rise, ST depression, ST elevation and any ventricular arrhythmia.

Left ventricular ejection fraction was the only variable included from radionuclide ventriculography.

Variables from 24 hour ambulatory electrocardiographic monitoring in the stepwise analysis included: more than five multiform premature ventricular complexes during any minute of the recording, and the presence of any ventricular couplet or ventricular tachycardia (runs of three or more ventricular complexes with a rate ≥ 100/min) during the 24 hour recording period.

The end point of the study was cardiac mortality during the first year after myocardial infarction. In a first pass, stepup analysis was done using an F value of 1.0, which entered in the discriminant function all variables remotely related to the outcome. In the second pass, a stepdown analysis was performed on the selected subgroup of variables using an F value of 4.0 or more. The discriminant functions resulting from the stepdown analysis were then used to predict the classification of the same group of patients for a range of threshold levels of the discriminant function.

Results

Prediction of survival by univariate analysis in all 596 hospital survivors (Tables 2 and 3). During the 1 year follow-up period there were 70 cardiac-related deaths: 37 sudden, 18 from reinfarction, 13 from heart failure and 2 perioperative. There were two noncardiac deaths, which were excluded from analysis. Death occurred within 3 months of the index infarction in 30 cases, between 3 and 6 months in 14 cases and between 6 and 12 months in 26 cases.

All clinical variables reflecting impaired left ventricular function were associated with poor survival. In addition, late ventricular tachycardia or fibrillation was significantly associated with late mortality. Early postinfarction angina was not followed by a higher mortality than that in patients

Table 2. Differences in Clinical Variables Before Discharge Between Late Survivors and Nonsurvivors Among 594 Hospital Survivors

Clinical Variables	Survivors	Nonsurvivors	p Value
No. of patients	524	70	—
Male (%)	79	74	NS
Age (yr)	57 ± 10	62 ± 12	0.0005
Previous angina (%)	36	53	0.01
Previous AMI (%)	26	60	0.0005
Anterior AMI (%)	34	38	NS
Killip class >II (%)	7	28	0.0005
Peak CK (IU/liter)	564 ± 481	590 ± 554	NS
Post-AMI angina (%)	25	27	NS
Late heart failure (%)	13	47	0.0005
Late VT or VF (%)	3	14	0.0005
CTR >50% (%)	20	57	0.0005
Digitalis at discharge (%)	18	56	0.0005
Diuretic therapy at discharge (%)	34	66	0.0005
Beta-blockers at discharge (%)	54	33	0.001
Cardiac surgery or PTCA (%)	12	3	0.01

The data of two patients who died of noncardiac causes are excluded. AMI = acute myocardial infarction; CK = serum creatine kinase; CTR = cardiothoracic ratio; NS = not significant; VF = ventricular fibrillation; VT = sustained ventricular tachycardia; other abbreviations as in Table 1.

Table 3. Differences in Predischarge Bicycle Ergometry, Radionuclide Ventriculography and 24 Hour Ambulatory Electrocardiographic Monitoring Between Late Survivors and Nonsurvivors in 594 Hospital Survivors

	Survivors	Nonsurvivors	p Value
Radionuclide ventriculography			
No. of patients	461	52	—
Ejection fraction (%)	47 ± 14	32 ± 15	0.0005
Bicycle ergometry			
No. of patients	374	29	—
Reason for interrupting the test (%)			
Fatigue	71	62	NS
Angina	6	7	NS
Dyspnea	18	17	NS
Pressure drop	2	13	0.001
Maximal work load (W)	114 ± 33	100 ± 23	0.02
Percent working capacity	79 ± 17	66 ± 15	0.0005
Angina (%)	20	20	NS
Heart rate at rest (beats/min)	82 ± 16	89 ± 18	0.01
Peak heart rate (beats/min)	130 ± 22	133 ± 27	NS
SBP at rest (mm Hg)	121 ± 15	121 ± 20	NS
Peak SBP (mm Hg)	163 ± 28	141 ± 25	0.0005
SBP rise (mm Hg)	42 ± 23	21 ± 19	0.0005
ST depression (%)*	46	53	NS
Work load at ST depression (W)	92 ± 31	82 ± 33	NS
ST elevation (%)*	44	53	NS
Ventricular ectopic activity (%)	22	34	NS
24 h ECG monitoring			
No. of patients	349	39	—
Multiform PVCs >5/min (%)	24	33	NS
Ventricular couplets (%)	31	58	0.001
Ventricular tachycardia (%)	13	38	0.0005

*ST depression or elevation ≥ 1 mm. The data of two patients who died of noncardiac causes during follow-up are excluded. PVCs = premature ventricular complexes; SBP = systolic blood pressure; other abbreviations as in Tables 1 and 2.

without angina; in contrast, a history of stable preinfarction angina was associated with a poor prognosis.

Radionuclide ejection fraction was significantly lower in nonsurvivors, consistent with the clinical findings.

An insufficient maximal work load and an insufficient blood pressure rise during the stress test were predictive of mortality, whereas markers of ischemia, such as angina and ST depression during exercise, were not predictive. Ventricular ectopic activity was more frequent in nonsurvivors, but not significantly so.

Finally, 24 hour ambulatory electrocardiographic monitoring was also predictive because the incidence of repetitive ventricular complexes was higher in nonsurvivors.

Prediction of survival from clinical variables, radionuclide ventriculography and bicycle ergometry in 449 patients treated medically (Tables 4 and 5). Radionuclide ventriculography was performed on 449 of the 520 patients treated medically (Table 1). Three hundred fifty-five patients were eligible for stress testing, whereas 94 were ineligible. Mortality was highest in patients ineligible for the exercise test (n = 25; 26%) and was 7% (n = 24) in patients who were judged eligible for the test. Baseline characteristics of the patients who were and were not eligible for stress testing are reported in Table 4. These data indicate that patients not eligible for testing were older, had more severe left ventricular dysfunction and a higher incidence of early postinfarction angina than did patients who completed the test.

The predictive value of clinical variables, stress testing and radionuclide ejection fraction by univariate analysis was comparable with that found in the whole group of 596 patients described in the previous section (Tables 2 and 3). Ejection fraction was lower in nonsurvivors than in survivors (31 ± 14 versus 47 ± 15%, respectively; $p < 0.0005$). The distribution of radionuclide ejection fraction values in the 449 patients is shown in Figure 1. Among stress test results, the contraindication for the test and the extent of blood pressure increase were the best predictors of prognosis.

The predictive value of radionuclide ejection fraction and stress testing (combined with the contraindication for the test and blood pressure increase) were comparable (Fig. 2), because the sensitivity and the specificity of the two tests largely overlap during the whole range of measurements. The cutoff points with the highest sensitivity and specificity

Table 6. Univariate Predictors of Mortality in 351 Patients With Complete Evaluation

	All Patients			Patients Eligible for Stress Testing			Patients Not Eligible for Stress Testing		
	Survivors	Nonsurv.	p Value	Survivors	Nonsurv.	p Value	Survivors	Nonsurv.	p Value
No. of patients	319	32		274	19		45	13	
Clinical variables									
Age (yr)*	56 ± 10	58 ± 12	NS	54 ± 10	52 ± 11	NS	65 ± 9	67 ± 8	NS
Males (%)	84	84	NS	86	95	NS	73	69	NS
Previous AMI (%)	22	53	0.001	20	47	0.001	29	62	0.02
Previous angina (%)	33	56	0.001	31	37	NS	40	85	0.005
Anterior AMI (%)	37	43	NS	36	53	NS	37	31	NS
Killip class >II (%)	6	25	0.001	5	11	NS	9	46	0.002
Post-AMI angina (%)	17	25	NS	14	21	NS	33	31	NS
Late heart failure (%)	14	50	0.001	12	42	0.001	24	62	0.001
Late VT or VF (%)	4	16	0.005	4	11	NS	4	23	0.05
CTR >50% (%)	20	50	0.001	24	26	NS	24	85	0.001
Digitalis at discharge (%)	16	59	0.001	13	53	0.001	27	69	0.001
Diuretic therapy at discharge (%)	34	72	0.001	32	63	0.01	44	85	0.02
Beta-blockers at discharge (%)	56	37	0.05	60	42	NS	29	31	NS
Radionuclide EF (%)*	47 ± 14	33 ± 16	0.001	48 ± 14	35 ± 18	0.001	45 ± 15	30 ± 12	0.002
24 h ECG monitoring									
Multiform PVCs >5/min (%)	24	34	NS	23	21	NS	29	54	NS
Ventricular couplets (%)	32	59	0.005	31	47	NS	33	77	0.005
Ventricular tachycardia (%)	12	37	0.001	13	21	NS	15	62	0.001

*Mean ± SD. Nonsurv. = nonsurvivors; other abbreviations as in previous tables.

rate) were identified with a blood pressure increase of 30 mm Hg or more and an intermediate risk group included 89 patients with a mortality rate of 12% who had a blood pressure rise of less than 30 mm Hg.

The discriminant function analysis (Table 8) applied to clinical variables only in the entire group of 351 patients resulted in three independent variables predictive of mortality at the 0.05 level of significance: use of digitalis at discharge, history of a previous myocardial infarction and persistence of heart failure after the acute phase of infarction. By adding the results of radionuclide ventriculography and of 24 hour ambulatory electrocardiographic monitoring, ejection fraction and the presence of ventricular tachycardia improved the predictive accuracy compared with that of clinical variables alone.

When a similar stepwise analysis was repeated in the group of patients eligible for the stress test, stress test results (the extent of blood pressure rise) slightly improved the prediction over that of clinical variables alone, but in this subset of patients ejection fraction and the results of 24 hour ambulatory electrocardiographic monitoring did not provide any additional information beyond that provided by the combination of clinical and stress test results.

Discussion

Left ventricular dysfunction, ventricular arrhythmias and residual myocardial ischemia are all important determinants of survival during the first year after myocardial infarction (1,2,6) when considered separately. Consequently, multiple

Table 7. Univariate Predictors of Survival in 293 Patients With Complete Evaluation: Stress Test Results

	Survivors	Nonsurvivors	p Value
No. of patients	274	19	—
Maximal work load (W)	115 ± 32	103 ± 23	NS
Working capacity (%)	79 ± 17	66 ± 14	0.002
Angina (%)	15	11	NS
Heart rate at rest (beats/min)	81 ± 16	93 ± 19	0.002
Peak heart rate (beats/min)	130 ± 22	139 ± 25	0.05
SBP at rest (mm Hg)	121 ± 15	120 ± 18	NS
Peak SBP (mm Hg)	161 ± 26	143 ± 27	0.002
SBP rise (mm Hg)	40 ± 22	24 ± 20	0.002
ST depression (%)	44	47	NS
Any ventricular arrhythmia (%)	22	26	NS

Abbreviations as in previous tables.

Table 8. Prediction of Mortality by Discriminant Function Analysis in 351 Patients With Complete Evaluation

	All Patients		Patients Eligible for Stress Test		
	Clinical Variables	Clinical Variables + EF + 24 h ECG	Clinical Variables	Clinical Variables + Stress Test	Clinical Variables + Stress Test + EF + 24 h ECG
Nonsurvivors (n)	32	32	19	19	19
Survivors (n)	319	319	274	274	274
Clinical variables (F value)					
Discharged on digitalis	20.5	26.4	19.1	15.8	15.8
History of previous AMI	14.1	12.7	7.5	5.8	5.8
Late heart failure	5.5	—	—	—	—
Radionuclide ventriculography (F value)					
Ejection fraction	—	5.2	—	—	—
24 h ECG monitoring (F value)					
Ventricular tachycardia	—	7.5	—	—	—
Stress testing (F value)					
SBP rise	—	—	—	5.0	5.0
Predictive accuracy (%)					
Sensitivity (%)	59	72	63	63	63
Specificity (%)	81	80	67	75	75
Predictive value positive (%)	24	26	12	15	15
Predictive value negative (%)	95	97	96	98	98
Total correct classification (%)	79	79	67	75	75
High risk group (%)	23	25	35	27	27
Risk ratio	5.0	7.7	3.2	4.5	4.5

Abbreviations as in Tables 1 and 2.

tests have been applied to postinfarction patients to improve the prediction of clinical outcome obtainable with clinical variables only (10,11). The questions now are: which of these tests is the most predictive and do we need them all in every patient? Indeed, the present study confirms that clinical variables, stress testing, radionuclide angiography and 24 hour ambulatory electrocardiographic monitoring are all useful in predicting late survival. When clinical information and these tests indicate left ventricular dysfunction and show complex ventricular arrhythmias, late survival is reduced (Table 6).

Surprisingly, early postinfarction angina and ST depression during the exercise test were not predictive of impaired survival. This is largely explained by the fact that 76 patients with more severe early postinfarction angina underwent coronary artery bypass or percutaneous transluminal coro-

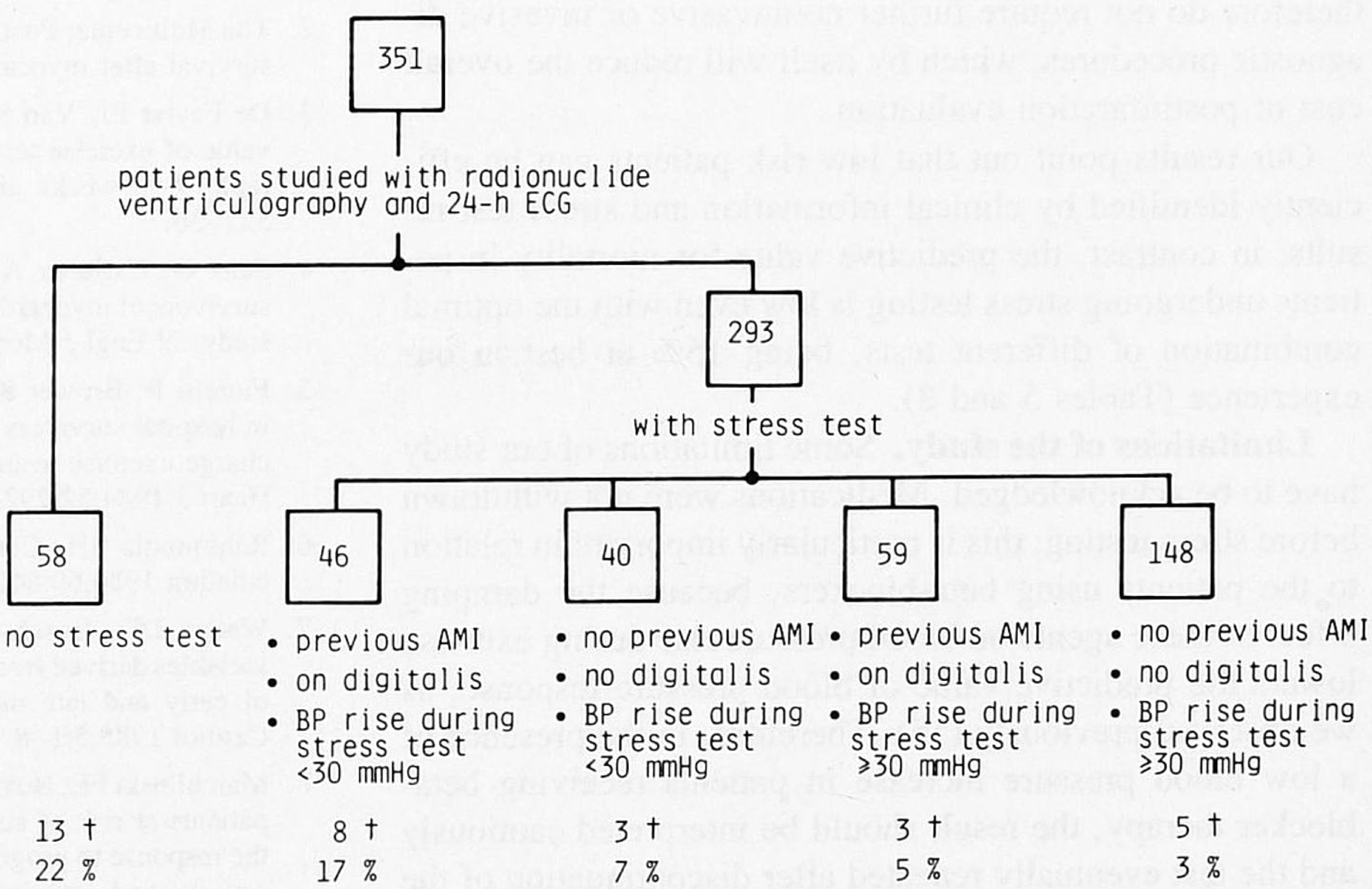

Figure 5. One year mortality after hospital discharge following acute myocardial infarction in subsets of patients based on clinical and exercise test results. AMI = acute myocardial infarction; BP = blood pressure; ECG = electrocardiogram.

nary angioplasty before hospital discharge (22,23) and, therefore, had to be excluded. However, other studies (24,25) have also failed to show ST depression during stress testing to have much prognostic relevance, even when patients undergoing revascularization were excluded (24).

Clinical variables versus multiple tests. Also consistent with previous studies (2,26), stress testing, radionuclide ventriculography and 24 hour ambulatory electrocardiographic monitoring do provide additional prognostic information to that provided by clinical data (Table 8). However, when multivariate analysis was restricted to those patients who completed a stress test, only the extent of blood pressure rise during exercise improved the prediction based on clinical data alone, whereas radionuclide ejection fraction and results of 24 hour ambulatory electrocardiographic monitoring were not additive. The failure of the ejection fraction determination to provide supplemental information is probably related to the better left ventricular function of the patients selected for stress testing compared with that of patients who were not eligible for stress testing (Table 4). Complex ventricular arrhythmias also added little new prognostic information in this group of patients. This finding also is consistent with the observations of many other investigators (1,27) who found that the prognostic relevance of complex ventricular arrhythmias is secondary to the assessment of ejection fraction.

Taken together, our results show that a large percentage of patients at low risk of mortality can be identified with easily obtainable and low cost techniques (Fig. 5). These findings are similar to those recently published by Krone et al. (12), who found a 1% mortality rate during the first year after acute myocardial infarction in patients with no signs of pulmonary congestion and a systolic blood pressure of 110 mm Hg or more during exercise. Such patients, who represent a substantial percentage of postinfarction patients, therefore do not require further noninvasive or invasive diagnostic procedures, which by itself will reduce the overall cost of postinfarction evaluation.

Our results point out that low risk patients can be efficiently identified by clinical information and stress test results; in contrast, the predictive value for mortality in patients undergoing stress testing is low even with the optimal combination of different tests, being 15% at best in our experience (Tables 5 and 8).

Limitations of the study. Some limitations of our study have to be acknowledged. Medications were not withdrawn before stress testing; this is particularly important in relation to the patients using beta-blockers, because the damping effect of these agents on blood pressure rise during exercise lowers the predictive value of blood pressure response, as we observed previously (15). Therefore, in the presence of a low blood pressure increase in patients receiving beta-blocker therapy, the result should be interpreted cautiously and the test eventually repeated after discontinuation of the beta-blocking agent. Furthermore, our results might have been influenced by the exclusion of some patients from analysis because of incomplete evaluation or early revascularization procedures.

Conclusions. We recommend a careful clinical assessment during hospitalization of patients with acute infarction. A history of previous myocardial infarction or requirement of digitalis on discharge by itself categorizes a high risk profile. A symptom-limited stress test should nevertheless be carried out at discharge as a routine procedure. Additional tests, such as radionuclide angiography and 24 hour ambulatory electrocardiographic monitoring, should be carried out only in patients with contraindications for stress testing or in those who complete the test and have an equivocal risk profile. In the low risk group it is unlikely that, unless indicated by symptoms, any particular medical treatment or any procedure of revascularization can significantly improve prognosis during the first year, although this should be prospectively verified. Long-term follow-up is required to determine whether the benign clinical course is maintained in these low risk patients. On the other hand, in the higher risk group, the appropriate treatment will also depend on the results of coronary arteriography. This procedure can be recommended with conviction on the basis of the predictive value of the noninvasive tests.

We gratefully acknowledge A. Peterse and S. Schenderling for the interpretation of 24 hour ambulatory electrocardiographic monitoring data and H. de Wolf for assisting in the preparation of the database.

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