Limitations on the prognostic value of predischARGE data after myocardial infarction

HENRI CLEEMPOEL, HARRY VAINSEL, MICHELE DRAMAIX,*
ANDRE LENAERS, EFISIO CONTU, MICHELINE HOYLAERTS,
BETTY DEMARET, MICHEL DE MARNEFFE, JEAN-LUC VANDENBOSSCHE,
MARC RENARD, RAYMOND HAARDT, MARC ENGLERT, HENRI DENOLIN,
ROLAND BERNARD

*From the Cardiology Department, Saint Peter's University Hospital; and the *School of Public Health, Free University of Brussels, Brussels, Belgium*

SUMMARY Clinical variables and those obtained by non-invasive techniques were studied prospectively in a series of 306 patients discharged from hospital after an acute myocardial infarction. The predictive value of the data at two and 12 months was assessed by univariate and multivariate analyses. The best correlation was found for age, hypertension, bundle branch block, early and late heart failure, x ray cardiothoracic ratio, digoxin use, the number of metabolic equivalents reached during the stress test, echocardiographic wall motion score index, left ventricular end diastolic diameter, left ventricular ejection fraction, and the presence of an aneurysm. The prognostic value of the same data at 12 months was studied in those surviving for two months. There was a noticeable decline in the relative risk of all but two of the factors (number of metabolic equivalents, ventricular arrhythmias). All of the predictive variables except the x ray cardiothoracic ratio, number of metabolic equivalents, and the presence of an aneurysm lost their discriminant power. The explanation for this is the strength of statistical relations of these variables with the outcome at two months. They continued to influence the score at 12 months even when the entire patient series was considered.

In conclusion, the study shows that the predictive value of most of the predischARGE variables usually taken into account in the assessment of risk in patients one year after infarction does not extend beyond the first two months.

In a previous prospective study we analysed the clinical data and information obtained by all currently available non-invasive techniques in a series of 202 patients in hospital with acute myocardial infarction.¹ The relevance and predictive values of some of the resulting indices were then established for a two month follow up period. The study was extended to 306 patients with the aim of assessing the validity of our previous work, extending the survey up to one year, and focusing more attention on follow up of those who survived two months.

Requests for reprints to Dr Henri Cleempoel, Hôpital Universitaire Saint Pierre, Département de Cardiologie, Rue Haute 322, B-1000 Brussels, Belgium.

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Patients and methods

We studied a continuous series of men aged < 70 who were admitted to the coronary care unit from January 1981 to March 1985 within 24 hours of the first clinical signs of myocardial infarction and left the hospital alive. The criteria for infarction were a peak serum concentration of creatine kinase MB that was $\geq 50\%$ of the upper normal limit and either the characteristic electrocardiographic signs of myocardial infarction or a history of prolonged chest pain consistent with this diagnosis. Three hundred and twenty two of the 905 patients admitted with myocardial infarction during this selection period met these criteria. Fifteen patients were excluded because of severe concurrent illnesses (6) or because they were foreigners who usually lived abroad (9). Of the remaining 307 patients considered for follow up, on

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died from a non-cardiac illness in the first two months of follow up and another died between the second and twelfth months. So 306 patients were included in the statistical analyses of the two month follow up and 305 were included in the 12 month follow up.

During hospital admission the patients were managed in accordance with the usual clinical indications. Forty five (15%) patients were treated with streptokinase. At the time of discharge, 150 (49%) subjects were taking β blockers, 34 (11%) anti-arrhythmic drugs, and 25 (8%) digoxin.

All patients were followed up for two and 12 months, with death as the end point. Only one patient was lost to one year follow up. The predictive value of the data collected before discharge was measured at two and 12 months. The predictive value at 12 months was also measured for those who survived the first two months.

VARIABLES

During the hospital stay 68 variables were investigated as described in our previous report.¹ They included history; clinical, electrocardiographic, and laboratory data; chest x ray cardiothoracic ratio, and the results of all of the non-invasive tests that were performed—that is treadmill exercise test, M mode and cross sectional echocardiography, gated equilibrium radionuclide ventriculography, and a 24 hour ambulatory electrocardiogram. These tests were carried out between 10 and 12 days after the myocardial infarction, before the date of discharge and without stopping drug treatment.

EXERCISE TEST

The exercise test was performed on a treadmill.² The maximum exercise level was expressed in metabolic equivalents and heart work was evaluated by the double product (systolic blood pressure $\times$ heart rate). ST changes were considered to be abnormal when there was a displacement of >1 mm in three consecutive complexes with a stable baseline. ST depression was measured 0.06 s after the RST (J) junction.

ECHOCARDIOGRAPHIC ANALYSIS

Echocardiograms were recorded on an ATL Mk 300. We measured long and short diameters of the left ventricle and the shortening fraction (%). Segmental wall motion was analysed by standard methods.³⁴ The left ventricle wall was divided into 16 segments and each segment was then assigned a number corresponding to the wall motion analysis (1 = normal, 2 = hypokinetic, 3 = akinetic, 4 = dyskinetic, 5 = aneurysm). The sum of these numbers multiplied by 10 and then divided by the

number of segments visualised gave the wall motion score index.

GATED EQUILIBRIUM RADIONUCLIDE VENTRICULOGRAPHY

Gated equilibrium radionuclide ventriculography was performed in the left anterior oblique (40°) and left posterior oblique (30°) projections a few minutes after intravenous injection of 15 mCi of technetium-99m labelled human serum albumin. The left ventricular end systolic and end diastolic volumes were measured and the left ventricular ejection fraction was calculated. We used a temporal Fourier transform to evaluate regional wall motion from functional images.^{5,6}

TWENTY FOUR HOUR ELECTROCARDIOGRAPHIC RECORDING

A patient was considered to have ventricular arrhythmias if 200 or more extrasystoles, runs, or ventricular tachycardia (≥ 5 beats) were recorded over a 24 hour period. The patients were active and able to walk about in the ward while the electrocardiograms were being recorded.

STATISTICAL ANALYSIS

The data collected during the hospital stay were analysed for correlations with the occurrence of cardiac death two and 12 months after admission to the coronary care unit. The predictive value of all of the variables was assessed by univariate statistical analysis and stepwise discriminant analysis for both follow up periods. The relative risks for all three periods (two months, 12 months, and from two to 12 months) were also calculated. All the analyses were performed with the Statistical Package for Social Sciences (SPSS), version 8 PO.⁷⁻⁹

Results

Fourteen (4.6%) patients died within two months of admission: eight suddenly, one from a recurrent myocardial infarction, and five from heart failure. A further 22 (7%) patients died between two and 12 months: nine from sudden death, six from another myocardial infarction, and seven from heart failure.

UNIVARIATE ANALYSIS

Predictive value at two and 12 months for all patients alive at the time of discharge

Clinical data (table 1).—The mean age difference between those who survived and those who died was significant at the one year follow up only. Hypertension was also predictive of death for the 12 month period only. No significant differences were found for a history of angina, previous infarctions, or

Table 1 Predictive value (%) at two and 12 months of clinical, electrocardiographic, and radiological data determined by univariate analysis (for all patients leaving the hospital alive)

Variables	2 months			12 months		
	Alive (n = 292)	Dead (n = 14)	p	Alive (n = 269)	Dead (n = 36)	p
Age (mean (SD))	56.0 (8.3)	58.8 (8.3)	NS	55.8 (8.4)	59.1 (6.6)	<0.05
Hypertension	26	43	NS	25	44	<0.05
Angina	33	50	NS	33	36	NS
Previous MI	26	50	NS	26	33	NS
Diabetes	25	36	NS	26	28	NS
Anterior MI	43	50	NS	42	52	NS
VT, VF	23	36	NS	24	22	NS
Bundle branch block	8	29	<0.05	8	19	<0.05
Early heart failure	17	86	<0.001	16	53	<0.001
Late heart failure	5	21	<0.05	4	17	<0.01
x ray C:T ≥ 50	39	86	<0.01	37	81	<0.001
Digoxin	7	36	<0.001	6	22	<0.01
β Blocking agent	50	36	NS	50	47	NS

MI, myocardial infarction; VT, ventricular tachycardia; VF, ventricular fibrillation; C:T, cardiothoracic ratio.

diabetes. Neither the infarction site nor the presence of ventricular tachycardia or fibrillation during hospital stay had any significant predictive value. The peak increase in plasma creatine kinase MB was lower in survivors at both two months (mean (SD) 50 (33) v 91.3 (98) $\mu\text{g/ml}$) and 12 months (mean 49 (91) v 71 (69) $\mu\text{g/ml}$). Nevertheless, the F test showed a highly significant difference in the variances in both groups. So a *t* test with "separate variance estimate" was chosen. This showed no significant difference between the mean plasma concentrations of creatine kinase MB. Complete right or left bundle branch block were less frequent at both two and 12 months in those who survived than in those who died. The variables related to deterioration of left ventricle function had especially high predictive values of death. Early heart failure (Killip classes II and III in the first three days after the acute myocardial infarction) was noted in 17% of the survivors and 86% of those who had died by two months and 16 and 53% of the survivors and those who had died by 12 months. Heart failure at the time of discharge (late heart failure) also showed a predictive value at two months

(5% v 21%) and 12 months (4% v 17%). A cardiothoracic ratio $\geq 50\%$ and digoxin use were also predictive of death before two and 12 months. Neither β blocking agents, nor antiarrhythmic treatment, nor angina at the time of discharge had discriminant value at two and 12 months. Streptokinase did not have any significant impact on prognosis, but only 45 patients received this drug. **Non-invasive procedures**—The exercise test (table 2) was undertaken by 295 patients. The one year mortality for this group was 11.5%, compared with 18% for the patients who were unable to perform the test because of heart related (arrhythmias, heart failure) or other reasons. Of the variables that were indicative of exercise capacity, only the mean peak workload, expressed in metabolic equivalents, achieved by the patients was higher in the survivors at two and 12 months. ST depression or elevation was not of predictive value. Even severe ST depression or elevation (> 2 mm) failed to have predictive value.

Several echocardiographic findings were of interest (table 3). The mean value of the wall motion

Table 2 Predictive value at two and 12 months after myocardial infarction of predischARGE exercise testing for surviving and dead patients determined by univariate analysis (for all patients leaving the hospital alive)

Variables	2 months			12 months		
	Alive (n = 282)	Dead (n = 13)	p	Alive (n = 261)	Dead (n = 33)	p
METs (mean (SD))	3.7 (1.7)	2.5 (1.5)	<0.01	3.8 (1.6)	2.4 (1.5)	<0.001
Max heart rate (mean (SD))	102 (15)	105 (15)	NS	102 (15)	102 (17)	NS
Double product (mean (SD))	14.2 (4)	12.8 (4)	NS	14.2 (4)	13.1 (4)	NS
ST depression > 1 mm (%)	42	25	NS	43	30	NS
ST elevation > 1 mm (%)	36	40	NS	35	36	NS
Severe ST depression or elevation (> 2 mm) (%)	24	17	NS	23	25	NS

METs, metabolic equivalents.

Table 3 Predictive value at two and 12 months of echocardiographic data for surviving and dead patients determined by univariate analysis (for all patients leaving the hospital alive)

Variables	2 months			12 months		
	Alive (n = 254)	Dead (n = 13)	p	Alive (n = 234)	Dead (n = 32)	p
WMSI (mean (SD))	15.9 (5.3)	22.5 (4.8)	<0.001	15.8 (5.3)	19.5 (5.7)	<0.001
WMSI > 22 (%)	13.4	76.9	<0.001	12.8	43.5	<0.001
LVEDD (mean (SD))	57.0 (6.9)	65.5 (5.7)	<0.001	57.0 (6.9)	60.8 (8.9)	<0.01
Aneurysm (%)	12	31	NS	11	28	<0.01

WMSI, wall motion score index; LVEDD, left ventricular end diastolic diameter.

score index and scores above 22 had discriminant value at two and 12 months. At two and 12 months the mean left ventricular end diastolic diameter was greater in those who died. Left ventricular aneurysms were statistically less frequent in those who were still alive at 12 months. Radionuclide ventriculography (table 4) showed higher mean left ventricular ejection fractions in survivors at two and 12 months. Left ventricular aneurysms were less frequent in survivors at two and 12 months. Ventricular arrhythmias (as defined above) were less common in the 24 hour electrocardiograms of survivors but the difference was significant at 12 months only.

Predictive values of the same variables at one year for those who survived the first two months (291 cases)

In order to establish their predictive value at 12 months the predischARGE data were re-examined for the group that survived the first two months. The non-predictive data for all patients remained non-predictive for this group.

Table 5 summarises the data with significant prognostic value for all patients (at two or 12 months or both). At 12 months only four of these variables continued to have a significant relation to the outcome in those who survived the first two months. These were a cardiothoracic ratio $\geq 50\%$, the functional capacity during the exercise test, isotopically detected left ventricular aneurysms, and ventricular arrhythmias in the 24 hour electrocardiographic recordings. The other variables lost their predictive, discriminant value.

Table 4 Predictive value at two and 12 months of radionuclide ventriculography for surviving and dead patients determined by univariate analysis (for all patients leaving the hospital alive)

Variables	2 months			12 months		
	Alive (n = 263)	Dead (n = 12)	p	Alive (n = 242)	Dead (n = 32)	p
LVEF (mean (SD))	48 (14)	30 (13)	<0.001	49 (13)	38 (15)	<0.001
LVEF ≤ 40 (%)	25	75	<0.001	24	56	<0.001
Aneurysm (%)	19	50	<0.05	17	47	<0.001

LVEF, left ventricular ejection fraction.

Table 5 Predictive value (%) at 12 months of clinical and technical variables determined by univariate analysis (for the patients surviving for the first two months)

Variables	Alive	Dead	p
Age (mean (SD))	55 (8.4)	59 (7.2)	NS
Hypertension	25	46	NS
Early heart failure	16	32	NS
Bundle branch block	8	14	NS
Late heart failure	4	14	NS
x ray C:T $\geq 50\%$	37	77	<0.001
Digoxin	6	14	NS
METs (mean (SD))	3.8 (1.6)	2.3 (1.5)	<0.001
WMSI (mean (SD))*	15.8 (5.3)	17.4 (5.6)	NS
LVEDD diameter (mean (SD))*	57 (6.9)	55.5 (7.8)	NS
Aneurysm*	11	26	NS
LVEF $\leq 40\%$ †	24	45	NS
Aneurysm†	17	55	<0.01
Ventricular arrhythmias‡	26	50	<0.05

C:T, cardiothoracic ratio; METs, metabolic equivalents; WMSI, wall motion score index; LVEDD, left ventricular end diastolic diameter.

*Echocardiographic data. †Radionuclide data. ‡24 hour electrocardiogram.

Relative risk of death

The relative risk of death for a given variable is the ratio of the mortality observed for the group with this factor to the mortality observed for the group without this factor. It was calculated for all variables showing a statistically significant predictive value for at least one of the periods investigated—that is two months, 12 months, and from two to 12 months (table 6).

Comparison of the relative risks of death for the three periods showed large intravariation differences between the periods and intervariable differences for

Table 6 Relative risk calculated at two and 12 months (for the entire population and for patients surviving for the first two months)

Variables	2 months	0-12 months	2-12 months
Hypertension	2	2.1	2.3
Early heart failure	23.8*	4.2*	2.2
Bundle branch block	4*	2.4*	1.8
x ray C:T $\geq$ 50%	8.5*	5.7*	5.1*
Late heart failure	4.4*	3.2*	2.9
Digoxin	6.2*	3.2*	3.1
METs < 3	2.4*	4.0*	6.4*
WMSI > 22†	17.5*	3.8*	1.7
Aneurysm†	3	2.6*	2.6
LVEF < 40%‡	7.9*	3.3*	2.4
Aneurysm‡	3.8	3.4*	3.4*
Ventricular arrhythmias§	1.7	2.2	2.6*

C:T, cardiothoracic ratio; METs, metabolic equivalents; WMSI, wall motion score index; LVEF, left ventricular ejection fraction.

*Predictors of mortality that were statistically significant by univariate analysis. †Echocardiographic data. ‡Radionuclide data. §24 h electrocardiogram.

the same period. At two months, the highest risks were associated with early heart failure (23.8) and an x ray cardiothoracic ratio of $\geq$ 50% (8.5) (for the clinical factors) and a wall motion score index above 22 (17.5) and an isotopically determined left ventricular ejection fraction $\leq$ 40% (17.9) (for the non-clinical variables). For all but two factors the relative risk at 12 months for all patients was lower than the relative risk at two months. For metabolic equivalents and arrhythmias the relative risk rose (from 2.4 to 4 and from 1.7 to 2.2 respectively). The decrease in risk was especially pronounced for the two factors that had the highest scores at two months, namely, early heart failure (decreasing from 23.8 to 4.2) and a wall motion score index above 22 (falling from 17.5 to 3.8). When the risks at 12 months for all of the patients included in the study were compared with those who survived the first two months there was a further decrease in the relative risk for most of the variables. The relative risk remained almost unchanged for the presence of an aneurysm but increased for the metabolic equivalents and ventricular arrhythmias.

Table 7 Independent predictors of death determined by multivariate analysis at two and 12 months follow up (for all patients and for the group surviving the first two months)

Variables	Standardised coefficient at:		
	2 months	12 months	2-12 months
Early heart failure	0.74***	0.35***	—
x ray C:T $\geq$ 50%	0.41**	0.57***	0.61**
METs	—	-0.46***	-0.57***
Aneurysm (radionuclide)	—	—	0.31*

C:T, cardiothoracic ratio; METs, metabolic equivalents.

*p < 0.05; **p < 0.01; ***p < 0.001.

MULTIVARIATE ANALYSIS

Stepwise discriminant analysis was performed at two months; it was repeated at 12 months for the entire sample group and for those who survived the first two months.

The following variables were introduced in the discriminant function in the first step: early heart failure, x ray cardiothoracic ratio, number of metabolic equivalents reached during the stress test, radioisotopically determined left ventricular ejection fraction, bundle branch block, wall motion score index, and ventricular arrhythmias. Except for heart failure, these variables were weakly correlated (maximum 0.30).

The following independent predictors of death listed by order of entry, emerged: at two months—early heart failure (standardised coefficient 0.74, p < 0.001) and x ray cardiothoracic ratio $\geq$ 50% (0.35, p < 0.01); at 12 months—early heart failure (0.35, p < 0.001), x ray cardiothoracic ratio $\geq$ 50% (0.57, p < 0.001), and the number of metabolic equivalents during the stress test (-0.46, p < 0.001). When the 12 month follow up was limited to those who survived the first two months, early heart failure disappeared as an independent predictive factor. Two variables remained significant. These were, by order of entry, x ray cardiothoracic ratio $\geq$ 50% (0.61, p < 0.01) and the number of metabolic equivalents (-0.57, p < 0.001), while a ventricular aneurysm detected by the radionuclide method was an independent predictive factor (0.31, p < 0.05). Heart failure, which was highly correlated with the other factors, was excluded in the second step. The same variables remained significant (table 7).

Discussion

A previous study of 202 patients emphasised the predictive value of simple clinical and non-invasive factors at two months.¹ The present study, including the first 202 patients and extended to 306 patients and in which all factors retained their earlier significance, confirmed the results of the first study.

The 12 month extended follow up, with only one patient lost to follow up, showed that the same factors continued to be of prognostic value, especially those that were indicative of impaired left ventricular function—that is early heart failure, an enlarged heart by radiography, a score < 3 metabolic equivalents during exercise testing, the echocardiographically determined wall motion score index, left ventricular ejection fraction, and the presence of an aneurysm (radionuclide method). A history of hypertension became significant. Nevertheless, the relative risk of death for all but two of the factors was lower at 12 months than at two months.

We did not find any relation between ST change and mortality, contrary to other investigators' reports.¹⁰⁻¹² Surprisingly, ST changes > 1 mm were more frequent among the survivors. Methodological differences, lower exercise levels (for the patients' safety, testing was stopped if relatively mild subjective and objective signs developed, as confirmed by the low maximum heart rate), and the administration of β blockers and digoxin may account, at least partially, for these differences. Nevertheless, the exercise test was carried out between days 10 and 12 in 96% of our subjects and was thus representative of the entire sample. Furthermore, others have reported the lack of correlation between ST segment changes and survival¹³⁻¹⁵ and bypass surgery performed in some of the patients during the first year of follow up may reduce the predictive value of ST depression.¹²⁻¹⁵ Fifty two of our patients had coronary artery bypass grafts between two and 12 months; the decision to operate was prompted by the results of the exercise test. Of this group, 61% showed significant ST depression during exercise. The 24 hour electrocardiographic monitoring was done rather early (between days 10 and 12), which may also account for the lack of prognostic value at two months.¹

When the 12 month follow up was limited to the two month survivors, most of the predictive factors were no longer discriminant (only four out of the 14 were still useful), while the relative risk of death associated with most of the factors declined.

The different statistical methods used (univariate and stepwise discriminant analysis) and relative risk calculations gave similar information. Specifically, the changes in the values of the different factors studied for the three follow up periods followed similar patterns.

The prognostic factors and indices were generally evaluated at 12 months after the acute event. While the results of our 12 month follow up were consistent with current knowledge for most of the variables, the study showed that the one year significance of most of the prognostic factors was influenced by the strength of their ability to predict death at two months. When the very ill patients who died within the two month follow up period were excluded, the findings for the remaining subjects for the two to 12 month follow up period were quite different. This explains why most prognostic variables lost their statistical significance. It is clear that the short term prognosis correlated strongly with the variables related to the size of the infarcted area and the degree of left ventricular dysfunction. After the two month period the long term prognosis is probably most dependent on other factors, such as the course of coronary disease. Further investigations at the end of the second month would probably improve the accuracy of the one year prognosis.

In conclusion, our findings show that the predictive value of most of the predischARGE clinical and technical data gathered on acute myocardial patients and used in establishing the 12 month prognosis is only valid in the short term. For two month survivors, more useful information could perhaps be gleaned from data obtained at that time.

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