

PREDISCHARGE ASSESSMENT OF PROGNOSIS AFTER MYOCARDIAL INFARCTION

BEPALING VAN DE PROGNOSE NA MYOCARD INFARCT
BIJ ONTSLAG UIT HET ZIEKENHUIS

PROEFSCHRIFT

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To the memory of my father

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CHAPTER 1

INTRODUCTION

CHAPTER 1

INTRODUCTION

Now that so many therapeutic modalities have become available, the identification of 'excess risk' in established coronary artery disease is an important step in secondary prevention in cardiology, in particular in patients after a recent myocardial infarction. Risk is here defined as the probability of mortality in the individual patient during a given period of time - and depends on different prognostic factors. The probability of mortality has to be derived from the relative frequencies of death in groups of patients observed in follow up studies, where the analysis focusses on relating the outcome to prognostic variables by means of statistical models. For economical reasons this risk identification should be carried out in the most 'efficient' way. The most 'efficient' way is defined here as the greatest information at the lowest possible cost. In fact, cost containment has become an important issue in cardiology in the past decade¹, a period where we have witnessed a rapid increase of the armamentarium available to the cardiologist for the evaluation of cardiac function. Non-invasive as well as invasive methods, such as echocardiography, radionuclide studies, electrophysiological studies, exercise tests and coronary angiography, all have proven to have some prognostic value in post-infarct patients. However, important questions remain: which of these tests are the most predictive? Do we need all of them in every patient? Do they provide relevant additional information for clinical management beyond that of usual routine clinical and laboratory findings such as demographic data, clinical history, physical examination, blood samples, 12-lead electrocardiogram and chest X-ray which are routinely available for all patients?

So far, few studies have addressed this problem in a sizable population of post-infarction patients studied at discharge with each of these test modalities².

The need to identify individuals with increased as well as negligible risk of mortality requires the following:

1. Optimal patient evaluation with the minimal number of tests, preferably of the non-invasive and low cost type;
2. Reassurance of those patients at low risk and "discharge" from the

system;

3. Risk modifications in patients with high and intermediate risk indicators by timely and appropriate intervention;

While the first two points can be achieved relatively easily, the third point is much more difficult. Can something be done to reduce the risk in patients with high and intermediate risk, once they are so identified? The answer must be positive since in the last few years, many large trials with drugs or mechanical interventions, such as coronary artery bypass surgery, have shown improved survival. Some secondary prevention trials, with different drugs, have shown mixed results^{3,4}. Trials with anti-arrhythmics^{5,6}, anticoagulants⁷⁻¹¹ and, with some exceptions, aspirin¹²⁻¹⁶ and sulfilpyrazone¹⁷⁻¹⁹, have failed to reduce the mortality rate after myocardial infarction in a significant manner.

In contrast it has been shown in numerous studies with beta-blockers, that they reduce cardiac mortality after myocardial infarction significantly³. In particular, the Beta Blocker Heart Attack Trial (BHAT)²⁰, and the MIAMI trial²¹ suggested that beta-blockers provided higher mortality reduction in the patients at highest risk, that is in those patients with most evidence of left ventricular dysfunction, while in the lowest risk groups, no major benefit could be demonstrated.

These data suggest that, while many physicians in practice treat with beta blockers low risk patients who will be unlikely to benefit in term of reduced mortality, it is the high risk patient who should to be treated with beta blockers, unless overt clinical signs or symptoms of left ventricular dysfunction provide a contraindication. Again, therefore a need to stratify.

Coronary revascularisation by coronary artery bypass grafting^{22,23} and, more recently percutaneous transluminal coronary angioplasty²⁴, have been shown to improve the prognosis of some subsets of postinfarct patients and this is another reason to classify patients after myocardial infarction appropriately. In a recent article, Julian reviewed the three most important coronary artery surgical trials²³, the Veteran Administration Study²⁵, the European Coronary Artery Surgery Study⁸ and the Coronary Artery Surgery Study²². He concluded²³ that "we can be reasonably confident that surgery improves prognosis in certain groups of patients with ischemic heart disease. The ones most likely to benefit are those with disease of the left main coronary artery and those with three vessel

disease or two vessel disease in which the proximal left anterior descending coronary artery is involved. Arteriography alone, however, provides an inadequate guide to prognosis, as it seems that surgery is most helpful when such anatomical features are accompanied by evidence of left ventricular dysfunction at rest or on exercise". He finally points out that, limited to patients with angina, "physicians should consider the possible effect of surgery on prognosis. In doing so, they should take into account symptoms and non-invasive indexes of left ventricular function, particular the response to exercise. If these features indicate a substantially worsened prognosis, coronary arteriography should be undertaken if the surgical approach seems a reasonable option". However, the large coronary artery surgery trials include a different population than that of the present study, which only consists of post-infarction patients evaluated at hospital discharge. Therefore, it is uncertain if the results of such trials completely apply to such a group, although the problem of residual ischemia is identical.

The development of coronary angioplasty in the last few years has provided a new and powerful tool for treatment for patients with coronary artery disease, which has been applied with success also in post-infarct patients with post-infarct angina²⁶. Its impact on relief of stable angina pectoris is already well established. The potential for improving prognosis by this technique appears promising but has not yet been proven.

All these observations underscore the importance of the non invasive, identification of the high-risk individuals. A clear protocol for those who should be referred for invasive evaluation is particularly important for the physician in district hospital who does not have immediate access to coronary arteriography.

Patient population and methods

In order to answer the questions posed earlier, we established a computerized data base which included the data obtained during hospitalization of 706 consecutive patients with a proven acute myocardial infarction, who had been admitted to the coronary care unit of the Thoraxcenter between March 1981 and December 1983. At hospital discharge all patients underwent symptom limited bicycle ergometry, unless contra-indicated. Five hundred and twenty patients also underwent resting radio-nuclide ventriculography and 24-hour ambulatory electrocardiographic

monitoring was performed in 389 patients. The latter two tests were not completed in all patients for organizational reasons, especially in the first year of the study and, in a few cases, because of refusal of the patients. We chose these three tests because they provide information on left ventricular function, myocardial ischemia and ventricular arrhythmias, and they allow quantification of the response to the tests.

Radionuclide ventriculography was chosen for the assessment of left ventricular function since it provides quantitative information of left ventricular ejection fraction in virtually all patients. Echocardiography provides in principle similar information, however quantification is possible in a lower percentage patients, of about 75%. For this reason echocardiography was not used in this study. After discharge, patients were followed for one year, mostly by regular out-patient visits. Only 6 patients were lost to follow-up. This data base therefore has been created prospectively and encompasses the complete spectrum of patients admitted to the Thoraxcenter with acute myocardial infarction over several years. The data base includes demographic and routine clinical variables collected during the different phases of hospitalization, variables from bicycle ergometry, variables from radionuclide ventriculography to include global left ventricular function and regional wall motion, variables from 24-hour ambulatory electrocardiographic monitoring and variables regarding follow-up (appendix A). Ten variables regarding left ventriculography and coronary angiography were also collected in those patients who underwent cardiac catheterization, even though cardiac catheterization was not the main part of this study.

Even if the primary aim of this study was that of finding the most 'efficient' procedure based on clinical and non-invasive tests for risk assessment, such a large and rather complete data base, allowed ancillary questions to be answered which arose while the study was underway. In fact we realized that one advantage of such a data base is that, if it is properly designed and maintained, one is not confronted with the need for creating a separate data collection and analysis system whenever a new problem or question is encountered.

An analysis of these results has been performed for the complete group of 706 patients in 2 of the reported studies (chapter 3 and 4), while the other chapters refer to the patient data collected during the first two years of the study, to include subsets of patients, as summarized in table 1. Actually, other reports have been published with even smaller numbers

Table 1: PATIENT POPULATION INCLUDED IN THE DIFFERENT STUDIES.

CHAPTER	ENTRY PERIOD	CCU ADMISSIONS with AMI	NUMBER OF PATIENTS	PREDICTORS STUDIED
2	March '81 - Dec. '82	529	405	- clinical variables - bicycle ergometry
3	March '81 - Dec. '83	706	449	- clinical variables - bicycle ergometry - radionuclide ventriculography - 24-h ECG monitoring
4	March '81 - Dec. '83	706	474	- clinical variables - 12-lead ECG
5	March '81 - Dec. '82	529	266	- peak serum CPK (in first infarction)
6	March '81 - Dec. '82	529	119	- clinical variables - bicycle ergometry after a first uncomplicated infarction.
7	March '81 - Dec. '82	529	68	- early post infarct angina: coronary artery bypass surgery versus medical therapy.

Abbreviations: AMI: acute myocardial infarction; ECG: electrocardiography;
CCU: coronary care unit; CPK: creatine phosphokinase;
24-h ECG: 24 hour ambulatory electrocardiographic monitoring.

of patients. They are not part of this thesis, but for completeness sake we report the abstracts of four of these in the appendix B. The role of table 1 is to demonstrate that the subsets of patients in the different studies are part of the total data base and can be considered to be representative.

Specific aim of the study

This study is a description of the follow up during the first year of 706 consecutive patients admitted at from the coronary care unit of the Thoraxcenter with a proven diagnosis of acute myocardial infarction between March 1981 and December 1983.

The main aim, outlined in this chapter, was to assess the relative value of the usual clinical variables compared to that of multiple non-invasive tests at discharge to predict survival after hospital discharge .

In chapter 2 we addressed the problem of comparing clinical variables and pre-discharge bicycle ergometry results to predict mortality and other non-fatal events during follow up. Patients judged non eligible for stress test were separately analyzed.

In chapter 3 we assessed the relative merits of clinical data, bicycle ergometry, radionuclide ventriculography and 24-hour ambulatory electrocardiographic monitoring to predict one year survival.

Since the 12-lead electrocardiogram is always performed at discharge and since there has recently been renewed interest in the prognostic value of the electrocardiogram in post-infarction patients, we studied in chapter 4 the prognostic value of different variables derived from the electrocardiogram. In particular the risk estimation compared to that obtained from other clinical variables was analyzed.

In chapter 5 the follow up is described during the first year of patients with a first myocardial infarction, in terms of their peak serum creatine phosphokinase. The rationale for that analysis was to test whether patients with a small initial infarct were subject to more or fewer ischemic events during follow-up, compared to those with intermediate or large size infarctions.

The prognosis of patients below 60 years who survived the hospital phase of a first myocardial infarction with an uncomplicated clinical course, was investigated in Chapter 6. Here the role of exercise testing in guiding the decision to proceed with coronary angiography formed the

main study object.

In chapter 7 a description is given of the clinical course of 34 patients who underwent coronary artery bypass surgery before hospital discharge, mostly because of "early" post-infarction angina. Their sequential events were compared to those of all other post-infarction patients and also with a subset retrospectively matched on the basis of demographic, clinical, ventriculographic and coronary angiographic data. The study was undertaken to assess the risk of coronary artery bypass surgery in the 'early' post-infarction patients with that of a similar group of patients treated medically.

In chapter 8 the recommendations are summarized for the assessment of post-infarct patients at hospital discharge, based on the results of these data and in the current experience in our hospital.

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CHAPTER 2

PREDICTION OF MORTALITY DURING THE FIRST YEAR AFTER
ACUTE MYOCARDIAL INFARCTION FROM CLINICAL VARIABLES
AND STRESS TEST AT HOSPITAL DISCHARGE.

By

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Prediction of Mortality During the First Year After Acute Myocardial Infarction from Clinical Variables and Stress Test at Hospital Discharge

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The predictive value of a predischarge symptom-limited stress test was studied in 405 consecutive survivors of acute myocardial infarction (AMI). Three hundred patients performed bicycle ergometry; 105 could not perform it. Among these latter 105 patients, the stress test was contraindicated in 43 because of angina or heart failure and in 62 because of noncardiac limitations. One-year survival was 44% in the "cardiac-limited" group (19 of 43) and 92% in the "non-cardiac-limited" group (57 of 62). One-year survival among the patients who performed an exercise test at discharge was 93% (280 out of 300). The best stress test predictor of mortality by univariate analysis was the extent of blood pressure (BP) increase: 42 ± 24 mm Hg in

280 survivors vs 21 ± 14 mm Hg in 20 nonsurvivors ($p < 0.001$). Among the 212 patients in whom BP increased 30 mm Hg or more, mortality was 3% ($n = 6$), while it was 16% ($n = 14$) among the 88 patients in whom BP increased less than 30 mm Hg. Angina, ST changes and arrhythmias were not as predictive. Stepwise discriminant function analysis showed inadequate BP increase to be an independent predictor of mortality. A high-risk group can be identified at discharge on clinical grounds in patients unable to perform a stress test, whereas intermediate- and low-risk groups can be identified by the extent of BP increase during exercise.

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Predischarge stress testing of hospital survivors of acute myocardial infarction (AMI) has become a routine procedure.¹⁻³ The stress test is considered a useful examination to individualize medication, specify subsequent activity programs⁴ and to establish the prognosis.^{5,6} However, only few studies have been designed to assess whether the stress test provides additional information independent of clinical data alone.⁶⁻⁸ Furthermore, little attention has been given to the definition of the baseline characteristics and the follow-up of patients who cannot perform the bicycle ergometry test. This prospective study assesses whether the test provides additional information beyond clinical data alone

in the prediction of mortality and other cardiac events during the first year.

Methods

We analyzed the records of 529 consecutive patients admitted to the coronary care unit of the Thoraxcenter between March 1, 1981, and December 31, 1983, with a diagnosis of AMI before their discharge. Diagnosis of AMI was based on at least 2 of the following criteria: (1) Typical prolonged chest pain at least 45 minutes in duration. (2) In transmural AMI, dynamic electrocardiographic changes such as evolving Q waves longer than 0.04 second with ST and T changes or in nontransmural AMI, T-wave inversion or ST depression persisting for at least 24 hours without new Q waves. Site was classified as undetermined in the case of complete left bundle branch block. (3) Typical increase and decrease of total serum creatine kinase level with a peak level of more than 100 IU/liter (twice the upper limit of normal values in this laboratory). Previous AMI was diagnosed by a history of AMI or diagnostic Q-wave abnormalities. During their hospital stay 72 patients died. Thirty-two patients underwent coronary artery bypass grafting and 16 underwent percutaneous transluminal coronary angioplasty before discharge for post-AMI angina re-

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TABLE I Baseline Characteristics of Patients Population, Subdivided According to Eligibility for Stress Testing

	No Stress Test		Stress Test Performed
	Cardiac Limitations	Noncardiac Limitations	
No. of pts	43	62	300
Age (yr)*	65 ± 9	66 ± 10	54 ± 10
Men (%)	74	63	84
Previous AMI (%)	56	26	27
Anterior AMI (%)	53	29	36
Killip class I (%)	23	68	74

* Mean ± standard deviation.

AMI = acute myocardial infarction.

fracture to medical therapy. Four patients required surgery for mechanical myocardial dysfunction.

To avoid a bias in interpretation of the results, these patients were excluded from the follow-up results. Of the remaining 405 patients participated in the study, 105 patients were judged ineligible for the test: 43 because of cardiac limitations (7 with angina and 36 with persistent heart failure) and 62 for noncardiac limitations (9 with peripheral vascular disease, 7 with lung disease, 5 with cerebrovascular disease, 5 with musculoskeletal disease, 22 with general disability and 14 for other medical noncardiac limitations). Advanced age was not considered a contraindication for the stress test. Some clinical characteristics of our patients are given in Table I. The median hospital stay was 15 days (range 7 to 70). Medication usage at discharge is detailed in Table II. Metoprolol, 50 or 100 mg twice daily, was given, when indicated, for angina or hypertension and also as a secondary preventive agent provided there were no contraindications or side effects.⁹

Before discharge, on average 13 days after AMI, a symptom-limited stress test with stepwise increments of 10 W/min was performed on a bicycle ergometer in 300 patients. Three Frank leads were constantly recorded and analyzed by a computer system.¹⁰ Blood pressure (BP) was measured every 2 minutes during exercise and during the recovery phase. The clinically prescribed medication was not discontinued before the test.

One hundred forty-five patients also underwent coronary angiography at discharge, 49 electively and 96 because of a study protocol, including patients in cardiogenic shock and those included in an ongoing randomized trial with intracoronary streptokinase.¹¹ After hospital discharge all patients were followed for 1 year by regular outpatient visits.

Statistical analysis: Univariate analysis with unpaired Student *t* test for continuous variables and chi-square or Fisher's exact test, were applied when appropriate, for the discrete variables. To compare and visualize the predictive value for mortality of different continuous variables, we used receiver-operator characteristics curves (ROC curves). In these curves, sensitivity vs specificity of a test are plotted, where sensitivity is a fraction of positive classification for all patients who satisfy the endpoint criteria and specificity is the fraction of all negative classifications for all patients who satisfy the non-endpoint criteria. These curves, when generated for different tests, provide a direct comparison of their results over the entire range of measurements.

In patients eligible for stress testing, the BMPD statistical package for stepwise discriminant analysis (P7M) was used to generate classification functions for 3 classes of information: clinical data only, exercise stress test data only, and clinical data and exercise stress test combined. The clinical variables consisted of age, sex, presence of a previous myocardial in-

TABLE II Medication at Hospital Discharge

	No Stress Test		Stress Test Performed
	Cardiac Limitations	Noncardiac Limitations	
Digitalis (%)	65	27	18
Diuretics (%)	76	45	31
Vasodilators (%)	56	34	29
β blockers (%)	15	27	52
Antiarrhythmics (%)	14	8	3
Anticoagulants (%)	53	29	14

farction, anterior location of the index infarction, the worst Killip class in the coronary care unit, angina pectoris present during the hospital stay, late sustained ventricular tachycardia, persistence of congestive heart failure after the stay in the coronary care unit, cardiomegaly on discharge (cardiothoracic ratio greater than 50%), and indication for digoxin or diuretic drugs at discharge. The exercise stress test variables included percent of predicted work capacity achieved, the workload achieved, angina pectoris present during the test, ventricular arrhythmias during the test, ST-segment depression, ST elevation (≥ 1 mm), extent of BP change during the test and maximal heart rate. The endpoint of major interest was cardiac mortality during the follow-up period. In a first pass, stepup analysis was done using an F to enter 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 to enter of 4.0. 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 in the discriminant function resulting in the specificity-sensitivity plots (ROC curves).

Results

Follow-up results: Complete follow-up information was available in all 405 patients. After discharge 49 patients (12%) died during the first year: 32 suddenly, 8 from a fatal reinfarction, 7 from progressive heart failure and 2 perioperatively after coronary artery bypass surgery. During the same period 18 patients (4%) had a nonfatal reinfarction; 33 underwent elective coronary artery bypass surgery, 5 other cardiac surgery and 5 percutaneous transluminal coronary angioplasty.

Prediction of mortality from clinical data in all patients: A comparison of medical history and clinical data between survivors and nonsurvivors is summarized in Table III. Univariate analysis indicates that late mortality was strongly associated with clinical variables that indicated a more advanced left ventricular dysfunction and less related to angina pectoris. The mortality rate was highest (24 deaths [57%]) among the 43 patients who could not perform the test because of cardiac limitations. The mortality rate among the 62 patients who could not perform the test for other reasons (5 deaths [8%]) was similar to that in 300 patients eligible for the test (20 deaths [7%]). The discriminant function analysis (Table IV) resulted in 4 independent variables predictive of mortality. The strongest predictor was the noneligibility for stress testing because of cardiac limitations, followed by the use of digitalis on discharge, a history of a healed AMI and cardiomegaly on chest radiograph.

Prediction of mortality from stress test data by univariate analysis: The stress test results of survivors and nonsurvivors are represented in Table V. ST changes were not significantly associated with mortality; in contrast, the extent of BP increase was; it was twice as high in survivors as in nonsurvivors. The predictive value for mortality of several stress test results are represented in Figure 1 as ROC curves. The distribution of mortality in patients eligible and in those not eligible for stress testing is summarized in Figure 2. The ROC curves in Figure 1 suggest that the most "advantageous" cutoff point of BP increase, i.e., that with the highest sensitivity and specificity, is 30 mm Hg. In this way a subgroup of 212 patients was identified that had a very low risk (mortality 3%, n = 6) provided they had a BP increase of 30 mm Hg or more (Fig. 2).

Prediction of cardiac events in patients eligible for stress test from clinical data and stress test results, by multivariate analysis (Table IV): The discriminant function analysis using exclusively the clinical information described in the Methods section resulted in 2 independent variables predictive of mortality at the 0.05 level of significance: history of a healed AMI and the use of digitalis on discharge (65% correct classifications). Similarly, using exclusively the exercise stress test data, only the BP change (the absence of a sufficient increase in BP during testing) was associated with mortality at the 0.05 level of significance (64% correct classifications). Combining both clinical and exercise information in the analysis resulted in the inclusion of the 3 above-mentioned variables with 76% correct classifications. The results of the sensitivity-specificity analysis with variable decision levels for classification are shown in Figure 3 and Table IV. When nonfatal reinfarction was added to mortality as the endpoint, the stress test lost its independent prognostic value relative to clinical information. However, stress test results appeared to have independent predictive value when other endpoints were added, such as late coronary artery bypass surgery, coronary angioplasty

TABLE III Differences in Historical and Clinical Data Collected During Hospital Stay Between Late Survivors and Nonsurvivors

	Survivors	Nonsurvivors	p Value
No. of pts	356	49	
Men (%)	80	77	NS
Age (yr)*	56 ± 11	62 ± 12	0.002
Previous angina (%)	15	24	NS
Previous AMI (%)	25	65	0.001
Anterior AMI (%)	36	41	NS
Peak CK, IU/liter*	583 ± 500	586 ± 491	NS
Killip class III or IV (%)	6	26	0.001
Late heart failure (%)	14	45	0.001
Late VT or VF (%)	4	12	0.02
Cardiomegaly (chest x-ray) (%)	19	57	0.001
Post-AMI angina (%)	15	24	NS
Discharged on digitalis (%)	19	67	0.001
Discharged on diuretics (%)	34	69	0.001
Discharged on β blockers (%)	47	22	0.001

* Mean ± standard deviation.
AMI = acute myocardial infarction; NS = not significant; VF = ventricular fibrillation; VT = ventricular tachycardia.

and persistent congestive heart failure. ST depression during stress testing did not provide independent additional information for any of the endpoints considered.

Discussion

Many studies have examined the prognostic value of predischARGE stress testing after AMI.² Only a few,^{5,7} however, include a detailed description of patients not eligible for the test or have tried to determine whether stress testing provides independent prognostic information compared with clinical variables alone. In our study group, after exclusion of patients who underwent coronary artery bypass surgery or percutaneous transluminal angioplasty for unstable angina (10% of discharge patients), 26% were judged not eligible for the stress testing (11% for cardiac and 15% for noncardiac limitations). The percentage of patients not eligible for the test in our study is somewhat lower than that previously reported.^{6,7} Consistent with the findings of Madsen and Gilpin⁶ and DeBusk et al,⁷ we also found a higher mortality in this group, which was further enhanced by subdividing the patients according to the contraindication (cardiac vs noncardiac). Patients with cardiac contraindications, usually heart failure, had a mortality rate of 57%. In contrast, the mortality rate of

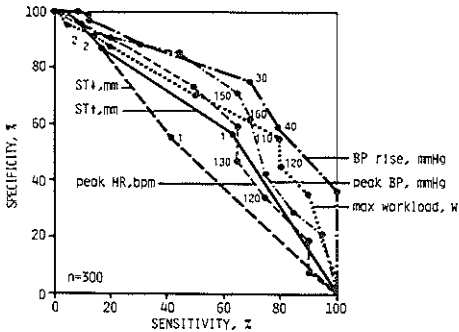


FIGURE 1. Specificity vs sensitivity for late mortality of exercise testing-derived data: maximal workload, peak heart rate (HR), peak systolic blood pressure (BP), systolic BP increase, ST elevation (ST↑) and ST depression (ST↓).

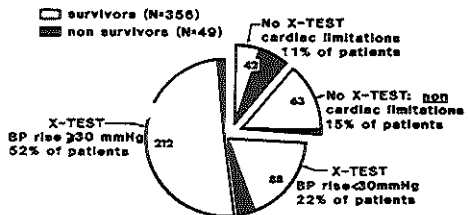


FIGURE 2. Incidence of mortality and exercise test (X-test) results. BP = blood pressure.

TABLE IV Prediction of Cardio Events During Follow-Up by Discriminant Function Analysis

	All Patients Death C	Patients Eligible for Stress Test											
		Death			Death or RMI			Death or RMI or CABG or PTCA			Death or RMI or CABG or PTCA or CHF		
		C	X	C + X	C	X	C + X	C	X	C + X	C	X	C + X
Clinical variables (F ratio)													
Previous AMI	24	31	...	27	13	...	13	14	...	16	11	...	10
Killip class > III or IV	12	...	11
Post-AMI angina	5
Cardiomegaly (chest x-rays)	7
Discharged on digitalis	25	33	...	27	34	...	34	18	...	19	28	...	20
Cardiac contraind. for x-test	47
X test variables (F ratio)													
BP rise	14	5	...	5	8	20	9
Max. workload
Ventricular arrhythmias	5	...
ST elevation	5	5	5	5
Angina	8	13
No patients													
Total	405		300			300			300			300	
Endpoint	49		20			36			60			80	
Non endpoint	356		280			264			240			220	
Predictive accuracy (%)													
Sensitivity	69	90	70	85	72	59	72	63	63	65	65	65	65
Specificity	93	63	63	75	64	57	64	65	66	75	67	61	75
Pred. value positive	58	15	12	20	21	15	21	31	30	38	42	37	48
Pred. value negative	96	99	97	98	94	91	94	88	88	90	84	83	86
Total correct classification	90	65	64	67	65	57	65	65	65	73	66	62	72
High-risk group	14	40	38	28	40	45	40	40	40	32	41	46	35

F ratio is the relative importance of each variable. C, X and C + X indicate that the prediction of the events is based on clinical information (C), stress testing results (X) or both (C + X).

Pred. value positive (negative) = predictive value of positive (negative) test. Total correct classification = number of patients correctly classified/total population. High risk group = number of patients with a positive test/total population.

AMI = acute myocardial infarction; BP = blood pressure; CABG = coronary artery bypass grafting; CHF = congestive heart failure; contraind. = contraindications; Max. = maximal; PTCA = percutaneous transluminal coronary angioplasty; RMI = nonfatal reinfarction.

patients not eligible for the test for noncardiac limitations and those eligible for the test had a low risk (8% and 7%, respectively). During 1-year follow-up, 20 of the 300 patients eligible for stress testing died. An adequate BP increase during exercise was the best single predictor of mortality (Tables IV and V); this confirms our previous observations in a smaller group of 167 patients.³ We did not confirm the association between stress test-induced ST depression and late mortality or nonfatal reinfarctions, contrary to previous findings.^{1,7,12} This discrepancy may be a result of many factors, such as patient selection, different techniques of stress testing (different lead systems, bicycle ergometry vs treadmill) and treatment during follow-up. In particular, the prognostic significance of an ischemic response during stress testing may have been underestimated by coronary artery bypass surgery or coronary angioplasty performed during follow-up. In fact, these patients more frequently had stress test-induced angina ($p < 0.001$) and ST depression ($p < 0.02$) than patients treated medically. However study results have been reported that are consistent with our results and fail to show any predictive value of ST depression, but emphasize the stronger association between mortality and left ventricular function.^{5,6,13-17} Factors such as maximal workload, the duration of exercise^{5,6} or the BP response^{13,14} are good indicators of left ventricular function. Scardi et al¹⁴ found that a "hypertensive response," i.e., BP in excess of 200/100 mm Hg, identified a low-risk subset of patients.

Although the extent of BP increase is related to left ventricular function, there was no correlation with ejection fraction at rest. This is not surprising because left ventricular dysfunction can be often detected only during physical exertion. In this series, the 30 patients with 3-vessel disease had a smaller BP increase than the 92 with less extensive coronary artery disease (26 ± 22 vs 42 ± 23 mm Hg, $p < 0.001$). An important finding of our study is that only 6 of 212 patients who had a BP increase of 30 mm Hg or more died, while none of the 107 patients with a BP increase of more than 50 mm Hg died. This group of patients at very low risk should not be considered for special additional investigations.

The use of β -blocking drugs in 139 patients who performed stress testing could have affected the results of our study because of the blunting effect on the increase in arterial pressure. The BP increase was only slightly lower in patients taking β -blocking drugs (38 ± 22 vs 43 ± 25 mm Hg, $p < 0.04$); however, the predictive accuracy for mortality of a BP increase of 30 mm Hg or more was higher in patients not using β -blocking drugs during the test (80% correct classifications compared to 65% for the whole group of patients) (Table IV). Therefore, an inadequate BP increase when β -blocking therapy is not discontinued before the test should be interpreted with caution.

The issue of whether stress testing yields prognostic information independent of routinely available clinical data is important and controversial.⁶⁻⁸ When clinical variables and stress test results were combined, the predictive accuracy for late mortality was improved compared with each variable by itself (Fig. 3, Table IV).

TABLE V Summary of Stress Test Results

	Survivors (n = 280)	Nonsurvivors (n = 20)	p Value
Reasons for interrupting the test			
Fatigue (%)	75	65	NS
Angina (%)	6	5	NS
Dyspnea (%)	17	20	NS
Pressure drop (%)	2	10	NS
Max. workload (W)	115 ± 33	98 ± 24	0.05
Rest heart rate (beats/min)	81 ± 16	93 ± 20	0.01
Max. heart rate (beats/min)	132 ± 23	142 ± 26	0.01
Rest BP (mm Hg)	121 ± 16	122 ± 22	NS
Max. BP (mm Hg)	164 ± 29	144 ± 24	0.01
BP rise (mm Hg)	42 ± 24	21 ± 15	0.001
Angina pectoris (%)	20	20	NS
ST depression (%)	44	40	NS
Workload at ST depression (W)	83 ± 43	96 ± 30	NS
ST elevation (%)	41	60	NS
Ventricular ectopic activity (%)	20	35	NS

ST depression or elevation of 1 mm or more. Data are expressed as percent of patients or as mean ± standard deviation.

Abbreviations as in Table IV.

A sensitivity of 85% and a specificity of 76% was thus achieved. At variance with our results, Madsen and Gilpin⁶ found that the prediction of death was not improved by exercise data. In their study correct predictions ranged from 67 to 71% for survivors and from 60 to 66% for nonsurvivors. They did not consider the BP response, which in our experience and that of Scardi et al¹² was the single best predictor. DeBusk et al,⁷ in a more recent study, also found that stress testing had an independent predictive value for subsequent "hard events," including death and reinfarction. The paucity of deaths in their group of patients who underwent stress testing (7 of 338 patients) did not allow multivariate analysis to predict mortality alone. Therefore we cannot compare their results with ours.

When nonfatal reinfarction was added to mortality as the endpoint, stress test results lost independent

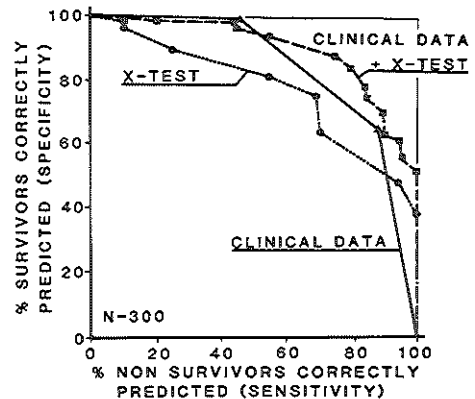


FIGURE 3. Specificity vs sensitivity for late mortality of discriminant function derived from clinical data alone, exercise test (X-test) alone and the combination of clinical and exercise test results.

predictive value relative to clinical variables.⁴ This is consistent with previous observations of our group and of others^{8,14,16} while Madsen and Gilpin⁶ found that stress testing provided a slight additional information. Stress testing gained again independent information when bypass surgery and/or coronary angioplasty were included on the endpoint (Table IV). This is not surprising, because these are not spontaneous events and the decision to perform these interventions is often influenced by the results of the stress test itself.

Implications: Patients who are not eligible for stress testing because of cardiac limitations have a high risk of dying during the subsequent year. These patients require intensive evaluation with other noninvasive methods and very careful management. Patients eligible for stress testing can be further stratified into low- and intermediate-risk groups by a combination of clinical and stress testing results; this combination improves the accuracy of the prognosis. Patients at very low risk do not require further investigation. Such attempts at stratification may allow for better utilization of increasingly costly health resources.

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ERRATA CHAPTER 2

Page 23: December 31, 1983 should be replaced by: December 31, 1982.

Page 26: Table IV: Killip class III or IV should be replaced by: Killip class III or IV.

CHAPTER 3

THE RELATIVE VALUE OF CLINICAL VARIABLES, BICYCLE
ERGOMETRY, RESTING RADIONUCLIDE VENTRICULOGRAPHY AND
24-HOUR AMBULATORY ELECTROCARDIOGRAPHIC MONITORING
AT DISCHARGE TO PREDICT ONE YEAR SURVIVAL AFTER
MYOCARDIAL INFARCTION.

By

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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.

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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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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	104 (14)
Discharged alive, with 1 year follow-up	596	72 (12)*
Lost to follow-up	6	—
Cardiac surgery or PTCA before discharge	76	2 (3)
Discharged on medical therapy	520	70 (13)*
With RV and XT	355	24 (7)
With RV and contraindication for XT	94	25 (26)
With RV, XT and 24 h ECG	293	19 (6)
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 min-

ute 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 \pm 10	62 \pm 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 \pm 481	590 \pm 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 post-infarction 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 4. Baseline Characteristics of 355 Patients Eligible and 94 Patients Not Eligible for Exercise Test, Treated Medically

	Eligible for Stress Testing	Not Eligible for Stress Testing	p Value
No. of patients	355	94	—
Age (yr)	54 ± 10	64 ± 9	0.001
Men (%)	83	69	0.005
Previous AMI (%)	23	40	0.001
Anterior AMI (%)	37	40	NS
Killip class >II (%)	5	24	0.0005
Late heart failure (%)	35	14	0.0005
Post-AMI angina (%)	28	16	0.01
Late VT or VF (%)	4	11	0.01
CTR >50% (%)	41	18	0.0005
Ejection fraction (%)	39 ± 16	47 ± 15	0.0005

Abbreviations as in Tables 1 and 2.

to predict survival were a blood pressure rise of 30 mm Hg for stress testing and an ejection fraction of 40%.

The discriminant function analysis (Table 5) using the clinical variables alone in the group of 355 patients eligible for stress testing resulted in two independent variables predictive of mortality at the 0.05 level of significance: a history of previous myocardial infarction and treatment with digitalis at discharge. The predictive accuracy was slightly improved when the result of stress testing, that is, extent of blood pressure increase, was included with the clinical variables. In contrast, radionuclide ejection fraction did not improve the prediction.

On the other hand, radionuclide ventriculography in patients ineligible for stress testing did provide an improvement in the prediction of survival compared with clinical variables alone, increasing the predictive value for mortality from 50 to 58%. The receiver-operator characteristic curves of the discriminant functions derived from clinical variables alone and combined with stress test and radionuclide results are shown in Figure 3 (patients eligible for the stress test) and Figure 4 (those not eligible). From these curves it appears that bicycle ergometry provides an improvement on the prognostic judgment compared with clinical variables alone in patients eligible for stress testing, while radio-

Table 5. Prediction of Cardiac Mortality by Discriminant Function Analysis in 449 Patients Studied With Radionuclide Ventriculography and Bicycle Ergometry (unless contraindicated)

	Patients Eligible for Stress Test			Patients Not Eligible for Stress Test	
	Clinical Variables	Clinical Variables + Stress Test	Clinical Variables + Stress Test + EF	Clinical Variables	Clinical Variables + EF
Nonsurvivors (n)	24	24	24	25	25
Survivors (n)	331	331	331	69	69
Clinical variables (F value)					
Previous AMI	18.4	15.4	15.4	5.1	—
Discharged on digitalis	22.6	18.6	18.6	—	—
CTR >50%	—	—	—	15.3	9.9
Late VT or VF	—	—	—	5.8	—
Stress testing (F value)					
SBP rise	—	5.4	5.4	—	—
Radionuclide ventriculography (F value)					
Ejection fraction	—	—	—	—	10.6
Predictive accuracy					
Sensitivity (%)	71	71	71	84	76
Specificity (%)	67	71	71	70	80
Predictive value positive (%)	13	15	15	50	58
Predictive value negative (%)	97	97	97	92	90
Total correct classification (%)	67	71	71	73	79
High risk group (%)	35	32	32	45	35
Risk ratio	4.4	5.2	5.2	6.5	5.9

EF = ejection fraction; other abbreviations as in Tables 1 and 2.

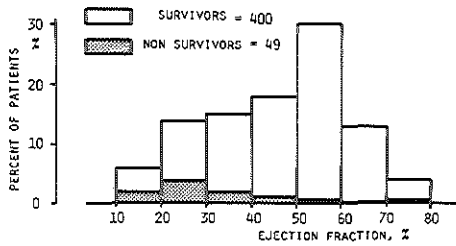


Figure 1. Histogram of ejection fraction relative to 1 year survival in 449 patients with acute myocardial infarction discharged receiving medical treatment.

nuclide ventriculography helps prognosis in those patients not eligible for exercise testing. However, it must be emphasized that bicycle ergometry and radionuclide ventriculography provide only a slight improvement beyond other routine clinical information.

Prediction of survival from clinical variables, radionuclide ventriculography, 24 hour ambulatory electrocardiographic monitoring and bicycle ergometry in 351 patients treated medically (Tables 6 to 8). The univariate analysis of these predictive variables was separately analyzed in patients eligible and not eligible for stress testing (Tables 6 and 7). Radionuclide ejection fraction was lower in patients not eligible for the stress test than in those eligible for the test (41 ± 15 versus $47 \pm 15\%$, respectively; $p < 0.01$). Patients with an ejection fraction of 40% or more ($n = 235$) had a mortality rate of 4% ($n = 9$) compared

Figure 2. Predictors of mortality after acute myocardial infarction. Specificity versus sensitivity for prediction of late cardiac mortality of radionuclide ejection fraction and exercise (X) testing (contraindication for the test or change of systolic arterial blood pressure [BP] during the test).

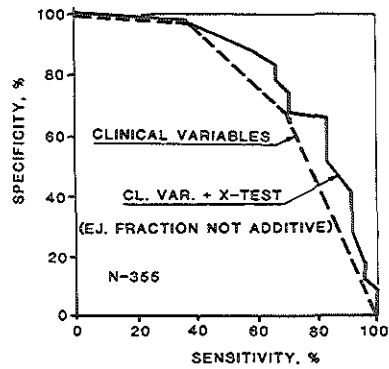
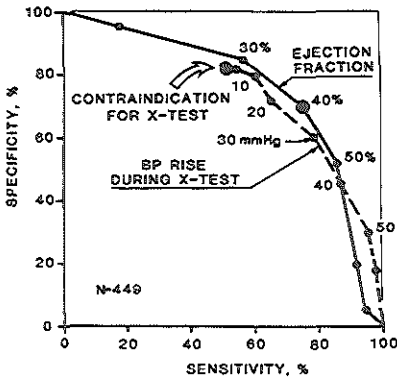


Figure 3. Specificity versus sensitivity for late mortality after acute myocardial infarction of discriminant function derived from clinical variables (CL. VAR.) alone and the combination of clinical and exercise (X) test results. EJ. = ejection.

with a mortality rate of 20% ($n = 23$) in 116 patients with an ejection fraction of less than 40%.

The presence of repetitive ventricular complexes (couplets or tachycardia) during 24 hour electrocardiographic monitoring was significantly associated with mortality only in patients not eligible for stress testing. In these patients the predictive value for mortality of repetitive ventricular complexes was 37%, compared with 9% in patients eligible for bicycle ergometry.

On the basis of the extent of blood pressure increase during stress testing, 204 patients at low risk (4% mortality

Figure 4. Specificity versus sensitivity for late mortality after acute myocardial infarction of discriminant function derived from clinical variables alone and the combination of clinical variables and radionuclide ventriculography, in 94 patients not eligible for stress testing. Abbreviations as in Figure 3.

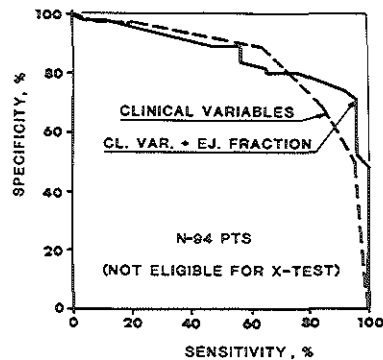


Table 6. Univariate Predictors of Mortality in 351 Patients With Complete Evaluation

	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									
Multi-form 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

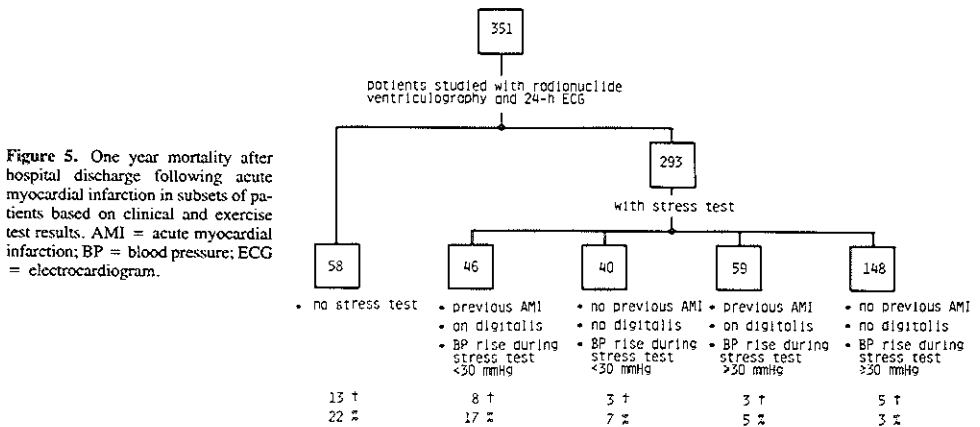
	All Patients		Patients Eligible for Stress Test		
	Clinical Variables	Clinical Variables + EF + 24 h ECG	Clinical Variables	Clinical Variables + Stress Test	Clinical Variables + Stress Test + EF + 24 h ECG
Nonsurvivors (n)	32	32	19	19	19
Survivors (n)	319	319	274	274	274
Clinical variables (F value)					
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 infor-

mation 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-



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 3). 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.

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CHAPTER 4

PROGNOSTIC VALUE OF PRE-DISCHARGE 12 LEAD ELECTROCARDIOGRAM AFTER MYOCARDIAL INFARCTION COMPARED TO OTHER USUAL CLINICAL DATA.

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ABSTRACT

The prognostic value of QRS score (Selvester), ST-depression, ST-elevation, premature ventricular contractions, P terminal force in V_1 and QTc from predischARGE 12 lead electrocardiogram, has been assessed in 474 patients after myocardial infarction without ventricular conduction defects and/or hypertrophy and/or atrial fibrillation. These results were compared with other usual clinical data for risk assessment. During follow-up 45 patients died.

By logistic regression analysis, QRS-score, ST-depression and QTc were independently predictive of cardiac mortality. However, when multivariate analysis was applied to clinical and electrocardiographic data, the 12-lead electrocardiogram did not provide independent information above other usual clinical and laboratory findings, such as a history of previous myocardial infarction, clinical signs of persistent heart failure, indication for digitalis or antiarrhythmic drugs at discharge, and enlarged heart on X ray. In conclusion, the electrocardiogram has important prognostic value, however it is not powerful enough to further improve the risk assessment of post-infarction patients.

Key words: 12 lead electrocardiogram, risk assessment after myocardial infarction.

INTRODUCTION

In the last few years cardiology has witnessed increased emphasis on a number of non-invasive as well as invasive tests which assess many different aspects of cardiac function. Some of these tests, (mainly related to the detection of myocardial ischemia, the quality of left ventricular function or the occurrence of ventricular arrhythmias) have been utilized to assess the risk of patients after myocardial infarction. However, it is apparent that there is considerable redundancy in information (1). Furthermore, since that many hospitals cannot support all these tests, which are costly and in some cases risky for the patient, it has become increasingly desirable to employ the usual clinical and laboratory findings in an optimal fashion.

Recently, different studies have shown that the 12 lead electrocardiogram has important prognostic value in patients after myocardial infarction (2-7). However, few studies have also included in their ana-

lysis, other clinical findings (2) or utilized a multivariate analysis for the prediction of survival. The routine 12 lead electrocardiogram could be a very attractive tool for risk assessment in postinfarction patients, as it provides information on the extent of myocardial damage (8), left atrium overload (7,9), presence of myocardial ischemia (2,10) arrhythmias (3) and electrical instability (4,5).

The aim of this study was to analyze the power of different variables extracted from predischARGE electrocardiogram to predict one year survival after myocardial infarction, and to establish whether they provide additional information beyond the routine clinical findings and tests. The study was based on 474 hospital survivors of myocardial infarction, without ventricular conduction defects, ventricular hypertrophy or atrial fibrillation.

PATIENTS AND METHODS

From March 1981 to December 1983, 706 consecutive patients were admitted to the coronary care unit of the Thoraxcenter with a confirmed diagnosis of acute myocardial infarction. Out of 602 hospital survivors, 474 patients formed the data base for this study (table 1). All these patients were followed up for one year with cardiac mortality as the end point. To predict mortality, we utilized different sets of information, derived from predischARGE 12 lead electrocardiogram and from the other clinical and laboratory findings obtained during the different phases of hospitalization.

Electrocardiographic variables.

Standard 12 lead electrocardiogram was obtained at discharge on a three channel Hewlett Packard 1513. A recorder at a paper speed of 25 mm/s. The following electrocardiographic variables have been measured: the presence of premature ventricular contractions, QRS score developed by Selvester (8), ST-depression (horizontal or downsloping) or elevation of one mm or more, P terminal force in V_1 (7,9), and QT-interval corrected for heart rate (QTc) (4,5). The measurements were performed by one cardiologist, blinded to the clinical outcome of the individual patients. In a previous study we showed a good agreement when QRS score was measured by two independent observers (6).

TABLE 1 Patient population.

	<u>N</u>	<u>1-year mortality</u>
<u>Admitted with acute myocardial infarction:</u>	706	174 (25%)
<u>Study group:</u>	474	45 (9%)
<u>Excluded from the study:</u>		
Hospital mortality	104	104
Lost to follow-up	6	-
Non-cardiac death	2	2
Missing or bad quality pre-discharge ECG	36	3 (8%)
With ventricular conduction defects or hypertrophy	8	19 (24%)
Atrial fibrillation	6	3 (50%)

Abbreviation : ECG : 12 lead electrocardiogram

Other clinical variables

The other "routine" variables consisted of age, sex, history of previous myocardial infarction, pre-infarction stable angina pectoris, the anterior location of the index infarction (Q-wave infarction), the worst Killip class while in the coronary care unit, early post-infarction angina, ventricular fibrillation any time before hospital discharge, "late" (72 hours or more after the infarction) ventricular fibrillation, "late" sustained ventricular tachycardia or supraventricular tacharrhythmias, persistent heart failure after discharge from the coronary care unit, resting heart rate at discharge, medication at discharge, cardiomegaly at discharge (cardiothoracic ratio > 50%) and radiological signs of pulmonary congestion. These variables were selected based on clinical experience and previous studies in our clinic. Other tests performed before discharge included radionuclide resting ventriculography in 417 patients, symptom limited bicycle ergometry in 340 patients and 24-hour ambulatory electrocardiographic monitoring in 310 patients, as previously described (1).

Cardiac catheterization with coronary arteriography was additionally performed in 235 of these patients for elective indications or as part of a randomized trial with intracoronary streptokinase (11-13). Medication at discharge included betablockers in 270 patients, digitalis in 94, diuretics in 166, antiarrhythmics in 17, nitrates or other vasodilators in 180 and calcium blockers in 128. Coronary artery bypass surgery was applied in 46 patients, and transluminal coronary angioplasty in 15 patients, before hospital discharge.

Statistical analysis

Univariate analysis for the different electrocardiographic and clinical variables was performed. Continuous variables were trichotomized. The 95% confidence interval (CI) for the respective risk ratio's (RR) were calculated according to Miettinen and Nurminen(10) with the first tertile considered as the reference group. If the 95% confidence interval exceeds 1, the association of the respective variable with the risk of dying within one year is statistically significant at the 5% level. For multivariate analysis the logistic regression model was used in order to predict mortality. Thus the objective was to find any combination of variables that predicted mortality to its nearest accuracy. As a general

principle, indicator variables were used. These are variables which assume the value of 1 if the property considered is present and 0 if absent. Continuous variables were trichotomized, so that indicator variables for the middle and high risk categories were considered for inclusion into the model. The BMDP package was used which selects stepwise predictor variables based on the maximum likelihood ratio (MLR). This provides a measure of significance and has an asymptotic chi-square distribution. Thus variables were included into the model, if they led to a substantial improvement of the log-likelihood ($P < 0.10$), or if their removal led to a substantial decrease ($p < 0.15$). Forward selection and backward elimination of the variables into the model yielded the same models.

Two models were developed, one based on the 12-lead electrocardiogram variables alone and the other on the clinical variables alone.

The regression coefficients of each model have a direct epidemiologic implication: each coefficient represents the log odds of dying while controlling for the other variables in the model. Its antilogarithm is the relative risk for the property considered. As an example, if the regression coefficient for old myocardial infarction is 1, its antilogarithm (e^1) is 2.7. This means that the risk of dying within one year for patients with a previous infarction is 2.7 times as high as that for patients who suffered no prior myocardial infarction. In fact, the coefficients concern relative odds, which are a good approximation for the relative risk, since mortality is a relatively rare event (45 out of 474 died, 9.5 %).

RESULTS

Prediction of mortality by univariate analysis

Table 2 gives the results of univariate analysis for the percent mortality and the risk ratios of the 474 patients included in the study. Of the 12-lead electrocardiographic variables, QRS score and ST depression gave significant values, while QTc and P terminal force in V_1 were less predictive. Of the clinical variables, previous myocardial infarction, pre-infarction angina, Killip class III or IV, late paroxysmal supraventricular tachycardia or fibrillation, late heart failure, heart rate at discharge greater than 75 beats/minute, pre-discharge cardiothoracic ratio greater than 50% and pulmonary congestion on X-rays all revealed significant risk ratios. From the medications administered at discharge, three reached significance: digitalis, diuretics and antiarrhythmics.

TABLE 2 Mortality, risk ratios and confidence intervals for the different electrocardiographic and clinical variables, by univariate analysis

	<u>N</u>	<u>Mortality (%)</u>	<u>Risk Ratio</u>	<u>95% Confidence Interval.</u>
<u>12-lead electrocardiogram</u>				
QRS SCORE				
< 2	144	9 (6.3%)	-	-
2-5	140	10 (7.1%)	1.1	0.5-2.7
> 5	190	26 (13.7%)	2.2	1.1-4.5
ST-SEGMENT DEPRESSION				
no	414 ¹	34 (8.2%)	-	-
yes	60	11 (18.3%)	2.2	1.2-4.0
ST-SEGMENT ELEVATION				
no	306	28 (9.2%)	-	-
yes	168	17 (10.1%)	1.1	0.6-1.9
PVCs				
no	455	43 (9.5%)	-	-
yes	19	2 (10.5%)	1.1	0.3-3.5
PTF				
< 10 mm msec	190	14 (7.4%)	-	-
10-20 mm msec	131	12 (9.2%)	1.2	0.6-2.6
> 20 mm msec	153	19 (12.4%)	1.7	0.9-3.2
QTc				
< 400 msec	147	12 (8.2%)	-	-
400-440 msec	182	13 (7.1%)	0.9	0.4-1.8
> 440 msec	145	20 (13.8%)	1.7	0.9-3.3
<u>Other clinical variables</u>				
AGE				
< 50, years	116	11 (9.5%)	-	-
50-60, years	165	11 (6.7%)	0.7	0.3-1.5
> 60, years	193	23 (11.9%)	1.3	0.6-2.5
SEX				
female	102	12 (11.8%)	-	-
male	372	33 (8.9%)	0.7	0.4-1.4
PREVIOUS AMI				
no	331	21 (6.3%)	-	-
yes	149	24 (16.8%)	2.6	1.5-4.6
PREVIOUS ANGINA				
no	301	23 (7.6%)	-	-
yes	173	22 (12.7%)	1.7	1.0-2.9
PEAK CK				
< 300, IU/l	194	14 (7.2%)	-	-
300-600, IU/l	121	16 (13.2%)	1.8	0.9-3.6
> 600, IU/l	159	15 (9.4%)	1.3	0.7-2.6
KILLIP CLASS				
I-II	439	36 (8.2%)	-	-
III-IV	35	9 (25.7%)	3.1	1.6-5.7

TABLE 2, continued

	<u>N</u>	<u>Mortality (%)</u>	<u>Risk Ratio</u>	<u>95% Confidence Interval.</u>
EARLY POST MI ANGINA				
no	351	32 (9.1%)	-	-
yes	123	13 (10.6%)	1.2	0.6-2.1
LATE VF OR VT				
no	460	40 (8.7%)	-	-
yes	14	5 (35.7%)	4.1	1.8-7.8
LATE SVT OR AF				
no	452	40 (8.8%)	-	-
yes	22	5 (22.7%)	2.6	1.1-5.3
LATE HEART FAILURE				
no	411	27 (6.6%)	-	-
yes	63	18 (28.6%)	4.3	2.5-7.3
HEART RATE AT DISCHARGE				
< 65 bpm	185	12 (6.5%)	-	-
65-75 bpm	144	12 (8.3%)	1.3	0.6-2.7
> 75 bpm	145	21 (14.4%)	2.2	1.2-4.3
PREDISCHARGE CTR > 50%				
no	379	24 (6.3%)	-	-
yes	95	21 (22.1%)	3.5	2.0-5.9
PULMONARY CONGESTION				
no	445	39 (9%)	-	-
yes	29	6 (20.7%)	2.3	1.1-4.7
MEDICATION AT DISCHARGE:				
DIGITALIS				
no	383	24 (6.3%)	-	-
yes	91	21 (23.1%)	3.7	2.1-6.2
DIURETICS				
no	312	19 (6.1%)	-	-
yes	162	26 (16.0%)	2.6	1.5-4.6
BETA-BLOCKERS				
no	205	24 (11.7%)	-	-
yes	269	21 (7.8%)	0.7	0.4-1.2
ANTIARRHYTHMICS				
no	459	40 (8.7%)	-	-
yes	15	5 (33.3%)	3.8	1.7-7.4
ANTICOAGULANTS				
no	384	32 (8.3%)	-	-
yes	90	13 (14.4%)	1.7	0.9-3.1

Abbreviations:

PVCs = premature ventricular complexes; PTF= P terminal force in V_1 ; AMI = acute myocardial infarction; CK = serum creatine phosphokinase; VF= ventricular fibrillation; VT = sustained ventricular tachycardia; SVT= paroxysmal supraventricular tachycardia; AF=paroxysmal atrial fibrillation or atrial flutter, CTR = cardio thoracic ratio.

Prediction of mortality by multivariate analysis

The results of stepwise logistic regression of one year mortality on the 12-lead electrocardiogram variables are shown in the upper part of table 3. QRS score >5, presence of ST depression and QTc > 440 msec were found to be of predictive value. In particular, the presence of a QRS score >5 or of QTc > 440 msec yields a 1.8 fold increase in the patient's risk of dying within one year and the presence of ST-depression multiplies the risk by 2.2.

The lower portion of table 3, summarizes the logistic regression results for the clinical variables. The presence of previous myocardial infarction, late heart failure, indication for digitalis at discharge or a cardiothoracic ratio > 50% and an indication for antiarrhythmic drugs (RR = 4.0) were of independent predictive value. The construction of the model is not straightforward here as there are three variables related to pump failure: clinical signs of late heart failure, use of digitals and cardiothoracic ratio > 50%. The regression model assumes multiplicity of the different factors. That is, if two factors are present each with a relative risk of 3, then the combined relative risk will be $3 \times 3 = 9$. As the three above variables measure to a large the same phenomenon, one may question the assumption of multiplicity. We investigated this using interaction terms in our model. We concluded that digitalis and a cardiothoracic ratio > 50% can be combined yielding a satisfying yet parsimonious model. The consequences are that the relative risk of a patient using digitalis or with cardiothoracic ratio > 50% remains 4.0. However, if clinical signs of late heart failure are present, the relative risk increases to 12.0, which is also the case if the latter is present with either of the other risk factors.

The addition of the 12-lead electrocardiogram variables to the model already containing the other clinical variables yielded only a marginal better fit to the data; the improvement of the log likelihood is 0.32 ($X^2=0.64$, $p > 0.60$). From this we concluded that the 12-lead electrocardiogram variables do not make an independent contribution to the prediction of one year mortality over that of the other clinical variables alone.

On the other hand, if such data are not available the 12 lead electrocardiogram can, to a certain extent substitute them. The mean predicted probability of dying for patients who actually died is 0.12, based the electrocardiographic model, and 0.23 based on the clinical model. This

TABLE 3 Variables eventually retained in the logistic function of the risk of dying within one year.

	coefficient	standard	relative risk	N	log-likelihood
<u>12 lead ECG</u>					
QRS SCORE > 5	0.6	0.3	1.8	190	} -142.2
ST SEGMENT DEPRESSION	0.8	0.4	2.2	60	
QTc > 440 msec	0.6	0.3	1.8	145	
CONSTANT	-2.9	0.3	-	474	
<u>Clinical variables</u>					
PREVIOUS AMI	1.1	0.3	3.0	143	} -122.7
LATE HEART FAILURE	1.1	0.4	3.0	63	
DIGITALIS OR CTR > 50%	1.4	0.4	4.1	148	
ANTIARRHYTHMICS	1.4	0.6	4.1	15	
CONSTANT	-3.7	0.3	-	474	

Abbreviations: N = number of patients in whom the property considered was present.
 AMI= acute myocardial infarction; CTR = cardio thoracic ratio;

demonstrates the greater ability of the clinical variables to identify patients who are going to die. The mean predicted probability of surviving (1-predicted probability of dying) for patients who actually survived is 0.91 based on the electrocardiographic models and 0.92 based on the clinical model, demonstrating that survival can equally well be predicted from the electrocardiographic and clinical variables.

DISCUSSION

Due to the proliferation of non-invasive and invasive tests, the armamentarium available to the cardiologist for assessing the risk of patients after myocardial infarction has considerably grown. Due to the overlap of information provided by different tests, the selection of the most efficient strategy (with the highest ratio of information to cost or risk to the patient) in an individual patient is not obvious.

In previous studies we addressed the problem of the prognostic value of tests which are not universally performed at discharge, like exercise testing, radionuclide ventriculography and the 24-hour ambulatory electrocardiogram compared to other clinical variables (1).

In this study, we assessed the prognostic value of the predischarge 12-lead electrocardiogram, which is not costly and is usually performed in order to establish whether it provides additional information beyond the known clinical information and tests.

As far as we know this is a unique study for the following reasons:

1. it includes a consecutive series of patients admitted to the same coronary care unit, which was sufficiently large to allow a multivariate analysis based on predischarge clinical and electrocardiographic variables; 2. it focusses on relatively low risk patients since those with conduction defects, ventricular hypertrophy and atrial fibrillation were excluded; 3. its electrocardiographic variables include among others the QRS score by Selvester (8) which in the last few years has become very popular for the assessment of the extent of myocardial damage and prognosis. However, its prognostic value has not been compared in other studies to that of other electrocardiographic or clinical variables by multivariate analysis. The only large study which addressed the relative prognostic value of clinical and electrocardiographic variables in post-infarction patients is that of the Coronary Drug Project (2). In this study, which includes 2035 patients followed for three years, it was concluded that ST-depression of 1 mm or more of the 'ischemic' type was

the most important independent risk predictor of all clinical and electrocardiographic findings studied, including, Q-waves, ventricular conduction defects, atrial fibrillation and premature ventricular complexes.

In our study we confirm that many electrocardiographic variables are predictive of survival (tables 2 and 3). The highest risk ratios for mortality at 2.2 were obtained for ST segment-depression. These figures are rather similar to those reported by the Coronary Drug Project (2). However, in contrast to their findings we did not confirm the predictive value of premature ventricular contractions and of ST-elevation. This could be related to the different population in the two studies. In fact the entry in the Coronary Drug Study was late (at least 3 months after the most recent infarction), and included also patients with ventricular conduction defects and atrial fibrillation. Also patients were followed for a longer period, up to three years. In contrast, our study was based on a consecutive series of patients evaluated at hospital discharge without conduction abnormalities and atrial fibrillation and the follow-up was for one year. When we recall that for hospital survivors of myocardial infarction, the mortality is highest in the first 3 to 6 months (1), it is clear that the two studies deal with a completely different population, particularly since early mortality is excluded in the Coronary Drug Project. In table 4 some predischarge variables of the 474 patients in the study group are compared to those of patients excluded from the study because of ventricular conduction defects, hypertrophy or atrial fibrillation. These data clearly indicate that patients with normal QRS pattern had much less extensive myocardial damage, consistent with a lower mortality during follow-up. It also means, that for the electrocardiogram to be helpful it must be dichotomized into either an electrocardiogram without conduction disturbance or hypertrophy in a relatively low risk group after myocardial infarction or when conduction defects are present be considered to carry highly significant prognostic information. The QRS-score and, to a lesser extent, P terminal force in V_1 and QTc were also predictive of mortality (table 2).

As QRS-score is directly related to the extent of myocardial damage (8), it has been shown to have a fair correlation with left ventricular ejection fraction. In the present series the correlation coefficient between radionuclide ejection fraction and QRS-score was -0.53 (SEE 11%) in 417 patients. The correlation coefficient was similar ($r=-0.57$, SEE 11%) when the analysis was limited to 296 patients with a first myocardial

infarction. These data are very close to previous findings by our group in a smaller population (6).

P terminal force measured from precordial lead V_1 has been shown by others to correlate to left atrium overload (9). Siltanen et al (7) recently described that P terminal force was the strongest independent predictor of mortality from predischARGE electrocardiogram in 457 post-infarction patients, followed by ST-segment abnormalities.

However, these authors did not measure the Selvester QRS score. Their population was also different. In fact they did not exclude patients with ventricular conduction abnormalities or ventricular hypertrophy. In our study these patients had a greater P terminal force in V_1 , indicating a more severe left ventricular dysfunction. Accordingly, these patients had also more frequently clinical signs of heart failure and a lower ejection fraction (table 4).

Mortality was higher in patients with prolonged QTc: Schwartz et al (4) found in 55 patients with a recent infarction that the finding of prolonged QTc (>440 msec) during serial electrocardiographic measurements constituted a 2.1 greater risk of sudden death, during a seven year follow-up. More recently, Ahnve et al (5) confirmed that a prolonged QTc is predictive of mortality in post-infarct patients. By using a cut-off of 440 msec, they found that QTc yielded a sensitivity of 77% and a specificity of 84%, limited to patients not on medical therapy, which might influence the QTc interval.

In contrast to QRS score and P terminal force in V_1 , which are related to pathophysiological phenomena such as the extent of myocardial damage and left atrium overload, ST-depression and QTc interval are difficult to interpret. In our study both were predictive of mortality. However the clinically prescribed medication was not discontinued. It is well known that medication is one of the many factors which affect both variables (5,11) .

When multivariate analysis was applied to the different electrocardiographic variables, ST-segment depression, QTc and QRS score were independent predictors of mortality (table 3). Of the clinical data the independent prognostic variables were persistent heart failure, a history of previous myocardial infarction, cardiomegaly from X-rays, the use of digitalis and antiarrhythmics at discharge. These variables all relate directly or indirectly to poor ventricular function, which is the stron-

TABLE 4. Differences of selected baseline characteristics between patients in the study group and those excluded from the study.

	<u>study group</u>	<u>excluded</u>	<u>p-value</u>
number of patients	474	84	-
age, years, mean(SD)	57 (11)	61 (10)	0.002
previous AMI, n(%)	146 (30)	26 (33)	ns
late heart failure, n(%)	66 (14)	27 (35)	0.0005
CTR >50%, n(%)	100 (21)	34 (44)	0.0005
EF, %, mean(SD)	47 (14)	37 (17)	0.0005
<u>Electrocardiographic variables</u>			
PVCs, n(%)	22 (5)	6 (8)	ns
PTF mm msec, mean(SD)	20 (15)	26 (18)	0.0005
<u>Follow up</u>			
one year mortality, n(%)	45 (9)	23 (27)	0.001

Abbreviations; AMI= acute myocardial infarction; CTR= cardio thoracic ratio; EF= left ventricular ejection fraction; PVCs= premature ventricular complexes; PTF= terminal force of P-wave in V₁.

gest prognostic factor. Therefore, several clinical and electrocardiographic variables provided useful prognostic information, however when multivariate analysis was applied to the combination of clinical and electrocardiographic variables, electrocardiographic variables were not strong enough to improve the prognostic information of the clinical data.

It is concluded that, pre-discharge electrocardiogram per se provides important prognostic information for post-infarction patients without conduction abnormalities, ventricular hypertrophy or atrial fibrillation, in whom clinical prescribed medication is not discontinued. From these electrocardiographic variables, persistent ST-segment depression, the Selevester QRS-score (8) and QTc are the independent predictors of survival. However, electrocardiographic variables by themselves are not sufficiently powerful to improve risk assessment when added to other information routinely collected during hospital stay.

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CHAPTER 5

PROGNOSIS OF PATIENTS WITH DIFFERENT PEAK SERUM CREATINE KINASE LEVELS AFTER FIRST MYOCARDIAL INFARCTION.

By

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Prognosis of patients with different peak serum creatine kinase levels after first myocardial infarction

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KEY WORDS: Myocardial infarction, serum creatine kinase.

The extent to which patients with low peak serum creatine kinase (CK) at their first myocardial infarction differ from patients with high CK levels in terms of risk for subsequent ischaemic events was investigated in 266 patients who survived the first 48 h from the onset of infarction. All patients were followed up for one year. Four groups were formed based on peak CK ≤ 200 , 201-400, 401-800 and > 800 IU l⁻¹. During follow-up the incidence of mortality was 15% (N=39), non-fatal re-infarction 9% (N=23), and angina 53% (N=140). Hospital mortality was significantly higher ($P < 0.02$) in the highest CK-group (16%), but the incidence of non-fatal re-infarction, angina pectoris and late mortality was similar in the four groups. In hospital survivors, ischaemic ST-changes during pre-discharge symptom limited bicycle stress test and multiple vessel disease were equally distributed in all four groups.

We conclude that while hospital mortality is directly related to peak CK, there is no relationship between peak CK and late mortality, non-fatal re-infarctions, or recurrent angina. Accordingly, diagnostic and therapeutic procedures in the individual patients are not influenced by the amount of serum CK released during acute infarction.

Introduction

Serial measurements of serum creatine kinase (CK) in the first few days after acute myocardial infarction is a routine procedure for proving the existence of infarction and is also used to estimate the extent of myocardial damage^[1]. It has been reported that this simple measurement also provides prognostic information since patients with high peak serum CK were found to have higher early mortality^[2]. However, it is uncertain to what extent patients with low peak CK levels at their first infarction differ from those with high CK levels in terms of their risk for other ischaemic events, such as angina and recurrent infarction.

Small myocardial infarctions are more often 'non Q-wave' infarctions and some investigators have reported that these patients carry a worse prognosis than patients with Q-wave infarctions^[3]. If this could be confirmed from enzyme studies,

a more aggressive diagnostic and therapeutic approach would be justified in these patients. However, other authors have not found any clinical differences between the two forms of infarction and have also failed to demonstrate that the concept of Q-wave versus non Q-wave infarction implies a pathologic distinction^[4].

To clarify the significance of the enzyme levels, we studied 266 consecutive patients with a first acute myocardial infarction and subdivided them into four subgroups with increasing peak serum CK levels. They were followed during the acute phase and during the year after recovery from the infarction.

The aims of this study were to determine the relation between peak serum CK and other clinical information reflecting infarct size, and to determine whether patients with a low peak serum CK have a different incidence of ischaemic events than those with larger infarctions, based on peak serum CK levels.

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Patients and methods

The records of 361 conse

admitted to the coronary care unit of the Thorax-center with a proven diagnosis of acute first myocardial infarction between 1 March 1981 and 31 December 1982 were considered for the study. The diagnosis of myocardial infarction was made in presence of at least 2 of the following criteria:

1. prolonged chest pain of at least 45 min;
2. dynamic electrocardiographic changes defined, in case of transmural infarctions, as evolving QR-complexes, Q-waves >0.04 s or $R > S$ in V_1 - V_2 with ST-T wave changes, or in case of non-transmural infarction, as ST- and/or T-wave changes persisting for at least 24 h without loss of R-wave voltage or new Q-waves. Site of infarction was defined as undetermined in case of complete left bundle branch block;
3. a typical rise and fall of total serum CK with a peak level >100 IU l^{-1} (twice the upper limit of the normal range).

Patients were graded in 4 groups according to peak CK <200 IU l^{-1} ($N=71$, median 123, range 90-200), 201-400 IU l^{-1} ($N=49$, median 290, range 220-400), 401-800 IU l^{-1} ($N=84$, median 583, range 403-795) and >800 IU l^{-1} ($N=62$, median 1373, range 814-2994). Serial serum CK was sampled every 6 h during the first day of admission and thereafter once a day for seven days. The CK was measured both in our center and in the referring hospital with the same method^[5]. The precision of the method is monitored by frequent analysis of commercially available control serum. Coefficients of variation in these lyophilized materials are in our laboratory 7-10%. When repeated analysis of fresh human serum is considered, variation coefficients are 3-6%.

Twenty three patients with a first myocardial infarction who died within 2 days from the onset of symptoms were excluded as the peak level of CK was possibly not reached. We also excluded from the study 19 patients admitted longer than two days from the beginning of symptoms and fifty three patients treated with intracoronary streptokinase, as part of an ongoing randomized clinical trial^[6], since the treatment with streptokinase is known to modify the patterns of enzyme release. The treatment during hospital stay followed the guidelines recently described^[7]. The data base therefore consisted of 266 patients.

At hospital discharge 188 patients were evaluated with a symptom limited bicycle stress test and 217 underwent a radionuclide ventriculography at rest^[8]. Stress testing was not performed in 58 hos-

pital survivors: in 14 because of recurrent angina, in 14 for persistent heart failure and in 30 for other limiting diseases or general disability. Eighty four patients underwent a coronary arteriography, elective in 58% of cases and in the others as part of a study protocol. After discharge patients were followed at the outpatient clinic. One year follow-up was complete. Mortality, recurrent infarction, persistent heart failure and typical angina pectoris were the end-points of the study.

Differences among groups of patients were assessed with analysis of variance for the continuous variables and with the Cochran modification of the chi square test for trend assessment of discrete variables.

Results

CK LEVELS, BASELINE CLINICAL DATA AND PRE-DISCHARGE EVALUATION (TABLES 1 AND 2)

Patients with a large infarction (CK >800) were slightly younger than those in the smaller infarction groups, but age was similar in the other groups. Sex and history of angina pectoris were evenly distributed. The percentage of patients referred from other hospitals for complications was 23% on average, being highest in patients with the largest infarcts (40%). As expected, the prevalence of non-transmural infarction was highest in the lowest CK-group (62%), while in the highest CK-group there was a prevalence of anterior infarctions (65%). Left ventricular ejection fraction progressively declined in the four CK-groups, and was on average 57, 56, 47 and 37%.

Stress testing could be performed in a similar fraction of each group—in 76% of patients on average. The maximal workload and the prevalence of ST-segment depression were equally distributed. Patients with the highest CK level had the lowest incidence of angina pectoris, but had the highest incidence of ST-segment elevation, the highest maximal heart rate and the lowest increment of systolic blood pressure, all indicators of impaired left ventricular function.

Coronary arteriography was performed in 37% of patients on average, and showed an even distribution of patients with multiple vessel disease in the four groups.

CLINICAL COURSE (TABLES 3 AND 4)

The incidence of mortality and severe heart failure during the hospital phase was significantly higher in patients with the highest peak CK-levels.

Table 1 Historical and clinical data in groups with different peak serum CK levels

Peak CK (IU l ⁻¹):	≤200	201-400	401-800	>800	P value
Number of patients	71	49	84	62	
Age (yrs: mean ± SD)	60 ± 11	57 ± 12	60 ± 11	53 ± 11	0.01
Males (%)	76	71	76	77	NS
Previous angina (%)	38	35	25	31	NS
Referred from other hospitals, (%)	14	18	18	40	0.01
Site of infarction					
anterior (%)	15	16	32	65	0.0001
inferior (%)	22	49	56	34	0.0001
non-transmural (%)	62	35	10	2	0.0001
unknown (%)	0	0	2	0	—
Peak α-HBDH (IU l ⁻¹)	190 ± 96 (N=64)	360 ± 173 (N=47)	598 ± 254 (N=78)	1048 ± 430 (N=56)	0.0001

If not specified, data are expressed by mean ± SD.

Table 2 Pre-discharge evaluation by radionuclide ventriculography, stress testing and coronary arteriography

Peak CK (IU l ⁻¹):	≤200	201-400	401-800	>800	P value
Ventriculography performed (%)	76	88	80	85	NS
LVEF (%)	57 ± 11	56 ± 11	47 ± 16	37 ± 17	0.001
Stress testing performed (%)	66	75	62	84	NS
max. workload (W)	119 ± 38	122 ± 43	112 ± 33	109 ± 28	NS
max. HR (bpm)	124 ± 25	133 ± 22	132 ± 21	141 ± 21	0.001
SAP rise (mmHg)	47 ± 25	45 ± 24	47 ± 27	34 ± 22	0.02
ST-depression (%)	40	52	48	25	NS
ST-elevation (%)	16	37	48	65	0.0001
angina (%)	28	40	19	3	0.002
Coronary angiography performed (%)	28	20	35	63	0.005
≥ 2 VD (%)	65	80	72	64	NS

Abbreviations: LVEF = left ventricular ejection fraction; HR = heart rate; SAP = systolic arterial pressure. ST-depression and -elevation ≥ 1 mm. If not specified, data are expressed as mean ± 1 SD.

Table 3 Hospital clinical course

Peak CK (IU l ⁻¹):	≤200	201-400	401-800	>800	P value
Mortality	N 1 % 1	2 4	7 8	10 16	0.02
Non-fatal re-infarctions	N 6 % 8	0 0	5 6	0 0	NS
Angina	N 18 % 25	11 22	16 19	10 16	NS
Killip class III-IV	N 2 % 3	2 4	9 11	17 27	0.0005

Table 4 Clinical course after hospital discharge during one year follow-up in 246 hospital survivors

Peak CK (IU l ⁻¹)		≤200	201-400	401-800	>800	P value
Number of patients		70	47	77	52	
Mortality	N	4	4	7	4	NS
	%	6	8	9	8	
Non-fatal re-infarctions	N	3	0	2	7	NS
	%	4	0	3	13	
Angina	N	25	17	23	15	NS
	%	36	36	30	29	
Heart failure	N	2	2	4	17	0-0001
	%	3	4	5	33	
CABG/PTCA	N	5/1	3/0	4/1	0/1	NS
	%	9	6	6	2	

CABG — coronary artery bypass grafting; PTCA — percutaneous transluminal coronary angioplasty.

Table 5 Treatment at hospital discharge

Peak CK (IU l ⁻¹)		≤200	201-400	401-800	>800	P value
Number of patients		70	47	77	52	
Beta blockers	N	45	27	31	10	0-0005
	%	64	57	40	19	
Nitrates	N	25	15	21	23	NS
	%	36	32	27	44	
Calcium blockers	N	21	12	15	6	NS
	%	30	26	19	46	
Digitalis	N	10	5	20	24	0-0005
	%	14	11	26	46	
Diuretics	N	19	10	30	30	0-005
	%	27	21	39	58	
Anticoagulants	N	5	2	16	23	0-0005
	%	7	4	21	31	
Antiarrhythmics	N	1	3	7	2	NS
	%	1	6	9	4	
No medication	N	10	9	11	3	NS
	%	14	19	14	6	
CABG/PTCA	N	7/3	1/1	3/2	2/0	NS
	%	17	4	6	4	

In contrast non-fatal re-infarctions and angina pectoris were similar in all groups. After hospital discharge, the follow-up data showed no differences in mortality, re-infarctions or angina pectoris during the first year. However, patients with the highest CK levels had the greatest incidence of persistent heart failure, which occurred in 33% of cases.

Discussion

Infarct size is well established as an important determinant of longterm outcome in patients who survive a first myocardial infarction^[1,2,9,10]. Peak serum CK is a simple measurement related to the extent of myocardial damage, which is routinely carried out in most coronary care units^[1].

Peak serum CK is a less accurate method to estimate the extension of myocardial necrosis than the calculation of total CK release^[1]. However, total CK release is not practical for routine work and certainly more expensive. Furthermore, Thomson *et al.*^[2], found a fair correlation between the two methods.

We found that peak serum CK is inversely related to left ventricular function as detected by clinical variables, pre-discharge radionuclide ventriculography, and stress testing. Left ventricular ejection fraction at discharge was inversely correlated with peak CK. The extent of blood pressure rise during the bicycle ergometry test, an index of left ventricular function^[8], was lowest in the highest CK-group. Also the incidence of ST-elevation during ergometry, an index of left ventricular dyskinesia, was highest in the highest CK-group. Therefore we confirm that peak CK, despite its limitations^[1], is for practical purposes a reliable indicator of residual left ventricular function and early prognosis after acute first myocardial infarction.

Other serum enzymes like CK-MB or α -HBDH have been reported to provide more specific information on the amount of myocardial necrosis than total serum CK^[11]. In the present study total CK was utilized since it was determined also in all referring hospitals. Furthermore, peak CK paralleled peak α -HBDH (Table 1), and therefore the use of total CK should not have invalidated our findings.

Hospital mortality and the incidence of advanced heart failure during the early phase was significantly higher in the highest CK-group (Table 3). In contrast, mortality after discharge during the first year follow-up was independent of peak CK, ranging from 5 to 8% in the four groups (Table 4). This is in partial agreement with the results of Thomson *et al.*^[2], who found that peak CK was more closely related to immediate than to late mortality. These investigators also found that the mode of death during follow-up was related to infarct size: patients with high peak CK died mostly from progressive heart failure while death was more often sudden in patients with a smaller infarction. In our series we could not confirm this last observation, since most of our patients who survived during follow-up died suddenly; however the incidence of heart failure was highest (25%) in the highest CK-group.

Another important issue is the relative incidence of angina pectoris and/or non-fatal re-infarctions

since it is uncertain whether their incidence is higher in patients with small infarctions, which would justify more aggressive management of these patients. Our results indicate that the incidence of angina and re-infarction is not related to peak CK either during the acute phase or during late follow-up (Tables 3 and 4). This is consistent with the similar frequency of ischemic electrocardiographic changes during stress testing and that of multiple vessel disease in the different CK-groups (Table 2).

Our results could have been biased by the many patients referred to us from peripheral hospitals because of complications. This would overestimate the severity of the disease compared to an unselected population. In fact, the prevalence of patients with multiple vessel disease in our series was higher than that described by Abraham *et al.* in a consecutive series of unselected patients with a first myocardial infarction who underwent coronary arteriography^[12]. This difference could also be due to the selection for coronary arteriography, mostly elective in our series.

The follow-up results could have been influenced by the treatment applied to the different CK-groups (Table 5). In particular, coronary artery bypass surgery and coronary angioplasty for the treatment of postinfarction angina were more frequently applied in the group of patients with a small CK rise. However, a recent study of our group^[13], partially based on the population of the present study, showed that coronary artery bypass surgery early after myocardial infarction did not influence survival or re-infarctions compared to a matched group treated medically.

As expected, at the other end of the spectrum, patients with the largest infarctions (CK > 800 IU⁻¹) were more frequently treated with digitalis, diuretics and anticoagulants and less frequently with beta blockers, because of the higher incidence of heart failure. However, most of these differences disappeared by excluding from the comparison the group with CK greater than 800 IU⁻¹. It is therefore unlikely that treatment different influence on the clinical outcome in those patients with a small or intermediate CK rise.

In summary, we confirm that in patients with first myocardial infarction, residual left ventricular function is inversely correlated with peak serum CK. Accordingly, patients with highest CK levels have the highest incidence of hospital mortality and heart failure. On the coronary, late mortality, non-fatal re-infarctions and angina were not

related to peak CK levels. Therefore, in patients with a first myocardial infarction, the diagnostic procedures and therapeutic policy should not be influenced by peak serum CK. In particular, patients with a small enzyme rise, do not require a more aggressive approach, unless indicated by persistent symptoms. Our results also indicate that when interventions are planned during the acute phase of infarction to salvage myocardium, beneficial effects on survival can be expected during the early phase, but not during the subsequent year.

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CHAPTER 6

PROGNOSE VAN HET ONGECOMPLICEERDE EERSTE HARTINFARCT BIJ PATIENTEN JONGER DAN 60 JAAR: REDEN TOT HARTCATHETERISATIE?

Door

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Prognose van het ongecompliceerde eerste hartinfarct bij patiënten jonger dan 60 jaar: reden tot hartcatheterisatie?

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INLEIDING

Onlangs beschreven Veenbrink et al. in dit tijdschrift de bevindingen bij coronairangiografie en inspanningselektrocardiografie na een eerste myocardinfarct.¹ Bij 80 patiënten zonder ernstige angina pectoris of decompensatio cordis, met een gemiddelde leeftijd van 48 jaar, vonden zij correlatie tussen daling van het ST-segment tijdens inspanning en een zogenaamde high risk-coronaria-aandoening. Hun conclusie luidde dat coronairangiografie beperkt zou kunnen blijven tot patiënten bij wie het inspanningsonderzoek na het eerste infarct in deze zin positief uitvalt.¹ Het artikel bevatte evenwel geen gegevens over de prognose van de onderzochte populatie.

Onlangs hebben wij bij 338 niet-geselecteerde patiënten die een infarct hadden doorgemaakt, de prognostische waarde nagegaan van het voor ontslag verrichte inspanningsonderzoek.² Daarbij bleek dat niet de ST-segmentdaling, maar de linker-kamerfunctie bij inspanning van prognostisch belang was. Om deze reden hebben we de prognose onderzocht van alle patiënten jonger dan 60 jaar, die in een periode van 22 maanden in ons centrum werden opgenomen wegens hun eerste ongecompliceerde infarct. De duur van het na-onderzoek bedroeg een jaar.

PATIËNTEN EN METHODEN

Tussen 1 maart 1981 en 31 december 1982 werden 529 achtereenvolgende patiënten opgenomen wegens een myocardinfarct. De diagnose werd op de gebruikelijke wijze gesteld met behulp van anamnese, typische ECG-veranderingen en enzymbeloop. Op grond van het ontbreken van de kenmerkende Q-golven in het eerste ECG van een gedocumenteerd infarct in het verleden kon bij 418 patiënten worden vastgesteld dat het een eerste infarct betrof. Van hen overleden 48 in het ziekenhuis. Van de 370 overlevende patiënten waren 213 jonger dan 60 jaar. Bij 94 hunner werd het herstel gecompliceerd door decompensatio cordis, angina pectoris dan wel door late, klinisch manifeste ritmestoornissen. Bij de overige 119 patiënten, jonger

SAMENVATTING

In dit artikel wordt een onderzoek beschreven naar de prognose in het eerste jaar na ontslag uit het ziekenhuis wegens een ongecompliceerd verlopen eerste hartinfarct van 119 achtereenvolgende patiënten jonger dan 60 jaar. Slechts één patiënt overleed plotseling binnen een jaar; bij 10 patiënten ontstond een recidiefinfarct. De dag voor ontslag werd door 110 patiënten een inspanningstest verricht. Er bleek verband te bestaan tussen het voorkomen van angina pectoris en ST-segmentdaling tijdens het inspanningsonderzoek en het optreden van angina pectoris in de periode van na-onderzoek. Bij de helft van de patiënten ontstond bij de inspanningstest een ST-segmentdaling van ten minste 0,1 mV. Inspanningsvariabelen bleken echter geen waarde te hebben voor de voorspelling van een recidiefinfarct. Geconcludeerd wordt dat ST-segmentdaling tijdens inspanningsonderzoek in deze groep patiënten geen indicatie is voor coronairangiografie.

dan 60 jaar met een eerste infarct, verliep het herstel van het infarct ongecompliceerd. Deze groep bestond uit 98 mannen en 21 vrouwen, in leeftijd variërend van 22 tot 59 jaar, gemiddeld 49 jaar. Van hen hadden 37 een voorwandinfarct, 54 een onderwandinfarct en 28 een niet-transmurale infarct.

Aan het einde van de ziekenhuisopname vond bij 54 patiënten hartcatheterisatie plaats. Dit onderzoek gebeurde bij 39 patiënten in verband met een gerandomiseerd onderzoek naar het effect van de toediening van streptokinase en bij 15 patiënten om electieve redenen.³ Een diametervernauwing van meer dan 50% in een of meer coronairarteriën werd als significant beschouwd.

De dag voor ontslag, gemiddeld 9 dagen na het infarct, verrichtten 110 patiënten een inspanningsproef op de fietsergometer, waarbij de belasting met 10 watt per minuut werd opgevoerd. Bij geen van de patiënten ontstonden ritmestoornissen, repolarisatiestoornissen of veranderingen in de bloeddruk, die noodzaakten tot beëindigen van het onderzoek. Het ECG werd met het afleidingsstelsel van Frank voortdurend geregistreerd en door een computer geanalyseerd.⁴ De bloeddruk werd om de minuut met een manchet gemeten. De voorgeschreven medicatie werd op de dag van het inspanningsonderzoek gecontinueerd. Wegens niet-cardiale contra-indicaties of om organisatorische redenen konden 9 patiënten, onder wie 4 gecatheteriseerde patiënten, het inspanningsonderzoek niet ondergaan. Na ontslag uit het ziekenhuis bezochten de patiënten regelmatig de

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TABEL 1. Resultaten van inspanningsonderzoek na ongecompliceerd verlopen eerste infarct

	alle patiënten (n = 110)	0-1-taksafw. (n = 40)	2-3-taksafw. (n = 10)
A. verschijnselen			
angina pectoris (%)	16 (15)	6 (15)	2 (20)
ventriculaire ritmestoornissen (%)	21 (19)	7 (17)	1 (10)
B. onderzoeksbevindingen			
behaalde max. belasting (%; SD)	81 (15)	78 (13)	78 (13)
0,1 mV ST-daling (%; SD)	40 (36)	15 (37)	5 (50)
0,2 mV ST-daling (%; SD)	13 (12)	4 (10)	1 (10)
0,1 mV ST-stijging (%; SD)	30 (27)	12 (30)	3 (30)
0,2 mV ST-stijging (%; SD)	17 (15)	7 (17)	-
max. hartfreq. (sl/min; SD)	136 (23)	141 (24)	129 (25)
max. syst. bloeddruk (mmHg; SD)	170 (27)	164 (24)	163 (27)
toename syst. bloeddruk (mmHg; SD)	45 (22)	45 (18)	36 (23)

polikliniek. Van alle patiënten waren de gegevens over een periode van een jaar na opname beschikbaar.

Bij de statistische bewerking werd de univariate analyse met Students t-toets voor continue variabelen en met Fishers exacte toets voor de discrete variabelen toegepast. Een p-waarde < 0.05 werd beschouwd als significant.

RESULTATEN

Slechts één patiënt overleed in het eerste jaar na het infarct, terwijl bij 10 patiënten een recidiefinfarct optrad. Angineuze klachten ontstonden bij 39 patiënten in de periode van na-onderzoek. In verband met de ernst van deze klachten werd bij 5 patiënten een bypass-operatie (CABG) uitgevoerd en bij 2 een percutane transluminale coronaire angioplastiek (PTCA).

Geen van de 54 patiënten bij wie hartcatheterisatie en coronairangiografie werd verricht aan het einde van de ziekenhuisopname, had een belangrijke vernauwing van de hoofdstam; 42 patiënten hadden een één-taksafwijking en 12 een twee- of drie-taksafwijking.

De bevindingen van het inspanningsonderzoek bij 110 patiënten zijn weergegeven in tabel 1. De inspanningsgegevens van de gecatheteriseerde patiënten waren vergelijkbaar met die van de niet-gecatheteriseerde patiënten. De gemiddelde behaalde belasting

bedroeg ongeveer 80% van de voor de leeftijd en lengte vastgestelde norm. Bij 16 patiënten ontstond tijdens de test angina pectoris en bij 53 een ST-segmentdaling van ten minste 0,1 mV.

In de gecatheteriseerde groep waren geen significante verschillen in behaalde belasting, mate van ST-segmentafwijking, maximale hartfrequentie en systolische bloeddruk tussen patiënten met 2- of 3-taksafwijkingen vergeleken met patiënten met afwijkingen in één tak van de coronairarteriën (zie tabel 1). Tabel 2 geeft het verband weer tussen het optreden van angina pectoris en ST-segmentdaling tijdens het inspanningsonderzoek bij ontslag en het klinische beloop in de periode van na-onderzoek. Geen van beide kenmerken bleek van waarde voor het voorspellen van een recidiefinfarct; wel bestond er verband tussen angina pectoris en ST-segmentdaling tijdens de test en het later optreden van angineuze klachten.

BESCHOUWING

Onze resultaten laten zien dat de éénjaarssterfte van jonge overlevenden na een ongecompliceerd verlopen eerste infarct bijzonder laag is. Van de 119 patiënten overleed slechts één in het eerste jaar na ontslag. Deze lage éénjaarssterfte bij patiënten jonger dan 60 jaar wordt ook door anderen gevonden: zo vermeldden Abraham et al. een éénjaarssterfte van 3% bij 197 niet-geselecteerde patiënten die een eerste infarct overleefden.⁵ Deze bevinding is niet zo verrassend, indien men bedenkt dat patiënten met klinische tekenen van decompensatio cordis van ons onderzoek werden uitgesloten.⁶ Deze selectie verklaart ook het geringe aantal patiënten met ernstige coronairaan- doeningen.⁵ In een poging om onze onderzoeksgroep zoveel mogelijk vergelijkbaar te maken met die van Veenbrink et al. werden de patiënten die angineuze klachten in het ziekenhuis hadden, uitgesloten. Niet-temin kregen 16 patiënten nieuwe angineuze klachten tijdens het inspanningsonderzoek en in de periode van na-onderzoek was er sprake van angina pectoris bij 39 patiënten. Veenbrink et al. namen bij 20 van de 80 patiënten angina pectoris waar, 2 tot 4 maanden na het infarct,¹ zodat ook in dit opzicht de patiëntengroepen goed overeenstemmen.

Wij hebben bij het inspanningsonderzoek bij ongeveer de helft van de patiënten een ST-segmentdaling

TABEL 2. Voorspellende waarde van angina pectoris en ST-segmentdaling tijdens inspanningsonderzoek

klinisch beloop in periode van na-onderzoek	inspanningsonderzoek								
	angina pectoris (aant. patiënten)			ST-segmentdaling (aant. patiënten)			angina en ST-segmentdaling (aant. patiënten)		
	+	-	p	+	-	p	+	-	p
	(n = 16)	(n = 94)		(n = 53)	(n = 57)		(n = 12)	(n = 98)	
overlijden	0	1 (1)	NS	0	1 (1)	NS	0	1 (1)	NS
recidiefinfarct (%)	3 (18)	5 (5)	NS	3 (6)	5 (10)	NS	0	8 (8)	NS
angina pectoris (%)	11 (69)	25 (27)	0,003	23 (38)	13 (23)	0,04	9 (75)	27 (28)	0,004
CABG of PTCA (%)	3 (19)	3 (3)	0,08	4 (8)	2 (4)	NS	3 (25)	3 (3)	0,03
geen complicaties (%)	5 (31)	65 (69)	0,01	29 (55)	41 (72)	NS	3 (25)	67 (68)	0,01

van ten minste 0,1 mV kunnen vaststellen; dit getal is ook door anderen gevonden.^{7,9} Veenbrink et al. namen een significante ST-segmentdaling waar bij 22% van hun patiënten; deze lagere incidentie wordt wellicht verklaard door een andere interpretatie van ECG-afwijkingen in de oude infarctgebieden, alsook door het latere tijdstip waarop de inspanningsproef werd uitgevoerd. De door Veenbrink et al. gevonden correlatie tussen de coronairangiografische en electrocardiografische bevindingen was in ons onderzoek minder duidelijk. Het is echter de vraag of deze verschillen van zoveel belang zijn. De prognostische waarde van ST-segmentdaling tijdens inspanning na een doorgemaakt infarct wordt immers door velen betwijfeld. Hoewel Theroux et al. destijds verband hebben gevonden tussen ST-segmentdaling en prognose,⁹ is dit door latere onderzoekers niet bevestigd.^{4,7,8,10-12} Bij eerder eigen onderzoek naar de prognostische waarde van de inspanningstest bij 338 ongeselecteerde overlevenden van een myocardinfarct bleek de éénjaarsprognose het beste gecorrigeerd te zijn aan de toename van de systolische bloeddruk tijdens de test.² Andere onderzoekers zijn eveneens van mening dat de uitkomsten van het inspanningsonderzoek die de mechanische functie van de linker kamer weergeven, de grootste prognostische betekenis hebben. Geringe inspanningstolerantie en lage maximale waarde van de systolische bloeddruk tijdens inspanning correleren volgens recente onderzoeken het beste met de sterfte na het infarct.^{7,8,10-12} Hier dringt zich de vergelijking op met de angiografische gegevens: ook daar is de functie van de linker kamer, behalve bij patiënten met een aandoening van de hoofdstam, prognostisch van groter belang dan de ernst van de anatomische afwijkingen in de coronairarteriën.¹³

Gezien de zeer lage éénjaarssterfte na een ongecompliceerd myocardinfarct, is het niet verrassend dat de bijdrage die inspanningsonderzoek kan leveren aan de prognostische indeling van deze patiënten, slechts gering is. Niettemin heeft het onderzoek ook in deze groep zijn waarde: zo is, bij afwezigheid van angina pectoris tijdens de test, de kans op cardiale complicaties tijdens het na-onderzoek zeer gering.

Hoewel uit de sterftcijfers van ons onderzoek de indruk zou kunnen ontstaan dat het doormaken van een ongecompliceerd infarct op jonge leeftijd niet zoveel betekenis heeft, mag niet uit het oog verloren worden dat een recidiefinfarct de prognose op langere termijn zeker nadelig zal beïnvloeden. In ons onderzoek ontstond bij 10% van de patiënten een niet-dodelijk recidiefinfarct binnen een jaar. Geen van de inspanningsgegevens bleek van waarde voor de voorspelling van deze gebeurtenis; resultaten van andere studies en eigen gegevens uit een andere populatie bevestigden deze slechte voorspelbaarheid.^{8,14}

Tenslotte moet met enige nadruk vermeld worden dat het niet duidelijk is welke waarde gehecht moet worden aan het vinden van een zogenaamde high risk-coronaria-aandoening bij patiënten met geen of

weinig klachten. Veenbrink et al. wezen hier reeds op.¹ Er is inmiddels aangetoond dat een bypassoperatie de prognose van deze patiënten niet verbetert.¹⁵ Hiermee vervalt de noodzaak om door middel van niet-invasief onderzoek patiënten te selecteren die ondanks de afwezigheid van klachten toch een uitgebreide coronaria-aandoening hebben.

CONCLUSIE

De uitkomsten van dit onderzoek bevestigen het goede éénjaarsoverlevingscijfer voor patiënten jonger dan 60 jaar, die hun eerste infarct overleven en bij wie geen recidiefinfarct, decompensatie, late ritmestoornissen of angina pectoris ontstaat in het ziekenhuis. Het verrichten van een inspanningstest vóór ontslag heeft dus prognostisch niet veel waarde, maar lijkt zinvol om andere redenen. De test kan het zelfvertrouwen van de patiënt doen toenemen, dan wel angineuze klachten provoceren die aanleiding kunnen zijn tot medicamenteuze therapie of eventueel coronairangiografie; bovendien kan het resultaat van de test een richtlijn zijn voor latere revalidatie. Het optreden van uitsluitend ST-segmentdaling tijdens de inspanning vormt echter geen reden tot coronairangiografie over te gaan.

SUMMARY

Prognosis of the uncomplicated first myocardial infarction in patients under 60: an indication for cardiac catheterization? - A follow-up study of 119 consecutive patients younger than 60 years one year after their discharge following hospitalization for an uncomplicated first myocardial infarction. Only one patient was found to have died suddenly within one year; 10 had had reinfarctions. 110 patients had been subjected to effort ECG one day before discharge. A correlation was observed between occurrence of angina pectoris and ST segment depression during the effort test and angina during the follow-up period. One-half of the patients had shown at least 0.1 mV depression of the ST segment. The effort test results proved to be irrelevant for prediction of reinfarction, however. It is concluded that depression of the ST segment during effort testing in this group of patients does not constitute an indication for coronary angiography.

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Aanvaard op 15 juli 1985

ERRATA CHAPTER 6

Table 1, page 70 : the first column should be as follows:

A <u>Verschijnselen</u>	
angina pectoris, n (%)	
ventriculaire ritmestoornissen, n (%)	
B <u>Onderzoek bevindingen</u>	
behaalde max. belasting,	% (SD)
0.1 mV ST-daling,	n (%)
0.2 mV ST-daling,	n (%)
0.1 mV ST-stijging,	n (%)
0.2 mV ST-stijging,	n (%)
max hartfrequentie,	sl/min (SD)
max syst bloeddruk,	mmHg (SD)
toenamse syst bloeddruk,	mmHg (SD)

Table 2, page 70 : the first column should be as follows:

overleden,	n (%)
recidief infarct,	n (%)
angina pectoris	n (%)
CABG of PTCA	n (%)
geen complicaties,	n (%)

CHAPTER 7

SURGICAL VERSUS NON-SURGICAL MANAGEMENT OF PATIENTS SOON AFTER ACUTE MYOCARDIAL INFARCTION

By

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Br Heart J 1985, 54: 460-465.

Surgical versus non-surgical management of patients soon after acute myocardial infarction

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SUMMARY Of 510 patients admitted to hospital with acute myocardial infarction, 34 had coronary artery bypass grafting before discharge (6-43 days (median 20) after infarction). The patients who were given grafts generally had a smaller infarction with less functional impairment than the 476 patients who were not. The outcome of coronary artery bypass grafting was investigated in a retrospective matched pair study. Patients were matched on the basis of the presence of post-infarction angina, left ventricular ejection fraction, location of the infarction, peak creatine kinase activity, Killip clinical class, and severity of coronary disease with 34 patients who were given medical treatment only. At one year follow up fewer of the operated patients had symptoms than did the matched non-operated patients. Survival at one year in the operated and non-operated groups respectively was 94% *vs* 91%; angina within one year occurred in 3% *vs* 68%; congestive heart failure in 3% *vs* 6%; and 0% *vs* 32% were referred for later bypass grafting or coronary angioplasty.

It is concluded that coronary artery bypass grafting can be performed safely soon after myocardial infarction provided that left ventricular function is not seriously compromised. Such treatment is more effective than medical treatment for relief of angina during the first year after infarction.

Referral for coronary artery surgery early after acute myocardial infarction presents a dilemma to the cardiovascular team. It has long been maintained that surgery at this stage carries substantial operative risks; recent reports, however, suggest that such estimates of operative mortality and complications may be unduly pessimistic.¹⁻³ DeWood *et al* and Berg *et al* have reported that surgery can be safely performed in the acute phase of infarction with excellent results.^{1,4} When pharmacologically uncontrolled angina indicates the likelihood of further deterioration, the indication for surgery is clear, especially since it may be possible to salvage the jeopardised myocardium. The possibility that surgery will improve long term survival or prevent reinfarction in this group of patients, however, has not been proven.

For the past few years we have referred patients

for coronary bypass surgery when recurrent angina was refractory to pharmacological treatment, in some patients soon after acute myocardial infarction and in others when angina was induced by mild exertion and associated with severe coronary lesions. It has been our impression that this could be done at low risk and with good long term results.

We have compared results in a group of patients operated on soon after infarction with results in all other patients seen over the same period who received only pharmacological treatment. We have also compared them with a matched pair series of patients at similar risk and with similar symptoms who were not operated on. Over a one year follow up we compared mortality, reinfarction, late referral to bypass surgery or coronary angioplasty, and recurrence of complaints.

The sole criterion for inclusion in the surgery group was that the patient had isolated coronary artery bypass grafting soon after an acute infarction and before hospital discharge. Most had angina pectoris at rest that was resistant to intensive medical treatment. There are always exceptional cases, how-

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ever, generally those with angina during mild exertion or advanced proximal lesions or both. In this study we have chosen to include all cases referred to surgery before hospital discharge after an acute myocardial infarction.

Patients and methods

Myocardial infarction was diagnosed when at least two of the following were present: typical prolonged chest pain lasting at least 45 minutes; evolving QR complexes or Q waves of more than 0.04 s duration with ST and T wave changes in the case of transmural infarction, or T wave inversion or ST depression persisting for at least 24 hours without loss of the R wave or development of new Q waves in the case of non-transmural infarction; a typical rise and fall of total creatine kinase with a peak activity greater than 100 IU/l (twice the upper limit for normal in our clinic).

From March 1981 to February 1983 there were 529 admissions with acute infarction. Hospital treatment followed the guidelines described by Simoons *et al.*⁵ Four cases were referred for surgery because of mitral valve incompetence, ventricular septal defect, or free wall ventricular rupture, and fifteen were treated by elective percutaneous transluminal angioplasty before discharge. These nineteen patients were excluded.

Of the remaining patients, 34 had coronary surgery during the admission for myocardial infarction and 476 did not. In 27 patients the indication for operation was persistent angina pectoris at

rest, refractory to medical treatment including beta blockers, calcium antagonists, and nitrates. Three of these patients were in Killip class III or IV during the acute phase of infarction. No patient was in severe heart failure or cardiogenic shock at the time of operation. The seven other patients did not have persisting angina at rest; three of them had angina during mild exertion and they were found to have severe proximal lesions, and four had severe proximal lesions in the infarct related artery after attempted intracoronary thrombolysis with streptokinase. Table I summarises the clinical data at entry to the trial. The coronary score⁶ was 15.5 (8.8) (mean (SD)), three patients were classified as having proximal three vessel disease, none had exclusively distal vessel disease.

Seventy three (15%) of the 476 patients who were not referred to surgery also had post-infarction angina, but they were not offered surgery for various reasons: angina became responsive to medication; there were contraindications to surgery because of severe non-cardiac disease; some refused surgery; and in a few the coronary anatomy was not suitable. Poor left ventricular function was not regarded as a contraindication to coronary bypass operation.

A subgroup of 34 non-operated patients was matched to the operated patients on the basis of age, presence of angina during the hospital stay, Killip class, left ventricular ejection fraction (radionuclide ventriculography) at discharge or before surgery, location of the infarction, peak serum creatine kinase activity, and anatomical severity of coronary artery disease (greater than 50% diameter stenosis, coded

Table 1 Key prognostic variables used to select matched pairs from the larger series of non-operated patients to match the group of operated patients

Variable	Operated	Matched non-operated	p	All non-operated	p
No. of cases	34	34	—	476	—
Age (years)	60.7 (6.1)	55.5 (8.9)	0.01	58.3 (11.6)	NS
Post-infarction angina at rest	27 (79%)	25 (74%)	NS	73 (15%)	0.0001
Ejection fraction	0.48 (0.14) (31 cases)	0.49 (0.11) (34 cases)	NS	0.45 (0.16) (358 cases)	*
Location of MI:			NS		0.025
Transmural anterior	9 (26%)	10 (29%)		189 (40%)	
Transmural inferior	10 (29%)	9 (26%)		177 (37%)	
Non-transmural	15 (44%)	15 (44%)		102 (21%)	
Undefinable/unknown	0	0		8	
Peak serum CK (IU/l)	420 (390)	420 (320)	NS	610 (530)	0.05
Killip class:			NS		0.025
I	25 (74%)	25 (74%)		278 (58%)	
II	6 (18%)	6 (18%)		113 (24%)	
III or IV	3 (9%)	3 (9%)		85 (18%)	
Anatomical severity:			NS		*
1 or 2 vessel disease	15 (44%)	18 (53%)		111 (23%)	
3 vessel or left main vessel disease	19 (56%)	16 (47%)		43 (9%)	
Unavailable	0	0		322 (68%)	

Data are reported as events and percentage of cases or as mean (SD). Statistical comparisons: non-operated *vs* operated; NS, difference not significant at the 0.05 level.

*No statistical comparison because large numbers of entries were missing.

MI, myocardial infarction; CK, creatine kinase.

as (a) one or two vessel disease or (b) three vessel disease or worse) (Table 1). Mean (SD) coronary score^a was 12.5(6.5), one case was classified as having proximal three vessel disease and five cases having exclusively distal vessel disease.

Medication in the operated patients (at referral to surgery) was compared with that in the non-operated matched pairs: beta blockers in 85% of operated vs 80% non-operated, calcium antagonists in 85% vs 60%, nitrates in 85% vs 70%, digoxin in 18% vs 15%, and diuretics in 29% vs 33%. Treatment at discharge for all 476 non-operated patients included beta blockers in 44%, calcium antagonists in 19%, nitrates in 33%, digoxin in 25%, and diuretics in 38%. The median duration from onset of the infarction to operation was 20 days (range 6 to 43 days); 97% were operated on within 35 days. For those patients referred for operation, treatment with analgesics and sedatives had already been started, hence additional premedication was usually not required. Intravenous fentanyl 15 µg/kg was used for induction of anaesthesia and 0.1 mg/kg pancuronium was given to facilitate intubation. Treatment with intravenous glyceryl trinitrate and inotropics was determined on the basis of arterial pressure monitoring and in principle drug treatment continued until extracorporeal circulation was established. The patient was ventilated with a servoventilator with a mixture of oxygen and nitrous oxide (40:60). Additional intravenous fentanyl and possibly pancuronium were given as required before sternotomy and later during operation.

Coronary artery bypass grafting was performed with moderate systemic hypothermia (28°C) and cardioplegic arrest in combination with topical cooling by means of a saline solution (4°C). Cardioplegic arrest was accomplished by use of at least 500 ml of St Thomas's solution (sodium chloride 91.6 mmol/l, potassium chloride 14.8 mmol/l, magnesium sulphate 1.2 mmol/l, magnesium chloride 15 mmol/l, potassium dihydrogen phosphate 1.2 mmol/l, calcium chloride 1.2 mmol/l, and hydrochloride pro-

caine 1.0 mmol/l). This was administered through the aortic root after cross clamping. If cross clamping lasted more than one hour after the initial infusion, cardioplegia was repeated every 60 minutes to maintain a flat electrocardiogram.

A jump graft was constructed with a saphenous vein graft to all coronary arteries which had stenosis of 50% or more. One sequential vein graft was routinely used and all distal anastomoses were made during cardioplegic arrest. The proximal anastomosis was made after removing the cross clamp during rewarmed. The average revascularisation rate was 3.5 grafts per patient (6 cases with 5 grafts, 11 with 4, 10 with 3, and 7 with 2). Sinus rhythm usually returned spontaneously. The left ventricle was always vented by means of a left ventricular drain.

Ventilation in the postoperative period was continued until the patient awoke and was haemodynamically stable. Hypertension was treated with nitroprusside. The patient was extubated on the same day as operation or the next morning.

Results

Compared with the 476 non-operated cases, the 34 operated cases had a greater frequency of non-transmural infarction, were more often in Killip class I, and had lower mean peak serum creatine kinase values, indicating less myocardial damage from the acute infarction. The ejection fraction, however, appeared to be similar in both groups, but it was not known in 61 of 70 (87%) of patients who died in hospital compared with 60 of 444 (14%) hospital survivors. The mean (SD) ejection fraction of 0.45 (0.16) for non-operated cases, because it is derived from the group containing the larger fraction of deaths, may therefore overestimate the true ejection fraction for this group. Finally, the in-hospital mortality rate was 3% for operated cases vs 14% for all 476 non-operated cases (Table 2). All these

Table 2 Clinical information before discharge from hospital

Variable	Operated	Matched non-operated	p	All non-operated	p
No. of cases	34	34	—	476	—
Males	27 (79%)	29 (85%)	NS	377 (79%)	NS
History of angina of more than 4 weeks	22 (65%)	11 (32%)	0.01	164 (34%)	0.0005
History of old MI	17 (50%)	17 (50%)	NS	145 (30%)	0.02
Wedge pressure (mm Hg) at admission	9.8 (6.1)	11.1 (4.5)	NS	15.3 (6.6)	0.05
Cardiac index in CCU at admission	3.1 (1.1)	2.8 (0.7)	NS	2.6 (0.8)	0.05
Systemic arterial pressure	119 (20)	126 (23)	NS	121 (25)	NS
Length of hospital stay	22 (10)	18 (15)	NS	12 (10)	0.0001
Recurrent MI in hospital	4 (12%)	3 (9%)	NS	24 (5%)	NS
Death in hospital	1 (3%)	1 (3%)	NS	69 (14%)	0.07

Data are reported as events and percentages of cases or as mean (SD). Statistical comparisons: non-operated vs operated; NS, difference not significant at the 0.05 level. MI, myocardial infarction; CCU, coronary care unit.

results indicate that patients referred for coronary artery bypass grafts were generally in a better condition overall after their myocardial infarction than were the non-operated patients. Therefore some form of matching is required to obtain a meaningful comparison between the operated and non-operated patients.

The size of the infarction appeared to have a bearing on the timing of operation; when peak serum creatine activity was <400 IU/l the median delay from date of myocardial infarction to operation was 14 days compared with 26 days when creatine kinase was \geq 400 IU/l.

One year survival in the operated cases was 94% compared with 91% in matched non-operated cases (Table 3). Two patients in the operated group died; both had had post-infarction angina and were in congestive heart failure in the acute phase of infarction. The first death, in a man aged 65, occurred in the perioperative period and 7 days after the infarction. He had an inferior infarction with peak serum creatine kinase activity of 530 IU/l, an ejection fraction of 0.37, and three vessel disease. Death was caused by low cardiac output syndrome. All grafts were found to be thrombosed. The second death, in a man aged 64, occurred 5 months after infarction and was caused by congestive heart failure. He had had an extensive inferior infarction with peak serum creatine kinase activity of 1595 IU/l.

There were three deaths in the matched non-operated group. The first occurred 26 days after infarction due to cardiac rupture in a 60 year old man (inferior infarction, peak serum creatine kinase activity 400 IU/l, ejection fraction 0.41, three vessel disease, and with congestive heart failure in the acute phase). This patient did not have post-infarction angina in the acute phase but the other two did. The second death occurred at 70 days due to progressive cardiac failure in a 50 year old man (anterior infarction, peak serum creatine kinase activity 1360 IU/l, ejection fraction 0.18, three vessel disease). The third death occurred at 67 days due to

congestive heart failure in a 67 year old man (anterior infarction, peak serum creatine kinase activity 130 IU/l, ejection fraction 0.24, history of previous infarctions, three vessel disease).

Among the survivors at one year (32 operated, 31 matched non-operated, and 356 non-operated cases) there were several highly significant differences. Cardiological events were infrequent in the operated cases; only one patient had angina and another had symptoms of congestive heart failure. Of the 356 survivors in the non-operated group, 143 reported angina by one year (43% of survivors), 57 had had an episode of congestive heart failure (16% of survivors), and 30 were eventually referred to coronary artery bypass graft surgery (8% of survivors). The comparison of operated survivors with the matched non-operated patients is even more striking. Of the 31 matched non-operated survivors, 23 (74%) had angina by one year (five with angina Killip class IV, six with class III, and twelve with class II) and 10 were referred for late coronary artery bypass surgery (32%). The frequency of recurrent infarction and congestive heart failure, however, is similar to that in the operated cases.

Since the indication for coronary artery bypass grafting shortly after an acute infarction is recurrent angina resistant to medical treatment, it is pertinent to ask whether these cases differ in any other important way from those without post-infarction angina. To avoid a selection bias, we considered only those patients who survived the first 72 hours after the acute event. Ninety eight patients presented with such post-infarction angina (21% of 472 patients surviving three days or more) (Table 4). There were no significant differences in the distribution of age, sex, or history of a previous infarction, although cases with recurrent angina do have a longer history of angina before the acute event. Ventricular function is virtually identical in the two groups as is one year survival. At discharge beta blockers, nitrates, and calcium antagonists were more frequently being given to patients with post-infarction angina.

Table 3 Follow up of patients after discharge from hospital

Variable	Operated	Matched non-operated	<i>p</i>	All non-operated	<i>p</i>
No. of cases	34	34	—	476	—
Death after discharge	1 (3%)	2 (6%)	NS	51 (11%)	NS
Survival at 1 year	32 (94%)	31 (91%)	NS	356 (75%)	0.02
Recurrent MI by 1 year	0 (0%)	0 (0%)	NS	27 (6%)	NS
Angina by 1 year	1 (3%)	23 (68%)	0.0001	153 (32%)	0.0001
CHF within 1 year	1 (3%)	2 (6%)	NS	57 (12%)	0.05
CABG within 1 year	0 (0%)	10 (29%)	0.001	30 (6%)	NS
PTCA within 1 year	0 (0%)	1 (3%)	NS	5 (1%)	NS

Data reported as events and percentage of cases. Statistical comparisons: non-operated *vs* operated; NS, difference not significant at the 0.05 level.

MI, myocardial infarction; CHF, congestive heart failure; CABG, coronary artery bypass graft surgery; PTCA, percutaneous transluminal coronary angioplasty.

Discussion

Earlier reports on the outcome of bypass operations performed soon after acute myocardial infarction were not encouraging. In 1974 Dawson *et al* reported a hospital mortality rate of 14.5% in 145 patients operated on within two months of an acute myocardial infarction and a rate of 38% in those operated within one week.⁷ At that time hospital mortality for elective coronary artery bypass graft surgery in patients without a recent myocardial infarction was 6.2% at the same hospital. Because this latter figure is considerably higher than that currently reported^{8,9} (less than 2% at most hospitals), it is likely that the surgical mortality for patients with acute infarction has also fallen, and, indeed, recent reports clearly demonstrate this fact. In 1985 Williams *et al* reported a hospital mortality rate of 2% in patients operated on within 30 days of infarction,² and Nunley *et al* reported a 3% operative mortality rate in those operated on within two weeks of infarction; this was in a subgroup of 66 patients with threatened extension of infarction.³ In our series the operative mortality is one case out of 34 (3%) while the one year survival (94%) accords with the recent reports mentioned above. The current operative mortality rate at our institution for all aortocoronary bypass surgery is 1.2% with a 5 year survival of 93.5%.¹⁰ While surgical mortality after acute infarction has apparently improved greatly over the past decade, it still falls somewhat short of the excellent results of elective surgery.

It should be borne in mind that our results are based on a retrospective study with all the limitations inherent in such an approach, and despite matching major differences remain between the two groups—these are responsiveness to medical treatment, unsuitable coronary anatomy for bypass surgery, and important non-cardiac disease. For example, five patients in the non-operated group had exclusively distal vessel disease whereas none of the operated group did.

There has been a substantial improvement in surgical technique and postoperative care since the early 1970s, and we agree with Nunley *et al*³ that current results do mitigate the concern about attempting an early operation in patients with post-infarction angina. Nevertheless, we should continue to exercise caution. Because the current policy generally excludes patients with extensive ventricular dysfunction, much of the risk of surgery has been eliminated at the outset. This is borne out by the fact that the two deaths in the operated group, one at 7 days and the other at 5 months, occurred in patients with poor left ventricular function. Furthermore, it has been our policy to select patients in whom the

infarction is small or caused relatively little functional impairment or both. Such patients would be expected to have a better prognosis whether or not they were operated on early, and this assumption is supported by the results in the matched pair series.

We found no significant difference in survival between patients with or without post-infarction angina (Table 4), nor was there a significant difference in survival between those operated on and the matched non-operated patients. It is doubtful whether operation would materially affect one year survival in any event since it was carried out too late to influence the primary infarct size itself.¹¹ DeWood *et al*¹ and Berg *et al*⁴ have reported that operation at a sufficiently early stage of infarction may limit infarct size and improve survival, although this can not be taken as proven since their patients formed a consecutive series without concurrent controls. The major benefit of surgery in our

Table 4 Comparison of patients without and with post-infarction angina who survived the first 72 hours after myocardial infarction (472 patients)

Variable	No post-MI angina	Post-MI angina	p
No of cases	374	98	—
Age (years)	57 (12)	60 (10)	NS
Males	301 (80%)	75 (77%)	NS
Length of stay (days)	12.9 (8.8)	18.8 (10.7)	0.001
Ejection fraction	0.45 (0.16)	0.46 (0.13)	NS
	(303 cases)	(86 cases)	
History of old MI	114 (30%)	36 (37%)	NS
History of AP for more than 4 weeks	110 (29%)	61 (62%)	0.001
Location of MI:			NS
Transmural anterior	144 (38%)	31 (32%)	
Transmural inferior	139 (37%)	34 (35%)	
Non-transmural	85 (23%)	32 (33%)	
Unknown/undefinable	6	1	
Peak serum CK (IU/l)	620 (540)	520 (420)	NS
Killip clinical class:			NS
I	237 (63%)	64 (65%)	
II	90 (24%)	24 (24%)	
III	23 (6%)	6 (6%)	
IV	24 (6%)	4 (4%)	
Wedge pressure (mm Hg)	12.9 (6.5)	11.3 (6.0)	NS
Cardiac index (l/min/m ²)	2.8 (0.8)	2.6 (0.8)	NS
Mean arterial pressure (mm Hg)	123 (22)	123 (20)	NS
Death in hospital	27 (7%)	5 (5%)	NS
Death after discharge			
within one year	39 (10%)	13 (13%)	NS
Non-fatal reinfarction	43 (11%)	12 (12%)	NS
Total one year survival	317 (85%)	83 (85%)	NS
Medication at discharge:			
Anticoagulants	74 (20%)	19 (19%)	NS
Beta blockers	147 (39%)	63 (64%)	0.001
Digoxin	88 (24%)	18 (18%)	NS
Diuretics	129 (34%)	37 (38%)	NS
Nitrates	91 (24%)	73 (74%)	0.001
Calcium antagonists	46 (12%)	60 (61%)	0.001
Antiarrhythmics	18 (5%)	4 (4%)	NS

Data reported as events and percentage of cases or as mean (SD). All percentages computed over entire series of 374 and 98 cases respectively. NS, difference not significant at the 0.05 level. MI, myocardial infarction; AP, angina pectoris; CK, creatine kinase.

series thus is the effective management of refractory post-infarction angina. Nevertheless, the decision to perform bypass grafting for this indication soon after infarction remains a matter requiring careful judgment in each patient.

These data were gathered during a period when percutaneous transluminal coronary angioplasty started to gain acceptance at our institution. It is clear that angioplasty is having an impact on our policy to refer patients for operation; more patients receive angioplasty first, and those with unsatisfactory results or complications are later referred for operation.¹² Meyer *et al* have reported that angioplasty can be carried out at low risk and with good early and late results in patients with unstable angina pectoris.¹³ But results from randomised trials designed to evaluate the long term success rate of this policy have not yet appeared. Also it remains to be seen what effect the widespread availability of thrombolytic agents such as recombinant tissue type plasminogen activator¹⁴ will have on the management of these patients.

In summary, the results presented here for coronary artery bypass surgery after acute myocardial infarction show that this procedure can be carried out with low operative mortality and one year mortality. In patients with post-infarction angina in whom an extension of infarction is threatened operation should be considered provided that the infarct is small and that left ventricular function is good. We must emphasise, however, that if angina can be controlled by medical treatment early after infarction, then this remains the preferred approach. The most striking difference between the operated and non-operated matched pairs is the recurrence of angina within one year that required aggressive medical treatment, angioplasty, or coronary bypass graft surgery.

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CHAPTER 8

GENERAL DISCUSSION AND RECOMMENDATIONS

CHAPTER 8

GENERAL DISCUSSION AND RECOMMENDATIONS

The identification of high and low risk subjects among those who have recovered from acute myocardial infarction is a major aim in clinical cardiology, now that so many therapeutic modalities are available. It is logical that this should be done in the most efficient way, that is, as was pointed out in the introduction, with a strategy which provides the greatest information at the lowest possible cost and discomfort to the patient.

In order to make such risk assessment and provide therapeutic recommendations, it is essential to have a knowledge of the mortality risk of the disease. Only then does it make sense to stratify patients in different risk subsets. Numerous studies have shown that the time course of mortality in hospital survivors of myocardial infarction is characterized by a first year mortality of 10 to 15% as an average, with a subsequent annual mortality rate of 3 to 5%. In particular the first six months after hospital discharge represent a high risk period^{1,2}. Our findings are consistent with the data reported in the literature, since overall one year cardiac mortality was 11,7% (70 out of 596 hospital survivors). Thirty patients died during the first three months after discharge, an additional 14 patients between 3 and 6 months. Thus, of the one year cardiac mortality after discharge, 63% occurred in the first 6 months. More than one half of these patients (53%) died suddenly, that is within one hour from the onset of symptoms or were found dead unexpectedly. All these factors underscore the importance of an early risk assessment of post infarction patients.

Prognostic stratification can be based on variables related to the amount of myocardial damage, the extent of coronary artery disease, or residual myocardial ischemia, and to the presence of ventricular arrhythmias.

Adequacy of left ventricular function or the extent of myocardial damage can directly or indirectly be judged from simple clinical signs^{2,4}, or can be quantified by non-invasive or invasive methods, such as hemodynamic monitoring^{5,7}, serum enzyme levels⁸, radionuclide studies^{9,10}, echocardiography¹¹, 12 lead electrocardiography¹², chest X ray¹³ or cardiac catheterization, including left ventricular angiography^{14,15}.

Residual myocardial ischemia can be shown by exercise stress testing¹⁶⁻¹⁹, pharmacological interventions, like dipyridamole test²⁰, atrial pacing stress testing²¹ and by ST changes from 24-hour ambulatory electrocardiographic analysis²².

Finally, ventricular arrhythmias can be detected by telemetry, 24-hour ambulatory electrocardiographic monitoring²³ or by provocative tests such as exercise²⁴ or electrophysiological testing^{25,26}.

Based in part on these observations, it has been suggested that an algorithm be developed to identify patients at high and intermediate risk in whom a more aggressive management would be indicated, as well as low risk group where multiple tests and special management are not warranted^{27,28}. Such an algorithm should use the most sensitive and specific tests and eliminate or obviate those which are costly and redundant. Furthermore, low risk patients should not undergo invasive evaluation. Although a great amount of information is available on the prognostic value of the individual tests, little information is available on the relative prognostic value of the different tests and on their additive value beyond that of usual clinical information and tests²⁹⁻³². Therefore the question which tests, in which sequence and for whom in the evaluation of post-infarction patients remained open for debate as recently as 1985³³.

Accordingly we investigated in the same patients recovered from myocardial infarction the prognostic value of symptom limited bicycle ergometry, resting radionuclide ventriculography and 24-hour electrocardiographic monitoring since these provide information on left ventricular function, myocardial ischemia and ventricular arrhythmias and since they are among those tests who are most commonly applied in post infarction patients. We then compared this information to the cheapest method of them all, the medical history and the in-hospital course.

Exercise electrocardiography

Exercise testing can detect a myocardial ischemia in different ways, such as the provocation of angina and the induction the induction of ST segment changes. At variance with the findings of Theroux³⁴ and those of the Stanford Cardiac Rehabilitation Program³⁰, an "ischemic" response to exercise testing has in our experience not been a significant factor in identifying patients with increased mortality risk after hospital dis-

Table 1 *Revascularisation procedures in the first year after myocardial infarction in patients who underwent predischARGE stress test.*

stress test results	number of patients	revascularisation procedure		p-value	
		N	%		
ST depression \geq 1 mm	yes	191	41	21	0.0005
	no	213	17	8	
Angina	yes	85	30	35	0.0005
	no	323	28	8	
Total		408	58	14	-

* missing data in 4 patients with intra ventricular conduction abnormalities.

charge (Chapters 2 and 3 and Figure 1).

This apparently surprising negative finding is consistent with several other recent reports^{14,29,31,32,35-38}. The reason for such differing findings is not immediately apparent. It is probably related to a variety of factors, the most important of which is the selection of patients for exercise testing (fig 1). In our population 191 patients (32%) were judged not eligible for the exercise test, in 55 cases due to severe angina. These patients may have formed an important section of the patients described by Theroux³⁴. Furthermore many patients with exercise induced angina and ST depression underwent coronary artery bypass surgery or percutaneous transluminal coronary angioplasty at discharge or during follow-up (table 1). These factors could have had biased the results by underestimating the prognostic value of an ischemic response to exercise testing (Fig 1). On the other hand, the studies more corresponding to ours, reported by Jennings et al³⁷, Birk Madsen and Gilpin²⁹ and Saunamaki and Anderson³⁵ also did not show a relationship of ST segment depression to mortality. It was significant that in their series no patient underwent a revascularisation procedure during follow-up. Even though we cannot draw definitive conclusions about the lack of association between ST segment depression during exercise and cardiac mortality in our hands, our policy remains not to refer asymptomatic patients to coronary angiography when ST segment depression is the only abnormal finding during the exercise test.

In contrast to the absence of the "ischemic response", as a significant prognostic factor, the hemodynamic response (and in particular the extent of systolic blood pressure rise by cuff measurement) and the maximum workload, achieved during bicycle ergometry, were highly predictive of mortality (chapters 2 and 3). The extent of blood pressure rise was the single best prognostic variable and it was the only one which by multivariate analysis provided more information than the other usual clinical variables.

This finding is in good agreement with recently published results of the Multicenter Postinfarction Research Group³², who found in 655 patients who underwent a submaximal treadmill test early after myocardial infarction, that the duration of exercise and the maximal blood pressure were the best prognostic variables which identified a large percentage of low risk patients. In this study 57 intermediate risk patients were found with a maximal blood pressure of less than 110 mmHg (10 deaths, mortality of 17%) and 598 low risk patients (20 deaths, mortality of 3%). They conclude,

PREDISCHARGE EVALUATION AND PROGNOSIS AFTER AMI

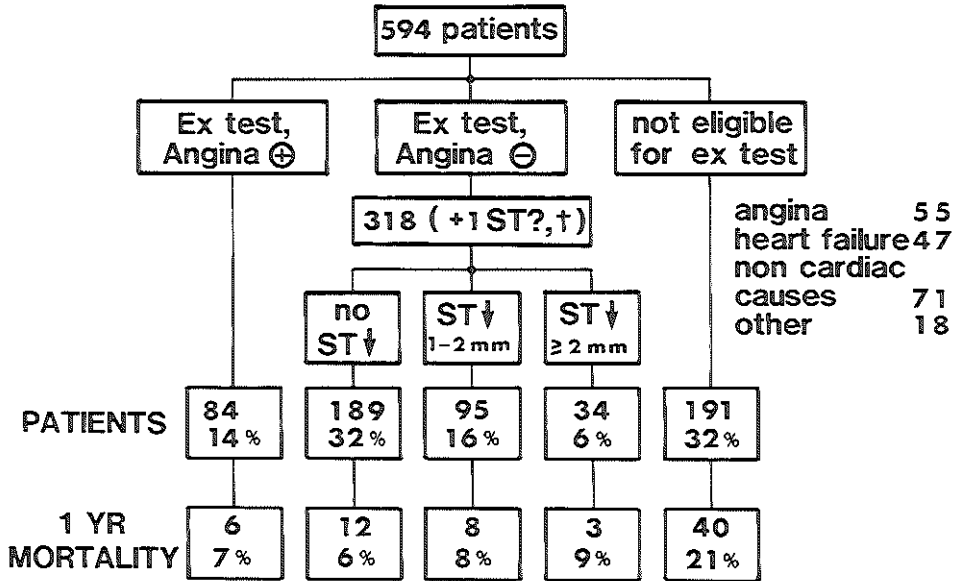


Fig. 1 Exercise test results and cardiac mortality during follow up in 594 hospital survivors of myocardial infarction.

like we, that it is very unlikely that drug therapy or revascularisation procedures will be of any value (unless indicated by symptoms) in such a low risk group. Also the execution of multiple tests is not indicated in this group. In our study, like in that of Krone et al³², patients were identified to be at high, intermediate and low risk based on the combination of their eligibility for exercise testing, a history of previous myocardial infarction, the indication for the use of digitalis at hospital discharge and the extent of blood pressure rise during exercise (see chapters 2 and 3). It appears that 40% of this population could be characterized as being eligible for the exercise test, not having spontaneous angina during exercise and with an "adequate" blood pressure response (30 mmHg or more) during exercise (Figure 2). This 40% had a very low mortality (3%), similar to the results described by Krone et al³². This is a subgroup of patients, for whom other tests and specifically invasive tests are not indicated.

Radionuclide ventriculography

Radionuclide ventriculography was confirmed to provide strong prognostic information (chapter 3) in agreement with many other studies^{9,14,15,-17,27,39}. The most efficient cut-off point, that is the point which provided the highest sensitivity and specificity, to stratify high and low risk patients was an ejection fraction of 40%. In agreement with the results of the Multicenter Postinfarction Research Group, we found that the risk of cardiac mortality progressively increased when the resting ejection fraction decreased below 40%.

However, an important finding of our study is that in patients who completed for exercise testing, the radionuclide ejection fraction did not provide additional prognostic information beyond that provided by clinical information and bicycle ergometry. This issue, as far as we know, has not been earlier addressed in the literature, and implies that the performance of a radionuclide study is only indicated in patients not eligible for stress testing, where it does provide independent information beyond clinical data (chapter 3). It is also helpful in those patients who appear at intermediate risk from clinical and exercise test results or in whom the test is equivocal. Even so, given the cost of this test in terms of apparatus and manpower requirements, it is an important conclusion that radionuclide testing can be reserved for a relatively small subset (about

PREDISCHARGE EVALUATION AND PROGNOSIS AFTER AMI

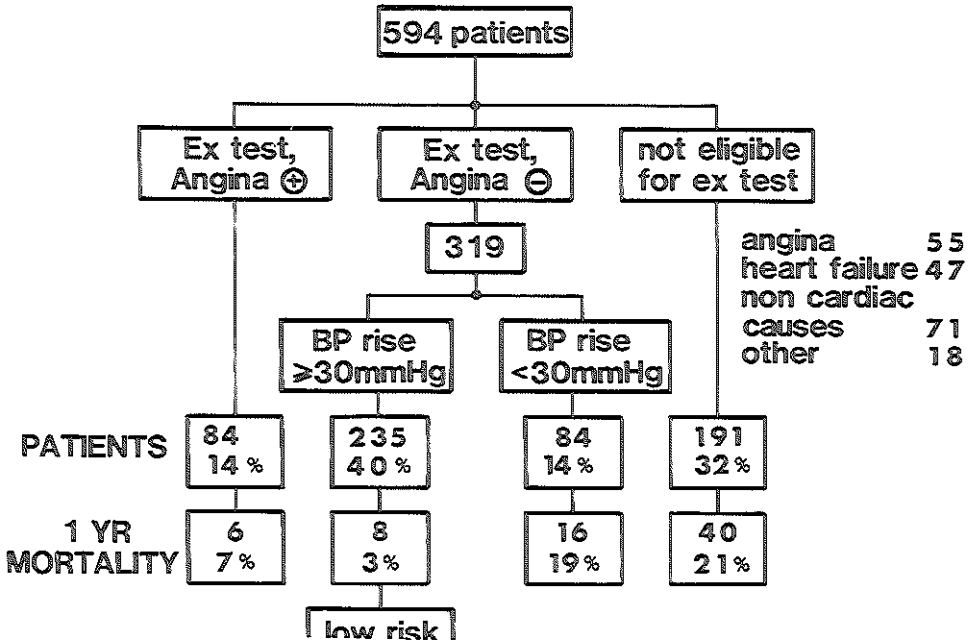


Fig. 2 Exercise test results and cardiac mortality during follow up in hospital survivors of myocardial infarction.

30%) of patients at the time of their discharge.

24-hour ambulatory electrocardiographic monitoring

With regard to the association between ventricular arrhythmias and subsequent cardiac mortality, the literature is virtually unanimous. In fact several studies have demonstrated a significant association between premature ventricular depolarizations (both in terms of frequency and patterns) and subsequent cardiac mortality^{1,23,39-42}. In particular, couplets and runs (3 or more complexes) of premature ventricular complexes are associated with the highest mortality⁴¹. Schultze et al⁴⁰ and Bigger et al⁴¹ found that the mortality was most elevated in patients with ventricular arrhythmias and left ventricular dysfunction. In particular, the results of the Multicenter Post-Infarction Research Group⁴¹ show that left ventricular dysfunction, assessed from ejection fraction and ventricular arrhythmias detected by 24-hour ambulatory electrocardiograms are independently related to mortality risk.

These data underscore that the clinical relevance of ventricular arrhythmias is dependent on the substrate, i.e. the degree of ventricular dysfunction. In keeping with these observations we found that ventricular arrhythmias were not significantly predictive of mortality in patients eligible for exercise testing (chapter 3, table 6), but were predictive in those not eligible for exercise testing, in whom the ejection fraction compared to that in patients eligible for exercise test was much lower ($39 \pm 16\%$ vs $47 \pm 15\%$, chapter 3, table 4).

Even when arrhythmias are found, the question remains whether reduction of ventricular arrhythmias can improve survival, particularly in those patients with decreased left ventricular function. Thus far, despite a consistent suppression of ventricular arrhythmias, no trial with anti-arrhythmic agents has demonstrated a reduction of cardiac mortality in post myocardial infarct patients^{41,42}. Different hypothesis have been formulated to explain this negative finding^{41,43}. The first hypothesis is that the suppression of ventricular arrhythmias does not improve prognosis at all. The second possible explanation is that the treatment of ventricular arrhythmias may prolong life, but that its benefit cannot be demonstrated since methodological limitations in the design of the trials and the relatively small number of patients participating prevent a small benefit from becoming evident. The last explanation is that no overall effect has been found as the control of ventricular arrhythmias may benefit some patients but harm others⁴⁵, thus cancelling each other.

In fact, a pro-arrhythmic effect of anti-arrhythmic drugs has been described⁴⁶, which may occur more frequently in patients with malignant ventricular arrhythmias and poor left ventricular dysfunction⁴⁶⁻⁴⁹. Accordingly our policy remains to treat ventricular arrhythmias, only when they are symptomatic, hence their systematic detection or induction has become less relevant.

Limitations of study

There are some limitations of this study, which should be discussed. Among these are the incompleteness of data, specifically regarding 24-hour ambulatory electrocardiographic monitoring and radionuclide ventriculography. Other problems are the relatively small number of end-points especially in the group of patients with complete tests (chapter 3) and the absence of an independent population to test the performance of the prognostic variables that were found.

The prognostic value of a low blood pressure response in patients on beta-blockers should be judged with some caution, because of the "blunting effect" of beta blocking on blood pressure rise. In these patients. The results of the test should be evaluated in the context of other variables of exercise tests related to left ventricular function or one might consider to repeat the test after withdrawal of beta blockers, if the clinical conditions of the patients allow this.

In chapter 5 the peak serum creatine kinase level was chosen as an indirect marker of infarct size. This has been done because this measurement is usually performed in most coronary care units. However, we acknowledge that this is a very crude measurement of myocardial damage. Other more specific enzymes like CK-MB or a-HBDH provide more specific information about myocardial necrosis and probably about prognosis, especially if time-concentration curves are derived from serial measurements^{4,9}. Furthermore, the use of thrombolytic agents in the treatment of acute myocardial infarction is increasing. Since they modify the pattern of enzyme release by including a rapid washout in cases of coronary reperfusion, it is likely that in an era where early coronary recanalisation will be increasingly applied, the clinical relevance of the peak serum enzyme levels will diminish.

Conclusions

Our current view is that the assessment of risk should be carried out in the least invasive way and in the most cost effective manner. It should begin by an accurate interpretation of the usual clinical variables supplemented by a symptom limited exercise test (figure 3). This can be performed on average 2 weeks after infarction in about 3/4 of the patients who do not present persistent heart failure, angina refractory to medical therapy or non-cardiac limitations. Exercise test should be symptom limited, since if patients are carefully selected, this is a safe procedure and is more accurate to detect signs and symptoms of myocardial ischemia than "submaximal" heart rate limited tests⁵¹⁻⁵⁴.

Additionally the symptom limited nature of the exercise protocol was crucial in our study, since the most valuable prognostic variables were the extent blood pressure rise from resting values to peak workload, and maximal working capacity itself. These data are consistent to recent findings of the Cardiac Rehabilitation Group in Stanford⁵⁵.

Patients not eligible for stress testing who have recurrent angina pectoris, marked heart failure, late sustained ventricular tachycardia or ventricular fibrillation, represent a very high risk subset with a mortality during the first year of up to 60%. In these patients multiple tests are indicated, according to the specific individual problem with the aim of detection ventricular malfunction. Cardiac catheterisation is recommended in all patients with angina pectoris. In patients with heart failure a non invasive evaluation with echocardiography and/or radionuclide ventriculography may be performed first and cardiac catheterisation should be limited to those in whom there is evidence of left ventricular aneurysm, ventricular septal defect or mitral regurgitation, lesions which might surgically be corrected. In this regard echocardiography with the recent addition of Doppler echocardiography may be superior to radionuclide studies for the more complete information, its repeatability and the lack of harmful radiation. However a drawback of this technique is that it allows less frequently than radionuclide ventriculography a quantification of ventricular function. Twenty four hour ambulatory electrocardiographic monitoring is recommended in patients with late symptomatic ventricular tachy-arrhythmias for the assessment of the effect of antiarrhythmic treatment.

Out of the 75% of hospital survivors eligible for the exercise test, more than 50% with an "adequate" systolic blood pressure response (of

PREDISCHARGE EVALUATION OF POST-INFARCTION PATIENTS

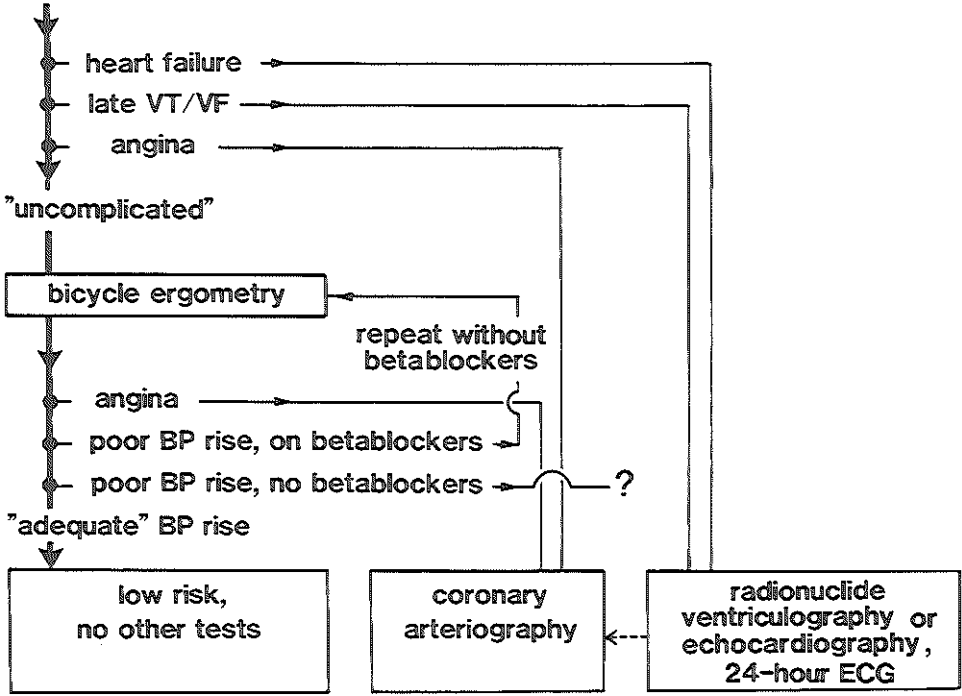


Fig. 3 Flow chart proposed for the evaluation at discharge of patients after myocardial infarction.

30mmHg or more) during exercise, represent a low risk subset (1 year mortality of 3%) and do not require additional tests, unless indicated by symptoms.

Patients with lower blood pressure response, even in absence of angina pectoris, represent an intermediate risk group, with an average mortality of 15 to 19% during the first year. Of this group of patients, which are asymptomatic, but still have an increased risk, it is unclear whether and which special tests or interventions are indicated. In fact it is reasonable to perform additional tests only if they can guide therapeutical procedure. For instance if coronary artery bypass surgery or percutaneous transluminal angioplasty are entertained, coronary angiography should be the additional first choice test without other tests before.

It is our opinion that the guidelines described above are preferable in practise because exercise testing is so effective in delineating low risk patients. As it is inexpensive and has similar prognostic information to that of radionuclide ventriculography, while providing information on myocardial ischemia, exercise tolerance and arrhythmias it is the most valuable approach for risk assessment. It also allows for the estimation of the amount of activity patient should be allowed after discharge and for developing a schedule of rehabilitation. Finally, it considerably improves the self confidence of patients recovering from myocardial infarction⁵⁶.

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CHAPTER 9

Samenvatting
Summary

SAMENVATTING

Het doel van deze studie is het geven van een zo compleet mogelijke beschrijving van de gegevens van na-onderzoek gedurende 1 jaar, verkregen bij een achtereenvolgende groep van 706 patiënten ontslagen uit het Thoraxcentrum gedurende de periode maart 1981 tot december 1983.

In het bijzonder hebben wij getracht de relatieve waarde van de gebruikelijke klinische variabelen, die van belang zijn voor de overleving na ontslag uit het ziekenhuis, vast te leggen. De waarde van deze klinische variabelen is bovendien vergeleken met het voor ontslag verrichte inspanningsonderzoek, met metingen van de linkerkamerfunctie door middel van radionuclide-angiografie en met 24-uurs-elektrocardiografie. Wij hebben laten zien dat bij patiënten, die in aanmerking kwamen voor de inspanningstest, de stijging van de bloeddruk gedurende de inspanning additionele prognostische informatie verschaftte ten opzichte van de reeds bekende klinische gegevens. De meting van de functie van de linkerkamer en langdurige registratie van het ECG bracht in de aldus gegeven prognostische indeling bij deze groep patiënten geen wijziging, ook niet indien er electrografische registratie sprake was van ventriculaire tachycardiën. Patiënten, die in staat waren de inspanningstest te verrichten, hadden een veel lagere mortaliteit dan patiënten bij wie het onderzoek op cardiale grond gecontraïndiceerd was (8% versus 56%). Op grond van klinische en inspanningsgegevens kon een groep patiënten geïdentificeerd worden met een zeer laag risico voor overlijden (mortaliteit 3%). Deze patiënten, 40% van alle patiënten ontslagen na het doorgemaakte myocardinfarct, zijn gekenmerkt door stijging van de systolische bloeddruk met meer dan 30 mmHg tijdens inspanning. Hieruit kan geconcludeerd worden dat in een omvangrijke groep patiënten het risico voor overlijden geschat kan worden op basis van een zorgvuldige klinische evaluatie en de gegevens van de inspanningstest. Aanvullende testen in deze patiënten lijken dan ook overbodig, tenzij bijkomende klachten deze onderzoeken zouden rechtvaardigen. Bij de patiënten bij wie het inspanningsonderzoek gecontraïndiceerd was, verschaften metingen van de functie van de linkerkamer en langdurige registratie van het ritme additionele prognostische informatie, ook indien er rekening werd gehouden met reeds bekende klinische gegevens. In deze groep patiënten lijken deze onderzoeken zeker zinvol.

In een groep patiënten met relatief laag risico, gekenmerkt door de afwezigheid van intraventriculaire geleidingsstoornissen en/of ventri-

culaire hypertrofie en/of atrium fibrillatie, werd de prognostische waarde van het 12 afleidingen ECG voor ontslag beoordeeld. Hoewel bij deze analyse bevestigd werd dat sommige variabelen van het 12 afleidingen ECG prognostisch van belang zijn, bleek bij multivariate analyse alleen de QRS-score als beschreven door Selvester, als ook persisterende ST segment daling en verlengd QT interval onafhankelijk geassocieerd met mortaliteit volgend op het infarct. De associatie van klinische variabelen met mortaliteit was echter veel sterker, zodat de toevoeging van de electrocardiografische gegevens de prognostische indeling van deze patiënten niet beïnvloedde.

De invloed die de maximale waarde van de creatine phosphokinase (CK) heeft op de prognose werd onderzocht bij patiënten, die een eerste infarct doormaakten. Er bleek een correlatie te bestaan tussen de CPK waarde's en de hoogste mortaliteit in het ziekenhuis. Gedurende het na-onderzoek werd echter geen relatie gevonden tussen maximale CPK waarde en mortaliteit, recidief infarct en angina. Hieruit kan geconcludeerd worden, dat men in deze groep patiënten het verdere diagnostisch of therapeutisch handelen niet van de maximale waarde van CK moet laten afhangen.

De betekenis van de voor ontslag verrichtte inspanningstest bij 119 achtereenvolgende patiënten die een ongecompliceerd infarct doormaakten en die jonger waren dan zestig jaar, werd duidelijk in het jaar volgend op het myocard infarct. Gedurende het na-onderzoek overleed slechts 1 patiënt, terwijl 10 een niet fataal recidief infarct doormaakten. De aanwezigheid van angina pectoris, en/of ST segment depressie tijdens inspanning bleek niet van waarde voor de voorspelling van het recidief infarct, maar deze variabelen correleerden wel met het optreden van late angina pectoris. Geconcludeerd wordt dat in deze groep patiënten coronaire angiografie niet noodzakelijk is op grond van de aanwezigheid van ST segment daling tijdens inspanningsonderzoek, daar de prognose van deze groep uitstekend is.

Tenslotte bestudeerden wij het effect van vroege bypass operatie na een doorgemaakt myocard infarct bij 34 geopereerde patiënten, die vergeleken werden met 34 anderen, medicamenteus behandeld. De twee groepen kwamen overeen voor wat betreft klinische, ventriculaire en coronaire angiografische gegevens. Indicatie voor operatie werd gevormd door post-infarct angina in 30 patiënten en doorgemaakt infarct in aanwezigheid van ernstige multiple proximale vatafwijkingen in de vier overige patienten. De operatie vond plaats na een mediaan interval van 20 dagen na het

infarct. Aan de directe gevolgen van de operatie overleed 1 patiënt. Tijdens het na onderzoek werd geen verschil gevonden in overleving of in het optreden van een niet fataal reinfarct tussen de geopereerde en niet geopereerde groep. De geopereerde patiënten hadden echter een lagere incidentie van angina pectoris. Op grond van de kleine aantal patiënten is het moeilijk hieruit een definitieve conclusie te trekken. Wel kan gesteld worden, dat een bypass operatie vroeg uitgevoerd na een myocard infarct een veilige procedure is die voor wat betreft het optreden van angina pectoris in het jaar na het myocard infarct effectiever lijkt dan behandeling met medicamenten.

In hoofdstuk 8 worden onze ervaringen vergeleken met de resultaten uit de literatuur, in het bijzonder wat betreft de waarde van de klinische variabelen en veelvoudige niet-invasieve methoden om het risico en het ontslagbeleid ten aanzien van hartinfarct patienten te bepalen. Voorzichtigheid is geboden bij het schatten van het risico op basis van klinische variabelen; het doen van een fietstest wordt altijd aanbevolen. Patienten, bij wie een fietstest gecontraïndiceerd is hebben de hoogste 1 jaar mortaliteit (20%). De mortaliteit is nog hoger (50%-60%) indien de contraïndicatie gebaseerd is op recidiverende angina of decompensatie cordis. In deze groep patienten moeten meerdere tests worden uitgevoerd, zoals echocardiografie, radionuclide ventriculografie, 24-uurs electrocardiogram of hartcatheterisatie, afhankelijk van het individuele probleem van de patient. Van de patienten, die één jaar na het hartinfarct nog leven, heeft 75% een inspanningstest ondergaan. De patienten met een inspanningstest hebben 10% minder risico om te overlijden gedurende één jaar na het infarct. Een stijging van de systolische bloeddruk met meer dan 30mmHg representeerde een lage risicogroep (3%), die 40% van alle overlevenden omvatte, terwijl patienten met een mindere stijging van de bloeddruk in de middelste risicogroep terecht kwamen (19%). Patienten in de lage risicogroep moeten geen additionele tests ondergaan, tenzij geïndiceerd door klachten. Verdere studie zou verricht moeten worden in de intermediaire risico groep, om de beste diagnostische en therapeutische strategie voor de individuele patient te bepalen.

SUMMARY

The aim of this study is to provide a comprehensive description of follow up data during the first year after myocardial infarction in a consecutive group of 706 patients discharged from the Thoraxcenter during a three year period, from March 1981 to December 1983.

In particular we wanted to assess the relative value of the usual clinical variables to predict survival after hospital discharge, compared to that of symptom limited bicycle ergometry, resting radionuclide ventriculography and the 24-hour ambulatory electrocardiogram.

It was shown that in patients eligible for predischARGE exercise testing, blood pressure rise during exercise provided additive prognostic information beyond clinical data. Radionuclide ventriculography and 24 hour ambulatory electrocardiogram even when demonstrating ventricular tachycardia, did not further refine the risk assessment in patients who completed for stress testing. Patients who were eligible for exercise testing had a much lower mortality than patients judged ineligible for the test for cardiac limitations (8% vs 56%). A low risk subset (3% mortality) was identified, encompassing 40% of hospital survivors, including patients who underwent bicycle ergometry and had an "adequate" blood pressure response during exercise (greater than 30 mmHg). From this it follows that in a substantial percentage of post-infarction patients a careful clinical evaluation and exercise testing are adequate for risk assessment, and that other tests are redundant, unless indicated by symptoms.

In contrast to patient eligible for exercise test, it was shown that radionuclide ventriculography and 24 hour ambulatory electrocardiography, did provide additional prognostic information beyond clinical data and were therefore useful for risk assessment.

The value of the predischARGE 12 lead electrocardiogram, compared to other usual clinical variables and tests to predict survival, was assessed in "low risk" patients without intra-ventricular conduction defects and/or ventricular hypertrophy and/or atrial fibrillation. While it was confirmed that several variables from the 12 lead electrocardiogram provided prognostic information, by multivariate analysis only the QRS score by Selvester, persistent ST segment depression and prolonged QT interval corrected for heart rate proved to be independent predictors. Since clinical variables were much stronger predictors than electrocardiographic variables, even the addition of electrocardiographic variables failed to

improve the risk assessment.

The clinical course of patients with different levels of peak serum creatine phosphokinase (CK), after their first myocardial infarction, showed that those with the highest peak CK value ($> 800 \text{ IU l}^{-1}$) had the greatest hospital mortality. However, during follow up after hospital discharge, different levels of peak CK were not associated with differences in mortality, recurrent infarction or angina. It is concluded that peak CK in patients after the first myocardial infarction should not influence the decision for further diagnostic or therapeutical procedures before hospital discharge.

The value of predischarge bicycle ergometry in 119 consecutive patients with uncomplicated first myocardial infarction younger than 60 years became evident in the first year after myocardial infarction; only one patient died while only 10 had a non fatal reinfarction. Exercise induced angina and/or ST depression were not predictive of non fatal reinfarction, but they predicted recurrent angina. It is concluded that coronary arteriography in this group of patients is not indicated even when there is exercise induced ST depression, since this subgroup has an excellent prognosis.

Finally, to study the effect of "early" coronary artery bypass surgery after myocardial infarction 34 patients were compared with 34 others treated medically. They were matched by clinical, ventriculographic and coronary arteriographic data. The indication for surgery was post infarction angina in 30 cases and infarction with severe proximal multiple vessel disease in four other patients. Patients were operated upon at a median interval of 20 days after the infarction and there was only one perioperative death. During one year follow up there was no difference in survival or non fatal reinfarctions between the operated and not operated group, however operated patients had a much lower incidence of angina pectoris. Because of the small numbers it is tentatively concluded that early coronary artery bypass surgery after myocardial infarction is a safe procedure which is more effective than medical treatment for the relief of angina pectoris during the first year after myocardial infarction.

APPENDIX A INVENTORY OF THE DATA BASE

1----- ADMINISTRATIVE INFORMATION #####

- 1-1. PATIENT NAME
No entry = 0, Valid = 706
- 1-2. SEX (1=MALE, 2=FEMALE)
No entry = 0, Valid = 706
Distribution: 554 152
- 1-3. BIRTH DATE (DDMMYY)
No entry = 0, Valid = 706
- 1-4. DATE ADMITTED CCU (DDMMYY)
No entry = 0, Valid = 706
- 1-5. DATE OF DISCHARGE (DDMMYY)
No entry = 66, Valid = 640
- 1-6. DATE OF LATEST FOLLOW-UP (DDMMYY)
No entry = 5, Valid = 701
- 1-7. DATE OF HOLTHER RECORDING (DDMMYY)
No entry = 316, Valid = 390
- 1-8. DATE OF EXERCISE TEST (DDMMYY)
No entry = 298, Valid = 408
- 1-9. DATE OF RADIONUCL. VENTRICULOGR. (DDMMYY)
No entry = 216, Valid = 490
- 1-10. DATE CARDIAC CATHETERISATION (DDMMYY)
No entry = 403, Valid = 303
- 1-11. DATE OF DEATH (DDMMYY)
No entry = 531, Valid = 175
- 1-12. DATE OF POST-DISCHARGE
RECURRENT NON-FATAL MI (DDMMYY)
No entry = 670, Valid = 36

2----- CCU DATA #####

- 2-1. DATE ADMITTED CCU (DDMMYY)
No entry = 0, Valid = 706
- 2-2. REFERRING INSTITUTION
1= not referred
2= referred from other hospital
No entry = 1, Valid = 705
Distribution: 519 186
- 2-3. OLD MYOCARDIAL INFARCTION (0=N, 1=Y)
No entry = 2, Valid = 704
Distribution: 478 226

- 2-4. HISTORY AP >4 WEEKS (0=N, 1=Y)
 No entry = 2, Valid = 704
 Distribution: 431 273
- 2-5. BEGIN OF MI SYMPTOMS
 1= at rest
 2= exercise
 3= normal activity
 4= other
 5= unknown
 No entry = 1, Valid = 705
 Distribution: 580 31 63 21 10
- 2-6. PREVIOUS CABG SURGERY (0=N, 1=Y)
 No entry = 2, Valid = 704
 Distribution: 671 33
- 2-7. PREVIOUS CHF (0=N, 1=Y)
 No entry = 2, Valid = 704
 Distribution: 690 14
- 2-8. PREVIOUS PTCA (0=N, 1=Y)
 No entry = 2, Valid = 704
 Distribution: 702 2
- 2-9. PREVIOUS OTHER HEART OPERATION (0=N, 1=Y)
 No entry = 2, Valid = 704
 Distribution: 702 2
- 2-10. DATE OF MYOCARDIAL INFARCTION (DDMMYY)
 No entry = 0, Valid = 706
- 2-11. LOCATION OF MI
 1= transmural anterior
 2= transmural inf/post
 3= unknown (LBBS)
 4= non-transmural
 5= undefinable
 No entry = 0, Valid = 706
 Distribution: 268 266 8 159 5
- 2-12. PEAK HBDH
 No entry = 95, Valid = 611
 Range = 74 TO 2500, Mean \pm SD = 542 \pm 389
- 2-13. PEAK CPK
 No entry = 48, Valid = 658
 Range = 14 TO 3500, Mean \pm SD = 610 \pm 539
- 2-14. MIRU CLASS, HEMODYNAMIC
 No entry = 313, Valid = 393
 Distribution: 143 131 67 52
- 2-15. KILLIP CLASS
 No entry = 1, Valid = 705
 Distribution: 401 169 60 75

- 2-16. HR (BPM), AT CCU ADMISSION
 No entry = 259, Valid = 447
 Range = 40 TO 160, Mean \pm SD = 85 \pm 21
- 2-17. WEDGE PRESSURE (mmHg), AT CCU ADM.
 No entry = 311, Valid = 395
 Range = 1 TO 35, Mean \pm SD = 13 \pm 6
- 2-18. CARDIAC INDEX (L/min/m2), AT CCU ADM.
 No entry = 333, Valid = 373
 Range = 0.8 TO 5.9, Mean \pm SD = 2.6 \pm 0.8
- 2-19. MIXED VENOUS O2 (%), AT CCU ADM.
 No entry = 362, Valid = 344
 Range = 40 TO 84, Mean \pm SD = 68 \pm 8
- 2-20. SYSTEMIC ARTERIAL P (mmHg), CCU ADM.
 No entry = 262, Valid = 444
 Range = 50 TO 200, Mean \pm SD = 120 \pm 24
- 2-21. HEMODYNAMIC PROGNOSTIC INDEX, CCU ADM.
 No entry = 350, Valid = 356
 Range = 1 TO 215, Mean \pm SD = 42 \pm 36
- 2-22. ANGINA DURING CCU STAY (0=N, 1=Y)
 No entry = 0, Valid = 706
 Distribution: 621 85
- 2-23. VF (0=N, 1=Y: <=72h, 2=Y: after 72 h)
 No entry = 0, Valid = 706
 Distribution: 660 38 8
- 2-24. RECURRENT NON-FATAL MYOCARDIAL INFARCTION
 0= none
 1= transmural anterior
 2= transmural inf/post
 3= unknown (LBBB)
 4= not transmural
 5= undefinable
 No entry = 1, Valid = 705
 Distribution: 681 10 9 0 2 3
- 2-25. DATE OF RECURRENT MI (DDMMYY)
 No entry = 683, Valid = 23
- 2-26. PEAK HSDE
 No entry = 690, Valid = 16
 Range = 154 TO 978, Mean \pm SD = 405 \pm 212
- 2-27. PEAK CPK
 No entry = 681, Valid = 25
 Range = 0 TO 1461, Mean \pm SD = 352 \pm 414
- 2-28. STREPTOKINASE INTERVENTION (0=N, 1=Y)
 No entry = 0, Valid = 706
 Distribution: 644 62

- 2-29. STREPTOKINASE AND PTCA INTERV. (0=N, 1=Y)
 No entry = 0, Valid = 706
 Distribution: 681 25
- 2-30. STREPTOKINASE CONTROL GROUP (0=N, 1=Y)
 No entry = 0, Valid = 706
 Distribution: 639 67
- 2-31. IABP INTERVENTION (0=N,1=Y)
 No entry = 0, Valid = 706
 Distribution: 640 66
- 2-32. DESTINATION AFTER CCU
 1= CARDIOLOGY DEPT: 1200
 2= CARDIOLOGY DEPT: 3 zuid
 3= other hospital department
 4= thorax surgery
 5= home
 6= mortality
 7= other
 No entry = 2, Valid = 704
 Distribution: 545 42 24 9 0 82 2
- 3----- POST-CCU DATA #####
- 3-1. AP DURING SPONTANEOUS EX (0=N, 1=Y)
 No entry = 83, Valid = 623
 Distribution: 575 48
- 3-2. AP AT REST (0=N, 1=Y)
 No entry = 83, Valid = 623
 Distribution: 534 89
- 3-3. DUBIOUS AP (0=N,1=Y)
 No entry = 83, Valid = 623
 Distribution: 604 19
- 3-4. CHF (0=N, 1=Y)
 No entry = 83, Valid = 623
 Distribution: 505 118
- 3-5. RECURRENT NON-FATAL MYOCARDIAL INFARCTION
 0= none
 1= transmural anterior
 2= transmural inf/post
 3= unknown (LBBB)
 4= not transmural
 5= undefinable
 No entry = 84, Valid = 622
 Distribution: 608 4 4 0 5 1
- 3-6. DATE OF RECURRENT NON-FATAL MI (DDMMYY)
 No entry = 694, Valid = 12
- 3-7. PEAK HSDH
 No entry = 698, Valid = 8
 Range = 0 TO 350, Mean \pm SD = 178 \pm 123

- 3-8. PEAK CPK
 No entry = 692, Valid = 14
 Range = 0 TO 420, Mean \pm SD = 170 \pm 191.
- 3-9. LATE VF (0=N, 1=Y)
 No entry = 84, Valid = 622
 Distribution: 606 16
- 3-10. SUSTAINED VT, >72 HRS AFTER MI (0=N,1=Y)
 No entry = 83, Valid = 623
 Distribution: 599 24
- 3-11. SUST. SVT/AF >72 HRS AFTER MI (0=N,1=Y)
 No entry = 83, Valid = 623
 Distribution: 587 36
- 3-12. CARDIOMEGALY,CTR>50 ON DISCH.(0=N,1=Y)
 No entry = 84, Valid = 622
 Distribution: 462 160
- 3-13. PULMONARY CONGESTION ON DISCH.(0=N,1=Y)
 No entry = 85, Valid = 621
 Distribution: 569 52
- 3-14. ECG ON DISCHARGE
 1= sinus rhythm
 2= atrial fibrillation
 3= other arrhythmia
 No entry = 2, Valid = 704
 Distribution: 690 14 0
- 3-15. ECG ON DISCHARGE
 1= LSH 2= RBBB 3= LBBB 4= none of these
 No entry = 2, Valid = 704
 Distribution: 0 53 32 13 606
- 3-16. ECG ON DISCHARGE
 1= AV block grade 1
 2= '' 2
 3= '' 3
 4= RBBB & LSH
 5= RBBB & LIH
 6= none of these
 No entry = 3, Valid = 703
 Distribution: 10 1 4 13 1 674
- 3-17. Q WAVES PRESENT (0=N, 1=Y)
 No entry = 7, Valid = 699
 Distribution: 152 547
- 3-18. ST ELEVATION (0=N, 1=Y)
 No entry = 176, Valid = 530
 Distribution: 326 204
- 3-19. ST DEPRESSION (0=N, 1=Y)
 No entry = 176, Valid = 530
 Distribution: 444 86

- 3-20. P.V.C.'s (0=N, 1=Y)
 No entry = 45, Valid = 661
 Distribution: 624 37
- 3-21. P TERMINAL FORCE
 No entry = 79, Valid = 627
 Range = 0 TO 80, Mean \pm SD = 21 \pm 16
- 3-22. CONDUCTION DEFECTICS, LVE
 1=LBBB
 2=RBBB
 3=RBBB, LSH
 4=RBBB, LIH
 5=LSH
 6=LIH
 7=LVE
 8=PACE MAKER
 No entry = 572, Valid = 134
 Distribution: 28 27 14 1 40 6 14 4
- 3-23. CORRECTED QT
 No entry = 179, Valid = 527
 Range = 0.298 TO 0.602, Mean \pm SD = 0.424 \pm 0.044
- 3-24. HEART RATE
 No entry = 179, Valid = 527
 Range = 38 TO 167, Mean \pm SD = 73 \pm 17
- 3-25. SELVESTER ECG SCORE
 No entry = 179, Valid = 527
 Range = 0 TO 20, Mean \pm SD = 5 \pm 3
- 3-26. DESTINATION ON DISCHARGE
 1= home
 2= dept thoracic surgery
 3= other hospital department
 4= mortality
 5= other
 No entry = 82, Valid = 624
 Distribution: 533 51 13 22 5
- 3-27. ANGINA
 1= no ECG changes
 2= isch. infarct zone
 3= isch. at a distance
 4= isch. at distance and reciproc
 5= no ECG recording or BBB
 6= No Angina
 No entry = 5, Valid = 701
 Distribution: 24 47 42 0 14 574
- 4----- THERAPY ON DISCHARGE #####
- 4-1. DATE OF DISCHARGE (DDMMYY)
 No entry = 66, Valid = 640

4-2. ANTI-COAGULANTS (0=N, 1=Y)
 No entry = 101, Valid = 605
 Distribution: 467 138

4-3. BETA-BLOCKERS ''
 No entry = 101, Valid = 605
 Distribution: 291 314

4-4. DIGOXIN ''
 No entry = 101, Valid = 605
 Distribution: 470 135

4-5. DIURETICS ''
 No entry = 101, Valid = 605
 Distribution: 375 230

4-6. NITRATES OR VASODILATORS ''
 No entry = 101, Valid = 605
 Distribution: 373 232

4-7. CALCIUM ANTAGONISTS ''
 No entry = 101, Valid = 605
 Distribution: 447 158

4-8. ANTI-ARRHYTHMICS ''
 No entry = 101, Valid = 605
 Distribution: 578 27

4-9. PACE MAKER ''
 No entry = 101, Valid = 605
 Distribution: 603 2

4-10. REFERRED CABG ''
 No entry = 100, Valid = 606
 Distribution: 550 56

4-11. REF. OTHER HEART SURGERY ''
 No entry = 1, Valid = 705
 Distribution: 696 9

4-12. REFERRED PTCA ''
 No entry = 101, Valid = 605
 Distribution: 589 16

4-13. NO THERAPY ''
 No entry = 102, Valid = 604
 Distribution: 547 57

5----- ONE YEAR FOLLOW UP OF PATIENTS #####

5-1. RECURRENT NON-FATAL MI (0=N, 1=Y)
 No entry = 107, Valid = 599
 Distribution: 563 36

5-2. DATE OF POST-DISCHARGE
 NON-FATAL RECURRENT MI (DDMMYY)
 No entry = 670, Valid = 36

- 5-3. LOCATION MI
 1= transmural anterior
 2= transmural inf/post
 3= unknown (LEBB)
 4= non-transmural
 5= undefined
 No entry = 570, Valid = 36
 Distribution: 9 13 0 8 6
- 5-4. PEAK CPK
 No entry = 681, Valid = 25
 Range = 79 TO 1550, Mean \pm SD = 539 \pm 417
- 5-5. PEAK HBDE
 No entry = 691, Valid = 15
 Range = 138 TO 1200, Mean \pm SD = 485 \pm 321
- 5-6. ANGINA PECTORIS (0=N, 1=Y)
 No entry = 107, Valid = 599
 Distribution: 385 214
- 5-7. CHF (0=N,1=Y)
 No entry = 107, Valid = 599
 Distribution: 518 81
- 5-8. CABG (0=N,1=Y)
 No entry = 107, Valid = 599
 Distribution: 564 35
- 5-9. DATE OF CABG (DDMMYY)
 No entry = 668, Valid = 38
- 5-10. PTCA (0=N, 1=Y)
 No entry = 107, Valid = 599
 Distribution: 588 11
- 5-11. DATE OF PTCA (DDMMYY)
 No entry = 695, Valid = 11
- 5-12. OTHER HEART SURGERY (0=N, 1=Y)
 No entry = 107, Valid = 599
 Distribution: 596 3
- 5-13. DATE OF OTHER H SURGERY (DDMMYY)
 No entry = 703, Valid = 3
- 5-14. SUSTAINED VT (0=N, 1=Y)
 No entry = 107, Valid = 599
 Distribution: 592 7
- 5-15. VF (0=N,1=Y)
 No entry = 108, Valid = 598
 Distribution: 596 2
- 5-16. DATE OF LATEST FOLLOW-UP (DDMMYY)
 No entry = 5, Valid = 701

- 5-17. DATE OF DEATH (DDMMYY)
No entry = 531, Valid = 175
- 5-18. CAUSE OF DEATH
1= Sudden, unexpected (<1 Hour)
2= Myocardial infarction
3= Non-cardiac 4= Peri-operative
5= Congestive heart failure 6= Other
7= Unknown
No entry = 634, Valid = 72
Distribution: 37 18 2 2 11 2 0
- 5-19. SOURCE OF MORTALITY INFORMATION
1= General practitioner 2= Hospital 3= Autopsy
4= Other (ENTER ONE CODE)
No entry = 633, Valid = 73
Distribution: 31 19 2 21
- 5-20. ANY COMPLICATION (0=N, 1=Y)
No entry = 0, Valid = 706
Distribution: 300 406
- 5-21. LOST TO FOLLOW-UP (0=N, 1=Y)
No entry = 103, Valid = 603
Distribution: 597 6
- 5-22. CARDIAC REHABILITATION
0= Not performed
1= Drop out because of death
2= ,, of other cardiac reason
3= ,, of medical non cardiac reason
4= ,, of non medical reason
5= Rehabilitation completed
No entry = 532, Valid = 174
Distribution: 2 4 5 8 13 142
- 5-23. DATE OF START REHABILITATION
No entry = 533, Valid = 173
- 5-24. DATE END REHABILITATION
No entry = 536, Valid = 170
- 5-25. BETA BLOCKERS, AT END REHAB. (0=N,1=Y)
No entry = 563, Valid = 143
Distribution: 67 76
- 5-26. MAX. WORKLOAD AT END REHABILITATION
No entry = 564, Valid = 142
Range = 60 TO 260, Mean \pm SD = 165 \pm 41
- 5-27. % MAX. WORKLOAD, %
No entry = 565, Valid = 141
Range = 30 TO 160, Mean \pm SD = 105 \pm 21
- 5-28. ANGINA DURING THE TEST (0=N, 1=Y)
No entry = 564, Valid = 142
Distribution: 121 21

- 5-29. RESTING HR, DURING EST AFTER REHAB.
 No entry = 566, Valid = 140
 Range = 45 TO 116, Mean \pm SD = 71 \pm 13
- 5-30. RESTING SBP DURING EST
 No entry = 566, Valid = 140
 Range = 100 TO 200, Mean \pm SD = 133 \pm 17
- 5-31. PEAK HR DURING EST
 No entry = 567, Valid = 139
 Range = 53 TO 191, Mean \pm SD = 141 \pm 23
- 5-32. PEAK SBP DURING EST
 No entry = 568, Valid = 138
 Range = 125 TO 240, Mean \pm SD = 175 \pm 27
- 5-33. BP RISE DURING EST AFTER REHAB
 No entry = 568, Valid = 138
 Range = -20 TO 120, Mean \pm SD = 41 \pm 23

5-34. REASONS FOR INTERRUPTING THE EST TEST

- 1= Fatigue
- 2= Angina
- 3= Dyspnoe
- 4= Other symptoms
- 5= HR too high
- 6= Pressure drop
- 7= ST changes
- 8= Arrhythmias
- 9= Other reasons
- 10=Unknown

No entry = 567, Valid = 139
 Distribution: 105 9 14 4 0 1 0 0 3 3

6----- HOLTER TAPE ANALYSIS #####

- 6-1. DATE OF RECORDING
 No entry = 316, Valid = 390
- 6-2. PVC UNF <5/MIN
 0= geen
 1= soms
 2= matig veel
 3= veel
 4= continu
 No entry = 316, Valid = 390
 Distribution: 281 97 11 1 0
- 6-3. PVC UNF >5/MIN
 No entry = 316, Valid = 390
 Distribution: 356 23 8 3 0
- 6-4. VNT BIG
 No entry = 316, Valid = 390
 Distribution: 312 67 11 0 0

6-5. PVC MTF <5/MIN
 No entry = 316, Valid = 390
 Distribution: 104 202 66 15 3

6-6. PVC MTF >5/MIN
 No entry = 316, Valid = 390
 Distribution: 293 57 23 15 2

6-7. PVC R OP T
 No entry = 317, Valid = 389
 Distribution: 385 4 0 0 0

6-8. VNT DBL
 No entry = 316, Valid = 390
 Distribution: 257 123 8 1 1

6-9. VNT RIT (>100) 3-10
 No entry = 316, Valid = 390
 Distribution: 335 51 4 0 0

6-10. VNT RIT (>100) >10
 No entry = 316, Valid = 390
 Distribution: 385 5 0 0 0

6-11. SLOW VT (<100)
 No entry = 316, Valid = 390
 Distribution: 354 35 0 1 0

7----- EXERCISE STRESS TEST #####

7-1. TEST STATUS
 1= test performed
 2= not performed due to AP
 3= '' CHF
 4= '' extra-cardiac med contraindication
 5= '' unknown or organizational problem
 No entry = 96, Valid = 610
 Distribution: 408 59 52 73 18

7-2. DATE OF STUDY (DDMMYY)
 No entry = 298, Valid = 408

7-3. DIGITALIS USED (0=N, 1=Y)
 No entry = 298, Valid = 408
 Distribution: 342 66

7-4. BETA-BLOCKER USED (0=N, 1=Y)
 No entry = 298, Valid = 408
 Distribution: 196 212

7-5. PERCENT MAX WORK CAPACITY (%)
 No entry = 298, Valid = 408
 Range = 32 TO 129, Mean \pm SD = 78 \pm 17

- 7-6. REASON FOR STOPPING TEST
 1= fatigue
 2= AP
 3= dyspnoe
 4= other symptoms
 5= HR to high
 6= pressure drop
 7= ST changes
 8= arrhythmias
 9= other medical reason
 No entry = 298, Valid = 408
 Distribution: 284 25 75 0 0 13 8 2 1
- 7-7. SYMPTOMS DURING TEST
 1= AP
 2= dyspnoe
 3= other
 4= none
 No entry = 298, Valid = 408
 Distribution: 85 10 1 312
- 7-8. MAXIMUM WORK LOAD ACHIEVED
 No entry = 298, Valid = 408
 Range = 40 TO 240, Mean \pm SD = 113 \pm 32.
- 7-9. REST HR
 No entry = 298, Valid = 408
 Range = 44 TO 142, Mean \pm SD = 82. \pm 16
- 7-10. REST SYSTOLIC BP (mmHg)
 No entry = 298, Valid = 408
 Range = 80 TO 175, Mean \pm SD = 121 \pm 16
- 7-11. MAXIMUM HR
 No entry = 298, Valid = 408
 Range = 76 TO 195, Mean \pm SD = 130 \pm 22
- 7-12. RECOVERY HR
 No entry = 374, Valid = 332
 Range = 47 TO 176, Mean \pm SD = 111 \pm 21
- 7-13. RECOVERY HR/REST HR RATIO
 No entry = 374, Valid = 332
 Range = 0.48 TO 1.11, Mean \pm SD = 0.85 \pm 0.08
- 7-14. MAXIMUM SYSTOLIC BP
 No entry = 298, Valid = 408
 Range = 100 TO 250, Mean \pm SD = 162 \pm 28
- 7-15. RECOVERY SYSTOLIC BP
 No entry = 374, Valid = 332
 Range = 100 TO 230, Mean \pm SD = 150 \pm 24
- 7-16. RECOVERY SYST BP/SYST BP RATIO
 No entry = 374, Valid = 332
 Range = 0.65 TO 1.23, Mean \pm SD = 0.93 \pm 0.08

- 7-17. INSUFFICIENT INCREASE PRESSURE (0=N, 1=Y)
 No entry = 298, Valid = 408
 Distribution: 345 63
- 7-18. ST SEGMENT CHANGES (0=N, 1=Y)
 No entry = 302, Valid = 404
 Distribution: 117 287
- 7-19. IF ST CHANGES, X ISCHAEMIC (mm)
 No entry = 302, Valid = 404
 Range = 0 TO 3, Mean \pm SD = 0.4 \pm 0.7
- 7-20. IF ST CHANGES, Y ISCHAEMIC (mm)
 No entry = 302, Valid = 404
 Range = 0 TO 3, Mean \pm SD = 0.2 \pm 0.5
- 7-21. IF ST CHANGES, Z ISCHAEMIC (mm)
 No entry = 302, Valid = 404
 Range = 0 TO 2, Mean \pm SD = 0.1 \pm 0.3
- 7-22. IF ST CHANGES, X WALL MOTION (mm)
 No entry = 302, Valid = 404
 Range = 0 TO 2, Mean \pm SD = 0.0 \pm 0.3
- 7-23. IF ST CHANGES, Y WALL MOTION (mm)
 No entry = 302, Valid = 404
 Range = 0 TO 2, Mean \pm SD = 0.1 \pm 0.4
- 7-24. IF ST CHANGES, Z WALL MOTION (mm)
 No entry = 303, Valid = 403
 Range = 0 TO 4, Mean \pm SD = 0.4 \pm 0.7
- 7-25. IF ST DEPRESSION, WORK LOAD
 No entry = 520, Valid = 186
 Range = 25 TO 200, Mean \pm SD = 91 \pm 31
- 7-26. IF ST DEPRESSION, % MAX WORK CAPACITY
 No entry = 521, Valid = 185
 Range = 15 TO 114, Mean \pm SD = 64 \pm 18
- 7-27. IF ST DEPRESSION, HR
 No entry = 521, Valid = 185
 Range = 76 TO 198, Mean \pm SD = 121 \pm 21
- 7-28. LBBB (0=N, 1=Y)
 No entry = 298, Valid = 408
 Distribution: 404 4
- 7-29. ARRYTHMIAS DURING TEST (VT> 3 BEATS)
 0= no
 1= yes
 No entry = 298, Valid = 408
 Distribution: 402 6

- 7-30. ARRHYTHMIAS DURING TEST (VF)
 0= no
 1= yes
 No entry = 298, Valid = 408
 Distribution: 407 1
- 7-31. ARRHYTHMIAS DURING TEST (COUPLETS)
 0= no
 1= yes
 No entry = 298, Valid = 408
 Distribution: 378 30
- 7-32. ARRHYTHMIAS DURING TEST (PVCs)
 0= no
 1= yes
 No entry = 298, Valid = 408
 Distribution: 314 94
- 7-33. NUMBER OF ARRHYTHMIAS DURING TEST (PVCs/MIN)
 No entry = 298, Valid = 408
 Range = 0 TO 44, Mean \pm SD = 1.8 \pm 5.1
- 7-34. ARRHYTHMIAS DURING TEST (VF or VT or COUPLETS)
 0= no
 1= yes
 No entry = 298, Valid = 408
 Distribution: 376 32
- 8----- GBP RADIONUCLIDE VENTRICULOGRAPHY #####
- 8-1. DATE OF STUDY (DDMMYY)
 No entry = 216, Valid = 490
- 8-2. EJECTION FRACTION
 No entry = 220, Valid = 486
 Range = 0.04 TO 0.8, Mean \pm SD = 0.45 \pm 0.16
- 8-3. REGIONAL WALL MOTION
 1= all regions normal
 2= worst segment hypokinetic
 3= '' akinetik
 4= '' dyskinetik
 5= ambiguous recording
 No entry = 218, Valid = 488
 Distribution: 61 108 198 118 3
- 8-4. REGIONAL EF, SEG 1
 No entry = 288, Valid = 418
 Range = 0 TO 0.18, Mean \pm SD = 0.06 \pm 0.03
- 8-5. '' 2
 No entry = 288, Valid = 418
 Range = 0 TO 0.14, Mean \pm SD = 0.05 \pm 0.03
- 8-6. '' 3
 No entry = 288, Valid = 418
 Range = 0 TO 0.21, Mean \pm SD = 0.07 \pm 0.04

8-7. '' 4
No entry = 288, Valid = 418
Range = 0 TO 0.18, Mean \pm SD = 0.06 \pm 0.036

8-8. '' 5
No entry = 288, Valid = 418
Range = 0 TO 0.8, Mean \pm SD = 0.06 \pm 0.04

8-9. '' 6
No entry = 288, Valid = 418
Range = 0 TO 0.7, Mean \pm SD = 0.06 \pm 0.04

8-10. LOCAL EF, SEG 1
No entry = 289, Valid = 417
Range = 0 TO 0.76, Mean \pm SD = 0.29 \pm 0.12

8-11. ,, 2
No entry = 289, Valid = 417
Range = 0 TO 0.66, Mean \pm SD = 0.29 \pm 0.14

8-12. ,, 3
No entry = 290, Valid = 416
Range = 0.04 TO 0.99, Mean \pm SD = 0.42 \pm 0.20

8-13. ,, 4
No entry = 290, Valid = 416
Range = 0.03 TO 1, Mean \pm SD = 0.50 \pm 0.23

8-14. ,, 5
No entry = 289, Valid = 417
Range = 0 TO 1, Mean \pm SD = 0.49 \pm 0.18

8-15. ,, 6
No entry = 289, Valid = 417
Range = 0 TO 0.87, Mean \pm SD = 0.37 \pm 0.13

9----- CARDIAC CATHETERISATION #####

9-1. DATE OF STUDY (DDMMYY)
No entry = 403, Valid = 303

9-2. REASON FOR CATHETERIZATION
1= elective
2= study protocol
3= unknown
No entry = 405, Valid = 301
Distribution: 0 155 145 1

9-3. EJECTION FRACTION
No entry = 466, Valid = 240
Range = 0.12 TO 0.76, Mean \pm SD = 0.46 \pm 0.14.

- 9-4. REGIONAL WALL MOTION
 1= all regions normal
 2= worst segment hypokinetic
 3= '' akinetik
 4= '' dyskinetik
 5= ambiguous recording
 No entry = 433, Valid = 273
 Distribution: 22 109 63 77 2
- 9-5. NUMBER OF VESSELS DISEASED
 0= no vessel disease
 1= one vessel disease
 2= two ''
 3= three ''
 4= main stem
 5= main stem & right
 6= ambiguous recording
 No entry = 405, Valid = 301
 Distribution: 8 96 103 87 0 7 0
- 9-6. LEAMAN CORONARY SCORE
 No entry = 410, Valid = 296
 Range = 0 TO 47, Mean \pm SD = 11. \pm 8.
- 9-7. MITRAL INSUFFICIENCY \geq GR 2 (0=N, 1=Y)
 No entry = 409, Valid = 297
 Distribution: 281 16
- 9-8. LV END DIAST PRESSURE
 No entry = 420, Valid = 286
 Range = 2 TO 45, Mean \pm SD = 20. \pm 8
- 9-9. LV END DIAST VOLUME
 No entry = 435, Valid = 271
 Range = 1 TO 255, Mean \pm SD = 90 \pm 29
- 9-10. LV END SYST VOLUME
 No entry = 454, Valid = 252
 Range = 6 TO 212, Mean \pm SD = 49 \pm 28
- 10—— SPECIAL DATA FILES (CREATED FROM EXISTING FILES) #####
- 10-1. AGE OF PATIENTS ON ADMISSION (YEARS)
 No entry = 0, Valid = 706
 Range = 22 TO 83.4, Mean \pm SD = 58 \pm 11
- 10-2. LENGTH OF STAY IN CCU (DAYS)
 No entry = 0, Valid = 706
 Range = 0 TO 78, Mean \pm SD = 13 \pm 9
- 10-3. EX. STR. TEST DONE (1=DONE, 2=NOT DONE)
 No entry = 96, Valid = 610
 Distribution: 408 202
- 10-4. HOLTER TAPE DONE (1=DONE, 2=NOT DONE)
 No entry = 0, Valid = 706
 Distribution: 390 316

- 10-5. AP DUR. CCU STAY OR DUR. SPON. EX OR AT REST
(0=NO, 1=YES)
No entry = 0, Valid = 706
Distribution: 539 167
- 10-6. LATE VF OR VT IN PCU (0=N, 1=Y)
No entry = 83, Valid = 623
Distribution: 590 33
- 10-7. ECG: RBBB OR RBBB & LSH OR RBBB & LIH (0=N, 1=Y)
No entry = 2, Valid = 704
Distribution: 656 48
- 10-8. MAX PRESSURE RATE PRODUCT DURING EST (MMEG*HR)
No entry = 298, Valid = 408
Range = 7600 TO 30430, Mean \pm SD = 15952 \pm 3695
- 10-9. CHANGE IN BP DURING EST (MMEG)
No entry = 298, Valid = 408
Range = -20 TO 125, Mean \pm SD = 40 \pm 24
- 10-10. EST ST CHANGES, MAX XYZ ISCHAEMIC (MM)
No entry = 302, Valid = 404
Range = 0 TO 3, Mean \pm SD = 0.6 \pm 0.7
- 10-11. EST ST CHANGES, MAX XYZ WALL MOTION (MM)
No entry = 302, Valid = 404
Range = 0 TO 4, Mean \pm SD = 0.5 \pm 0.7
- 10-12. EF RADIONUCLIDE OR ANGIO
No entry = 162, Valid = 544
Range = 0.04 TO 0.8, Mean \pm SD = 0.45 \pm 0.16
- 10-13. ARRHYTHMIAS DURING EST (1=SOME, 2=NONE)
No entry = 298, Valid = 408
Distribution: 94 314
- 10-14. ARRHYTHMIAS DURING HOL.(1=SOME, 2=NONE)
No entry = 316, Valid = 390
Distribution: 155 235
- 10-15. DURATION OF FOLLOW-UP AFTER MI (DAYS)
No entry = 5, Valid = 701
Range = 0 TO 608, Mean \pm SD = 283. \pm 150.
- 10-16. DURATION OF FOLLOW-UP AFTER DISCH.
No entry = 67, Valid = 639
Range = -12 TO 597, Mean \pm SD = 294. \pm 129.
- 10-17. REF. CABG DURING HOSP. STAY
1= PURE CABG
2= OTHER HEART SURGERY WITH OR WITHOUT CABG
3 =NO HEART SURGERY
No entry = 0, Valid = 706
Distribution: 51 9 646

- 10-18. DEATH IN HOSPITAL (0=N, 1=Y)
 No entry = 0, Valid = 706
 Distribution: 602 104
- 10-19. VERDOUW HEMODYN. INDEX AT ADM.
 No entry = 362, Valid = 344
 Range = -9.415 TO 9.385, Mean \pm SD = 2.899 \pm 3.209
- 10-20. WOLFENBUTTEL HEM. INDEX AT ADM.
 No entry = 333, Valid = 373
 Range = 1.97740112994 TO 487.5, Mean \pm SD = 50. \pm 53
- 10-21. REGIONAL LV WALL MOTION GEP OR ANGIO
 1= all regions normal
 2= worst segment hypokinetic
 3= '' akinetik
 4= '' dyskinetic
 5= ambiguous recording
 No entry = 153, Valid = 553
 Distribution: 69 125 218 137 4
- 10-22. ST-depr.and DIGITALIS, PRE DISCH. ECG
 (0=No ST-depr,1=ST- with DIG,2=ST- without DIG)
 No entry = 216, Valid = 490
 Distribution: 426 27 37
- 10-23. RECURRENT NON-FATAL MI FROM CCU & PCU
 0= none
 1= transmural anterior
 2= transmural inf/post
 3= unknown (LBBB)
 4= not transmural
 5= undefinable
 No entry = 1, Valid = 705
 Distribution: 668 13 13 0 7 4

CURRICULUM VITAE

The author of this thesis was born in Trieste (Italy) on 21 may 1944.

Educational and clinical experience

- 1962 : Schooling degree, Liceo Scientifico
G. Oberdan, Trieste (Italy)
- 1962-1968 : Medical studies, graduated cum laude,
Università degli Studi, Milano (Italy)
- 1968-1969 : Department of Internal Medicine,
Università degli Studi, Milano (Italy)
- 1969-1970 : Department of Cardiology, Università
degli Studi di Pavia (Italy)
- 1970-1977 and
1979-1981 : Department of Cardiology, Ospedale
Maggiore, Trieste (Italy)
- 1977 : Registration as Cardiologist in The
Netherlands
- 1977-1979 and
1981 till present : Thoraxcenter, Department of
Cardiology, Erasmus University,
Rotterdam (The Netherlands)

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APPENDIX B

Prediction of mortality in hospital survivors of myocardial infarction

Comparison of predischarge exercise testing and radionuclide ventriculography at rest

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SUMMARY The relative merits of resting ejection fraction measured by radionuclide angiography and predischarge exercise stress testing were compared for predicting prognosis in hospital survivors of myocardial infarction. Two hundred and fourteen survivors of myocardial infarction out of 338 consecutive patients with acute myocardial infarction were studied over a 14 month period. Hospital mortality was 13% (45 of 338) whereas 19 additional patients out of 214 died in the subsequent year (9%). High, intermediate, and low risk groups could be identified by left ventricular ejection fraction measurement. Mortality was 33% for nine patients with an ejection fraction <20%, 19% for 58 patients with an ejection fraction between 20% and 39%, and 3% for 147 patients with an ejection fraction >40%. Mortality was high (23%) in 47 patients who were unable to perform the stress test because of heart failure (19) or other limitations (28). The patients could be stratified further into intermediate and low risk groups according to the increase in systolic blood pressure during exercise: six deaths occurred in 46 patients with a blood pressure increase of <30 mm Hg and two deaths occurred in 121 patients with an increase \geq 30 mm Hg. Maximum workload, angina, ST changes, and ventricular arrhythmias were less predictive than blood pressure changes.

It is concluded that the prognostic value of radionuclide angiography at rest and of symptom limited exercise testing is similar. The latter investigation should be the method of choice since it provides more specific information for patient management.

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Ineligibility for predischarge exercise testing after myocardial infarction in the elderly: Implications for prognosis

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KEY WORDS: Myocardial infarction, exercise test, prognosis, old age.

This study describes the clinical profile and prognosis of elderly patients not eligible for predischarge exercise testing. The database consisted of 133 patients 55-64 years of age, and 111 patients older than 64 years of age who survived an acute myocardial infarction. Follow-up was one year. In the younger age group, 24 (18%) patients were unable to perform the test, in contrast to 63 (57%) of the elderly subjects. In these two groups, one-year mortality rates were 13% and 37%, compared with 6% and 4% for the respective patients eligible for stress testing. Clinical profile and radionuclide ejection fraction between ineligible patients in both age groups were similar. Ejection fraction measurement was the best predictor of late mortality in those patients who did not have an exercise test. It is concluded that ineligibility for predischarge exercise test identifies a high-risk group, especially in patients older than 64 years of age.

Limitations of a QRS scoring system to assess left ventricular function and prognosis at hospital discharge after myocardial infarction

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SUMMARY The value of a QRS scoring system derived from 12 lead electrocardiograms to estimate left ventricular ejection fraction was assessed in a prospective study of 285 hospital survivors of myocardial infarction. In these patients both the QRS score and ejection fraction were measured by radionuclide ventriculography at discharge. The correlation between ejection fraction and QRS score was weak. In 22 patients who died during six to 12 months follow up the ability of the ejection fraction and QRS score to predict mortality was assessed in terms of sensitivity, specificity, predictive value of a positive and negative test, and efficiency. For ejection fraction <40% and a QRS score ≥ 6 sensitivity was respectively 73% and 64%, specificity 73% and 56%, predictive value of a positive test 18% and 11%, predictive value of a negative test 97% and 95%, and efficiency 73% and 56%.

Both ejection fraction and QRS score may be used to identify patients at low and high risk during one year follow up, but, contrary to initial expectations, the QRS score appears to be of little value in estimating ejection fraction and is less accurate than ejection fraction in predicting late survival in hospital survivors of myocardial infarction.

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Predischarge stress test after myocardial infarction in the old age: Results and prognostic value

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KEY WORDS: Stress test, myocardial infarction, old age.

The aim of this study was to evaluate the results of predischarge stress testing in the elderly, and to assess the prognostic value of the test during one-year follow-up. The database consisted of 48 patients older than 64 years of age and 109 patients 55-64 years of age, who survived acute myocardial infarction, out of 532 consecutive patients admitted for myocardial infarction. Stress-test results were not different in the two groups. During one-year follow-up mortality was 6% in the younger patients and 4% in the older group, and the incidence of non-fatal reinfarctions was 8% in both groups. Mortality was best predicted by the extent of blood pressure rise (43 ± 26 mmHg in survivors vs 19 ± 15 mmHg in non-survivors, $P < 0.001$). Stress-test results were no more predictive when non-fatal reinfarction was added to mortality as an end-point. We conclude that for patients in whom the stress test is not contraindicated, (1) age does not affect stress test results, (2) the extent of blood pressure rise during a stress test is the best single predictor of mortality, (3) stress tests are not predictive of reinfarctions.

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