European Heart Journal (1997) **18**, 1873–1881

Prognostic value of residual ischaemia assessed by exercise electrocardiography and dobutamine stress echocardiography in low-risk patients following acute myocardial infarction

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Background Risk stratification after uncomplicated myocardial infarction is a major clinical problem. In particular, the prognostic value of residual inducible ischaemia is still controversial. We compared the relative prognostic value of exercise ECG and dobutamine stress echocardiography performed in the early post-infarction period.

Methods Four hundred and six patients (53 female) aged 57 ± 9 years, undergoing maximal exercise ECG and dobutamine stress echocardiography within 10 days of an uncomplicated myocardial infarction off therapy, were prospectively followed-up for 8·8 months. Age, sex, diabetes, smoking habit, hypertension, dyslipidaemia, infarct location, thrombolysis and resting wall motion score index were taken into account among clinical variables. Prognostic correlations were made vs spontaneous events (cardiac death, non-fatal reinfarction and unstable angina requiring hospitalization) whilst patients undergoing revascularization (by means of percutaneous transluminal coronary angioplasty or coronary artery bypass surgery) at the time of the procedure were censored.

Results One hundred and twenty-seven events occurred during the follow-up: 41 (10%) were spontaneous (five deaths, 12 reinfarctions and 24 unstable angina) and 86 procedural (27 angioplasty and 59 bypass surgery). Spontaneous events were not predicted by any clinical, exercise ECG or dobutamine stress echocardiography variable, but the negative predictive value of both tests was excellent (91% and 90%, respectively). With a multivariate Cox analysis, male gender, positive low-workload (<100 W) exercise ECG ($P<0·0001$), positive low-dose dobutamine stress echocardiography ($P<0·0001$) and rest–stress wall motion score index variation ($P<0·001$) were found to predict cumulative cardiac events with an independent and additive value. Dobutamine stress echocardiography was significantly more sensitive ($P<0·05$) and less specific ($P<0·01$) in predicting the outcome of patients with anterior infarction, whilst exercise ECG was significantly more sensitive ($P<0·05$) in patients with non-Q wave infarction.

Conclusions (1) Spontaneous events are poorly predicted by provocative tests in low-risk patients after uncomplicated myocardial infarction. (2) However, both exercise ECG and dobutamine stress echocardiography can predict a favourable outcome with a very high negative predictive value. (3) Dobutamine stress echocardiography should be considered a secondary option in cases where the exercise ECG is equivocal or when the location of ischaemia is a relevant issue. (4) The possibility that the two tests have a differential utility depending on the infarct location and type (Q wave vs non-Q wave) may be clinically relevant and deserves further evaluation.
(Eur Heart J 1997; 18: 1873–1881)

Key Words: Prognosis after myocardial infarction, risk stratification, exercise ECG, stress echocardiography, dobutamine.

Introduction

Non-invasive risk stratification is a well established principle of patient management following the acute phase of myocardial infarction. Its goal is to identify

Revision submitted 3 February 1997, and accepted 24 February 1997.

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0195-668X/97/121873+09 $18.00/0

subjects at high risk for hard events who may benefit from properly targeted therapeutic interventions[1]. Clinical data and exercise ECG are routinely used for assessing post-myocardial infarction risk[2]. The prognostic value of exercise ECG has been assessed by a large number of studies[3–5], and it has been clearly demonstrated that patients unable to exercise have the highest incidence of hard events[6–8]. On the other hand, methods of inducing ischaemia by exercise failed to identify a high-risk subgroup among patients with normal or mildly impaired left ventricular function[9–11]. These patients account for more than 50% of the post-infarction population[12], so their risk stratification is a major clinical problem.

In the last few years, pharmacological stress echocardiography has emerged as a safe and effective diagnostic tool in the post-infarction setting. It has been employed for identifying multivessel coronary artery disease[13–16], for defining the anatomical status of the culprit vessel[13], for assessing the presence of jeopardized myocardium[17] and to predict prognosis[18,19]. However, few data exist concerning the direct comparison of its prognostic value with that of exercise ECG after myocardial infarction, so that the relative clinical yield of the two tests remains to be established.

With this aim in mind, we prospectively assessed the prognostic importance of residual ischaemia assessed by exercise ECG and dobutamine stress echocardiography in a consecutive series of low-risk patients <75 years of age, with left ventricular ejection fraction >40%, recovering from uncomplicated myocardial infarction.

Methods

Study population

The original study population consisted of 653 consecutive patients off cardioactive therapy undergoing, in a random order, dobutamine stress echocardiography and exercise ECG within 15 days of a first episode of acute myocardial infarction. Two hundred and forty-seven were excluded for the following reasons: early complications, such as recurrent myocardial ischaemia, overt heart failure, shock or severe ventricular arrhythmias (59 patients), ejection fraction <40% (51 patients), uninterpretable exercise ECG (14 patients), age >75 years (20 patients), poor acoustic window (41 patients), inability to exercise maximally (46 patients), evaluation on therapy (16 patients). The remaining 406 patients, whose clinical characteristics are reported in Table 1, formed the study population and were prospectively followed-up for a mean period of 8·8 (range 1–25) months. Age, sex, thrombolytic therapy, diabetes, smoking habit, hypertension and dyslipidaemia were considered as clinical variables potentially associated with increased risk of further coronary events.

Table 1 Clinical characteristics of study population

Number of patients	406
Age	57 ± 9
Sex (m/f)	353/53
Q wave infarction	355 (87%)
anterior	137 (34%)
inferior	211 (52%)
lateral	7 (1%)
Non-Q wave infarction	51 (13%)
Thrombolysis	220 (54%)
Smoking habit	248 (61%)
Diabetes	52 (13%)
Hypertension	87 (21%)
Dyslipidaemia	150 (37%)

Exercise stress testing

Patients performed a symptom-limited, bicycle exercise stress test (25 W incremental loading every 3 min) 1 to 3 days before or after dobutamine stress echocardiography. A 12-lead ECG was continuously monitored throughout the test by means of a computer-assisted Marquette Case 15 System. The occurrence of significant anginal pain, ventricular tachycardia, major conduction abnormalities, ST depression ≥3 mm, limiting symptoms (such as dyspnoea, dizziness, fatigue, cramp in legs, etc.) an excessive increase (above 230 mmHg) or decrease (≥30 mmHg) in systolic blood pressure were regarded as interruption criteria. Both ST depression in one or more leads, excluding aVR and V_1, and ST elevation in leads without pathological Q waves were considered. The presence of horizontal or downsloping ST depression ≥1 mm measured 80 ms after the J point and of ST elevation >1 mm measured 40 ms after the J point were regarded as positive criteria. Positive was defined as 'low-threshold' if occurring at rate-pressure product <20 000 or at workload <100 W.

Dobutamine stress echocardiography

Dobutamine stress echocardiography was performed 10·2 ± 3·7 days after the infarction using a Hewlett-Packard Sonos 1500 or Acuson XP10 echo equipment and recorded on connected 3/4 inch U-Matic tape (video recorder Panasonic AG-7350), with the patient in the left lateral decubitus position. Dobutamine (Dobutrex, Eli Lilly) was infused using a volumetric pump, according to a protocol based on 3-min stages of 5, 10, 20, 30 and 40 $\mu g \cdot kg^{-1} \cdot min^{-1}$ plus additional atropine (0·25 up to 1 mg) in patients not achieving the 85% of their age-predicted maximum heart rate, as previously suggested[20]. Throughout the dobutamine infusion, a 12-lead ECG and a two-dimensional echocardiogram were continuously monitored. The 12-lead ECG was recorded each minute and cuff blood pressure was taken at the end of each infusion stage. Metoprolol and sublingual nitrates were at hand as antagonists. Achievement of 85% of age-predicted maximal heart rate, ST depression ≥3 mm, ST elevation ≥1 mm in leads not directly

facing the infarcted area, severe chest pain, significant arrhythmias, decrease in blood pressure ≥ 30 mmHg, severe worsening of preexisting asynergies or appearance of obvious new wall motion abnormalities were considered as test end-points. Standard apical and parasternal views were recorded in a closed cine-loop quad-screen format on super-VHS video-tape in order to get a better comparison of rest and stress images. All echocardiograms were analysed by two experienced observers. When there was a disagreement about the results, a third observer reviewed the images without knowledge of previous assessment and a majority decision was achieved. The readers were 'blinded' to the exercise ECG results at the time of reading dobutamine studies and vice versa. For the semiquantitative assessment, the left ventricular wall was divided into 16 segments[21] and scored using a 4-point scale: 1=normal, 2=hypokinetic, 3=akinetic, 4=dyskinetic. A wall motion score index (WMSI) was calculated, as usual, by adding the numeric value assigned to each segment and dividing by the number of visualized segments. The test was considered positive where there was worsening wall motion in asynergic regions or new wall motion abnormalities developed in normokinetic regions. The test was 'homozonally' positive if the wall motion abnormalities were detected in the culprit vessel area or 'heterozonally' positive if they were detected in a different vascular territory. However, the test was defined as negative if there was no evident change or development of hyperkinetic wall motion observed during the dobutamine infusion. The 30 $\mu g \cdot kg^{-1} \cdot min^{-1}$ dose was regarded as a cut-off value to distinguish between 'low-' and 'high-threshold' positive tests. The vascular attribution of echocardiographic territories to the conventional anatomical distribution of major coronary arteries was done according to the American Society of Echocardiography[22]. The left ventricular ejection fraction was measured by means of two-dimensional echocardiography using Simpson's rule[22].

Follow-up

Follow-up information was obtained from outpatient visits (every 3 months during the first 2 years and every 6 months thereafter), by discharge reports from other hospitals, following emergency admission (19 cases), and by telephone interview with the patient, his close relative or referring physician. This latter method was used when the patient did not comply with the follow-up programme (31 cases) and at study end, if the last visit dated back more than 2 months (14 cases).

Two groups of end-points were considered: spontaneous (cardiac death, non-fatal reinfarction and unstable angina requiring hospitalization) and procedural (percutaneous transluminal coronary angioplasty and coronary artery bypass surgery). Death was defined as cardiac if strictly related to proved cardiac causes (such as fatal reinfarction, malignant arrhythmias, etc.); reinfarction was diagnosed on the basis of documented electrocardiographic changes and typical cardiac enzyme release; finally, unstable angina was defined as 'crescendo angina' and rest or minimal effort angina in the absence of clear-cut electrocardiographic and cardiac enzyme changes indicating myocardial infarction. The decision to perform revascularization was taken by a team of cardiologists and cardiac surgeons, unaware of the study aim, on the basis of the clinical characteristics and coronary anatomy of the individual patient. Subjects undergoing revascularization were excluded from further follow-up (or were censored) at the time of procedure, since it was considered to cause underestimation of the spontaneous event rate. Only the first event, either spontaneous or procedural, was taken into account for statistical analysis, so that there was no overlap between the two groups.

Statistical analysis

Values are expressed as mean ± SD. The 95% confidence interval (CI) is reported when appropriate. Kaplan–Meier life table estimates of event-free time were used to summarize the follow-up result. Sensitivity, specificity, positive and negative predictive values and accuracy in predicting the outcome relied on standard definitions.

Continuous variables were compared by the unpaired two-sample t-test. Categorical variables were compared by the chi-square statistic. Fisher's exact test was used when appropriate. Sensitivity and specificity were compared using the McNemar's test. A P value <0.05 was considered as statistically significant.

The individual effect of exercise ECG and dobutamine stress echocardiography variables on event-free survival was evaluated using the Cox's proportional hazard model[23]. According to a stepwise forward procedure, the variables were included in the model on the basis of a computed significance probability. The variable showing the most significant relationship to dependent outcome was entered first in the model, whilst the remaining were included only if they further improved outcome prediction. At each step a significance of 0·1 was required to enter into the model.

The differences among survival curves were evaluated by means of a log-rank test. The area under a receiver operating characteristic (ROC) curve method[24] was used to select the cut-off value of wall motion score index change providing the best discrimination of risk.

Data were analysed by means of SPSS (release 4.1 for VAX/VMS) and SAS statistical packages.

Results

No complication occurred during exercise ECG. Four cases of non-sustained and one of sustained ventricular tachycardia occurred during dobutamine stress echocardiography. Atropine administration was required by 168 (41%) patients.

Table 2 Exercise ECG and dobutamine stress echocardiography results

Positive exercise ECG	128
Maximal heart rate	121·6 ± 13·2
Maximal systolic blood pressure	170·2 ± 18·6
Maximal workload (W)	94 ± 30
Low-threshold (RPP <20 000)	101
Low-threshold (<100 W)	158
Negative exercise ECG	278
Maximal heart rate	140·8 ± 15·5
Maximal systolic blood pressure	180·2 ± 19·7
Maximal workload (W)	108 ± 27·8
Positive DSE	192
Homozonal	140
Heterozonal	52
Low dose ($\leq$30 μg . kg^{-1} . min^{-1})	62
High-dose (>30 μg . kg^{-1} . min^{-1})	130
WMSI at peak DSE	1·5 ± 0·3
ΔWMSI	0·09 ± 0·13
Total atropine administrations	168
Negative DSE	214

RPP=rate pressure product; DSE=dobutamine stress echocardiography; ΔWMSI=stress–rest wall motion score index variation.

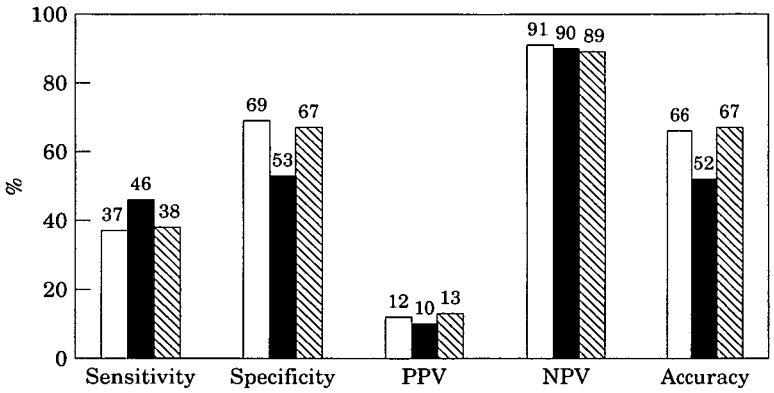

Figure 1 **Sensitivity, specificity, predictive value and accuracy of exercise ECG (□) and dobutamine stress echocardiography (■) in predicting spontaneous events. PPV=positive predictive value; NPV=negative predictive value; ▨=combined.**

The results of the two tests are reported in Table 2. A positive result was less frequently observed with exercise ECG than with dobutamine stress echocardiography (P<0·0001), but the positive low-threshold was more frequent with exercise ECG (P<0·0001). The two tests showed a concordant result in 255 (both negative in 169 and both positive in 86) and a discordant result in 152 patients. Among those with discordant result, the only positive test was exercise ECG in 46 and dobutamine stress echocardiography in 106 patients. Dobutamine-induced new wall motion abnormalities were homozonal in 140 (34%) and heterozonal in 52 (13%) patients.

Patient compliance with the follow-up programme was 92%. One hundred and twenty-seven new cardiac events occurred during the follow-up: 41 were spontaneous (5 deaths, 12 non-fatal reinfarctions and 24 unstable angina) and 86 procedural (27 percutaneous transluminal coronary angioplasty and 59 coronary artery by-pass grafting). Exercise ECG was less sensitive but more specific than dobutamine stress echocardiography in predicting spontaneous events; both tests, however, showed an excellent negative predictive value (Fig. 1). Dobutamine stress echocardiography was, in particular, significantly more sensitive and less specific in predicting the outcome of patients with anterior infarction, whilst exercise ECG was significantly more sensitive in patients with non-Q wave infarction (Fig. 2).

The ROC curve analysis method indicated 0·13 as the optimal stress–rest wall motion score index variation (ΔWMSI) for identifying an increased risk of cardiac events.

Spontaneous events were not predicted by any clinical, exercise ECG or dobutamine stress echocardiography variable. The multivariate Cox analysis showed only male gender, low workload (<100 W), positive exercise ECG, positive low-dose dobutamine

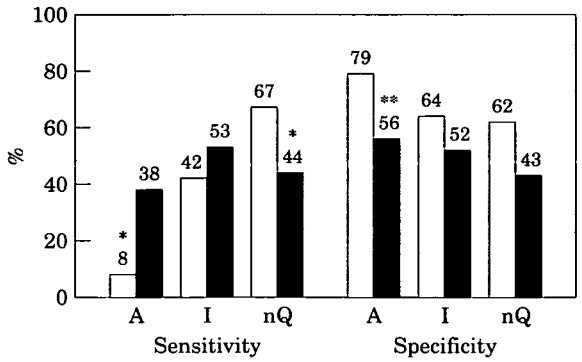

Figure 2 **Sensitivity and specificity of exercise ECG (□) and dobutamine stress echocardiography (■) in predicting spontaneous events according to infarct location. *$P<0.05$; **$P<0.01$.**

stress and ΔWMSI >0·13 to have an independent and additive value in predicting cumulative (spontaneous and procedural) cardiac events (Table 3).

The Kaplan–Meier survival curves of patients, according to the results of exercise ECG and dobutamine stress echocardiography, are reported in Fig. 3. A statistically significant ($P<0.0001$) difference was found only when cumulative cardiac events were considered, whilst no significant prediction of spontaneous events was provided by either test.

Discussion

The increasing availability of new and more sophisticated diagnostic tools has been making the functional evaluation of patients with recent myocardial infarction more complex in the last few years. Nevertheless, a great deal of evidence supports the concept that clinical history and in-hospital course can identify those at greatest risk, for which an aggressive diagnostic and therapeutic approach is advisable[6–8,10,11,25]. Patients with uncomplicated myocardial infarction represent an increasing population in the thrombolytic era and are at low or intermediate risk of subsequent cardiac events[26]. Their prognostic stratification generally deals with the detection of residual ischaemia by means of non-invasive tests, since the benefit from the routine use of coronary angiography has not been definitely proven[27]. Exercise ECG still remains the cornerstone of non-invasive evaluation and is almost uniformly performed after myocardial infarction. However, it has important shortcomings, which include its inability to identify the location and extent of coronary artery disease, and its dependence on the patient's exercise capacity and motivation. Indeed, although exercise test variables reflecting serious left ventricular impairment are useful for identifying a large proportion of subjects at low risk of 1-year mortality[6–8], the evidence of residual ischaemia was of insufficient or no positive predictive value[8–11].

The use of functional imaging after myocardial infarction has sought to overcome these limitations. Myocardial perfusion scintigraphy after exercise or pharmacological stress is the most widely used imaging technique for detecting myocardial ischaemia and has been shown to identify high cardiac risk more effectively than exercise ECG or coronary angiography[28]. However, it is expensive and time-consuming; moreover transient perfusional defects reflect a heterogeneity of regional flow that is not necessarily associated with 'true' myocardial ischaemia. Stress echocardiography is increasingly used for detecting coronary artery disease presence and extent. In particular, in detecting residual ischaemia after myocardial infarction a higher specificity has been recently reported as compared with nuclear perfusion techniques[29].

The results of this study demonstrate that stress echocardiography is a feasible and reasonably safe alternative to standard exercise ECG for detecting residual ischaemia in patients recovering from acute myocardial infarction, thereby confirming the findings of large studies including heterogeneous populations[30,31]. Mortality rate (1·2%) and incidence of non-fatal reinfarction (2·9%) were similar to those reported by previous large studies in low-risk populations of post-infarction patients[32]. In keeping with the results of previous studies[9–11,33], we found that stress-induced ischaemia was not associated with increased incidence of spontaneous events. Indeed, the link between residual ischaemia and reinfarction is known to be elusive, since an important proportion of myocardial infarctions occur as a consequence of the abrupt development of coronary occlusions from preexisting mildly stenotic plaques without ischaemic potential[34,35]. Conversely, all five patients who died during the follow-up had at least one positive test and in three of them both tests were positive. An excess of positive dobutamine stress echocardiography as compared with exercise ECG has been found in this study. This has two main explanations, in our opinion: first, it may reflect true ischaemia detected only by the more sensitive 'mechanical' marker, particularly in patients with anterior infarctions in which the ECG signal has the lowest sensitivity; second, since the specificity of dobutamine stress echocardiography has been shown to be relatively lower than its sensitivity in detecting coronary artery disease[36], a number of 'false positive' results has to be expected. Their potential source may include inadequate endocardial visualization, 'mild' myocardial ischaemia associated with intermediate or low-grade coronary stenoses and 'non-ischaemic' wall motion abnormalities, such as those related to tethering phenomenon, particularly in the basal segments of the posterior myocardial circulation[37].

Comparison with previous studies

In the EPIC study[18], the wall motion abnormalities during dipyridamole stress were the most powerful univariate predictors of spontaneous events and showed an independent predictive value in post-infarction patients.

Table 3 Multivariate predictors of cumulative cardiac events

Variable	Wald chi-square	*P*	RR
Low workload (<100 W) ExT positivity	20·55	0·0001	2·42
ΔWMSI >0·13	12·70	0·0004	2·08
Low-dose (≤30 mcg/kg/min) DSE positivity	5·64	0·0176	1·68
Male gender	4·66	0·0309	2·12

ExT=exercise ECG stress test; ΔWMSI=stress–rest wall motion stress index variation; DSE=dobutamine stress echocardiography; RR=risk ratio.

Furthermore, Neskovic *et al.*[38] found the sensitivity, specificity and accuracy of dipyridamole stress echocardiography to be 75%, 74% and 74%, respectively, for predicting spontaneous events. Three main explanations, besides the difference between the two pharmacological agents utilized, could account for the discrepancy between these findings and the results of present study. First of all, exercise ECG was not included in the protocol of these studies and, therefore, its contribution was not tested in the multivariate statistical model; in addition, the study populations were unselected and included patients with poor ventricular function; finally, recurrence of anginal symptoms was considered only on anamnestic basis.

In a direct comparison between exercise ECG and dipyridamole echocardiography in post-infarction patients, Severi *et al.*[39] found the latter to be a more powerful predictor of cumulative event-free survival. However, this study included patients referred to the author's institution for chest pain recurrence, thereby increasing the pre-test probability of subsequent cardiac events; moreover, revascularization procedures were considered as an end-point.

Both exercise ECG and dobutamine stress echocardiography showed an excellent negative predictive value in the present study, thus helping to identify a very low-risk subgroup of patients in whom further investigations are not justified upon Bayesian grounds. Similar findings have been reported by large studies addressing either exercise ECG[11] or dipyridamole stress echocardiography[18] in unselected populations of post-infarction patients. It is interesting to note that infarct location affected the accuracy of both tests. In particular, the sensitivity of dobutamine stress echocardiography was significantly better in anterior infarctions, in which the resting modifications of the ECG signal are known to hinder the interpretation of exercise-induced changes; conversely, it appeared to be worse in non-Q wave infarctions and further investigations are needed to better clarify the pathophysiological and clinical significance of this finding.

Study limitations

Some limitations of the present study should be taken into account. Firstly, it deals with a very low risk population of post-infarction patients aged <75 years and with left ventricular ejection fraction >40%; so its results cannot be extrapolated to different groups with higher event rates. Moreover, it is possible that the more aggressive approach to patients with evidence of inducible ischaemia has introduced a post-referral bias, causing the prognostic value of this finding to be underscored. This aspect, however, represents an intrinsic limitation of all observational studies aimed to evaluate the prognostic impact of a diagnostic test result. Finally, some concerns could arise as to the withdrawal of cardioactive therapy, in particular beta-blockers, early following acute myocardial infarction. Indeed, the choice of performing stress testing for prognostic purposes on or, respectively, off therapy represents a well known 'vessata questio'. In particular, previous studies that included patients recovering from recent myocardial infarction showed controversial results[40–42].

Exercise stress testing can provide the clinician with two main pieces of information for post-infarction patients: residual left ventricular function and extent of coronary artery disease. Moreover, as further demonstrated by the present study, the negative predictive value is the most accurate prognostic parameter obtained by exercise ECG, provided that maximal heart rate is achieved. It is known that beta-blockers can interfere with both ventricular function and myocardial oxygen balance during exercise, thus increasing the specificity and decreasing the sensitivity of the test[43]. A similar influence of therapy on test results has been described for pharmacological stress echocardiography[44]. On the other hand, low-risk patients seem to gain no immediate advantage from beta-blockade in the subacute phase of myocardial infarction[45]; moreover, the prognostic impact of beta-blocker therapy has not been adequately evaluated in the thrombolytic era. So, in our opinion, the potential risk from a short-term in-hospital pharmacological wash-out in this kind of population can be considered as negligible.

Clinical implications

This study confirms that the majority of new cardiac events in low-risk post-infarction patients is not predicted by inducible ischaemia. This fits the available pathophysiological as well as angiographic evidence that plaque factors[46], other than the degree of stenosis[47], are major determinants of acute coronary events. Stress

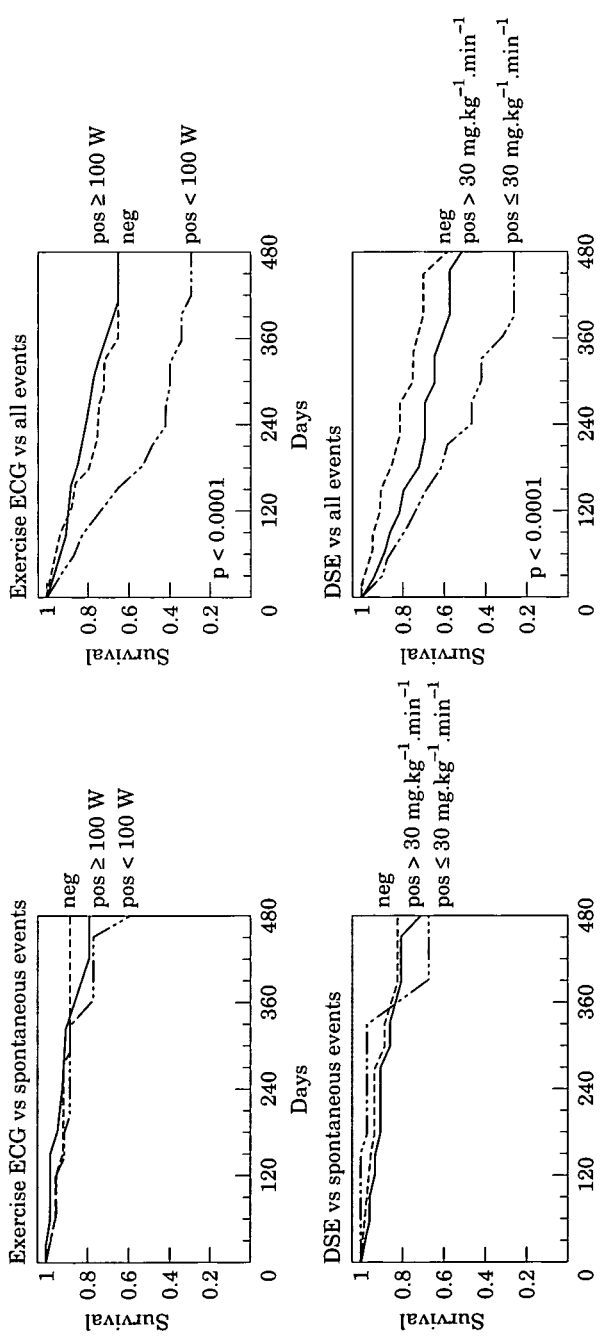

Figure 3 Kaplan–Meier event-free survival curves according to the result of exercise ECG and dobutamine stress echocardiography. neg = negative; pos ≥ 100 W = high-threshold exercise ECG positivity; pos < 100 W = low-threshold exercise ECG positivity; pos > 30 μg = high-dose dobutamine stress echocardiography positivity; pos ≤ 30 μg = low-dose dobutamine stress echocardiography positivity.

tests can only indirectly identify the extent and severity of a general pathological process[48] whose prognostic evolution is still largely unpredictable. Questions could arise, however, as to the relative role of pharmacological stress echocardiography and exercise ECG in patients at low or moderate risk. Our results confirm the 'first line' role of a diagnostic exercise ECG. Dobutamine stress echocardiography should be considered as a secondary option in cases where the exercise ECG is equivocal or when the location of ischaemia is a relevant issue. This strategy may be an alternative to the application of thallium perfusion scintigraphy as a second-line test, but offers clear advantages in terms of cost containment, patient convenience and availability.

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