meta-analysis, that is, the study of families, may be preferable. In such a study design, an affected individual and other members of the family (parents if available, otherwise siblings) are ascertained and the probability of transmission of the different alleles at the locus under study from parents to the affected individual calculated. Because transmission is being studied, there is no problem with population substructure between cases and controls, although extreme care still needs to be paid to the technical issues of genotyping. We would suggest that any positive association discovered in a case-control study, however strongly supported by meta-analyses and appropriately sized studies, be regarded as preliminary until family studies confirm that the association is due to identity or proximity of the genotyped polymorphism to a causative genetic variant on the chromosome. Until such time, it seems prudent to adhere to the epidemiological principles of large size in individual studies and inclusivity in meta-analysis.

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European Heart Journal (2001) **22,** 273–276
doi:10.1053/euhj.2000.2435, available online at http://www.idealibrary.com on IDEAL®

The post myocardial infarction exercise test: still worthy after all of these years

See page 300 for the article to which this Editorial refers

While the prognostic value of exercise testing post-myocardial infarction has been established by meta-analysis, both pre[1] and post[2] the thrombolytic era, there are other benefits of performing the test. Hospital discharge can be optimized and expediated. The patients' response to exercise, their work capacity, and limiting factors at the time of discharge can be assessed. Guidelines for exercise at home can be formulated and reassurance given of physical status, and risk of complications. The test provides a safe basis for advice on return to work, and can demonstrate to the patient, relatives, or employer the effect of the myocardial infarction on the capacity for physical performance. It can cause an improvement in the patients' self-confidence by making them less anxious about daily physical activities[3]. The test has been helpful in reassuring spouses of post-myocardial infarction patients of their physical capabilities[4]. The psychological impact of performing well on the exercise test is impressive and in fact many patients increase their activity and actually rehabilitate themselves after being encouraged and reassured by their response to this test.

Exercise testing remains useful after hospital discharge. It is an important tool for activity counselling and in exercise training, as part of comprehensive cardiac rehabilitation, where it can be used to develop and modify the exercise prescription, and assess the patient's progress. For all these reasons, national guidelines call for exercise testing post-myocardial infarction[5].

In this issue, Domínguez *et al.*[6] heighten our understanding of the post-myocardial infarction

Table 1 Contraindications to exercise testing

Absolute	Relative
Within 2 days of myocardial infarction	Hypertension >200/110
An acute coronary syndrome — without 48 h pain free	Hypertrophic cardiomyopathy with outflow tract obstruction
Severe aortic stenosis	High degree atrioventricular block
Severe left ventricular dysfunction	Electrolyte abnormalities
Endocarditis, myocarditis, pericarditis	Physical disability such as claudication, arthritis or deformity
	Other exertion limiting conditions such as smoking related lung disease

exercise test by presenting an analysis of 15 years follow-up of exercise tests carried out early after the event. The study is particularly significant, not just for the length of follow-up, but for the fact that the tests were carried out before the age of thrombolysis and in the context of only rare intervention. Thus the story presented is 'clean' and gives a guide to the true long-term risk of myocardial infarction and how it relates to post event exercise variables. Such a study would not be possible today — indeed, such a 'retrospective' approach represents one answer to the problem of 'work-up bias' (data can only be gathered within the bounds of contemporary clinical practice).

Perhaps the most consistent finding in the post-myocardial infarction exercise test studies that included a follow-up for cardiac end-points is that patients who met the criteria to undergo exercise testing were at lower risk than those excluded from testing. This finding, the primary conclusion from the present study, supports the clinical judgement of the skilled clinician in identifying high risk patients. In relation to the test itself, the earlier meta-analysis suggested that only an inadequate systolic blood pressure response or low exercise capacity were significantly associated with a poor outcome[1].

The DUKE meta-analysis[2] demonstrated that electrocardiographic, symptomatic, or scintigraphic markers of ischaemia were less sensitive (around 44%) than markers of both left ventricular dysfunction and ischaemia (exercise duration, exertional hypotension, and peak left ventricular ejection fraction). Further, markers of left ventricular dysfunction, or both dysfunction and ischaemia were better predictors than markers of myocardial ischaemia alone.

The GISSI-2 database enabled re-evaluation of the prognostic role of exercise testing in the thrombolytic era[7]. In this study, the 6 month mortality rate was 7·1% among patients who did not have an exercise test (40% of the population studied), 1·7% for those with an ischaemic test, 0·9% for those who had a normal test, and 1·3% for those whose tests were non-diagnostic. Independent predictors of mortality were symptomatic-induced ischaemia, ischaemia at a submaximal workload, low total work capacity, and abnormal systolic blood pressure (relative risks 2·5, 2·3, 2, and 1·9, respectively). However, when these variables were considered simultaneously, only symptomatic-induced ischaemia and low work capacity were confirmed as independent predictors of mortality. The GISSI investigators concluded, as have others[8], that patients with a normal exercise response have an excellent medium-term prognosis and do not need further investigation. Like us, they recommend evaluation be concentrated on those patients who cannot undergo exercise testing, since the mortality is five to seven (Shaw estimates four[2]) times greater in that group.

These analyses, spanning a total of 80 studies and over 37 000 patients, find that markers of left ventricular dysfunction are more predictive of adverse cardiac events after myocardial infarction than measures of exercise-induced ischaemia. Further, the biggest risk factor is not being able to take the test at all. The strength of this last finding demands some explanation. Exclusion criteria were generally not broken down in detail in the studies, although in the GISSI database, those excluded tended to be 'female, with a history of myocardial infarction, hypertension, diabetes, or anterior wall infarction'. Non-cardiac contraindications were, however, almost three times as common as cardiac. Commonly accepted contraindications to exercise testing are shown in Table 1. The key question is what puts this population at such high risk (higher even than those with signs of left ventricular dysfunction)? Although a diverse group, the simplest explanation is that some of these patients had sufficiently *severe* left ventricular dysfunction as to contraindicate exercise testing. However, we also know that physical inactivity is a 'major' risk factor for cardiovascular disease[9,10]. Thus, physical disability in the form of, say, arthritis or even aortic stenosis would both contraindicate exercise testing and predict risk through an inactive lifestyle. The psychological correlates of inactivity[11] would

amplify those accompanying myocardial infarction and compound the risk[12]. In addition, features such as claudication might suggest more widespread and severe arterial disease.

Notwithstanding debate over the merits of discussing poor prognosis with the patient in the absence of modifiable risk, to know who is at high risk is helpful only in so far as it identifies those with most to gain from intervention. Here again, we must address two groups: those who complete an exercise test and those who do not. In the latter group, clinical judgement is once again called to answer, because the contraindication will be different in each case. Thus we must look to secondary prevention measures known to save lives: pharmacological (aspirin, statins, beta-blockers, ACE inhibitors, spironolactone) and lifestyle (smoking, exercise, diet, weight loss). Although all our patients should receive close secondary prevention monitoring, our knowledge of the high risk of this population should lead us to be especially careful with them. The question of angiographic intervention in this group is more difficult, but their high risk demands some other form of assessment of modifiable disease. Of the newer non-invasive tests, pharmacological stress echo, and in particular the rest–stress wall motion index look to be particularly promising[13].

For those who do complete the test, we have the benefit of exercise variables to elucidate more clearly their risk. However, as with the latter group, the greatest risk seems to be associated with that about which we can do least, namely left ventricular dysfunction, while those whose arteries can be stented or bypassed seem to have lower risk. This presumably reflects the fact that, in the presence of an already reduced effective muscle mass, a less critical occlusion results in a proportionately larger loss. This may not be absolute, however, because of the presence of hibernating myocardium[14]. Viable but akinetic myocardium which recovers its function following revascularization may provide a reason to look more closely at this group. Of note, in the randomized trials of bypass grafting[15], benefit is concentrated in those with ejection fractions of 30 to 50%. Suspicion of hibernation prompted by a low exercise capacity, or an inadequate systolic blood pressure response to exercise in the presence of a low peak enzyme rise with no previous history of myocardial infarction, should lead to further investigation (and several possible tests are available[16]).

Other causes of low exercise capacity should also be considered. Depression affects one in five patients following myocardial infarction and is known to be associated with poor outcome[17]. It is likely that patients who are depressed will perform poorly during an exercise test and have lower estimated capacity. Although intervention has been shown to improve quality of life measures, no study has yet demonstrated an improvement in mortality[18].

Ironically, however, there is perhaps more we can do for those with lower risk. Bypass grafting improves survival in patients with triple vessel disease, left main disease, or two vessel disease including the proximal LAD[15]. Bearing in mind the lack of localization of exercise ECG changes and the fact that the diagnostic characteristics of the test are not compromised by beta-blockade[19], severe myocardial ischaemia on exercise testing should lead to coronary angiography with a view to bypass grafting or stent intervention. Severe ischaemia is characterized by ST segment depression (lead V_5 in recovery is repeatedly shown to have the highest sensitivity) and/or angina at a double product (HR × systolic blood pressure) less than 20 000 or an exercise capacity less than 5 METS. It is worth noting that despite the promise of the rest–stress wall motion index[13] it is not yet clear that this measure outperforms simple exercise electrocardiography[20] and given the significantly lower cost of the latter, it is too early to recommend other than simple exercise testing for routine use in the post-myocardial infarction population. In fact, although the sensitivity is lower in one or two vessel disease, the exercise ECG is approximately 90% sensitive for triple vessel or left main disease.

Exercise testing post-myocardial infarction is a vital part of the continuing management of the cardiac patient. It provides reassurance and benefit to the patients and their families, allows optimization of cardiac rehabilitation, and facilitates risk stratification relevant for up to 15 years following the test[6]. Planning exercise tests in all post-myocardial infarction patients allows secondary prevention efforts (and more expensive tests) to be directed towards those with contraindications to the test, in line with their extremely high risk. While low work capacity and inadequate systolic blood pressure response highlight a high risk group, it is not entirely clear if this group gains from angiographic intervention. Ironically, there may be more to gain in the lower risk inducible ischaemia group.

The exercise test plays a pivotal role in the recovery from myocardial infarction. In identifying those at greatest risk, it promotes directed intervention, tailored rehabilitation, and optimal secondary prevention. Domínguez *et al.* have provided one more reason to be grateful for its simplicity.

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European Heart Journal (2001) **22,** 276–279
doi:10.1053/euhj.2000.2437, available online at http://www.idealibrary.com on IDEAL®

Coronary risk factor modification after the acute event — why are effects not maintained?

See page 307 for the article to which this Editorial refers

Coronary artery disease is a chronic pathogenic process. In most patients it takes years or even decades before development of the underlying coronary pathology leads to clinical manifestations. When an acute clinical event occurs, however, it often comes as a complete surprise and a shock for the patient. Modern cardiology and emergency medicine have