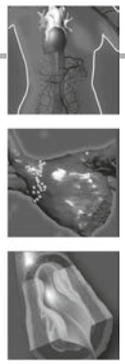

The role of exercise testing in the interventional era: a shift of focus

The role of exercise testing has changed in the last decade, due to the development of new interventional treatment options, new cardiac biomarkers, as well as emerging noninterventional imaging techniques. The increasing prevalence of lifestyle-related disease, such as obesity and diabetes mellitus, highlights the role of exercise for primary/secondary prevention and treatment of coronary artery disease. In stable coronary artery disease, the trend of an increasing number of percutaneous coronary interventions, has been questioned, with smaller studies indicating equally good treatment results by aggressive medical treatment and lifestyle changes. Thus, while the role of the exercise test in the evaluation of acute chest pain and early in the setting of an acute coronary syndrome has decreased, it remains an important clinical tool. The exercise test today, has a pivotal and increasing role in tailored exercise prescriptions, with a shift of focus towards giving information on prognosis, functional capacity and safety of prescriptions.

KEYWORDS: exercise prescription ■ exercise test ■ prognosis ■ risk predictor

Mats Borjesson*[1,2] & Mikael Dellborg[3,4]

[1]The Swedsih School of Sport & Health Sciences, Stockholm, Sweden
[2]Karolinska University Hospital, Stockholm, Sweden
[3]Department of Molecular & Cardiovascular Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
[4]Adult Congenital Heart Center, Department of Medicine, Sahlgrenska University Hospital/Östra, Gothenburg, Sweden
**Author for correspondence: mats.brjesson@telia.com*

For a long time, the exercise test (ET) has been the main evaluation method recommended for most patients with suspected myocardial ischemia [1,2]. Furthermore, the ET has been used widely as the main decision tool for deciding clinical strategy – that is, interventional or conservative approach [1], but the ET can also be used for risk evaluation [3] and for exercise prescription [4].

However, in recent years, the role of the ET has shifted. Recent developments of new imaging methods have put the role of the ET in chest pain evaluation and for deciding upon a suitable treatment method, into question [5]. At the same time, an increasing body of scientific knowledge accumulated over the last 10 years has shed light on the importance of regular physical activity for prevention of cardiovascular morbidity and mortality, and have highlighted the role of the ET for providing prognostic information in patients with coronary artery disease (CAD) [6,7], and also for prescribing individualized physical activity to these patients [4,8,9].

The role of the ET in the investigation of patients with chest pain

The ET has been the main evaluation method in patients presenting with suspected CAD for the last few decades – that is, for those without resting-ECG changes that would not interfere with interpretation of the test, as well as those able to exercise sufficiently [1]. While having certain disadvantages, such as a low specificity in low-risk patients and especially women [10], the ET is readily available and relatively cheap. The important advantage of the ET over myocardial scintigraphy is the absence of radiation. Regarding CT angiography, while in most cases providing good anatomical information on prevalence of high-grade stenosis and/or calcifications in the proximal coronaries, the main limitation remains its inability to provide information on ischemia burden and ultimately prognosis, in addition to being less (not universally) available and subjecting the patient to significant doses of radiation.

Recently, the use of the ET in evaluation of chest pain in patients who had a normal resting ECG and no prior revascularization, was found to be cost effective, compared with modern stress imaging methods [11]. In fact, the ET showed a similar diagnostic yield and was considerably cheaper, compared with available stress imaging methods [11]. Thus, the ET still seems to have a given role, at least in a male chest-pain population.

However, a more invasive strategy has been increasingly popular clinically. Due to the almost universal availability of coronary angiography, and studies such as FRISC II [12] that have shown that a generally invasive strategy is advantageous, the use of ET has declined in the acute setting. This shift in the use of the ET is partly due to scientific developments, showing the superiority of an invasive strategy in unstable disease [12],

Future Medicine part of fsg

but is also due to the logistic organization of acute cardiac care. Today, the widespread availability of angiographic/interventional laboratories, makes it (in many places) easier and faster to perform a coronary angiography to rule out significant CAD, than to get additional stress imaging, such as myocardial scintigraphy or stress echocardiography. However, the evidence in favor of a strategy of routine intervention is not so solid for all patient groups, such as women and low-risk patients [13], and certainly not for stable CAD [8,14], although the number of studies directly comparing percutaneous coronary interventions (PCI) to exercise is rather small and not very numerous [8,14].

Emerging imaging methods and the development of new biochemical markers for increased risk prediction [15], has shifted the focus away from the standard ET in risk stratification of chest pain patients. Regarding biomarkers, myocardial damage markers such as cardiac troponin T and high-sensitive troponin T; natriuretic peptides involved in cardiac remodelling, such as NT-pro-BNP, as well as components of the acute phase response, such as C-reactive protein, have all been associated with higher risk in nonselected patients with chest pain, in the acute setting [15–17]. However, the role of coronary calcium score in the evaluation of chest pain remains to be fully understood [18]. Importantly, imaging methods, such as computed tomography angiography and cardiac MRI, have the potential to give even more detailed information on coronary artery anatomy and plaque morphology [19,20], but its role in routine chest pain evaluation, in the acute setting, remains to be established.

Women with chest pain have a lower incidence of CAD than men. In women with suspected myocardial ischemia, the ET is still a recommended first-line evaluation procedure [21], and has been shown to exclude CAD more effectively, than in men [22]. Due to the high false-positive rate of the ET, in women [10], additional and higher cost procedures have been suggested [5]. However, the evidence base for choosing the most suitable method for evaluation of women with suspected myocardial ischemia has been limited. The recent WOMEN study concluded that in low-risk women, a diagnostic strategy that includes the ET yields similar 2-year outcomes, as a strategy using myocardial perfusion imaging, and at a significantly lower cost [21]. The authors suggested that "in women capable of exercising, a strategy using the ET alone, was still the preferred evaluation method for those with suspected myocardial ischemia" [21]. In patients with a low-risk score, more often women, there is at present no evidence that any additional imaging method, will add to the prognostic information gathered from the ET [1]. Stress echocardiography [23] or myocardial scintigraphy [1,5] are recommended as additional evaluation methods of chest pain, in patients with intermediate-risk ET score.

All in all, the role of the ET in chest pain evaluation has declined in recent years, not only for scientific reasons (better imaging methods available), but also for logistical reasons and because of the way we organize acute care.

The role of the ET as a tool for selecting patients for acute/subacute coronary intervention

The ET is safe, conferring a low risk for serious adverse events (myocardial infarction [MI]/death) in low-risk patients seeking medical attention for unspecified chest pain [1], but also in stabilised unstable angina. Historically, the most important prognostic message from the ET has in fact been the initial evaluation, whether the patient is capable of performing the exercise at all, or not. The patients who are excluded from the ET have a generally poorer prognosis [24].

The aim of noninvasive testing has been to identify patients suitable for revascularization and patients with severe left ventricular heart failure [1,25,26]. Clinical studies randomizing patients with an acute coronary syndrome to early intervention or to a more conservative approach, have shown that an interventional strategy most often is the preferred strategy [27]. However, in women, in the elderly and in patients with very low or very high risk, this is less clear. Elderly patients have a higher risk of intervention, but also have potentially more to gain from an intervention. Clinically, an intervention will often be based on identifying those patients that benefit the most from an intervention – that is, being at higher than average risk [1], especially in areas and countries where an acute coronary intervention is not readily available to all. The ET has a high accuracy for identifying such high-risk patients [11]. In addition, one of the advantages of the ET is to detect possible exercise-induced arrhythmias.

Possibly, there is also a gender difference regarding the application of a universal invasive approach. The results regarding an interventional strategy in women are lacking compared with what has been demonstrated in men, for example in the FRISC II study [12]. In fact,

no studies have clearly shown that an invasive strategy is significantly better than a more noninvasive approach in women with acute coronary syndrome. Not only in low-risk women [21], but also possibly in the growing elderly population, a strategy involving stabilization and risk evaluation with the ET, before deciding upon an interventional treatment or not, may still be the preferred approach.

Therefore, while generally declining in importance in the decision-making approach in acute coronary syndrome, the ET remains an important tool, especially in the subset of women with acute coronary syndrome. The ET still has a definitive role in identifying patients where a significant symptomatic effect of a revascularization can be expected.

The role of the ET as a risk predictor in different settings

A low cardiorespiratory fitness level (low $VO_{2\,max}$) has been shown to be at least as important a risk factor, as elevated systolic blood pressure, smoking, obesity and diabetes for mortality in CAD [28]. Fitness is also a predictor of CAD and of progression of atherosclerosis [28]. In fact, fitness represents one of the strongest independent predictors of mortality, also with underlying CAD [7], emphasizing the importance of the ET for fitness evaluation, in everyday clinical practice.

Different risk scoring charts are commonly used to assess the individual cardiovascular risk profile, for example the European SCORE system [29]. This important decision tool, may help the clinician's treatment and follow-up, as well as providing the patient with incentive and motivation to adhere to treatments, and thereby achieve a reduction in estimated risk. The problems with today's risk scoring system, is the limited number of risk factors included in the risk-assessment (hypertension, smoking, age, sex and total cholesterol) [29]. The addition of information on the individual fitness level would increase the prognostic power of the SCORE risk assessments [30].

An early meta-analysis of the ET in post-MI patients, demonstrated that clinical judgment can be used to identify high-risk patients, and that ST-segment shifts are not as predictive of high risk as an abnormal systolic blood pressure response or having a poor exercise capacity [31].

In patients with stable coronary heart disease, studies considering angiographic findings, cardiac events and the differential outcome of coronary artery bypass surgery as compared with medical therapy, have shown the ET to have prognostic power [3]. Later, as PCI emerged as a therapeutical alternative, the classical electrocardiographic changes seen in myocardial ischemia (ST-depression) were more unreliable as prognostic markers [32]. However, the ET was still a useful prognostic tool, as the blood pressure response and exercise capacity remained good predictors of prognosis, also post-PCI [32], and especially in stable angina [8,14]. The ET in the interventional era, will thus still add valuable prognostic information [33].

From this perspective, it is obvious that there is much information supporting the use of ET as the first noninvasive step after the history, physical examination and resting ECG in the prognostic evaluation of patients with CAD [1]. The result of the ET may predict both the severity of the underlying coronary disease, as well as give information on the patient's prognosis. In addition, the ET will also help making recommendations for optimal treatment of the disease.

The role of the ET in giving the patient tailored physical activity prescriptions

Successful primary prevention of CAD remains one main goal for the healthcare systems of the future. However, CAD is increasing in many countries worldwide, for example in China [34,101], because of the imbalance between a rise in classical risk factors (overweight, diabetes, hypertension and smoking) compared with the results of lifestyle advice (smoking cessation, diet and increasing physical activity) and pharmaceutical treatment options (e.g., β-blockers, cholesterol-lowering agents and so on). Increments in noncommunicable diseases, like CAD, is now a universal problem, as highlighted by the WHO [101]. Therefore, secondary prevention will continue to be an important part of the CAD management in the foreseeable future [4,35]. Presently, the level of secondary prevention is insufficient, particularly regarding lifestyle advice, as shown by national registries [36] and patient surveys [37], demonstrating the great potential benefits of improvements in this area.

Specifically, cardiac rehabilitation programs, typically post-MI, have been successful in increasing functional capacity [38] and to reduce complications and even mortality [39], at least in the short term. While the effect of such programs in a longer perspective, remains to be demonstrated, regular physical activity has been shown to be equally effective as PCI, in addition to conventional medical therapy, in stable angina [8]. The COURAGE study demonstrated that in patients

with stabilized CAD, if optimal medical therapy was given, as assessed by measuring the HDL fraction of cholesterol, and prescription of exercise was added, the addition of PCI meant that more patients became free from angina in the short term (months), while having no positive effect and no effect on hard end points, such as recurrent infarction or death [14]. In addition, cardiac rehabilitation seems to be of benefit (even to reduce mortality) to patients undergoing invasive PCI [40,41]. Furthermore, the Corpus Christi study showed that the risk of a new MI, in patients with a recent MI, was halved in patients who increased their level of physical activity or remained physically active [42].

In Sweden, the National Board of Health and Welfare recently, after extensively reviewing the available literature, published national guidelines for methods to prevent disease (addressing smoking cessation, bad diet, alcohol consumption and a low physical activity level) as treatment [102]. It was clearly stated that for all patients that are insufficiently physically active, the healthcare system, should give structured advice on physical activity, accompanied by adjuvants such as prescriptions on exercise or activity diaries, as well as follow-up these measures regularly [102].

Also in the context of prescription of exercise to patients with CAD, as part of the treatment regime, the ET may play an important and increasing future role. Especially, patients who have had a recent MI or have undergone interventional therapy, require counseling regarding their ability to perform daily activities and exercise [4,9]. ET can be a useful tool in establishing physical activity guidelines for these individuals.

Clinically, exercise prescription for CAD patients, is recommended to be based on a thorough clinical individual evaluation, which includes risk scoring, assessing the intended level of activity and performing an ET [4,43]. The individual training intensity could be determined as a percentage of symptom free maximal exercise capacity, as measured by the standard ET [4]. Alternatively, the $VO_{2\,peak}$ and/or the first ventilatory threshold (ventilatory anaerobic threshold), using a more extensive cardiopulmonary ET, may be used [44].

In clinical practice, the maximal workload in watts (J/s) achieved by the patient, without him/her experiencing any signs of ischemia and/or cardiac or respiratory failure, may be used for an approximation of the suitable exercise capacity. The training intensity is prescribed as percentage of the maximal workload, or calculated from the heart rate reserve (maximal heart rate minus resting heart rate) and/or as percentage of the maximal heart rate (training heart rate) from the test [4,44].

In CAD patients treated with β-blockers the training heart rate, could be determined either as percentage of $VO_{2\,peak}$ [45], or by measuring the ventilatory aerobic threshold [44]. In patients with chronotropic incompetence and atrial fibrillation, exercise prescription could alternatively be based on the maximal work load achieved during the ET [4].

Importantly, if the status of the patient's individual cardiorespiratory fitness is regularly evaluated by further ETs, this provides valuable information on potential CAD progression [4]. The heart rate recovery index (heart rate at a standardized workload minus heart rate after 2 min) is a practical tool for follow-up of a physical activity prescription [4].

In summary, the individually tailored exercise prescription has to consider pre-existing risks and limitations (i.e., exercise-induced ischemia or arrhythmias, cardiac function, limiting comorbidities and disabilities), the baseline fitness level, individual preferences on exercise modalities, potential psychological, social and/or cultural barriers, gender as well as age-related needs and limitations. Thus, the potential role of the ET in exercise prescription is vast, but it is still underutilized in clinical practice.

Conclusion

In combination with adequate imaging and biochemical tests, the ET is still a valuable tool in the work-up of patients admitted for chest pain. In selected patients with acute coronary syndrome (elderly, women, patients in remote or socioeconomically less favored areas) careful selection of patients for revascularization may be guided by ET. In primary and secondary prevention, the last decade has provided us with an abundance of studies indicating not only the importance of physical activity but also the importance of exercise prescription for treatment of patients with CAD. The ET is an excellent tool to identify the suitable physical activity, and to help motivate patients with CAD to change their lifestyle.

Future perspective

The role of ET in evaluation and risk stratification of acute chest pain will possibly continue to decrease in the near future, due to emerging noninterventional imaging techniques. Importantly, methods, such as computed tomography angiography could add valuable

information, to conventional coronary angiography and coronary calcium score, by providing information on coronary artery anatomy [19]. Cardiac MRI has the potential to give even more detailed information on coronary plaque morphology [20], but its role in routine chest pain evaluation, in the acute setting remains to be established. Further development in imaging methods, will probably decrease the role of the ET in risk stratification of chest pain in the future.

In the setting of an acute coronary syndrome, ET will remain obsolete for many patients during the initial hospital stay, but will be used more in early out-patient rehabilitation. As lifestyle -related diseases continue to increase worldwide [101], currently already constituting a great part of the 'noncommunicable diseases', there will be an even greater focus on preventing these diseases in the near future. Therefore, preventive measures involving lifestyle behavioral changes, such as increasing the level of physical activity, will be more emphasized, possibly involving the political, social and healthcare settings.

In addition, lifestyle treatments such as prescribed physical activity, will be more widely used in healthcare as a basic treatment modality, supplemented by pharmacological treatment according to national and international treatment guidelines, for both cardiovascular risk factors and in established stable CAD [4]. Potentially, the overall benefits of increasing the level of physical activity as part of an improved secondary prevention of CAD, may be even greater than the benefits of any developments of new pharmacological or interventional therapies, in the near future. Revascularization in moderately symptomatic patients with stable angina will be replaced by more aggressive and structured lifestyle changes and medical therapy, in the coming years.

In this context, the role of the ET will certainly improve in the development of exercise programs for a growing number of individuals with cardiovascular disease. Specifically, the ET will also be used more widely and routinely, to assess risk, for prognosis and for assessment of functional capacity.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Executive summary

The role of the exercise test in the investigation of patients with chest pain

- With novel biomarkers and emerging imaging techniques, the role of the exercise test (ET) has decreased in the investigation of patients with chest pain of unknown etiology.

The role of the ET as a tool for selecting patients for acute/subacute coronary intervention

- While the role of the ET in the setting of an acute coronary syndrome has decreased overall, it remains important, especially in patients at low risk, in women and in areas with limited availability of immediate interventional strategies.

The role of the ET as a risk predictor in different settings

- The use of the ET has an increased role, in both primary and secondary prevention of coronary artery disease, to risk stratify the patients.

The role of the ET in giving the patient tailored physical activity prescriptions

- The use of the ET remains underutilized, as a clinical tool for prescribing individualized physical activity, as treatment for coronary artery disease.

References

Papers of special note have been highlighted as:
- ▪ of interest
- ▪▪ of considerable interest

1 Gibbons RJ, Balady GJ, Bricker JT *et al.* ACC/AHA 2002 guideline update for exercise testing: summary article. A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. *J. Am. Coll. Cardiol.* 40, 1531–1540 (2002).

2 Goldhammer S, Scherf D. Elektrokardiographische untersuchungen bei kranken mit angina pectoris ('ambulatorischer Typus'). *Ztschr. f. Klin. Med.* 122, 134 (1932).

3 Wackers FJT, Zaret BL. Risk stratification soon after acute infarction. *Circulation* 100, 2040–2042 (1999).

4 Vanhees L, Rauch B, Piepoli M *et al.* Importance of characteristics and modalities of physical activity and exercise in the management of cardiovascular health in individuals with cardiovascular disease (part III). *Eur. J. Prev. Cardiol.* doi:10.1177/2047487312437063 (2012) (Epub ahead of print).

5 Hansen CL, Goldstein RA, Akinboboye OO *et al.* Myocardial perfusion and fucnction. *J. Nucl. Cardiol.* 14, E39–E60 (2007).

6 Kavanagh T, Mertens DJ, Hamm LF *et al.* Predicition of long-term prognosis in 12 169 men referred for cardiac rehabilitation. *Circulation* 106, 666–671 (2002).

▪ **Well conducted, large study demonstrating the prognostic value of physical capacity in patients with coronary heart disease.**

7 Myers J, Prakash M, Froelicher V, Do D, Parlington S, Atwood JE. Exercise-capacity

and mortality among men referred for exercise testing. *N. Engl. J. Med.* 346, 793–801 (2002).

▪ **Well conducted, large study demonstrating the prognostic value of physical capacity in patients with coronary heart disease.**

8 Hambrecht R, Walther C, Mobius-Winkler S *et al.* Percutaneous coronary angioplasty compared with exercise training in patients with stable coronary artery disease. *Circulation* 109, 1371–1378 (2004).

▪▪ **Pivotal study that randomized patients with stable angina to angioplasty or daily exercise with the latter treatment coming out significantly better regarding complications as well as morbidity.**

9 *Physical Activity on Prescription-FYSS.* Professional Associations for Physical Activity (YFA) (Eds). The Swedish National Institute of Public Health, Stockholm, Sweden (2010).

10 Mieres JH, Shaw LJ, Arai A *et al.* Role of noninvasive testing in the clinical evaluation of women with suspected coronary artery disease. *Circulation* 111, 682–696 (2005).

11 Miller TD. Stress testing: the case for the standard treadmill test. *Curr. Opin. Cardiol.* 26, 363–369 (2011).

12 Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. FRagmin and Fast Revascularisation during InStability in Coronary artery disease Investigators. *Lancet* 354, 708–715 (1999).

13 Swahn E, Alfredsson J, Afzal R *et al.* Early invasive compared with a selective invasive strategy in women with non-ST-elevation acute coronary syndromes: a substudy of the OASIS 5 trial and a meta-analysis of previous randomized trials. *Eur. Heart J.* 33, 51–60 (2012).

▪ **Most recent randomized trial and meta-analysis, indicating little or no benefit of aggresive revascularization versus a more conservative approach in women with acute coronary syndromes.**

14 Boden WE, O'Rourke RA, Teo KK *et al.* Optimal medical therapy with or without PCI for stable coronary disease. *N. Engl. J. Med.* 356, 1503–1516 (2007).

▪▪ **Large multicenter study comparing optimal medical therapy versus without revascularization. If medical therapy, including exercise, is pushed far enough, there is a small short-term positive effect on symtoms but no effect on hard end points or long-term outcomes and/or symtoms.**

15 Eggers KM, Dellborg M, Oldgren J, Swahn E, Venge P, Lindahl B. Risk prediction in chest pain patients by biochemical markers including estimates of renal function. *Int. J. Cardiol.* 128, 207–213 (2008).

16 Jernberg T, Lindahl B, Siegbahn A *et al.* N-terminal pro-brain natriuretic peptide in relation to inflammation, myocardial necrosis, and the effect of an invasive strategy in unstable coronary artery disease. *J. Am. Coll. Cardiol.* 42, 1909–1916 (2003).

17 Tsimikas S, Willerson JT, Ridker PMJ. C-reactive protein and other emerging blood biomarkers to optimize risk stratification of vulnerable patients. *J. Am. Coll. Cardiol.* 47(Suppl. 8), C19–C31 (2006).

18 Versteylen MO, Joosen IA, Winkens MH *et al.* Combined use of exercise electrocardiography, coronary calcium score and cardiac CT angiography for the prediction of major cardiovascular events in patients presenting with stable chest pain. *Int. J. Cardiol.* doi:10.1016/j.ijcard.2011.12.016(2012) (Epub ahead of print).

19 Halpern EJ. Clinical applications of cardiac CT angiography. *Insights Imaging* 1, 205–222 (2010).

20 Ehara S, Hasegawa T, Nakata S *et al.* Hyperintense plaque identified by magnetic resonance imaging relates to intracoronary thrombus as detected by optical coherence tomography in patients with angina pectoris. *Eur. Heart J. Cardiovasc. Imaging* 13(5), 394–399 (2012).

21 Shaw LJ, Mieres JH, Hendel RH *et al.* Comparative effectiveness of exercise electrocardiography with or without myocardial perfusion single photon emission computed tomography in women with suspected coronary artery disease. Results from the what is the optimal method for ischemia evaluation in women (WOMEN) trial. *Circulation* 124, 1239–1249 (2011).

22 Alexander KP, Shaw LJ, Shaw LK *et al.* Value of exercise treadmill testing in women. *J. Am. Coll. Cardiol.* 32, 1657–1664 (1998).

23 Marwick TH, Case C, Vasey C *et al.* Prediction of mortality by exercise echocardiography: a strategy for combination with the Duke treadmill score. *Circulation* 103, 2566–2571 (2001).

24 Navare SM, Mather JF, Shaw LJ, Fowler MS, Heller GV. Comparison of risk stratification with pharmacologic and exercise stress myocardial perfusion imaging: a meta-analysis. *J. Nucl. Cardiol.* 11, 551–561 (2004).

25 Madsen JK, Grande P, Saunamaki K *et al.* Danish multicenter randomized study of invasive versus conservative treatment in patients with inducible ischemia after thrombolysis in acute myocardial infarction (DANAMI). DANish trial in Acute Myocardial Infarction. *Circulation* 96, 748–755 (1997).

26 Shaw LJ, Peterson ED, Shaw LK *et al.* Use of a prognostic treadmill score in identifying diagnostic coronary disease subgroups. *Circulation* 98, 1622–1630 (1998).

27 Fox KA, Clayton TC, Damman P *et al.* FIR Collaboration. Long-term outcome of a routine versus selective invasive strategy in patients with non-ST-segment elevation acute coronary syndrome: a meta-analysis of individual patient data. *J. Am. Coll. Cardiol.* 55, 2435–2445 (2010).

28 Laukkanen JA, Kurl S, Salonen JT. Cardiorespiratory fitness and physical activity as risk predictors of future atherosclerotic cardiovascular diseases. *Curr. Atheroscler. Rep.* 4, 468–476 (2002).

29 Conroy RM, Pyörälä K, Fitzgerald AP *et al.* Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur. Heart J.* 24, 987–1003 (2003).

30 Mora S, Redberg RF, Sharnett R, Blumenthal RS. Enhanced risk assessment in asymptomatic individuals with exercise testing and Framingham Risk Scores. *Circulation* 112, 1566–1572 (2005).

31 Froelicher VF, Duarte GM, Oakes DF, Klein J, Dubach PA, Janosi A. The prognostic value of the exercise test. *Dis. Mon.* 34, 677–735 (1988).

32 Valeur N, Clemmensen P, Sauramäki K, Grande P. The prognostic value of pre-discharge exercise testing after myocardial infarction treated with either primary PCI or fibrinolysis: a DANAMI-2 substudy. *Eur. Heart J.* 26, 119–127(2005).

33 Börjesson M, Dellborg M. Exercise-testing post-MI: still worthwhile in the interventional era? *Eur. Heart J.* 26, 105–106 (2005).

34 Critchley J, Liu J, Zhao D, Wei W, Capewell S. Explaining the increase in coronary heart disease mortality in Beijing between 1984 and 1999. *Circulation* 110, 1236–1244 (2004).

35 Graham I, Atar D, Borch-Johnsen K *et al.*; European Society of Cardiology (ESC) Committee for Practice Guidelines (CPG). European guidelines on cardiovascular disease prevention in clinical practice: executive summary: fourth joint task force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts). *Eur. Heart J.* 28, 2375–2414 (2007).

36 Bellman C, Hambraeus K, Lindbäck J, Lindahl B. Achievement of secondary preventive goals after acute myocardial infarction: a comparison between participants and nonparticipants in a routine patient education program in Sweden. *J. Cardiovasc. Nurs.* 24, 362–368 (2009).

37 Held C, Iqbal R, Lear SA *et al.* Physical activity levels, ownership of goods promoting

sedentary behaviour and risk of myocardial infarction: results of the INTERHEART study. *Eur. Heart J.* 33, 452–466 (2012).

▪ **Large study that clearly demonstrates the cardiovascular risk associated with a physically inactive lifestyle.**

38 Clark AM, Hartling L, Vandermeer B, McAlister FA. Meta analysis: secondary prevention programs for patients with coronary artery disease. *Ann. Intern. Med.* 143, 659–672 (2005).

39 Taylor RS, Brown A, Ebrahim S *et al.* Exercise-based rehabilitation for patients with coronary heart disease: systematic review and meta-analysis of randomised controlled trials. *Am. J. Med.* 116, 682–692 (2004).

40 Suaya JA, Statson WB, Ades PA, Normand SL, Shepard DS. Cardiac rehabilitation and survival in older coronary patients. *J. Am. Coll. Cardiol.* 54, 25–33 (2009).

41 Goel K, Lennon RJ, Tilbury RT, Squires RW, Thomas RJ. Impact of cardiac rehabilitation on mortality and cardiovascular events after percutaneous coronary intervention in the community. *Circulation* 123, 2344–2352 (2011).

42 Steffen-Baty L, Nichaman MZ, Goff DC *et al.* Change in level of physical activity and risk of all-cause mortality or reinfarction. The Corpus Christi Heart Project. *Circulation* 102, 2204–2209 (2000).

43 Borjesson M, Urhausen A, Kouidi E *et al.* Cardiovascular evaluation of middle-aged/senior individuals engaged in leisure-time sport activities: position stand from the section of exercise physiology and sports cardiology of the European Association of Cardiovascular Prevention and Rehabilitation. *Eur. J. Cardiovasc. Prev. Rehabil.* 18, 446–458 (2011).

44 Mezzani A, Agostini P, Cohen-Solal A *et al.* Standards for the use of cardiopulmonary exercise testing for the functional evaluation of cardiac patients: a report from the exercise physiology section of the European association for cardiovascular prevention and rehabilitation. *Eur. J. Cardiovasc. Prev. Rehabil.* 16, 249–267 (2009).

45 Tabet JY, Meurin P, Teboul F, Et A. Determination of exercise training level in coronary artery disease patients on β blockers. *Eur. J. Cardiovasc. Prev. Rehabil.* 15, 67–72 (2008).

■ Websites

101 WHO: cardiovascular diseases, fact sheet No. 317 (2011). www.who.int/mediacentre/factsheets/fs317/en/index.html

102 The National Board of Health and Welfare: national guidelines for methods of preventing disease (2011). www.socialstyrelsen.se/english