Risk Stratification for Coronary Artery Disease in Marathon Runners

a report by

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Low to moderate amounts of regular physical activity reduce cardiovascular (CV) risk factor burden, improve morbidity of CV and other chronic diseases and reduce CV mortality.[1–6] Aerobic endurance activities such as walking, jogging and running are popular and advocated ways to improve and maintain health across all age groups. Marathon running is an extreme form of such endurance exercise and poses a challenge to the runner and his or her CV system. Bouts of exercise may in fact increase the short-term risk of coronary events, not only in persons unaccustomed to exercise but also in joggers and marathon runners.[7–12] At a younger age, i.e. <35–40 years, CV events in athletes are predominantly attributable to cardiomyopathies (40%), coronary artery anomalies including myocardial bridging (19%), left ventricular (LV) hypertrophy (8%) and myocarditis (6%).[8] In those aged >35–40 years, coronary artery disease (CAD) is the most frequent cause of CV events (80%), followed by valvular heart disease (16%) and hypertrophic cardiomyopathy (3%).[13]

CV event rates in association with marathon running are low. However, nine deaths during running events in Germany in 2007 alone[14] sustain the debate on the necessity and methods of pre-participation CV screening and risk stratification in recreational athletes. Current American Heart Association (AHA) guidelines recommend a detailed personal and family history and a physical examination for baseline screening,[15] followed by further testing as appropriate, which may include exercise stress testing. European Society of Cardiology (ESC), International Olympic Committee (IOC) and German guidelines also advise routine baseline resting ECG screening.[16–20] However, pre-participation screening of marathon runners is not obligatory for recreational runners in most countries, and the cardiovascular work-up of athletes contains potential pitfalls. As a prudent measure, many marathons now provide defibrillators along the course,[9] but early detection of subclinical disease should clearly be the first-line approach to prevent CV events in marathon runners.

We have performed a prospective study on the prevalence of CV risk factors and coronary atherosclerosis in healthy marathon runners aged ≥50 years.[21,22] The purpose of this review is to discuss our findings in light of current practice in cardiovascular risk stratification and existing guidelines on cardiovascular pre-participation screening in athletes.

The Marathon Study Cohort

The study design and initial results have been presented in detail elsewhere.[21] In brief, the Marathon Study was designed to assess the prevalence of CV risk factor burden and coronary atherosclerosis in experienced marathon runners ≥50 years of age. Participants were eligible if they had no known CV disease, no symptoms of CV disease and no diabetes and had completed at least five full-distance marathon events during the previous three years. On average, they were 57±6 years old, had completed 20 marathons (median: 20; 25th/75th percentile: 14/42) and had been running marathons regularly for the past nine years (median value).[22] Data were compared with controls from the Heinz Nixdorf Recall study, which was designed to determine the prognostic value of subclinical atherosclerosis compared with established risk factors in the general unselected population.[23,24]

Risk Stratification in the General Population

Risk stratification algorithms such as the Framingham risk score,[25] the Münster Heart Study (PROCAM) score[26] and the European Systematic Coronary Risk Evaluation (SCORE) system[27,28] are used to assess an individual's global 10-year risk. Conventional risk factors are measured and weighted and attributed to an empirically determined absolute risk of cardiovascular events, e.g. cardiac death and myocardial infarction:[29]

- low-risk = <1% per year or <10% in 10 years;
- intermediate-risk = 1–2% per year or 10–20% in 10 years; and
- high-risk = >2% per year or >20% in 10 years.

This classification was slightly modified by the 2004 update of National Cholesterol Education Program (NCEP) guidelines, in that it separates the intermediate-risk group into moderate-risk and a moderately high-risk

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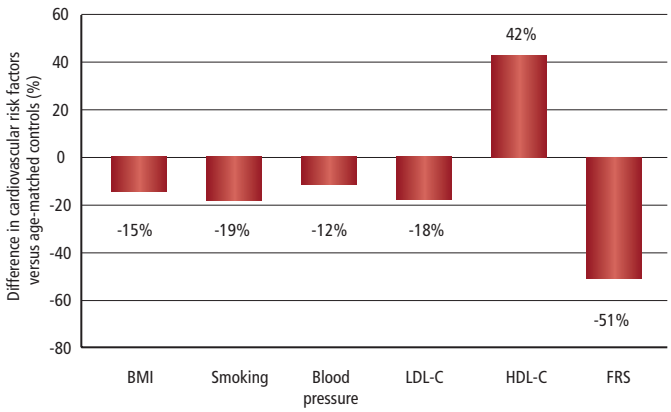
Table 1: American Heart Association Consensus Panel – Recommendations for Pre-participation Screening

Family history
1. Premature sudden death
2. Heart disease in surviving relatives
Personal history
3. Heart murmur
4. Systemic hypertension
5. Fatigability
6. Syncope
7. Exertional dyspnoea
8. Exertional chest pain
Physical examination
9. Heart murmur*
10. Femoral pulses
11. Stigmata of Marfan syndrome
12. Blood pressure measurements

** Pre-cordial auscultation is recommended in both supine/sitting and standing positions to identify heart murmurs consistent with dynamic left ventricular outflow tract obstruction.*

Figure 1: Difference in Conventional Cardiovascular Risk Factors in Marathon Runners



Difference in conventional cardiovascular risk factors in marathon runners compared with age-matched controls from the Heinz Nixdorf Recall Study. The values indicated average risk factors in marathon runners. The lower risk factor burden results in a Framingham risk score that is only half of that seen in age-matched controls from the unselected general population. 'Smoking' indicates 'ever smoked'. BMI = body mass index; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; FRS = Framingham risk score.

groups based on the number of risk factors present.[30] It is argued that persons at high risk, including those with established CAD or with risk equivalents, will most likely benefit from intensive risk modification, while persons at low risk are generally advised to adhere to a healthy lifestyle and guideline-based treatment of individual risk factors when present. However, in persons at intermediate risk there remains a diagnostic gap. Further tests such as coronary artery calcium (CAC) scanning,[31] measuring intima media thickness (IMT), the ankle arm index (AAI) or exercise stress testing may be useful in distinguishing individuals who are at a high risk from those at a low risk,[29] hopefully leaving few at an intermediate risk. However, it should be noted that the Framingham risk score does not take into account lifestyle factors such as diet, exercise and body mass index (BMI), all of which are usually favourable in marathon runners. Neither does the score reflect a positive family history of CV disease. The extent of atherosclerotic disease burden, autonomic dysfunction, chronic inflammation, lipoprotein subfractions, blood thrombogenicity, the myocardial propensity to develop life-threatening arrhythmias and unmeasurable genetic factors are also not part of the conventional risk assessment. Direct quantitative measuring of the extent of the disease – preferably in its early subclinical stages – may better reflect lifelong overall exposure to all risk factors, and may overcome the limitations of cross-sectional assessment of risk factor burden at one specific point in time.

Current Guidelines for Cardiovascular Risk Stratification in Athletes

To determine the risk of a CV event in presumably healthy marathon runners, a simple 12-element CV screening algorithm has been proposed by the AHA[13] (see *Table 1*). It comprises a detailed personal and family history as well as a physical examination including auscultation and blood pressure measurements. IOC,[18] ESC[17,19,20] and German[16] guidelines also recommend a routine 12-lead resting electrocardiogram (ECG) as part of the initial evaluation. In cases of abnormal findings on initial screening, additional tests – including exercise ECG, echocardiography and Holter-ECG – may be warranted to obtain further information on CV morphology and function, as prognosis for athletes with diagnosed CAD worsens with the extent of disease, LV systolic dysfunction, inducible ischaemia and electrical instability.[32]

The 36th Bethesda Conference was dedicated to establishing eligibility recommendations for competitive athletes with cardiovascular abnormalities. It was recommended that competitive athletes with established CAD (as defined by a history of CAD events, significant angiographic CAD, angina symptoms, inducible myocardial ischaemia and a coronary artery calcification [CAC] score >100 [see below]) should have their LV function assessed.[32] If exercise testing is considered necessary, it is recommended to approximate as closely as possible the cardiovascular and metabolic demands of the planned competitive event and its training regime. In marathon runners, this is often difficult to accomplish and cannot replicate the CV stress produced by sustained bouts of exercise during marathons and the required training. Furthermore, strong evidence from basic and clinical research suggests that regular exercise improves coronary microvascular function to such a degree that it can compensate for epicardial atherosclerosis even in advanced stages of the disease.[2,33] Standard clinical exercise tests may not always help to identify occult CAD in marathon runners.[32]

Risk Factor Burden in Marathon Runners

Regular physical activity has a beneficial impact on most modifiable CV risk factors.[34] In normotensive subjects, average resting systolic and diastolic blood pressures are reduced by 3.4 and 2.4mmHg, respectively, with a much greater effect in hypertensive persons.[34] High-density lipoprotein (HDL) cholesterol levels can be expected to increase by 3.0–4.6%, while triglyceride and LDL-cholesterol concentrations may decrease by 0.6–3.7% and 0.8–5.0%, respectively.[34–36] Exercise programmes help to maintain smoking cessation[37] and weight loss,[38] and beneficially affect glucose metabolism in diabetics.[39] In the Marathon Study cohort, all established risk factors were improved compared with age-matched controls (see *Figure 1*). In addition, runners had lower heart rates than controls (64.8±10 versus 76.4±11.8 beats per minute, respectively; $p<0.0001$) as well as lower high sensitivity C-reactive protein (hs-CRP) levels (0.1±0.2 versus 0.3±0.6mg/dl, respectively; $p<0.0001$) and leukocyte levels (5.3±1.2 versus 7.1±1.9nl, respectively; $p<0.0001$). The Framingham risk score in marathon runners (7.0±3.6% in 10 years) was even lower compared with women of a similar age from the general population (7.6±4.9% in 10 years).[22,23] These findings suggest that long-term regular aerobic exercise may improve CV risk factor burden beyond previous observations from controlled prospective studies with follow-up periods of often not more than six to 12 months.

Coronary Artery Calcium

CAC is a measure of the extent of total coronary atherosclerosis as it closely correlates with total coronary plaque burden.[31] It is not an index for stenosis severity at the site of CAC, but an increasing CAC burden increases the likelihood of a significant and potentially vulnerable lesion somewhere else in the coronary tree. This concept seems to hold in marathon runners.[33] The CAC score has been suggested to have value for improved risk stratification in intermediate-risk subjects[31] and to add prognostic information beyond established CV risk factors in the general population.[40] Historically, the CAC score is classified into groups of 0–10 (none to minimal), 10–100 (mild), 100–400 (moderate), 400–1,000 (severe) and >1,000 (extensive).[41] As age and gender are the main determinants of CAC burden, a CAC value >75th age- and sex-specific percentile is also advocated for clinical use in addition to absolute score values.[5]

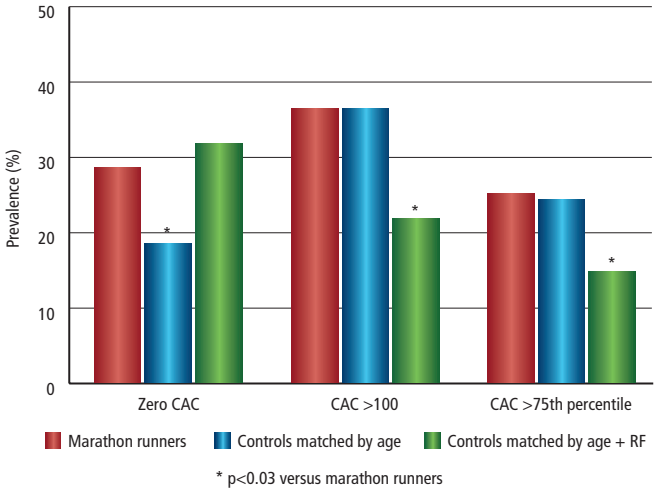
Coronary Atherosclerosis in Marathon Runners

In the 1970s, marathon running was still believed to induce 'immunity against coronary atherosclerosis', a theory referred to as the 'Bassler Hypothesis'. This hypothesis was invalidated in the late 1970s and early 1980s, initially by Noakes et al.,[42] then by others.[35,43] It is now established that coronary atherosclerosis accounts for the majority of CV events in older athletes.[13,15] Interestingly, studies of exercise-related acute myocardial infarction demonstrate less extensive CAD in sport participants than in controls,[44,45] which may reflect either selection bias for less severe atherosclerosis in those capable of exercising at high intensity or the ability of exercise to provoke events in individuals with less severe disease.[6]

In the Marathon Study, we have measured the prevalence and extent of calcified coronary atherosclerosis and found an unexpectedly high CAC burden that did not differ from that in age-matched controls from an unselected general population (see *Figure 2*) even though the Framingham risk score was only half of that in age-matched controls (7.0±3.6 versus 14.3±8.2% in 10 years; p<0.0001; see *Figure 1*). When the CAC score in marathon runners was compared with that in males from the general population with a similar risk factor profile, marathon runners had an even higher CAC score. A CAC score >100 was present in 36% of runners. A CAC score below 15, which has been suggested as a threshold below which high-intensity sports such as marathon running are safely recommendable,[32] was found in only 43% of runners.

We found no association of CAC burden with any of the exercise-related variables such as numbers of marathon completed, training mileage and frequency or years of regular marathon running. Hence, currently it is unclear whether frequent exhaustive exercise such as marathon running has direct pro-atherosclerotic effects. This is unlikely given the substantial evidence on the benefits of regular physical activity on coronary atherosclerosis, but no epidemiological studies have so far examined individuals engaged in such prodigious amounts of exercise. It is possible that the observed mismatch between a low risk factor burden and a high CAC score may be explained by a higher risk factor exposure earlier in life in marathon runners, and supports the limitations of conventional risk-stratification algorithms in master athletes. Alternatively, repetitive bouts of exhaustive exercise with the associated oxidant and inflammatory cytokine bursts may have contributed to the development of coronary atherosclerosis. The CAC burden is an independent predictor for myocardial damage and seems to contain prognostic information in marathon runners like in other asymptomatic cohorts (see below).[39,31] The implication of our findings is that the true CV risk in marathon runners may be underestimated if it is assessed based on established risk factors alone.

Figure 2: Prevalence of Coronary Artery Calcium in Marathon Runners



Marathon runners have a higher rate of no CAC compared with age-matched controls, indicating that regular marathon running may delay or even prevent atherosclerosis onset in runners free from atherosclerosis. However, runners have a very similar prevalence of CAC >100 and CAC >75th percentile, which is even higher compared with controls matched by age and risk factors. These controls may have had lifelong protection from the atherosclerotic effect of risk factor exposure, while marathon runners may have had a more unfavourable risk factor profile earlier in life. CAC = coronary artery calcium; RF = risk factors.

Myocardial Late Gadolinium Enhancement

Using cardiac magnetic resonance imaging (cMRI), the prevalence of myocardial damage can be directly visualised by late myocardial enhancement after infusion of gadolinium. 'Myocardial damage' is a term that we use here to summarise a variety of causes that can contribute to this imaging phenomenon, such as myocardial infarction, myocarditis, cardiomyopathy and vasculitis.[46] Myocardial late gadolinium enhancement (LGE) has been shown to be associated with an impaired prognosis in a population-based cohort including many subjects with known CAD.[47]

Out of 102 runners who were studied with cMRI, 12 (12%) had evidence of LGE.[22] This is a three-fold higher prevalence compared with an age-matched control group derived from a CV screening programme (4%).[48] The extent of CAC burden and the number of marathons completed were independent predictors of LGE. The mechanisms underlying this observation are as yet unclear. Coronary microembolisation from epicardial plaque material after superficial plaque fissuring or erosion due to epicardial shear stress and mechanical forces may play a role.[49] Furthermore, microthrombi from the surface of epicardial plaque or due to an increased systemic thrombogenicity, in part triggered by catecholamine-induced platelet aggregation or an imbalance in fibrinolytic/prothrombotic factors,[5,51] may obstruct intra-myocardial microvessels. Repeat inflammation during exhaustive marathon running and its required training may challenge endothelial antioxidative capacity, impair intramyocardial microvascular integrity and accelerate the atherosclerotic disease process.

Therefore, we cannot exclude the possibility that frequent marathon running itself has contributed to myocardial damage in our runners via mechanisms that still need to be determined. Irrespective of their aetiology, such areas of damaged myocardium could be the substrate for catecholamine-triggered arrhythmic activity during exercise.

Cardiovascular Event Rates

In healthy adult marathon runners, CV death is estimated to be in the range of 0.3–2.7 events per 10,000 person-hours of exercise.[6] Others have estimated an annual fatal event rate of one per every 15,000–18,000 joggers[10,52] and fatal events in one per 50,000–220,000 marathon race finishers.[3,9] In our Marathon Study, we observed no deaths during two years of follow-up. However, two out of 108 presumably healthy runners experienced aborted sudden death related to exercise and underwent subsequent revascularisation procedures. Two other runners received coronary stents without prior heart events.[22,33] None of the events occurred in relation to a marathon competition. All runners had CAC scores >100. Notably, the event rate increased from 0 of 69 (0%) in men with CAC <100 to two of 25 (8%) in men with CAC 100–400, and to two of 14 (14.3%) in men with CAC >400 (log-rank: p=0.018). Thus, 10% of 39 marathon runners with CAC >100 underwent revascularisation procedures during two years of follow-up, while their Framingham risk – which is designed to estimate cardiac death and myocardial infarction – was calculated to be only 7.9±3% (median: 7.0%, 25/75th percentile: 6/9%) in 10 years.

Implications for Risk Stratification

The 12-element approach to risk stratification (see *Table 1*) should be the first step in risk stratification in marathon runners.[15] In addition, lipid values and resting glucose levels should be assessed following NCEP, ESC and other guidelines.[5,28,53] In our experience, these screening tools alone will leave many runners with occult advanced CAD undetected. In asymptomatic persons with diabetes (class IIa recommendation) and in asymptomatic men >45 years of age and women >55 years of age (class IIb recommendation) the American College of Cardiologists (ACC), AHA[54] and the ACSM[55] recommend exercise testing before engaging in vigorous exercise training programs. However, participants in the Marathon Study were not diabetic and had been running regularly for many years. Twelve-lead ECGs at rest and during exercise are expected to miss relevant CAD in many of such runners due to coronary artery remodelling and the beneficial effects of exercise on endothelial and microvascular function, as outlined above.

Due to these difficulties in risk assessment, a gradual training programme that progressively leads to more vigorous levels of physical exertion is generally encouraged in master athletes.[15] In addition, we suggest that master marathon runners who have a history of modifiable risk factors such as smoking, elevated blood pressure, being overweight, former unhealthy eating habits, etc. may be appropriate candidates for atherosclerosis imaging, even if they are at low CV risk based on conventional risk factor assessment.

In runners with a CAC score >100, regular aspirin and lipid-lowering drugs should be considered with LDL treatment goals that are recommended for secondary prevention of CAD, i.e. LDL-C <100mg/dl, preferably <70mg/dl.[5,28,30] Runners should be advised to train at moderate intensity levels, which must be determined individually. Running in groups during training or the use of mobile phones may be reasonably advised. Most importantly, primary care practitioners, cardiologists and sports medicine specialists should be aware of limitations of the current risk stratification algorithms and conventional screening tests, and of the high prevalence of occult coronary atherosclerosis in marathon runners. At present, these considerations are not evidence-based, but are prudent measures to prevent CV events in runners who intend to participate in marathons. Further studies are required to determine whether our findings hold in other cohorts of marathon runners, which should then have an impact on current guidelines on pre-participation screening and recommendations for diagnostic testing, including modern imaging techniques. ■

1. Haskell WL, Lee IM, Pate RR, et al., *Circulation*, 2007;116: 1081–93.
2. Kojda G, Hambrecht R, *Cardiovasc Res*, 2005;67:187–97.
3. Mittleman MA, Maclure M, Tofler GH, et al., *N Engl J Med*, 1993;329:1677–83.
4. Mora S, Cook N, Buring JE, et al., *Circulation*, 2007;116(19): 2110–18.
5. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report, *Circulation*, 2002;106:3143–3421.
6. Thompson PD, Franklin BA, Balady GJ, et al., *Circulation*, 2007;115(17):2358–68.
7. Albert CM, Mittleman MA, Chae CU, et al., *N Engl J Med*, 2000;343(19):1355–61.
8. Maron BJ, Shirani J, Poliac LC, et al., *JAMA*, 1996;276:199–204.
9. Roberts WO, Maron BJ, *JACC*, 2005;46:1374–5.
10. Siscovick DS, Weiss NS, Fletcher RH, Lasky T, *N Engl J Med*, 1984;311:874–7.
11. Tunstall Pedoe DS, *Sports Med*, 2007;37(4–5):448–50.
12. Van Camp SP, Bloor CM, Mueller FO, et al., *Med Sci Sports Exerc*, 1995;27:641–7.
13. Maron BJ, Thompson PD, Ackerman MJ, et al., *Circulation*, 2007;115;1643–55.
14. German Road Races. 2008; Available at: www.germanroad races.de/24-0-2975-berlinmarathon-anlauf-zum-tod-die. html?npi=2
15. Maron BJ, Araújo CGS, Thompson PD, et al., *Circulation*, 2001;103;327–34.
16. Boldt F, Hansel J, Huonker M, et al., Available at: www.germanroadraces.de/files/leitlinie2404.pdf
17. Corrado D, Pelliccia A, Bjørnstad HH, et al., *Eur Heart J*, 2005;26:516–24.
18. International Olympic Committee Medical Commission. Sudden CV Death in Sport: Lausanne Recommendations: Pre-participation CV Screening, 2004; Available at: http://multimedia.olympic.org/pdf/en_report_886.pdf
19. Pelliccia A, Fagard R, Bjørnstad HH, et al., *Eur Heart J*, 2005;26:1422–45.
20. Pelliccia A, *Eur Heart J*, 2007;28(22):2703–5.
21. Möhlenkamp S, Schmermund A, Kröger K, et al., *Herz*, 2006;31(6):575–85.
22. Möhlenkamp S, Lehmann N, Breuckmann F, et al., *Eur Heart J*, 2008; published online on April 22nd 2008.
23. Erbel R, Möhlenkamp S, Lehmann N, et al., *Dtsch Ärztebl*, 2008;105(1/2):1–8.
24. Möhlenkamp S, Moebus S, Schmermund A, et al., *Herz*, 2007;32(2):108–20.
25. Wilson PW, D'Agostino RB, Levy D, et al., *Circulation*, 1998;97:1837–47.
26. Assmann G, Cullen P, Schulte H, *Circulation*, 2002;105:310–15.
27. Conroy RM, Pyorala K, Fitzgerald AP, et al., *Eur Heart J*, 2003;24:987–1003.
28. European guidelines on CVD prevention in clinical practice: Executive summary. Fourth Joint Task Force of the ESC and other societies on CVD prevention in clinical practice, *Eur J Cardiovasc Prev Rehab*, 2007;14(Suppl. 2):E1–40.
29. Smith SC, Greenland P, Grundy SM, *Circulation*, 2000;101: 111–16.
30. Grundy SM, Cleeman JI, Merz CN, et al., *JACC*, 2004;44: 720–32.
31. Greenland P, Bonow RO, Brundage BH, et al., *Circulation*, 2007;115:403–26.
32. Thompson PD, Balady GJ, Chaitman BR, et al., *J Am Coll Cardiol*, 2005;45(8):1348–53.
33. Möhlenkamp S, Böse D, Mahabadi AA, et al., *Nature Clin Pract Cardiovasc Med*, 2007;4(7):396–401.
34. Thompson PD, Buchner D, Piña IL, et al., *Circulation*, 2003;107(24):3109–16.
35. Burke AP, Farb A, Malcom GT, et al., *JAMA*, 1999;281:921–6.
36. Leon AS, Rice T, Mandel S, et al., *Metabolism*, 2000;49:513–20.
37. Marcus BH, Albrecht AE, King TK, et al., *Arch Intern Med*, 1999;159:1229–34.
38. Wing RR, Hill JO, *Annu Rev Nutr*, 2001;21:323–41.
39. Knowler WC, Barrett-Connor E, Fowler SE, et al., *N Engl J Med*, 2002;346:393–403.
40. Detrano R, Guerci AD, Carr JJ, et al., *N Engl J Med*, 2008;358:1336–45.
41. Erbel R, Möhlenkamp S, Kerkhoff G, et al., *Heart*, 2007;93(12): 1620–29.
42. Noakes TD, Opie LH, Rose AG, et al., *N Engl J Med*, 1979;301: 86–9.
43. Virmani R, Robinowitz M, McAllister HA, *Am J Med*, 1982;72: 874–82.
44. Ciampricotti R, Deckers JW, Taverne R, et al., *Am J Cardiol*, 1994;73:219–22.
45. Giri S, Thompson PD, Kiernan FJ, et al., *JAMA*, 1999;282:1731–6.
46. Hunold P, Schlosser T, Vogt FM, et al., *Am J Roentgenol*, 2005;184(5):1420–26.
47. Kwong RY, Chan AK, Brown KA, et al., *Circulation*, 2006;113(23):2733–43.
48. Breuckmann F, Nassenstein K, Sievers B, et al., Available at: www.abstractsonline.com/viewer/SearchResults.asp
49. Skyschally A, Leineweber K, Gres P, et al., *Basic Res Cardiol*, 2006;101:373–82.
50. Bärtsch P, *Lancet*, 1999;354:1747–8.
51. Siegel AJ, Stec JJ, Lipinska I, et al., *Am J Cardiol*, 2001;88(8):918–20.
52. Thompson PD, Funk EJ, Carleton RA, Sturner WQ, *JAMA*, 1982;247:2535–8.
53. Gohlke H, Kübler W, Mathes P, et al., *Z Kardiol*, 2005;94 (Suppl. 3):113–15.
54. Gibbons RJ, Balady GJ, Bricker JT, et al., Available at: http:// www.acc.org/clinical/guidelines/exercise/dirIndex.htm
55. American College of Sports Medicine, *Guidelines for Exercise Testing and Prescription, 7th ed*, Baltimore, MD: Lippincott Williams & Wilkins, 2005.

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