Substantial data have established that higher levels of physical activity (PA), participating in exercise training (ET), and higher overall cardiorespiratory fitness (CRF) provide considerable protection in the primary and secondary prevention of coronary heart disease (CHD). This review surveys data from epidemiological and prospective ET studies supporting the favorable impact of PA, ET, and CRF in primary CHD prevention. Clearly, cardiac rehabilitation and ET (CRET) programs have been underutilized for patients with CHD, particularly considering the effect of CRET on CHD risk factors, including CRF, obesity indices, fat distribution, plasma lipids, inflammation, and psychological distress, as well as overall morbidity and mortality. These data strongly support the routine referral of patients with CHD to CRET programs and that patients should be vigorously encouraged to attend CRET following major CHD events. (Circ J 2013; 77: 281–292)

Key Words: Cardiac rehabilitation; Coronary heart disease; Exercise; Fitness

The American Heart Association has established that a sedentary lifestyle is a major modifiable risk factor for coronary heart disease (CHD). Nevertheless, a sizable percentage of the United States’ population is sedentary or at least relatively inactive. Based on substantial data, many health organizations have recommended increased physical activity (PA) and exercise training (ET) to increase cardiorespiratory fitness (CRF), which are reviewed in the current joint positions from the American College of Sports Medicine (ACSM) and the 2008 Federal Physical Activity Guidelines.

In this review, we discuss the interaction of PA, obesity, and CRF on overall cardiovascular (CV) risk, including the effect of occupational PA and ET studies. Also, the role of formal CRF on overall cardiovascular (CV) risk, including the effect of chronic coronary heart disease (CHD) is reviewed.

PA Levels and CV Risk

Epidemiological data demonstrate that low levels of PA are associated with a higher prevalence of hypertension (HTN), obesity, type 2 diabetes mellitus (T2DM), and metabolic syndrome (MetSyn). Similarly, ample published data demonstrate a strong inverse association between PA levels and CV mortality. In the Harvard Alumni study (n=12,516) observed a significant trend for lower CHD risk in middle-aged and older men with highest tertile (≥12,600 KJ/week, relative risk: 0.73) of PA levels compared to those in the lowest tertile (<2,100 KJ/week, referent). Additionally, men with PA levels greater than 4,200 KJ/week (consistent with 30 min of PA on most days of the week) were associated with a 38% reduction in CV mortality (not including CHD) compared to low levels in men who were London civil servants. In the Whitehall study (n=6,702), Smith et al observed a 38% reduction in CV mortality (not including CHD) with high levels of leisure-time PA compared to low levels in middle-aged and older men with highest tertile (≥12,600 KJ/week, relative risk: 0.73) of PA levels compared to those in the lowest tertile (<2,100 KJ/week, referent). Additionally, men with PA levels greater than 4,200 KJ/week (consistent with 30 min of PA on most days of the week) had approximately 19–20% reduction in CHD risk.

In the Women’s Health Study (n=39,372), Lee et al observed that higher levels of energy expenditure were associated with a lower relative risk of CHD in middle-aged and older women. In addition, walking at least 1.0 h or more per week was associated with >50% reduction in CHD risk in...
multivariate models. Li et al observed that women in the Nurse’s Health Study (n=88,393) who were moderately active (1–3.49 h/week) and active (≥3.5 h/week), had 43% and 58% lower risk of CHD, respectively, compared to sedentary women (<1 h/week).24 Hu et al25 in their study of Finish participants (n=47,840) observed that a high level of leisure-time PA was associated with 16% and 23% reductions in CHD risk for men and women, respectively, compared to those with low levels of PA. A recent meta-analysis by Li and Siegrist26 observed that in men, moderate and high levels of leisure-time PA had 20% and 24% reductions in CHD risk, respectively. In women, they were associated with 18% and 27% reductions in CHD risk, respectively. Similarly, a meta-analysis by Soft et al observed that moderate and high levels of PA were associated with 12% and 27% reductions in CHD incidence, respectively.27

High levels of PA have also been shown to reduce CV mortality in higher risk populations, such as individuals with T2DM and the elderly. Hu et al observed 16% and 31% reductions in CV mortality (n=3,316) with moderate and high levels, respectively, of leisure-time PA in Finish adults with T2DM.17 In the Zutphen Elderly Study (n=802), Bijnen et al27 observed a significant trend for lower 10-year CV mortality (15%), but not CHD mortality, with higher levels of PA in elderly Dutch men (age: 64–84 years). In the same study, men classified as active (20 min of exercise at least 3 times per week) had a 34% reduction in 10-year CV mortality compared to men classified as inactive. Thus, the available evidence strongly suggests an inverse association exists between PA level and CV mortality and CHD risk.

Interactions Among Obesity, PA and CV Risk
Several studies have evaluated the potential interaction between PA level and obesity on CV mortality risk. The consensus among studies is that higher levels of PA attenuate, but do not completely eliminate, the elevated CV mortality risk associated with obesity. Hu et al16 in the Nurses’ Health Study (n=116,564) observed that the relative risk of CV mortality was markedly reduced in obese women with higher levels of PA compared to those with lower levels. However, obese women still had elevated risk compared to normal-weight (body mass index [BMI] <25 kg/m²) women with high levels of PA. Similarly, Fang et al,28 using National Health and Nutrition Examination Survey data (n=9,790), observed using Cox regression analyses that obese individuals (BMI >30 kg/m², hazard ratio: 1.24) and those in the lowest tertile of PA (hazard ratio: 1.32) were at an elevated risk of CV mortality even after multivariable adjustments. Weinstein et al in the Women’s Health Study (n=38,987) observed that active overweight (hazard ratio: 1.5) and obese (hazard ratio: 1.87) women had elevated CHD risk compared to normal-weight individuals.29 A limitation of all these studies is that PA was assessed by self-report questionnaires, which are quite inaccurate and lead to substantial misclassification. This likely means that these studies potentially do not adequately adjust for PA when evaluating the effects of obesity on health outcomes.

Changes in PA Level and CV Risk
The available evidence from epidemiologic studies suggests that increasing the level of PA is associated with reductions in CV mortality and CHD risk. Paffenbarger et al30 in the Harvard Alumni Study (n=10,269) observed that sedentary individuals who increased the amount of moderate to vigorous PA had a 41% lower risk of CHD compared to those who remained sedentary. However, increasing PA levels (defined as an increase in 2,000 kcal/week determined through questionnaire) were not associated with a reduction in all-cause mortality or CHD risk. In older women (n=7,553, median follow-up: 5.7 years), Gregg et al observed that increasing the level of PA, based on the Harvard Alumni Questionnaire, was associated with a 36% reduction in CV mortality in sedentary older women.31 Lastly, Wannemethee et al observed that in middle-aged British men (n=5,936, 4 years follow-up) increasing the level of PA from inactive to at least lightly active was associated with a 45% reduction in CV mortality compared to those that were inactive at both examinations.32

Occupational PA and CV Risk
Several studies have explored PA and CV risk in occupational settings, with much of the available data from Finish cohorts. Slattery et al33 observed that male US railroad workers (n=3,043) who were sedentary (expended ≤40 kcal/wk) based on PA questionnaires, had a 39% greater risk of CHD compared to men with higher PA (3,632 kcal/wk).28 Similarly, Hu et al observed that in middle-aged Finnish men and women (n=47,840) free of CHD or stroke at baseline, a high level of occupational PA was associated with 10% and 20% reductions in the risk of CHD in men and women, respectively, after adjustment for covariates and commuting and leisure-time PA.18 Hu et al, in a different study, observed that among Finnish adults with T2DM (n=5,516, mean follow-up: 18.4 years) high moderate/vigorous occupational PA was independently associated with a 31% reduction in CV mortality, even after adjustments for age, sex, BMI, systolic blood pressure, and commuting and leisure-time PA.17

CRF and CV Risk
Similar to low levels of PA, a low level of CRF is a well-recognized risk factor for CV and CHD mortality. In general, epidemiological studies define CRF as the highest level of estimated metabolic equivalents (METs) (or in some cases peak or maximal oxygen consumption) achieved during a maximal exertion treadmill test. Participants generally exercise to at least 85% of age-predicted maximum heart rate or to volitional exhaustion.35 High levels of CRF have been associated with reduced prevalence of several CV risk factors such as HTN 34,35 and obesity 36,37 and lower incidence rates of MetSyn 38-40 and T2DM.41-43

Epidemiologic data suggest an inverse association between CRF level and CV mortality. Blair et al, in the Aerobics Center Longitudinal Study (ACLS; n=25,341 men and 7,080 women), observed a substantially higher relative risk of CV mortality in men and women categorized as having low CRF even after multivariate adjustments compared to adults with high levels of CRF.44 Mora et al,45 in the Lipid Research Clinics Prevalence Study (n=2,994), observed that low levels of CRF (defined as ≤ median value) were associated with almost a 2-fold increase in CV mortality risk in asymptomatic women after 20 years of follow-up. Furthermore, an estimated one MET increase in CRF was associated with a 17% increased risk in CV mortality. A recent meta-analysis by Kodama et al observed that a 1 MET increase in CRF was associated with 13% and
15% reductions in all-cause and CVD/CHD mortality, respectively. In addition, the authors defined minimum levels of CRF associated with lower event rates in both men (40 years: 9 METs, 50 years: 8 METs, 60 years: 7 METs) and women (40 years: 7 METs, 50 years: 6 METs, 60 years: 5 METs) based on age.

High levels of CRF are also associated with lower CV mortality risk in otherwise high-risk individuals. Katzmarzyk et al, using ACLS data, observed that in men with MetSyn (n=3,757), a low level of CRF was associated with a 2.6-fold higher CV mortality risk compared to men with a higher level of CRF.47 Similarly, Leyer et al,48 also using ACLS data, observed that in women (n=3,044) with pre-diabetes or undiagnosed T2DM, moderate and high levels of CRF were associated with reduced mortality by approximately 37% and 39%, respectively, compared to women with low CRF.48 McAuley et al, in the Veterans Exercise Testing study (n=7,775), observed that in men with T2DM (without baseline CVD) those with high CRF had 2.5- and 3.8-fold reductions in all-cause mortality risk compared to men in the moderate or low CRF categories, respectively, after multivariate adjustments.49 Berry et al observed in men in the ACLS dataset (n=11,049) that low levels of CRF were associated with a higher lifetime risk of CV mortality to age 80 years, with markedly lower rates at 45 (high CRF: 3.4 vs. low CRF: 12.2%), 55 (high CRF: 4.9 vs. low CRF: 19.6%) and 65 (high CRF: 5.6 vs. low CRF: 12.2%) years old compared to those with low levels of CRF.46 Especially notable in their findings, men with a high burden of traditional CV risk factors, but with a high level of CRF, had lifetime CV mortality rates that were similar to those with a low burden of traditional CVD risk factors.48 In summary, these data suggest that increasing or maintaining a high level of CRF may be of particular importance in individuals with known CVD risk factors.

Independent Effects of CRF and Obesity
Several researchers have evaluated the independent effects of CRF and obesity on CV mortality. Overwhelming evidence exists that high levels of CRF attenuates the CV mortality risk in overweight and obese individuals.51-55 Wei et al observed in men in the ACLS dataset (n=25,714) that low levels of CRF elevated the relative risk of CV mortality similarly in normal weight (1.7), overweight (1.9) and obese men (2.0) compared to normal-weight men without low CRF.56 Stevens et al, in the Lipid Research Clinics Study (n=5,366), demonstrated that men and women (RR=1.39 for both) classified as fat and fit did not have a significantly higher relative risk of CV mortality compared to the reference group who were both fit and lean, although the relationship for men did approach significance (P<0.06).55 Lee et al, using the ACLS dataset (n=21,925), evaluated this relationship using body fat (≥25.0%) as a measure of obesity and observed that the relative risk of CV mortality was substantially lower in men who were obese and fit (1.35) compared to men who were obese and unfit (4.08), but not significantly different from the reference group (men who were lean and fit).56 Church et al, studying men with T2DM in the ACLS dataset, observed a significant reduction in the relative risk of CV disease mortality in normal weight (low: 2.7, high: 1.0) and obese individuals (low: 2.7, moderate/high: 1.5) with T2DM and a trend for similar effects in individuals classified as overweight (low: 2.7, high: 1.5, P-trend=0.07).57 Thus, the available epidemiological evidence suggests that a high level of CRF is associated with markedly reduced CV mortality risk, regardless of BMI or adiposity.

Importantly, most of the available data suggest that even in lean and normal-weight individuals, CV mortality is increased with low levels of CRF. Lee et al observed an approximately 3-fold increase in CV mortality in lean men who were unfit compared to lean, fit men.56 Similarly, Stevens et al observed >50% increase in CV mortality in men categorized as unfit/not fat compared to fit/not fat men.53

Changes in CRF and CV Risk
The few studies that have evaluated the effect of a change in CRF on CV mortality endpoints have observed that improving the level of CRF generally has a protective effect on CV mortality. The best-known study in this area was conducted by Blair et al, using ACLS data (n=9,777), in which they showed that men classified as unfit at the first examination and fit at the second examination had a 52% reduction in CV mortality compared to men who were unfit at both examinations.57 Erikssen et al58 observed that among middle-aged men (n=2,014), there was an inverse association between the change in CRF (defined as the ratio of the maximum cycle ergometer workload of the 2nd examination divided by the 1st examination) and CV mortality (50% and 53% reductions in risk in the 2 highest quartiles compared to the lowest quartile).58 Lee et al,59 using the ACLS dataset (n=14,345), evaluated the long-term effects of a change in CRF on CV mortality (mean follow-up, 11.4 years) and observed a significant reduction in CV mortality in men who had either no change (27%) or increased CRF (42%) at the second examination separated by 6.3 years that persisted even after adjustments for change in BMI. Furthermore, for every 1 MET increase in CRF over time, there were 15% and 19% reductions in all-cause and CV mortality, respectively. Although cause and effect relationships cannot be determined based on these epidemiological studies and similar data confirming these relationships in women are needed, the studies presented provide strong evidence that improving the level of CRF has a favorable effect on CV mortality.

Is PA or CRF Level the Best Predictor of CV Mortality?
Some studies have compared the relative importance of the CRF and PA levels on CV mortality. The available data in this area suggests that CRF is the more clinically important predictor of CV and mortality outcomes.40,61 after controlling for CV risk factors.62 However, it is important to consider (as stated in a recent review article by Blair et al63) that much of the epidemiological data evaluating PA and CVD risk has been determined through self-report questionnaires whereas high CRF, after accounting for genetic heritability (which is extremely important),64 is primarily determined by regular PA. Simply stated, CRF may be a better measure of habitual PA than are responses to self-report questionnaires.

Public Health Recommendations for PA
Increasing the amount of PA or ET is recommended by a variety of health organizations.65-67 to reduce the risk of CV disease in sedentary adults, because of the favorable effects of exercise on CRF and other CVD risk factors. The current joint position stand from the ACSM2 and the 2008 Federal Physical Activity Guidelines3 recommend that adults obtain at least 150 min of moderate-intensity PA per week or 75 min of vigorous-intensity PA per week, and specifically state that all adults should avoid inactivity. For individuals who are unable to attain the current recommendations for PA, some PA likely has health benefits over remaining sedentary.2,3,67 The Guide-
lines also set a higher recommendation of 300 min of moderate-intensity activity per week or 150 min of vigorous activity per week to obtain even greater health benefits. The Guidelines also indicate that a person can combine moderate and vigorous intensity to reach the recommendations, with 1 min of vigorous being equal to 2 min of moderate. Thus, 25 min of vigorous intensity (2×25) combined with 100 min of moderate intensity would meet the basic recommendation of 150 min/week.

**ET and CRF**
As mentioned earlier in this review, CRF is important for predicting CV mortality. Aerobic ET of sufficient intensity and volume has well-established effects on improving CRF. The ACSM recommends moderate or vigorous aerobic ET in order to maintain or increase CRF. Evidence from large randomized controlled trials supports that increases in CRF can be achieved with moderate-intensity aerobic ET programs. Kraus et al, in the Studies of Targeted Risk Reduction Interventions through Defined Exercise (STRRIDE; n=111), observed a significant increase in CRF level following 8 months of moderate-intensity (45–55% VO2max) aerobic ET in sedentary overweight men and women. Church et al, in the Dose Response to Exercise in Women (DREW; n=464) study, observed significant increases in CRF in postmenopausal women following 6 months of moderate-intensity cycle ergometer ET (50% VO2max), and a greater improvement in CRF with a greater amount of ET. Thus, for sedentary adults, moderate-intensity ET is likely a sufficient stimulus to improve CRF.

In terms of the effect of aerobic ET intensity on CRF, the prevailing view is that larger gains in CRF may be obtained with higher intensity aerobic ET (training at a higher percentage of maximal CRF levels). Crouse et al observed a greater increase in CRF in men exercising at high intensity as opposed to moderate intensity (measured via peak VO2) in middle-aged men (n=26) following 24 weeks of cycle ergometer exercise. Similarly, O’Donovan et al observed a greater increase in CRF following 24 weeks of high-intensity cycle ergometer ET in sedentary men (n=64) compared to moderate-intensity ET matched for ET energy costs. In addition, several studies suggest that high-intensity aerobic ET is associated with greater responses in glucose control, insulin sensitivity, and visceral fat loss compared to moderate-intensity ET.

Thus, the available evidence suggests that vigorous ET confers equal or enhanced health benefits when compared to moderate ET when matched for total caloric expenditure. In addition, when moderate- and vigorous-intensity aerobic ET are matched for total exercise time, a greater caloric expenditure is achieved with higher ET intensities, which has the potential to produce additional health benefits. It is important to keep in mind that most of the studies in this area have small sample sizes with varying methodologies/study populations, and have had mixed results. Therefore, more empirical evidence from large clinical trials is still needed to confirm and expand the findings in regard to CRF and other CV risk factors.

**Effect of ET on Traditional CV Risk Factors**

**Cholesterol**
The most consistent effect of aerobic ET on lipids tends to be restricted to improvements in high-density lipoprotein-cholesterol (HDL-C). Kraus et al observed a significant increase in HDL-C in overweight adults with high level and high-intensity aerobic ET, but not with low levels of aerobic ET (at either high or low intensities). In the same study, Kraus et al showed that all ET groups (regardless of amount or intensity) had beneficial changes in low-density lipoprotein (LDL) particle size. A recent review article by Tamilselvan et al reported an increase in HDL-C of approximately 9.8% in studies utilizing moderate-intensity aerobic ET. Similarly, Kodama et al, in a recent meta-analysis, observed that aerobic ET resulted in an increase in HDL-C of 2.5 mg/dl, and that both ET duration and caloric expenditure were significantly associated with increases in HDL-C.

**Glucose Control**
ET is recommended by the Joint Position Stand by ACSM and the American Diabetes Association, specifically the combination of aerobic and resistance training when feasible to maximize the improvement in glucose control in individuals with T2DM. Both Church et al and Sigal et al observed the greatest reductions in hemoglobin A1c (HbA1c) levels in adults with T2DM following combination ET programs (using both aerobic and resistance ET), whereas the improvements in HbA1c with aerobic or resistance training alone were inconsistent in the 2 studies. The reduction in HbA1c with ET has been associated with a reduction in both body fat and central adiposity, and an increase in CRF. Muralidhar et al, in the Heritage Family Study, observed a 32% reduction in MetSyn prevalence following 20 weeks of aerobic ET.

**Weight and Adiposity**
Weight loss solely from ET (without dietary caloric restriction) is generally modest (ie, <3% of body weight) in controlled ET studies. The ACSM Position Stand on this topic notes that public health recommendations of 150 min/week of moderate PA have generally not shown clinically significant weight loss, and have the potential for modest absolute weight loss (<2.5 kg). In addition, adoption of PA levels below those recommended is unlikely to produce clinically significant weight loss. Church et al, in the DREW study (n=464), observed no significant changes in body weight in postmenopausal women exercising at low-to moderate-intensity levels consistent with public health recommendations (−2.2 kg) or 50% above (−0.6 kg) or 50% below those recommendations (−0.4 kg). Donnelly et al, in the Midwest Exercise Trial, observed clinically significant weight loss in men (−5.2 kg, −5.5% of baseline body weight), but not women (0.6 kg) after 16 weeks (225 min/week) of aerobic ET. Although clinically significant weight loss generally does not occur in ET trials, other favorable cardiometabolic changes, such as improvements in insulin sensitivity, waist circumference, HDL-C, and total fat, visceral fat, and interleukin-6 concentration have been observed following aerobic ET without weight loss. Thus, it is important to remember that PA is beneficial whether or not significant weight loss occurs.

**Blood Pressure**
Following ET, there appears to be a beneficial effect on HTN; however, the magnitude of the effects on resting blood pressure among studies tends to be variable. Whelton et al, in a meta-analysis of 54 controlled trials, observed that ET was associated with reductions of −3.8 and −2.6 mmHg in systolic and diastolic blood pressure, respectively. Similarly, a recent meta-analysis by Cornelissen et al demonstrated that aerobic ET was associated with reductions of blood pressure in participants with normal blood pressure (systolic: −2.4, diastolic: −1.6 mmHg), pre-HTN (systolic: −1.7, diastolic: −1.7 mmHg), and HTN (systolic: −6.9, diastolic: −4.9 mmHg). Based on their additional analyses, the authors concluded that the hypotensive effects of aerobic ET may be related to reductions in systemic vascular resistance (−7.1%), plasma norepinephrine concentration (−28.7%) and plasma renin activity (−19.8%).
ET and Secondary CHD Prevention

Those Who Think They Have No Time for Bodily Exercise Will Sooner or Later Have to Find Time for Illness
– Earl of Derby

Several observational studies, as well as randomized controlled trials, have established the benefits of PA and ET in cohorts with established CHD.97–99 Perhaps the best example of ET and secondary CHD prevention comes from data collected in formal CRET secondary prevention programs. A broad range of patients, with defined clinical characteristics, benefit from formal CRET programs, which is summarized in Table 1.

Effect of CRET on Exercise Capacity

Probably the most important benefit of formal CRET is the improvement in CRF.97–99 Our studies have noted considerable discrepancy between estimated maximal METs as determined by peak treadmill speed and grade and maximal CRF assessed by gas exchange (peak VO2).100–102 Because this terminology is confusing, we prefer clinically to define CRF as either estimated METs or measured peak VO2. Our studies of CHD patients demonstrate that estimated maximal METs significantly overestimate measured CRF, both before but, particularly, following an ET program (and even more so in younger than in older patients). Nevertheless, considerable data that have estimated CRF (discussed earlier), as well as studies using gas exchange, have determined that measures of CRF are a major predictor of mortality in CHD patients.100–103 Although patients with low CRF benefit more from CRET than do patients with high CRF, we have demonstrated that even patients with high CRF obtain marked improvements following CRET.104 In a study of CRET for nearly 15,000 men and women, every 1 mEq·h−1·min−1 increase in directly measured peak VO2 showed a nearly 10% reduction in major CV mortality.105,106 In another study, total mortality fell by 2% for every 1% increase in peak VO2 with CRET.107

Effect of CRET on Lipids and Inflammation

The overall effects of CRET on levels of LDL-cholesterol are minimal, especially considering the current extremely high background use of statins, more so at high doses.108–110 Many CHD patients have dyslipidemia, including low levels of HDL-C and/or high levels of triglycerides (TGs) that often markedly improve following formal CRET.97–99 Typically, the improvements in HDL-C and TG concentrations are modest (eg, +6% and −15%, respectively) following CRET, although greater improvements are typically observed in patients with abnormal baseline lipid values.111–113 The Ochsner group and others have demonstrated the significance of systemic inflammation, particularly as assessed by levels of high-sensitivity C-reactive protein (hs-CRP), in both primary and secondary prevention.114,115 Additionally, we have reviewed the potential improvements in hs-CRP with PA and ET, and the improvement in overall CRF.116

In a study of 277 patients with stable CHD following major CHD events, we demonstrated that hs-CRP fell by almost 40% in 235 patients who completed formal CRET, with no improvement noted in the 42 controlled patients who did not attend CRET (Figure 1).117 We also demonstrated that CHD patients with MetSyn had approximately 2-fold higher levels of hs-CRP compared with CHD patients without MetSyn, but both groups of patients had approximately 40% reductions in hs-CRP following formal CRET programs.118 Whereas lean CHD patients had <20% reductions in hs-CRP following CRET, which were not statistically significant, the obese patients had nearly 45% reductions in hs-CRP following CRET.119 In a more recent study, we assessed the relationship between hs-CRP and weight loss with CRET, and we demonstrated that overweight/obese individuals who had greater than median weight loss (average reduction in weight, 5%) with CRET, also had a 40% reduction in hs-CRP, whereas those without a significant weight loss only had a minimal (6%) reduction in hs-CRP (Figure 2).120 Others have reported significant improvements in hs-CRP with CRET.121,122

Effect of CRET on Obesity

Considering the extremely high prevalence of overweight/obesity in Western society and, particularly, in patients with CHD, the potential important benefit of formal CRET programs is promotion of weight reduction and weight maintenance.97–99 Although the Ochsner group and others have published extensively on the obesity paradox in patients with CV diseases, including CHD,123–135 we believe that most data still support the benefits of purposeful weight reduction.136 Further, data from CRET programs have established the efficacy and safety of weight loss in patients with CHD, especially in those with MetSyn, where a 37% reduction in the prevalence of MetSyn has occurred following CRET.118

In a small group of 45 obese patients with CHD from our CRET program who successfully lost weight following CRET

<table>
<thead>
<tr>
<th>Table 1. Benefits of Formal Cardiac Rehabilitation and Exercise Training Programs</th>
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<tr>
<td><strong>Improvement in exercise capacity</strong></td>
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<tr>
<td>1. Estimated METs +35%</td>
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<td>2. Peak VO2 +15%</td>
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<tr>
<td>3. Peak anaerobic threshold +11%</td>
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<tr>
<td><strong>Improvement in lipid profiles</strong></td>
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<tr>
<td>1. Total cholesterol –5%</td>
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<tr>
<td>2. Triglycerides −15%</td>
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<tr>
<td>3. HDL-C +6% (higher in patients with low baseline)</td>
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<td>4. LDL-C –2%</td>
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<tr>
<td>5. LDL-C/HDL-C –5% (higher in certain subgroups)</td>
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<tr>
<td><strong>Reduction in inflammation</strong></td>
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<tr>
<td>hs-CRP –40%</td>
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<tr>
<td><strong>Reduction in indices of obesity</strong></td>
</tr>
<tr>
<td>1. BMI –1.5%</td>
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<tr>
<td>2. % fat –5%</td>
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<tr>
<td>3. Metabolic syndrome –37%</td>
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<tr>
<td><strong>Improvements in behavioral characteristics</strong></td>
</tr>
<tr>
<td>1. Depression</td>
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<td>2. Anxiety</td>
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<td>3. Hostility</td>
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<td>4. Somatization</td>
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<tr>
<td>5. Overall psychological distress</td>
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<tr>
<td><strong>Improvements in quality of life and components</strong></td>
</tr>
<tr>
<td>1. Increased heart rate recovery</td>
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<td>2. Increased heart rate variability</td>
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<td>3. Reduced resting pulse</td>
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<tr>
<td><strong>Improvements in blood rheology</strong></td>
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<td><strong>Reduction in hospitalization costs</strong></td>
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<td><strong>Reduction in major morbidity and mortality</strong></td>
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BMI, body mass index; hs-CRP, high-sensitivity C-reactive protein; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol.
(>5% weight loss; mean 10%), we noted statistically greater improvements in CRF and plasma lipids compared with 81 obese patients who did not lose weight. A recent study of 377 consecutive patients from the CRET program at the Mayo Clinic demonstrated that weight loss was associated with reductions in total mortality plus major CV events, and these improvements were noted even among those CRET patients with baseline BMI <25 kg/m², as well as in those in the higher BMI groups. Data from Ades et al demonstrated that greater weight loss with CRET, utilizing a high-caloric-expenditure (3,000–3,500 kcal/week) ET program, was associated with reduced insulin resistance, improved lipids (reductions in TGs and increases in HDL-C), as well as reduced plasminogen activator inhibitor I concentration and blood pressure. Finally, a study of more than 1,500 overweight/obese CHD patients demonstrated that those patients with depression who completed CRET had >70% reduction in 3-year mortality (8% vs. 30%, P<0.001) compared with a control group of depressed CHD patients who did not attend CRET. However, patients who remained depressed had 4-fold higher 3-year mortality (P<0.001).

In order to make the link between improvements in CRF and depression-related mortality, we divided patients into those who achieved mild improvement in peak VO₂ following CRET (≤10%; n=135), those who had more marked improvements in peak VO₂ (>10%; n=285), and those who did not improve CRF (n=102). We demonstrated that only a small improvement in peak VO₂ is required to produce significant reductions in depression and depression-related increased mortality risk, which were very similar to the improvements noted in those who achieved more marked improvements in peak VO₂ (Figure 4). Very recently, we demonstrated similar marked improvements following CRET in depression and depression-related mortality risk in high-risk CHD patients with systolic heart failure.

Similar benefits of CRET are noted in patients with high total scores for PS, as well as in those with high PS-associated increased mortality risk.

**Effect of CRET on Psychological Risk Factors**

*It is exercise alone that supports the spirit, and keeps the mind in vigor – Cicero* –

Perhaps some of the most important data on the effect of CRET is in the area of psychological stress (PS), including levels of depression, hostility, anxiety, and total PS. We have documented a high prevalence of PS risk factors in patients with CHD, with marked benefits following formal CRET programs (Figure 3). For example, we have demonstrated that those patients with depression who completed CRET had >70% reduction in 3-year mortality (8% vs. 30%, P<0.001) compared with a control group of depressed CHD patients who did not attend CRET. However, patients who remained depressed had 4-fold higher 3-year mortality (P<0.001).

In order to make the link between improvements in CRF and depression-related mortality, we divided patients into those who achieved mild improvement in peak VO₂ following CRET (≤10%; n=135), those who had more marked improvements in peak VO₂ (>10%; n=285), and those who did not improve CRF (n=102). We demonstrated that only a small improvement in peak VO₂ is required to produce significant reductions in depression and depression-related increased mortality risk, which were very similar to the improvements noted in those who achieved more marked improvements in peak VO₂ (Figure 4). Very recently, we demonstrated similar marked improvements following CRET in depression and depression-related mortality risk in high-risk CHD patients with systolic heart failure.

Similar benefits of CRET are noted in patients with high total scores for PS, as well as in those with high PS-associated increased mortality risk.

**Effect of CRET on Morbidity and Mortality**

Although sometimes more difficult to demonstrate, perhaps the most important benefit of referring patients to formal CRET after major CHD events is the marked effects on major CV morbidity and mortality. One of the first major meta-analyses of CRET programs by O’Connor et al in 1989 included 22 randomized controlled trials in 4,551 CHD patients who were post-myocardial infarction (MI). This major meta-analysis demonstrated reductions in total and CV mortality of 20% and 25%, respectively, at 3-year follow-up after CRET. Addition-
ally, there was a significant 37% reduction in sudden cardiac death after 1 year, with strong trends for reductions in sudden cardiac death at 2- and 3-year follow-up. A more recent meta-analysis of 8,440 participants from 32 randomized controlled trials demonstrated a 31% reduction in CV mortality following CRET. Although there have been many advances in medical and interventional therapies that have improved prognosis following MI, a recent analysis of 1,821 post-MI patients from the Mayo Clinic (Olmsted County, Minnesota residents) demonstrated that the benefits of CRET were greater during the past decade compared to several decades previously, suggesting that the benefits of CRET are not decreasing over time. Although most of the CRET benefits have been described in post-MI patients, these benefits have recently been assessed by Goel et al utilizing Olmsted County, Minnesota Registry data from patients following percutaneous coronary intervention (PCI). In 2,395 consecutive post-PCI patients, participation in formal CRET was associated with a 45% reduction (P<0.001) in all-cause mortality during a 6-year follow-up, with a strong trend for a reduction in CV mortality among those who participated in CRET, with the benefits of CRET seen regardless of type of PCI (elective or urgent), sex, and age.

![Figure 3. Effect of formal cardiac rehabilitation and exercise training programs on prevalence of adverse psychological stress parameters (depression, anxiety, and hostility) in younger and older patients with coronary heart disease (data adapted from Lavie and Milani).](image)

![Figure 4. Prevalence of depression and subsequent mortality based on changes in peak oxygen consumption (VO2) during cardiac rehabilitation and exercise training. *P<0.001 compared with VO2 loss (data adapted from Milani and Lavie).](image)
In fact, recent data on CRET have been particularly noteworthy in elderly patients. Suaya et al\textsuperscript{153} demonstrated that among elderly Medicare beneficiaries who attended CRET, 5-year mortality was reduced by 34%. Moreover, a very strong relationship between greater CRET attainment (eg, number of sessions) and mortality reduction was demonstrated. Hamill et al also demonstrated the benefits of CRET in elderly Medicare CHD patients, also noting a powerful relationship between CRET attendance and lower mortality.\textsuperscript{142}

### Exercise Prescription in CHD

As mentioned earlier, there are guidelines for PA and ET in primary prevention.\textsuperscript{219} In general, these recommendations also apply to secondary prevention.\textsuperscript{97–99} In CRET programs and in many clinicians’ offices, the prescription of aerobic and resistance ET is needed and this frequently includes directions on the mode of PA and ET, frequency, duration and intensity of ET, which are all summarized in Table 2. Although most of the emphasis in ET and secondary prevention is directed at aerobic ET, we have recently demonstrated the importance of muscular strength to predict survival in men with HTN,\textsuperscript{153} as well as other populations,\textsuperscript{156} further supporting the performance of resistance ET as the major means of improve muscular strength.

In CRET programs, the ET prescription is the major focus.\textsuperscript{97–99} However, whether patients with CHD are enrolled in formal CRET or not, CHD patients should still be advised to perform ET for at least 30 min (≥35 min to provide greater caloric expenditure for the large number of overweight/obese patients with CHD) on most days (at least 4–5 days/week, but preferably 6–7 days/week). During CRET, intensity recommendations are provided, based on exercise stress results and depend on whether the exercise test was performed with ventilatory expired gas exchange, as well as on the presence and severity of exercise-induced ischemia. A major area of controversy currently involves the relative risks vs. benefits of high-intensity ET as opposed to low-moderate-intensity continuous ET, and details on this topic are beyond the scope of this review. In patients who are also shown to repeatedly demonstrate that their exercise heart rate corresponds to a predicted level of perceived exertion, the Borg Scale of perceived exertion or another simple scale can be used to monitor exercise intensity.

In the office setting, outside of CRET programs, many clinicians have the opportunity to provide exercise prescription for patients with CHD, as well as those at high risk of CHD, and on many occasions, recent formal exercise stress testing results may not be available. In these circumstances, ET intensity is generally recommended at a “moderate” level (eg, the patient should be able to speak during ET, but the exercise intensity should be high enough such that one would prefer not to speak for the majority of the ET session). As in many other instances of medical care, if a simple 10-point perceived exertion scale is used to describe exercise intensity, with 10 representing the highest ET intensity possible and 0 describing rest, most ET should be performed in the moderate range (approximately 5–7/10 intensity range).

### Conclusions

Regular PA and ET and maintenance of high levels of CRF have an important role in reducing CHD in both primary and secondary prevention. In patients with CHD, CRET services are markedly underutilized.\textsuperscript{157,158} Evidence suggests that ET programs produce marked benefits in CRF, obesity indices, lipids, inflammation, psychological risk factors, and other areas, thus leading to reduction in major CV morbidity and mortality in primary and secondary prevention. Through automatic referral and incentive-based systems geared to improve the quality and delivery of medical care, greater emphasis must be placed on the referral of all appropriate patients to CRET secondary prevention programs after major CHD events.\textsuperscript{97–99,157,158}

### Disclosures

Financial Disclosure: None.

### References


### Table 2. Exercise Prescription in Primary and Secondary Prevention of Coronary Heart Disease

<table>
<thead>
<tr>
<th>Mode</th>
<th>Duration</th>
<th>Frequency</th>
<th>Intensity</th>
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<tbody>
<tr>
<td><strong>Aerobic</strong></td>
<td>At least 20–30 min (preferably 30–45 min)</td>
<td>Most days (at least 4–5 d/wk and preferably 6–7 d/wk)</td>
<td>Close to anaerobic threshold: 50–75% of peak VO₂, 65–85% of maximal heart rate or 60–70% of heart rate reserve; 10–15 beats/min below the level of ischemia. Perceived exertion scales can be used</td>
</tr>
<tr>
<td><strong>Resistance</strong></td>
<td>10–15 repetitions; 1–3 sets of 8–10 different exercises for both upper and lower body</td>
<td>2–3 sessions weekly (non-consecutive days)</td>
<td>Moderate intensity (should not be straining on last repetitions)</td>
</tr>
</tbody>
</table>

- `Walking, jogging, cycling, ergometry, elliptical trainers, stair climbing, rowing, cross-country ski, aerobic dance`
- `Hand weights, elastic bands, calisthenics, weight machines`
Exercise and Coronary Prevention


