

## Cardiac Rehabilitation 2012 Advancing the Field Through Emerging Science

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**B**urgeoning research in the field of preventive cardiology over the past 20 years has fostered the evolution of cardiac rehabilitation programs, once limited to exercise training, into comprehensive secondary prevention centers. Data demonstrate that contemporary cardiac rehabilitation/secondary prevention (CR/SP) programs reduce cardiovascular risk and event rates, foster healthy behaviors, and promote active lifestyles.<sup>1,2</sup> Accordingly, every recent major evidence-based guideline from the American Heart Association (AHA) and the American College of Cardiology Foundation regarding the management and prevention of coronary heart disease provides a class 1 level recommendation (ie, procedure/treatment should be performed/administered) for referral to a CR/SP program<sup>3,4</sup> for those patients with recent myocardial infarction (MI) or acute coronary syndrome, chronic stable angina, or heart failure, or for those patients following coronary artery bypass surgery or percutaneous coronary intervention. CR/SP programs are also indicated for those patients following valve surgery or cardiac transplantation.<sup>3</sup> Emerging science will undoubtedly advance the field further, as clinicians translate data to foster future change. In this brief review, we provide a focused update on recently published studies that have great potential to move the field of cardiac rehabilitation forward. These studies address the following topic areas: utilization of CR/SP services and associated survival benefits; novel exercise protocols; and emerging applications in the management of diabetes mellitus, heart failure, pulmonary hypertension, peripheral arterial disease, and congenital heart disease.

### Use of Cardiac Rehabilitation Services and Survival Benefits

Despite the wealth of evidence supporting the proven benefits of CR/SP programs, the services are greatly underutilized. Of eligible patients, only 14% to 35% of heart attack survivors and 31% of patients after coronary artery bypass surgery participate in CR/SP programs.<sup>5,6</sup> To reduce the gap between indication and implementation, a joint American Association of Cardiovascular and Pulmonary Rehabilitation/American College of Cardiology Foundation/AHA committee has recently revised the performance measures for referral to these services.<sup>3</sup> The newly published AHA Presidential Advisory

on the referral, enrollment, and delivery of CR/SP programs highlights the patient-oriented, medical, and healthcare system factors associated with suboptimal participation.<sup>2</sup> In particular, patients who are women, belong to ethnic minorities, are elderly, and have low socioeconomic status have lower participation rates than white men and represent specific high-risk groups to be targeted for referral.<sup>1</sup> Healthcare system factors interfering with utilization include proximity and accessibility of services incorporating home-based exercise programs together with facility-based supervised training sessions can help improve participation (see later for discussion on home-based training for patients with diabetes mellitus and peripheral arterial disease). Disease management and lifestyle-coaching interventions can be delivered remotely via telephone, Internet-based portals, electronic mail, or social media outlets. A recent similar strategy promoting weight loss through encouragement of goal setting and exercise has successfully affected weight loss to a similar degree as in-person support.<sup>7</sup> Such efforts should be used as an adjunct to existing facility-based services to reach the large majority of eligible patients who currently do not participate in CR/SP programs.

Addressing factors that limit participation is particularly important given recent data that demonstrate an inverse relationship between CR/SP program participation and adverse cardiovascular events. The relationship between the number of CR/SP sessions attended and cardiovascular outcomes was recently evaluated in an analysis of Medicare claims data including 30 161 patients with CAD (with recent coronary artery bypass surgery, MI, or acute coronary syndrome) who attended at least 1 CR/SP session.<sup>8</sup> After 4 years of follow-up, patients who attended 36 sessions had a 14% lower risk of death and a 12% lower risk of MI than those who attended 24 sessions; a 22% lower risk of death and a 23% lower risk of MI than those who attended 12 sessions; and a 47% lower risk of death and a 31% lower risk of MI than those who attended 1 session (Figure). However, only 18% of the patients completed the maximum 36 sessions. This dose-dependent improvement further highlights the importance of patient retention in CR/SP programs. Clinical outcomes following percutaneous coronary intervention were recently assessed in a retrospective analysis of 2395 patients (40% of whom attended CR).<sup>9</sup> Participation in CR was associated with decreased all-cause mortality (hazard ratio 0.53–0.55,  $P < 0.001$ ), although no effect on cardiac death or MI was noted.

These important and recent findings further support the recommendations provided in clinical guidelines, and reimbursement policy instituted by the Centers for Medicare and Medicaid Services, as well.

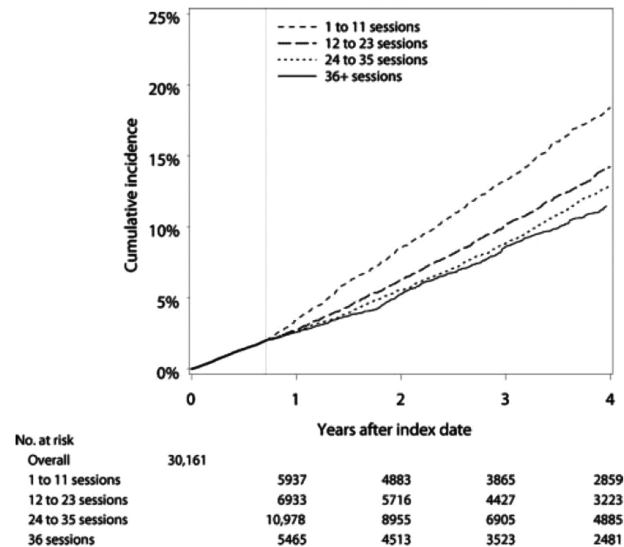
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**Figure.** Cumulative incidence of death by number of cardiac rehabilitation sessions attended. Reproduced from Hamill et al,<sup>8</sup> with permission of the publisher.

### Novel Exercise Protocols

Standard exercise protocols involve a combination of aerobic and resistance training. Moderate-intensity exercise training (50% to 80% of maximum heart rate [ $HR_{peak}$ ]) is recommended for aerobic exercise achieved via continuous or interval training.<sup>10</sup> Aerobic interval training involves alternating 3- to 4-minute periods of exercise at high intensity (90%–95%  $HR_{peak}$ ) with exercise at moderate intensity (60%–70%  $HR_{peak}$ ). Such training for  $\approx 40$  minutes, 3 times per week has been recently evaluated by Wisløff and colleagues, who randomly assigned 27 patients with postinfarction heart failure (mean left ventricular ejection fraction [LVEF] 29%).<sup>11</sup> They demonstrated that improvement in peak oxygen uptake ( $VO_2$ ) was greater in patients enrolled in aerobic interval training than standard moderate-intensity exercise (46% versus 14%,  $P < 0.001$ ). Similarly, an evaluation of patients after coronary artery bypass surgery showed that the improvement of peak  $VO_2$  was more sustained after a short prescription of aerobic interval training than moderate-intensity training.<sup>12</sup>

With the rising incidence of overweight and obesity in patients with CAD, CR/SP programs take on the additional role of facilitating weight loss. Energy expenditure in traditional programs is modest (700–800 kcal/wk).<sup>13</sup> High-caloric-expenditure exercise training, during which 3000 to 3500 kcal/wk is expended, represents a strategy to further reduce risk in obese patients. In a randomized trial of 74 overweight and obese patients (mean body mass index, 32.2  $kg/m^2$ ) with CAD, those enrolled in high-caloric-expenditure exercise lost more weight (8.2 versus 3.7 kg,  $P < 0.001$ ), fat mass (5.9 versus 2.8 kg,  $P < 0.011$ ), and waist circumference (–7 versus –5 cm,  $P = 0.02$ ), and had improved lipid profiles after 5 months in comparison with those in a traditional program.<sup>14</sup> Overall, the prevalence of metabolic syndrome was reduced from 59% to 31%.

## Expanding Applications

### Diabetes Mellitus

The rising epidemic of diabetes mellitus has been attributed to the growing prevalence of obesity and overweight. Beneficial effects of exercise training include improved glycemic control, reduction of body fat and body mass index, reduced hypoglycemic medication requirement, and improved exercise capacity.<sup>15</sup> The 2009 AHA scientific statement on Exercise Training in Type 2 Diabetes Mellitus recommends 150 min/wk of moderate-intensity cardiorespiratory exercise (class I) or a combination of vigorous cardiorespiratory and resistance exercise (class I). The Health Benefits of Aerobic and Resistance Training in Individuals with Diabetes (HART-D) trial sought to clarify the benefits of different exercise prescriptions while maintaining a similar weekly exercise duration. A diverse group of 262 previously sedentary patients with diabetes mellitus (baseline glycated hemoglobin [HbA1c] 7.7%) were randomly assigned to aerobic, resistance, or combined exercise.<sup>16</sup> Patients who participated in combined training had modest, statistically significant improvements in HbA1c (–0.34%; 95% CI, –0.64% to –0.03%;  $P = 0.03$ ), whereas those in isolated aerobic or resistance programs had no significant improvement. This reinforces the synergistic effect of combined exercise modalities in this patient population as described in previous studies.<sup>17</sup>

However, access to structured, facility-based exercise programs is limited relative to the growing number of patients with type 2 diabetes. A meta-analysis performed by Umpierre and colleagues, including 47 randomized, controlled trials and 8538 subjects, evaluated the benefit of physical activity advice in comparison with structured exercise.<sup>18</sup> Whereas the greatest reduction in HbA1c was observed in patients with combined aerobic and resistance training at least 150 minutes weekly (–0.89%; 95% CI, –1.26% to –0.51%), a similarly significant effect was noted in patients who received advice in addition to dietary counseling (–0.58%). Thus, the development of home-based counseling and training CR/SP programs represents an opportunity to effectively impact patients with diabetes mellitus.

### Systolic Heart Failure

Exercise training for patients with systolic heart failure was given a class I recommendation as an “adjunctive approach to improve clinical status” in the 2009 Focused Update to the American College of Cardiology Foundation/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults.<sup>19</sup> This was further addressed in the recently published Heart Failure: A Controlled Trial Investigation Outcomes of Exercise Training (HF-ACTION) study, the largest study evaluating exercise training in heart failure.<sup>20</sup> Subjects with New York Heart Association class II to IV heart failure ( $n = 2331$ ) and at least moderate systolic dysfunction (LVEF  $< 35\%$ ) were randomly assigned to 36 sessions of moderate-intensity exercise training followed by home-based training, versus usual care. All subjects were followed up for a median of 30 months. A nonsignificant reduction in the primary combined end point of all-cause mortality or hospitalization

was found (hazard ratio 0.93;  $P=0.13$ ). Following adjustment for several prespecified predictors of mortality (duration of the cardiopulmonary exercise test, LVEF, Beck Depression Inventory II score, history of atrial fibrillation), the primary end point became modestly significant (hazard ratio 0.89;  $P=0.03$ ). Additional analysis revealed no significant difference in mortality (16% versus 17%) between groups. There was only a modest but significant improvement in measured peak  $\text{VO}_2$  in the exercise group in comparison with the control group (0.6 versus 0.2 mL/kg per min, respectively) at 3 months, which was similar at 1 year. Self-reported health status improvement was greater in the exercise training group.<sup>21</sup> These findings should be considered in the context of the disappointingly low adherence rate to exercise in the training group, whereby only 30% of subjects exercised at or above the target number of minutes per week. Furthermore, at least 8% of the control patients reported that they were exercising throughout the entire study period. These important factors likely contributed to the limited improvement in exercise tolerance in the exercise group, and may have attenuated differences in outcomes between the exercise and control groups.

A recently published study evaluated the effects of exercise training among 37 patients with very advanced chronic heart failure (New York Heart Association class IIIb).<sup>22</sup> After 12 weeks of exercise training, improvements were seen in New York Heart Association functional class, peak  $\text{VO}_2$ , and LVEF. Further study is needed to assess the safety of exercise in such patients. For a more detailed discussion, the reader is referred to the recent comprehensive review by Downing and Balady.<sup>23</sup>

### Heart Failure With Preserved Ejection Fraction

Although >50% of patients with heart failure have preserved ejection fraction, evidence-based treatments are limited. Training programs to target the main symptom of heart failure with preserved ejection fraction, exercise intolerance, have been recently evaluated in 2 similar randomized clinical trials involving patients with heart failure symptoms and LVEF  $\geq 50\%$ . Forty-six patients (mean age, 70 years) with isolated heart failure with preserved ejection fraction (without significant coronary, valvular, or pulmonary disease) were randomly assigned to moderate-intensity supervised exercise training or usual care.<sup>24</sup> Improvement of peak  $\text{VO}_2$  (change,  $2.3 \pm 2.2$  mL/kg per min versus  $-0.3 \pm 2.1$  mL/kg per min;  $P=0.0002$ ) and physical quality-of-life (QOL) measures ( $P=0.03$ ), although not overall QOL ( $P=0.11$ ) were noted in the exercise group. The exercise training in diastolic heart failure (Ex-DHF) pilot study ( $n=64$ ) showed similar functional improvement.<sup>25</sup> In addition, there was echocardiographic evidence of reverse left atrial remodeling (change in indexed left atrial volume  $-4.0$  mL/m<sup>2</sup>,  $P<0.001$ ) and significantly improved left ventricular diastolic function as assessed by  $E/e'$  measurement. Patients with diastolic heart failure represent an important group in whom exercise training can potentially improve clinical outcomes.

### Pulmonary Arterial Hypertension

Patients with pulmonary arterial hypertension also experience exercise intolerance and reduced QOL despite appropriate

disease-targeted treatment. A recent landmark randomized controlled trial evaluated the risks and benefits of moderate-intensity exercise and respiratory training in 30 patients with chronic, severe pulmonary hypertension (mean pulmonary artery pressure 50 mm Hg).<sup>26</sup> After 15 weeks of therapy, individuals randomly assigned to activity training (compared with usual care) had significant improvement in 6-minute walk distance by 22%, QOL scores, World Heart Organization functional classification, and peak  $\text{VO}_2$  (from 13.2 mL/kg per min to 15.4 mL/kg per min,  $P<0.05$ ). Further trials are needed to evaluate the effect of activity training on clinical outcomes in this high-risk group.

### Congenital Heart Disease

Historically, conservative restriction in physical activity had been imposed on individuals with congenital heart disease. However, as reparative surgery has become commonplace, up to 90% of patients survive to adulthood. Participation in physical activity and exercise is now recommended in American and European guidelines, although evidence has been limited and based primarily on pediatric populations.<sup>27,28</sup> Recently, Dua and colleagues evaluated the effect of home-based walking in 61 adults with congenital heart disease.<sup>29</sup> Increased treadmill test duration and improved QOL measures were noted. Holloway and colleagues noted similar improvement in exercise tolerance when 11 patients were enrolled in a formal cardiac rehabilitation program with appropriate exercise prescriptions.<sup>30</sup> For a detailed discussion on cardiac rehabilitation in children with congenital heart disease, the reader is referred to the recent comprehensive review by Rhodes et al.<sup>31</sup>

### Peripheral Arterial Disease

Exercise training has a well-established role in patients with peripheral arterial disease, specifically those with claudication. In the American College of Cardiology/AHA 2005 Practice Guidelines for the Management of Patients with Peripheral Arterial Disease, supervised exercise training was given a class I recommendation, and unsupervised training received a class IIb recommendation.<sup>32</sup> Despite this recommendation, supervised exercise is still not covered by major medical insurance providers. Home-based programs can increase accessibility to these interventions. A recent and important randomized trial involving 119 patients with intermittent claudication compared quantified home-based exercise (using a step activity monitor) with traditional supervised exercise and usual care controls.<sup>33</sup> Adherence to both exercise interventions was high (exceeding 80%). In comparison with controls, patients in the home-based and supervised exercise groups had similar improvement in claudication onset time (increase by 165 and 134 seconds, respectively,  $P<0.05$  for both groups compared with control) and peak walking time (increase by 215 and 124 seconds, respectively,  $P<0.05$  for both groups compared with control) after 12 weeks. There was no statistically significant difference in the improvement between the home-based and structured exercise groups ( $P>0.05$ ). Similar home-based quantified protocols could be expanded to other conditions for which exercise programs are beneficial. For a recent detailed discussion on exercise



rehabilitation in peripheral artery disease, the reader is referred to the review by Hamburg and Balady.<sup>34</sup>

### Conclusion

The benefits of CR/SP programs are now well established for patients with CAD. However, insurance coverage for expanded applications beyond the clinical center and for other diagnoses lags behind. With health insurance reform, emphasis on preventive care is ever increasing. As the role of exercise training is further evaluated for conditions such as heart failure (both systolic and diastolic), diabetes mellitus, pulmonary hypertension, and congenital heart disease, data-driven policy changes that will affect the millions of people with cardiovascular disease have the potential to foster an overall healthier population. Across-the-board improvement in referral and enrollment in CR/SP programs is essential<sup>2</sup>; however, scientific discovery is fundamental to this entire process.

### Disclosures

None.

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