

COUNCIL PERSPECTIVES

Heart Failure as a Newly Approved Diagnosis for Cardiac Rehabilitation

Challenges and Opportunities



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ABSTRACT

Many see the broadened eligibility of cardiac rehabilitation (CR) to include heart failure with reduced ejection fraction (HFrEF) as a likely catalyst to high CR enrollment and improved care. However, such expectation contrasts with the reality that CR enrollment of eligible coronary heart disease patients has remained low for decades. In this review, entrenched obstacles impeding utilization of CR are considered, particularly in relation to potential HFrEF management. The strengths and limitations of the HF-ACTION (Heart Failure—A Controlled Trial Investigating Outcomes of Exercise Training) trial to advance precepts of CR are considered, as well as gaps that this trial failed to address, such as the utility of CR for patients with heart failure with preserved ejection fraction and the conundrum of poor patient adherence. (J Am Coll Cardiol 2015;65:2652-9) © 2015 by the American College of Cardiology Foundation.

The recent decision by the U.S. Center for Medicare Services (CMS) to extend cardiac rehabilitation (CR) coverage to patients with heart failure with reduced ejection fraction (HFrEF) (1) caps years of cumulative research showing the benefits of exercise training, lifestyle modifications, medication adherence, education, and other CR elements to moderate HFrEF pathophysiology and improve clinical outcomes (2-4). Many healthcare experts anticipate that the new CMS eligibility will translate rapidly into CR enrollment by HFrEF patients (5). However, CMS coverage of CR for coronary heart disease (CHD) is longstanding and has been

reinforced over time by data demonstrating improved outcomes among CHD patients who attended CR (i.e., consistently beyond the evolving standards of contemporary care), yet underenrollment has persisted (6). Therefore, irrespective of CMS eligibility, CR implementation for HFrEF patients may constitute more of a challenge than many presume.

HISTORICAL PERSPECTIVE: CR FOR CHD

CR was formulated as a safe, effective program to guide exercise progression for myocardial infarction (MI) patients as part of a shift from standards of

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prolonged bed rest to standards of earlier activity and greater emphasis on self-care (6). Subsequently, evolving insights regarding atherosclerosis initiation, progression, and regression indicated that CR not only had potential to reduce morbidity and mortality by moderating the sequelae of sedentary behaviors (e.g., pulmonary emboli, deconditioning), but that it also could more fundamentally moderate the pathophysiology of atherosclerosis (6). Overall, the rationale for CR for acute coronary syndromes, revascularization, and/or chronic CHD has progressed over time, but utilization has persistently lagged (6).

The inherent weakness of CR research has contributed to poor CR utilization for CHD. CR benefits were originally based predominantly on small single-site investigations (7) that tended to enroll mostly middle-aged, ethnically homogeneous males who were also usually better educated and motivated than patients who did not attend CR. Given the limited statistical power of such studies, assessments of CR mortality benefits relied on meta-analyses (8), and were subject to the inherent limitations of such secondary analyses.

Nonetheless, recent analyses of large contemporary databases corroborate CR benefits for patients across spectra of different ages, sexes, and therapies (including both revascularization and adjunctive treatments). The Rochester Epidemiologic Project (9) showed that CR benefits on mortality and recurrent MI were greater as cardiac care advanced over time. Suaya et al. (10) used propensity-based matching, regression modeling, and instrumental variables to show mortality reductions in all demographic and clinical subgroups, including patients with acute MI and revascularization procedures.

IS CR FOR HFREF DIFFERENT?

Evolving over 20 years, multiple smaller HFREF exercise training trials demonstrated wide-ranging physiological and clinical benefits, including improved exercise capacity, favorable cardiac remodeling, and improved autonomic balance (11). However, most of the formative trials were completed at single centers with implicit selection bias akin to the CR for CHD literature. Moreover, skepticism regarding the utility of exercise therapy for HFREF was magnified by safety concerns. In comparison to patients with CHD, HFREF patients tend to be more prone to arrhythmia, hemodynamic instability, and fluid overload, and are often older and frailer, and have more comorbidities. Concerns were particularly intensified when 1 exercise trial reported adverse remodeling in patients who had sustained recent anterior Q-wave MIs (12).

Remarkably, that study engendered widespread apprehension regarding exercise training for heart failure (HF), despite its small size (only 13 patients) and that only 3 patients had HF. Proponents of exercise training for HFREF countered with assertions regarding the predominant safety of exercise training in multiple other studies (13).

Amid such contention, the HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) trial was designed to definitively assess the safety and efficacy of exercise training for HF, and to potentially justify changes in practice standards (4). The National Heart, Lung, and Blood Institute made a forward-thinking decision to invest appreciably in the promise of therapeutic exercise. The HF-ACTION trial was large (targeting 3,000 patients), resource-intensive, and expensive (approximately \$40 million) (personal communication, C. M. O'Connor, January 2015).

WHAT THE HF-ACTION TRIAL ACCOMPLISHED

The HF-ACTION trial assessed the safety and efficacy of exercise training for medically stable patients with HFREF (left ventricular ejection fraction $\leq 35\%$, New York Heart Association functional class II to IV). Notable features included the large and diverse study population, the randomized controlled trial design, and the requirement for optimal medical management, including pharmacologic therapy with an angiotensin-converting enzyme inhibitor and beta-blockers. Approximately 40% of patients (exercise group and controls) had implanted cardiac defibrillators, and 18% had biventricular pacing. Given such comprehensive baseline care, the trial's capacity to assess additive benefits of a CR-like intervention were intended to be unambiguous.

The HF-ACTION exercise group began with 36 supervised training sessions for 30 min of exercise 3 times per week, with an individualized exercise prescription on the basis of cardiopulmonary exercise testing (CPX). Halfway through this training period, patients received, at no cost, a home treadmill or stationary bicycle and a heart-rate monitor for personal use. They were instructed to exercise 5 times per week at moderate intensity for 40 min. In contrast, the usual-care group was only given instructions regarding the benefits of exercise training at moderate intensity for 30 min per day, as recommended by the existing American College of Cardiology/American Heart Association guidelines (14).

ABBREVIATIONS AND ACRONYMS

CHD	= coronary heart disease
CMS	= Center for Medicare Services
CPX	= cardiopulmonary exercise testing
CR	= cardiac rehabilitation
HF	= heart failure
HFpEF	= heart failure with preserved ejection fraction
HFREF	= heart failure with reduced ejection fraction
LVAD	= left ventricular assist devices
MI	= myocardial infarction
VO₂	= oxygen uptake

All patients (exercise group and controls) received educational resources, adherence recommendations, and close supportive care from the research team. This support may have been more effectual in the exercise group because these elements were implicitly reinforced by integration with the regular exercise sessions (15).

Only 2,331 of the 3,000 HFrEF subjects originally targeted for the study were enrolled into the HF-ACTION trial. Power calculations for the trial were reassessed after approximately 2,000 patients had been enrolled, and, on the basis of a higher event rate than originally anticipated, only 2,300 patients were deemed necessary for 90% statistical power. Correspondingly, the target sample size was reduced (4).

The HF-ACTION trial's composite primary endpoint was all-cause mortality or all-cause hospital stay. After a median follow-up of 30 months, there was a nonsignificant reduction in the primary combined endpoint (hazard ratio: 0.93; 95% confidence interval: 0.84 to 1.02; $p = 0.13$). However, after adjusting for baseline characteristics strongly predictive of these clinical outcomes (duration of the cardiopulmonary exercise test; left ventricular ejection fraction; Beck Depression Inventory II score; history of atrial fibrillation) the primary endpoint was significant (hazard ratio: 0.89; 95% confidence interval: 0.81 to 0.99; $p = 0.03$). The secondary endpoint of cardiovascular mortality or HF hospitalization was also significantly improved by the exercise training intervention after adjusting for prognostic baseline characteristics (hazard ratio: 0.85; 95% confidence interval: 0.74 to 0.99; $p = 0.03$) (4).

HALF FULL OR HALF EMPTY?

Some interpret the HF-ACTION trial as an important success, as it demonstrated the safety of exercise training in a large, diverse HFrEF population, with benefits that extended beyond optimal pharmacological and device therapies. Exercise training was associated with an 11% reduction in all-cause mortality/hospitalizations, as well as a 15% reduction in cardiovascular mortality/HF hospitalizations. In addition, a substudy demonstrated improved quality of life using the Kansas City Cardiomyopathy Questionnaire (16).

In a subsequent analysis, Keteyian *et al.* (17) demonstrated that patients who achieved increased exercise volume during the HF-ACTION trial had relatively better outcomes, supporting the concept of a dose-response relationship. Exercise volume was a significant ($p = 0.001$) predictor of reduced mortality (all cause or cardiac) or hospitalization (all cause or HF.

Moderate exercise volumes of 3 to 7 metabolic equivalent hours per week were associated with reductions in risk exceeding 30%. Swank *et al.* (18) reported similarly improved outcomes in the HF-ACTION trial patients who achieved increased peak oxygen uptake (VO_2) over the course of the exercise-training program.

Others regard the HF-ACTION trial more critically (19). Some impugn the conclusions because statistically significant benefits of exercise training were only evident after statistical methods adjusted for predictive factors for the same outcomes. Others criticize the HF-ACTION trial's need to extend enrollment to 79 study sites in the United States and abroad in order to achieve enrollment goals, inferring that exercise training is inherently problematic, especially considering the reduction in enrollment targets more than halfway through the trial. Similarly, despite multiple methods to reinforce adherence, only approximately 30% of those in the HF-ACTION trial's exercise arm exercised at or above the target number of minutes per week. Furthermore, the demonstration of greater mortality benefits in HFrEF patients who were able to sustain exercise therapy implicitly calls attention to the erosion of the treatment effect targeted in the original trial design by poor exercise adherence.

Notably, a related HF-ACTION trial analysis showed that poor adherence was not predictable at enrollment using standard assessment criteria (20). However, it is also noteworthy that while female sex and nonwhite race are commonly associated with poor CR enrollment and high attrition, women and self-identified black patients in the HF-ACTION trial achieved significant exercise training benefits (21,22). Both women and black patients had lower peak VO_2 and 6-min walk distance at baseline than male and white patients, respectively, but training effects and clinical benefits were preserved. Risk reduction of the primary endpoint (all-cause mortality and hospitalization) was greater in women than in men, with a significant treatment by sex interaction ($p = 0.027$) (21).

THE HF-ACTION TRIAL AND CR: AN IMPORTANT ADVANCE, BUT WITH GAPS TO FILL

The HF-ACTION trial provides a greater rationale to justify CMS financing for CR for HFrEF than any prior single study has done to justify CR for other diagnoses, yet still leaves residual concerns and questions, particularly due to its limited enrollment and suboptimal adherence. Home-based exercise adherence by the exercise group fell from a weekly

median of 95 min (interquartile range: 26 to 184 min) in months 4 to 6 to only 50 min (interquartile range: 0 to 140 min) during year 3 (4). Many interpret the poor enrollment and adherence as supporting a mandate to consider novel CR strategies to better implement and sustain wellness behaviors (e.g., home-based CR, mobile device CR, or other technological options in the burgeoning field of telehealth) (6).

Some critics also question the basic assumption that the HF-ACTION trial can be associated with contemporary CR because HFrEF may differ from CR's primary orientation to CHD (23). The distinctive risks and needs of HFrEF patients may necessitate new CR program designs and technologies. The expertise of CR personnel may also need to be modified to meet the needs of a different patient population (5).

More practically, the HF-ACTION trial focused primarily on the safety and rudimentary efficacy of aerobic exercise for HFrEF, but avoided many other challenges germane to contemporary HFrEF management. Participants could not be enrolled until 6 weeks after hospitalization for decompensated HF; thus, the safety and potential efficacy of earlier enrollment in CR to decrease HFrEF readmissions are unknown. Similarly, the HF-ACTION trial utilized CPX and 6-min walk testing as metrics by which to assess exercise training efficacy and as standards to ensure clinical safety and stability prior to exercise training. While this builds on a tradition of formalized functional assessments before CR, many see such stringencies as inherent barriers to exercise training, especially for patients who have been presumably stabilized on medications, implanted cardiac defibrillators, and other provisions of care (24). It is possible that the poor enrollment into the HF-ACTION trial was exacerbated by the protocol's rigid requirements for CPX, walking tests, and site-based exercise training (and the inherent logistic difficulties). Options to use exercise assessments and exercise supervision more selectively, to potentially make exercise training more accessible and uncomplicated to relatively more stable subsets of HFrEF patients, were not considered or assessed.

The HF-ACTION trial also enrolled few adults >75 years of age, and failed to address advanced age complexities germane to HFrEF care (e.g., multimorbidity, polypharmacy, frailty). Likewise, the HF-ACTION trial utilized only 1 approach to exercise (moderate intensity, continuous aerobic exercise), but did not incorporate other modalities (e.g., strength and inspiratory training) and intensities (e.g., high-intensity interval training) that might better suit different clinical contexts (e.g., frailty, obesity) and/or patient populations (e.g., women,

elderly). HF with preserved ejection fraction (HFpEF), the dominant form of HF among older adults (25), was entirely omitted. Exercise training for HFrEF patients with left ventricular assist devices (LVADs), an increasingly common HFrEF management option, was also not included.

THE NEED FOR MORE RESEARCH

CR FOR HFpEF. Reports show an already large and growing prevalence of HFpEF (25,26), especially because of the dual effects of intrinsic age-related susceptibility to HFpEF and the expanding older adult population. The related literature highlights the high morbidity and mortality associated with HFpEF (27). The evidence for the benefits of exercise training in HFpEF is rapidly increasing (28,29), and there have been many calls for additional exercise-oriented research (30,31), especially after a succession of unsuccessful HFpEF pharmacological trials (32,33).

Many conceptualize HFpEF as primarily a disease of abnormal lusitropic physiology, and assume that exercise benefits will be manifest principally as improved diastolic filling properties (34). However, seminal research (28) suggests that training benefits for HFpEF are more likely to be mediated by peripheral effects, particularly involving skeletal muscle quality and intrinsic oxygen utilization. Studies show increased interstitial fat and relatively reduced aerobic (type I) skeletal muscle fibers in HFpEF patients compared with age-matched controls, suggesting the potential for their modification by exercise (35). Other studies suggest that at least some HFpEF patients may achieve central and peripheral vascular benefits (and improved ventricular-vascular coupling) from exercise training and wellness therapies (36). Furthermore, HFpEF is particularly associated with comorbidity (even more than HFrEF) (37), and many comorbid conditions (e.g., diabetes, peripheral arterial disease, hypertension, CHD) are likely to benefit from exercise therapy.

Given the evolving perspectives on HFpEF pathophysiology and steps that can moderate the disease, further research is essential, including on the utility of CR. Persistent uncertainties regarding the fundamental mechanisms of disease add to the challenge of meaningful CR trials in terms of patient selection, type, and intensity of exercise training (38), and the effectiveness of adjunctive therapies (e.g., diet and pulmonary pharmacological enhancements, such as phosphodiesterase inhibitors and possibly even skeletal muscle enhancements) (39,40).

CR FOR VERY OLD HF PATIENTS. The recently National Institute on Aging-funded REHAB-HF (Trial of

Rehabilitation Therapy in Older Acute Heart Failure Patients) trial (41) will study the utility of exercise training for older patients with acute decompensated HF including both HFrEF and HFpEF subtypes, and will particularly target issues salient to advanced age. The primary outcome measure is improved physical function, as measured by the short physical performance battery (42); the secondary outcome measure is rehospitalization. Other assessments include frailty, multimorbidity, polypharmacy, and other age-related complexities of care.

CR FOR LVAD PATIENTS. LVAD patients face some unique barriers to exercise training, including limitations in mobility due to device drive lines and consoles, as well as dyspnea due to adjacent hemidiaphragm compression (43). As the majority of LVAD patients are currently implanted with continuous-flow pumps, and many are implanted with concomitant pacemakers, heart rate and ECG often cannot be used as markers of exercise intensity or safety (44,45). Furthermore, patients with continuous-flow LVADs are sensitive to small volume shifts that significantly affect pump flow (46).

The Rehab-VAD (Cardiac Rehabilitation in Patients With Continuous Flow Left Ventricular Assist Devices) trial (47) showed that moderate intensity aerobic training yielded significantly improved health status (measured by the Kansas City Cardiomyopathy Questionnaire), total treadmill time, and leg strength (measured using an isokinetic dynamometer) in continuous LVAD patients, but without improvements in peak VO_2 . Safety of CR in LVAD patients was suggested by only 1 event (syncope) in over 300 sessions.

ACCOMPLISHING ADHERENCE. The World Health Organization defines adherence to long-term therapy as “the extent to which a person’s behavior—taking medication, following a diet, and/or executing lifestyle changes—corresponds with agreed recommendations from a health care provider” (48). A key implication is that adherence difficulties usually entail more than 1 barrier, and a single-factor approach usually achieves only limited effectiveness.

Multiple impediments to exercise adherence among HFrEF patients have consistently been identified (49,50). Patients are generally older and have age-related limitations, commonly including multimorbidity, polypharmacy, disability, frailty, visual and hearing deficits, incontinence, falls, and cognitive deficits, all compounding management complexity and impediments to adherence. HF symptoms, such as fatigue and dyspnea, may detract from the capacity of patients to achieve consistent exercise and physical activity patterns. Recurrent HF exacerbations

and associated comorbidities often precipitate recurrent hospitalizations that lead to more deconditioning, which may hamper ongoing motivation to resume activities (51). Psychological barriers to adherence among HF patients are additionally encumbering. Depressive symptoms are found in nearly 30% of patients with HF and are associated with increased risk of mortality, rehospitalization, and cardiac events (52).

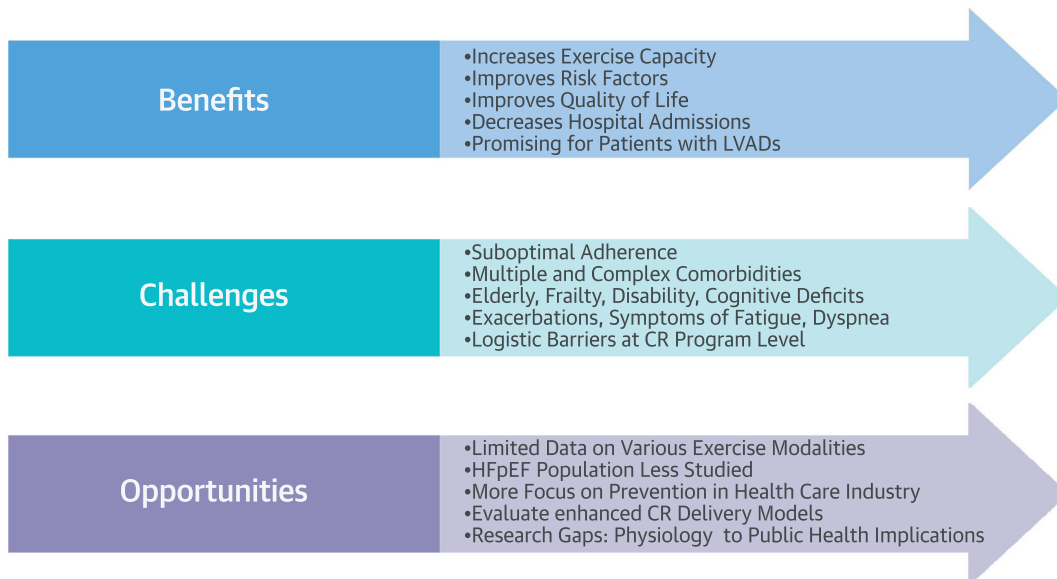
Tierney *et al.* (53) focused on exercise adherence among HF patients and suggests components of social cognitive theory to reinforce exercise adherence: 1) increase knowledge of the risks and benefits of exercise; 2) promote self-efficacy and confidence in being able to perform or control the behavior; 3) promote outcome expectations of the desired outcomes; and 4) promote facilitators and minimize barriers to perform the desired behavior.

Supportive practitioners can help by providing clear information, which in many cases will need to be repeated frequently. Studies focusing on dietary interventions for HF highlight a generalizable problem wherein patients recurrently deny knowing that healthful recommendations exist (50). Practitioners can also build their patients’ self-confidence and inclinations for physical activity by accepting and accommodating their sense of limitations, being flexible, and encouraging realistic activities and goals. Overall, behavior change theory constructs include therapeutic patient-provider communication, patient engagement in realistic goal setting, self-monitoring of progress, and mutual problem-solving to reduce barriers and foster social support.

EXPANDING MODELS OF EXERCISE ASSESSMENT AND TRAINING TO IMPROVE CR UTILIZATION AND ADHERENCE

There is emerging evidence on the effectiveness of complementary or alternative CR models that may be particularly useful in addressing the adherence challenges of HF patients. In select populations, home-based CR has been demonstrated to be as effective as center-based CR in improving exercise capacity, risk factor control, and health-related quality of life (54). Other promising models include interventions tailored to an individual’s risk profile and delivered through telehealth, web-based platforms, and community-based or home-based programs (55). Structured telephone support and telemonitoring have been demonstrated to be effective in reducing the risk of all-cause mortality and HF-hospitalizations in HFrEF patients, and also in improving quality of life, reducing costs, and improving evidence-based

CENTRAL ILLUSTRATION Heart Failure and CR: Challenges and Opportunities



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Cardiac rehabilitation (CR) provides proven benefits for heart failure with reduced ejection fraction patients, particularly functional gains, improved quality of life, and decreased hospitalizations. Still, key challenges remain: poor adherence, logistical barriers, comorbidity, and geriatric syndromes are among the impediments that erode CR's utility in contemporary management. Research is needed to clarify models of cardiac rehabilitation and exercise training that best surmount these challenges. Research is also essential to clarify the presumed benefits of CR for heart failure with preserved ejection fraction (HFpEF). LVAD = left ventricular assist device.

prescribing (56). Emerging evidence shows promise in the feasibility and acceptability of mobile technology interventions in CR (57). Recently, a mobile care delivery platform was integrated within a CR program and enhanced both patient and physician perceptions of the CR caregiving process (58).

Whereas CR is now structured as a relatively formulaic fee-for-service model with specific criteria required to document participation and payment, a recent AHA advisory calls for consideration of new models of care that achieve more convenient exercise training and wellness objectives that are more likely to be successful (59). As models of CR care evolve, it is incumbent on investigators to prove the efficacy of new CR models in terms of costs, safety, enrollment, adherence, and qualitative/quantitative outcomes.

PERTINENT CHANGES IN U.S. HEALTHCARE DYNAMICS

CR delivery will potentially be transformed in the greater context of changes in American healthcare. The Affordable Care Act was initiated in 2010 as a means to ensure that patients receive high-value

healthcare that better responds to each individual's own sense of priority and wellness (60). Accountable Care Organizations are models of care fostered by the Affordable Care Act to facilitate prevention strategies and treatment that maximize efficiencies and value. As a comprehensive program that fosters more efficacy and quality of care, CR has the potential to become an effective Accountable Care Organization instrument (61). CR can be applied to optimize prevention in relation to aggregate risk (including age), thereby facilitating increased prevention, earlier mobilization, better transitions of care, and greater overall value of care. Aligning incentives among providers and eliminating disincentives to patients (e.g., copayments) add to the potential for more patients to enroll and participate in CR, including women, minorities, the elderly, and those in lower socioeconomic brackets.

CONCLUSIONS

CR is at a critical juncture. While there is a strong rationale for exercise and wellness therapy for HFpEF, persistent underutilization of CR for patients with

CHD bodes inauspiciously for its application to those with HF_rEF. Major changes in U.S. healthcare are still evolving that seem likely to shift priorities and standards towards increased emphasis on CR. Therefore, the recent decision by CMS to include HF_rEF as an eligible diagnosis for CR payment is an important step, but only part of the solution (**Central Illustration**). Additional insights regarding the efficacy and dissemination of CR to HF_rEF and

HFpEF patients of all ages, and related issues of adherence, safety, efficacy, and financial feasibility are needed to realize CR's full potential.

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