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AHA/ACC SCIENTIFIC STATEMENT

Supervised Exercise Training for Chronic Heart Failure With Preserved Ejection Fraction: A Scientific Statement From the American Heart Association and American College of Cardiology

This statement is endorsed by the Heart Failure Society of America, the American Association of Cardiovascular and Pulmonary Rehabilitation, and the American Association of Heart Failure Nurses.

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ABSTRACT: Heart failure with preserved ejection fraction (HFpEF) is one of the most common forms of heart failure; its prevalence is increasing, and outcomes are worsening. Affected patients often experience severe exertional dyspnea and debilitating fatigue, as well as poor quality of life, frequent hospitalizations, and a high mortality rate. Until recently, most pharmacological intervention trials for HFpEF yielded neutral primary outcomes. In contrast, trials of exercise-based interventions have consistently demonstrated large, significant, clinically meaningful improvements in symptoms, objectively determined exercise capacity, and usually quality of life. This success may be attributed, at least in part, to the pleiotropic effects of exercise, which may favorably affect the full range of abnormalities—peripheral vascular, skeletal muscle, and cardiovascular—that contribute to exercise intolerance in HFpEF. Accordingly, this scientific statement critically examines the currently available literature on the effects of exercise-based therapies for chronic stable HFpEF, potential mechanisms for improvement of exercise capacity and symptoms, and how these data compare with exercise therapy for other cardiovascular conditions. Specifically, data reviewed herein demonstrate a comparable or larger magnitude of improvement in exercise capacity from supervised exercise training in patients with chronic HFpEF compared with those with heart failure with reduced ejection fraction, although Medicare reimbursement is available only for the latter group. Finally, critical gaps in implementation of exercise-based therapies for patients with HFpEF, including exercise setting, training modalities, combinations with other strategies such as diet and medications, long-term adherence, incorporation of innovative and more accessible delivery methods, and management of recently hospitalized patients are highlighted to provide guidance for future research.

Key Words: AHA Scientific Statements ■ aged ■ cardiac rehabilitation ■ exercise therapy ■ exercise tolerance ■ heart failure

There have been several exercise-based therapeutic trials in patients with chronic heart failure (HF) with preserved ejection fraction (HFpEF). In contrast to the pharmacological trials, most of them reported positive primary outcomes with relatively large, clinically meaningful effect sizes. Whereas pharmacological studies focused on clinical outcomes, the smaller exercise-based trials focused primarily on aerobic exercise capacity and quality of life, and

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none were adequately powered for events. However, exercise capacity (ie, cardiorespiratory fitness) is an independent, clinically meaningful patient outcome, and its measurement is valid, objective, and reproducible. These positive data on exercise capacity for patients with chronic HFpEF provided the impetus for the current American Heart Association and American College of Cardiology scientific statement, which describes the quantification of exercise intolerance and its underlying mechanisms, critically examines currently available data on exercise-based therapies, and discusses the rationale for their promotion and wider dissemination.

BACKGROUND

HF Definition and Classification

Ejection fraction (EF) has traditionally been used to classify patients with HF because of its prognostic and therapeutic implications. The definitions of HFpEF have varied over time and among the studies cited, including both exercise and pharmacological trials. Thus, interpretation of results for any subgroup of HF could differ somewhat depending on study population selection criteria. Clinical trials have used an EF ≤35% or 40% to define HF with reduced EF (HFrEF). HFpEF trials have used variable EF thresholds of >40%, 45%, or 50% for patient selection. In 2021, a universal definition of HF was proposed: "HF is a clinical syndrome with symptoms and/or signs caused by a structural and/or functional cardiac abnormality and corroborated by elevated natriuretic peptide levels and/or objective evidence of pulmonary or systemic congestion."[1] In addition, the following classifications were proposed and have been incorporated into the most recent HF guidelines[2]: HFrEF includes patients with an EF ≤40%; HF with mildly reduced EF (HFmrEF) includes those with an EF of 41% to 49%; and HFpEF includes those with an EF ≥50%.[1]

Epidemiology of HFpEF

HFpEF affects approximately half of all patients with HF (ie, >3 million Americans), with women disproportionately affected compared with men. Its prevalence is increasing relative to HFrEF,[3–5] largely because of the aging of the population and an increasing burden of comorbidities that contribute to its development.[4–7] HFpEF has profound health consequences, including severe exercise intolerance manifested by exertional dyspnea and early-onset fatigue with even brief bouts of mild physical activity, impaired health-related quality of life, frequent hospitalizations, loss of functional independence, increased death, and high healthcare use and costs.[8]

Common Comorbidities

Comorbid medical conditions not only are highly prevalent in HFpEF but also are linked to the underlying mechanisms for its development and prognosis.[4,5,9,10] Hypertension is a major risk factor for HF development and is highly prevalent in those with HFpEF. Although there is evidence that treatment of hypertension may prevent HFpEF development,[11] there appears to be less effect from blood pressure lowering on reducing morbidity and death once HFpEF is established.[11] Overweight or obesity is present in >80% of patients with HFpEF,[12] making excess adiposity and the associated metabolic derangements the most common HFpEF phenotype. Multiple lines of evidence indicate that body habitus, particularly excess intra-abdominal fat stores,[12] plays a pivotal role in the development of obese or metabolic HFpEF and independently influences the severity of outcomes, including both exercise capacity and subsequent clinical events.[13] Approximately 25% to 50% of patients with HFpEF have diabetes, and this proportion is expected to increase. Diabetes has adverse prognostic significance in patients with HFpEF, likely because of overlapping pathophysiological sequelae, including neurohormonal activation, inflammation, and impaired skeletal muscle function. Coronary artery disease is common in patients with HFpEF and is associated with a greater deterioration in left ventricular systolic function and worse outcomes.[14] Pulmonary hypertension is common in HFpEF and develops as a result of elevated left atrial pressures and progressive pulmonary vascular disease. There is a bidirectional relationship between the heart and kidney dysfunction that mediates volume overload and congestion and is correlated with poor clinical outcomes.[7]

There is a high burden of sarcopenia and frailty in patients with HFpEF, and these factors are associated with worse quality of life and increased clinical events.[15,16] Reduced physical activity with aging and low cardiorespiratory fitness are important contributors to the development of HFpEF,[17,18] and emerging evidence demonstrates that among patients with HFpEF, these impairments can be improved with exercise training interventions.[19]

Clinical Management of HFpEF

Patients with HFpEF may have frequent episodes of acute decompensation with volume overload and congestion, often leading to hospitalizations.[4,20] However, even when their congestion has been effectively treated and they are well-compensated, stable, and nonedematous, patients with chronic, stable HFpEF often experience severe exercise intolerance, exertional fatigue, and dyspnea. Indeed, exercise intolerance is the primary manifestation of chronic HFpEF and is associated with poor health-related quality of life[4] and other adverse outcomes. Acknowledging the importance of exercise capacity and quality of life in these patients,[7] a recent US Food and Drug Administration statement emphasized that reducing symptoms and enhancing physical function are valid end points for HF drug development.[21]

Until recently, most HFpEF trials of pharmacological therapy were neutral on their primary outcomes of clinical events (eg, HF hospitalizations and cardiovascular death).[4,22] In February 2021, the US Food and Drug Administration reviewed data on the effect of sacubitril/valsartan and spironolactone treatment for HFpEF and granted approval for the use of sacubitril/valsartan in selected patients with HFpEF based largely on the PARAGON-HF (Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction) trial.[22] Despite promising results from post hoc analyses of data from the TOPCAT trial (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist),[23] no final determination on spironolactone use was issued. Results from 2 unequivocally positive trials for HFpEF, EMPEROR PRESERVED (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction)[24] and DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure),[25] were recently published and showed a reduction in the combined risk of HF hospitalizations or cardiovascular death with empagliflozin and dapagliflozin treatment.

In HFpEF drug trials that evaluated exercise capacity as a primary or secondary end point, changes in exercise capacity with most drugs,[4] including spironolactone (mean difference in peak oxygen uptake [$\dot{V}o_2$] compared with control subjects, −0.4 mL·kg^{-1}·min^{-1}; P=0.38),[26] sacubitril/valsartan (mean difference in 6-minute walk distance [6MWD], −2.5 m; P=0.42),[27] and empagliflozin (mean difference in 6MWD, 4 m; P=0.37),[28] have been disappointing. In October 2021, the first drug trial to improve exercise capacity and quality of life in patients with HFpEF was published. The PRESERVED-HF trial[29] (Dapagliflozin in Preserved Ejection Fraction Heart Failure) showed that dapagliflozin significantly improved the Kansas City Cardiomyopathy Questionnaire Clinical Summary score by 5.8 points at 12 weeks, and an increase (8.2%) in the 6MWD was observed. As previously noted, these trials used varying EF thresholds (40%, 45%, 50%) for inclusion of patients.

Several device-based solutions to relieve symptoms and to improve the clinical course of patients with HFpEF have been evaluated. Use of a wireless pulmonary artery pressure monitoring device reduced hospitalizations in all patients with HF[30]; an exploratory subgroup analysis found that this effect was also seen in patients with HFpEF.[31] Placement of an interatrial shunt device to reduce pulmonary capillary wedge pressure during exercise did not reduce HF events in patients with HFpEF.[32] However, prespecified analyses showed that latent pulmonary vascular disease in one-third of patients identified worse outcomes, suggesting that two-thirds of patients may benefit.[33] Despite this recent progress in drugs and devices, a paucity of interventions for HFpEF remains, highlighting the need to evaluate potentially therapeutic lifestyle interventions.

Current Guidelines for HFpEF Management

A new version of the American College of Cardiology/American Heart Association guidelines for HF management was recently released, and HFpEF treatment recommendations have been added for sodium-glucose cotransporter 2 inhibitors (Class of Recommendation 2a), mineralocorticoid receptor antagonists (Class of Recommendation 2b), and angiotensin receptor neprilysin inhibitors (Class of Recommendation 2b).[2] Current guidelines also include a Class 1 recommendation (Level of Evidence A) for exercise training in patients with HF.[2] Although this recommendation does not distinguish between HFpEF and HFrEF, the supporting evidence for this recommendation emanates largely from studies of supervised exercise training (SET) in patients with chronic HFrEF. Guidelines also include comorbidity management in the treatment of HFpEF, and patients with hypertension, obesity, and diabetes may also benefit from SET.

ASSESSMENT AND QUANTITATION OF EXERCISE INTOLERANCE IN HFpEF

Aerobic exercise capacity can be quantified objectively and reproducibly in patients with HFpEF as peak $\dot{V}o_2$ by expired gas analysis.[34] Peak $\dot{V}o_2$ is physiologically meaningful because it measures the ability to transport (cardiac output) and use (arteriovenous O_2 difference) oxygen. Peak $\dot{V}o_2$ is severely reduced by ≈30% in patients with HFpEF compared with age-matched healthy individuals and is similar to that in age-matched patients with HFrEF (13–14 mL·kg^{-1}·min^{-1}).[35] This reduced level of peak $\dot{V}o_2$ is below established thresholds required for functional independence, including normal activities of daily living such as carrying groceries.[36] Peak $\dot{V}o_2$ also has significant prognostic value in patients with HFpEF,[37] potentially greater than in patients with HFrEF.[38] However, in contrast to SET studies in patients with HFrEF,[39] the relationship between changes in peak $\dot{V}o_2$ and clinical outcomes in HFpEF has not been examined. The most commonly used practical alternative for assessing exercise performance in HFpEF is the 6MWD, demonstrating values that are comparable to those in patients with HFrEF and markedly reduced relative to control subjects. However, there are few or no data correlating this parameter with clinical event outcomes in patients with HFpEF.[40,41]

MECHANISMS OF EXERCISE INTOLERANCE IN CHRONIC HFpEF AND BENEFITS FROM EXERCISE TRAINING

Several pathophysiological mechanisms are responsible for the severely reduced aerobic exercise capacity in patients with HFpEF. These can be broadly categorized as cardiac,

pulmonary, vascular, and skeletal muscle. Other factors that contribute to exercise intolerance in these patients involve common, coexisting risk factors and comorbidities, including sedentary behavior; atrial fibrillation, which is accompanied by a worse prognosis[10,42]; and obesity, which may be associated with increased plasma volume, cardiac remodeling, and potentially pericardial restraint.[43] Excess intra-abdominal adiposity is pivotal and has been linked to systemic inflammation, mitochondrial dysfunction, capillary rarefaction, and reduced nitric oxide bioavailability.[10,13]

Cardiac and Pulmonary Mechanisms

Impaired cardiac output reserve during exercise is attributable to modest blunting of stroke volume augmentation and to chronotropic incompetence, which occurs in up to ≈50% of patients with HFpEF.[44] The blunting of stroke volume occurs despite an exaggerated increase in filling pressures with exercise.[45] Left ventricular systolic and diastolic dysfunction and left atrial dysfunction may also impair exercise capacity.

Chronically elevated left ventricular filling pressures lead to pulmonary vascular remodeling and impaired gas exchange with decreased lung diffusion capacity and alveolar ventilation.[46] Pulmonary hypertension is present in >50% of patients with HFpEF; right ventricular dysfunction is seen in approximately one-third of patients; and both can contribute to exercise intolerance and a poor prognosis.[36]

Vascular Mechanisms

Exercise intolerance in patients with HFpEF is also associated with abnormalities in central artery (ie, proximal thoracic aorta) distensibility, peripheral (eg, femoral, brachial) artery vasodilator capacity, and microvascular diffusive function (O_2 movement from hemoglobin to mitochondria).[47] Specifically, increased central artery stiffness correlates with the observed reduction in peak $\dot{V}o_2$.[48] Among patients who are free of clinically manifest coronary atherosclerosis, flow-mediated endothelial function is abnormal compared with younger healthy individuals; however, this may be an age-related phenomenon because the reduction in vasodilatory responsiveness is apparently not different when patients with HFpEF are compared with healthy age-matched control subjects.[49,50] Last, microvascular function, which influences the diffusion of O_2 within both the myocardium and skeletal muscle and is partly dependent on both local autoregulatory mechanisms and capillary density, is reduced in individuals with HFpEF compared with age-matched control subjects.[51]

Skeletal Muscle Mechanisms

Although reduced exercise cardiac output is sometimes assumed to be the primary mechanism for severe exercise intolerance in HFpEF, a reduced arteriovenous O_2 difference accounts for >50% of the reduction in peak $\dot{V}o_2$ and is a stronger independent predictor of peak $\dot{V}o_2$ than exercise cardiac output.[44,52] Reduced peak exercise arteriovenous O_2 difference in HFpEF may be attributed to the aforementioned convective and diffusive oxygen delivery abnormalities, as well as multiple skeletal muscle abnormalities that impair oxygen utilization, including reduced muscle mass, excess adipose infiltration, and, most important, impaired mitochondrial function.[53–59]

The strongest evidence that abnormal skeletal muscle mitochondrial function contributes to aerobic exercise intolerance was provided by phosphorous magnetic resonance spectroscopy measurement of ATP and creatine phosphate concentrations and turnover rates during and after handgrip exercise using a small mass of exercising muscle, a model that excluded any limitation in cardiac output as a contributor.[59] These studies showed that patients with HFpEF have rapid muscle ATP depletion, which was observed early during exercise, further excluding abnormalities in cardiac output and muscle blood flow reserve as causes.

The presence of multiple skeletal muscle abnormalities[53,54,56,58,59] suggests that, independently of any limitations in cardiac output, patients with HFpEF have a skeletal muscle myopathy similar to that described in HFrEF.[53,60] Furthermore, these abnormalities are not merely secondary to deconditioning because (1) they develop even when physical activity is maintained during the development of HF[60] and (2) the pattern of abnormalities differs from deconditioning, particularly the fiber-type shift, which is the opposite of that seen in deconditioning. The intrinsic nature of skeletal muscle dysfunction is consistent with the current HFpEF paradigm that it is a systemic syndrome, likely triggered by circulating factors such as inflammatory cytokines that cause dysfunction in multiple organ systems.[10]

Mechanisms of Benefits From Exercise Training

Studies indicate that peripheral adaptations, particularly in skeletal muscle, are the primary mechanism for improvement in peak $\dot{V}o_2$ after exercise training in patients with HFpEF.[6] The reason may be that, compared with cardiac muscle, skeletal muscle is more plastic and has potential for rapid, large improvements in function after even a brief period of exercise.[61]

Exercise has a broad range of benefits that are relevant to HFpEF, including anti-inflammatory, rheological, lipid-lowering, antihypertensive, positive inotropic, positive lusitropic, negative chronotropic, vasodilation, diuretic, weight-reducing, hypoglycemic, hypnotic, and antidepressive qualities.[62] These pleiotropic systemic effects (Figure 1) are potentially well suited for the treatment of both the cardiac and, in particular, the extracardiac abnormalities that contribute to exercise intolerance in HFpEF.[6,63]

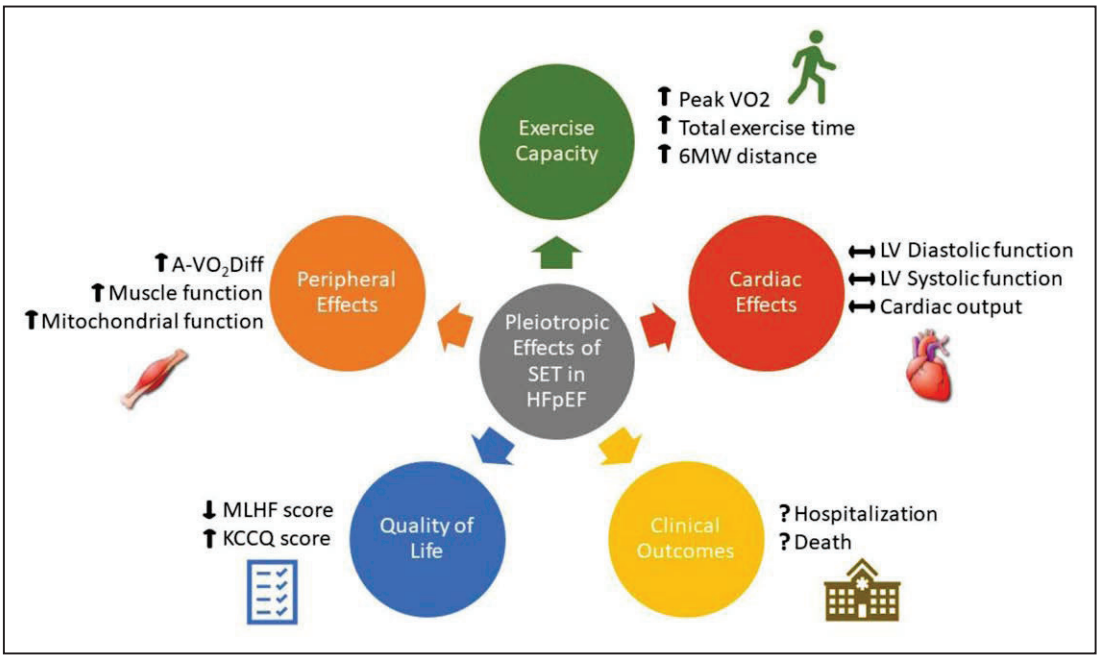

Figure 1. Pleiotropic effects of SET in chronic HFpEF.
A-$\dot{V}o_2$Diff indicates arteriovenous O_2 difference; HFpEF, heart failure with preserved ejection fraction; KCCQ, Kansas City Cardiomyopathy Questionnaire; LV, left ventricular; MLHF, Minnesota Living With Heart Failure Questionnaire; and SET, supervised exercise training.

Many studies have demonstrated improvements in physical function with exercise training in patients with HFpEF and have shown favorable cardiac adaptations (increased maximal cardiac output), peripheral vascular changes, and skeletal muscle adaptations (increased oxidative muscle fibers, reduced muscle wasting).[6,61,64–66] Compared with most drugs that have failed to show benefits, exercise training has shown consistent improvements in exercise capacity in patients with HFpEF.

CRITICAL ANALYSIS OF DATA FROM AEROBIC EXERCISE TRAINING TRIALS IN CHRONIC HFpEF

Because earlier randomized controlled trials (RCTs) of SET in HF were not blinded for assessment of outcome measures,[41] this scientific statement focuses on single-blinded HFpEF trials from 2010 onward (Table 1 and Supplemental Table 1).[67–77] Trials included in this analysis were identified from a 2019 Cochrane review of exercise-based cardiac rehabilitation (CR) for adults with HF[78] and related reviews and meta-analyses from PubMed.[79–83] Studies were required to have aerobic exercise capacity parameters as outcomes, and those that enrolled both patients with HFpEF and patients with HFrEF were excluded if results for HFpEF were not presented separately. Two exercise training studies were excluded because of a lack of randomization, and 5 studies of other exercise forms (classes, functional electrical stimulation, tai chi, resistance training only) were excluded (Supplemental Figure 2).

Of the 11 RCTs included in this review (Table 1), 8 had data available to calculate the effect of SET on the baseline–to–follow-up change in peak $\dot{V}o_2$. Two of the studies did not have a control group,[76,77] and 1 study did not have a peak $\dot{V}o_2$ measurement.[75] With regard to the evolving definition of HFpEF and its classification, 6 of 8 trials included in the meta-analysis used the current EF classification of HFpEF. One study used an EF of 40% and 1 used 45%; both of these studies included patients with HF with mildly reduced EF and patients with HFpEF based on current definitions.

Demographics of the Patient Population and Potential Limitations

There was substantial variation in the baseline characteristics of patients with chronic HFpEF who underwent aerobic exercise interventions. Some studies excluded patients with atrial fibrillation, chronic obstructive pulmonary disease, and coronary artery disease, despite the fact that these comorbidities are common in individuals with HFpEF. Moreover, individuals with demographic characteristics prevalent in population studies of HFpEF were often underrepresented, including older adults, women, individuals of lower socioeconomic status, and underrepresented racial and ethnic groups. Similar to SET studies in HFrEF, patients were clinically stable with no recent acute hospitalization. Accordingly, these exclusions limit somewhat the generalizability of the results and preclude extrapolation to patients with more severe disease, particularly those with recent hospitalization who have much more severe and broader deficits in physical

Table 1. RCTs of Facility-Based SET in HFpEF

Study author, year	Aim of study	Study size: exercise/control (blinded: yes/no)	Centers, n	Patient population	Type of ET	SET program	Primary end points (unless otherwise noted)	Cardiac and vascular end points	QOL end points
Kitzman et al,[67] 2010	To evaluate the effect of ET on peak $\dot{V}o_2$ and QOL	26 ET/27 control (yes)	1	EF ≥50%, NYHA II–III, age 70±6 y, 17% male	Walking	3 times per wk for 4 mo	Improved peak $\dot{V}o_2$, ex test time, 6MWD	No change in cardiac parameters	No change in MLHF or SF36 score
Edelmann et al,[68] 2011	To evaluate the effect of ET on functional capacity, cardiac function, and QOL	44 ET/20 control (yes)	3	EF ≥50%, NYHA II–III, age 64±8 y, 45% male	Bike+resistance	3 times per wk, 35 min each, for 6 mo	Improved peak $\dot{V}o_2$, ex test time, 6MWD	Decreased E/e' and LAVI	Improved MLHF, SF36 score
Smart et al,[69] 2012	To evaluate the effect of ET on functional capacity, cardiac function, and QOL	14 ET/16 control (echo blinded, not mentioned for exercise testing)	2	EF ≥45%, NYHA II–III, age 67±6 y, 58% male	Bike	3 times per wk, 30 min each, for 4 mo	Improved peak $\dot{V}o_2$	No change in cardiac parameters	No change in MLHF score
Kitzman et al,[70] 2013	To evaluate the effect of ET on FMD, arterial stiffness, and peak $\dot{V}o_2$	24 ET/30 control (yes)	1	EF ≥50%, NYHA II–III, age 70±7 y, 28% male	Walking+arm aerobics	3 times per wk for 4 mo	Improved peak $\dot{V}o_2$, ex test time, 6MWD (secondary)	No change in FMD (primary), arterial stiffness, or cardiac parameters	Improved SF36 score, no change in MLHF score
Kaltsatou et al,[71] 2014	To compare dancing vs ET vs control on functional capacity	18 dancing, 17 ET/16 control (yes)	1	EF ≥40%, NYHA II–III, age 67±7 y, 100% male	Greek dance vs bike/treadmill+resistance vs control	3 times per wk, 30 min each, for 1 mo	Both dancing and ET improved peak $\dot{V}o_2$, ex test time	None	Both dancing and ET improved SF36 score
Fu et al,[72] 2016	To explore how aerobic interval training affects central and peripheral hemodynamics	30 ET/29 control (echo blinded, not mentioned for exercise testing)	1	HFpEF, HFrEF, 2 control groups; EF ≥50%, NYHA II–III, age 61±3 y, 67% male	Bike (3-min intervals)	3 times per wk, 30 min each, for 3 mo	Improved peak $\dot{V}o_2$	Decreased E/e' ratio	Improved MLHF, SF36 scores
Kitzman et al,[73] 2016	To determine whether caloric restriction or SET improves exercise capacity and QOL	46 ET/46 control (yes)	1	EF ≥50%, NYHA II–III, age 67±6 y, 20% male, BMI ≥30 kg/m^2	2×2 factorial: diet, walking, both, control	3 times per wk, 60 min each, for 5 mo	Improved peak $\dot{V}o_2$, ex test time, 6MWD	No change in cardiac function, arterial stiffness unchanged	No change in MLHF, KCCQ, or SF36 score
Mueller et al,[74] 2021	To compare HIIT, MCT, and guideline-based physical activity on peak $\dot{V}o_2$ change	58 HIIT/58 MCT/60 control (no)	5	EF ≥50%, HF/high filling pressures and BNP, mean age 70 y, 33% male, mean BMI 30 kg/m^2	HIIT cycle (4-min intervals) vs MCT vs control	3 times per wk all, 3 mo SET, follow-up to 12 mo	Improved peak $\dot{V}o_2$ at 3 mo in HIIT and MCT groups	No change in diastolic function or NT-proBNP	No change in KCCQ score at 3 mo; improvement in MCT group at 12 mo
Alves et al,[75] 2012	To investigate the effect of ET on exercise tolerance and cardiac function	31 HFpEF, 33 HFmrEF/34 HFrEF (yes)	1	HFpEF (EF >55%), HFmrEF (EF 45%–54%), HFrEF (EF <45%), control; age 63±10 y, 71% male	Treadmill or bike	3 times per wk for 4 mo	Improved METs in HFpEF and HFmrEF groups	EF, E/A increased; DT decreased in HFpEF and HFmrEF groups	None
Angadi et al,[76] 2015	To determine whether HIIT improves peak $\dot{V}o_2$, endothelial dysfunction, and diastolic dysfunction vs aerobic continuous training	9 HIIT/6 MCT (yes)	2	NYHA II–III, age 69±6 y, 89% male	HIIT treadmill (2-min intervals) vs MCT	3 times per wk, 60 min each, for 8 mo	HIIT improved peak $\dot{V}o_2$ (secondary)	HIIT did not change FMD (primary), HIIT improved diastolic function	None
Donelli da Silveira et al,[77] 2020	To compare the effectiveness of HIIT vs MCT in HFpEF	10 HIIT/9 MCT (yes)	1	EF ≥50%, NYHA II–III, age 60±9 y, 37% male	HIIT treadmill (4-min intervals) vs continuous	3 times per wk for 3 mo	Peak $\dot{V}o_2$ improved 22% with HIIT, 11% with MCT	E/e' ratio improved in both groups	MLHF score improved

BMI indicates body mass index; BNP, brain natriuretic peptide; DT, deceleration time; EF, ejection fraction; ET, exercise training; ex test time, exercise test time or duration; FMD, flow-mediated dilation; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HIIT, high-intensity interval training; KCCQ, Kansas City Cardiomyopathy Questionnaire; LAVI, left atrial volume index; MCT, moderate continuous training; MET, metabolic equivalent; MLHF, Minnesota Living With Heart Failure Questionnaire; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association class; QOL, quality of life; RCT, randomized controlled trial; SET, supervised exercise training; SF36, 36-item Short Form Health Survey; 6MWD, 6-minute walk distance; and $\dot{V}o_2$, oxygen consumption.

function and may be better served by interventions other than standard aerobic-based SET.[84,85]

Types of Exercise Used in Clinical Trials

Exercise studies in patients with chronic, stable HFpEF used various approaches for training, including walking, stationary cycle ergometry, high-intensity interval training (HIIT), strength training, and dancing.[67–73,75–77] Eleven studies[47,67–72,74–77] used facility-based SET (Table 1), and 4 studies[86–89] used home-based exercise training (Supplemental Table 1). HIIT studies used 2- to 4-minute exercise bouts with the treadmill or cycle ergometer.[74,76,77] Although the training frequency was generally 3 sessions per week, the duration ranged from 1 to 8 months, and the intensity of training, when specified, varied considerably (40%–90% of exercise capacity), as did the individual session length (25–60 min).

Outcome Measures in SET Trials

Patients with HFpEF are often older and frail with severe, chronic symptoms that significantly compromise quality of life. Thus, it is not surprising that they may place higher value on improving symptoms rather than prolonging survival compared to other groups. In the 2017 American Heart Association statement "Prioritizing Functional Capacity as a Principal End Point for Therapies Oriented to Older Adults With Cardiovascular Disease," Forman et al[90] emphasized that a large body of literature demonstrates that older adults respond favorably to and value the benefits of exercise training programs. Patient-reported surveys indicate that improved physical function and quality of life are preferred outcomes.[91] Accordingly, primary outcome measures for most SET studies reviewed here included exercise capacity, expressed as peak $\dot{V}o_2$, exercise test time or duration, 6MWD, or a combination of these measures.

Meta-Analysis of the Effect of SET on Exercise Capacity

For this scientific statement, we conducted a random-effects meta-analysis of 8 RCTs of aerobic exercise training that indicated that SET significantly improved peak $\dot{V}o_2$, total exercise test time, and 6MWD. Among the patients randomized to SET (n=258), baseline peak $\dot{V}o_2$ increased by 14% (2.2 mL·kg^{-1}·min^{-1}; from 15.8 to 18.0 mL·kg^{-1}·min^{-1}), whereas control subjects (n=245) had a 2% decrease (0.3 mL·kg^{-1}·min^{-1}; from 16.2 to 15.9 mL·kg^{-1}·min^{-1}; P=0.002; absolute treatment effect, 2.5 mL·kg^{-1}·min^{-1}; DerSimonian-Laird[92] meta-analysis treatment effect, 2.8 mL·kg^{-1}·min^{-1}; Figure 2; Supplemental Table 1 provides details). Among the 6 studies that used EF ≥50% for the definition of HFpEF, baseline peak $\dot{V}o_2$ in patients randomized to SET (n=228) increased by 12% (2.0 mL·kg^{-1}·min^{-1}; from 15.7 to 17.7 mL·kg^{-1}·min^{-1}), whereas control subjects (n=212) had a 2% decrease (0.4 mL·kg^{-1}·min^{-1}; from 16.0 to 15.6 mL·kg^{-1}·min^{-1}; P=0.001; absolute treatment effect, 2.4 mL·kg^{-1}·min^{-1}; DerSimonian-Laird meta-analysis treatment effect, 2.2 mL·kg^{-1}·min^{-1}; Supplemental Figure 2). Previous meta-analyses[79–81,93,94] reported similar training-related increases in peak $\dot{V}o_2$ ranging from 1.7 to 2.7 mL·kg^{-1}·min^{-1}. An increase of peak $\dot{V}o_2$ >6% to 7% (≈1.0 mL·kg^{-1}·min^{-1}) is considered a clinically meaningful improvement in patients with HFrEF,[95,96] suggesting that the training-related increases observed with SET in HFpEF are meaningful.

Although 5 of the 8 trials in this meta-analysis are single-center studies (Table 1), the recently published multicenter OptimEx-Clin study[74] (Optimising Exercise Training in Prevention and Treatment of Diastolic Heart Failure), the largest trial of exercise training for chronic, stable HFpEF to date (n=176), also found substantial improvements in peak $\dot{V}o_2$ after 3 months of HIIT (1.1 mL·kg^{-1}·min^{-1}) and moderate-intensity continuous training (MCT; 1.6 mL·kg^{-1}·min^{-1}) compared with control subjects (−0.6 mL·kg^{-1}·min^{-1}). Although the trial did not meet its overly ambitious, large a priori threshold of a 2.5 mL·kg^{-1}·min^{-1} improvement, there were clear benefits in both exercise arms, particularly with MCT, which may be a preferable approach in the older, frail, chronic HFpEF population. This trial used an EF criterion of ≥50%, which is consistent with the current definition of HFpEF.

In 5 studies, total exercise time was measured and shown to be increased by 21% (1.9 minutes) in the SET group compared with a 1% decrease (0.1 minutes) in control subjects (P=0.003). For comparative purposes, a 1-minute or 10% increase in exercise time is considered meaningful and has been used by the US Food and Drug Administration for approval of drugs for angina pectoris. In the 4 studies that measured 6MWD, distance in the SET group increased 9% (40 m) compared with a 3% (12 m) increase in control subjects (P=0.03).

Impact of SET on Quality of Life

The effects of SET on general quality-of-life metrics have been assessed in RCTs using the 36-item Short Form Health Survey[67,68,70–73] and on disease-specific quality of life with the Minnesota Living With Heart Failure Questionnaire[67–70,72,73,77] and Kansas City Cardiomyopathy Questionnaire.[73] Although some studies show no change in quality-of-life measures,[67,70,73] others report significant improvements after SET.[68,71,72,74,77] Effect sizes from previous meta-analyses[79–81,93,94] also show varied results, with improvement (decrease) in Minnesota Living With Heart Failure Questionnaire scores ranging from 4.0 to 9.1 units from baseline to follow-up.

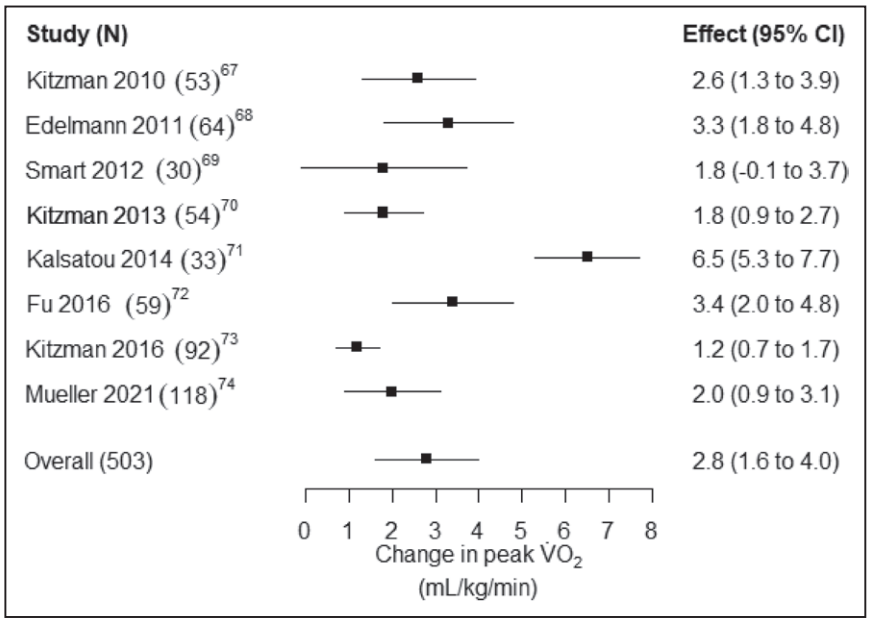

Figure 2. Forest plot of peak $\dot{V}o_2$ increase in randomized exercise training trials in chronic HFpEF.
HFpEF indicates heart failure with preserved ejection fraction.

Cardiovascular and Peripheral Effects of SET

Multiple studies have examined the cardiovascular and peripheral effects of SET in patients with HFpEF to better understand the mechanisms underlying the pleiotropic effects (Figure 1). Among studies that examined alterations in selected cardiac parameters, some reported no change,[67,69,70,73,74,87] whereas others found improvement in diastolic function measures.[68,72,75–77,88] In an observational study in which 7 of 11 patients with HFpEF underwent cardiac catheterization before and after 12 months of SET,[97] there was no discernible impact on left ventricular filling pressures or pressure-volume loops, suggesting that ventricular compliance and cardiac index remained largely unchanged.

Peripheral measures of flow-mediated dilation and arterial stiffness in patients with HFpEF have demonstrated abnormalities at baseline but no significant changes in large-vessel function after SET.[70,73,76] Studies evaluating peripheral adaptations have reported increases in peak arteriovenous O_2 difference after SET with no significant changes in peak exercise cardiac output or stroke volume.[65,72] These findings suggest that improvements in peak $\dot{V}o_2$ after SET are attributable predominantly to peripheral adaptations (eg, increased mitochondrial density and function, myoglobin content, capillary density, blood flow redistribution) that result in increased diffusion capacity and oxygen extraction by the exercising muscles.[61,66] These improvements in the skeletal muscle myopathy of HFpEF are not unexpected and represent a promising target for novel interventions because skeletal muscle has a much greater capacity for repair and regeneration after SET than cardiac muscle.[61]

Effect of SET on Clinical Outcomes

Higher aerobic exercise capacity is associated with fewer subsequent cardiovascular events and improved survival in patients with and without cardiovascular disease[98,99]; however, this relationship has not been systematically examined in patients with HFpEF. To clarify this outcome, some studies of home-based exercise training in HFpEF have explored its impact on clinical events. Although none of the studies had adequate statistical power, a recent pilot study of 50 patients[86] reported fewer hospitalizations in the exercise intervention group. Similarly, a rehabilitation program that included home-based exercise in 85 patients with HFpEF showed a trend toward fewer cardiac events in the exercise training group.[88] The inadequacy of current data highlights the need for larger-scale, longer-term studies to examine the effects of SET on clinical events in HFpEF.

Safety of SET in Chronic, Stable HFpEF

Although regular physical activity reduces the risk of cardiovascular disease, vigorous physical activity, particularly when episodic and performed by unfit, inactive individuals with known or occult coronary artery disease, can trigger acute cardiovascular events.[100] Nonetheless, the safety of SET has been consistently demonstrated in selected middle-aged and older patients with chronic, stable HFpEF. A meta-analysis of 276 patients from 6 RCTs reported no exercise-related major adverse events.[79] Two of the trials noted occasional minor, although expected, adverse exercise responses (eg, palpitations, musculoskeletal discomfort, transient hypoglycemia).[68,70] Studies of home-based exercise training reported no serious events. The safety of exercise in these studies may be attributed partly to the careful selection of clinically stable patients with compensated chronic HF, no recent hospitalization, and monitoring and medical supervision during exercise.

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Adherence to SET and Long-Term Maintenance

Data on patient adherence to the exercise program were provided in 7 of the 11 SET trials summarized here. Completion rates ranged from 84% to 90% in 5 studies.[67,70,71,73,76] One study reported that one-third of patients completed >90% of sessions and half completed 70% to 90%,[68] and the largest study (OptimEx-Clin) reported that 80% of the HIIT group and 76% of the MCT group completed >70% of the exercise sessions.[74] Interventions to promote uptake and adherence to exercise-based therapy may require targeting of patient-specific barriers to enrollment and participation.[101]

Most SET trials have been relatively short term (3–6 months) and were unable to address long-term adherence. Indeed, an important limitation of these studies is the relatively poor long-term maintenance of benefit, partly the result of challenges associated with continued patient adherence.[41] In the SET trial with the longest duration,[76] an 8-month HIIT regimen improved peak $\dot{V}o_2$, whereas MCT showed no improvement.[76] In the recent OptimEx-Clin trial, which had a home-based exercise phase for months 4 to 12, adherence decreased to 56% of the HIIT group and 60% of the MCT group completing >70% of sessions by 12 months. Long-term adherence to exercise training remains a critical challenge regardless of the regimen used and should be addressed in future studies.

Effect of Combining SET and Caloric Restriction

Given the high prevalence of the obese HFpEF phenotype and well-documented adverse effects of excess adiposity on aerobic exercise capacity, interventions combining SET and caloric restriction may have independent and additive benefits in this population. In a single-center 2×2 factorial trial of obese patients with HFpEF (body mass index ≥30 kg/m^2) who were ≥60 years of age and randomized to caloric restriction, SET, both, or neither, Kitzman et al[73] found that caloric restriction (ie, ≈400 fewer kcal/d for 20 weeks) resulted in significantly greater weight loss compared with no restriction (−7 kg [95% CI, −9 to −5]; $P<0.001$). Exercise also resulted in significantly greater weight loss than no exercise (−3 kg [95% CI, −5 to −1]; $P<0.001$) and significantly improved indices of inflammation and cardiac remodeling. Peak $\dot{V}o_2$ improved similarly with caloric restriction (1.3 mL·kg^{-1}·min^{-1} [95% CI, 0.8–1.8]; $P<0.001$) and SET (1.2 mL·kg^{-1}·min^{-1} [95% CI, 0.7–1.7]; $P<0.001$). Both diet and SET resulted in significant improvement in HF-specific quality-of-life measures by the Kansas City Cardiomyopathy Questionnaire, and the combination of caloric restriction and SET doubled the improvement in peak $\dot{V}o_2$ (2.5 mL·kg^{-1}·min^{-1}); exercise time and 6MWD also showed large improvements.

Alternative Exercise Training Models: Home-Based and Hybrid Exercise Training

To the best of our knowledge, only 4 trials of home-based exercise training for patients with chronic HFpEF have been published (Supplemental Table 1).[86–89] All reported improved exercise capacity and quality-of-life metrics. However, because of the short duration (3–6 months) and small number of exercising subjects (n=67) included, the safety and efficacy of these training regimens remain unproven. Home-based CR is a relatively new strategy that incorporates remote coaching and supervision of exercise interventions that may be used alone or in combination with facility-based training (hybrid CR). To date, no studies have compared these 2 approaches in patients with HFpEF. Hybrid models, in which patients participate initially in medically supervised followed by home-based activities, may reduce cost and enhance accessibility for eligible patients.[102] The widespread availability of activity trackers, smartphones, telehealth, and internet-based programs markedly enhances the ability to monitor patient adherence to, responses to, and progress in home-based CR programs. Future research is needed to evaluate integration of other technology applications and novel strategies and to assess their impact on patient adherence and outcomes.

CURRENT APPLICATIONS OF EXERCISE-BASED THERAPIES FOR HFpEF AND COMPARISON WITH OTHER CONDITIONS

There are several types of exercise-based therapies. Self-directed exercise training is performed without supervision and with no formal exercise prescription. Contemporary guidelines for all Americans recommend ≥150 min/wk of moderate-intensity physical activity (eg, 30 minutes on 5 d/wk) and ≥2 d/wk of muscle-strengthening activities.[103] However, there are no data on the safety and efficacy of self-directed exercise in patients with HFpEF, who have far greater functional impairments, symptomatology, and cardiovascular risk.

In clinical practice, SET is prescribed by health care professionals to improve both aerobic exercise capacity and quality of life. It is most often conducted in a clinical setting with monitoring and typically includes at least 3 sessions per week of aerobic-type exercises such as walking on a treadmill or stationary cycling. Other types of activities such as muscle strengthening may also be included, and 36 visits are generally prescribed/allowed by third-party payers within a 12-week period. Structured disease management interventions are not included in this model.

Exercise-based CR combines SET with education that targets risk factor modification, tailored behavioral interventions and counseling, psychosocial assessments, and outcome (eg, clinical, behavioral, physiological)

assessment. For covered conditions, the Centers for Medicare & Medicaid Services (CMS) typically allows 36 CR visits over a 36-week period, thus providing patients with more flexibility over time.

To illustrate the different SET therapies possible for patients with HFpEF, we describe the exercise models that are currently part of guideline-based therapy and are covered by Medicare for 2 other patient populations who present with similar clinical challenges (eg, multiple comorbidities, exercise intolerance). Specifically, patients with chronic, stable HFrEF have been eligible for exercise-based CR coverage since 2014.[104] However, patients with HFpEF were specifically excluded from Medicare coverage because of insufficient evidence at that time. Patients with symptomatic peripheral artery disease (PAD) have been eligible specifically for SET coverage as defined by CMS since 2017.[105] It is notable that CMS reimbursement approvals of exercise therapy, including exercise-based CR programs for most conditions (ie, coronary artery disease, PAD, and HFrEF), were based primarily on SET trials alone. As described, there is now considerable evidence for the safety and efficacy of SET for patients with chronic, stable HFpEF, including exercise capacity improvements that appear similar to or greater than those observed in patients with HFrEF.

How HFpEF and HFrEF Trials Compare

After many single-site studies demonstrated the benefits of SET on exercise capacity in patients with HFrEF, the multicenter HF-ACTION trial (Heart Failure and a Controlled Trial to Investigate Outcomes of Exercise Training) was implemented to determine the effect of aerobic exercise training on clinical outcomes. This trial randomized 2331 patients with chronic HFrEF to usual care compared with usual care plus 36 supervised exercise sessions followed by home exercise training.[41] All-cause death or hospitalization was nonsignificantly reduced in the exercise group compared with the usual care group (hazard ratio, 0.93 [95% CI, 0.84–1.02]; P=0.13). After adjustment for highly prognostic baseline characteristics chosen by a prespecified, treatment-blinded selection algorithm, exercise training was associated with a significant reduction in this combined end point (0.89 [95% CI, 0.81–0.99]; P=0.03). Largely on the basis of these findings, the American Heart Association/American College of Cardiology established SET as a Class 1 recommendation for the treatment of patients with HF (regardless of EF criteria), and HFrEF was added by the CMS as an indication for CR that is covered for Medicare beneficiaries.[104] However, subsequent meta-analyses in chronic HFrEF have shown conflicting results, with 1 analysis of 18 trials showing no significant difference in death or hospitalizations[106] and another showing some reduction in hospitalizations,[78] thus shifting the focus of SET benefits back to improvement of exercise capacity and quality of life.

HF-ACTION showed a modest, statistically significant improvement (0.6 mL·kg^{-1}·min^{-1} [4%]) in peak $\dot{V}o_2$ with exercise training. This effect size, which is at the lower end of a clinically meaningful change, was likely attenuated by suboptimal adherence; moreover, improvement in quality of life was also observed.[107] Although interstudy comparisons should be interpreted with caution, SET studies in HFpEF have generally shown larger increases in peak $\dot{V}o_2$ (≈14%), above the clinically meaningful threshold of a 6% to 7% increase.[95] In the only trial directly comparing the effects of SET in older patients with chronic HFpEF and those with chronic HFrEF, at the 4-month follow-up, there was a large, significant peak $\dot{V}o_2$ improvement in HFpEF but not in HFrEF (18.7±17.6% versus −0.3±15.4%; P<0.001).[108] Overall, available data suggest that the magnitude of improvement in exercise capacity from SET in patients with chronic HFpEF is at least as great as and potentially greater than that seen in patients with chronic HFrEF.

Comparison of SET Trials in Chronic HFpEF With Trials in PAD

The current status of SET for patients with HFpEF is chronologically similar to that for patients with PAD 4 to 5 years ago. Numerous studies had consistently demonstrated a benefit in walking distance after SET in patients with PAD and intermittent claudication (Supplemental Table 2). In 2017, the CMS evaluated evidence on the effects of SET compared with usual care in patients with PAD and found that "absolute change in maximum walking distance and quality of life were considered the most important outcomes in measuring the success of exercise therapy."[105] On the basis of these outcomes, the CMS approved SET coverage for patients with PAD and intermittent claudication.[105] The American Heart Association/American College of Cardiology clinical practice guidelines also recommend SET as first-line therapy for this patient subset to improve functional status and quality of life and to reduce symptomatology.[109] Medically supervised PAD exercise programs are typically conducted in hospitals or associated outpatient facilities, most often within the constructs of a comprehensive CR service.[109] The current evidence supporting improvements in exercise capacity and quality of life after SET in patients with HFpEF closely parallels that for PAD and supports the rationale for extending exercise-based therapy to patients with HFpEF.

IMPLEMENTATION OF CURRENT KNOWLEDGE, EXISTING GAPS, AND FUTURE RESEARCH DIRECTIONS

The strength of currently available data on SET for chronic, stable HFpEF and the paucity of effective pharmacological therapies provide substantial rationale for increasing

Table 2. Critical Gaps in Exercise-Based Therapy in HFpEF

Recommended focus areas for future trials
Setting: supervised, community based, home based, or hybrid
Modalities: HIIT, continuous aerobic training, strength training, or combination
Combination with other lifestyle interventions or medications: dietary weight loss, comprehensive CR, or ET alone
Strategies for long-term adherence: most trials are short-term and long-term maintenance is modest
Strategies to increase accessibility: particularly for underresourced populations
Minimize costs: can specific settings/modalities improve access and minimize costs
Role in management of recently hospitalized, older adults: frailty, impaired balance, and cognition may require innovative interventions
Effect on clinical events (hospitalization, death): larger studies and long-term follow-up are necessary
Preventing the development of HFpEF: supervised or home-based training in patients with multiple risk factors

CR indicates cardiac rehabilitation; ET, exercise training; HFpEF, heart failure with preserved ejection fraction; and HIIT, high-intensity interval training.

efforts to promote and implement exercise-based therapies for this large, inadequately treated, growing patient population. Many RCTs have demonstrated that SET is safe and effective for the entire spectrum of chronic HF, including HFpEF. Implementation efforts are warranted and include frameworks for improving referral rates, strategies to increase access to exercise-based programs, and methods to facilitate adherence. Exercise training is significantly underused in patients with HF, with much lower participation among women and Black patients highlighting existing disparities.[110] Several strategies have been proposed to address this implementation gap, including educating patients and physicians about the benefits of SET, addressing logistical and social determinants of health challenges for patients and communities, and broadening criteria for referrals and reimbursement.[110]

Simultaneously, additional research is needed to extend access to exercise-based therapy for patients with HFpEF. Although implementation of SET for chronic, stable HFpEF appears reasonable on the basis of the considerable volume of data, available evidence on the safety and efficacy of exercise therapy in other settings such as community and home-based programs is more limited and is especially important for underrepresented groups. The coronavirus disease 2019 (COVID-19) pandemic has increased the urgency of defining alternative rehabilitation delivery models that are effective for patients with chronic HF. These are key areas of focus for future research efforts. Additional important evidence gaps include the following (Table 2): clarifying the optimal exercise modalities; delineating the independent and additive benefits of combining exercise interventions with other lifestyle interventions and medications; identifying strategies to increase long-term adherence; improving accessibility of these interventions to underresourced populations; using innovative technology to facilitate cost-effectiveness; and implementing larger, longer-term trials to determine the potential effect of exercise-based therapies on hospitalization, death, cardiovascular events, and health care expenditures. Our meta-analysis included only 2 studies that enrolled both patients with HFpEF and patients with HF with mildly reduced EF according to current definitions. Therefore, more studies on the HF with mildly reduced EF subgroup may help clarify their response to SET. Although there is sufficient evidence to support improvement in exercise capacity with exercise-based treatments in patients with HFpEF, there may also be a role for these interventions in the prevention of HFpEF. Further studies of SET and home-based exercise to prevent the development of HFpEF in patients with multiple risk factors are warranted.

An additional key evidence gap concerns the use of exercise therapy in patients recently hospitalized with acute, decompensated HF, a high-risk population distinct from those with chronic, stable HF. Such patients have high rates of frailty (>90%) and marked impairments in balance, mobility, and strength, in addition to poor endurance,[20] which is the primary domain impairment in chronic, stable HF. Exposing such patients to standard SET can potentially limit efficacy and increase injuries and falls.[111] In the recent REHAB-HF trial (Rehabilitation Therapy in Older Acute Heart Failure Patients), which included patients with HFrEF and HFpEF, a novel, tailored, progressive, transitional, multidomain physical rehabilitation intervention initiated during hospitalization improved frailty, physical function, and quality of life but had no significant effect on rehospitalization or death.[112] A secondary analysis of the trial found that at baseline, among the 53% of patients with HFpEF, frailty, physical function, and quality of life were significantly worse than in those with HFrEF, and benefits appeared greater in patients with HFpEF.[19] There also appeared to be a trend for reduced rehospitalization and death in patients with HFpEF but not in those with HFrEF.[19] However, this was an exploratory analysis of an underpowered, phase 2 trial; a larger trial is needed to definitively test this novel rehabilitation strategy for patients recently hospitalized with acute HFpEF.[19] A recently instituted National Institutes of Health–sponsored multicenter, RCT (NCT05525663) is specifically designed to address this key gap.

CONCLUSIONS

Improved management of the large, inadequately treated population of patients with HFpEF represents an urgent unmet need. HFpEF prevalence continues to increase as a result of aging of the population and the growing prevalence of risk factors such as obesity and diabetes. It is now well accepted that despite similar clinical presentations for all patients with HF, HFrEF and HFpEF are mechanistically distinct diseases. In support of this concept is the lack of efficacy of multiple drug classes

in HFpEF trials although they had been proven effective in patients with HFrEF. HFpEF is a complex and heterogeneous clinical syndrome with pathophysiological mechanisms linked to chronic systemic inflammation and metabolic stress from comorbid conditions. Although outcomes remain poor for all patients with HF, population and clinical trials of chronic, stable HFpEF show lower death and cardiovascular hospitalization rates compared with HFrEF, making a large clinical trial for these events in HFpEF more challenging.

Our review demonstrates that in multiple RCTs of SET in selected patients with chronic, stable HFpEF, exercise is safe and provides substantial, clinically relevant improvements in aerobic exercise capacity and quality of life. Surveys in older patients have shown that they value these as important outcomes, and these outcomes are considered to be appropriate end points for drug development by the US Food and Drug Administration. The magnitude of benefits on exercise capacity and quality of life appears comparable to or potentially greater than that for other cardiovascular conditions (eg, HFrEF, PAD) for which exercise-based therapies (eg, CR) are now typically covered by third-party payers such as Medicare. These findings highlight the importance of exercise-based therapies for chronic, stable HFpEF and for pursuing referral, adherence, and coverage efforts during implementation. Future research should focus on maximizing the benefits and accessibility of SET for chronic HFpEF; extending its availability to medically supervised group, home-based, and hybrid CR settings; and addressing common barriers to long-term adherence.

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