

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.

Vandana Sachdev, MD, Chair*†; Kavita Sharma, MD, Vice Chair; Steven J. Keteyian, PhD; Charina F. Alcaín, DNP, ACNP-BC; Patrice Desvigne-Nickens, MD†; Jerome L. Fleg, MD, FAHA†; Viorel G. Florea, MD, PhD; Barry A. Franklin, PhD, FAHA; Maya Guglin, MD, PhD; Martin Halle, MD; Eric S. Leifer, PhD†; Gurusher Panjra, MD, FAHA; Emily A. Tinsley, PhD†; Renee P. Wong, PhD†; Dalane W. Kitzman, MD, FAHA*; on behalf of the American Heart Association Heart Failure and Transplantation Committee of the Council on Clinical Cardiology; Council on Arteriosclerosis, Thrombosis and Vascular Biology; and American College of Cardiology

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

*V. Sachdev and D.W. Kitzman contributed equally.

†Disclaimer: The content of this manuscript is solely the responsibility of the authors and does not necessarily reflect the official views of the National Heart, Lung, and Blood Institute, National Institutes of Health, or the US Department of Health and Human Services.

Supplemental Material is available at <https://www.ahajournals.org/doi/suppl/10.1161/CIR.0000000000001122>.

© 2023 by the American Heart Association, Inc., and the American College of Cardiology Foundation.

Circulation is available at www.ahajournals.org/journal/circ

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 $\leq 35\%$ 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 guidelines²: HFrEF includes patients with an EF $\leq 40\%$; HF with mildly reduced EF (HFmrEF) includes those with an EF of 41% to 49% ; and HFpEF includes those with an EF $\geq 50\%$.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 life⁴ 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, $-0.4 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$; $P=0.38$),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 trial²⁹ (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 HF³⁰; 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 $\approx 30\%$ in patients with HFpEF compared with age-matched healthy individuals and is similar to that in age-matched patients with HFrEF ($13\text{--}14 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$).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 $\approx 50\%$ 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 exer-

cise 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 HF⁶⁰ 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}

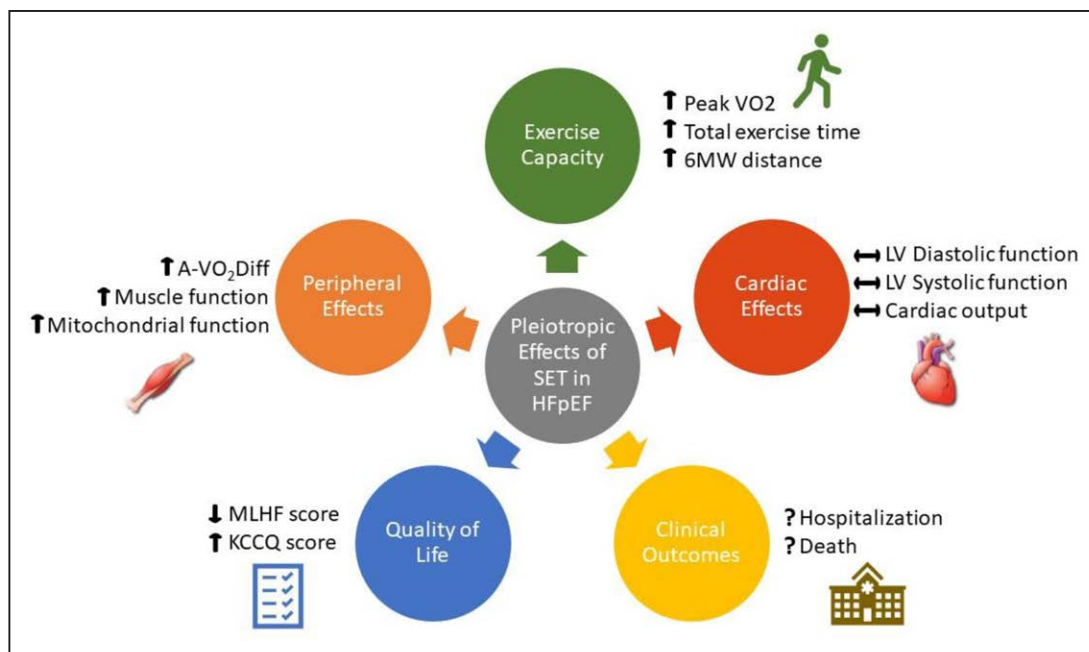


Figure 1. Pleiotropic effects of SET in chronic HFpEF.

A- VO_2Diff 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 HF⁷⁸ 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 $\dot{V}\text{O}_2$. Two of the studies did not have a control group,^{76,77} and 1 study did not have a peak $\dot{V}\text{O}_2$ 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 \geq 50%, NYHA II–III, age 70 \pm 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 \geq 50%, NYHA II–III, age 64 \pm 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 \geq 45%, NYHA II–III, age 67 \pm 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 \geq 50%, NYHA II–III, age 70 \pm 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 \geq 40%, NYHA II–III, age 67 \pm 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 \geq 50%, NYHA II–III, age 61 \pm 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 \geq 50%, NYHA II–III, age 67 \pm 6 y, 20% male, BMI \geq 30 kg/m ²	2 \times 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 \geq 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 \pm 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 \pm 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 \geq 50%, NYHA II–III, age 60 \pm 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 al⁹⁰ 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-Laird⁹² 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 $\geq 50\%$ 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 HFpEF,^{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 study⁷⁴ (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 $\geq 50\%$, 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.

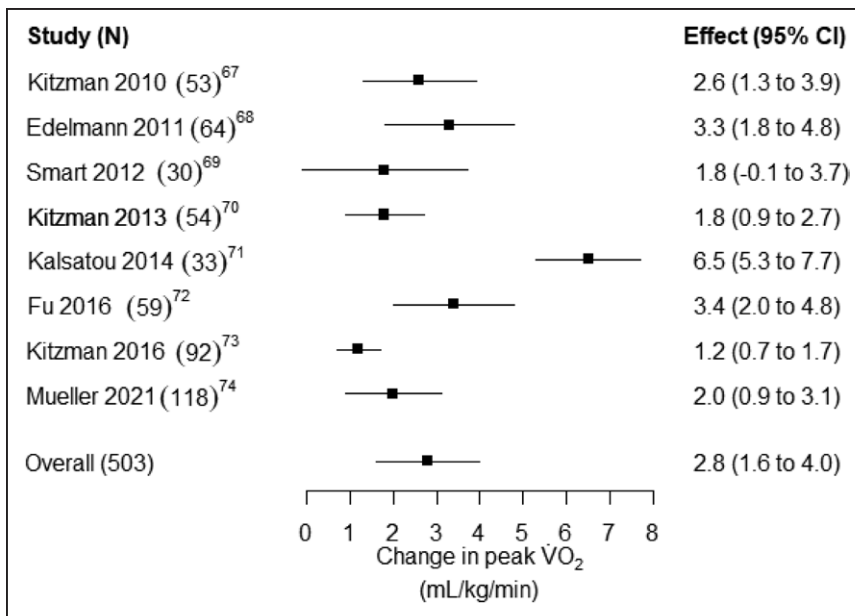


Figure 2. Forest plot of peak $\dot{V}O_2$ increase in randomized exercise training trials in chronic HFpEF. HFpEF indicates heart failure with preserved ejection fraction.

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 im-

proved 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 patients⁸⁶ 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.

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 $\dot{V}O_{2p}$, 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/m²) who were ≥60 years of age and randomized to caloric restriction, SET, both, or neither, Kitzman et al⁷³ 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 pre-specified, 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 hospitalizations¹⁰⁶ 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 ($0.6 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ [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 $\dot{V}O_2$ ($\approx 14\%$), 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 ($18.7\pm 17.6\%$ versus $-0.3\pm 15.4\%$; $P<0.001$).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.

Disclosures

Writing Group Disclosures

Writing group member	Employment	Research grant	Other research support	Speakers' bureau/honoraria	Expert witness	Ownership interest	Consultant/advisory board	Other
Vandana Sachdev	National Heart, Lung, and Blood Institute	None	None	None	None	None	None	None
Kavita Sharma	Johns Hopkins University School of Medicine	Amgen (research grant funding)†; AHA†	None	Amgen*; Bayer*; Janssen*	None	None	Alleviant (unpaid)*; AstraZeneca*; Bayer*; Boehringer-Ingelheim*; Novartis*; NovoNordisk*; RIVUS*	None
Charina F. Alcain	University of Chicago	None	None	None	None	None	None	None
Patrice Desvigne-Nickens	National Heart, Lung, and Blood Institute	None	None	None	None	None	None	None
Jerome L. Fleg	National Heart, Lung, and Blood Institute	None	None	None	None	None	None	None
Viorel G. Florea	Minneapolis VA Health Care System	None	None	None	None	None	None	None

(Continued)

ARTICLE INFORMATION

The American Heart Association and the American College of Cardiology make every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

This document was approved by the American Heart Association Science Advisory and Coordinating Committee September 12, 2022, and the American Heart Association Executive Committee September 26, 2022, and the American College of Cardiology Clinical Policy Approval Committee September 26, 2022.

The American Heart Association requests that this document be cited as follows: Sachdev V, Sharma K, Keteyian SJ, Alcain CF, Desvigne-Nickens P, Fleg JL, Florea VG, Franklin BA, Guglin M, Halle M, Leifer ES, Panjra G, Tinsley EA, Wong RP, Kitzman DW; on behalf of the American Heart Association Heart Failure and Transplantation Committee of the Council on Clinical Cardiology; Council on Arteriosclerosis, Thrombosis and Vascular Biology; and American College of Cardiology. Supervised exercise training for chronic heart failure with preserved ejection fraction: a scientific statement from the American Heart Association and American College of Cardiology. *Circulation*. 2023;147:e699–e715. doi: 10.1161/CIR.0000000000001122

This article has been copublished in the *Journal of the American College of Cardiology*.

Copies: This document is available on the websites of the American Heart Association (professional.heart.org) and the American College of Cardiology (www.acc.org). A copy of the document is also available at <https://professional.heart.org/statements> by selecting the "Guidelines & Statements" button. To purchase additional reprints, call 215-356-2721 or email Meredith.Edelman@wolterskluwer.com.

The expert peer review of AHA-commissioned documents (eg, scientific statements, clinical practice guidelines, systematic reviews) is conducted by the AHA Office of Science Operations. For more on AHA statements and guidelines development, visit <https://professional.heart.org/statements>. Select the "Guidelines & Statements" drop-down menu near the top of the webpage, then click "Publication Development."

Permissions: Multiple copies, modification, alteration, enhancement, and distribution of this document are not permitted without the express permission of the American Heart Association. Instructions for obtaining permission are located at <https://www.heart.org/permissions>. A link to the "Copyright Permissions Request Form" appears in the second paragraph (<https://www.heart.org/en/about-us/statements-and-policies/copyright-request-form>).

Writing Group Disclosures Continued

Writing group member	Employment	Research grant	Other research support	Speakers' bureau/honoraria	Expert witness	Ownership interest	Consultant/advisory board	Other
Barry A. Franklin	Beaumont Health Preventive Cardiology and Cardiac Rehabilitation	None	None	None	None	None	None	None
Maya Guglin	Indiana University	None	None	None	None	None	None	None
Martin Halle	Technische Universitaet Muenchen (Germany)	NIH (clinical trial)†	None	None	None	None	None	Medical Park Rehabilitation Group (medical supervisor)†
Steven J. Keteyian	Henry Ford Health	NIH (clinical trial)†	None	None	None	None	Abt, Inct	None
Dalane W. Kitzman	Wake Forest University School of Medicine	Novo Nordisk (clinical trial)†; NIH (funded clinical studies)†; Rivus (clinical trial)†; Pfizer (clinical study)†; Astra Zeneca (clinical study)†; Bayer (clinical study)†	None	None	None	None	NIH*; Novo Nordisk†; Rivust Boehringer-Ingelheim†; Astra Zenecat	None
Eric S. Leifer	National Heart, Lung, and Blood Institute	None	None	None	None	None	None	None
Gurusher Panjra	George Washington University	None	None	None	Defendant†	None	None	None
Emily A. Tinsley	National Heart, Lung, and Blood Institute	None	None	None	None	None	None	None
Renee P. Wong	National Heart, Lung, and Blood Institute	None	None	None	None	None	None	None

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives \$5000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns \$5000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

Reviewer Disclosures

Reviewer	Employment	Research grant	Other research support	Speakers' bureau/honoraria	Expert witness	Ownership interest	Consultant/advisory board	Other
Susan D'Anna	Dartmouth Hitchcock Medical Center	None	None	None	None	None	None	None
Nasrien Ibrahim	Massachusetts General Hospital	None	None	None	None	None	None	None
Richard Josephson	University Hospitals	None	None	None	None	None	None	None
Ran Lee	Cleveland Clinic Foundation	None	None	None	None	None	None	None
Ambarish Pandey	University of Texas Southwestern Medical Center	None	None	None	None	None	None	None
David Whellan	Thomas Jefferson University	None	None	None	None	None	None	None

This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives \$5000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns \$5000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

REFERENCES

1. Bozkurt B, Coats AJ, Tsutsui H, Abdelhamid M, Adamopoulos S, Albert N, Anker SD, Atherton J, Bohm M, Butler J, et al. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. *J Card Fail.* 2021;27:P387–P413. doi: 10.1016/j.cardfail.2021.01.022
2. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, Deswal A, Drazner MH, Dunlay SM, Evers LR, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines [published corrections appear in *Circulation.* 2022;145:e1033 and *Circulation.* 2022;146:e185]. *Circulation.* 2022;145:e895–e1032. doi: 10.1161/CIR.0000000000001063
3. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Delling FN, et al; American Heart

Downloaded from http://ahajournals.org by on March 26, 2024

Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2020 update: a report from the American Heart Association. *Circulation*. 2020;141:e139–e596. doi: 10.1161/CIR.0000000000000757

4. Upadhyia B, Pisani B, Kitzman DW. Evolution of a geriatric syndrome: pathophysiology and treatment of heart failure with preserved ejection fraction. *J Am Geriatr Soc*. 2017;65:2431–2440. doi: 10.1111/jgs.15141
5. Sharma K, Kass DA. Heart failure with preserved ejection fraction: mechanisms, clinical features, and therapies. *Circ Res*. 2014;115:79–96. doi: 10.1161/CIRCRESAHA.115.302922
6. Pandey A, Shah SJ, Butler J, Kellogg DL Jr, Lewis GD, Forman DE, Mentz RJ, Borlaug BA, Simon MA, Chirinos JA, et al. Exercise intolerance in older adults with heart failure with preserved ejection fraction: JACC state-of-the-art review. *J Am Coll Cardiol*. 2021;78:1166–1187. doi: 10.1016/j.jacc.2021.07.014
7. Shah SJ, Borlaug BA, Kitzman DW, McCulloch AD, Blaxall BC, Agarwal R, Chirinos JA, Collins S, Deo RC, Gladwin MT, et al. Research priorities for heart failure with preserved ejection fraction: National Heart, Lung, and Blood Institute Working Group summary. *Circulation*. 2020;141:1001–1026. doi: 10.1161/CIRCULATIONAHA.119.041886
8. Steinberg BA, Zhao X, Heidenreich PA, Peterson ED, Bhatt DL, Cannon CP, Hernandez AF, Fonarow GC; Get With The Guidelines Scientific Advisory Committee and Investigators. Trends in patients hospitalized with heart failure and preserved left ventricular ejection fraction: prevalence, therapies, and outcomes. *Circulation*. 2012;126:65–75. doi: 10.1161/CIRCULATIONAHA.111.080770
9. Kitzman DW. Outcomes in patients with heart failure with preserved ejection fraction: it is more than the heart. *J Am Coll Cardiol*. 2012;59:1006–1007. doi: 10.1016/j.jacc.2011.12.011
10. Shah SJ, Kitzman DW, Borlaug BA, van Heerebeek L, Zile MR, Kass DA, Paulus WJ. Phenotype-specific treatment of heart failure with preserved ejection fraction: a multiorgan roadmap. *Circulation*. 2016;134:73–90. doi: 10.1161/CIRCULATIONAHA.116.021884
11. Upadhyia B, Rocco M, Lewis CE, Oparil S, Lovato LC, Cushman WC, Bates JT, Bello NA, Aurigemma G, Fine LJ, et al; SPRINT Research Group. Effect of intensive blood pressure treatment on heart failure events in the Systolic Blood Pressure Reduction Intervention Trial. *Circ Heart Fail*. 2017;10:e003613. doi: 10.1161/CIRCHEARTFAILURE.116.003613
12. Pandey A, Patel KV, Vaduganathan M, Sarma S, Haykowsky MJ, Berry JD, Lavie CJ. Physical activity, fitness, and obesity in heart failure with preserved ejection fraction. *JACC Heart Fail*. 2018;6:975–982. doi: 10.1016/j.jchf.2018.09.006
13. Kitzman DW, Nicklas BJ. Pivotal role of excess intra-abdominal adipose in the pathogenesis of metabolic/obese HFpEF. *JACC Heart Fail*. 2018;6:1008–1010. doi: 10.1016/j.jchf.2018.08.007
14. Hwang SJ, Melenovsky V, Borlaug BA. Implications of coronary artery disease in heart failure with preserved ejection fraction. *J Am Coll Cardiol*. 2014;63(pt A):2817–2827. doi: 10.1016/j.jacc.2014.03.034
15. Bekfani T, Pellicori P, Morris DA, Ebner N, Valentova M, Steinbeck L, Wachter R, Elsner S, Slizuk V, Scheffold JC, et al. Sarcopenia in patients with heart failure with preserved ejection fraction: impact on muscle strength, exercise capacity and quality of life. *Int J Cardiol*. 2016;222:41–46. doi: 10.1016/j.ijcard.2016.07.135
16. Sanders NA, Supiano MA, Lewis EF, Liu J, Claggett B, Pfeffer MA, Desai AS, Sweitzer NK, Solomon SD, Fang JC. The frailty syndrome and outcomes in the TOPCAT trial. *Eur J Heart Fail*. 2018;20:1570–1577. doi: 10.1002/ehf.1308
17. Pandey A, LaMonte M, Klein L, Ayers C, Psaty BM, Eaton CB, Allen NB, de Lemos JA, Carnethon M, Greenland P, et al. Relationship between physical activity, body mass index, and risk of heart failure. *J Am Coll Cardiol*. 2017;69:1129–1142. doi: 10.1016/j.jacc.2016.11.081
18. Pandey A, Patel KV, Bahnson JL, Gaussoin SA, Martin CK, Balasubramanyam A, Johnson KC, McGuire DK, Bertoni AG, Kitzman D, et al; Look AHEAD Research Group. Association of intensive lifestyle intervention, fitness, and body mass index with risk of heart failure in overweight or obese adults with type 2 diabetes mellitus: an analysis from the Look AHEAD trial. *Circulation*. 2020;141:1295–1306. doi: 10.1161/CIRCULATIONAHA.119.044865
19. Mentz RJ, Whellan DJ, Reeves GR, Pastva AM, Duncan P, Upadhyia B, Nelson MB, Chen H, Reed SD, Rosenberg PB, et al. Rehabilitation intervention in older patients with acute heart failure with preserved versus reduced ejection fraction. *JACC Heart Fail*. 2021;9:747–757. doi: 10.1016/j.jchf.2021.05.007
20. Warraich HJ, Kitzman DW, Whellan DJ, Duncan PW, Mentz RJ, Pastva AM, Nelson MB, Upadhyia B, Reeves GR. Physical function, frailty, cognition, depression, and quality of life in hospitalized adults ≥ 60 years with acute decompensated heart failure with preserved versus reduced ejection fraction. *Circ Heart Fail*. 2018;11:e005254. doi: 10.1161/CIRCHEARTFAILURE.118.005254
21. US Food and Drug Administration. Treatment for heart failure: endpoints for drug development guidance for industry. 2019. Accessed September 21, 2022. <https://www.fda.gov/media/128372/download>
22. Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, Martinez F, Packer M, Pfeffer MA, Pieske B, et al; PARAGON-HF Investigators and Committees. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med*. 2019;381:1609–1620. doi: 10.1056/NEJMoa1908655
23. Pfeffer MA, Claggett B, Assmann SF, Boineau R, Anand IS, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, et al. Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial. *Circulation*. 2015;131:34–42. doi: 10.1161/CIRCULATIONAHA.114.013255
24. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, Brunner-La Rocca HP, Choi DJ, Chopra V, Chuquiuire-Valenzuela E, et al; EMPEROR-Preserved Trial Investigators. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med*. 2021;385:1451–1461. doi: 10.1056/NEJMoa2107038
25. Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF, Inzucchi SE, Kosiborod MN, Lam CSP, Martinez F, et al; DELIVER Trial Committees and Investigators. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. *N Engl J Med*. 2022;387:1089–1098. doi: 10.1056/NEJMoa2206286
26. Upadhyia B, Hundley WG, Brubaker PH, Morgan TM, Stewart KP, Kitzman DW. Effect of spironolactone on exercise tolerance and arterial function in older adults with heart failure with preserved ejection fraction. *J Am Geriatr Soc*. 2017;65:2374–2382. doi: 10.1111/jgs.14940
27. Pieske B, Wachter R, Shah SJ, Baldrige A, Szczepoedy P, Ibram G, Shi V, Zhao Z, Cowie MR; PARALLAX Investigators and Committee Members. Effect of sacubitril/valsartan vs standard medical therapies on plasma NT-proBNP concentration and submaximal exercise capacity in patients with heart failure and preserved ejection fraction: the PARALLAX randomized clinical trial. *JAMA*. 2021;326:1919–1929. doi: 10.1001/jama.2021.18463
28. Abraham WT, Lindenfeld J, Ponikowski P, Agostoni P, Butler J, Desai AS, Filippatos G, Gniot J, Fu M, Gullestad L, et al. Effect of empagliflozin on exercise ability and symptoms in heart failure patients with reduced and preserved ejection fraction, with and without type 2 diabetes. *Eur Heart J*. 2021;42:700–710. doi: 10.1093/eurheartj/ehaa943
29. Nassif ME, Windsor SL, Borlaug BA, Kitzman DW, Shah SJ, Tang F, Khariton Y, Malik AO, Khumri T, Umpierrez G, et al. The SGLT2 inhibitor dapagliflozin in heart failure with preserved ejection fraction: a multicenter randomized trial. *Nat Med*. 2021;27:1954–1960. doi: 10.1038/s41591-021-01536-x
30. Abraham WT, Adamson PB, Bourge RC, Aaron MF, Costanzo MR, Stevenson LW, Strickland W, Neelagaru S, Raval N, Krueger S, et al; CHAMPION Trial Study Group. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. *Lancet*. 2011;377:658–666. doi: 10.1016/S0140-6736(11)60101-3
31. Adamson PB, Abraham WT, Bourge RC, Costanzo MR, Hasan A, Yadav C, Henderson J, Cowart P, Stevenson LW. Wireless pulmonary artery pressure monitoring guides management to reduce decompensation in heart failure with preserved ejection fraction. *Circ Heart Fail*. 2014;7:935–944. doi: 10.1161/CIRCHEARTFAILURE.113.001229
32. Shah SJ, Borlaug BA, Chung ES, Cutlip DE, Debonnaire P, Fail PS, Gao Q, Hasenfuß G, Kahwash R, Kaye DM, et al; REDUCE LAP-HF II Investigators. Atrial shunt device for heart failure with preserved and mildly reduced ejection fraction (REDUCE LAP-HF II): a randomised, multicentre, blinded, sham-controlled trial. *Lancet*. 2022;399:1130–1140. doi: 10.1016/S0140-6736(22)00016-2
33. Borlaug BA, Blair J, Bergmann MW, Bugger H, Burkhoff D, Bruch L, Celermajer DS, Claggett B, Cleland JGF, Cutlip DE, et al; REDUCE LAP-HF-II Investigators. Latent pulmonary vascular disease may alter the response to therapeutic atrial shunt device in heart failure. *Circulation*. 2022;145:1592–1604. doi: 10.1161/CIRCULATIONAHA.122.059486
34. Scott JM, Haykowsky MJ, Eggebeen J, Morgan TM, Brubaker PH, Kitzman DW. Reliability of peak exercise testing in patients with heart failure with preserved ejection fraction. *Am J Cardiol*. 2012;110:1809–1813. doi: 10.1016/j.amjcard.2012.08.015
35. Kitzman DW, Little WC, Brubaker PH, Anderson RT, Hundley WG, Marburger CT, Brosnihan B, Morgan TM, Stewart KP. Pathophysiological characterization of isolated diastolic heart failure in comparison to systolic heart failure. *JAMA*. 2002;288:2144–2150. doi: 10.1001/jama.288.17.2144

36. Nayor M, Houstis NE, Namasivayam M, Rouvina J, Hardin C, Shah RV, Ho JE, Malhotra R, Lewis GD. Impaired exercise tolerance in heart failure with preserved ejection fraction: quantification of multiorgan system reserve capacity. *JACC Heart Fail*. 2020;8:605–617. doi: 10.1016/j.jchf.2020.03.008
37. Shafiq A, Brawner CA, Aldred HA, Lewis B, Williams CT, Tita C, Schairer JR, Ehrman JK, Velez M, Selektor Y, et al. Prognostic value of cardiopulmonary exercise testing in heart failure with preserved ejection fraction: the Henry Ford Hospital CardioPulmonary EXercise Testing (FIT-CPX) project. *Am Heart J*. 2016;174:167–172. doi: 10.1016/j.ahj.2015.12.020
38. Nadruz W Jr, West E, Sengelov M, Santos M, Groarke JD, Forman DE, Claggett B, Skali H, Shah AM. Prognostic value of cardiopulmonary exercise testing in heart failure with reduced, midrange, and preserved ejection fraction. *J Am Heart Assoc*. 2017;6:e006000. doi: 10.1161/JAHA.117.006000
39. Swank AM, Horton J, Fleg JL, Fonarow GC, Keteyian S, Goldberg L, Wolfel G, Handberg EM, Bensimhon D, Illiuc MC, et al; HF-ACTION Investigators. Modest increase in peak $\dot{V}O_2$ is related to better clinical outcomes in chronic heart failure patients: results from Heart Failure and a Controlled Trial to Investigate Outcomes of Exercise Training. *Circ Heart Fail*. 2012;5:579–585. doi: 10.1161/CIRCHEARTFAILURE.111.965186
40. Guazzi M, Dickstein K, Vicenzi M, Arena R. Six-minute walk test and cardiopulmonary exercise testing in patients with chronic heart failure: a comparative analysis on clinical and prognostic insights. *Circ Heart Fail*. 2009;2:549–555. doi: 10.1161/CIRCHEARTFAILURE.109.881326
41. O'Connor CM, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ, Leifer ES, Kraus WE, Kitzman DW, Blumenthal JA, et al; HF-ACTION Investigators. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA*. 2009;301:1439–1450. doi: 10.1001/jama.2009.454
42. Keteyian SJ, Ehrman JK, Fuller B, Pack QR. Exercise testing and exercise rehabilitation for patients with atrial fibrillation. *J Cardiopulm Rehabil Prev*. 2019;39:65–72. doi: 10.1097/HCR.0000000000000423
43. Obokata M, Reddy YNV, Pislaru SV, Melenovsky V, Borlaug BA. Evidence supporting the existence of a distinct obese phenotype of heart failure with preserved ejection fraction. *Circulation*. 2017;136:6–19. doi: 10.1161/CIRCULATIONAHA.116.026807
44. Haykowsky MJ, Brubaker PH, John JM, Stewart KP, Morgan TM, Kitzman DW. Determinants of exercise intolerance in elderly heart failure patients with preserved ejection fraction. *J Am Coll Cardiol*. 2011;58:265–274. doi: 10.1016/j.jacc.2011.02.055
45. Pandey A, Khera R, Park B, Haykowsky M, Borlaug BA, Lewis GD, Kitzman DW, Butler J, Berry JD. Relative impairments in hemodynamic exercise reserve parameters in heart failure with preserved ejection fraction: a study-level pooled analysis. *JACC Heart Fail*. 2018;6:117–126. doi: 10.1016/j.jchf.2017.10.014
46. Kitzman DW, Guazzi M. Impaired alveolar capillary membrane diffusion: a recently recognized contributor to exertional dyspnea in heart failure with preserved ejection fraction. *JACC Heart Fail*. 2016;4:499–501. doi: 10.1016/j.jchf.2016.03.020
47. Kitzman DW, Haykowsky MJ. Vascular dysfunction in heart failure with preserved ejection fraction. *J Card Fail*. 2016;22:12–16. doi: 10.1016/j.cardfail.2015.11.004
48. Hundley WG, Kitzman DW, Morgan TM, Hamilton CA, Darty SN, Stewart KP, Herrington DM, Link KM, Little WC. Cardiac cycle-dependent changes in aortic area and distensibility are reduced in older patients with isolated diastolic heart failure and correlate with exercise intolerance. *J Am Coll Cardiol*. 2001;38:796–802. doi: 10.1016/s0735-1097(01)01447-4
49. Haykowsky MJ, Herrington DM, Brubaker PH, Morgan TM, Hundley WG, Kitzman DW. Relationship of flow-mediated arterial dilation and exercise capacity in older patients with heart failure and preserved ejection fraction. *J Gerontol A Biol Sci Med Sci*. 2013;68:161–167. doi: 10.1093/gerona/gjs099
50. Hundley WG, Bayram E, Hamilton CA, Hamilton EA, Morgan TM, Darty SN, Stewart KP, Link KM, Herrington DM, Kitzman DW. Leg flow-mediated arterial dilation in elderly patients with heart failure and normal left ventricular ejection fraction. *Am J Physiol Heart Circ Physiol*. 2007;292:H1427–H1434. doi: 10.1152/ajpheart.00567.2006
51. Mohammed SF, Majure DT, Redfield MM. Zooming in on the microvasculature in heart failure with preserved ejection fraction. *Circ Heart Fail*. 2016;9:e003272. doi: 10.1161/CIRCHEARTFAILURE.116.003272
52. Dhakal BP, Malhotra R, Murphy RM, Pappagianopoulos PP, Baggish AL, Weiner RB, Houstis NE, Eisman AS, Hough SS, Lewis GD. Mechanisms of exercise intolerance in heart failure with preserved ejection fraction: the role of abnormal peripheral oxygen extraction. *Circ Heart Fail*. 2015;8:286–294. doi: 10.1161/CIRCHEARTFAILURE.114.001825
53. Haykowsky MJ, Tomczak CR, Scott JM, Paterson DI, Kitzman DW. Determinants of exercise intolerance in patients with heart failure and reduced or preserved ejection fraction. *J Appl Physiol (1985)*. 2015;119:739–744. doi: 10.1152/jappphysiol.00049.2015
54. Haykowsky MJ, Brubaker PH, Morgan TM, Kritchevsky S, Eggebeen J, Kitzman DW. Impaired aerobic capacity and physical functional performance in older heart failure patients with preserved ejection fraction: role of lean body mass. *J Gerontol A Biol Sci Med Sci*. 2013;68:968–975. doi: 10.1093/gerona/glt011
55. Kitzman DW, Nicklas B, Kraus WE, Lyles MF, Eggebeen J, Morgan TM, Haykowsky M. Skeletal muscle abnormalities and exercise intolerance in older patients with heart failure and preserved ejection fraction. *Am J Physiol Heart Circ Physiol*. 2014;306:H1364–H1370. doi: 10.1152/ajpheart.00004.2014
56. Molina AJ, Bharadwaj MS, Van Horn C, Nicklas BJ, Lyles MF, Eggebeen J, Haykowsky MJ, Brubaker PH, Kitzman DW. Skeletal muscle mitochondrial content, oxidative capacity, and mfn2 expression are reduced in older patients with heart failure and preserved ejection fraction and are related to exercise intolerance. *JACC Heart Fail*. 2016;4:636–645. doi: 10.1016/j.jchf.2016.03.011
57. Bhella PS, Prasad A, Heinicke K, Hastings JL, Arbab-Zadeh A, Adams-Huet B, Pacini EL, Shibata S, Palmer MD, Newcomer BR, et al. Abnormal haemodynamic response to exercise in heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2011;13:1296–1304. doi: 10.1093/eurjhf/hfr133
58. Haykowsky MJ, Kouba EJ, Brubaker PH, Nicklas BJ, Eggebeen J, Kitzman DW. Skeletal muscle composition and its relation to exercise intolerance in older patients with heart failure and preserved ejection fraction. *Am J Cardiol*. 2014;113:1211–1216. doi: 10.1016/j.amjcard.2013.12.031
59. Weiss K, Schär M, Panjath GS, Zhang Y, Sharma K, Bottomley PA, Golozar A, Steinberg A, Gerstenblith G, Russell SD, et al. Fatigability, exercise intolerance, and abnormal skeletal muscle energetics in heart failure. *Circ Heart Fail*. 2017;10:e004129. doi: 10.1161/CIRCHEARTFAILURE.117.004129
60. Middlekauff HR. Making the case for skeletal myopathy as the major limitation of exercise capacity in heart failure. *Circ Heart Fail*. 2010;3:537–546. doi: 10.1161/CIRCHEARTFAILURE.109.903773
61. Kitzman DW, Haykowsky MJ, Tomczak CR. Making the case for skeletal muscle myopathy and its contribution to exercise intolerance in heart failure with preserved ejection fraction. *Circ Heart Fail*. 2017;10:e004281. doi: 10.1161/CIRCHEARTFAILURE.117.004281
62. Roberts WC. An agent with lipid-lowering, antihypertensive, positive inotropic, negative chronotropic, vasodilating, diuretic, anorexigenic, weight-reducing, cathartic, hypoglycemic, tranquilizing, hypnotic and antidepressant qualities. *Am J Cardiol*. 1984;53:261–262. doi: 10.1016/0002-9149(84)90725-2
63. Fleg JL, Cooper LS, Borlaug BA, Haykowsky MJ, Kraus WE, Levine BD, Pfeffer MA, Piña IL, Poole DC, Reeves GR, et al; National Heart, Lung, and Blood Institute Working Group. Exercise training as therapy for heart failure: current status and future directions. *Circ Heart Fail*. 2015;8:209–220. doi: 10.1161/CIRCHEARTFAILURE.113.001420
64. Coats AJ, Forman DE, Haykowsky M, Kitzman DW, McNeil A, Campbell TS, Arena R. Physical function and exercise training in older patients with heart failure. *Nat Rev Cardiol*. 2017;14:550–559. doi: 10.1038/nrcardio.2017.70
65. Haykowsky MJ, Brubaker PH, Stewart KP, Morgan TM, Eggebeen J, Kitzman DW. Effect of endurance training on the determinants of peak exercise oxygen consumption in elderly patients with stable compensated heart failure and preserved ejection fraction. *J Am Coll Cardiol*. 2012;60:120–128. doi: 10.1016/j.jacc.2012.02.055
66. Tucker WJ, Angadi SS, Haykowsky MJ, Nelson MD, Sarma S, Tomczak CR. Pathophysiology of exercise intolerance and its treatment with exercise-based cardiac rehabilitation in heart failure with preserved ejection fraction. *J Cardiopulm Rehabil Prev*. 2020;40:9–16. doi: 10.1097/HCR.0000000000000481
67. Kitzman DW, Brubaker PH, Morgan TM, Stewart KP, Little WC. Exercise training in older patients with heart failure and preserved ejection fraction: a randomized, controlled, single-blind trial. *Circ Heart Fail*. 2010;3:659–667. doi: 10.1161/CIRCHEARTFAILURE.110.958785
68. Edelmann F, Gelbrich G, Dungen HD, Fröhling S, Wachter R, Stahrenberg R, Binder L, Töpper A, Lashki DJ, Schwarz S, et al. Exercise training improves exercise capacity and diastolic function in patients with heart failure with preserved ejection fraction: results of the Ex-DHF (Exercise training in Diastolic Heart Failure) pilot study. *J Am Coll Cardiol*. 2011;58:1780–1791. doi: 10.1016/j.jacc.2011.06.054
69. Smart NA, Haluska B, Jeffriess L, Leung D. Exercise training in heart failure with preserved systolic function: a randomized controlled trial of the

- effects on cardiac function and functional capacity. *Congest Heart Fail* 2012;18:295–301. doi: 10.1111/j.1751-7133.2012.00295.x
70. Kitzman DW, Brubaker PH, Herrington DM, Morgan TM, Stewart KP, Hundley WG, Abdelhamed A, Haykowsky MJ. Effect of endurance exercise training on endothelial function and arterial stiffness in older patients with heart failure and preserved ejection fraction: a randomized, controlled, single-blind trial. *J Am Coll Cardiol*. 2013;62:584–592. doi: 10.1016/j.jacc.2013.04.033
 71. Kaltsatou AC, Kouidi EI, Anifanti MA, Douka SI, Deligiannis AP. Functional and psychosocial effects of either a traditional dancing or a formal exercising training program in patients with chronic heart failure: a comparative randomized controlled study. *Clin Rehabil*. 2014;28:128–138. doi: 10.1177/0269215513492988
 72. Fu TC, Yang NI, Wang CH, Cherng WJ, Chou SL, Pan TL, Wang JS. Aerobic interval training elicits different hemodynamic adaptations between heart failure patients with preserved and reduced ejection fraction. *Am J Phys Med Rehabil*. 2016;95:15–27. doi: 10.1097/PHM.0000000000000312
 73. Kitzman DW, Brubaker P, Morgan T, Haykowsky M, Hundley G, Kraus WE, Eggebeen J, Nicklas BJ. Effect of caloric restriction or aerobic exercise training on peak oxygen consumption and quality of life in obese older patients with heart failure with preserved ejection fraction: a randomized clinical trial. *JAMA*. 2016;315:36–46. doi: 10.1001/jama.2015.17346
 74. Mueller S, Winzer EB, Duvinage A, Gevaert AB, Edelmann F, Haller B, Pieske-Kraigher E, Beckers P, Bobenko A, Hommel J, et al; OptimEx-Clin Study Group. Effect of high-intensity interval training, moderate continuous training, or guideline-based physical activity advice on peak oxygen consumption in patients with heart failure with preserved ejection fraction: a randomized clinical trial. *JAMA*. 2021;325:542–551. doi: 10.1001/jama.2020.26812
 75. Alves AJ, Ribeiro F, Goldhammer E, Rivlin Y, Rosenschein U, Viana JL, Duarte JA, Sagiv M, Oliveira J. Exercise training improves diastolic function in heart failure patients. *Med Sci Sports Exerc*. 2012;44:776–785. doi: 10.1249/MSS.0b013e31823cd16a
 76. Angadi SS, Mookadam F, Lee CD, Tucker WJ, Haykowsky MJ, Gaesser GA. High-intensity interval training vs. moderate-intensity continuous exercise training in heart failure with preserved ejection fraction: a pilot study. *J Appl Physiol (1985)*. 2015;119:753–758. doi: 10.1152/jappphysiol.00518.2014
 77. Donelli da Silveira A, Beust de Lima J, da Silva Piardi D, Dos Santos Macedo D, Zanini M, Nery R, Laukkanen JA, Stein R. High-intensity interval training is effective and superior to moderate continuous training in patients with heart failure with preserved ejection fraction: a randomized clinical trial. *Eur J Prev Cardiol*. 2020;27:1733–1743. doi: 10.1177/2047487319901206
 78. Long L, Mordi IR, Bridges C, Sagar VA, Davies EJ, Coats AJ, Dalal H, Rees K, Singh SJ, Taylor RS. Exercise-based cardiac rehabilitation for adults with heart failure. *Cochrane Database Syst Rev*. 2019;1:CD003331. doi: 10.1002/14651858.CD003331.pub5
 79. Pandey A, Parashar A, Kumbhani D, Agarwal S, Garg J, Kitzman D, Levine B, Drazner M, Berry J. Exercise training in patients with heart failure and preserved ejection fraction: meta-analysis of randomized control trials. *Circ Heart Fail*. 2015;8:33–40. doi: 10.1161/CIRCHEARTFAILURE.114.001615
 80. Gomes-Neto M, Durães AR, Conceição LSR, Roever L, Liu T, Tse G, Biondi-Zoccai G, Goes ALB, Alves IGN, Ellingsen Ø, et al. Effect of aerobic exercise on peak oxygen consumption, VE/VCO₂ slope, and health-related quality of life in patients with heart failure with preserved left ventricular ejection fraction: a systematic review and meta-analysis. *Curr Atheroscler Rep*. 2019;21:45. doi: 10.1007/s11883-019-0806-6
 81. Fukuta H, Goto T, Wakami K, Kamiya T, Ohte N. Effects of exercise training on cardiac function, exercise capacity, and quality of life in heart failure with preserved ejection fraction: a meta-analysis of randomized controlled trials. *Heart Fail Rev*. 2019;24:535–547. doi: 10.1007/s10741-019-09774-5
 82. Leggio M, Fusco A, Loreti C, Limongelli G, Bendini MG, Mazza A, Coraci D, Padua L. Effects of exercise training in heart failure with preserved ejection fraction: an updated systematic literature review. *Heart Fail Rev*. 2020;25:703–711. doi: 10.1007/s10741-019-09841-x
 83. Upadhyia B, Haykowsky MJ, Kitzman DW. Therapy for heart failure with preserved ejection fraction: current status, unique challenges, and future directions. *Heart Fail Rev*. 2018;23:609–629. doi: 10.1007/s10741-018-9714-z
 84. Reeves GR, Whellan DJ, Patel MJ, O'Connor CM, Duncan P, Eggebeen JD, Morgan TM, Hewston LA, Pastva AM, Kitzman DW. Comparison of frequency of frailty and severely impaired physical function in patients ≥60 years hospitalized with acute decompensated heart failure versus chronic stable heart failure with reduced and preserved left ventricular ejection fraction. *Am J Cardiol*. 2016;117:1953–1958. doi: 10.1016/j.amjcard.2016.03.046
 85. Reeves GR, Whellan DJ, O'Connor CM, Duncan P, Eggebeen JD, Morgan TM, Hewston LA, Pastva A, Patel MJ, Kitzman DW. A novel rehabilitation intervention for older patients with acute decompensated heart failure: the REHAB-HF pilot study. *JACC Heart Fail*. 2017;5:359–366. doi: 10.1016/j.jchf.2016.12.019
 86. Lang CC, Smith K, Wingham J, Eyre V, Greaves CJ, Warren FC, Green C, Jolly K, Davis RC, Doherty PJ, et al; REACH-HF Investigators. A randomised controlled trial of a facilitated home-based rehabilitation intervention in patients with heart failure with preserved ejection fraction and their caregivers: the REACH-HFpEF pilot study. *BMJ Open*. 2018;8:e019649. doi: 10.1136/bmjopen-2017-019649
 87. Palau P, Domínguez E, Núñez E, Schmid JP, Vergara P, Ramón JM, Mascarell B, Sanchis J, Chorro FJ, Núñez J. Effects of inspiratory muscle training in patients with heart failure with preserved ejection fraction. *Eur J Prev Cardiol*. 2014;21:1465–1473. doi: 10.1177/2047487313498832
 88. Andryukhin A, Frolova E, Vaes B, Degryse J. The impact of a nurse-led care programme on events and physical and psychosocial parameters in patients with heart failure with preserved ejection fraction: a randomized clinical trial in primary care in Russia. *Eur J Gen Pract*. 2010;16:205–214. doi: 10.3109/13814788.2010.527938
 89. Palau P, Domínguez E, López L, Ramón JM, Heredia R, González J, Santas E, Bodí V, Miñana G, Valero E, et al. Inspiratory muscle training and functional electrical stimulation for treatment of heart failure with preserved ejection fraction: the TRAINING-HF trial. *Rev Esp Cardiol (Engl Ed)*. 2019;72:288–297. doi: 10.1016/j.rec.2018.01.010
 90. Forman DE, Arena R, Boxer R, Dolansky MA, Eng JJ, Fleg JL, Haykowsky M, Jahangir A, Kaminsky LA, Kitzman DW, et al; on behalf of the American Heart Association Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; Council on Quality of Care and Outcomes Research; and Stroke Council. Prioritizing functional capacity as a principal end point for therapies oriented to older adults with cardiovascular disease: a scientific statement for healthcare professionals from the American Heart Association. *Circulation*. 2017;135:e894–e918. doi: 10.1161/CIR.0000000000000483
 91. Stanek EJ, Oates MB, McGhan WF, Denofrio D, Loh E. Preferences for treatment outcomes in patients with heart failure: symptoms versus survival. *J Card Fail*. 2000;6:225–232. doi: 10.1054/jcaf.2000.9503
 92. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177–188. doi: 10.1016/0197-2456(86)90046-2
 93. Dieberg G, Ismail H, Giallauria F, Smart NA. Clinical outcomes and cardiovascular responses to exercise training in heart failure patients with preserved ejection fraction: a systematic review and meta-analysis. *J Appl Physiol (1985)*. 2015;119:726–733. doi: 10.1152/jappphysiol.00904.2014
 94. Chan E, Giallauria F, Vigorito C, Smart NA. Exercise training in heart failure patients with preserved ejection fraction: a systematic review and meta-analysis. *Monaldi Arch Chest Dis*. 2016;86:759. doi: 10.4081/monaldi.2016.759
 95. Keteyian SJ, Brawner CA, Ehrman JK, Ivanhoe R, Boehmer JP, Abraham WT; PEERLESS-HF Trial Investigators. Reproducibility of peak oxygen uptake and other cardiopulmonary exercise parameters: implications for clinical trials and clinical practice. *Chest*. 2010;138:950–955. doi: 10.1378/chest.09-2624
 96. Pandey A, Kitzman DW. Searching for the optimal exercise training regimen in heart failure with preserved ejection fraction. *JAMA*. 2021;325:537–539. doi: 10.1001/jama.2020.26347
 97. Fujimoto N, Prasad A, Hastings JL, Bhella PS, Shibata S, Palmer D, Levine BD. Cardiovascular effects of 1 year of progressive endurance exercise training in patients with heart failure with preserved ejection fraction. *Am Heart J*. 2012;164:869–877. doi: 10.1016/j.ahj.2012.06.028
 98. Franklin BA, Brinks J, Sacks R, Trivax J, Friedman H. Reduced walking speed and distance as harbingers of the approaching grim reaper. *Am J Cardiol*. 2015;116:313–317. doi: 10.1016/j.amjcard.2015.04.024
 99. Keteyian SJ, Brawner CA, Savage PD, Ehrman JK, Schairer J, Divine G, Aldred H, Ophaug K, Ades PA. Peak aerobic capacity predicts prognosis in patients with coronary heart disease. *Am Heart J*. 2008;156:292–300. doi: 10.1016/j.ahj.2008.03.017
 100. Franklin BA, Thompson PD, Al-Zaiti SS, Albert CM, Hivert MF, Levine BD, Lobelo F, Madan K, Sharrief AZ, Eijsvogels TMH; on behalf of the American Heart Association Physical Activity Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; and Stroke Council. Exercise-related acute cardiovascular events and potential deleterious adaptations following long-term exercise training: placing the risks into perspective—an update:

- a scientific statement from the American Heart Association. *Circulation*. 2020;141:e705–e736. doi: 10.1161/CIR.0000000000000749
101. Keteyian SJ, Squires RW, Ades PA, Thomas RJ. Incorporating patients with chronic heart failure into outpatient cardiac rehabilitation: practical recommendations for exercise and self-care counseling—a clinical review. *J Cardiopulm Rehabil Prev*. 2014;34:223–232. doi: 10.1097/HCR.000000000000073
 102. Thomas RJ, Beatty AL, Beckie TM, Brewer LC, Brown TM, Forman DE, Franklin BA, Keteyian SJ, Kitzman DW, Regensteiner JG, et al. Home-based cardiac rehabilitation: a scientific statement from the American Association of Cardiovascular and Pulmonary Rehabilitation, the American Heart Association, and the American College of Cardiology. *Circulation*. 2019;140:e69–e89. doi: 10.1161/CIR.0000000000000663
 103. Physical Activity Guidelines for Americans. 2018. Accessed September 21, 2022. https://health.gov/sites/default/files/2019-09/Physical_Activity_Guidelines_2nd_edition.pdf
 104. Centers for Medicare & Medicaid Services. Decision memo for cardiac rehabilitation (CR) programs—chronic heart failure (CAG-00437N). 2014. Accessed September 21, 2022. <https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=270>
 105. Centers for Medicare & Medicaid Services. Decision memo for supervised exercise therapy (SET) for symptomatic peripheral artery disease (PAD) (CAG-00449N). 2017. Accessed September 21, 2022. <https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=287>
 106. Taylor RS, Walker S, Smart NA, Piepoli MF, Warren FC, Ciani O, O'Connor C, Whellan D, Keteyian SJ, Coats A, et al; ExTraMATCH II Collaboration. Impact of exercise-based cardiac rehabilitation in patients with heart failure (ExTraMATCH II) on mortality and hospitalisation: an individual patient data meta-analysis of randomised trials. *Eur J Heart Fail*. 2018;20:1735–1743. doi: 10.1002/ejhf.1311
 107. Flynn KE, Piña IL, Whellan DJ, Lin L, Blumenthal JA, Ellis SJ, Fine LJ, Howlett JG, Keteyian SJ, Kitzman DW, et al; HF-ACTION Investigators. Effects of exercise training on health status in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA*. 2009;301:1451–1459. doi: 10.1001/jama.2009.457
 108. Pandey A, Kitzman DW, Brubaker P, Haykowsky MJ, Morgan T, Becton JT, Berry JD. Response to endurance exercise training in older adults with heart failure with preserved or reduced ejection fraction. *J Am Geriatr Soc*. 2017;65:1698–1704. doi: 10.1111/jgs.14867
 109. Gerhard-Herman MD, Gornik HL, Barrett C, Barshes NR, Corriere MA, Drachman DE, Fleisher LA, Fowkes FGR, Hamburg NM, Kinlay S, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [published correction appears in *Circulation*. 2017;135:e790]. *Circulation*. 2017;135:e686–e725. doi: 10.1161/CIR.0000000000000470
 110. Pandey A, Keshvani N, Zhong L, Mentz RJ, Piña IL, DeVore AD, Yancy C, Kitzman DW, Fonarow GC. Temporal trends and factors associated with cardiac rehabilitation participation among Medicare beneficiaries with heart failure. *JACC Heart Fail*. 2021;9:471–481. doi: 10.1016/j.jchf.2021.02.006
 111. Reeves GR, Whellan DJ, Duncan P, O'Connor CM, Pastva AM, Eggebeen JD, Hewston LA, Morgan TM, Reed SD, Rejeski WJ, et al; REHAB-HF Trial Investigators. Rehabilitation Therapy in Older Acute Heart Failure Patients (REHAB-HF) trial: design and rationale. *Am Heart J*. 2017;185:130–139. doi: 10.1016/j.ahj.2016.12.012
 112. Kitzman DW, Whellan DJ, Duncan P, Pastva AM, Mentz RJ, Reeves GR, Nelson MB, Chen H, Upadhyia B, Reed SD, et al. Physical rehabilitation for older patients hospitalized for heart failure. *N Engl J Med*. 2021;385:203–216. doi: 10.1056/NEJMoa2026141