Advances in the pathophysiology and treatment of heart failure with preserved ejection fraction

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Abstract

Purpose of review—With the failure of multiple trials to identify a successful therapy for heart failure with preserved ejection fraction (HFpEF), attention has shifted to defining specific phenotypes within the HFpEF spectrum in an effort to develop a targeted approach to treatment. Here we summarize the most recent studies investigating the pathophysiology and clinical features of HFpEF, and discuss recent clinical trials in the context of developing treatments that look toward the underlying cause of this disorder.

Recent findings—Advances in basic science and clinical research have further characterized HFpEF, identifying multiple pathophysiological mechanisms that ultimately lead to exercise intolerance and volume overload. The success of small studies focused on specific subsets of the HFpEF population has promoted the concept that there may not be one treatment strategy that can universally be applied to HFpEF.

Summary—HFpEF is associated with significant morbidity and mortality and accounts for approximately half of patients with chronic heart failure. HFpEF is a complex disease, encompassing a diverse cohort of patients and marked by the presence of multiple etiological mechanisms. The failure to develop successful therapies for the management of HFpEF may be because of inadequate standardization of the HFpEF diagnosis, overly broad inclusion criteria and inadequate differentiation of disease subtypes. Given the heterogeneity among patients with HFpEF, much of the current research is focused on understanding of pathophysiology and identifying disease phenotypes that may respond to a targeted treatment approach. Several newer approaches, including neprilysin inhibition and device therapy, offer promise for a new era of HFpEF treatment.

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INTRODUCTION

Among patients with chronic heart failure, approximately 50% have a preserved ejection fraction (HFpEF) [1]. The prevalence of heart failure with a preserved ejection fraction (HFpEF) is expected to increase with more clinical recognition of this disease and the aging of the population [2]. HFpEF has a substantial impact on health care costs, and patients with HFpEF have reduced survival, although overall mortality is not as severe as for patients with an overt systolic dysfunction [3■]. No clinical trial to date has identified a therapy that improves survival in HFpEF. This may be because of the complex pathophysiology of HFpEF as well as failures of trial design. Unlike patients with HFrEF, whose symptoms can be directly tied to the consequences of systolic dysfunction, the cause of dyspnea in patients with HFpEF has remained more opaque. HFpEF is a heterogeneous disorder with multiple identified mechanisms and a wide variety of clinical presentations. Identifying a narrow set of disease-specific inclusion criteria for clinical studies has been a challenge. In addition, HFpEF patients have a high prevalence of comorbidities (hypertension, diabetes, chronic kidney disease, obesity) that can contribute significantly to the morbidity and mortality associated with the disease, making the identification of HFpEF-specific therapies more difficult. Much of the current research in this field is focused on the underlying pathophysiological mechanisms, with the goal of identifying disease phenotypes that may respond to a targeted treatment approach. In this review, we summarize the most recent data on the pathophysiology of HFpEF and discuss emerging evidence from clinical trials of HFpEF therapies.

KEY POINTS

- HFpEF represents approximately half of all heart failure, and leads to significant morbidity and mortality.

- Patients with HFpEF typically have multiple comorbidities, and disease presentation varies depending on the comorbidity profile.

- Exercise intolerance is the primary manifestation of HFpEF and has multiple etiological mechanisms, including diastolic dysfunction, chronotropic incompetence, pulmonary hypertension and subtle abnormalities of systolic dysfunction.

- Unlike HFrEF, no clinical trial to date has identified a therapy that improves survival in HFpEF. This may be related to inadequate understanding of pathophysiology and the application of broad therapies to a heterogeneous disorder.

- Classification of HFpEF phenotypes will allow the use of targeted therapies such as exercise training or rate-adaptive pacing for subgroups of the HFpEF population.

PATHOPHYSIOLOGY AND CLINICAL FEATURES OF HEART FAILURE WITH PRESERVED EJECTION FRACTION

HFpEF is characterized by abnormalities of both diastolic and systolic function that result in exercise intolerance. Animal models have highlighted the role of the cytoskeletal protein titin in promoting passive stiffness that underlies the development of diastolic dysfunction [4■,5■,6]. Diastolic dysfunction is considered a crucial component of HFpEF, and impaired ventricular relaxation has been well documented by both echocardiography and invasive hemodynamics [7,8]. Recently, human studies have focused on measuring abnormalities of cardiac performance not captured by ejection fraction, a highly load-dependent measure of systolic function. Using speckle tracking imaging, these studies have demonstrated that HFpEF is associated with abnormalities of global and longitudinal strain, dyssynchrony and impaired left atrial function[9■■,10■,11■]. In addition, a series of elegant exercise studies have demonstrated marked impairment of chronotropy and cardiovascular reserve among HFpEF patients [12,13].

The comorbidities associated with HFpEF play a significant role in its morbidity and mortality [14■,15]. Both atrial fibrillation and renal dysfunction are associated with worsened parameters of systolic and diastolic function, and the presence of atrial fibrillation has a significant impact on exercise capacity [16■,17■]. Diabetic patients have an increased burden of comorbidities, higher levels of inflammatory markers, worsened functional status and increased risk of hospitalizations [18■]. Likewise, HFpEF patients with coronary artery disease have an increased risk of mortality and subsequent decline in systolic function [19■]. Noninvasive measures of endothelial function have also been associated with adverse events in the HFpEF population [20]. Paulus and Tschope [21■■] have proposed a unifying hypothesis that comorbidities underlie the syndrome of HFpEF by inducing a proinflammatory state with multiple consequences, including endothelial dysfunction, dysregulation of myocyte hypertrophy and collagen deposition.

Designing therapeutic interventions for HFpEF has been complicated by the heterogeneity of this disorder. As a result, attention has been devoted to better defining HFpEF phenotypes. An autopsy study found that 19% of HFpEF subjects showed evidence of wild-type transthyretin amyloid deposition, which was associated with excess fibrosis [22■]. Identifying this subset of HFpEF will take on increased importance with the emergence of therapies that stabilize the transthyretin protein. One medication, tafamidis, has shown promise in the treatment of amyloid neuropathy and is currently under investigation in a Phase 3 trial for patients with familial or wild-type amyloid cardiomyopathy (NCT01994889). Large clinical trials with echocardiographic core laboratories have characterized the diversity of ventricular structure present in HFpEF, with most patients exhibiting concentric remodeling or concentric hypertrophy, but a significant percentage with eccentric hypertrophy [23■]. Sex differences are present, with women exhibiting increased left ventricular wall thickness and ventricular stiffness [24]. Increasing attention is being directed at the role of the right ventricle. Right ventricular dysfunction is a feature of HFpEF that carries a strong association with mortality, andmay be a good target for pulmonary vasodilator therapies [25,26■–28■].

THERAPEUTIC TARGETS FOR HEART FAILURE WITH PRESERVED EJECTION FRACTION

Clinical trials of therapies for HFpEF have explored multiple pathways, based on proposed pathophysiological mechanisms as well as extrapolation from treatments that have shown benefit in HFrEF. To date, no therapy has proven to improve survival in HFpEF. The mainstays of treatment are diuretics and guideline-directed management of comorbidities. The importance of extracellular volume management was highlighted by a subgroup analysis from the CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients (CHAMPION) trial, in which HFpEF patients with an implantable pulmonary artery pressure monitoring system had a 50% reduction in the incidence of heart failure hospitalization over 18 months, primarily because of augmentation of diuretic therapy [29■■]. Exercise training has been studied as nonpharmacological therapy, and has shown success in improving exercise capacity in patients with exertional dyspnea, although it has failed to alter other pathophysiological abnormalities characteristic of HFpEF [30■,31■].

Targeting the renin–angiotensin–aldosterone system

The renin–angiotensin–aldosterone system (RAAS) was the most obvious target for potential HFpEF therapies because of the experience with inhibition of RAAS in HFrEF as well as the association of neuro-hormonal activation with hypertension and volume retention. Preventing the adverse effects of angiotensin II [with angiotensin-converting enzyme (ACE) inhibitors or aldosterone receptor blockers (ARB)] was studied in three trials: Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM)-Preserved, Perindopril in elderly people with chronic heart failure (PEP-CHF) and Irbesartan in Heart Failure with Preserved Ejection Fraction (I-Preserve) [32–34]. All three studies failed to find any mortality benefit from RAAS inhibition (Table 1). CHARM-Preserved identified a reduction in heart failure hospitalizations, a secondary endpoint, with candesartan as compared with placebo, although the use of a left ventricular ejection fraction (LVEF) of 40% as the lower limit for the inclusion criteria raises the question of whether it was truly a HFpEF population that was studied. PEP-CHF found a reduction in multiple secondary endpoints, including exercise capacity and heart failure hospitalizations, with the ACE-inhibitor perindopril as compared with placebo [33]. However, PEP-CHF was a relatively small trial that was underpowered because of a low event rate, making it difficult to draw significant conclusions from secondary endpoints. The I-Preserve trial, which used an LVEF more than 45% as an inclusion criterion (and therefore may more closely represent a true HFpEF population), failed to find a difference in any of its secondary endpoints, including quality of life and heart failure hospitalizations [34].

Blocking the downstream effects of aldosterone is appealing in the treatment of HFpEF because of aldosterone's association with volume retention and ventricular fibrosis. Two trials have investigated aldosterone antagonism in HFpEF: Aldosterone Receptor Blockade in Diastolic Heart Failure (ALDO-DHF) and Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) (Table 1) [35,36■■]. ALDO-DHF failed to find an improvement in functional outcomes, despite improvement in diastolic function

(E/E′) on echocardiography, and was not designed to look at hospitalizations or survival [35].

The TOPCAT trial is a large, randomized study that was powered to investigate the effect of aldosterone antagonism on clinical outcomes in HFpEF [36■■]. In TOPCAT, patients with symptomatic heart failure, an LVEF of 45% or greater, and either a prior hospitalization for heart failure within the past year or an elevated natriuretic peptide level were randomized to spironolactone or placebo. A total of 3445 patients were randomized, the median age was 68, and 50% were women. At a mean follow-up of 39 months, there was no significant difference in the primary endpoint of death from cardiovascular causes, aborted cardiac arrest or hospitalization for heart failure (18.6 versus 20%, P=0.14). Although the primary endpoint was neutral, there was a lower incidence of hospitalization for heart failure in the spironolactone group (12.0 versus 14.2%, P=0.04).

TOPCAT's patients were reflective of a contemporary HFpEF population, with high rates of hypertension (91%), obesity (55%), diabetes (32%), chronic kidney disease (38%), atrial fibrillation (35%) and coronary artery disease (59%). The study may have been limited by having broad inclusion criteria and by the enrollment of patients at varying stages of disease progression, as there was marked geographical variation in event rates [37■]. A similar finding has recently been reported from a review of multiple HFpEF trials, suggesting discrepancies in the definition of HFpEF across study sites [38■].

Targeting pulmonary hypertension

With the negative results of spironolactone in TOPCAT added to the previous failure of other RAAS inhibitors to alter mortality in HFpEF, the focus of clinical efforts has turned toward therapies that more specifically target pathophysiological abnormalities. Pulmonary hypertension has been described in a significant percentage of the HFpEF population, and is associated with increased morbidity and mortality, making pulmonary vasodilation an attractive therapeutic strategy [39■]. In addition to vasodilation, inhibition of phosphodiesterase-5 has been shown to reverse cardiac hypertrophy, fibrosis and contractile dysfunction [40]. The use of sildenafil in HFpEF was initially examined in a small study by Guazzi *et al.*, which randomized 44 patients with HFpEF and pulmonary hypertension to sildenafil or placebo [41]. Large improvements were seen in right atrial pressure, pulmonary artery pressure and right ventricular function after 6 months. Of note, baseline right atrial pressure was markedly elevated in this study (23 mmHg), suggesting that this study population had severe right ventricular dysfunction and may not be reflective of the larger population with HFpEF.

The Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure with Preserved Ejection Fraction (RELAX) trial compared sildenafil with placebo in 216 patients with symptomatic heart failure, LVEF greater than 50%, decreased peak oxygen consumption and either an elevated NT-proBNP or evidence of resting or exercise-induced elevation of filling pressures [42■■]. At a mean follow-up of 24 weeks, there was no difference between the two groups in the primary endpoint of change in peak oxygen consumption (−0.20 versus −0.20 ml/kg/min, P=0.90). There was also no difference in any of the secondary endpoints, including parameters of diastolic function, change in 6-

min walk distance or clinical status as measured by a hierarchical composite score. Pulmonary hypertension was not required for entry into the study, which may have limited the efficacy of a therapeutic strategy that targets the pulmonary vasculature. An ongoing study will assess the impact of sildenafil on pulmonary pressures in HFpEF patients with pulmonary hypertension documented by invasive hemodynamics (Table 2).

Targeting heart rate

Heart rate is a marker of sympathetic activation and has been correlated with adverse outcomes in HFpEF. A substudy of the I-Preserve trial found an inverse association between heart rate (in sinus rhythm) and the incidence of cardiovascular death or heart failure hospitalizations [44■]. Ivabradine, an I_f-channel inhibitor, works directly on the sinus node to reduce heart rate without negative inotropic effects. This approach holds promise in diastolic dysfunction, as slower heart rates permit greater time for ventricular filling, and may be particularly well suited for patients whose symptoms predominantly occur with exercise. Favorable data from an animal model indicated improvements in vascular stiffness, ventricular elastance, and diastolic function following selective heart rate reduction with ivabradine [47■]. One clinical study has recently reported on the short-term use of ivabradine in HFpEF [43■■]. Sixty-one patients were randomized to take ivabradine or placebo for 7 days. Ivabradine therapy resulted in an increase in peak VO_2 of 3.0 ± 3.6 ml/kg/min as compared with an increase of 0.4 ± 1.2 ml/kg/min for placebo ($P=0.003$). Additionally, patients in the ivabradine arm had a reduction in the change of E/E′ with exercise (3.1 ± 2.7 prior to treatment as compared with 1.3 ± 2.0 following treatment; $P=0.004$), whereas there was no significant change in this parameter during exercise in the placebo group (Table 2).

Targeting the natriuretic peptide system

The natriuretic peptides play a crucial role in fluid homeostasis. They are released in response to ventricular stretch, resulting in vasodilation, natriuresis and myocardial relaxation. One method of augmenting natriuretic peptide activity is through the inhibition of neprilysin, a protease that degrades biologically active natriuretic peptides.

The Prospective Comparison of ARNI With ARB on Management of Heart Failure with Preserved Ejection Fraction (PARAMOUNT) trial was a Phase II trial that compared LCZ696 (an angiotensin receptor neprilysin inhibitor) with valsartan in 308 patients with symptomatic heart failure, LVEF of at least 45% and elevated NT-proBNP levels [45]. At 12 weeks, NT-proBNP levels were significantly reduced in the LCZ696 arm compared with the valsartan group (ratio of change LCZ696/valsartan 0.77, $P=0.005$). At 36 weeks, NT-proBNP levels remained reduced from baseline in the LCZ696 group; however, the difference between the study groups was no longer significant ($P=0.20$). Heart failure symptoms were improved in a greater percentage of the LCZ696 group at 36 weeks ($P=0.05$). Blood pressure was reduced to a greater extent with LCZ696, although a subsequent analysis suggested that the benefits observed in the trial were independent of the blood pressure effect [48]. Prospective Comparison of ARN with ARB Global Outcomes in Heart Failure with Preserved Ejection Fraction (PARAGON-HF), a large Phase III trial investigating the impact of LCZ696 on cardiovascular death and heart failure hospitalizations in HFpEF, is currently enrolling patients (Table 2).

FUTURE DIRECTIONS

Table 2 outlines a selection of ongoing investigations of novel therapies for HFpEF. Renal denervation is an approach that has attracted significant attention. The potential benefits of renal denervation in the HFpEF population include suppression of the excess sympathetic activity associated with heart failure and stricter control of hypertension. Several studies are currently evaluating the effect of renal denervation on changes in ventricular structure and measures of diastolic function.

Soluble guanylate cyclase stimulators enhance production of cyclic guanosine monophosphate, inducing vasodilation and inhibiting the development of fibrosis. Riociguat was recently studied in pulmonary hypertension associated with HFrEF and failed to meet its primary endpoint of change in mean pulmonary artery pressure, although it did improve cardiac index and reduce pulmonary vascular resistance [49]. Acute Hemodynamic Effects of Riociguat in Patients with Pulmonary Hypertension Associated with Diastolic Heart Failure (DILATE-1), a small study of short-term administration of riociguat in HFpEF, failed to demonstrate a reduction in pulmonary artery pressures as compared with placebo, but did find an improvement in stroke volume and right ventricular end-diastolic area [27■]. A Phase II study of vericiguat, Soluble Guanylate Cyclase Stimulator in Heart Failure Study (SOCRATES-PRESERVED), is in progress [46].

Device therapy for the treatment of HFpEF is an area of active investigation. Chronotropic incompetence has increased prevalence in the HFpEF population and limits the ability of HFpEF patients to augment their cardiac output during exercise [50]. Restoration of chronotropic competence has promise for reducing exercise-induced dyspnea in HFpEF, but unfortunately, a prospective assessment of rate-adaptive pacing was terminated because of insufficient enrollment [51]. Another approach is to pace the left atrium through a coronary sinus lead to restore left atrial filling in patients with 'atrial dyssynchrony syndrome,' which is characterized by interatrial conduction delay and increased left atrial stiffness. A pilot study showed increased 6-min walk distance during active pacing, as well as improvement in left atrial and left ventricular filling [52]. The Left Atrial Pacing in Diastolic Heart Failure trial will attempt to confirm these results in a larger cohort. Mechanical circulatory support has not been tested in HFpEF; however, a small series of left ventricular assist device therapy in patients with restrictive or hypertrophic cardiomyopathies suggested an increased incidence of right ventricular failure after implantation [53].

There are several structural devices in development for the treatment for HFpEF. Percutaneous creation of an interatrial shunt has been developed as a method to reduce left atrial pressure, with the aim of reducing exertional dyspnea. In a computer model, the addition of the interatrial shunt resulted in a reduction of pulmonary capillary wedge pressure by 3mmHg at rest and 11mmHg during peak exercise. These changes were accompanied by a decrease in left ventricular cardiac output and an increase in right ventricular cardiac output [54]. The InterAtrial Shunt Device (DC Devices, Inc., Tewksbury, MA, USA) is a percutaneously implanted 8-mm shunt and has been tested in a pilot study of 11 patients with an LVEF higher than 45% [55■]. In this nonrandomized study, pulmonary capillary wedge pressure (PCWP) was reduced by 5.5mmHg at 30 days, and was

accompanied by a reduction in NYHA class in all but one patient. The safety and efficacy of this device are currently being investigated in the Reduce Elevated Left Atrial Pressure in Patients with Heart Failure (REDUCE LAP-HF) Trial (NCT01913613). The V Wave device (V Wave Ltd, Hod HaSharon, Israel) applies the same approach to creating an interatrial shunt, but has the addition of a pericardial tissue valve to ensure one-way shunting. It recently underwent its first-in-man implantation in a patient with systolic dysfunction, and recruitment to a Phase 1 study is ongoing [56].

The CORolla device (Corassist Cardiovascular Ltd, Herzliya, Israel) is the first nonpharmacological approach to the problem of impaired ventricular relaxation. An elastic spring that is implanted in the left ventricular apex, the CORolla, absorbs energy during ventricular systole and then applies expansion forces to the septum and lateral wall during diastole, permitting increased ventricular filling. At this time, the device must be implanted surgically, but a transapical approach is under development.

CONCLUSION

HFpEF is characterized by a complex pathophysiology, encompassing multiple etiological mechanisms and exhibiting a diversity of clinical presentations. With a lack of proven therapies other than diuretics, HFpEF continues to have excessive morbidity and mortality. The failure to develop successful therapies for the management of HFpEF may be because of an overly broad disease definition and inadequate differentiation of disease subtypes. Developments in the understanding of pathophysiology, including the stages of disease, are fueling new therapies directed at improving both symptoms and survival (Table 3). Future trials may have greater success through targeting of specific subgroups or specific phases of disease development [57]. Recent successful physiological studies of heart rate reduction with ivabradine and neprilysin inhibition with LCZ696 have moved the field forward, and renewed excitement about new strategies for treating HFpEF. The results of the PARAGON-HF study are eagerly awaited, as are the conclusion of multiple device trials that are currently in progress.

Acknowledgments

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Table 1

Features and results of clinical trials targeting the renin–angiotensin–aldosterone system in heart failure with a preserved ejection fraction

Trial	Therapy	Inclusion criteria	N	Follow-up	Primary endpoint	Trial result
CHARM-preserved	Candesartan	NYHA Class II–IV LVEF >40% Prior cardiac hospitalization	3023	3 years	Cardiovascular death or heart failure hospitalization	Negative (22 versus 24%; $P = 0.118$)
PEP-CHF	Perindopril	Age >70 Diastolic dysfunction LV wall motion index >1.4 Prior heart failure hospitalization	850	2.1 years	All-cause mortality and heart failure hospitalization	Negative (25.1 versus 23.6%; $P = 0.545$)
I-PRESERVE	Irbesartan	NYHA Class II–IV LVEF >45% Prior heart failure hospitalization	4128	4.1 years	Death from any cause or cardiovascular hospitalization	Negative (36 versus 37%; $P = 0.35$)
ALDO-DHF	Spironolactone	NYHA Class II–III LVEF >50% Diastolic dysfunction	422	1 year	Change in E/E′ Change in peak VO_2	Mixed results: E/E′: −0.6 versus +0.8 ($P < 0.001$) VO_2: +0.5 versus +0.5 ml/kg/min ($P = 0.81$)
TOPCAT	Spironolactone	NYHA Class II–IV LVEF >45% Prior heart failure hospitalization or elevated BNP	3445	3.25 years	Cardiovascular death, aborted cardiac arrest, or heart failure hospitalization	Negative (18.6 versus 20%; $P = 0.14$)

BNP, B-type natriuretic peptide; LV, left ventricular; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; VO_2, oxygen uptake.

Table 2

Recently completed or current investigations of novel therapies for HFpEF

Therapy	Trial name	Design	Inclusion criteria	N	Primary outcome measure	Results/status
PDE-5 inhibitor	RELAX [42■■]	Sildenafil versus placebo	LVEF >50%	216	Change in peak VO$_2$ at 6 months	No difference in change in peak VO$_2$ between sildenafil and placebo
	NCT01726049		VO$_2$ <60% predicted			
			NT-proBNP >400 pg/ml			
			LVEF >45%	52	Reduction in mean PAP at 3 months	Enrollment complete
			Mean PAP >25 mmHg			
			PCWP >15 mmHg			
I$_f$-channel inhibitor	Kosmala *et al.* [43■■]	Ivabradine versus placebo	LVEF >50%	61	Change in peak VO$_2$	Increase in peak VO$_2$ with ivabradine (3.0 versus 0.4; $P = 0.003$)
			Diastolic dysfunction			
Angiotensin receptor neprilysin inhibitor	PARAMOUNT [45]	LCZ696 versus valsartan	LVEF >45%	308	Change in NT-proBNP at 3 months	Ratio of change in proBNP for LCZ696/valsartan 0.77 ($P = 0.005$)
			NT-proBNP >400 pg/ml			
	PARAGON		LVEF >45%	4300	Cumulative number of cardiovascular death and heart failure hospitalization	Enrolling
			Elevated NT-proBNP or heart failure hospitalization			
sGC inhibitor	SOCRATES-PRESERVED [46]	Vericiguat versus placebo	LVEF >45%	470	Change of NT-proBNP and LAVI	Enrolling
			Worsening heart failure			
Renal denervation	DIASTOLE	Renal denervation versus optimal medical therapy	LVEF >50%	60	Change in E/E′ and LAVI at 12 months	Enrolling
			Diastolic dysfunction			
			SBP >140/90			
	RESPECT-HF		ADHF with LVEF >50%	144	Change in LAVI or LVMi on cMRI at 6 months	Enrolling
			E/E′ >15 or NT-proBNP >220 pg/ml			

Therapy	Trial name	Design	Inclusion criteria	N	Primary outcome measure	Results/status
Interatrial septal shunt device	REDUCE LAP-HF	Single arm trial of IASD System (DC Devices)	Age >40	100	Incidence of death, stroke, MI, or systemic embolic event at 6 months	Enrolling
			LVEF >40%			
			Elevated PCWP/LVEDP that is greater than CVP			

ADHF, acute decompensated heart failure; CMRI, cardiac magnetic resonance imaging; CVP, central venous pressure; DIASTOLE, Denervation of the Renal Sympathetic Nerves in Heart Failure with Normal LV Ejection Fraction; HFpEF, heart failure with preserved ejection fraction; LAVI, left atrial volume index; LVEDP, left ventricular end diastolic pressure; LVEF, left ventricular ejection fraction; LVMi, left ventricular mass index; MI, myocardial infarction; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PAP, pulmonary artery pressure; PARAGON, Prospective Comparison of ARN with ARB Global Outcomes in Heart Failure with Preserved Ejection Fraction; PARAMOUNT, Prospective Comparison of ARNI With ARB on Management of Heart Failure with Preserved Ejection Fraction; PCWP, pulmonary capillary wedge pressure; PDE-5, phosphodiesterase-5; REDUCE LAP-HF, Reduce Elevated Left Atrial Pressure in Patients with Heart Failure; RESPECT-HF, Renal Sympathectomy in Heart Failure; sGC, soluble guanylate cyclase; SOCRATES, Soluble Guanylate Cyclase Stimulator in Heart Failure Study; VO$_2$, oxygen uptake.

Table 3

Examples of targeted therapies based on specific pathophysiologic mechanisms in HFpEF

Targeted etiological mechanisms	Potential therapies
Exertional dyspnea (exercise-induced diastolic dysfunction)	Ivabradine exercise training, interatrial shunt devices
Volume overload	Pulmonary artery pressure monitor, angiotensin receptor neprilysin inhibitor
Pulmonary hypertension and right ventricular dysfunction	Phosphodiesterase-5 inhibitors, soluble guanylate cyclase stimulators
Impaired ventricular relaxation	Intraventricular spring with diastolic expansion
Chronotropic incompetence	Rate-adaptive atrial pacing
Atrial dyssynchrony	Left atrial pacing

HFpEF, heart failure with preserved ejection fraction.