Curr Treat Options Cardio Med (2019) 21: 20
DOI 10.1007/s11936-019-0709-4

Heart Failure (W Tang, Section Editor)

Treatment of Heart Failure With Preserved Ejection Fraction (HFpEF): the Phenotype-Guided Approach

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Published online: 13 April 2019

This article is part of the Topical Collection on *Heart Failure*

Keywords Heart failure with preserved ejection fraction · Treatment · Phenotype

Abstract

The syndrome of heart failure with preserved ejection (HFpEF) continues to rise in prevalence without persuasive evidence of current pharmacologic interventions that can reduce mortality. Clinical trials thus far have generally enrolled "all-comers" with the clinical syndrome of heart failure and objective evidence of a preserved ejection fraction. However, HFpEF is increasingly understood to be a heterogeneous syndrome likely borne from the interplay of genetic predisposition, lifestyle factors, and high burden of associated comorbidities with each contributing to a variety of incompletely understood pathophysiologic abnormalities. Complicating management further, such abnormalities appear to be present to varying degrees among individual patients. Ongoing studies, along with the use of computational statistics/machine learning, offer the hope of clarifying the pathophysiological substrates giving rise to the syndrome of HFpEF in different patient subsets. With better understanding of the syndrome's underpinnings, there will be the potential for development of truly targeted therapies. However, for now, there is substantial evidence for the use of currently available pharmacologic device and lifestyle therapy for the optimized management of patients. Such therapy can be tailored to presently identifiable patient clusters—called "phenotypes"—distinguished by both the presence of predominant presenting symptoms and/or predominant comorbidity profiles. Examples of clinical presentation phenotypes include lung congestion, chronotropic incompetence, pulmonary hypertension, or skeletal muscle weakness as

predominant features. Additionally, such patients may have underlying metabolic syndrome, systemic (arterial) hypertension, renal dysfunction, atrial fibrillation, and/or coronary artery disease as principal underlying comorbidities. Here, we review a "phenotype-guided" approach to the management of patients with HFpEF, based on a stepwise method of making the HFpEF diagnosis, identifying the prominent sources of organ dysfunction, and treating accordingly.

Introduction

Heart failure with preserved ejection fraction (HFpEF) poses a growing burden to the healthcare system with rising prevalence paired with substantial morbidity and mortality [1, 2]. However, the syndrome of HFpEF has failed to respond to the "one-size-fits-all" recipe of renin-angiotensin-aldosterone antagonism and neurohormonal blockade that, over the course of the last two decades, has provided remarkable success in the stabilization and even reversal of heart failure with reduced ejection fraction (HFrEF). There has been much frustration borne out of the failure of major clinical trials performed thus far to reach positive primary outcomes, with no medications proven to reduce mortality or increase activity levels in patients with HFpEF. This failure to find a single therapy beneficial to all-comers with HFpEF has been attributed at least in part to the marked heterogeneity among patients with the syndrome, highlighting the fact that no single unifying disease process underlies the dysfunction seen in all patients who are affected [3, 4].

Defining the problem

Although it is understood that there are certain aberrations present in all patients with HFpEF—elevated left atrial pressures (at rest and/or with exertion) and renal sodium retention—there is considerable diversity with regard to the presence and severity of cardiac and extracardiac abnormalities attributed to systemic inflammation, fibrosis, endothelial dysfunction, cardiomyocyte dysfunction, and skeletal muscle dysfunction [5, 6]. While recent work has brought this paradigm of multiorgan dysfunction to the forefront, a method by which clinicians can readily determine the degree to which such pathophysiologic processes are present in a specific patient with HFpEF does not yet exist. So too, the way such underlying dysfunction manifests with regard to outward phenotype remains an active area of investigation.

In recent years, studies integrating multiple layers of patient data (e.g., echocardiographic, laboratory, and morphologic data along with comorbidity profiles) and utilizing computational statistics (e.g., machine learning) have made progress in revealing distinguishable clusters of patients characterized by predominant symptoms and comorbidities—referred to as phenotypes—among cohorts of HFpEF patients [7–9]. Although current endeavors have utilized several forms of phenotypic data, future studies may utilize additional data from patient transcriptomes/proteomes, cardiac and skeletal muscle biopsies, and sophisticated multiorgan imaging [10]. While such methods will continue to mature and ultimately be necessary to appropriately characterize the underlying disease states giving rise to the syndrome of HFpEF, certain phenotypes are currently identifiable and will be discussed below.

Making the diagnosis

Proper treatment of HFpEF begins with ensuring that the diagnosis is made. Although symptoms of volume overload, exercise intolerance, and fatigue should always raise suspicion for the presence of underlying heart failure, patients with HFpEF may not present with "classic" symptoms and may instead have very subtle clinical presentations. While the presence of an elevated serum B-type natriuretic peptide (BNP) level can be helpful in ruling in heart failure, a normal level does not rule out the presence of HFpEF, as up to one third of outpatients may have a BNP level that is below typical diagnostic thresholds [11–13]. An echocardiogram with Doppler is critical in the assessment of the patient, allowing measurement of the ejection fraction, chamber morphology (e.g., LV hypertrophy, atrial enlargement) diastolic function (e.g., e'E/e', E/A), right ventricular (RV) size/function, PA systolic pressure, and estimated filling pressures. Even so, if the diagnosis of HFpEF remains in doubt, right heart catheterization with measurement of filling

pressures at rest and with exercise or volume challenge should be performed to confirm the diagnosis [14, 15].

In the process of making the diagnosis of HFpEF, ruling out potential "zebras" that can masquerade as HFpEF, but which have unique prognostic implications and therapy, is imperative. Careful review of the physical exam, electrocardiogram, echocardiogram, and invasive hemodynamic data can ensure that infiltrative cardiomyopathies such as amyloidosis and sarcoidosis, constrictive pericarditis, and hypertrophic cardiomyopathy (HCM) are not overlooked.

Characterizing the phenotype

While ongoing population studies attempt to provide deeper understanding of the mechanisms that give rise to different subgroups of HFpEF, there nonetheless remain phenotypic subclasses that are identifiable and can be used as a framework for management (3; 16). One stratification schema focuses on associated comorbidities as "etiology/pathophysiology phenotypes" and include (1) predominant metabolic syndrome (often referred to as "garden variety" HFpEF), (2) coronary artery disease, (3) pulmonary hypertension, (4) atrial fibrillation, (5) HCM-like hypertensive heart disease, (6) valvular heart disease, (7) high-output heart failure, or (8) other causes such as restrictive or constrictive cardiomyopathies. Each of these phenotypic variants can be targeted with rational therapy (Fig. 1) that is described in greater detail below. In addition to stratification based on etiology/pathophysiology, patients can also be classified by "clinical presentation phenotype," based on typical clinical presentations that include (1) exercise intolerance with elevated LV filling pressures, (2) volume overload, or (3) right heart failure. Undoubtedly, there is overlap, with an individual patient likely to have diabetes, obesity, chronic hypertension, and coronary artery disease with predominant symptoms of exercise intolerance, for example. However, a focus on

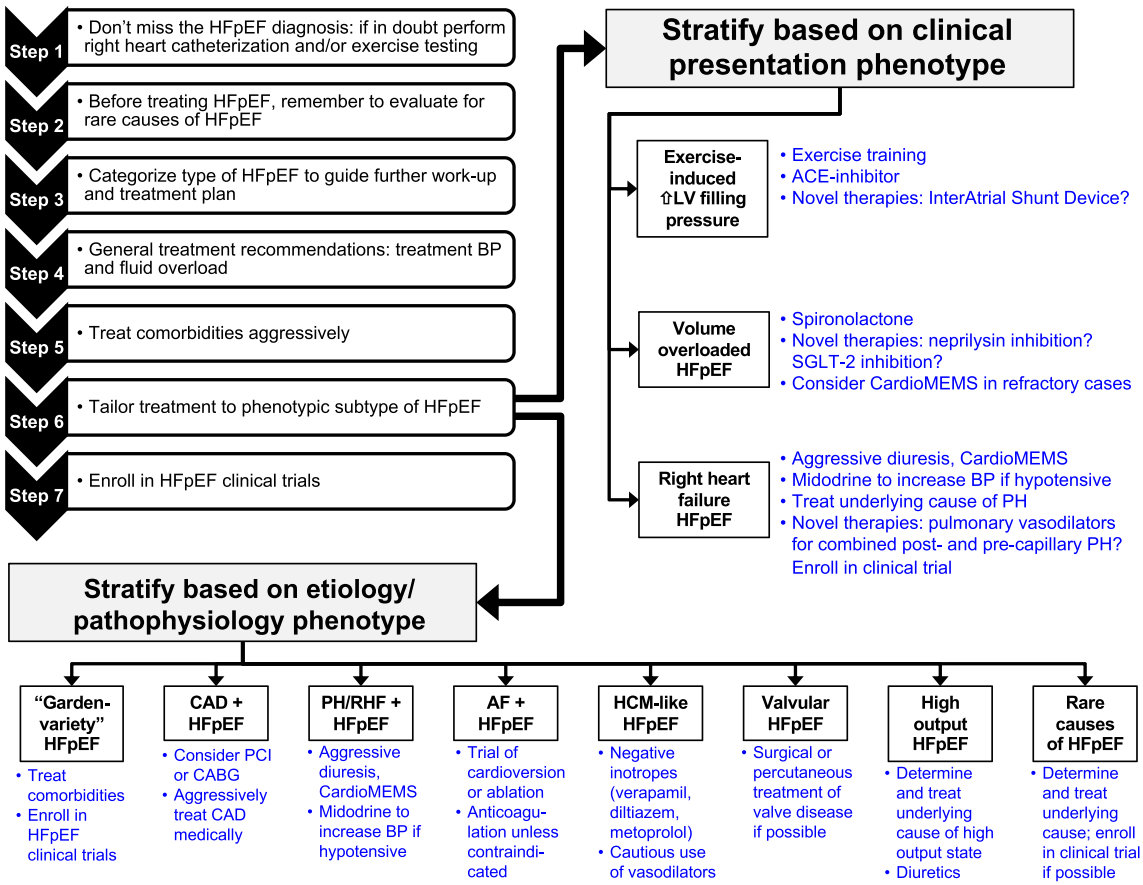

Fig. 1. Stepwise approach to the treatment of heart failure with preserved ejection fraction: general approaches and tailored treatment based on phenotypic subtypes.

Table 1. Management of comorbidities in heart failure with preserved ejection fraction

Comorbidity	Management strategies
Systemic hypertension	• Consider ACE inhibitor/ARB, thiazide diuretic, and vasodilating beta-blocker (e.g., carvedilol), if no evidence of chronotropic incompetence as first-line agents • Thiazide and thiazide-like diuretics (e.g., chlorthalidone, indapamide) prevent HFpEF • Consider and work-up secondary causes of hypertension in patients with difficult to control blood pressure • Most patients can be treated with a combination of vasodilating beta-blocker, ACE inhibitor/ARB, thiazide, loop diuretic, spironolactone (and hydralazine/nitrates or dihydropyridine calcium channel blocker, if needed); therefore, avoid clonidine, minoxidil, atenolol as these drugs are either ineffective or have several unwanted side effects
Coronary artery disease	• Although drugs such as beta-blockers and ACE inhibitors/ARBs, used to treat CAD, have not shown clear mortality benefit in HFpEF clinical trials; these drugs were not specifically tested in the subset of patients with HFpEF-CAD; therefore, we still recommend treating with these drugs in patients with HFpEF-CAD • There is no known clear benefit of coronary revascularization in HFpEF (data is limited). However, revascularization can be helpful for exclusion of diagnosis of HFpEF when there is diagnostic dilemma (HFpEF vs. CAD) regarding the causes of signs and symptoms in the individual patient • Aspirin and statins in all patients unless contraindicated for primary or secondary prevention of myocardial infarction
Atrial fibrillation	• Trial of restoration of normal sinus rhythm in all patients (this could include cardioversion, percutaneous ablation, or surgical maze procedure, as indicated depending on symptoms in the setting of atrial fibrillation) • Rate control strategy with beta-blockers or non-dihydropridine calcium channel blockers (diltiazem or verapamil) is usually preferred due to potential side effects of rhythm control agents. • Drugs to control rhythm reserved for patients who have worsening of HF with loss of atrial kick. • Anticoagulation with warfarin or novel oral anticoagulants (NOACs) unless contraindicated
Obesity	• Diet counseling (including sodium and fluid restriction) for all patients • Consider referral to obesity management program (and bariatric surgery in select patients with morbid obesity)
Chronic kidney disease	• Consider co-management with a nephrologist in patients with GFR < 30 mL/min/1.73 m^2 • Patients with right heart failure can develop renal venous congestion, especially if systemic blood pressure is low; these patients can present as "pre-renal" but require diuresis to improve renal blood flow • Patients with symptoms of HFpEF who have "normal" renal function with "normal" serum creatinine (i.e., < 1.2 mg/dL) often have a falsely low creatinine due to hemodilution; in these patients, look for signs of volume overload; and increased creatinine with diuresis in this setting may simply be a sign of hemoconcentration
Obstructive sleep apnea	• Risk factors for HFpEF (i.e., obesity) overlap with OSA; thus, HFpEF and OSA often co-exist. OSA can result in LVH and diastolic dysfunction as well as pulmonary hypertension and right heart failure, both of which can exacerbate HFpEF. • HFpEF can be associated with oropharyngeal and laryngeal edema which can cause OSA; patients with severe HFpEF can also have central sleep apnea • Consider overnight polysomnography testing after initial diuresis in all patients, and all patients with documented OSA should undergo treatment for OSA • Co-management with a sleep specialist is key for patients with HFpEF who have (1) CPAP intolerance; (2) mixed apnea; or (3) persistent evidence of sleep apnea despite treatment with CPAP
Chronic lung disease	• Even mild chronic lung disease can cause significant hypoxemia, dyspnea, and exercise intolerance in the HFpEF patient

Table 1. (Continued)

Comorbidity	Management strategies
	• Given exquisite sensitivity to pulmonary edema/fluid overload, patients with both chronic lung disease and HFpEF often require frequent monitoring and judicious use of diuretics • Aggressive treatment of chronic lung disease such as COPD may help improve symptoms and quality of life

HF heart failure, *HFpEF* heart failure with preserved ejection fraction, *ACE* angiotensin-converting enzyme, *ARB* angiotensin receptor blocker, *CAD* coronary artery disease, *CKD* chronic kidney disease, *GFR* glomerular filtration rate, *OSA* obstructive sleep apnea, *LVH* left ventricular hypertrophy, *CPAP* continuous positive airway pressure, *COPD* chronic obstructive pulmonary disease

these phenotypes can be utilized to systematically provide optimized care based on current, available therapies [17]. Either method of characterization allows for a "phenotype-guided" treatment strategy utilizing available therapies to manage comorbidities, minimize symptoms, and improve quality of life.

General treatment strategies

The typical, "garden variety," patient with HFpEF will have some components of the metabolic syndrome (overweight/obese, type 2 diabetes mellitus, hyperlipidemia, etc.) and typical symptoms of lung congestion. Thus, a starting point for most patients with HFpEF is centered on risk reduction, comorbidity management, and the use of diuretics with loop diuretics as a mainstay but thiazide diuretics and the addition of mineralocorticoid antagonists also available as valuable options. Lifestyle changes including low-sodium diet, decrease in caloric intake, and regular aerobic exercise should be undertaken in most patients with HFpEF, with proof of safety and effective symptom relief in obese, elderly patients with HFpEF [18, 19]. Additionally, statins should be used to manage dyslipidemia as directed by ACC/AHA guidelines but may also have a unique role in treatment of HFpEF due to their reduction in systemic inflammation [20–22]. Optimal management of glycemic control, whether in preventing progression of impaired fasting glucose to diabetes mellitus or in reaching hemoglobin-A1C goals in patients already diagnosed with diabetes mellitus, can also reduce systemic inflammation, reduce complications such as neuropathy that minimize physical activity, and protect against development of renal dysfunction which is linked with promotion of HFpEF through increased systemic inflammation, endothelial dysfunction, and decreased nitric oxide bioavailability [23]. A more specific comorbidity management schema is displayed in Table 1 and further details about individual interventions follow in the "Treatment" section.

Treatment

Pharmacologic treatment

Angiotensin-converting enzyme inhibitors

- Angiotensin-converting enzyme (ACE) inhibitors were tested prospectively in elderly HFpEF patients with LVEF > 40% and New York Heart Association (NYHA) class II-IV symptoms in the PEP-CHF trial after their success in reducing mortality in HFrEF had already been shown. Although it was thought that similar benefits from antagonism of the renin-angiotensin-aldosterone axis and beneficial remodeling would occur in HFpEF patients, the PEP-CHF trial showed no significant reduction in all-cause mortality and/or heart failure-related hospitalizations in patients receiving perindopril compared to placebo. However, there was significant increase

in 6-min walk test distance at 52 weeks as well as decreased heart failure hospital admission at 1 year [24].

- Observational and retrospective studies, including an analysis from the Swedish Heart Failure registry evaluating the use of ACE inhibitors or angiotensin receptor blockers (ARBs) in patients with heart failure and an ejection fraction > 40% suggested that patients on either therapy had significantly reduced all-cause mortality [25]; however, this contrasts with the only large-scale, prospective study performed to date (PEP-CHF).

Phenotype-guided use: Beneficial as a first-line agent for treatment of hypertension or in patients with diabetes mellitus for renal protection.

Standard dosage: Dosing and frequency is dependent on the specific ACE inhibitor used. Initiation of an ACE inhibitor should start with a low dose and progressively uptitrated over serial visits as tolerated by blood pressure, renal function, and potassium levels.

Contraindications: History of angioedema, hypotension (systolic blood pressure < 80 mmHg), serum creatinine > 3.0 mg/dL, serum potassium > 5.5 mEq/L, anuric renal failure, or bilateral renal artery stenosis are the primary contraindications to ACE inhibitor use.

Main drug interactions: Due to their actions on the proximal and distal tubules and risk for kidney injury, non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided with concurrent use of ACE inhibitors.

Main side effects: Angioedema, cough, hyperkalemia, hypotension, or renal dysfunction.

Angiotensin receptor blockers

- ARBs were tested prospectively in HFpEF patients in the CHARM-Preserved (Candesartan) and I-PRESERVE (Irbesartan) studies for their ability to reduce cardiovascular death/hospital admission and all-cause death/hospitalization, respectively. While neither study showed significant reduction in the primary outcome with use of ARBs, candesartan in the CHARM-Preserved trial did significantly reduce the number of heart failure hospital admissions [26–28].

Phenotype-guided use: Beneficial as a first-line agent for treatment of hypertension as an alternative to ACE inhibitors with the potential to reduce frequency of hospitalization.

Standard dosage: dosing and frequency is dependent on the specific ARB used. Initiation of an ARB should start at a low dose and progressively uptitrated over serial visits as tolerated by blood pressure, renal function, and potassium levels.

Contraindications: hypotension (systolic blood pressure < 80 mmHg), serum creatinine > 2.5 mg/dL, estimated GFR < 30 ml/min/1.73 m^2, or potassium > 5.0 mEq/L.

Main side effects: Hyperkalemia, hypotension, renal dysfunction.

Beta-blockers

- Two randomized, placebo-controlled trials have been performed to assess the role of beta-blockers vs. placebo in HFpEF, with carvedilol tested in the

J-DHF trial and nebivolol tested in the ELANDD trial [29, 30]. The former was designed to test for a difference in primary composite outcome of cardiovascular death and unplanned hospitalization for heart failure while the latter tested for a primary outcome of increased exercise capacity at 6 months as measured by change in the 6-min walk test. Neither study showed a clinical benefit from the use of beta-blockers, although J-DHF suggested that response might be dose-dependent with greater benefit derived from higher dose of beta-blocker than doses tested in the trial. Although the SENIORS trial is often mentioned as a trial of beta-blockers in HFpEF, patients in that trial had a range of EF, with the majority of patients with "preserved" EF in that trial with mid-range EF.

Phenotype-guided use: The use of a beta-blocker should be tailored to the specific clinical scenario. In patients with hypertension, non-selective beta-blockers with alpha-1 blocking activity may be beneficial for their vasodilating activity, whereas in patients with atrial tachyarrhythmias, selective beta-1 blocking beta-blockers are ideally suited to help control heart rates. Likewise, beta-blockers may be used in HFpEF patients with associated comorbidities such as coronary artery disease with history of myocardial infarction. However, before initiating a beta-blocker, exercise testing should be performed to evaluate for chronotropic incompetence, in which case a beta-blocker could worsen the patient's symptoms.

Standard dosage: Dosing and frequency is dependent on the specific beta-blocker used and indication. Initiation of a beta-blocker should start with the lowest possible dose and progressively uptitrated over serial visits as tolerated by blood pressure, heart rate, and subjective symptoms.

Contraindications: Hypotension (systolic blood pressure < 80 mmHg), chronotropic intolerance, restrictive cardiomyopathy, history of bronchospasm, 2nd/3rd degree atrioventricular block, frequent episodes of hypoglycemia.

Main drug interactions: Beta-blockers can potentiate hypotension, particularly when used with other classes of anti-hypertensives and can result in bradyarrhythmias when administered with other AV nodal blocking agents.

Main side effects: Hypotension, symptomatic bradycardia, dry mouth, sexual side effects.

Calcium channel blockers

- Several small studies have been performed to evaluate for any clinical benefit from calcium channel blockers in HFpEF; however, no well-designed recent studies have shown any clinical benefit.

Phenotype-guided use: There is little evidence to support routine use of calcium channel blockers in HFpEF; however, refractory hypertension can benefit from the use of dihydropyridine calcium channel blockers whereas tachyarrhythmias can benefit from non-dihydropyridine calcium channel blockers.

Standard dosage: dosing and frequency is dependent on the specific calcium channel blocker used and indication.

Contraindications: Hypotension (systolic blood pressure < 80 mmHg), bradycardia (for non-dihydropyridine agents), chronotropic intolerance (for non-dihydropyridine agents).

Main side effects: Hypotension, symptomatic bradycardia, peripheral edema (for dihydropyridine agents).

Digoxin

- The DIG-PEF study showed no long-term effect on mortality or incidence of heart failure hospitalizations in patients with EF of > 45% [31].

Phenotype-guided use: There is no evidence to support the use of digoxin in patients with HFpEF and growing evidence suggesting potential adverse outcomes in patients treated with digoxin. However, digoxin may be useful in patients who have RV dysfunction for its effects on RV inotropy.

Loop diuretics

- Although there are no major clinical trials directly studying loop diuretics in patients with chronic HFpEF, they remain a mainstay of treatment for maintenance of euvolemia and relief of pulmonary congestion.
- The loop diuretic torsemide/torasemide can affect collagen cross-linking and in patients with hypertensive heart disease has been shown to improve left ventricular diastolic dysfunction [32].
- The CHAMPION trial utilized direct hemodynamic monitoring with the use of the CardioMEMS heart monitor (see below) to direct titration of diuretics to reduce LV diastolic pressures and prevent transition to decompensated heart failure. The study showed that treatment with loop diuretics guided by this implantable pulmonary artery pressure monitor significantly decreased the frequency of heart failure hospitalization in patients with HFpEF [33, 34].

Phenotype-guided use: The use of loop diuretics to lower LV filling pressures, reduce pulmonary artery pressures, and improve loading of the right ventricle plays a primary role in most patients with HFpEF as a means of reducing symptoms of dyspnea and exercise intolerance. They should be used as a first-line diuretic agent in patients with diabetes mellitus and have utility when more powerful diuresis is needed than can be obtained from thiazide/thiazide-like diuretics. In patients with evidence of diuretic resistance or with lower glomerular filtration rates, the use of a higher potency agent with greater bioavailability such as bumetanide or torsemide is preferable. Once initial diuresis is achieved and the HFpEF patient is euvolemic, the dose of loop diuretic should be minimized with PRN dosing for intermittent fluid overload.

Standard dosage: Dosing and frequency is dependent on the specific loop diuretic used along with patients underlying renal function. Hypotension, acute kidney injury, or hypokalemia may limit dosing.

Contraindications: Anuric renal failure, severe hypotension (SBP < 80 mmHg).

Main side effects: Hypotension, acute kidney injury, hypokalemia, sulfa allergy (if sulfa allergy is present, ethacrynic acid can be used).

Thiazide diuretics

- Although prospective trials testing thiazide and thiazide-like diuretics in patients with HFpEF have not been performed, two studies have shown

benefit from their use in preventing the development of HFpEF. The ALLHAT trial showed chlorthalidone to significantly reduce the occurrence of new-onset, hospitalized HFpEF compared with alternative anti-hypertensives including the ACE inhibitor lisinopril [35].

- The HYVET study showed significant benefits in very elderly (> 80 years old) patients with the use of indapamide (with or without additional ACE inhibitor to achieve target blood pressures of less than 150/80 mmHg) with reduction in incidence of heart failure, cardiovascular mortality, and stroke [36].

Phenotype-guided use: Thiazide and thiazide-like diuretics may be used as a diuretic/anti-hypertensive agent when possible given their ability to reduce occurrence of new-onset heart failure, and in patients already diagnosed with HFpEF for their ability to potentially reduce HF exacerbation events. Higher-potency thiazide diuretics such as metolazone can be useful as adjunctive therapy to loop diuretics in patients with significant volume overload such as in right-sided HF with the cardiorenal syndrome outcomes.

Standard dosage: Dosing and frequency, just as with other diuretics and anti-hypertensives used is dependent on the specific drug and indication. Initiation should begin with the lowest possible dose and progressively be uptitrated over serial visits as required for target blood pressure.

Contraindications: Creatinine clearance < 10 mL/min (ineffective), hypotension (SBP < 80 mmHg), or in patients with impaired fasting glucose/diabetes mellitus (relative contraindication) [37, 38].

Main side effects: Hypokalemia, hypochloremic alkalosis, hypomagnesemia, hyponatremia (electrolyte disturbances can be minimized when used in conjunction with ACE inhibitors or ARBs), gout (hyperuricemia), or sulfa allergy.

Mineralocorticoid receptor antagonists

- The mineralocorticoid receptor antagonist (MRA) spironolactone was tested in HFpEF patients in the TOPCAT trial where it failed to significantly reduce the primary endpoint (death from cardiovascular causes, aborted cardiac arrest, or hospitalization for management of heart failure) in the overall trial population, a point of significance as subsequent analysis of the study revealed considerable regional disparities between patients enrolled in the Americas vs. the Russian Federation [39]. In patients enrolled in the Americas, there was a significant reduction in the primary composite outcome, suggesting inconsistencies in enrollment or a patient population without heart failure incapable of benefit from the study drug primarily enrolled in Russia and Georgia [40]. Furthermore, a recent report of serum samples evaluated from patients Russia/Georgia randomized to receive spironolactone revealed an absence of detectable metabolites from the drug suggesting that many were not actually receiving the therapy.
- It is thought that in addition to the benefits from spironolactone's anti-hypertensive and diuretic properties, it may exert saltatory antifibrotic effects on patients with advanced collagen deposition and cardiac remodeling.

Phenotype-guided use: Spironolactone is a mainstay of treatment in HFpEF and should be considered in all patients with elevated BNP, prior history of HF hospitalization, or evidence of volume overload. In any patient on loop diuretics in whom potassium supplementation is considered, spironolactone should be administered instead (if not contraindicated) [41]. MRAs added in sequential blockade to the nephron can be synergistic with loop diuretics, helping to compensate for the resistance that may develop in chronic heart failure and balancing potassium homeostasis. In patients with early-stage HFpEF without overt volume overload, MRAs have not been shown to improve exercise tolerance based on the results of the ALDO-DHF trial.

Standard dosage: Spironolactone is typically started at 12.5 or 25 mg and uptitrated serially to daily doses as high as 100 mg as tolerated by blood pressures and with monitoring for hyperkalemia or acute kidney injury.

Contraindications: hypotension (systolic blood pressure < 80 mmHg), serum creatinine > 2.5 mg/dL, estimated GFR < 30 ml/min/1.73 m^2, or potassium > 5.0 mEq/L.

Main side effects: Hyperkalemia, hypotension, renal dysfunction, gynecomastia (eplerenone, equivalent dose = 2 × spironolactone dose, can be used in patients who develop gynecomastia).

Nitrates

- Nitrates in HFpEF were studied in the NEAT-HFpEF trial in which therapy with isosorbide mononitrate failed to show any significant increase in activity levels as measured by accelerometer [42]. The study revealed a trend towards reduced activity levels in patients receiving higher doses of the study medication. The somewhat negative outcomes from the trial may be explained at least in part by increased hypotension/decreased preload, pharmacologic tolerance, and increased cerebral vasodilation compared to systemic vasodilation (resulting in headaches).

Phenotype-guided use: There is no role for nitrates in the routine treatment of HFpEF, and in general, their use should be avoided except in patients with known epicardial coronary artery disease or microvascular dysfunction with symptoms of angina.

Phosphodiesterase-5 inhibitors

- The phosphodiestase-5 inhibitor sildenafil was tested in a small, prospective, randomized, placebo-controlled study evaluating its role in HFpEF with concurrent (post-capillary) pulmonary hypertension and showed significant improvement in pulmonary pressures, RV function, LV relaxation, and several other hemodynamic measures compared with placebo [43].
- The results of the larger, multicenter, placebo-controlled randomized clinical trial RELAX-HF showed no significant effect on exercise capacity, clinical status, quality of life, LV remodeling, diastolic function, or pulmonary artery systolic function [44].

Phenotype-guided use: The results of the RELAX-HF trial suggest that there is no role for PDE-5 inhibitor therapy in the general HFpEF population. There

may be a role, however, for PDE-5 inhibitors in a subclass of patients with elevated pulmonary arterial pressures and right ventricular dysfunction such as is in HFpEF patients with combined post- and pre-capillary pulmonary hypertension [45]. This assertion has not been adequately, however. Given the lack of evidence, routine use of pulmonary vasodilators, even in patients with HFpEF and combined post- and pre-capillary pulmonary hypertension, is not recommended. Rather, enrollment in clinical trials such as SERENADE (endothelin receptor antagonist), SOUTHPAW (prostacyclin), or HELP-PH-HFpEF (levosimendan) is recommended for these patients.

Statins

- Observational studies and small phase 2 clinical trials have suggested improved outcomes in patients with HFpEF treated with statins [46, 47]. The benefits are thought to be derived primarily from the systemic anti-inflammatory effects provided with statin use which can also improve endothelial function, rather than the lipid-lowering effects [20].

Phenotype-guided use: Statins should be used at a baseline for management of cholesterol levels per ACC/AHA guidelines as well as would normally be indicated in patients with diagnosis of coronary artery disease, diabetes mellitus, or chronic kidney disease. However, if a patient does not otherwise have a classical indication, it would not be unreasonable to initiate a statin medication, justified by its anti-inflammatory effects.

Standard dosage: dosing is agent-dependent and typically can be directed per AHA/ACC "Treatment of Blood Cholesterol to Reduce ASCVD Risk" guidelines, although specific dosing and choice of statin has not been compared prospectively in HFpEF patients specifically [22].

Contraindications: Class intolerance to statin medications, acute liver disease, unexplained transaminitis, pregnancy.

Main side effects: Transaminitis, myalgias/arthralgias, myopathy.

Device therapy

Implantable pulmonary artery hemodynamic sensor (CardioMEMS)

- The CardioMEMS was approved for us in the USA by the FDA in October of 2014 for patients with NYHA class III symptoms and a prior hospitalization for heart failure based on the results of the CHAMPION CardioMEMS trial, where an implantable pulmonary artery pressure sensor allowed for remote hemodynamic monitoring and early response to the progressive rise in LV pressures that typically precede decompensated heart failure hospitalization. The original study enrolled 550 patients with heart failure and included patients with both reduced and preserved ejection fractions and showed a marked reduction in heart failure admissions [34].
- Subsequent analysis of the patients with HFpEF enrolled in the CHAMPION trial revealed reduced hospitalizations and that much of the benefit seen in the trial was attributable to patients with HFpEF [34].

Phenotype-guided use: The CardioMEMS device should be considered in any patient with HFpEF and NYHA III symptoms who has been previously hospitalized for heart failure exacerbation, and is ideal for those patients in whom finding optimal balance of diuretic dosing and kidney function is a challenge (these patients are more often those with right-sided HF and the cardiorenal syndrome).

Standard procedure: The CardioMEMS HF system is a sensor that is implanted in a cardiac catheterization lab and comes attached to an over-the-wire delivery catheter accommodating an exchange-length guidewire. Venous access is obtained via the right common femoral vein, although off-label right internal jugular venous access may be considered in patients with morbid obesity or severe tricuspid regurgitation. Venous access does not routinely require interruption of anticoagulation, nor is anticoagulation required for the procedure. Selective pulmonary angiography and pressure monitoring is performed with use of ~ 10 cc of contrast in the average patient. The ideal sensor location is within an inferior and lateral branch of the left pulmonary artery due to its more posterior orientation, allowing optimal wireless communication of the device (stronger signal strength) and placement is confirmed with ~ 2 min of fluoroscopy. A Swan-Ganz catheter is inserted concurrently to measure pulmonary artery pressures and to calibrate the device, and a wireless communication "wand" is tested while the patient remains in the catheterization lab. Subsequent follow-up utilizes a dedicated portable wireless transmission device for the patient so that hemodynamic data can be sent to the patient's providers.

Contraindications: Patients must be able to take dual anti-platelet agent or anticoagulants for 1 month post implant.

Complications: Challenges may arise in the presence of severe tricuspid regurgitation which can make a trans-femoral approach difficult, entrapment of the delivery catheter in the tricuspid valve apparatus, non-optimal sensor location upon deployment, sensor movement following deployment, anatomical complications (inability to advance the guidewire), bleeding events (groin hematoma), or delivery system failure (which would require a snare to remove the delivery system), although in experienced centers, these complications are very rare.

Special points: The use of a CardioMEMS device requires continued follow-up of remotely accessible pressure-monitoring data and often benefits from a dedicated program including a multidisciplinary team for follow-up.

Cost/cost-effectiveness: Analysis of the results from the CHAMPION clinical trial using economic modeling suggested that the use of the CardioMEMS pulmonary artery pressure-monitoring device was a cost-effective measure (based on healthcare utilization, survival, and quality of life) over a 5-year follow-up period, with 2.56 vs. 2.15 quality-adjusted life years in the treatment group vs. control group, respectively [48].

Lifestyle modifications

Caloric restriction and aerobic exercise

- A recent randomized examined the effects of diet, exercise, or both in older, obese patients with chronic HFpEF, with primary outcomes of peak oxygen consumption and quality of life. Both caloric restriction and aerobic exercise were shown to significantly increase

peak oxygen consumption, although only caloric restriction significantly improved quality of life scores. The study provided objective evidence for improvement in exercise capacity with a short course of guided therapy, with likely additive effects from combined caloric restriction and aerobic exercise [19].

Phenotype-guided use: Dietary counseling and encouragement to participate in regular aerobic exercise should be encouraged for any patient with HFpEF. Caloric restriction targets the multiple adverse effects attributed to increased body adiposity, including its contribution to pro-inflammatory environment that yields multi-system dysfunction.

Emerging therapies

There are numbers of promising therapies in various stages of testing for patients with HFpEF, many targeted towards the systemic abnormalities now understood to be present in most patients with the syndrome, but some more targeted towards specific patient phenotypes. In either case, one of the central debates at the root of designing subsequent clinical trial regards the most appropriate selection of endpoints, with the dilemma of whether a reduction in mortality in a patient group characterized by elderly age, multiple comorbidities, and considerable debility is indeed most appropriate. Or, rather, whether a focus on targeting increased activity levels, improved quality of life, and/or reduction in hospitalizations might be of greater value to patients and the healthcare system at large. Future trials may shift focus to these more novel endpoints, as some already have.

Neprilysin inhibitors

- The neprilysin inhibitor sacubitril aims to target the multi-faceted and beneficial effects of protein kinase-G (PKG) signaling in the cardiomyocyte, including antifibrotic, antihypertrophic, and lusitropic effects (with the latter provided via its phosphorylation of the giant molecular protein spring, titin). PKG itself is stimulated either through NO-dependent activation of soluble guanylate cyclase (sGC) or via natriuretic peptide receptor-associated guanylate cyclase (rGC). The use of a neprilysin inhibitor is proposed to reduce natriuretic peptide (NP) breakdown, and thus promotes guanylate cyclase signaling, leading to increased PKG stimulation and its multiple beneficial downstream effects [49–51].
- The phase 2 PARAMOUNT trial prospectively evaluated the angiotensin receptor blocker/neprilysin inhibitor (ARNI) valsartan/sacubitril vs valsartan alone in HFpEF patients, with a primary endpoint of reduced NT-proBNP. The study showed a significant reduction in serum NP levels in the arm receiving the ARNI at 12 weeks, paving the way for the PARAGON-HF trial, an ongoing Phase 3 clinical trial evaluating the efficacy of valsartan/sacubitril compared to valsartan on morbidity and mortality in patients with HFpEF.

Contraindications/limitations: Use limited by anti-hypertensive effects and renal function.

Soluble guanylate cyclase stimulators

- As an alternative means to stimulate sGC, increase cGMP, and ultimately activate PKG, an sGC stimulator (vericiguat) was tested in HFpEF patients in the SOCRATES-PRESERVED trial, a phase IIb randomized clinical trial [52], and was found to be ineffective in reducing NTproBNP and LA volume. However, there was a suggestion of improved physical activity at the highest doses of vericiguat. The VITALITY (vericiguat) and CAPACITY (praliciguat, another sGC stimulator) are trials currently examining the effect of sGC stimulators on exercise tolerance in HFpEF.
- Although sGC stimulators have been shown to improve exercise tolerance as well as quality of life surveys in patients with various forms of pulmonary hypertension, they are limited by potent blood pressure lowering in some patients.

Contraindications/limitations: nitrates and PDE5 inhibitors.

Sodium-glucose transporter-2 (SGLT-2) inhibitors

- SGLT-2 inhibitors have been shown in the EMPA-REG and DECLARE trials to reduce HF hospitalizations in high-risk patients with diabetes, and are currently being tested in dedicated trials of patients with HFpEF and HFrEF, with and without diabetes.
- While we await the results of these clinical trials, in patients with diabetes and HFpEF, SGLT-2 inhibitors can be used for refractory fluid retention and/or to minimize exposure to high-dose loop diuretics.

Transcatheter interatrial shunt device

- Based on the common thread in HFpEF of a exaggerated rise in left atrial pressures with exercise, there has been consideration given for targeting of the left atrium with device therapy aimed at ameliorating such inappropriate pressure elevation. Such a device, a transcatheter-delivered interatrial shunt device (IASD), was tested in a phase 1 open-label clinical trial, called "REDUCE LAP-HF", evaluating feasibility and safety of the device in patients with HFpEF, an elevated pulmonary capillary wedge pressure (PCWP) > 15 mmHg at rest (or > 25 mmHg during exercise), and LVEF > 40%. The study showed promise in 64 patients who underwent placement of the IASD, with no major adverse events or peri-procedural complications and more than half of patients with a reduction in PCWP at rest and with exercise after 6 months [53].
- With the promising results of the phase I study, a follow-up prospective, multicenter, randomized controlled study (REDUCE LAP-HF I) to evaluate the IASD system in HFpEF patients > 40 years old with NYHA class III/IV symptoms was performed and revealed that those patients randomized to IASD had a significant reduction in PCWP during exercise at 1 month, and through 1 year of follow-up had no significant differences in safety endpoints compared to control patients [54–56]. A pivotal trial (REDUCE

LAP-HF II) is now underway to examine the effect of the IASD on clinical outcomes in HFpEF.

Conclusions

HFpEF remains a challenging clinical syndrome to manage but is not untreatable. Using currently available therapies, patients can be optimized to enjoy increased exercise capacity and reduced HF hospitalizations. Much work remains to help deepen our understanding of the different disease states at play among different HFpEF phenotypes targeted therapies may continue to be developed. However, therapeutics currently being tested in clinical trials offer real hope for effective new tools to be added to the arsenal with which we treat this syndrome.

Compliance with Ethical Standards

Conflict of Interest

Dr. Silverman reports no conflicts of interest.

Dr. Shah reports receiving research grants from the National Institutes of Health (R01 HL107577, R01 HL127028, and R01 HL140731), Actelion, AstraZeneca, Corvia, and Novartis; and has served as a consultant/advisory board member for Abbott, Actelion, AstraZeneca, Amgen, Bayer, Boehringer-Ingelheim, Cardiora, Coridea, CVRx, Eisai, Ionis, Ironwood, Merck, MyoKardia, Novartis, Pfizer, Sanofi, Tenax, and United Therapeutics.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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