JAMA | Review

Heart Failure With Preserved Ejection Fraction
A Review

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IMPORTANCE Heart failure with preserved ejection fraction (HFpEF), defined as HF with an EF of 50% or higher at diagnosis, affects approximately 3 million people in the US and up to 32 million people worldwide. Patients with HFpEF are hospitalized approximately 1.4 times per year and have an annual mortality rate of approximately 15%.

OBSERVATIONS Risk factors for HFpEF include older age, hypertension, diabetes, dyslipidemia, and obesity. Approximately 65% of patients with HFpEF present with dyspnea and physical examination, chest radiographic, echocardiographic, or invasive hemodynamic evidence of HF with overt congestion (volume overload) at rest. Approximately 35% of patients with HFpEF present with "unexplained" dyspnea on exertion, meaning they do not have clear physical, radiographic, or echocardiographic signs of HF. These patients have elevated atrial pressures with exercise as measured with invasive hemodynamic stress testing or estimated with Doppler echocardiography stress testing. In unselected patients presenting with unexplained dyspnea, the H2FPEF score incorporating clinical (age, hypertension, obesity, atrial fibrillation status) and resting Doppler echocardiographic (estimated pulmonary artery systolic pressure or left atrial pressure) variables can assist with diagnosis (H2FPEF score range, 0-9; score >5 indicates more than 95% probability of HFpEF). Specific causes of the clinical syndrome of HF with normal EF other than HFpEF should be identified and treated, such as valvular, infiltrative, or pericardial disease. First-line pharmacologic therapy consists of sodium-glucose cotransporter type 2 inhibitors, such as dapagliflozin or empagliflozin, which reduced HF hospitalization or cardiovascular death by approximately 20% compared with placebo in randomized clinical trials. Compared with usual care, exercise training and diet-induced weight loss produced clinically meaningful increases in functional capacity and quality of life in randomized clinical trials. Diuretics (typically loop diuretics, such as furosemide or torsemide) should be prescribed to patients with overt congestion to improve symptoms. Education in HF self-care (eg, adherence to medications and dietary restrictions, monitoring of symptoms and vital signs) can help avoid HF decompensation.

CONCLUSIONS AND RELEVANCE Approximately 3 million people in the US have HFpEF. First-line therapy consists of sodium-glucose cotransporter type 2 inhibitors, exercise, HF self-care, loop diuretics as needed to maintain euvolemia, and weight loss for patients with obesity and HFpEF.

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In the US, it is estimated that more than 6 million persons have heart failure (HF), and HF is the second most common cause of hospitalization among adults.[1] HF has been classified into subgroups according to left ventricular ejection fraction (EF) at HF diagnosis. HF with reduced EF (HFrEF) is defined by an EF of 40% or less, HF with mildly reduced EF is defined by an EF of 41% to 49%, and HF with preserved EF (HFpEF) is defined by an EF of 50% or greater.[2] Currently, HFpEF accounts for approximately 50% of all diagnoses of HF. HFpEF is challenging to diagnose, pathophysiologic mechanisms remain incompletely understood, and effective treatment is limited. This review summarizes current evidence regarding the epidemiology, pathophysiology, clinical presentation, diagnosis, and treatment of HFpEF.

Methods

A PubMed literature search was conducted for English-language articles published from January 1, 2000, to December 6, 2022, using the terms "HFpEF" and "heart failure, diastolic." Articles with larger sample sizes, longitudinal studies, and randomized clinical trials were prioritized for inclusion, along with guideline statements. Of 105 included articles, 28 were randomized clinical trials, 4 were meta-analyses, 6 were guidelines, 23 were reviews, and 44 were cross-sectional or longitudinal observational studies.

Epidemiology

By the year 2030, the prevalence of HF (with any EF) in the US is projected to reach approximately 8 million cases, representing about 3.0% of people 18 years and older.[3] Globally, more than 64 million persons are estimated to have HF.[4] In persons surviving to 45 years of age, estimates of the subsequent lifetime risk of HF from different cohorts vary by sex and race and range from 20% to 46%.[5,6] Approximately 50% of patients with HF have HFpEF.[7,8] The prevalence of HFpEF among persons hospitalized for HF increased from approximately 38% in 1987 to approximately 54% in 2001,[9] with increases due in part to improved recognition.[8,10] The prevalence of HFpEF relative to HFrEF may

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Table 1. Multisystem Structural and Functional Perturbations in Heart Failure With Preserved Ejection Fraction (HFpEF)

Abnormality	Frequency, %
Cardiac[11,15-25]	
Altered left ventricular geometry; concentric hypertrophy or remodeling	60
Abnormal left ventricular diastolic function (impaired relaxation, increased stiffness)	80-90
Myocardial fibrosis	Mild, 66; moderate, 17; severe, 10
Myocardial microvascular dysfunction and/or reduced density of microvessels	80
Increased left ventricular systolic stiffness	70
Subtle resting left ventricular systolic dysfunction and impaired systolic reserve	70
Left atrial enlargement and/or systolic and diastolic dysfunction	70
Increased epicardial fat	40-50 among patients with obesity
Pericardial alteration that limits filling of the left ventricle (constraint)	30
Chronotropic incompetence (inability to increase heart rate appropriately)	70-80
Atrial fibrillation	40-50
Epicardial coronary artery disease	50-65
Pulmonary[26-29]	
Postcapillary or combined pre- and postcapillary group 2 pulmonary hypertension	80
Pulmonary arterial, venous, and small vessel remodeling	20
Restrictive pulmonary physiology	Mild, 40-50; moderate, 10
Decreased diffusing capacity for carbon monoxide	Mild, 50-60; moderate, 20
Right side of the heart[30-32]	
Right ventricular diastolic dysfunction	50
Right ventricular dilatation and systolic dysfunction	30
Right atrial enlargement and/or systolic and diastolic dysfunction	50
Vascular[17,22,33]	
Increased arterial stiffness	70
Impaired systemic microvascular function	70
Reduced systemic venous compliance and capacitance	70
Systemic[11,22,34]	
Obesity	60-70
Dysglycemia/insulin resistance	60-70
Neurohumoral activation	30
Reduced skeletal muscle mass with contractile dysfunction and fatty replacement	60
Skeletal muscle microvascular dysfunction and rarefaction	50
Increased visceral fat	70
Kidney[35]	
Reduced glomerular filtration rate	60
Reduced sodium excretion	70
Hepatic[36]	
Nonalcoholic fatty liver disease	40-50
Congestive hepatopathy	10

continue to increase due to a combination of improved recognition, reductions in death from other comorbidities that can lead to HFpEF, increases in the age of the population, and increasing prevalence of obesity.[8,11] Older age and obesity are risk factors for HFpEF.

The incidence of HFpEF varies from 1 to 4 cases per 1000 person-years depending on cohort characteristics and time period of study.[1,12-14] In a large, multicohort incidence study,[13] risk factors for incident HFpEF included older age (hazard ratio [HR], 2.0 per 10-year increment), hypertension (HR, 1.7), obesity (HR, 1.3 per 4-unit increase in body mass index), diabetes (HR, 1.8), and coronary artery disease (HR, 1.6) (absolute rates not provided).[13] Although observational studies[7] reported that 55% to 65% of patients with HFpEF were women, in the multicohort incidence study, adjusting for age and other risk factors, the incidence of HFpEF was numerically but not statistically significantly higher in women vs men.[13] In contrast, the incidence of HFrEF was substantially lower among women than men, even after adjusting for age and other risk factors.[13] Data regarding associations between race, ethnicity, and social determinants of health and HFpEF epidemiology and outcomes are needed.[8]

Pathophysiology

There are multisystem abnormalities present in HFpEF, including cardiac,[11,15-25] pulmonary,[26-29] right side of the heart,[30-32] vascular,[17,22,33] systemic metabolic and skeletal muscle,[11,22,34] kidney,[35] and hepatic[36] structural and functional changes (**Table 1**). Paradigms hypothesized to explain the pathophysiologic processes resulting in these changes have evolved (**Figure 1**). Most patients with HFpEF have a history of hypertension. Randomized clinical trials have shown that treatment of hypertension with the strategies outlined in the American College of Cardiology (ACC)/American Heart Association (AHA) hypertension treatment guidelines[37] reduces HFpEF incidence by up to 40% over 2 to 8 years.[38,39] This evidence suggested that suboptimally controlled hypertension is part of the biological pathway to developing HFpEF (Figure 1A) and implied that all patients with HFpEF have hypertension-induced ventricular hypertrophy and pathological myocardial fibrosis. However, less than 50% of patients with HFpEF meet criteria for ventricular hypertrophy, myocardial fibrosis was shown to be significantly but modestly greater in individuals with HFpEF (median fibrosis area, 9.6% [95% CI, 6.8%-13.5%]) than controls (median fibrosis area, 7.1% [95% CI, 5.1%-9.0%]), and both changes in myofilament protein (titin) stiffness and myocardial fibrosis are associated with diastolic dysfunction in HFpEF.[19,21,25] These observations and others suggested alternative hypotheses for the multisystem alterations (Table 1) seen in HFpEF. Proinflammatory comorbid conditions may promote HFpEF through cardiac microvascular endothelial cell inflammation, increased oxidative stress with decreased nitric oxide–soluble guanylate cyclase-protein kinase G signaling, and impaired processes that clear dysfunctional proteins (unfolded protein response) with resultant myocardial structural and functional impairment and coronary microvascular dysfunction (Figure 1B).[40] However, large clinical trials have not yet investigated the effect of anti-inflammatory drugs on clinical outcomes in HFpEF, and clinical trials of agents designed to treat impaired nitric oxide signaling have shown no benefit in HFpEF.[41] Thus, the role of inflammation and reduced nitric oxide bioavailability in the development of HFpEF remains unclear. It is possible that multiple biological pathways result in HFpEF, with manifestations that may require distinct therapies (Figure 1C). Identifying HFpEF phenogroups with unique and therapeutically relevant pathophysiology is a major area of ongoing research in HFpEF.[41,42]

Clinical Presentation

The most common presenting symptom of HF is dyspnea, either on exertion only or at rest and with exertion. Approximately 65% of patients with HFpEF present with dyspnea and overt congestion,

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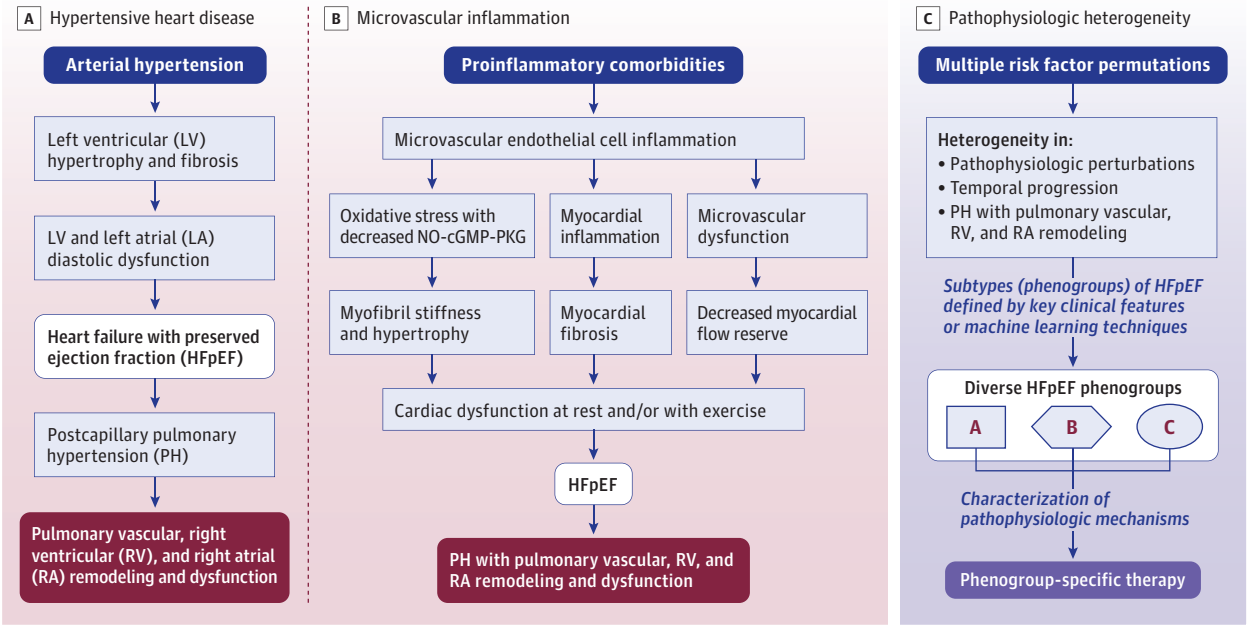
Figure 1. Pathophysiologic Paradigms in Heart Failure With Preserved Ejection Fraction



The pathophysiology paradigms are shown as a progression, although some processes are occurring simultaneously. Phenogroups A-C are theoretical phenogroups that could be based on various physiologic characteristics.

NO-cGMP-PKG indicates nitric oxide–soluble guanylate cyclase-protein kinase G signaling.

suggested by clinical signs such as peripheral edema, ascites, jugular venous distention, S_3 gallop sounds, or elevated cardiac filling pressures[43] (**Figure 2**). Other patients (approximately 35%) present with dyspnea on exertion but do not have evidence of congestion on physical examination.[43] These individuals have "unexplained dyspnea" (Figure 2) and require further diagnostic testing as outlined below to establish the presence of HFpEF.[2,16,44,45]

In patients with confirmed HFpEF, pulmonary disease (obstructive or restrictive lung disease; approximately 30%), anemia (approximately 50%), frailty (up to 50%), and atrial fibrillation (approximately 40% at diagnosis) are common.[24,46-48] Evaluating patients with dyspnea and HF risk factors for HFpEF, even if they have comorbid conditions, is important because multifactorial dyspnea is common and specific therapy for HFpEF exists.

Some patients may experience relatively rapid onset of volume overload with elevation in cardiac filling pressures and worsening of symptoms and signs of HF (acute decompensation).[2,49] Factors contributing to acute decompensation vary with cohort characteristics[50,51] and are unknown in up to 50% of patients, but, in 1 study,[51] included poorly controlled hypertension (13%), atrial fibrillation (AF) with rapid heart rate (9%), nonadherence to medications or dietary (sodium) restrictions (13%), or another physiological stressor (eg, anemia, infection, thyroid dysfunction, nonsteroidal anti-inflammatory drug use).

Diagnosis

All patients with HF symptoms should undergo echocardiography (Figure 2) to assess EF, diastolic function, atrial and ventricular size, ventricular wall thickness (global or regional wall thickening), valve disease, or wall motion abnormalities suggesting prior myocardial infarction.[2,49] A diagnosis of HFpEF requires evidence of increased cardiac filling pressures (right atrial pressure, pulmonary capillary wedge pressure, or left ventricular end-diastolic pressure) at rest or with exercise.[2] Increased cardiac filling pressures can be detected by direct measurement at right heart catheterization (RHC) or can be inferred by findings on physical examination, chest radiography, echocardiography, or natriuretic peptide assays or the H2FPEF score (Figure 2).[2,44,45]

Patients with HFpEF and congestion (Figure 2) present with the physical signs noted above and symptoms including exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea, fatigue, and edema. Bendopnea refers to dyspnea associated with bending over,[52] occurs in approximately 30% to 50% of patients with HF (regardless of EF),[52,53] and is associated with a further elevation of filling pressures while bending over or while in a bent position.[52] Patients with overtly congested HFpEF usually have chest radiographic evidence of cardiomegaly and pulmonary vascular congestion and Doppler echocardiography findings consistent with HF (Figure 2).[2,49-51]

In HFpEF presenting as "unexplained dyspnea" (Figure 2), dyspnea on exertion, bendopnea, and fatigue are common, and patients may have chest pain even in the absence of epicardial coronary disease. In these patients, physical signs (as above) and chest radiographic and echocardiographic evidence of congestion are usually absent (Figure 2); symptoms may be attributed to obesity and/or deconditioning if further assessment with stress hemodynamics is not performed.

Brain natriuretic peptide (BNP; biologically active) and N-terminal fragment of the prohormone BNP (NT-proBNP; biologically inert biomarker) are produced by cleavage of a precursor molecule (proBNP) in normal cardiomyocytes. Their production and release into the circulation are increased with elevated systolic or diastolic intracardiac pressures that increase transmural ventricular wall stress and cardiomyocyte stretch.[54,55] Based on multiple clinical studies in the emergency department evaluation of patients with acute dyspnea and

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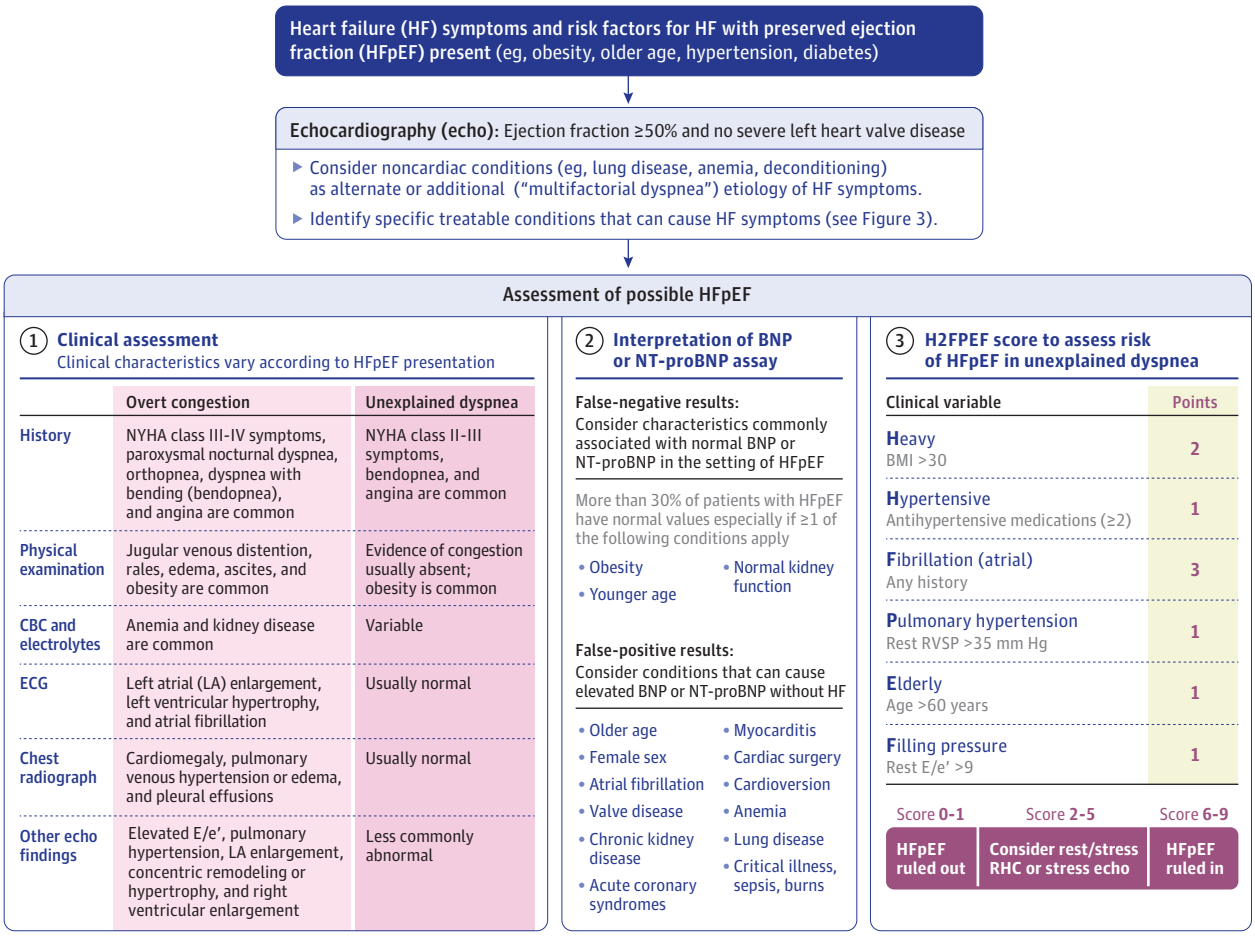
Figure 2. Diagnostic Algorithm for Heart Failure With Preserved Ejection Fraction



An approach to the assessment of patients with suspected HFpEF is shown. BMI indicates body mass index; CBC, complete blood count; E/e', ratio of early diastolic mitral inflow blood velocity to mitral annular tissue velocity; ECG, electrocardiogram; NT-proBNP, N-terminal prohormone brain natriuretic peptide; NYHA, New York Heart Association; RHC, right heart catheterization; RVSP, right ventricular systolic pressure.

in patients presenting with dyspnea in nonacute care settings, HF guidelines[2,49] indicate partition values to "rule out" HF in the acute (BNP <100 pg/mL or NT-proBNP <300 pg/mL)[49] and nonacute (BNP <35 pg/mL or NT-proBNP <125 pg/mL)[2,49] care settings, with negative predictive values for these ranges estimated to be approximately 94% to 98%.[49] However, at least 30% of patients with HFpEF and elevated resting atrial pressures documented at the time of RHC have plasma levels of BNP less than 100 pg/mL or NT-proBNP levels less than 125 pg/mL.[56,57] Patients with normal vs elevated levels of BNP/NT-proBNP are younger (63 vs 71 years), more often obese (79% vs 57%), have better kidney function (estimated glomerular filtration rate, 72 vs 57 mL/min/1.73 m^2), and have lower prevalence of permanent atrial fibrillation (7% vs 34%).[56,57] Normal levels of BNP/NT-proBNP in certain subsets of patients with HFpEF are attributed to differences in factors that affect natriuretic peptide production and clearance.[54,58,59] At the optimal discriminatory value (NT-proBNP >275 pg/mL), sensitivity (59%) and specificity (77%) to detect HFpEF are poor in patients with exertional dyspnea but no overt congestion.[44] In addition, several cardiac and noncardiac conditions (eg, atrial fibrillation, acute coronary syndromes, pulmonary embolism, advanced age, lung disease, kidney dysfunction) can cause elevated BNP levels in the absence of HF (false-positive results; Figure 2).[2] In summary, the predictive characteristics of BNP/NT-proBNP assays are insufficient to rule out HFpEF, particularly in younger patients, those with sinus rhythm, and those with obesity and/or normal kidney function.

Approximately 50% to 60% of patients presenting with dyspnea without low EF or other apparent etiologies have HFpEF, which can be identified based on elevated filling pressures with exercise when evaluated with direct invasive measurement of atrial pressures at RHC[2,16,44,45] or with exercise echocardiography.[60] The H2FPEF score (Figure 2; range, 0-9)[44] is recommended by the 2022 ACC/AHA HF guidelines[2] to estimate the likelihood of HFpEF in patients with unexplained dyspnea. Although the predictive values of risk scores vary with disease prevalence, in a consecutive series of patients with normal EF and unexplained dyspnea (HFpEF prevalence of 50%-60%),[44,45] a score of 6 or higher was associated with more than 95% probability of HFpEF, whereas a score of 0 or 1 was associated with less than a 25% probability of HFpEF. Additional testing (rest/exercise RHC or rest/exercise Doppler echocardiography) is required in patients with intermediate (2-5) scores.[44,45]

The RHC directly measures atrial pressures and is considered the criterion standard (100% sensitivity and specificity; C statistic, 1.0) for

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Figure 3. Heart Failure With Preserved Ejection Fraction (HFpEF) Differential Diagnosis

Treatable conditions that can cause heart failure (HF) symptoms with a preserved ejection fraction (EF)

Condition	Suggestive echo findings	Potential diagnostic evaluation	Treatment
Hypertrophic cardiomyopathy	Asymmetric or global increase in left ventricular (LV) wall thickness	▸ Cardiac magnetic resonance imaging (MRI) and genetic testing ▸ Typical characteristics include young age, family history of HF or sudden death, and no history of hypertension (HTN)	▸ Genetic counseling ▸ Medical, surgical, or transcatheter therapies for patients with obstruction ▸ Medications targeting sarcomere abnormalities (ie, myosin inhibitors)
Amyloid cardiomyopathy	Global increase in LV wall thickness	▸ Calculate transthyretin amyloid cardiomyopathy (ATTR-CM) score Age 60-69 y +2; Age 70-79 y +3; Age ≥80 y +4 Male sex +2; HTN diagnosis −1; EF <60% +1 Posterior wall thickness ≥12 mm +1; Relative wall thickness >0.57 +2 (ATTR-CM score range, 1-10) ▸ If ATTR-CM score ≥6, obtain ATTR-CM scintigraphy ▸ If scintigraphy result is positive, rule out AL amyloid and familial amyloid	▸ Chemotherapy or transplant for AL amyloid ▸ Medical therapies targeting transthyretin deposition (currently transthyretin stabilizers such as tafamids)
High-output heart failure	Elevated cardiac index ≥3.54	▸ Evaluate for suspected etiology ▸ Common etiologies include obesity, arteriovenous shunts, liver disease, lung disease, and myeloproliferative disease	▸ Treat according to etiology
Group 1, 3, 4, or 5 pulmonary hypertension (PH)	PH tricuspid regurgitation velocity >3.4 m/s	▸ Consider group 1, 3, 4, or 5 PH vs HFpEF with advanced group 2 PH ▸ Physical examination findings: loud P_2, right ventricular (RV) lift, clubbing, sclerodactyly, telangiectasia, calcinoses ▸ ECG findings: right atrial enlargement, RV strain, rightward axis ▸ Radiographic findings: central pulmonary artery or right heart enlargement ▸ Consider ventilation perfusion scan, pulmonary function tests (DLCO), and connective tissue disease serology ▸ Right heart catheterization is needed to confirm group 2 vs non-group 2 PH	▸ PH clinic referral ▸ Pulmonary vasoactive therapy ▸ Etiology-specific therapies ▸ Transplant consideration

Condition	Clinical setting	Potential diagnostic evaluation	Treatment
Constrictive pericarditis	• Chest surgery or trauma • Pericarditis history • Connective tissue disease • Few HF risk factors	▸ Cardiac MRI with contrast ▸ Cardiac computed tomography with contrast ▸ Echocardiography with focused respirometry Doppler examination ▸ Hemodynamic catheterization with respiratory examination	▸ Consider anti-inflammatory therapies in patients with active pericardial inflammation ▸ Pericardiectomy
Cardiac sarcoidosis	• Ventricular arrhythmia • Younger age • Extracardiac sarcoid	▸ Cardiac MRI ▸ Fluorodeoxyglucose PET (cardiac and trunk) ▸ Biopsy of PET positive or clinically involved extracardiac sites	▸ Immunosuppression ▸ Sarcoid clinic referral ▸ Rheumatology referral
Coronary artery disease	• Atherosclerosis with or without chest pain	▸ Consider coronary angiography or stress testing because dyspnea can be anginal equivalent ▸ Chest pain is common in HFpEF without epicardial coronary disease ▸ Microvascular disease is common	▸ Observational evidence indicates revascularization improves HFpEF outcomes

DLCO indicates diffusing capacity of the lung for carbon monoxide; echo, echocardiography; PET, positron emission tomography; P_2, pulmonic component of the second heart sound.

HFpEF diagnosis,[61,62] whereas rest/exercise Doppler echocardiography uses surrogate measures for atrial pressures provided by a combination of Doppler variables (E/e' [ratio of early diastolic mitral inflow blood velocity to mitral annular tissue velocity], tricuspid regurgitation velocity, and early diastolic mitral annular tissue velocity [or e']).[63] However, RHC with exercise is not universally available, requires skilled operators, is costly, and is associated with adverse events that include bleeding (0.07%), arrhythmias requiring treatment (0.05%), and major cardiovascular complications (0.2%).[64] Exercise Doppler echocardiography is more widely available, noninvasive, and less costly than RHC. However, the sensitivity of exercise Doppler echocardiography for diagnosing HFpEF is 34% and the specificity is 83% (C statistic, 0.65).[62] An alternative test is cardiopulmonary exercise testing, which measures oxygen consumption and carbon dioxide production and can document the severity of exercise limitation in patients with dyspnea.[65] The sensitivity of cardiopulmonary exercise testing using the peak oxygen consumption value that maximizes discrimination (<17 mL/kg/min) is 80% and the specificity is 76% (C statistic, 0.78) for the diagnosis of HFpEF, making cardiopulmonary exercise testing an inadequate tool for use in isolation.[66]

Differential Diagnosis

It is important to consider conditions that cause HF symptoms but have distinct etiologies and treatments (**Figure 3**), including epicardial coronary artery disease, infiltrative cardiomyopathies such as amyloidosis, causes of pulmonary hypertension not due to HF (groups 1, 3, 4,

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and 5 pulmonary hypertension), constrictive pericarditis, hypertrophic cardiomyopathy, cardiac sarcoidosis, and high-output HF.

Amyloid cardiomyopathy may present with signs and symptoms similar to HFpEF and can be due to monoclonal protein (light chains; AL amyloidosis) or (more commonly) transthyretin (transthyretin amyloid cardiomyopathy [ATTR-CM]) deposition in the heart.[67] ATTR-CM can occur without ("wild type") or with ("familial") TTR gene variants. In studies largely restricted to White persons, ATTR-CM was present in 6% to 17% of older (>60 years) patients (primarily men) presenting with clinical HF, normal EF, and increased left ventricular wall thickness,[68,69] with ATTR-CM prevalence increasing from 5% in the sixth decade to 20% in the ninth decade.[68] The electrocardiogram findings may show low voltage and/or Q waves (despite normal wall motion). Echocardiography and cardiac magnetic resonance imaging can show other suggestive findings. AL amyloid diagnosis relies on measurement of serum-free light chains, serum and urine immunoelectrophoresis, and specific stains if tissue sample (fat, kidney, heart) is obtained.[67] Scintigraphy is 99% sensitive and 86% specific for ATTR-CM if AL amyloidosis has been ruled out.[67] The ATTR-CM score[70] has a range of −1 to 10 and can be used to estimate the likelihood of ATTR-CM (Figure 3), with a C statistic of 0.89; a score of 6 or higher has a sensitivity of 93% and a specificity of 62% for ATTR-CM. Patients with scores of 6 or higher should undergo scintigraphy and, if results are positive, AL amyloidosis should be ruled out and genetic testing should be performed to rule out familial ATTR-CM, even in older persons. Chemotherapy and stem cell transplant are effective for managing AL amyloidosis. In ATTR-CM, TTR stabilizers (currently tafamidis) reduce risk of cardiovascular hospitalization by 32% and mortality by 30%.[67,71]

Prognosis

Patients with HFpEF and normal resting, but abnormal exercise, atrial pressures have higher risk for the combined outcome of mortality or hospitalization for HF compared with people without HFpEF (20 events among 187 patients [10.7%] vs 9 events among 193 patients [4.7%] over a median follow-up of 2.7 years; HR, 2.44 [95 CI, 1.11-5.36]).[43] In-hospital mortality for HFpEF is approximately 2% to 5%.[7] At 5 years after a hospitalization for HFpEF, rehospitalization rates are approximately 80% and mortality rates are approximately 50% to 75%.[7] Overall, patients with HFpEF are hospitalized approximately 1.4 times per year,[7] and annual mortality for HFpEF is approximately 15% in observational studies, with higher mortality rates in older people.[72]

Treatment

First-line therapy for HFpEF includes a sodium-glucose cotransporter type 2 (SGLT2) inhibitor for patients without contraindications, education regarding HF self-care, exercise, weight loss for patients with obesity, and diuretics (usually a loop diuretic) for patients with overt congestion (**Figure 4**).

Two randomized clinical trials of 5988 and 6263 patients (**Table 2**) demonstrated benefit of SGLT2 inhibitors (empagliflozin[76] or dapagliflozin[73] 10 mg orally once daily) vs placebo in patients with HFpEF and New York Heart Association HF class II to IV symptoms, structural heart disease (left atrial enlargement or left ventricular hypertrophy) or a recent HF hospitalization, elevated BNP assay level, and EF greater than 40%. Both studies demonstrated an 18% to 21% reduction in the rate of HF hospitalization or cardiovascular death with SGLT2 inhibitors. Event rates per 100 patient-years were 8.7 with placebo vs 6.9 with empagliflozin (HR, 0.79 [95% CI, 0.69-0.90])[76] and 9.6 with placebo vs 7.8 with dapagliflozin (HR, 0.82 [95% CI, 0.73-0.92]).[73] In both clinical trials, benefit was due to lower rates of HF hospitalizations, with no significant reduction in cardiovascular mortality (Table 2). There were statistically significant, but not clinically meaningful, improvements (relative to placebo) in quality of life scores with both agents (increase in Kansas City Cardiomyopathy score of 1.32 [95% CI, 0.45-2.19] points with empagliflozin and 1.11 [95% CI, 1.03-1.21] points with dapagliflozin) (Table 2). The Kansas City Cardiomyopathy score has a range of 0 to 100 (higher scores are more favorable), with a change in score greater than 5 considered clinically meaningful. A meta-analysis of 5 trials of SGLT2 inhibitors in HF demonstrated similar impact on the rate of HF hospitalizations or cardiovascular death regardless of age, sex, EF, presence of diabetes, body mass index, or kidney function (range allowed in the trials: estimated glomerular filtration rate >20-25 mL/min/1.73 m^2).[74] In smaller studies of 3 months duration, treatment with dapagliflozin (but not empagliflozin) resulted in clinically meaningful improvements in patient-reported Kansas City Cardiomyopathy scores compared with placebo (placebo-corrected change, 5.8 points [95% CI, 2.3-9.2]) and 6-minute walk distance (placebo-corrected change, 20.1-m increase [95% CI, 5.6-34.7]) in patients with HFpEF (Table 2).[75,77]

SGLT2 inhibitors are contraindicated in patients with type 1 diabetes, history of ketoacidosis, recurrent genitourinary infections, or estimated glomerular filtration rate less than 20 mL/min/1.73 m^2. Small (0.2-0.4 mg/dL) increases in serum creatinine, glucosuria, and increases in hematocrit (approximately 2%) are expected based on SGLT2 inhibitor physiology. Some patients have a larger diuretic response to SGLT2 inhibitors, but neither symptomatic hypotension (6.6% vs 5.2%) nor acute kidney injury (12.1% vs 12.8%) were more common in patients with HFpEF treated with SGLT2 inhibitors.[76] Small increases in creatinine with initiation of SGLT2 inhibitors should not dissuade continuation of therapy because SGLT2 inhibitors have favorable effects on kidney function over time.[73,76,86] Uncomplicated urinary tract (9.9% vs 8.1%) and genital (2.2% vs 0.7%) infections were more common in patients treated with empagliflozin vs placebo.[76] Only serious urinary infections were reported in the dapagliflozin HFpEF trial and were not increased with dapagliflozin vs placebo (1% vs 1%).[73] Episodes of ketoacidosis were rare (≤0.2%), only occurred in patients with diabetes, and were not more common with SGLT2 inhibitor treatment.[73,76]

Heart failure self-care is defined as adherence to medications and sodium, calorie, and fluid restrictions along with exercise and monitoring of weight, vital signs, and HF symptoms. Patients should be instructed on therapeutic interventions (eg, diuretic increases) and who to contact if their clinical status is worsening so that early interventions can be implemented to avoid hospitalizations. Ideally, the HF self-care plan education and its implementation is delivered by a multidisciplinary team specializing in HF and including cardiologists, nurses, and pharmacists who work with the patient's primary care team. The ACC/AHA guidelines for HF recommend education in HF self-care for all patients with symptomatic HF regardless of EF. This recommendation is based on multiple meta-analyses of randomized clinical trials that demonstrated an association of interventions to improve HF self-care with statistically significant reductions in hospitalizations (for HF and all-cause) and mortality and improvements in quality of life measures

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compared with usual care.[2] The relative effect of these interventions in HFpEF vs HFrEF is not known.[87]

In addition to pharmacologic treatment, aerobic exercise training[88,89] and aerobic exercise training plus diet-induced weight loss[90] produced clinically meaningful improvements in exercise capacity as assessed by peak oxygen consumption (increase of 1.66 [95% CI, 0.97-2.35] mL/min/kg) and quality of life (reduction in Minnesota Living with HF Questionnaire score of 9.1 [95% CI, 3.1-15.0] points; range, 0-105, with lower scores indicating better quality of life; minimal clinically meaningful difference, 5 points) in a pooled analysis of clinical trials in patients with HFpEF.[89] Cardiac rehabilitation with a tailored, multidomain (endurance, strength, balance, and mobility) intervention improved functional performance relative to placebo in frail, older patients recently hospitalized with HF (53% with HFpEF).[91] However, most government or commercial insurance policies currently cover cardiac rehabilitation for HFrEF but not for HFpEF. For unsupervised exercise training, current functional capacity and frailty/gait stability are important considerations in the types of exercise training undertaken by patients to avoid injury. Nonfrail patients should be instructed to advance continuous moderate-intensity endurance exercises (eg, cycling, elliptical, walking) gradually from 20 to 60 minutes per session 3 to 5 days per week.[88] For frail or more sedentary patients, starting with multiple shorter exercise sessions is reasonable.

For patients with obesity and HFpEF, modest (ie, 6.6%) weight loss induced through caloric restriction (prepared meals to achieve reduction in energy intake by 400 kcal/d) improved functional status (change in peak oxygen consumption of 1.3 [95% CI, 0.8-1.8] mL/kg/min compared with attention control; n = 100).[90] In observational studies, greater relative weight loss (22%, such as with bariatric surgery) has been associated with favorable changes in cardiac structure and function in people with obesity without HF.[92]

First-line therapy for patients with overt congestion includes loop diuretics, such as furosemide, torsemide, or bumetanide, which reduce cardiac filling pressures to improve symptoms of dyspnea. Diuretics may also cause volume depletion, orthostatic hypotension, and acute kidney injury. In HF, the elimination half-life for torsemide is 6 hours and is longer than furosemide (2.7 hours) or bumetanide (1.3 hours). Both torsemide and bumetanide have higher bioavailability than furosemide. However, a 2023 open-label, pragmatic clinical trial randomized 2859 patients (25% with HFpEF) to receive torsemide vs furosemide and showed no significant difference in rates of hospitalization after 12 months (940 total hospitalizations among 536 patients in the torsemide group and 987 total hospitalizations among 577 participants in the furosemide group; rate ratio, 0.94 [95% CI, 0.84-1.07]), regardless of EF.[93]

AF occurs in approximately 66% of patients with HFpEF and may occur prior to, concurrent with, or after HFpEF diagnosis.[24] Patients should be treated with anticoagulation and risk factors for AF (sleep apnea, obesity, thyroid disease, or valve disease) should be addressed in accordance with 2019 ACC/AHA AF guidelines.[94] A propensity-matched observational study of 1352 patients with HF and AF showed that, compared with absence of ablation (868 patients), ablation (484 patients) was associated with lower rates of the combined end point of all-cause mortality or first HF hospitalization (12.0 [95% CI, 10.3-14.0] vs 24.7 [95% CI, 24.4-25.0] events per 100 patient-years; HR, 0.78 [95% CI, 0.65-0.94]) after a median follow-up of 2.6 years, and benefit was independent of HF type (HFpEF vs HFrEF).[95] However, there are currently insufficient data to provide recommendations regarding whether patients with HFpEF and AF should be treated with a rate vs rhythm control strategy.[94]

Figure 4. Treatment of Heart Failure With Preserved Ejection Fraction

Treatment of heart failure with preserved ejection fraction (HFpEF)

STRONGLY RECOMMENDED

- **Sodium-glucose cotransporter type 2 inhibitor**
  Unless type 1 diabetes, history of diabetic ketoacidosis, or estimated glomerular filtration rate (eGFR) <20 mL/min/1.73 m^2
- **HF self-care plan education**
  Includes adherence to medications and sodium, calorie, and fluid restrictions, along with monitoring of weight, vital signs, and HF symptoms
- **Aerobic exercise training**
- **Diet-induced weight loss plus aerobic exercise for patients with obesity**
- **Loop diuretics for patients with fluid overload**
- **Manage hypertension (HTN) according to HTN guidelines**

CAN BE BENEFICIAL

- **Manage atrial fibrillation (AF) according to AF guidelines**

MAY BE CONSIDERED

- **Mineralocorticoid receptor antagonist such as spironolactone if:**
  EF <60%, elevated brain natriuretic peptide (BNP) assay, recent HF hospitalization, eGFR >30 mL/min/1.73 m^2 or creatinine <2.5 mg/dL, serum potassium <5.0 mmol/L, and adherent to laboratory monitoring
- **Angiotensin receptor-neprilysin inhibitor such as sacubitril valsartan if:**
  EF <45% for men or <60% for women and there are risk factors for HF hospitalization (elevated BNP assay, structural heart disease, or recent HF hospitalization)
- **Angiotensin receptor blocker such as candesartan if EF <55%**
- **Pulmonary artery pressure-guided therapy to reduce HF hospitalizations if:**
  NYHA class II-III symptoms of HF and elevated BNP/NT-proBNP or recent HF hospitalization

POTENTIALLY HARMFUL OR NONBENEFICIAL
(No benefit on exercise capacity or quality of life)

- **Nitrates, sildenafil, and soluble guanylate cyclase stimulators in patients with HFpEF**
- **Rate-adaptive atrial pacing in patients with HFpEF and chronotropic incompetence**

NT-proBNP indicates N-terminal fragment of the prohormone brain natriuretic peptide.

A multinational randomized clinical trial of 3445 patients with HFpEF reported that, compared with placebo, spironolactone (15-45 mg per day) did not significantly improve the combined rate of cardiovascular death, HF hospitalization, or cardiac arrest at 3.3 years of follow-up (18.6% vs 20.4%; HR, 0.89 [95% CI, 0.77-1.04]).[96] Compared with other sites (US, Canada, Brazil, and Argentina), event rates in participants enrolled in Russia and Georgia were dramatically lower[81] and spironolactone metabolite levels in participants randomized to undergo active therapy in these regions were lower,[97] raising concern for veracity of the HF diagnosis and study drug adherence at these sites. A post hoc analysis restricted to patients enrolled in the US, Canada, Brazil, and Argentina showed benefit on the primary end point (Table 2).[81] However, adverse effects during the trial, such as doubling of creatinine (17.8% vs 11.6%) and hyperkalemia (25.2% vs 8.9%), were more common in patients treated with spironolactone compared with placebo. Other post hoc analyses[82,98] of the adverse effect risk vs therapeutic benefit ratio

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Table 2. Clinical Trials of Pharmacologic Therapy for Heart Failure With Preserved Ejection Fraction (HFpEF)

Therapy	Sample size	Comparator	Effect on primary end point	NNT for 1 y to prevent 1 primary end point[a]	Effect on mortality	Placebo-corrected change in quality of life score (95% CI)	Placebo-corrected change in 6MWD (95% CI), m	Adverse effects	Post hoc analyses findings
SGLT2 inhibitor: dapagliflozin 10 mg once daily[73-75]	6263	Placebo	7.8 vs 9.6 per 100 patient-years (HR, 0.82 [95% CI, 0.73 to 0.92])[b]	61	CV: HR, 0.88 (95% CI, 0.74 to 1.05) Overall: HR, 0.94 (95% CI, 0.83 to 1.07)	At 8 mo: 2.4 (1.5 to 3.4)[c] At 3 mo: 5.8 (2.3 to 9.2)[d]	At 3 mo: 20.1 (5.6 to 34.7)	6263 patients followed up for 2.3 y[e] Dapagliflozin vs placebo: DKA, 0.1% vs 0.0%[f] Major hypoglycemia, 0.2% vs 0.2% Volume depletion, 1.3% vs 1.0% Serious kidney event, 2.3% vs 2.9% UTI, 1.0% vs 1.0% Total SAEs, 43.5% vs 45.5%	Combined analysis[52] of the 2 trials of SGLT2 inhibitors showed therapeutic effect size does not vary by EF, sex, or diabetic status and showed trend toward (P = .052) reduction in CV death, but not all-cause death (P = .48)
SGLT2 inhibitor: empagliflozin 10 mg once daily[74,76,77]	5988	Placebo	6.9 vs 8.7 per 100 patient-years (HR, 0.79 [95% CI, 0.69 to 0.90])	60	CV: HR, 0.91 (95% CI, 0.76 to 1.09) Overall: HR, 1.00 (95% CI, 0.87 to 1.15)	At 12 mo: 1.32 (0.45 to 2.19)[d] At 3 mo: 2.08 (−2.08 to 6.25)[c]	At 3 mo: 4.0 (−5.0 to 13.0)	5988 patients followed up for 2.2 y[e] Empagliflozin vs placebo: DKA, 0.1% vs 0.2%[f] Hypoglycemia, 4.3% vs 4.5%[f] Acute kidney failure, 12.1% vs 12.8% UTI, 9.9% vs 8.1%[g] Genital infections, 2.2% vs 0.7%[g] Total SAEs, 47.9% vs 51.6%[g]	
ARNI: sacubitril/valsartan; starting dose, 24/26 mg; goal dose, 97/103 mg twice daily[78-80]	4822	Valsartan	12.8 vs 14.6 per 100 patient-years (RR, 0.87 [95% CI, 0.75 to 1.01])[h]	64	CV: HR, 0.95 (95% CI, 0.79 to 1.16) Overall: HR, 0.97 (95% CI, 0.84 to 1.13)	At 8 mo: 1.0 (0.0 to 2.1)[d] At 6 mo: 0.52 (0.93 to 1.97)[d]	At 6 mo: −2.5 (−8.5 to 3.5)	4822 patients followed up for 2.9 y[e] Sacubitril/valsartan vs valsartan Hypotension, 15.8% vs 10.8%[g] Hyperkalemia, 13.2% vs 15.3%[g] Elevated creatinine, 10.8% vs 13.7%[g] Angioedema, 0.6% vs 0.2%[g] Total SAEs, 58.9% vs 58.9%	Therapeutic effect more evident in women and with lower EF (EF < approximately 60% in women or < approximately 45% in men)
MRA: spironolactone; starting dose, 12.5-25 mg; goal dose, 25-50 mg once daily[81-83]	1767	Placebo	10.4 vs 12.6 per 100 patient-years (HR, 0.82 [95% CI, 0.69 to 0.98])[i,j]	51	CV: HR, 0.74 (0.57 to 0.97) Overall: HR, 0.83 (0.68 to 1.02)	At 12 mo: 0 (−2 to 2)[k]	At 12 mo: −12 (−27 to −2)	1767 patients followed up for 3.3 y[e] Spironolactone vs placebo: Doubling of creatinine, 17.8% vs 11.6%[g] Hyperkalemia, 25.2% vs 8.9%[g] Hypokalemia, 15.2% vs 26.2%[g] Total SAEs, not reported	Therapeutic effect more evident with lower EF (EF < approximately 55%)

(continued)

of spironolactone demonstrated a favorable ratio only in younger patients with lower EF, better kidney function, and higher risk as indicated by recent HF hospitalization or higher BNP assay levels (Figure 4). A smaller trial of spironolactone vs placebo in HFpEF showed no benefit on exercise ability or quality of life.[83]

In a randomized clinical trial of 4822 patients with HFpEF, sacubitril/valsartan did not significantly reduce the combined end point of cardiovascular death and total HF hospitalizations compared with valsartan (12.8 vs 14.6 events per patient-year) at a median follow-up of 35 months (rate ratio, 0.87 [95% CI, 0.75-1.01]).[78] Additional post hoc

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Table 2. Clinical Trials of Pharmacologic Therapy for Heart Failure With Preserved Ejection Fraction (HFpEF) (continued)

Therapy	Sample size	Comparator	Effect on primary end point	NNT for 1 y to prevent 1 primary end point[a]	Effect on mortality	Placebo-corrected change in quality of life score (95% CI)	Placebo-corrected change in 6MWD (95% CI), m	Adverse effects	Post hoc analyses findings
ARB: candesartan; starting dose, 4-8 mg; goal dose, 32 mg once daily[84,85]	3023	Placebo	8.1 vs 9.1 per 100 patient-years (HR, 0.89 [95% CI, 0.77 to 1.03])	100	CV: HR, 0.99 (95% CI, 0.80 to 1.22) Overall: HR, 1.10 (95% CI, 0.79 to 1.52)[l]	Not reported	Not reported	3025 patients followed up for 3 y[e] Candesartan vs placebo: Hypotension, 2.4% vs 1.1%[g] Doubling of creatinine, 6% vs 3%[g] Hyperkalemia (≥6.0), 2% vs 1%[g] Total SAEs, 17.8% vs 13.5%[g]	Post hoc analyses: Therapeutic effect more evident with lower EF (EF < approximately 55%)

Abbreviations: 6MWD, 6-minute walk test distance; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; CV, cardiovascular; DKA, diabetic ketoacidosis; HR, hazard ratio; MRA, mineralocorticoid receptor antagonist; NNT, number needed to treat; RR, rate ratio; SAE, serious adverse event; SGLT2, sodium-glucose cotransporter type 2; UTI, urinary tract infection.

[a] NNT calculations were performed using ClinCalc NNT calculator (https://clincalc.com/Stats/NNT.aspx).

[b] Primary composite end point of hospitalizations or emergency department visits for HF or cardiovascular death.

[c] Kansas City Cardiomyopathy Questionnaire total symptom score.

[d] Clinical summary scores both have a range of 0 to 100, with higher score indicating better quality of life and a change ≥5 considered clinically meaningful.

[e] Median follow-up.

[f] In patients with diabetes.

[g] Adverse events statistically different between treatment groups.

[h] Primary composite end point of total HF hospitalizations or cardiovascular death.

[i] Data shown for post hoc analysis confined to patients with HFpEF enrolled in North or South America in the TOPCAT trial.

[j] Primary end point composite of hospitalizations for HF, cardiovascular death, or aborted cardiac arrest.

[k] Minnesota Living with Heart Failure Questionnaire scores range from 0-105, with higher scores indicating worse clinical status and a change ≥5 considered clinically meaningful.

[l] Noncardiovascular deaths.

patient-level analyses combining trials of sacubitril/valsartan in HFpEF and HFrEF[79] showed that sacubitril/valsartan, compared with valsartan or enalapril, respectively, reduced the risk of HF hospitalization or cardiovascular mortality at EF up to approximately 45% in men and 60% in women. A trial of 2572 patients with HFpEF randomized patients with elevated NT-proBNP assay levels to receive sacubitril/valsartan vs an angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, or neither (placebo) depending on what medication the patient was prescribed at the time of study entry. Relative to the comparator therapy, sacubitril/valsartan had no effect on 6-minute walk distance (co–primary end point) or quality of life scores (secondary end point) in individuals with HFpEF. The co–primary end point of NT-proBNP level was significantly reduced with sacubitril/valsartan vs comparator therapy (adjusted geometric mean ratio, 0.84 [95% CI, 0.80-0.88]), indicating a biological effect of sacubitril/valsartan. However, this biological impact was insufficient to improve the tested clinical end points (Table 2).[80]

In a trial of 3023 patients with HF and EF greater than 40%, there was no significant effect of candesartan compared with placebo on the primary end point of HF hospitalization or cardiovascular death (333 [22.0%] vs 366 [24.3%] events over a median follow-up of 36.6 months; HR, 0.89 [95% CI, 0.77-1.03]; $P = .118$)[84] (Table 2). Post hoc analyses suggested a benefit in patients with lower EF[85] (Table 2). The ACC/AHA guidelines for HF[2] stipulate that treatment with angiotensin receptor blockers can be considered to prevent hospitalization, although in another trial of 4128 patients with HFpEF, irbesartan did not reduce the risk of death or cardiovascular hospitalization for any cause over a mean follow-up of 49.5 months (primary event rates of 10.0 vs 10.5 per 100 patient-years in the irbesartan vs placebo group; HR, 0.95 [95% CI, 0.86-1.05]).[99]

A trial of pulmonary artery pressure–guided HF therapy (primarily adjusting diuretics) reduced hospitalizations in those with HF overall[100] and in the subset of patients with HFpEF,[101] where there were 29 HF hospitalizations in the guided management group vs 59 in the standard care group during a mean of 17.6 months of follow-up (risk reduction, 0.50 [95% CI, 0.35-0.70]). This management strategy requires RHC for implantation of a pressure sensor in the pulmonary artery and resources for consistent monitoring of sensor data and therapy adjustments, but can be considered in patients at risk for HF hospitalization.[2]

Trials of agents targeting deficient nitric oxide signaling, including nitrates, sildenafil, or soluble guanyl-cyclase stimulators, did not improve exercise ability or symptoms among individuals with HFpEF (Figure 4).[2,41,102,103] Inability to increase heart rate with activity (chronotropic incompetence) is common in HFpEF and associated with worse exercise capacity. In a randomized clinical trial, rate-responsive atrial pacing increased early and peak exercise heart rate, but did not improve exercise performance or quality of life (Figure 4).[104]

Both hypertension and HF guideline statements recommend that hypertension should be treated to target a systolic blood pressure goal of less than 130 mm Hg in patients with HFpEF to prevent morbidity.[2,37] Although the evidence that managing hypertension to a goal of these targets prevents HF is strong,[37,105] there are no randomized clinical trials of hypertension treatment strategies in patients with HFpEF. Similarly, other important comorbidities (eg, epicardial coronary artery disease, hyperlipidemia, chronic kidney disease) can impact clinical course in HFpEF, but lacking HFpEF-specific data, discussion of their management is beyond the scope of this review.

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Limitations

This review has limitations. First, this was not a systematic review. Second, the quality of included studies was not evaluated formally. Third, some relevant papers may have been missed. Fourth, the data were not available for the precise prevalence of some clinical or pathophysiologic characteristics and required estimation-based available evidence.

Conclusions

Approximately 3 million people in the US have HFpEF. First-line therapy consists of SGLT2 inhibitors, exercise, HF self-care, loop diuretics to maintain euvolemia, and weight loss for patients with obesity and HFpEF.

ARTICLE INFORMATION

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Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

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