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THE PRESENT AND FUTURE

JACC SCIENTIFIC STATEMENT

Heart Failure With Preserved Ejection Fraction

JACC Scientific Statement

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ABSTRACT

The incidence and prevalence of heart failure with preserved ejection fraction (HFpEF) continue to rise in tandem with the increasing age and burdens of obesity, sedentariness, and cardiometabolic disorders. Despite recent advances in the understanding of its pathophysiological effects on the heart, lungs, and extracardiac tissues, and introduction of new, easily implemented approaches to diagnosis, HFpEF remains under-recognized in everyday practice. This under-recognition presents an even greater concern given the recent identification of highly effective pharmacologic-based and lifestyle-based treatments that can improve clinical status and reduce morbidity and mortality. HFpEF is a heterogenous syndrome and recent studies have suggested an important role for careful, pathophysiological-based phenotyping to improve patient characterization and to better individualize treatment. In this *JACC* Scientific Statement, we provide an in-depth and updated examination of the epidemiology, pathophysiology, diagnosis, and treatment of HFpEF.
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During the past 20 years, the diagnostic approach to heart failure with preserved ejection fraction (HFpEF) has markedly evolved in parallel with our scientific understanding of this complex clinical syndrome.[1] Indeed, with the publication of recent pivotal sodium-glucose transport protein-2 inhibitor (SGLT2i) trials and their widespread therapeutic implications,[2,3] the absence of noninvasive gold standard diagnostic tests for HFpEF is more apparent than ever. Recent efforts have garnered consensus around a new universal definition, anchored clinically to the syndrome of heart failure (HF) caused by structural and/or functional cardiac abnormalities, with HFpEF defined as a left ventricular ejection fraction (LVEF) ≥50% further corroborated by either elevated natriuretic peptide (NP) levels or other evidence of congestion.[4]

As we examine the global scope and secular trends of this disease, it is important to recognize that this clinical definition has varying degrees of overlap with data we rely on to define HFpEF epidemiology and outcomes (**Table 1**). For example, relying on hospitalization or International Classification of Diseases (ICD)-9 codes alone may reduce specificity, increase associations with mortality, and reduce estimates of prevalence. Relying on easily measured biomarkers of congestion, such as the NPs, misses approximately one-third of all affected patients and may disproportionately affect patients with obesity or African ancestry.[5,6] Indeed, HFpEF remains underdetected in many settings, particularly in patients with obesity,

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HIGHLIGHTS

- HFpEF is an increasingly common cause of exercise intolerance linked to obesity and sedentary behavior.
- Despite advances in understanding of pathophysiological mechanisms, diagnosis, and treatment, HFpEF remains under-recognized.
- Further research is needed to characterize HFpEF phenotypes to promote individualized management and to improve outcomes.

likely accounting for substantial underappreciation of its actual scope.[7,8]

A number of specific diseases cause the clinical syndrome of HF in tandem with a normal LVEF, but have their own unique pathophysiology, natural history, and treatments (Table 2). These etiologies should not be considered to represent true "garden variety" HFpEF because of their distinct features and treatments, and the present text does not apply to these "masqueraders." In this *JACC* Scientific Statement, we examine the epidemiology, pathophysiology, diagnosis, and treatment of HFpEF in the context of these recognized limitations and the available evidence.

EPIDEMIOLOGY OF HFpEF

HFpEF INCIDENCE, PREVALENCE, AND LIFETIME RISK. Although the overall incidence of HF in the United States appears to be stable or even decreasing, the incidence of HFpEF specifically continues to rise (Figure 1).[9,10] Across 4 community-based cohorts, the incidence rate of HFpEF is estimated at ~27 cases per 10,000 person-years.[11] Over the span of 2 decades, secular trends in the Framingham Heart Study suggest a >50% higher incidence rate in 2000-2009 vs 1990-1999. Similarly, the prevalence of HFpEF is increasing and is expected to exceed that of heart failure with reduced ejection fraction (HFrEF) in the near future.[12] Specifically, data from the national inpatient sample demonstrate that the number of HFpEF hospitalizations more than doubled from 189,260 in 2008 to 495,095 in 2018.[13] Using pooled data from the CHS (Cardiovascular Health Study) and MESA (Multi-Ethnic Study of Atherosclerosis), the estimated lifetime risk of HFpEF at age 45 years is >10% in both men and women.[14] Taken together, these data suggest that the total burden of HFpEF is projected to become the dominant HF subtype in the future, affecting approximately 1 in 10 adults during their lifetime. Therefore, clinicians should have a low threshold for considering HFpEF as a potential (and increasingly common) diagnosis in patients with dyspnea or exercise intolerance.

SEX AND RACE DIFFERENCES IN HFpEF EPIDEMIOLOGY. Important sex differences in HF subtypes have been described. Although the incidence of HFpEF is similar among men and women, the prevalence of HFpEF is higher in women compared with men (Figure 1).[15,16] In one study, women outnumbered men 2:1 with respect to HFpEF hospitalizations. This is further reflected in lifetime risk estimates of HF: the lifetime risk of HFpEF is nearly double that of HFrEF among women (10.7% vs 5.8%), whereas the lifetime risk of HFpEF and HFrEF are similar among men.[14]

Studies on race/ethnic differences in HFpEF burden are evolving. Data from the ARIC (Atherosclerosis Risk In Communities) study of HF-related hospitalizations in 4 U.S. communities between 2005 and 2014 show that average event rates for first HFpEF hospitalization were highest among Black women (7.4 per 1,000 person-years [95% CI: 6.7-8.1 per 1,000 person-years]) when compared with Black men (6.2 per 1,000 person-years [95% CI: 5.5-7.0 per 1,000 person-years]), White women (5.9 per 1,000 person-years [95% CI: 5.5-6.2 per 1,000 person-years]), and White men (4.9 per 1,000 person-years [95% CI: 4.5-5.3 per 1,000 person-years]). During this time period, annual percent change for first HFpEF hospitalization increased for all 4 race-sex groups and was particularly pronounced among Black women.[17] These racial disparities in HFpEF prevalence may actually be underestimated given lower NP levels in Black individuals compared with other race/ethnic groups, which likely leads to underdiagnosis.[6]

HFpEF ACROSS THE HF STAGES: FROM RISK FACTORS TO DISEASE

HFpEF RISK FACTORS (STAGE A). Most traditional HF risk factors are shared and increase susceptibility for both HFpEF and HFrEF, including older age, hypertension, and ischemic heart disease.[18] However, it is important to note that obesity, metabolic dysfunction, and physical inactivity appear to specifically predispose to HFpEF more so than HFrEF

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation
BMI = body mass index
cGMP = cyclic guanosine monophosphate
CMD = coronary microvascular dysfunction
EF = ejection fraction
HF = heart failure
HFpEF = heart failure with preserved ejection fraction
HFrEF = heart failure with reduced ejection fraction
LA = left atrium
LV = left ventricle
LVEF = left ventricular ejection fraction
ML = machine learning
NO = nitric oxide
NP = natriuretic peptide
PCWP = pulmonary capillary wedge pressure
PH = pulmonary hypertension
PVD = pulmonary vascular disease
RV = right ventricle
SGLT2i = sodium glucose cotransporter-2 inhibitor

TABLE 1 HFpEF Definitions and Considerations Across Different Studies

HFpEF Definition	Criteria	Use Cases	Considerations
Universal definition[4]	Clinical HF with structural and/or functional cardiac abnormality, corroborated by ↑natriuretic peptide levels and/or objective evidence of pulmonary or systemic congestion	Clinical practice	Developed in 2021–data evolving on stage A, B, and C reclassifications (especially stage B)
Hemodynamic definition[1,112,119]	Elevated PCWPs at rest (≥15 mm Hg) or with exercise (PCWP ≥25 mm Hg supine or PCWP/CO slope >2 upright)	CPET, physiology-based studies	"Gold standard" physiological evidence of HF but relies on tertiary referral centers with greater expertise
Epidemiologic studies[1,112]	Combination of signs, symptoms, and objective evidence, eg, Framingham Heart Study criteria	Prospective longitudinal cohorts	Robust for overtly congested patients with advanced HF, "specific but not sensitive," may miss outpatient diagnoses
HF hospitalization criteria[151]	Combination of signs, symptoms, and objective evidence, eg, Cardiovascular Trials Initiative and U.S. Food and Drug Administration	Clinical trials	Expert clinical endpoint adjudication, "specific but not sensitive," relies on chart documentation, may miss outpatient diagnoses
ICD billing codes[1,23]	Variable ICD codes used: AHA Get With the Guidelines and others	Outcomes research, claims-based datasets	Misclassification has been described, especially with complex medical conditions including HFpEF, "sensitive but not as specific," missed most outpatient diagnoses, many non-HF diagnoses included[152]

AHA = American Heart Association; CO = cardiac output; CPET = cardiopulmonary exercise testing; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; ICD = International Classification of Diseases; PCWP = pulmonary capillary wedge pressure.

(Figure 2). Among 4 community-based cohorts, higher body mass index (BMI) and insulin resistance were differentially associated with future HFpEF, particularly among women vs men.[19] In addition, physical inactivity was associated with higher risk of HFpEF compared with HFrEF in a dose-dependent manner.[20] Excess body fat leads to development of HFpEF through a variety of mechanisms (Figure 2), and, with continued increases in the obesity and physical inactivity epidemics and associated cardiometabolic consequences, current trends in increasing HFpEF incidence and prevalence will continue to compound in the future.[8] Further study is required to better understand the mechanisms linking adiposity and deconditioning with HFpEF.

CARDIOVASCULAR REMODELING IN PRECLINICAL HFpEF (STAGE B). How individuals progress from risk factors (stage A) to cardiac remodeling and preclinical HFpEF (stage B) and eventual HFpEF (stages C and D) remains incompletely understood. In contrast to stage B HFrEF, which is easily recognized as asymptomatic left ventricular (LV) systolic dysfunction, readily prompting a change in clinical management, stage B HFpEF remains nebulous. The most recent consensus document defined patients with stage B HF as individuals free of HF symptoms, with evidence of structural heart disease (eg, LV hypertrophy, chamber enlargement), abnormal cardiac function (eg, elevated filling pressures or diastolic dysfunction), or elevated NP or cardiac troponin levels.[4]

Evolving studies will need to more clearly define how to apply these criteria to preclinical HFpEF. The diagnosis of stage B HF requires establishing the absence of HF symptoms; however, clinicians may be less likely to rigorously test for symptoms such as exercise intolerance in patients with abnormal cardiac structure/function associated with HFpEF (eg, LV hypertrophy, left atrial enlargement, diastolic dysfunction) compared with patients with asymptomatic LV systolic dysfunction. If exercise intolerance is present, determining whether it is due to cardiac vs extracardiac abnormalities can also be challenging. Furthermore, it is known that NP concentrations are lower among individuals with overt HFpEF vs HFrEF.[1] Whether the same cutpoints in preclinical HFpEF vs preclinical HFrEF adequately capture risk remains to be seen, but seems unlikely as roughly one-third of patients with stage C HFpEF have NP levels below typical thresholds used for HF diagnosis.[5] A recent study has shown that even among patients where HFpEF has been excluded, an increasing burden of HFpEF risk factors and functional abnormalities based on echocardiography are strongly correlated with hemodynamic and aerobic limitations typical of (but less severe than) those observed in patients with overt, stage C HFpEF.[21] As we consider the role of potential preventive therapies for HFpEF, clearly defining preclinical HFpEF will be paramount.

UNDER-RECOGNITION OF HFpEF (STAGE C). Recently developed scoring systems (discussed later in this paper) now provide a means to screen larger

patient populations and estimate the potential scope of undiagnosed HFpEF in the community. Among individuals with unexplained dyspnea but without diagnosis of HFpEF in ARIC, the H_2FPEF score was high risk (≥5) in 35%, indicating that a substantial proportion of older adults with HFpEF in the community are likely undiagnosed (Figure 3).[22] This underdiagnosis may be even more problematic among Black patients, who are known to have lower NP levels than White individuals,[6] and who made up a larger proportion of patients with undiagnosed dyspnea as H_2FPEF scores increased in the analysis from ARIC (20.7% Black in the lowest score category and 38.3% in the highest risk category; $P < 0.001$).[22] The problem of HFpEF under-recognition is even greater now given the emergence of SGLT2is as highly effective treatments.

CLINICAL OUTCOMES AMONG PATIENTS WITH HFpEF

SURVIVAL AND HF READMISSIONS. Patients with HFpEF have similarly poor survival when compared with HFrEF (Figure 1). In community-based cohorts, the incidence rate of all-cause mortality among individuals with newly diagnosed HFpEF vs HFrEF was 394 vs 459 events per 10,000 person-years, respectively.[11] Among individuals in the Get With The Guidelines-HF registry with linked Medicare data through 2014, the 5-year mortality rate was 75.3% among those with HFpEF, and 75.7% among those with HFrEF.[23] Despite similarly poor outcomes, the mode of death differs by HF subtype, with a lesser proportion of cardiovascular compared with noncardiovascular deaths in HFpEF vs HFrEF.[24] Among a nationwide study of patients admitted with HFpEF in 2017, the 30-day all-cause readmission rate was 21%, but only a minority (9.2%) of these readmissions was due to acute HFpEF.[25] Similar to mode of death, the proportion of cardiovascular and HF-specific readmissions appears lower in HFpEF vs HF with mid-range ejection fraction (EF), underscoring the importance of management of noncardiac comorbidities in HFpEF.[26]

RACE AND SEX DIFFERENCES IN HFpEF OUTCOMES. In the ARIC study, age-adjusted 28-day and 1-year case fatality rates after HFpEF hospitalization were higher among White vs Black individuals. Specifically, 28-day age-adjusted case fatality was 11.7% (White males), 10.1% (White females), 7.2% (Black females), and 7.6% (Black males).[17] However, within a clinical trial sample, Black patients with HFpEF had worse outcomes including HF hospitalization compared with White patients, with no difference in cardiovascular mortality.[27] As compared with women, men with HFpEF consistently display greater risk for mortality as well as HF hospitalization, and this also contributes to the greater prevalence of HFpEF in women as compared with men (Figure 1).[28]

PATHOPHYSIOLOGY OF HFpEF

COMMON DISEASE MECHANISM HYPOTHESES. HFpEF was first considered to be caused by diastolic dysfunction caused by hypertensive LV remodeling in isolation, exacerbated by abnormal ventricular-arterial coupling and chronotropic incompetence. These mechanisms were initially observed in HFpEF patients with predominantly hypertensive heart disease, where the primary mechanistic hypotheses centered around hypertension leading to LV hypertrophy with stiff and relatively small LVs and, eventually, overt HF.[29-32] Over the past 2 decades the predominant clinical phenotype in HFpEF has shifted from older adults with isolated hypertensive heart disease to multimorbid patients with obesity, diabetes, and metabolic syndrome,[8,33] focusing greater attention toward systemic inflammation, endothelial dysfunction, altered myocardial energetics, and abnormalities in skeletal muscle.[34-37]

HYPERTENSIVE VENTRICULAR STIFFENING. Passive myocardial stiffness is often increased in HFpEF and has been considered an important contributor to pathophysiology.[31,32] The causes for myocardial stiffening include factors influencing the extracellular matrix and those intrinsic to the cardiomyocyte itself.[37] Myocardial fibrosis is a well-established feature of HFrEF, and total collagen volume is similarly increased in HFpEF endomyocardial biopsy tissue.[38-41] Both collagen type I and type III expression and tissue staining are elevated in HFpEF and are coupled to reduced collagenase, metalloproteinase-1, but increased tissue inhibitor of metalloproteinase expression, which may further enhance fibrosis. In addition to altering matrix turnover, cross-linking of collagen including the formation of advanced glycation end products contributes to fibrosis and stiffening. Potential mechanisms for the altered matrix structure include inflammation, diabetes, and neurohumoral activation. Although increases in passive stiffness are commonly attributed exclusively to myocardial fibrosis, in the largest endomyocardial biopsy study of HFpEF to date, moderate or greater myocardial fibrosis was only present in the minority (27%) of patients.[38] Alterations in isotype expression and phosphorylation of sarcomeric proteins such as titin

TABLE 2 Clues, Evaluation, and Treatment Options for HFpEF Masqueraders

Clues to the Possible Presence of an HFpEF Masquerader
Definite HFpEF (high natriuretic peptides, high PCWP, and/or HF hospitalization) with low H_2FPEF score
Kussmaul's sign: ↑JVP with inspiration
↓Voltage ECG relative to ↑LV wall thickness LVH without a history of hypertension or progression withdrawal of antihypertensives due to progressively low BP
Inability to up-titrate or initiate neurohormonal therapy; history of recently coming off all antihypertensive therapy
Known risk factor for infiltrative/restrictive cardiomyopathy HFpEF in a young patient (age <55 y, unless obese or diabetic)
Prominent musculoskeletal or neurologic features: eg, bilateral carpal tunnel syndrome, lumbar spinal stenosis, biceps tendon rupture, significant peripheral neuropathy

Etiology	Clinical Clues	Diagnostic Evaluation	Treatment Options
Cardiac amyloidosis	Progressively lower BP, recent BP medication withdrawal, or orthostatic hypotension; bilateral carpal tunnel syndrome, lumbar spinal stenosis, biceps tendon rupture; peripheral neuropathy; persistent low-level ↑ troponin, low tissue Doppler velocities (e', a', s' <5 cm/s), low-voltage ECG with ↑ LV wall thickness.	Serum immunofixation, free light chains, urine protein electrophoresis, prealbumin, strain echocardiography (relative apical sparing ratio >0.87, LVEF/GLS ratio >4.1), cardiac MRI with T1 mapping (high ECV, difficulty nulling the myocardium), nuclear scintigraphy, biopsy.	Chemotherapy (for light chain amyloidosis), tafamidis (for transthyretin amyloidosis), consider anticoagulation (high risk for cardioembolic complications), avoid nondihydropyridine CCBs, ACE inhibitor, ARB, ARNIs.
Hypertrophic cardiomyopathy	Family history; symptoms due to LV obstruction; ECG with increased voltage out of proportion to hypertension history; ECG with deep T-wave inversions in precordial leads (apical HCM).	Echocardiography with strain imaging (asymmetric septal hypertrophy, LV outflow tract or intracavitary obstruction, SAM, apical hypertrophy, specific bullseye patterns such as focal anteroseptal or apical abnormalities); cardiac MRI.	Mavacamten (for LV outflow tract obstruction); weigh risk/benefit of septal reduction surgery/ablation; beta-blockers, nondihydropyridine CCBs; avoid vasodilators.
Cardiac sarcoidosis	History of extracardiac sarcoidosis; prominent ventricular arrhythmias despite preserved LVEF; high-grade AV block (especially if age <60 y).	Echocardiography (septal thinning); cardiac MRI (septal thinning, midmyocardial or subepicardial scar); FDG-PET; biopsy.	Immunosuppression.
Hemochromatosis	Family history; history of frequent transfusions; presence of liver disease + diabetes.	Ferritin, *HFE* genetic testing, cardiac MRI with T2* imaging; cardiac biopsy.	Chelation therapy; therapeutic phlebotomy.
Fabry disease	Echocardiogram with infiltrative appearance but ECG shows increased voltage; rash in bathing suit distribution; significant proteinuria.	Alpha-galactosidase level, genetic testing, cardiac biopsy (with electron microscopy).	Enzyme replacement therapy.
High-output HF	Echocardiography with 4-chamber enlargement and/or increased LV outflow tract VTI.	Evaluate for underlying cause of high output state (eg, anemia, thiamine deficiency, fistula, cirrhosis, AVMs).	Treat underlying cause (eg, correction of anemia, thiamine replacement, fistula ligation for shunts, liver transplantation for cirrhosis, embolization for AVMs).
Myocarditis	History of flu-like illness (or diagnosed COVID or influenza) prior to onset of symptoms; troponin elevation.	Cardiac MRI (epicardial or subepicardial late gadolinium enhancement), cardiac biopsy.	Immunosuppression for specific types (eg, giant cell, eosinophilic myocarditis).
Congenital heart disease	History of other congenital anomalies, elevated hemoglobin (suggests secondary polycythemia due to chronic hypoxemia). Common forms of congenital heart disease that can present late in life include ASD, PAPVR, VSD (perimembranous, supracristal), PDA.	Echocardiography, cardiac MRI, cardiac CT, invasive hemodynamics with saturations. ASD will cause RA/RV enlargement; PAPVR will cause RV/PA enlargement and diastolic septal flattening (volume overload); small VSDs typically affect the left side of the heart > right side of the heart, will cause LA/LV enlargement; PDA will cause LA/LV enlargement.	Percutaneous or surgical correction of congenital anomaly.
Valvular heart disease	Differentiate primary from secondary causes of valve disease (patients with HFpEF can develop significant MR due to LA enlargement and TR due to RA enlargement [or RV failure], particularly in the setting of atrial fibrillation/flutter).	Echocardiography, invasive hemodynamics, CT (for calcific valve disease).	Surgical or percutaneous valve interventions.
Coronary artery disease	All patients with signs and symptoms of HFpEF should be evaluated for CAD.	Stress testing; coronary CT angiography; invasive coronary angiography.	Revascularization, aspirin, statin, beta-blockers, nitrates.

Continued on the next page

modify cardiomyocyte stiffness leading to increased passive LV chamber stiffness in patients with HFpEF.[34,37,42,43] Heightened pericardial constraint (eg, due to increased epicardial and pericardial fat in obese HFpEF) can also effectively increase LV stiffness (Figure 4).[44,45]

OBESITY-CARDIOMETABOLIC STRESS. Myocardial stiffness estimated based on echocardiography is

TABLE 2 Continued

Etiology	Clinical Clues	Diagnostic Evaluation	Treatment Options
Toxins	History of toxin exposure (eg, chemotherapy or radiation [even if remote], illicit drug use, hydroxychloroquine, heavy metals).	Clinical history, blood testing, endomyocardial biopsy.	Removal of offending toxin; evaluate and treat for coronary, valvular, and pericardial disease in patients with history of XRT.
Pulmonary arterial hypertension	Risk factor for PAH (eg, autoimmune disease, anorexigen exposure, HIV, liver disease, congenital heart disease, chronic lung disease, OSA, pulmonary embolism); exertional lightheadedness.	Echocardiography (elevated PA systolic pressure [>50 mm Hg] with E/A ratio <1 or lateral E/e' ratio <8; systolic interventricular septal flattening; RA > LA size and/or interatrial septum bows right-to-left); right heart catheterization.	Pulmonary vasodilators; treatment of underlying cause of PAH if secondary (eg, lung disease, OSA, chronic thromboembolic pulmonary hypertension).
Predominant lung disease with cor pulmonale	Patients with risk factors for severe lung disease including long smoking history, environmental exposures, severe sleep apnea, oxygen dependence, severe abnormalities on spirometry.	Right heart catheterization to define whether hemodynamic congestion is present, spirometry, lung mechanics and alveolar diffusion capacity, high-resolution chest CT. Note that mild to moderate abnormalities in spirometry and lung diffusion are also common in HFpEF.	Inhaled therapies for COPD/reactive airways disease, nocturnal oxygen or continuous positive airway pressure, interstitial lung disease treatments.
Pericardial disease (constrictive pericarditis, chronic pericardial effusion)	History of pericarditis, pericardial effusion, radiation therapy, cardiac surgery, autoimmune disease; low BP; exertional lightheadedness/dizziness; prominent right-sided heart failure (eg, hepatic congestion, ascites); low output state.	Echocardiography (constriction: diastolic septal bounce; respiratory variation in mitral inflow; septal e' ≥ lateral e'; diastolic flow reversal in hepatic vein flow during expiration), CT, MRI with T2 imaging and LGE, invasive hemodynamics (discordance in LV/RV pressure tracings during inspiration in patients with constrictive physiology).	Constrictive pericarditis: immuno-suppression for active pericardial inflammation (↑ CRP, ↑ ESR, pericardial edema on cardiac MRI T2 imaging); pericardiectomy for advanced disease without evidence of inflammation. Pericardiocentesis, drain, or window for pericardial effusion.
Anatomic causes (extrinsic cardiac compression)	Significant symptoms and/or diuretic use despite relatively normal cardiac structure/function; obscured echocardiography images.	CT or MRI; other diagnostic imaging based on cause of extracardiac compression.	Correction of anatomic cause of cardiac compression (eg, hiatal hernia, dilated esophagus, tumor).

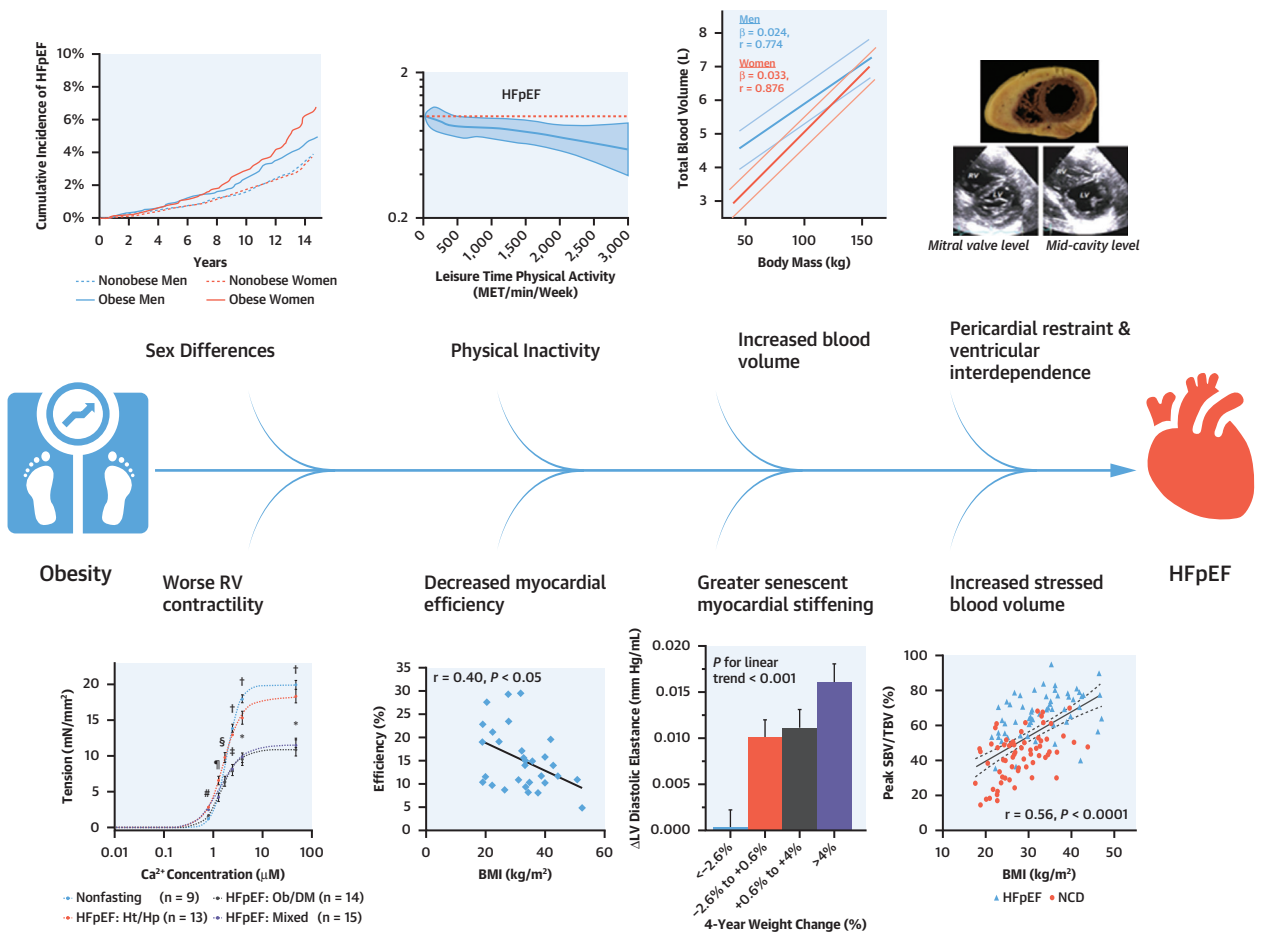
↑ = increased; ↓ = decreased; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor/neprilysin inhibitor; ASD = atrial septal defect; AV = atrioventricular; AVM = arteriovenous malformation; BP = blood pressure; CAD = coronary artery disease; CCB = calcium-channel blocker; COPD = chronic obstructive pulmonary disease; CRP = c-reactive protein; CT = computed tomography; ECG = electrocardiogram; ESR = erythrocyte sedimentation rate; FDG-PET = fluorodeoxyglucose-positron emission tomography; HCM = hypertrophic cardiomyopathy; JVP = jugular venous pressure; GLS = global longitudinal strain; LA = left atrial; LGE = late gadolinium enhancement; LV = left ventricular; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; MRI = magnetic resonance imaging; OSA = obstructive sleep apnea; PA = pulmonary artery; PAH = pulmonary arterial hypertension; PAPVR = partial anomalous pulmonary venous return; PDA = patent ductus arteriosus; RA = right atrial; RV = right ventricular; SAM = systolic anterior motion; TR = tricuspid regurgitation; VSD = ventricular septal defect; VTI = velocity time integral; XRT = radiation therapy; other abbreviation as in Table 1.

FIGURE 1 Epidemiology of HFpEF

	HFpEF Incidence	HFpEF Prevalence	HFpEF Clinical Outcomes
	• 27 cases per 10,000 person-years • Lifetime risk: 1 in 10 at age 45 years	• 1.0%-1.5% of population • Highly age dependent	• 5-year mortality: 75.3% (GWTG registry) • 30-day all-cause readmission rate: 21%
Secular trends	↑ incidence over time	↑ prevalence over time	?
Sex differences	↔	>	<
HFpEF vs HFrEF	HFpEF incidence rising relative to HFrEF	HFpEF prevalence rising relative to HFrEF	Similarly poor survival ↓ CV death in HFpEF vs HFrEF

Summary of current understanding of HF incidence, prevalence, and outcomes and influence of sex drawn from references 10-17 and 24-27.
CV = cardiovascular; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; GWTG = AHA Get With The Guidelines.

FIGURE 2 Pathophysiology of Obesity-Related HFpEF

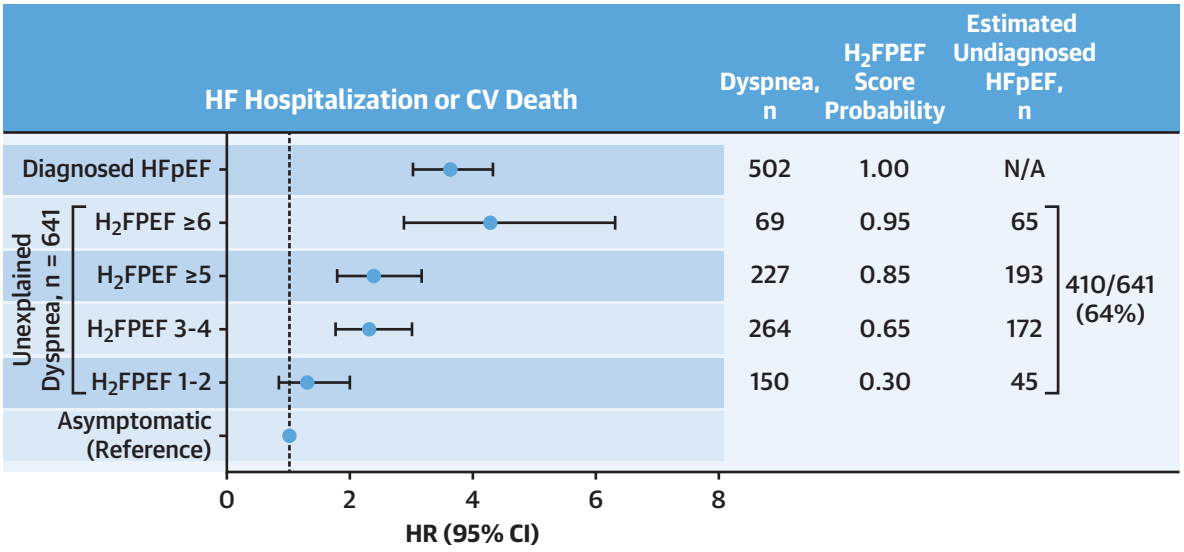


Obesity is a major risk factor for HFpEF, particularly in women, in addition to reductions in physical activity. TBV is strongly related to body mass, with a stronger relationship in women. Cardiomegaly due to chamber remodeling and increases in epicardial fat in obesity to enhance pericardial restraint and ventricular interaction. As compared with nonobese patients, those with increasing BMI display impaired RV sarcomere function, reduced myocardial efficiency, and more severe increases in SBV and ratio of SBV to TBV, reflected in reduced venous capacitance in obese patients with HFpEF. Age-related diastolic LV stiffening is exaggerated in patients with greater weight gain. Figure adapted with permission.[19,20,44,46,47,49-51,150] BMI = body mass index; LV = left ventricular; RV = right ventricular; SBV = stressed blood volume; TBV = total blood volume; other abbreviations as in Figure 1.

increased in patients with obesity, and the increases in LV chamber stiffness with aging are amplified among patients with greater weight gain (Figure 2).[46] Blood and plasma volumes increase with greater body weight,[47] a relationship that is steeper in women than men,[47] and patients with obesity-related HFpEF display higher blood volume and greater sensitivity of filling pressures on plasma volume.[44,48] Even in the absence of frank volume overload, abnormal distribution of blood volume (increased stressed blood volume) due to impaired venous capacitance is present in HFpEF, and notably is associated with increasing BMI (Figure 2), resulting in even greater elevations in cardiac filling pressures.[49]

Direct tissue analyses are shedding new light as well. In human myocardial tissue biopsy samples from a contemporary obese HFpEF cohort, cardiomyocyte hypertrophy and fibrosis were common in HFpEF, although the severity of each was mild to moderate.[38] In a follow-up study from the same group, patients with Class II or greater obesity exhibited substantially reduced right ventricular (RV) systolic sarcomere function, but less passive cardiomyocyte stiffness compared with cardiomyocytes from patients with a primarily hypertensive phenotype of HFpEF (Figure 2).[50] However, there are major and fundamental differences between the RV and LV at the chamber, matrix, and cardiomyocyte levels,

FIGURE 3 Scope of Undiagnosed HFpEF in the Community

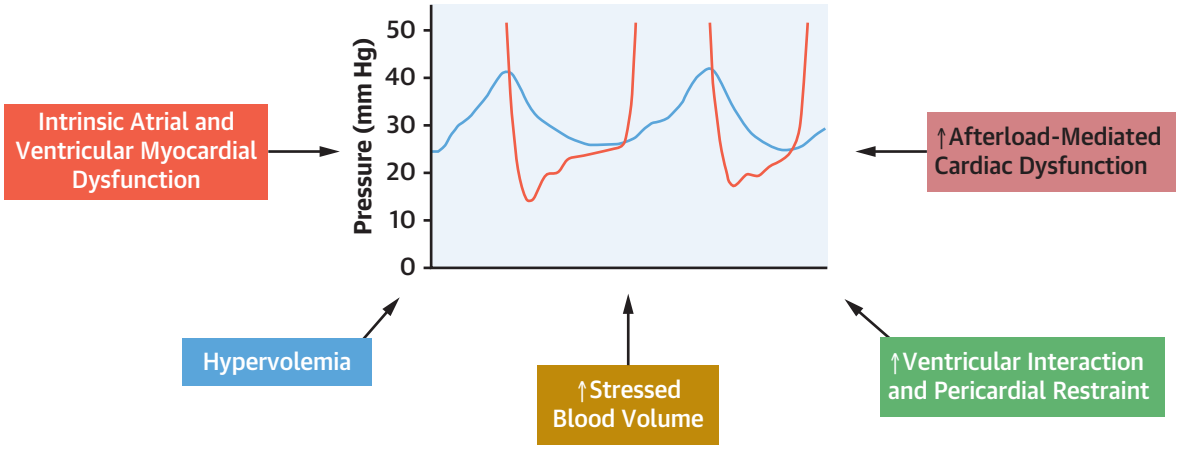


Among 4,892 community-dwelling older adults participating in the ARIC study, 76.6% had no dyspnea, 10.3% had been diagnosed with HFpEF, and 13.1% had moderate or greater dyspnea, but no diagnosis of HFpEF. Among those with unexplained dyspnea, 35% had high-risk H_2FPEF scores. If we extrapolate HFpEF risk from prior work[117] to this sample from ARIC[22] it becomes clear that a substantial proportion of older adults with HFpEF in the community potentially remain undiagnosed and, therefore, untreated. ARIC = Atherosclerosis Risk in Communities; other abbreviations as in Figure 1.

and it remains unknown whether such differences would be observed in LV specimens.

Myocardial work increases and efficiency decreases with increasing BMI and insulin resistance in women without HF,[51] which may relate to greater myocardial reliance on fat vs carbohydrate oxidation.[8,51] Recent studies have demonstrated that myocardial energetics are abnormal in HFpEF[52] and

FIGURE 4 Mechanisms of Hemodynamic Congestion in HFpEF



Increases in pulmonary capillary wedge pressure **(blue)** and left ventricular end diastolic pressure **(red)** develop through a variety of pathophysiological perturbations in HFpEF, many of which coexist within the same patient, but some that do not, and may require different treatments. Abbreviation as in Figure 1.

notably reverse with weight loss among patients with obesity but no HF.[53] Myocardial gene expression signatures differ in obese HFpEF compared with HFrEF and controls, with uniquely up-regulated genes in HFpEF enriched for mitochondrial adenosine triphosphate synthesis/electron transport, pathways that are down-regulated in HFrEF, further evidencing fundamental differences in the HF subtypes.[54] HFpEF down-regulated genes included endoplasmic reticulum stress, autophagy, and angiogenesis pathways.

In a hemodynamic study of obese HFpEF compared with nonobese HFpEF and controls, those with obesity demonstrated worse exercise capacity (lower peak oxygen consumption), higher biventricular filling pressures, and depressed pulmonary artery vasodilatory reserve.[44] Furthermore, obese patients with HFpEF were more likely to have RV dysfunction as well as cardiomegaly due to increased epicardial fat, leading to enhanced pericardial restraint and ventricular interaction (**Figure 2**).[44,55] Similar findings were noted in a post hoc analysis of the RELAX (PhosphdiesteRasE-5 Inhibition to Improve CLinical Status and EXercise Capacity in Diastolic Heart Failure) trial, in which obese patients with HFpEF had worse peak oxygen consumption and 6-minute walk distance compared with nonobese patients with HFpEF, with greater evidence of systemic inflammation (higher c-reactive protein levels).[56]

MICROVASCULAR INFLAMMATION. In 2013, Paulus and Tschope[34] proposed a new model wherein comorbidities, such as obesity, diabetes, chronic lung disease and hypertension, induce a proinflammatory state in which coronary microvascular endothelial dysfunction develops, leading to downstream reduction in nitric oxide (NO) bioavailability, cyclic guanosine monophosphate (cGMP), and eventual protein kinase G activity in cardiomyocytes. Studies of LV endomyocardial biopsy and analyses of inflammatory cell markers suggested increased oxidative stress and depressed NO signaling resulting in inflammation play a key role in this syndrome.[34,37,42] This cascade was proposed to explain maladaptive changes including myocyte hypertrophy, increased myocyte tension, and interstitial fibrosis. However, therapies targeting this pathway have not shown efficacy in clinical trials,[57-60] although it is difficult to discern whether these therapies effectively improved intracellular cGMP- protein kinase G signaling.

Several studies have reported associations between elevated inflammatory biomarkers and incident HFpEF, prevalent HFpEF severity, and outcomes.[61-64] The PROMIS-HFpEF (Prevalence and correlates of coronary microvascular dysfunction in heart failure with preserved ejection fraction) study investigated the prevalence of coronary microvascular dysfunction (CMD) and its association with endothelial dysfunction, myocardial dysfunction, and HF severity in patients with HFpEF.[65] Nearly 75% of patients in the study had evidence of CMD, similar to other invasive studies,[66,67] and patients with worse coronary flow reserve were associated with higher N-terminal pro brain natriuretic peptide, markers of endothelial dysfunction such as higher urinary albumin-to-creatinine ratio, and worse RV function.[65] In a substudy analysis of proteomics from the PROMIS-HFpEF study, comorbidity burden was associated with worse structural and functional parameters by echocardiography and with inflammatory proteins; proteins involved in inflammation mediated the relationship between comorbidity burden and markers of hemodynamics and RV function.[68] Chronically, CMD may promote vascular rarefaction, which has been demonstrated in autopsy studies in HFpEF, showing associations with fibrosis.[69] Population-based studies have also supported the role of endothelial adhesion molecules (eg, intercellular adhesion molecule-1 [ICAM-1] and vascular cell adhesion molecule-1 [VCAM-1], key drivers of leukocyte infiltration across the vascular endothelium and into the heart and other organs) in HFpEF pathogenesis by relating elevated circulating levels of these proteins to both the echocardiographic substrate for HFpEF and incident HFpEF.[70,71]

More recent studies have expanded and reshaped the Paulus hypothesis to include metabo-inflammation, wherein obesity and nutrient overload leads to chronic microvascular inflammation, enhanced activation of inducible NO synthase, nitrosative stress, metabolic inflexibility, disrupted NO/cGMP signaling, and altered protein folding and cellular quality control.[35,72] The primary origin of metabo-inflammation in HFpEF remains unclear. Adipocytes and adipose macrophages may secrete inflammatory adipokines, such as interleukin-6, and increases in visceral fat are independently associated with risk of HFpEF[73] and hemodynamic disease severity, especially in women.[74,75] Myocardial tissue may also be a source, as evidenced by increased monocyte infiltration[38] and inducible NO synthase expression in RV tissue.[72] Emerging data suggest that SGLT2is work at least in part by enhancing nutrient deprivation signaling in multiple cell types, resulting in improved cell quality control and reduced inflammation and oxidative stress.[76] Further study is required to better understand the primary source(s) of inflammation, preferably from human tissue, and

examining cardiomyocytes from the left and right sides of the heart.

CARDIAC PATHOPHYSIOLOGY. Impairments in cardiac structure and function are the most conspicuous abnormalities in HFpEF and span all 4 chambers.[1] Alterations in LV relaxation and increases in chamber stiffness are present and importantly contribute to elevation in filling pressures.[31,32,77] Over time, chronic, sustained or intermittent elevation in LV filling pressures in HFpEF cause remodeling and dysfunction of the left atrium (LA), frequently culminating in the development of atrial fibrillation (AF), which may be considered as a "biomarker" of underlying LA myopathy and an indicator of more advanced HFpEF (**Central Illustration**).[78-80] Indeed, abnormalities in LA function are more predictive of adverse outcome than those of the LV,[80] and impairments in LA strain have been shown to be the most robust imaging markers distinguishing HFpEF from noncardiac causes of dyspnea.[81-83] Although LV dysfunction precedes LA dysfunction in the majority of patients with HFpEF, a subset of patients with HFpEF may develop a primary LA myopathy as the cause of elevated LA pressure and reduced LV filling (resulting in insufficient cardiac output augmentation during exertion).

Regardless of the cause, sustained elevation in LA pressures leads to worsening pulmonary hypertension (PH), especially in patients with more severe LA myopathy.[84] Roughly 80% of patients with HFpEF have PH,[85,86] which starts as a passive result of downstream LA pressure elevation, but in many patients ultimately leads to pulmonary vascular disease (PVD), characterized by a combination of vascular remodeling and vasoconstriction that affects the pulmonary veins, capillaries, and small arteries, leading to worsening exercise capacity, lung congestion, pulmonary diffusion abnormalities, and increased mortality (**Central Illustration**).[87-89]

Development of PVD is then associated with increased risk of RV dysfunction, secondary tricuspid regurgitation, and systemic venous congestion,[90,91] which are also markers of advanced or "Stage D" HFpEF (**Central Illustration**). However, recent studies have extended the importance of earlier stages of PVD progression in HFpEF as well. For example, PVD that is "latent," or apparent only during exercise, is associated with increased risk for adverse events, and significantly modifies the response to novel therapies such as shunt devices,[92] leading to an excessive increase in pulmonary artery pressure as lung perfusion increases during exercise.[93]

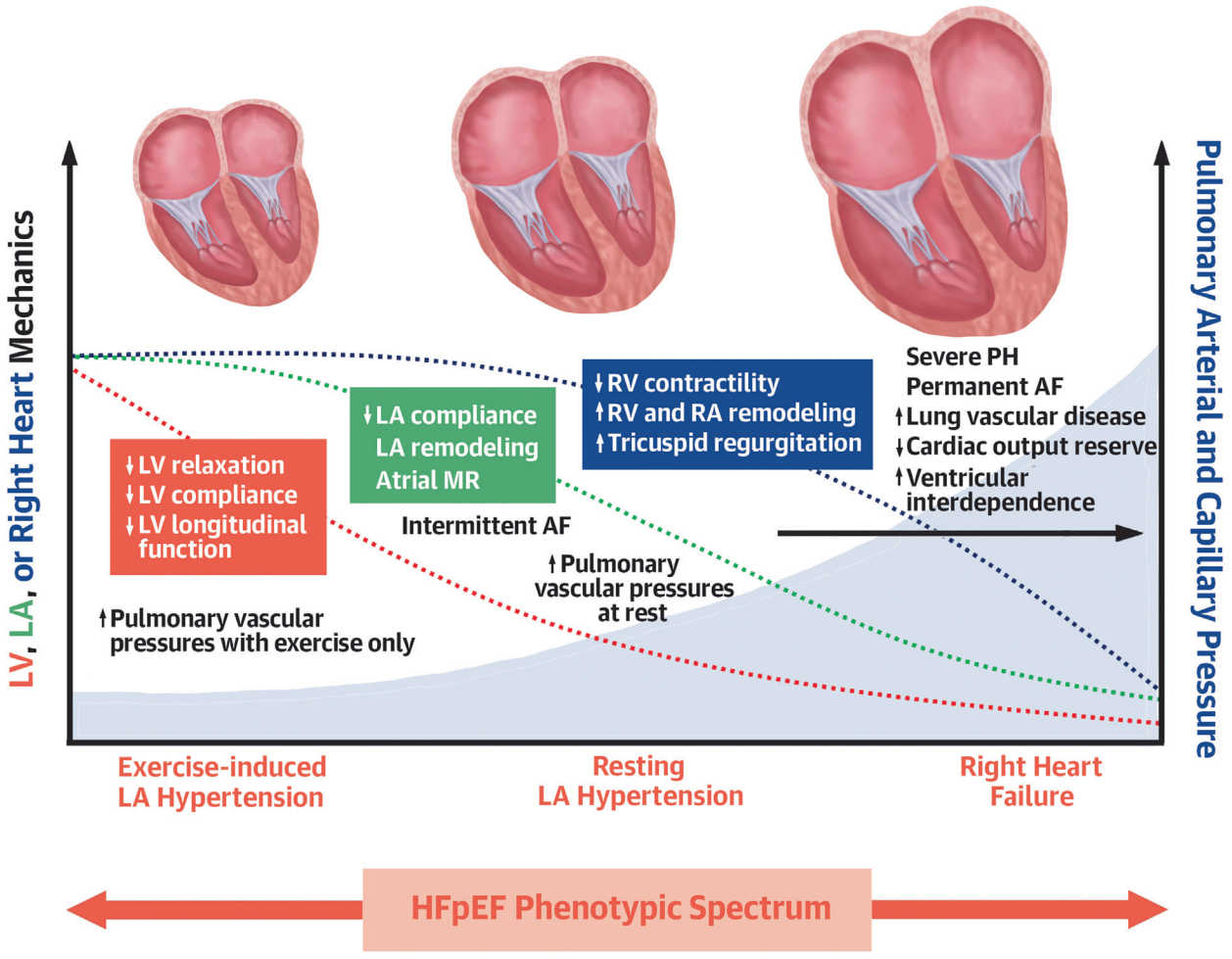
Patients with HFpEF have systemic endothelial dysfunction, which may also affect the coronary microvasculature, as indicated earlier in this paper.[65,66,94] Thus, in some patients RV dysfunction can occur in concert with LV dysfunction due to coronary microvascular dysfunction and/or metabolic abnormalities in both ventricles simultaneously. Indeed, the RV in patients with HFpEF exhibits heightened afterload sensitivity in response to pulmonary artery pressure elevation compared with patients without HF.[90]

Although there is evidence to support sequential causal linkages in disease progression, such as atrial myopathy leading to PVD and RV dysfunction,[91] recent studies have also shown that atrial and biventricular dysfunction can progress across both sides of the heart in parallel, not just in series as shown in the **Central Illustration**,[95] suggesting a common response to shared inflammatory, metabolic, or ischemic insults. It is likely that such insults also affect extracardiac organ function in parallel (as mentioned later in this paper).

NONCARDIAC MECHANISMS. Numerous extracardiac mechanisms importantly contribute to the pathophysiology of HFpEF,[36] some with differing impacts in women and men.[74,75,96] These include abnormalities in conduit arterial vessels,[96,97] the endothelium and microvasculature,[65,66,94] skeletal muscle,[98,99] lung,[89,100] kidney,[84] and adipose tissue, especially among patients with excess visceral fat.[8,74,75] According to the Fick principle, peak O_2 consumption during exercise is determined by the product of cardiac output and arterial-venous O_2 content difference, and, in patients with HFpEF, each component contributes ~50% to deficits in peak VO_2.[99,101] Autonomic dysfunction is also common in HFpEF because many patients display chronotropic incompetence,[30,102] blunted arterial baroreflex sensitivity,[30] and abnormalities in venous capacitance that importantly contribute to elevation of filling pressures.[49,103] In patients with diagnosed HFpEF, it is important to consider alternative, noncardiac contributors to each identified pathophysiological abnormality given the potential to treat these contributors. For example, in patients with evidence of HFpEF and PVD, noncardiac contributors to PVD (eg, chronic lung disease) should be identified and treated.

MULTIPLE PHENOTYPE HYPOTHESIS. Hemodynamic abnormalities that cause tissue congestion are consistent across all patients with HFpEF (by definition),[4] but this does not mean that all patients reach this characteristic signature of hemodynamic abnormalities through a common mechanism. In contrast to the hypothesis that HFpEF is predominantly a single

CENTRAL ILLUSTRATION **Temporal Disease Progression in Heart Failure With Preserved Ejection Fraction**

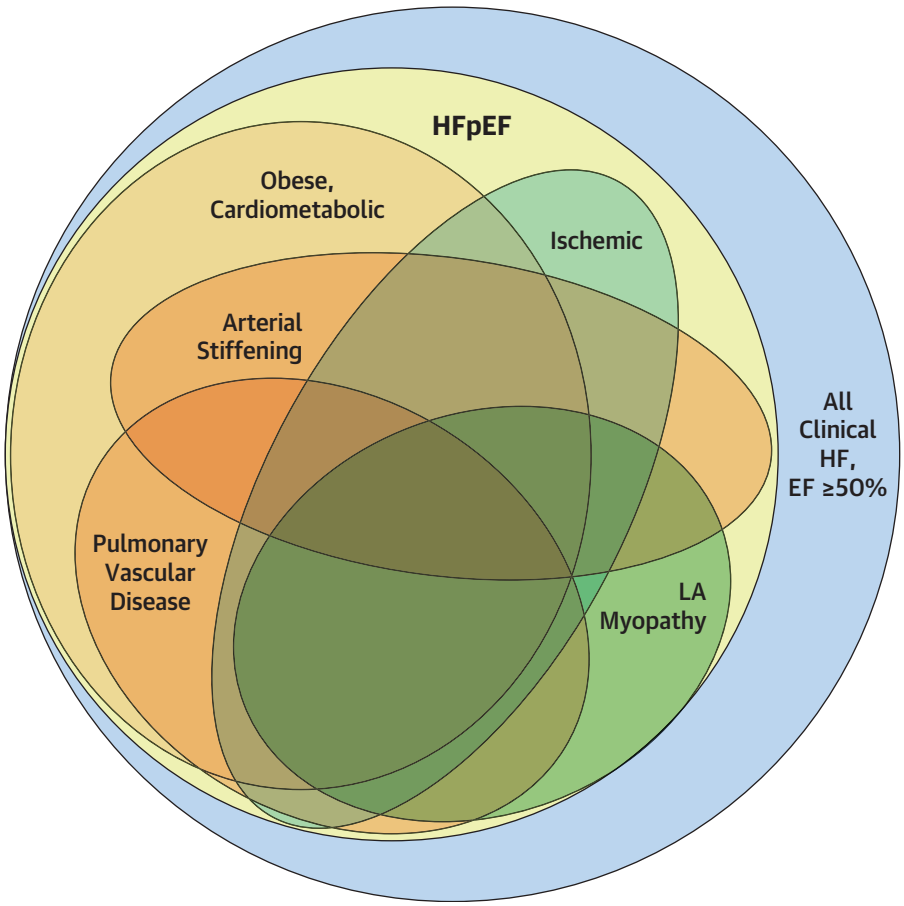


Borlaug BA, et al. J Am Coll Cardiol. 2023;81(18):1810–1834.

Initially HFpEF is characterized by relatively little cardiac remodeling and mild impairment in LV mechanics, with elevation in LV filling pressures exclusively during exercise. With time, there is progressive deterioration in LA function and remodeling leading to secondary atrial functional MR and development of paroxysmal AF. Mild elevation in LV filling pressures at rest may develop at this stage. With further progression, LA remodeling/dysfunction progress further, with transition to permanent AF, worsening PH, pulmonary vascular remodeling and vasoconstriction, RV and RA dysfunction, more severely impaired cardiac output, and increased pericardial restraint, findings of advanced HFpEF. Patients present at any time during this progression, and treatments may differ depending on presentation. Progression through these stages is not inevitable and may follow distinct tempos. Comorbidities, inflammation, and endothelial dysfunction can manifest differently among individuals, further increasing heterogeneity. AF = atrial fibrillation; HFpEF = heart failure with preserved ejection fraction; LA = left atrial; LV = left ventricular; MR = mitral regurgitation; PH = pulmonary hypertension; RA = right atrial; RV = right ventricular.

disorder caused by singular inciting mechanisms, multiple lines of evidence now suggest that HFpEF is more accurately conceptualized as a combination of pathophysiological phenotypes that converges to produce this common hemodynamic signature of elevated LV filling pressures at rest or with exercise, even as the individual causes differ from a cellular, organ, and tissue basis, and, in most patients with HFpEF, multiple mechanisms interact in a complex fashion to cause hemodynamic abnormalities (Figure 5, Table 3).[104,105] A key unanswered question is to what extent the different phenogroups

FIGURE 5 Phenotypic Spectrum of HF With Normal EF



The **area of the outer circle** represents all patients with the clinical syndrome of HF and an EF ≥50%. Even after excluding non-HFpEF "masqueraders" (Table 2), shown here by the **shaded blue area**, multiple pathophysiologically distinct phenogroups exist within the broader spectrum of HFpEF **(yellow circle)**. These individual phenogroups are sometimes singular but typically display considerable overlap with one another, complicating schemes to separate them into discrete cohorts. The area of each ellipsoid is not based on direct data but included for illustrative purposes. EF = ejection fraction; LA = left atrial; other abbreviation as in Figure 1.

represent distinct disorders or merely different stages in the spectrum of disease progression (Central Illustration).[106,107]

There is abundant data to support the concept of different phenotypes, but the optimal phenotypic nosology is not yet resolved and represents an important knowledge gap in the field.[108] Phenotypes may be categorized based on the severity or pattern of organ dysfunction or hemodynamics, as suggested by the cardiac and noncardiac mechanisms described earlier in this paper (Table 3), or phenotypes may be separated based on the presence or absence of comorbid conditions such as obesity[8,44] or coronary disease.[65,67] Recent work has further explored whether machine learning (ML) techniques can better categorize patients into phenotypes, using combinations of comorbidities, measures of cardiac and extracardiac structure/function, and multilayered omics.[109,110] This characterization is one of the key goals of the National Heart, Lung, and Blood Institute-funded HeartShare clinical research network, which is part of the Accelerating Medicines Partnership HF project.[111] Although ML studies of HFpEF continue to proliferate in the literature, they are merely the starting point for deeper investigation into the pathobiology of identified HFpEF subtypes. Ultimately, any nosologic phenotype system must be tied to both pathophysiology and, most importantly, treatment response, and this will require further study in appropriately powered prospective trials.

TABLE 3 Mechanisms of Abnormal Hemodynamics in HFpEF

Mechanism	Specific Causes	Relevant Phenogroups
Intrinsic myocardial dysfunction[a]	Pressure-overload hypertrophy/remodeling Vascular rarefaction Interstitial fibrosis Ischemia Cardiomyocyte energy deprivation Oxidative/nitrosative stress Insulin resistance	Stiff vasculature/hypertensive Ischemic (epicardial or microvascular) Obese LA myopathy
Hypervolemia	Obesity Renin-angiotensin-aldosterone activation Chronic kidney disease	Obese Chronic kidney disease
↑Stressed blood volume	Obesity Excessive sympathoexcitation	Obese Autonomic dysfunction
↑Ventricular interaction & pericardial restraint	Obesity Right-sided heart remodeling & dysfunction Tricuspid regurgitation	Pulmonary vascular disease Obesity Atrial tricuspid regurgitation
Afterload-mediated myocardial dysfunction	Systolic hypertension Aortic stiffening	Stiff vasculature/hypertensive Chronic kidney disease

[a]May affect myocardium in atria, ventricles, or both
Abbreviations as in Tables 1 and 2.

DIAGNOSIS OF HFpEF

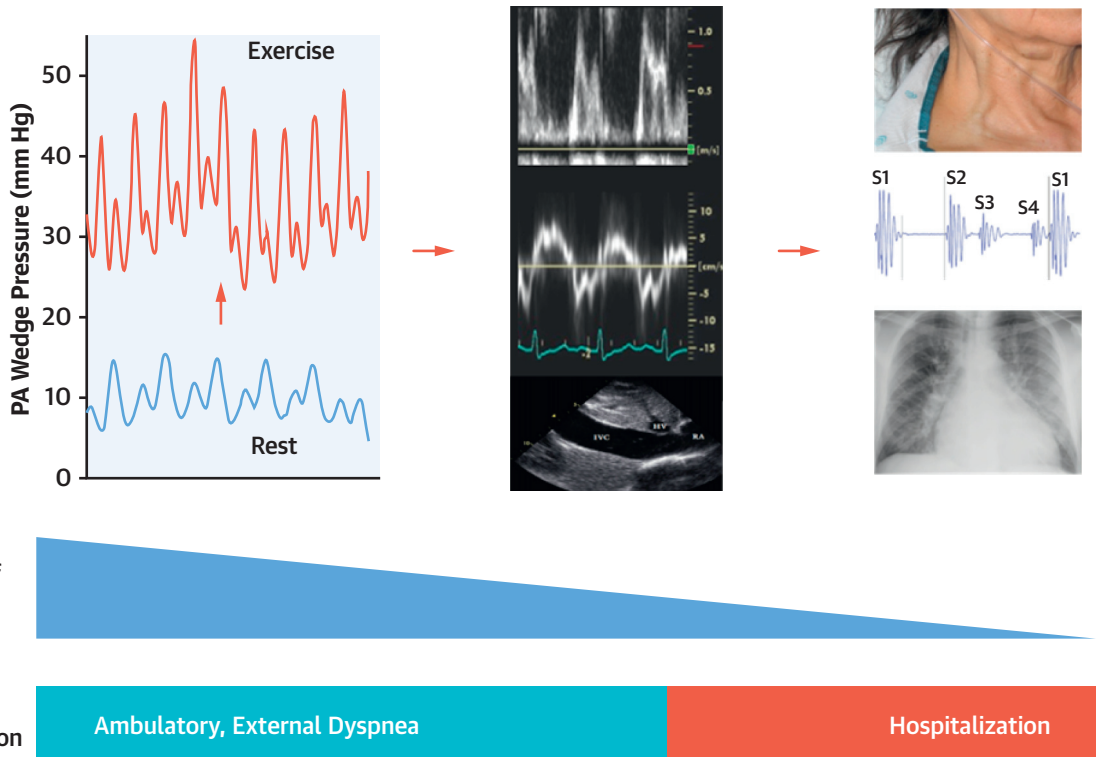
Diagnosis of HFpEF relies on history revealing symptoms of dyspnea and fatigue coupled with objective evidence of congestion and an EF ≥50%.[1,4,112] Evidence of congestion may be apparent based on physical examination findings, but these findings are often absent among ambulatory patients (Figure 6).[113] Plasma NPs may be elevated reflecting congestion, but as reviewed earlier in this paper, roughly one-third of patients with HFpEF display NP values below typically used clinical thresholds for HF diagnosis despite elevated LV filling pressures at rest or with exercise,[5,114] particularly among patients with obesity-related HFpEF.[9,44] Several other causes of NP deficiency have been identified, including lower LV diastolic wall stress for any given elevation in LV diastolic pressure,[7] African ancestry, *NPPB* polymorphisms, insulin resistance, and increased androgenicity in women.[6] Thus, normal NP levels cannot be used to rule out HFpEF. Imaging may be useful to evaluate for ambient or chronic markers of congestion, such as increases in the E/e' ratio, left atrial enlargement, reduced left atrial reservoir strain, increases in estimated pulmonary artery pressures, and distention of the inferior vena cava (Figure 6).[115]

The presence of echocardiographic and NP indicators of congestion is useful to increase the likelihood that HFpEF is present, but their absence is not helpful to exclude HFpEF.[116,117] This is partly related to insensitivity of these estimations and partly related to the fact that in approximately one-third of patients with HFpEF, LV filling pressures are normal at rest and only increase during exercise.[86] Exercise testing is required in these patients to diagnose or exclude HFpEF. The gold standard diagnostic test involves rest and exercise hemodynamic assessment during right heart catheterization (Table 1), which is consistent with the new universal definition that requires objective evidence of congestion.[1,4,118,119] An increase in pulmonary capillary wedge pressure (PCWP) at rest (≥15 mm Hg) or exercise (≥25 mm Hg) made at end expiration confirms the diagnosis during supine exercise.[118] An increase in PCWP relative to the increase in cardiac output during exercise >2 mm Hg/L/min has also been used to establish the diagnosis of HFpEF,[120] but this metric may only apply to upright exercise as pressures are much higher in the supine position, and application to supine exercise may reclassify a significant minority of patients into the wrong diagnostic category.[121]

Although invasive exercise testing provides definitive diagnosis, it is not universally available and carries greater cost and requirement for expertise compared with noninvasive imaging modalities. Alternative provocative maneuvers have been tested, including saline infusion and passive leg raise. An increase in PCWP ≥18 mm Hg with saline or ≥19 mm Hg with leg raise may also help to identify patients with HFpEF.[122,123] Although these alternative tests are superior to resting assessment alone, they do not replicate the patient's experience of dyspnea during exertion, are less physiologically relevant, and do not challenge the cardiovascular system to the extent observed with exercise, where increases in heart rate, contractility, loading conditions, and autonomic signaling to a much greater magnitude.[124] Exercise stress echocardiography is also used as an alternative to invasive hemodynamic exercise testing and offers incremental value to resting echocardiography in isolation, but is often limited by the ability to acquire diagnostic quality imaging during stress and false-negative results as a number of patients with HFpEF may not display elevation in E/e' or other surrogate markers with exertion.[116,125]

Diagnostic scoring systems have been developed to aid medical decision making regarding the need for invasive exercise testing in the evaluation of patients with possible HFpEF, including the H_2FPEF and HFA-PEFF (Heart Failure Association Pre-test assessment,

FIGURE 6 Clinical Presentation of HFpEF



Patients with earlier stage HFpEF display elevation in PA wedge pressures only during exercise **(red tracing)**, despite normal values at rest **(blue tracing)**. With more dramatic elevation in cardiac filling pressures at rest, evidence of congestion becomes apparent at rest, with elevation in the E/e' ratio and dilation/loss of collapsibility of the inferior cava. Patients with the most overt congestion fulfilling the Framingham criteria (Table 1) present with jugular distention, S3 gallops, and radiographic edema. These patients typically require hospitalization and represent only a small fraction of the broader HFpEF spectrum. PA = pulmonary artery; other abbreviation as in Figure 1.

Echocardiography & natriuretic peptide, Functional testing, Final aetiology) scores (Figure 7).[117,118] Low or high scores with either scheme are used to exclude or diagnose HFpEF, respectively, and patients with intermediate scores are best referred for exercise testing. In a large multicenter comparative study with invasive hemodynamic confirmation of diagnoses, both scores were validated as accurate tools to discriminate HFpEF from noncardiac causes of dyspnea, but the H_2FPEF score was shown to be more sensitive, with greater overall accuracy and discrimination than the HFA-PEFF score, despite requirement for fewer input variables.[121] It is important to note that the H_2FPEF score was derived and validated in patients with unexplained dyspnea. In patients with overt signs and symptoms of HF (Figure 6) and elevated NPs, a low H_2FPEF score does not exclude HFpEF, but may point to atypical causes of the HFpEF syndrome such as infiltrative cardiomyopathies.

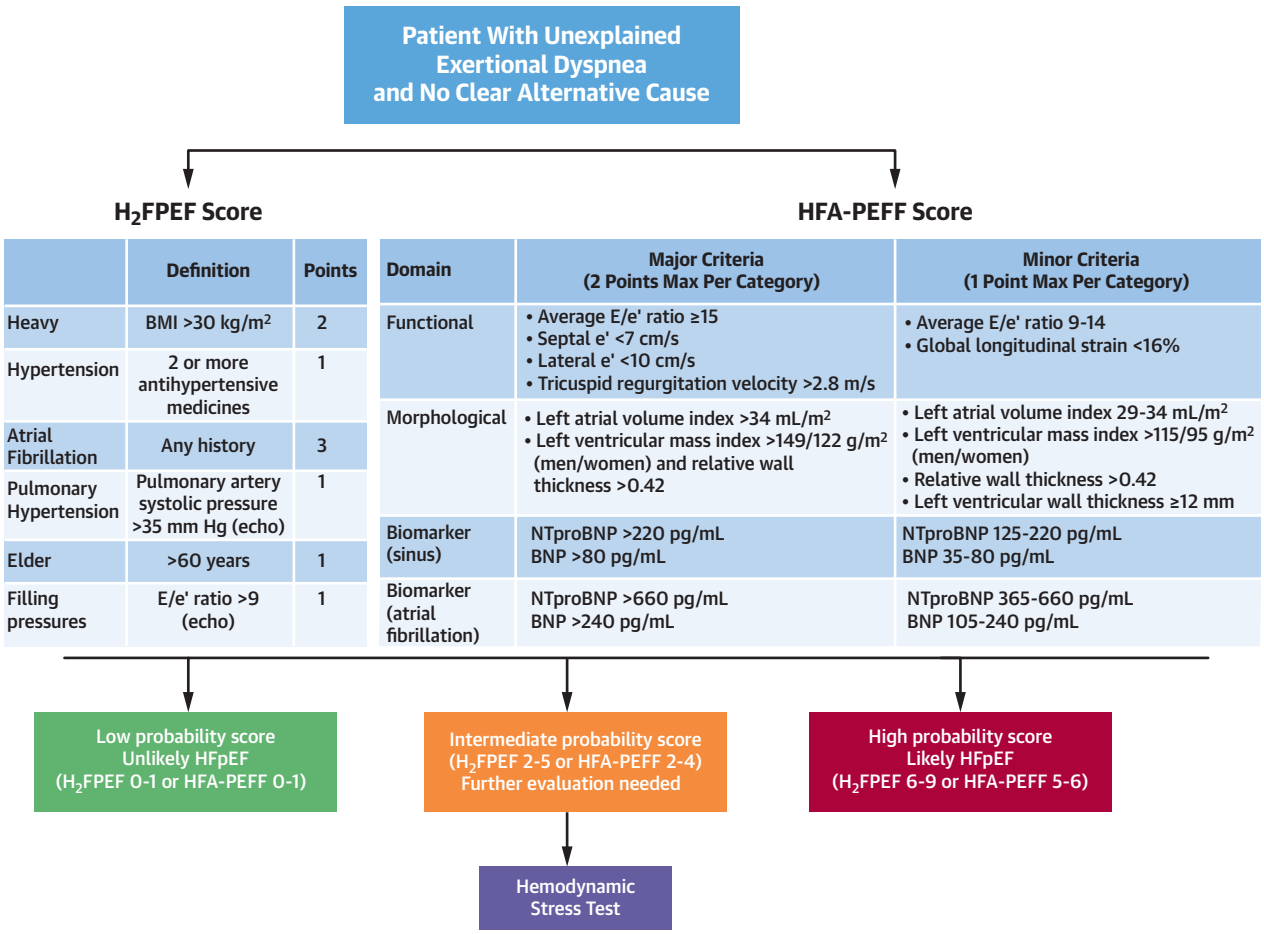
Once the diagnosis of clinical HF has been made in a patient with normal EF, it is essential to rule out HFpEF "masqueraders," disorders with their own specific etiologies, natural histories, and treatments, which differ from "garden variety" HFpEF and have specific treatments that differ from HFpEF (Table 2).

TREATMENT OF HFpEF

Once HFpEF has been diagnosed and alternate diagnoses have been excluded, systematic treatment of HFpEF, which includes management of comorbidities and pharmacologic and nonpharmacologic therapies, should be instituted (Figure 8). Systematic laboratory investigation of patients with HFpEF is also critical for optimal management of these patients (Table 4).

COMORBIDITY MANAGEMENT. Blood pressure control in accordance with clinical practice guidelines

FIGURE 7 Diagnostic Evaluation of HFpEF



	Definition	Points
Heavy	BMI >30 kg/m²	2
Hypertension	2 or more antihypertensive medicines	1
Atrial Fibrillation	Any history	3
Pulmonary Hypertension	Pulmonary artery systolic pressure >35 mm Hg (echo)	1
Elder	>60 years	1
Filling pressures	E/e' ratio >9 (echo)	1

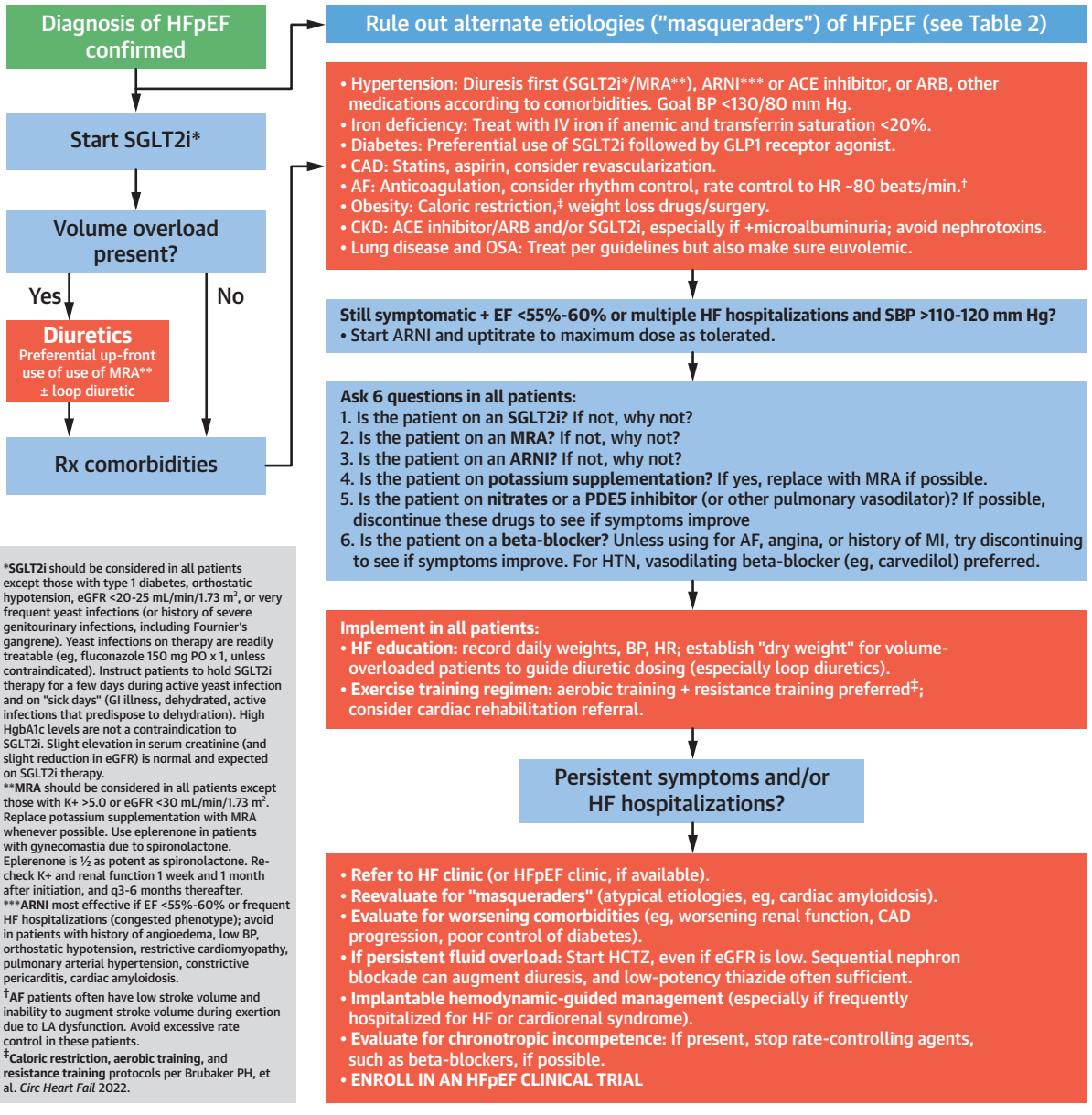
Domain	Major Criteria (2 Points Max Per Category)	Minor Criteria (1 Point Max Per Category)
Functional	• Average E/e' ratio ≥15 • Septal e' <7 cm/s • Lateral e' <10 cm/s • Tricuspid regurgitation velocity >2.8 m/s	• Average E/e' ratio 9-14 • Global longitudinal strain <16%
Morphological	• Left atrial volume index >34 mL/m² • Left ventricular mass index >149/122 g/m² (men/women) and relative wall thickness >0.42	• Left atrial volume index 29-34 mL/m² • Left ventricular mass index >115/95 g/m² (men/women) • Relative wall thickness >0.42 • Left ventricular wall thickness ≥12 mm
Biomarker (sinus)	NTproBNP >220 pg/mL BNP >80 pg/mL	NTproBNP 125-220 pg/mL BNP 35-80 pg/mL
Biomarker (atrial fibrillation)	NTproBNP >660 pg/mL BNP >240 pg/mL	NTproBNP 365-660 pg/mL BNP 105-240 pg/mL

In patients with unexplained dyspnea and normal EF, the probability of underlying HFpEF can be estimated by the H_2FPEF score or HFA-PEFF score. Patients with intermediate probability scores should undergo additional hemodynamic exercise stress testing to establish the diagnosis. HFA-PEFF = Heart Failure Association Pre-test assessment, Echocardiography & natriuretic peptide, Functional testing, Final aetiology; other abbreviations as in Figures 1, 3, and 5.

(target <130/80 mm Hg) is important in the management of HFpEF, with selection of antihypertensive agents driven by the presence of other comorbidities and other indications.[126] AF is highly prevalent in HFpEF and is associated with more advanced disease, poorer exercise capacity, and increased mortality (Central Illustration).[79,127] Goals of therapy include prevention of thromboembolism, modification of contributing risk factors, and control of symptoms.[126] Emerging data suggest a greater role for more aggressive rhythm control, including catheter ablation, although prospective trial data is required.[128] Notably, aggressive rate control may be deleterious in HFpEF patients with AF due to significant LA dysfunction resulting in low stroke volume and inability to increase stroke volume during exertion.

Obesity is highly prevalent in HFpEF and weight loss through lifestyle-based interventions is indicated. Kitzman et al[129] showed in a randomized trial that weight loss through caloric restriction improves exercise capacity, health status, and markers of inflammation in patients with obesity-related HFpEF. Weight loss through bariatric surgery and other interventions may also improve cardiac function,[130] as well as hemodynamic abnormalities,[131] but further prospective study is required. Epicardial coronary disease is observed in two-thirds of patients with HFpEF and is often challenging to diagnose.[69,132] When CMD is included, coronary disease is observed in an even greater proportion of patients (Figure 5).[65-67] Although prospective data are lacking, observational studies have shown that complete revascularization in patients with HFpEF

FIGURE 8 Treatment of HFpEF



Summary of key points for treatment of HFpEF, with emphasis on evaluation and treatment of congestion with diuretics and SGLT2 inhibitors, treatment of comorbidities, lifestyle interventions, and vigilant consideration for HFpEF masqueraders that are treated differently. For caloric restriction, aerobic training, and resistance training protocols, see Brubaker et al.[153] SGLT2 = sodium glucose cotransporter-2; other abbreviation as in Figure 1.

and coronary disease is associated with improved outcomes.[132] Further study is required to determine the optimal treatment for CMD in HFpEF. Approximately 50% of patients with HFpEF in clinical trial cohorts have diabetes mellitus.[133] SGLT2i should be considered first-line therapy for glucose control in patients with HFpEF and diabetes given their reduction in HF hospitalizations and cardiovascular-related death in patients with and without diabetes.[2,3]

PHARMACOLOGIC TREATMENTS. The EMPEROR-Preserved (EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction) and DELIVER (Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure) trials demonstrated

TABLE 4 Laboratory Evaluation of Patients With Suspected or Diagnosed HFpEF

Test	Interpretation/notes
Complete blood cell count with differential	Elevated neutrophil-to-lymphocyte ratio is associated with worse prognosis. If anemia is present, evaluate further for the etiology and potential treatment options. Hematocrit can be followed to evaluate for hemoconcentration. Elevated hemoglobin is uncommon in HFpEF and should prompt evaluation for causes of polycythemia, particularly congenital heart disease or chronic hypoxia.
Basic chemistry panel	Sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine (with eGFR). Hypokalemia: consider hyperaldosteronism, if on loop diuretics, add MRA. Hyponatremia and elevated BUN are poor prognostic signs. If creatinine is normal and the patient has evidence of fluid overload, consider hemodilution or sarcopenia. Most patients with overt HFpEF will have abnormal renal function.
Liver function tests	Total bilirubin, AST, ALT, alkaline phosphatase, albumin, total protein. Elevated total bilirubin and/or alkaline phosphatase can be a sign of hepatic congestion due to right-sided heart failure.
BNP/NTproBNP	Clinical thresholds for the diagnosis of HF in current use (eg, BNP >100 pg/mL), should not be used to rule out the diagnosis of HFpEF given the high prevalence (~30%) of natriuretic peptide deficiency in HFpEF. MRA use results in lower natriuretic peptide levels. NTproBNP should be used in patients on sacubitril/valsartan. Factors associated with natriuretic peptide deficiency include obesity, African ancestry, insulin resistance, *NPPB* polymorphisms, increased androgenicity in women, corticosteroid use, and factors associated with lower diastolic wall stress (eg, small LV cavity, LV hypertrophy). Levels can be elevated in the presence of atrial fibrillation, pulmonary arterial hypertension, primary RV dysfunction, and pulmonary embolism.
High-sensitivity troponin	Persistent low-level elevations can be a clue to the presence of cardiac amyloidosis, hypertrophic cardiomyopathy, other atypical etiologies (eg, cardiotoxicity or other causes of infiltrative cardiomyopathy), or reduced subendocardial perfusion due to coronary microvascular dysfunction. Low-level troponin elevation also points to a more "myocardial" phenotype of HFpEF.
Uric acid	Indirect sign of abnormal renal function and/or endothelial dysfunction. Uric acid can be elevated in patients on loop diuretics; if gout is present, consider lowering loop diuretic dose in favor of other diuretics (eg, SGLT2i or MRA).
Prealbumin	Low-normal or reduced levels can be indicative of ATTR cardiomyopathy (prealbumin = transthyretin, and the assay only detects TTR in its tetrameric form).
Serum free light chains, serum immunofixation, UPEP	Serum protein electrophoresis is neither sensitive nor specific, so serum immunofixation should be used for the evaluation of a plasma cell dyscrasia. Abnormal free light chains (especially elevated kappa/lambda ratio) can occur in the setting of chronic kidney disease.
Iron studies, ferritin	Low ferritin or transferrin saturation <20% indicate iron deficiency, which should be evaluated and treated if indicated.
TSH	Hyperthyroidism and hypothyroidism can mimic HFpEF and are treatable.
Autoimmune panel	Consider ANA testing in patients with signs and symptoms of connective tissue disease. Reflex testing can be performed if ANA is abnormal.
Intact PTH, 25-OH vitamin D, calcium, phosphorous	Indirect measures of abnormal renal function. Secondary hyperparathyroidism in a patient with normal creatinine and eGFR can be a clue to the presence of chronic kidney disease.
Urine albumin-to-creatinine ratio	Alternate measure of abnormal renal function, which is helpful when eGFR is normal due to hemodilution. Consider addition of renoprotective medications (eg, SGLT2i, ARNI, ACE inhibitor, or ARB) if present.
Hemoglobin A1c	Evaluate for and treat diabetes.
Lipid profile	Besides work-up for potential untreated hypercholesterolemia or hypertriglyceridemia, low levels of total cholesterol, HDL, and LDL can be seen in the setting of hepatic congestion due to advanced HFpEF, in which case ApoB may be more helpful.

ALT = alanine aminotransferase; ANA = antinuclear antibody; ApoB = apolipoprotein B; AST = aspartate aminotransferase; ATTR = transthyretin amyloid cardiomyopathy; BNP = B-type natriuretic peptide; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MRA = mineralocorticoid receptor antagonists; NTproBNP = N-terminal pro brain natriuretic peptide; PTH = parathyroid hormone; SGLT2i = sodium glucose cotransporter-2 inhibitor; TSH = thyroid-stimulating hormone; TTR = transthyretin; UPEP = urine protein electrophoresis; other abbreviations as in Tables 1 and 2.

that treatment with the SGLT2is empagliflozin and dapagliflozin, respectively, was associated with an 18% to 21% reduction in the primary endpoints of HF hospitalization or cardiovascular death among patients with HF and EF >40%.[2,3] Dapagliflozin has also been shown to improve quality of life and exercise capacity measured using 6-minute walk distance.[134] Benefits from SGLT2i apply similarly to patients with and without diabetes, and across the spectrum of EF.[135]

Diuretics are indicated to relieve the congestive symptoms in patients with HFpEF.[126] Mineralocorticoid receptor antagonists may decrease risk of HF hospitalizations, particularly in those with lower range LVEF. The TOPCAT (Treatment Of Preserved Cardiac function heart failure with an Aldosterone antagonist Trial) trial of spironolactone in HFpEF failed to show a reduction in the primary composite endpoint of HF hospitalization or cardiovascular death,[136] but there was substantial geographic heterogeneity, and, in the Americas, spironolactone use was associated with improved outcomes including the primary composite endpoint and HF hospitalizations.[137] The combined angiotensin receptor/neprilysin inhibitor sacubitril/valsartan did not significantly reduce the risk of HF hospitalization or cardiovascular death in the PARAGON-HF (Prospective Comparison of ARNI with ARB Global Outcomes in HF With Preserved Ejection Fraction) trial (P = 0.06).[138] Benefit was greater in

women and among patients with lower EF, but, in the subsequently published PARALLAX (Prospective Comparison of ARNI vs Comorbidity-Associated Conventional Therapy on Quality of Life and Exercise Capacity) trial, there was no salutary effect of sacubitril/valsartan on health status or submaximal exercise capacity,[139] in contrast to the favorable effects observed with SGLT2i.[134]

NONPHARMACOLOGIC THERAPIES. Exercise training improves aerobic capacity and quality of life in HFpEF and moderate intensity training appears equivalent to higher intensities.[140,141] Pulmonary artery pressure monitoring has demonstrated benefit in the treatment of HFpEF, as seen in the CHAMPION (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients) trial with a 50% reduction in HF hospitalization compared with standard care during the follow-up period of 18 months with an overall number needed to treat of 2 to prevent 1 HF hospitalization.[142] Implantation of a rate-adaptive atrial pacemaker to enhance heart rate responses to exercise in patients with HFpEF and chronotropic incompetence was not shown to improve exercise performance or quality of life in the RAPID-HF (Rate-Adaptive Atrial Pacing in Diastolic Heart Failure) trial.[143]

Treatment with an atrial shunt device in REDUCE LAP-HF II (Randomized trial to REDUCE Elevated Left Atrial Pressure in Patients with Heart Failure II) had no significant effect on the primary composite outcome of cardiovascular death, stroke, HF events, and change in health status.[144] However, a post hoc analysis showed that patients with latent pulmonary vascular disease (elevated exercise pulmonary vascular resistance >1.74 WU, which is the upper limit of normal in healthy older individuals) were harmed by shunt therapy, whereas those with normal pulmonary vascular resistance with exercise appeared to improve.[92] Pericardiotomy to reduce external constraint on the LV has been shown to improve hemodynamics in animal models and in pilot human studies,[145,146] but further study is required. Preliminary analyses from the open-label roll-in phase of the REBALANCE-HF (Endovascular Ablation of the Right Greater Splanchnic Nerve in Subjects Having HFpEF) trial testing endovascular splanchnic nerve ablation revealed improvements in LV filling pressures during exercise and patient-reported health status, although the results of the blinded, sham-controlled trial are not yet available.[147] A large number of clinical trials are under way for the identification of promising HFpEF therapies (Table 5), which should be more frequently offered to patients with HFpEF as potential additive treatment options given the high morbidity and mortality of HFpEF (which rivals most cancers).

KNOWLEDGE GAPS AND FUTURE DIRECTIONS

The past 20 years have witnessed major strides in improved understanding of HFpEF epidemiology, pathophysiology, molecular mechanisms, diagnosis, and treatment. After decades of neutral trials in HFpEF, a proven therapy (SGLT2i) now exists. Nevertheless, major unmet needs and knowledge gaps are still present (Table 6). As outlined earlier in this paper, HFpEF prevalence is increasing, too often remains undetected, and, even when diagnosed, is associated with high rates of hospitalization and rehospitalization. Despite the success of SGLT2i, both the DELIVER and EMPEROR-Preserved trials only showed a 3% absolute risk reduction in the primary outcome, which was driven by HF hospitalization and not cardiovascular mortality.[2,3] Thus, improved diagnosis and treatment of HFpEF is essential.

We now understand that HFpEF is a systemic, "reserve dysfunction" syndrome that involves multiple organs, not just the heart, and one that often requires perturbational testing to assist with diagnosis and treatment selection. Improved understanding of HFpEF in this manner has expanded the potential treatment landscape beyond conventional HF therapies to those that have beneficial effects in multiple organs. Indeed, a likely reason for the broad success of SGLT2i is the ability to improve the metabolic health of multiple organs while also promoting renoprotective diuresis. Successful future therapeutics will likely fall into 1 of 2 categories: 1) broadly applicable therapeutics such as SGLT2i that ameliorate abnormalities in multiple organs; and 2) tailored therapies that are directed toward specific subtypes of HFpEF (ie, a precision medicine approach to HFpEF).

Despite numerous major differences between HFpEF and HFrEF indicating that these are 2 distinct syndromes,[148] both of the aforementioned categories of therapeutics also open up the possibility of EF-agnostic HF therapeutics. Like SGLT2i, some therapies developed for HFpEF may be beneficial to all HF patients, especially as we understand that the comorbidity-inflammation-endothelial dysfunction paradigm may extend to many patients with HFrEF as well. On the other hand, precision therapeutics developed for HFpEF subtypes may be beneficial across the HF spectrum. For example, novel therapies for HFpEF that reduce interstitial fibrosis, targeted to

TABLE 5 Ongoing and Upcoming Clinical Trials in HFpEF

Trial Name (NCT #)	Therapy	Population/Key Enrollment Criteria	Primary Outcome
Cardiometabolic drug trials			
STEP HFpEF & STEP HFpEF-DM (NCT04788511, NCT04916470)	Semaglutide vs placebo	EF ≥45% and NYHA functional class II-IV BMI ≥30 kg/m^2 without or with T2DM	Change in KCCQ and change in body weight at 12 mo
SUMMIT (NCT04847557)	Tirzepatide vs placebo	EF ≥50% and NYHA functional class II-IV Elevated NT-proBNP BMI ≥30 kg/m^2	Composite: all-cause mortality, HF events, 6-min walk distance, KCCQ
CAMEO-SEMA (NCT05371496)	Semaglutide vs placebo	EF ≥50% and NYHA functional class II-IV BMI ≥30 kg/m^2 Exercise PCWP ≥25 mm Hg	Change in PCWP incorporating rest and exercise measurements at 1 y
CAMEO-DAPA (NCT04730947)	Dapagliflozin vs placebo	EF ≥50% and NYHA functional class II-IV Exercise PCWP ≥25 mm Hg	Change in PCWP incorporating rest and exercise measurements at 6 mo
HuMAIN (NCT05284617)	HU6 vs placebo	EF ≥50% and NYHA functional class II-IV BMI ≥30 kg/m^2 and T2DM	Change in body weight at 6 mo
Neurohormonal drug trials			
FINEARTS-HF (NCT04435626)	Finerenone vs placebo	EF >40% and NYHA functional class II-IV Structural heart disease Elevated NT-proBNP	Total number of CV deaths and HHF
SPIRRIT (NCT02901184)	Spironolactone vs standard of care	EF ≥40% and NYHA functional class II-IV NT-proBNP >300 ng/L or >750 ng/L in AF	Time to CV death or first HHF
SPIRIT-HF (NCT04727073)	Spironolactone vs placebo	EF ≥40% and NYHA functional class II-IV NT-proBNP >300 ng/L or >900 ng/L in AF	Total number of CV deaths and HHF
PARAGLIDE-HF (NCT03988634)	Sacubitril/Valsartan vs Valsartan	EF >40% Hospitalized with acute decompensated HFpEF Elevated NT-proBNP or BNP during hospitalization	Change in NT-proBNP from baseline to the average of wk 4 and 8
Pulmonary hypertension due to HFpEF trials			
CADENCE (NCT04945460)	Sotatercept vs placebo	EF ≥50% with combined pre- and postcapillary PH PVR ≥4 WU, PCWP >15 but <30 mm Hg	Pulmonary vascular resistance
PH-HFpEF (NCT03015402)	Sodium nitrite vs placebo oral capsule	PH-HFpEF confirmed diagnosis by RHC	PAP during submaximal exercise
Metformin for PH-HFpEF (NCT03629340)	Metformin vs placebo	PH-HFpEF confirmed within the past 6 mo ≥3 features of metabolic syndrome	Mean PAP during submaximal exercise at 12 wk
Open-Label Rollover Study of Levosimendan in PH-HFpEF (NCT03624010)	Open label levosimendan	Completed double-blind therapy in a PH-HFpEF clinical study of levosimendan sponsored by Tenax Therapeutics, Inc.	Clinical safety measured by number of adverse events at 2 y
Nitric oxide/cGMP/PKG-activating drug trials			
INABLE-Training (NCT02713126)	Sodium nitrite vs placebo solution	EF ≥50% and NYHA functional class II-IV Previous HHF, elevated PCWP (rest or exercise) or NT-proBNP >400 pg/mL or BNP >200 pg/mL	Change in peak VO_2 at 12 wk
KNO_3CK OUT HFpEF (NCT02840799)	Potassium nitrate vs potassium chloride	EF >50% and NYHA functional class II-III Elevated filling pressures	Change in peak VO_2 and change in total work performed during a maximal-effort exercise test

Continued on the next page

patients with HFpEF with high extracellular volume content on cardiac magnetic resonance imaging,[149] could be expanded to all patients with HF (regardless of EF) who have evidence of substantial interstitial myocardial fibrosis.

Therefore, future therapeutic strategies will benefit from deep, multimodal, and multiorgan phenotyping coupled with hypothesis-driven and ML-guided approaches to uncover novel HFpEF mechanisms, subtypes, and therapeutic targets. Given the heterogeneity of the HFpEF syndrome, development of automated techniques to enhance the diagnosis, subtyping, and therapeutic decision-making in patients with HFpEF may also be of significant utility.

CONCLUSIONS

HFpEF is one of the most pressing diagnostic and therapeutic challenges in clinical medicine today given its increasing prevalence, underdiagnosis, poor prognosis, limited therapeutic options, and substantial burden on the health care system worldwide. Despite these challenges, the success of recent SGLT2i trials has shown that HFpEF is treatable. Ongoing large-scale studies of HFpEF pathobiology, an increasing number of translational studies spanning the gap between the bedside and the bench, and numerous clinical trials of novel therapeutics in HFpEF offer a glimpse of hope toward a future of reduced prevalence, morbidity, and mortality

TABLE 5 Continued

Trial Name (NCT #)	Therapy	Population/Key Enrollment Criteria	Primary Outcome
Trials targeting left atrial myopathy and atrial fibrillation			
RESPONDER (NCT05425459)	Atrial shunt device vs sham	LVEF ≥40% and NYHA functional class II-IV Elevated PCWP during exercise, without high PVR or pacemaker device	Composite of HF event rates and KCCQ at 12 mo
RELIEVE-HF (NCT03499236)	Atrial shunt device vs sham	HFpEF and HFpEF, NYHA functional class II-IV HHF and/or elevated NP levels	Composite of death, transplant or LVAD, HHF, worsening outpatient HF events, and change in KCCQ
FROST-HF (NCT03751748)	Atrial shunt device vs sham	LVEF >45%, NYHA functional class II-IV, and LA enlargement 6MWT distance <80% predicted. PCWP ≥25 mm Hg during supine exercise test	Change in 6-min walk distance at 12 mo
RELAXIN-LA (NCT05592275)	Relaxin analogue vs placebo	EF ≥50% and NYHA functional class II-IV Recent HF hospitalization or urgent outpatient treatment for congestion with NTproBNP >300 or >900 in AF	Change in LA reservoir strain at 26 wk
CABA-HFPEF (NCT05508256)	Catheter ablation vs usual care	LVEF ≥40% and NYHA functional class II-IV Paroxysmal or persistent AF NT-proBNP >300 ng/L or >900 ng/L (AF) or HF hospitalization	Time free of CV death and total (first and recurrent) unplanned cardiovascular hospitalizations
Trials targeting inflammation			
Myeloperoxidase (MPO) inhibitor with exercise in HFpEF (NCT03611153)	MPO inhibitor vs placebo	EF ≥50% and NYHA functional class II-IV PCWP ≥15 at rest or PCWP ≥25 with exercise	Exercise PCWP
ENDEAVOR (NCT04986202)	MPO inhibitor vs placebo	EF ≥40% and NYHA functional class II-IV NT-proBNP >200-250 ng/L or >400-500 ng/L in AF (based on BMI)	Change in KCCQ and change in 6-min walk distance
HERMES (NCT05636176)	Ziltivekumab vs placebo	EF ≥40% and NYHA functional class II-IV NT-proBNP >300 or >600 in AF C-reactive protein >2 mg/L	Time to HF hospitalization, cardiovascular death, or urgent outpatient HF visit
ColPET (NCT04857931)	Colchicine vs placebo	EF ≥45% and NYHA functional class II-IV NT-proBNP >300 ng/L or >900 ng/L in AF BMI >30 kg/m^2, T2DM, or CRP >2 mg/L	Change in C-reactive protein at 6 mo
Colchicine in patients with HFpEF (NCT05637398)	Colchicine vs usual care	EF ≥50% and NYHA functional class II-IV NT-proBNP >300 or >600 in AF, structural heart disease BMI >30 kg/m^2 or T2DM	Change in sST2 at 12 wk
Device-based trials			
Rebalance-HF (NCT04592445)	Right greater splanchnic nerve ablation vs sham	LVEF ≥50% and NYHA functional class II-IV Elevated NP, prior HHF, or increased diuretic requirement Elevated PCWP during exercise	Change in PCWP incorporating rest and exercise measurements at 1 mo
AIM HIGHer (NCT05064709)	Cardiac contractility modulation vs sham	LVEF ≥40% and ≤60% and NYHA functional class II-IV Elevated NP levels	Change in 6-min walk distance and KCCQ at 6 mo
HERACLES-HFpEF (NCT04782908)	Transvascular tricuspid valve repair	LVEF ≥50% and NYHA functional class II-IV Severe tricuspid regurgitation	Change in LV end diastolic pressure volume relationship
Other trials			
IRONMET-HFpEF (NCT04945707)	Ferric Derisomaltose vs placebo	EF ≥50% and NYHA functional class II-IV Iron deficiency	Change in peak VO_2
REHAB-HFpEF (NCT05525663)	Rehabilitation intervention vs attention control	Age ≥60 y EF ≥45% Hospitalization for acute decompensated HF	Combined all-cause rehospitalization and death at 6 mo
AMETHYST (NCT04327024)	Verinurad and allopurinol vs placebo	EF ≥45% and HF symptoms Hyperuricemia	Change in peak VO_2

AF = atrial fibrillation; BMI = body mass index; cGMP = cyclic guanosine monophosphate; CV = cardiovascular; EF = ejection fraction; HHF = hypertensive heart failure; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVAD = left ventricular assist device; MPO = myeloperoxidase; NP = natriuretic peptide; NYHA = New York Heart Association; PAP = pulmonary artery pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; RHC = right heart catheterization; sST2 = soluble suppression of tumorigenicity-2; T2DM = type 2 diabetes mellitus; other abbreviations as in Tables 1, 2, and 4.

TABLE 6 Key Knowledge Gaps and Unmet Needs in HFpEF

Category	Knowledge Gap or Unmet Need
Diagnosis	1. Noninvasive tests with similar accuracy to invasive gold standard 2. Accurate markers of congestion (improvement over natriuretic peptides) 3. Improved detection of HFpEF given the high frequency of underdiagnosis 4. Valid, reproducible, easily applied definitions for preclinical HFpEF
Mechanism	5. Unraveling mechanisms linking adiposity and physical inactivity with HFpEF 6. Determinants of progression from stage A to stage B to stage C/D HFpEF 7. Repositories of cardiac and extracardiac tissue from HFpEF patients, including atrial tissue as well as biopsy or necropsy material from both ventricles 8. Preclinical models that recapitulate human HFpEF 9. Unraveling effects of HF on the lungs and pulmonary vasculature in HFpEF 10. Improved understanding of the interactions and directionality between extracardiac organ dysfunction and the heart in HFpEF
Phenotyping and natural history	11. Understanding natural history and disease trajectory across HFpEF phenogroups or in the context of multimorbidity 12. Creation of an optimal phenotypic classification system for HFpEF 13. Identify and test in novel therapies targeting specific phenogroups in prospective trials
Therapy	14. Therapies that prevent the development of HFpEF 15. Investigations focused on obesity and physical inactivity and the role in HFpEF, including weight loss and increasing activity levels/training 16. Phenotype-guided vs general strategies to treat HFpEF 17. Therapies targeting cardiometabolic perturbations in HFpEF 18. Novel therapies targeting peripheral determinants of exercise intolerance 19. Therapies that improve ventricular compliance, relaxation, and cardiac reserve 20. Therapies that target pulmonary vascular disease in HFpEF 21. Therapies targeting outside the cardiovascular system such as adipose tissue, inflammation, and skeletal muscle 22. Treatment of epicardial coronary artery disease 23. Treatment of coronary microvascular disease 24. Optimal treatment of atrial fibrillation and role of catheter ablation

Abbreviations as in Table 1.

associated with HFpEF, which would be a major advance for population health.

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REFERENCES

1. Pfeffer MA, Shah AM, Borlaug BA. Heart failure with preserved ejection fraction in perspective. *Circ Res*. 2019;124:1598–1617.

2. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med*. 2021;385:1451–1461.

3. Solomon SD, McMurray JJV, Claggett B, et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. *N Engl J Med*. 2022;387:1089–1098.

4. Bozkurt B, Coats AJS, Tsutsui H, et al. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure: endorsed by Canadian Heart Failure Society, Heart Failure Association of India, the Cardiac Society of Australia and New Zealand, and the Chinese Heart Failure Association. *Eur J Heart Fail*. 2021;23:352–380.

5. Verbrugge FH, Omote K, Reddy YNV, Sorimachi H, Obokata M, Borlaug BA. Heart failure with preserved ejection fraction in patients with normal natriuretic peptide levels is associated with increased morbidity and mortality. *Eur Heart J*. 2022;43:1941–1951.

6. Shah SJ. BNP: biomarker not perfect in heart failure with preserved ejection fraction. *Eur Heart J*. 2022;43:1952–1954.

7. Obokata M, Reddy YNV, Melenovsky V, Sorimachi H, Jarolim P, Borlaug BA. Uncoupling between intravascular and distending pressures leads to underestimation of circulatory congestion in obesity. *Eur J Heart Fail*. 2022;24:353–361.

8. Borlaug BA, Jensen MD, Kitzman DW, Lam CSP, Obokata M, Rider OJ. Obesity and heart failure with preserved ejection fraction: new insights and pathophysiologic targets. *Cardiovasc Res*. 2023;118:3434–3450.

9. Gerber Y, Weston SA, Redfield MM, et al. A contemporary appraisal of the heart failure epidemic in Olmsted County, Minnesota, 2000 to 2010. *JAMA Intern Med*. 2015;175:996–1004.

10. Tsao CW, Lyass A, Enserro D, et al. Temporal trends in the incidence of and mortality associated with heart failure with preserved and reduced ejection fraction. *J Am Coll Cardiol HF*. 2018;6:678–685.

11. Bhambhani V, Kizer JR, Lima JAC, et al. Predictors and outcomes of heart failure with mid-range ejection fraction. *Eur J Heart Fail*. 2018;20:651–659.

12. Steinberg BA, Zhao X, Heidenreich PA, et al. Trends in patients hospitalized with heart failure and preserved left ventricular ejection fraction: prevalence, therapies, and outcomes. *Circulation*. 2012;126:65–75.

13. Clark KAA, Reinhardt SW, Chouairi F, et al. Trends in heart failure hospitalizations in the US from 2008 to 2018. *J Card Fail*. 2022;28:171–180.

14. Pandey A, Omar W, Ayers C, et al. Sex and race differences in lifetime risk of heart failure with preserved ejection fraction and heart failure with reduced ejection fraction. *Circulation*. 2018;137:1814–1823.

15. Ho JE, Lyass A, Lee DS, et al. Predictors of new-onset heart failure: differences in preserved versus reduced ejection fraction. *Circ Heart Fail*. 2013;6:279–286.

16. Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. *Nat Rev Cardiol*. 2017;14:591–602.

17. Chang PP, Wruck LM, Shahar E, et al. Trends in hospitalizations and survival of acute decompensated heart failure in four US communities (2005-2014): ARIC Study Community Surveillance. *Circulation*. 2018;138:12-24.

18. Ho JE, Enserro D, Brouwers FP, et al. Predicting heart failure with preserved and reduced ejection fraction: the international collaboration on heart failure subtypes. *Circ Heart Fail*. 2016;9:e003116. https://doi.org/10.1161/CIRCHEARTFAILURE.115.003116

19. Savji N, Meijers WC, Bartz TM, et al. The association of obesity and cardiometabolic traits with incident HFpEF and HFrEF. *J Am Coll Cardiol HF*. 2018;6:701–709.

20. Pandey A, LaMonte M, Klein L, et al. Relationship between physical activity, body mass index, and risk of heart failure. *J Am Coll Cardiol*. 2017;69:1129–1142.

21. Koepp KE, Reddy YNV, Obokata M, et al. Identification of patients with preclinical heart failure with preserved ejection fraction using the H2FPEF score. *Nat Cardiovasc Res*. 2022;1:59–66.

22. Selvaraj S, Myhre PL, Vaduganathan M, et al. Application of diagnostic algorithms for heart failure with preserved ejection fraction to the community. *J Am Coll Cardiol HF*. 2020;8:640–653.

23. Shah KS, Xu H, Matsouaka RA, et al. Heart failure with preserved, borderline, and reduced ejection fraction: 5-year outcomes. *J Am Coll Cardiol*. 2017;70:2476–2486.

24. Vaduganathan M, Patel RB, Michel A, et al. Mode of death in heart failure with preserved ejection fraction. *J Am Coll Cardiol*. 2017;69:556–569.

25. Jha AK, Ojha CP, Krishnan AM, Paul TK. Thirty-day readmission in patients with heart failure with preserved ejection fraction: Insights from the nationwide readmission database. *World J Cardiol*. 2022;14:473–482.

26. Desai AS, Vaduganathan M, Cleland JG, et al. Mode of death in patients with heart failure and preserved ejection fraction: insights from PARAGON-HF trial. *Circ Heart Fail*. 2021;14:e008597.

27. Lewis EF, Claggett B, Shah AM, et al. Racial differences in characteristics and outcomes of patients with heart failure and preserved ejection fraction in the treatment of preserved cardiac function heart failure trial. *Circ Heart Fail*. 2018;11:e004457.

28. Wang X, Vaduganathan M, Claggett BL, et al. Sex differences in characteristics, outcomes and treatment response with dapagliflozin across the range of ejection fraction in patients with heart failure: insights from DAPA-HF and DELIVER. *Circulation*. 2023;147:624–634.

29. Kawaguchi M, Hay I, Fetics B, Kass DA. Combined ventricular systolic and arterial stiffening in patients with heart failure and preserved ejection fraction: implications for systolic and diastolic reserve limitations. *Circulation*. 2003;107:714–720.

30. Borlaug BA, Melenovsky V, Russell SD, et al. Impaired chronotropic and vasodilator reserves limit exercise capacity in patients with heart failure and a preserved ejection fraction. *Circulation*. 2006;114:2138–2147.

31. Zile MR, Baicu CF, Gaasch WH. Diastolic heart failure–abnormalities in active relaxation and passive stiffness of the left ventricle. *N Engl J Med*. 2004;350:1953–1959.

32. Lam CS, Roger VL, Rodeheffer RJ, et al. Cardiac structure and ventricular-vascular function in persons with heart failure and preserved ejection fraction from Olmsted County, Minnesota. *Circulation*. 2007;115:1982–1990.

33. Ng ACT, Delgado V, Borlaug BA, Bax JJ. Diabesity: the combined burden of obesity and diabetes on heart disease and the role of imaging. *Nat Rev Cardiol*. 2021;18:291–304.

34. Paulus WJ, Tschope C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *J Am Coll Cardiol*. 2013;62:263–271.

35. Schiattarella GG, Rodolico D, Hill JA. Metabolic inflammation in heart failure with preserved ejection fraction. *Cardiovasc Res*. 2021;117:423–434.

36. Pandey A, Shah SJ, Butler J, et al. Exercise intolerance in older adults with heart failure with preserved ejection fraction: JACC STATE-OF-THE-ART REVIEW. *J Am Coll Cardiol*. 2021;78:1166–1187.

37. Paulus WJ, Zile MR. From systemic inflammation to myocardial fibrosis: the heart failure with preserved ejection fraction paradigm revisited. *Circ Res*. 2021;128:1451–1467.

38. Hahn VS, Yanek LR, Vaishnav J, et al. Endomyocardial biopsy characterization of heart failure with preserved ejection fraction and prevalence of cardiac amyloidosis. *J Am Coll Cardiol HF*. 2020;8:712–724.

39. Rosch S, Kresoja KP, Besler C, et al. Characteristics of heart failure with preserved ejection fraction across the range of left ventricular ejection fraction. *Circulation*. 2022;146:506–518.

40. van Heerebeek L, Borbély A, Niessen HWM, et al. Myocardial structure and function differ in systolic and diastolic heart failure. *Circulation*. 2006;113:1966–1973.

41. van Heerebeek L, Hamdani N, Handoko ML, et al. Diastolic stiffness of the failing diabetic heart: importance of fibrosis, advanced glycation end products, and myocyte resting tension. *Circulation*. 2008;117:43–51.

42. van Heerebeek L, Hamdani N, Falcão-Pires I, et al. Low myocardial protein kinase g activity in heart failure with preserved ejection fraction. *Circulation*. 2012;126:830–839.

43. Zile MR, Baicu CF, Ikonomidis JS, et al. Myocardial stiffness in patients with heart failure and a preserved ejection fraction: contributions of collagen and titin. *Circulation*. 2015;131:1247–1259.

44. Obokata M, Reddy YN, Pislaru SV, Melenovsky V, Borlaug BA. Evidence supporting the existence of a distinct obese phenotype of heart failure with preserved ejection fraction. *Circulation*. 2017;136:6–19.

45. Borlaug BA, Reddy YNV. The role of the pericardium in heart failure: implications for pathophysiology and treatment. *J Am Coll Cardiol HF*. 2019;7:574–585.

46. Wohlfahrt P, Redfield MM, Lopez-Jimenez F, et al. Impact of general and central adiposity on ventricular-arterial aging in women and men. *J Am Coll Cardiol HF*. 2014;2:489–499.

47. Feldschuh J, Enson Y. Prediction of the normal blood volume. Relation of blood volume to body habitus. *Circulation*. 1977;56:605–612.

48. Miller WL, Borlaug BA. Impact of obesity on volume status in patients with ambulatory chronic heart failure. *J Card Fail*. 2020;26:112–117.

49. Sorimachi H, Burkhoff D, Verbrugge FH, et al. Obesity, venous capacitance, and venous compliance in heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2021;23:1648–1658.

50. Aslam MI, Hahn VS, Jani V, Hsu S, Sharma K, Kass DA. Reduced right ventricular sarcomere contractility in heart failure with preserved ejection fraction and severe obesity. *Circulation*. 2021;143:965–967.

51. Peterson LR, Herrero P, Schechtman KB, et al. Effect of obesity and insulin resistance on myocardial substrate metabolism and efficiency in young women. *Circulation*. 2004;109:2191–2196.

52. Burrage MK, Hundertmark M, Valkovič L, et al. Energetic basis for exercise-induced pulmonary congestion in heart failure with preserved ejection fraction. *Circulation*. 2021;144:1664–1678.

53. Rayner JJ, Peterzan MA, Watson WD, et al. Myocardial energetics in obesity: enhanced ATP delivery through creatine kinase with blunted stress response. *Circulation*. 2020;141:1152–1163.

54. Hahn VS, Knutsdottir H, Luo X, et al. Myocardial gene expression signatures in human heart failure with preserved ejection fraction. *Circulation*. 2021;143:120–134.

55. Koepp KE, Obokata M, Reddy YNV, Olson TP, Borlaug BA. Hemodynamic and functional impact of epicardial adipose tissue in heart failure with preserved ejection fraction. *J Am Coll Cardiol HF*. 2020;8:657–666.

56. Reddy YNV, Lewis GD, Shah SJ, et al. Characterization of the obese phenotype of heart failure with preserved ejection fraction: a RELAX trial ancillary study. *Mayo Clin Proc*. 2019;94:1199–1209.

57. Redfield MM, Anstrom KJ, Levine JA, et al. Isosorbide mononitrate in heart failure with preserved ejection fraction. *N Engl J Med*. 2015;373:2314–2324.

58. Borlaug BA, Anstrom KJ, Lewis GD, et al. Effect of inorganic nitrite vs placebo on exercise capacity among patients with heart failure with preserved ejection fraction: the INDIE-HFpEF randomized clinical trial. *JAMA*. 2018;320:1764–1773.

59. Udelson JE, Lewis GD, Shah SJ, et al. Effect of praliciguat on peak rate of oxygen consumption in patients with heart failure with preserved ejection fraction: the CAPACITY HFpEF randomized clinical trial. *JAMA*. 2020;324:1522–1531.

60. Armstrong PW, Lam CSP, Anstrom KJ, et al. Effect of vericiguat vs placebo on quality of life in patients with heart failure and preserved ejection fraction: the VITALITY-HFpEF randomized clinical trial. *JAMA*. 2020;324:1512–1521.

61. Sanders-van Wijk S, van Empel V, Davarzani N, et al. Circulating biomarkers of distinct pathophysiological pathways in heart failure with preserved vs. reduced left ventricular ejection fraction. *Eur J Heart Fail*. 2015;17:1006–1014.

62. Kalogeropoulos A, Georgiopoulou V, Psaty BM, et al. Inflammatory markers and incident heart failure risk in older adults: the Health ABC (Health, Aging, and Body Composition) study. *J Am Coll Cardiol*. 2010;55:2129–2137.

63. Markousis-Mavrogenis G, Tromp J, Ouwerkerk W, et al. The clinical significance of interleukin-6 in heart failure: results from the BIOSTAT-CHF study. *Eur J Heart Fail*. 2019;21:965–973.

64. Sabbah MS, Fayyaz AU, de Denus S, et al. Obese-inflammatory phenotypes in heart failure with preserved ejection fraction. *Circ Heart Fail*. 2020;13:e006414.

65. Shah SJ, Lam CSP, Svedlund S, et al. Prevalence and correlates of coronary microvascular dysfunction in heart failure with preserved ejection fraction: PROMIS-HFpEF. *Eur Heart J*. 2018;39:3439–3450.

66. Yang JH, Obokata M, Reddy YNV, Redfield MR, Lerman A, Borlaug BA. Endothelium-dependent and independent coronary microvascular dysfunction in patients with heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2020;22:432–441.

67. Rush CJ, Berry C, Oldroyd KG, et al. Prevalence of coronary artery disease and coronary microvascular dysfunction in patients with heart failure with preserved ejection fraction. *JAMA Cardiol*. 2021;6:1130–1143.

68. Sanders-van Wijk S, Tromp J, Beussink-Nelson L, et al. Proteomic evaluation of the comorbidity-inflammation paradigm in heart failure with preserved ejection fraction: results from the PROMIS-HFpEF study. *Circulation*. 2020;142:2029–2044.

69. Mohammed SF, Hussain S, Mirzoyev SA, Edwards WD, Maleszewski JJ, Redfield MM. Coronary microvascular rarefaction and myocardial fibrosis in heart failure with preserved ejection fraction. *Circulation*. 2015;131:550–559.

70. Patel RB, Colangelo LA, Bielinski SJ, et al. Circulating vascular cell adhesion molecule-1 and incident heart failure: the Multi-Ethnic Study of Atherosclerosis (MESA). *J Am Heart Assoc*. 2020;9:e019390.

71. Patel RB, Colangelo LA, Reiner AP, et al. Cellular adhesion molecules in young adulthood and cardiac function in later life. *J Am Coll Cardiol*. 2020;75:2156–2165.

72. Schiattarella GG, Altamirano F, Tong D, et al. Nitrosative stress drives heart failure with preserved ejection fraction. *Nature*. 2019;568:351–356.

73. Rao VN, Zhao D, Allison MA, et al. Adiposity and incident heart failure and its subtypes: MESA (Multi-Ethnic Study of Atherosclerosis). *J Am Coll Cardiol HF*. 2018;6:999–1007.

74. Sorimachi H, Omote K, Omar M, et al. Sex and central obesity in heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2022;24:1359–1370.

75. Sorimachi H, Obokata M, Takahashi N, et al. Pathophysiologic importance of visceral adipose tissue in women with heart failure and preserved ejection fraction. *Eur Heart J*. 2021;42:1595–1605.

76. Packer M. Critical reanalysis of the mechanisms underlying the cardiorenal benefits of SGLT2 inhibitors and reaffirmation of the nutrient deprivation signaling/autophagy hypothesis. *Circulation*. 2022;146:1383–1405.

77. Borlaug BA, Jaber WA, Ommen SR, Lam CSP, Redfield MM, Nishimura RA. Diastolic relaxation and compliance reserve during dynamic exercise in heart failure with preserved ejection fraction. *Heart*. 2011;97:964–969.

78. Melenovsky V, Hwang S-J, Redfield MM, Zakeri R, Lin G, Borlaug BA. Left atrial remodeling and function in advanced heart failure with preserved or reduced ejection fraction. *Circ Heart Fail*. 2015;8:295–303.

79. Reddy YNV, Obokata M, Verbrugge FH, Lin G, Borlaug BA. Atrial dysfunction in patients with heart failure with preserved ejection fraction and atrial fibrillation. *J Am Coll Cardiol*. 2020;76:1051–1064.

80. Freed BH, Daruwalla V, Cheng JY, et al. Prognostic utility and clinical significance of cardiac mechanics in heart failure with preserved ejection fraction: importance of left atrial strain. *Circ Cardiovasc Imag*. 2016;9:e003754. https://doi.org/10.1161/CIRCIMAGING.115.003754

81. Reddy YNV, Obokata M, Egbe A, et al. Left atrial strain and compliance in the diagnostic evaluation of heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2019;21:891–900.

82. Telles F, Nanayakkara S, Evans S, et al. Impaired left atrial strain predicts abnormal exercise haemodynamics in heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2019;21:495–505.

83. Backhaus SJ, Lange T, George EF, et al. Exercise stress real-time cardiac magnetic resonance imaging for noninvasive characterization of heart failure with preserved ejection fraction: the HFpEF-Stress trial. *Circulation*. 2021;143:1484–1498.

84. Verbrugge FH, Guazzi M, Testani JM, Borlaug BA. Altered hemodynamics and end-organ damage in heart failure: impact on the lung and kidney. *Circulation*. 2020;142:998–1012.

85. Lam CS, Roger VL, Rodeheffer RJ, Borlaug BA, Enders FT, Redfield MM. Pulmonary hypertension in heart failure with preserved ejection fraction: a community-based study. *J Am Coll Cardiol*. 2009;53:1119–1126.

86. Omote K, Verbrugge FH, Sorimachi H, et al. Central hemodynamic abnormalities and outcome in patients with unexplained dyspnea. *Eur J Heart Fail*. 2023;25:185–196.

87. Vanderpool RR, Saul M, Nouraie M, Gladwin MT, Simon MA. Association between hemodynamic markers of pulmonary hypertension and outcomes in heart failure with preserved ejection fraction. *JAMA Cardiol*. 2018;3:298–306.

88. Fayyaz AU, Edwards WD, Maleszewski JJ, et al. Global pulmonary vascular remodeling in pulmonary hypertension associated with heart failure and preserved or reduced ejection fraction. *Circulation*. 2018;137:1796–1810.

89. Omote K, Sorimachi H, Obokata M, et al. Pulmonary vascular disease in pulmonary hypertension due to left heart disease: pathophysiologic implications. *Eur Heart J*. 2022;43:3417–3431.

90. Melenovsky V, Hwang SJ, Lin G, Redfield MM, Borlaug BA. Right heart dysfunction in heart failure with preserved ejection fraction. *Eur Heart J*. 2014;35:3452–3462.

91. Obokata M, Reddy YNV, Melenovsky V, Pislaru S, Borlaug BA. Deterioration in right ventricular structure and function over time in patients with heart failure and preserved ejection fraction. *Eur Heart J*. 2019;40:689–697.

92. Borlaug BA, Blair J, Bergmann MW, et al. Latent pulmonary vascular disease may alter the response to therapeutic atrial shunt device in heart failure. *Circulation*. 2022;145:1592–1604.

93. Ho JE, Zern EK, Lau ES, et al. Exercise pulmonary hypertension predicts clinical outcomes in

patients with dyspnea on effort. *J Am Coll Cardiol*. 2020;75:17–26.

94. Borlaug BA, Olson TP, Lam CSP, et al. Global cardiovascular reserve dysfunction in heart failure with preserved ejection fraction. *J Am Coll Cardiol*. 2010;56:845–854.

95. Sorimachi H, Verbrugge FH, Omote K, et al. Longitudinal evolution of cardiac dysfunction in heart failure and preserved ejection fraction with normal natriuretic peptide levels. *Circulation*. 2022;146:500–502.

96. Lau ES, Panah LG, Zern EK, et al. Arterial stiffness and vascular load in HFpEF: differences among women and men. *J Card Fail*. 2022;28:202–211.

97. Reddy YNV, Andersen MJ, Obokata M, et al. Arterial stiffening with exercise in patients with heart failure and preserved ejection fraction. *J Am Coll Cardiol*. 2017;70:136–148.

98. Kitzman DW, Nicklas B, Kraus WE, et al. Skeletal muscle abnormalities and exercise intolerance in older patients with heart failure and preserved ejection fraction. *Am J Physiol Heart Circ Physiol*. 2014;306:H1364–1370.

99. Houstis NE, Eisman AS, Pappagianopoulos PP, et al. Exercise intolerance in heart failure with preserved ejection fraction: diagnosing and ranking its causes using personalized O2 pathway analysis. *Circulation*. 2018;137:148–161.

100. Olson TP, Johnson BD, Borlaug BA. Impaired pulmonary diffusion in heart failure with preserved ejection fraction. *J Am Coll Cardiol HF*. 2016;4:490–498.

101. Haykowsky MJ, Brubaker PH, John JM, Stewart KP, Morgan TM, Kitzman DW. Determinants of exercise intolerance in elderly heart failure patients with preserved ejection fraction. *J Am Coll Cardiol*. 2011;58:265–274.

102. Sarma S, Stoller D, Hendrix J, et al. Mechanisms of chronotropic incompetence in heart failure with preserved ejection fraction. *Circ Heart Fail*. 2020;13:e006331.

103. Fudim M, Kaye DM, Borlaug BA, et al. Venous tone and stressed blood volume in heart failure: JACC review topic of the week. *J Am Coll Cardiol*. 2022;79:1858–1869.

104. Shah SJ, Kitzman DW, Borlaug BA, et al. Phenotype-specific treatment of heart failure with preserved ejection fraction: a multiorgan roadmap. *Circulation*. 2016;134:73–90.

105. Sorimachi H, Omote K, Borlaug BA. Clinical phenogroups in heart failure with preserved ejection fraction. *Heart Fail Clin*. 2021;17:483–498.

106. Ho JE, Redfield MM, Lewis GD, Paulus WJ, Lam CSP. Deliberating the diagnostic dilemma of heart failure with preserved ejection fraction. *Circulation*. 2020;142:1770–1780.

107. Senni M, Caravita S, Paulus WJ. Do existing definitions identify subgroup phenotypes or reflect the natural history of heart failure with preserved ejection fraction? *Circulation*. 2019;140:366–369.

108. Peters AE, Tromp J, Shah SJ, et al. Phenomapping in heart failure with preserved ejection fraction: insights, limitations, and future directions. *Cardiovasc Res*. 2023;118:3403–3415.

109. Shah SJ, Katz DH, Selvaraj S, et al. Phenomapping for novel classification of heart failure with preserved ejection fraction. *Circulation*. 2015;131:269–279.

110. Ahmad FS, Luo Y, Wehbe RM, Thomas JD, Shah SJ. Advances in machine learning approaches to heart failure with preserved ejection fraction. *Heart Fail Clin*. 2022;18:287–300.

111. Shah SJ, Butler J, Shah SH, Kamphaus TN, Sachdev V. Accelerating therapeutic discoveries for heart failure: a new public-private partnership. *Nat Rev Drug Discov*. 2022;21:781–782.

112. Borlaug BA. Evaluation and management of heart failure with preserved ejection fraction. *Nat Rev Cardiol*. 2020;17:559–573.

113. Jering K, Claggett B, Redfield MM, et al. Burden of heart failure signs and symptoms, prognosis, and response to therapy: the PARAGON-HF trial. *J Am Coll Cardiol HF*. 2021;9:386–397.

114. Anjan VY, Loftus TM, Burke MA, et al. Prevalence, clinical phenotype, and outcomes associated with normal B-type natriuretic peptide levels in heart failure with preserved ejection fraction. *Am J Cardiol*. 2012;110:870–876.

115. Obokata M, Reddy YNV, Borlaug BA. Diastolic dysfunction and heart failure with preserved ejection fraction: understanding mechanisms by using noninvasive methods. *J Am Coll Cardiol Img*. 2020;13:245–257.

116. Obokata M, Kane GC, Reddy YN, Olson TP, Melenovsky V, Borlaug BA. Role of diastolic stress testing in the evaluation for heart failure with preserved ejection fraction: a simultaneous invasive-echocardiographic study. *Circulation*. 2017;135:825–838.

117. Reddy YNV, Carter RE, Obokata M, Redfield MM, Borlaug BA. A simple, evidence-based approach to help guide diagnosis of heart failure with preserved ejection fraction. *Circulation*. 2018;138:861–870.

118. Pieske B, Tschöpe C, de Boer RA, et al. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur Heart J*. 2019;40:3297–3317.

119. Omote K, Hsu S, Borlaug BA. Hemodynamic assessment in heart failure with preserved ejection fraction. *Cardiol Clin*. 2022;40:459–472.

120. Eisman AS, Shah RV, Dhakal BP, et al. Pulmonary capillary wedge pressure patterns during exercise predict exercise capacity and incident heart failure. *Circ Heart Fail*. 2018;11:e004750.

121. Reddy YNV, Kaye DM, Handoko ML, et al. Diagnosis of heart failure with preserved ejection fraction among patients with unexplained dyspnea. *JAMA Cardiol*. 2022;7:891–899.

122. D'Alto M, Badesch D, Bossone E, et al. A fluid challenge test for the diagnosis of occult heart failure. *Chest*. 2021;159:791–797.

123. van de Bovenkamp AA, Wijkstra N, Oosterveer FPT, et al. The value of passive leg raise during right heart catheterization in diagnosing heart failure with preserved ejection fraction. *Circ Heart Fail*. 2022;15:e008935.

124. Andersen MJ, Olson TP, Melenovsky V, Kane GC, Borlaug BA. Differential hemodynamic effects of exercise and volume expansion in people with and without heart failure. *Circ Heart Fail*. 2015;8:41–48.

125. Maeder MT, Thompson BR, Brunner-La Rocca HP, Kaye DM. Hemodynamic basis of exercise limitation in patients with heart failure and normal ejection fraction. *J Am Coll Cardiol*. 2010;56:855–863.

126. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2022;79:e263–e421.

127. Zakeri R, Chamberlain AM, Roger VL, Redfield MM. Temporal relationship and prognostic significance of atrial fibrillation in heart failure patients with preserved ejection fraction: a community-based study. *Circulation*. 2013;128:1085–1093.

128. Reddy YNV, Borlaug BA, Gersh BJ. Management of atrial fibrillation across the spectrum of heart failure with preserved and reduced ejection fraction. *Circulation*. 2022;146:339–357.

129. Kitzman DW, Brubaker P, Morgan T, et al. Effect of caloric restriction or aerobic exercise training on peak oxygen consumption and quality of life in obese older patients with heart failure with preserved ejection fraction: a randomized clinical trial. *JAMA*. 2016;315:36–46.

130. Sorimachi H, Obokata M, Omote K, et al. Long-term changes in cardiac structure and function following bariatric surgery. *J Am Coll Cardiol*. 2022;80:1501–1512.

131. Reddy YNV, Anantha-Narayanan M, Obokata M, et al. Hemodynamic effects of weight loss in obesity: a systematic review and meta-analysis. *J Am Coll Cardiol HF*. 2019;7:678–687.

132. Hwang SJ, Melenovsky V, Borlaug BA. Implications of coronary artery disease in heart failure with preserved ejection fraction. *J Am Coll Cardiol*. 2014;63:2817–2827.

133. Jackson AM, Rørth R, Liu J, et al. Diabetes and pre-diabetes in patients with heart failure and preserved ejection fraction. *Eur J Heart Fail*. 2022;24:497–509.

134. Nassif ME, Windsor SL, Borlaug BA, et al. The SGLT2 inhibitor dapagliflozin in heart failure with preserved ejection fraction: a multicenter randomized trial. *Nat Med*. 2021;27:1954–1960.

135. Jhund PS, Kondo T, Butt JH, et al. Dapagliflozin across the range of ejection fraction in patients with heart failure: a patient-level, pooled meta-analysis of DAPA-HF and DELIVER. *Nat Med*. 2022;28:1956–1964.

136. Pitt B, et al. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med*. 2014;370:1383–1392.

137. Pfeffer MA, Pfeffer MA, Assmann SF, et al. Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial. *Circulation*. 2015;131:34–42.

138. Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med*. 2019;381:1609–1620.

139. Pieske B, Wachter R, Shah SJ, et al. Effect of sacubitril/valsartan vs standard medical therapies on plasma NT-proBNP concentration and submaximal exercise capacity in patients with heart failure and preserved ejection fraction: the PARALLAX randomized clinical trial. *JAMA*. 2021;326:1919–1929.

140. Pandey A, Parashar A, Kumbhani D, et al. Exercise training in patients with heart failure and preserved ejection fraction: meta-analysis of randomized control trials. *Circ Heart Fail*. 2015;8:33–40.

141. Mueller S, Winzer EB, Duvinage A, et al. Effect of high-intensity interval training, moderate continuous training, or guideline-based physical activity advice on peak oxygen consumption in patients with heart failure with preserved ejection fraction: a randomized clinical trial. *JAMA*. 2021;325:542–551.

142. Adamson PB, Abraham WT, Bourge RC, et al. Wireless pulmonary artery pressure monitoring guides management to reduce decompensation in heart failure with preserved ejection fraction. *Circ Heart Fail*. 2014;7:935–944.

143. Reddy YNV, Koepp KE, Carter R, et al. Rate-adaptive atrial pacing for heart failure with preserved ejection fraction: the RAPID-HF randomized clinical trial. *JAMA*. 2023;329:801–809.

144. Shah SJ, Borlaug BA, Chung ES, et al. Atrial shunt device for heart failure with preserved and mildly reduced ejection fraction (REDUCE LAP-HF II): a randomised, multicentre, blinded, sham-controlled trial. *Lancet*. 2022;399:1130–1140.

145. Borlaug BA, Schaff HV, Pochettino A, et al. Pericardiotomy enhances left ventricular diastolic reserve with volume loading in humans. *Circulation*. 2018;138:2295–2297.

146. Jain CC, Pedrotty D, Araoz PA, et al. Sustained improvement in diastolic reserve following percutaneous pericardiotomy in a porcine model of heart failure with preserved ejection fraction. *Circ Heart Fail*. 2021;14:e007530.

147. Fudim M, Fail PS, Litwin SE, et al. Endovascular ablation of the right greater splanchnic nerve in heart failure with preserved ejection fraction: early results of the REBALANCE-HF trial roll-in cohort. *Eur J Heart Fail*. 2022;24:1410–1414.

148. Borlaug BA, Redfield MM. Diastolic and systolic heart failure are distinct phenotypes within the heart failure spectrum. *Circulation*. 2011;123:2006–2013. discussion 2014.

149. Lewis GA, Dodd S, Clayton D, et al. Pirfenidone in heart failure with preserved ejection fraction: a randomized phase 2 trial. *Nat Med*. 2021;27:1477–1482.

150. Borlaug BA, Maleszewski JJ. The heavy heart of HFpEF. *Eur Heart J*. 2020;41:3447.

151. Hicks KA, Mahaffey KW, Mehran R, et al. 2017 cardiovascular and stroke endpoint definitions for clinical trials. *J Am Coll Cardiol*. 2018;71:1021–1034.

152. Cunningham JW, Singh P, Reeder C. Natural language processing for adjudication of heart failure in the electronic health record. *J Am Coll Cardiol HF*. 2023 Mar 5;S2213-1779(23)00098-7.

153. Brubaker PH, Nicklas BJ, Houston DK, et al. A randomized, controlled trial of resistance training added to caloric restriction plus aerobic exercise training in obese heart failure with preserved ejection fraction. *Circ Heart Fail*. 2023;16(2):e010161.

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