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EXPERT CONSENSUS DECISION PATHWAY

Management of Heart Failure With Preserved Ejection Fraction: 2026 ACC Expert Consensus Decision Pathway

A Report of the American College of Cardiology Solution Set Oversight Committee

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1. INTRODUCTION

Despite advances in therapy, heart failure (HF) remains a major cause of morbidity and death worldwide, with a lifetime risk at age 40 years of approximately 20%.[1] Although the incidence of overall HF in the United States appears to be stable or even declining, the incidence of heart failure with preserved ejection fraction (HFpEF) continues to rise.[2-4] HFpEF accounts for >50% of cases of HF,[5] with outcomes comparable to heart failure with reduced ejection fraction (HFrEF).[6] HFpEF is often underrecognized and results in substantial resource utilization.[7]

Historically, a dearth of effective options has been available to improve quality of life and reduce morbidity in HFpEF. However, the conceptual framework of HFpEF has evolved to a complex, multisystem syndrome driven by visceral adiposity, inflammatory adipokines,[8] and metabolic dysfunction,[9] with recognition of distinct phenotypic subgroups.[10] Remarkable advances in the past decade have yielded novel, effective interventions. Given recent favorable clinical trials, particularly with sodium glucose-cotransporter 2 (SGLT2) inhibitors,[11,12] nonsteroidal mineralocorticoid receptor antagonists (MRA),[13] and incretin-based therapies,[14,15] as well as evidence that these therapies have additional cardiovascular-kidney-metabolic benefits,[16] an increasing urgency for accurate diagnosis and timely implementation of optimal medical therapy is needed. These pivotal advances in HFpEF motivated this update to the 2023 expert consensus decision pathway (ECDP).[17] Table S1 in the Supplemental Appendix summarizes changes to the 2026 revised ECDP.

In accordance with the American College of Cardiology's (ACC's) relationship with industry and other entities (RWI) policy, relevant disclosures for the writing committee and comprehensive disclosures for external peer reviewers are available in Appendixes 1 and 2. To ensure complete transparency, a comprehensive RWI table for the writing committee, including relationships not pertinent to this document, has also been created and is

included in the Supplemental Appendix. For additional details concerning ECDPs,[18] please consult the Preface and Methods also included in the Supplemental Appendix.

2. ASSUMPTIONS AND DEFINITIONS

To limit inconsistencies in interpretation, specific assumptions (eg, treatment effects in varied populations) were considered by the writing group in development of the ECDP. References are supplied when applicable or appropriate.

2.1. Assumptions

1. The principal focus of this effort, including ECDP considerations, applies to individuals with HFpEF.
2. The writing committee endorses the evidence-based approach to HF diagnosis and management recommended in the 2022 guideline for the management of HF.[19]
3. Optimal care decisions should properly reflect the individual's preferences and priorities as well as those of the managing clinician. A shared decision-making model regarding care decisions is appropriate, particularly when clinical equipoise exists in areas of treatment uncertainty.
4. This ECDP is not intended to supersede good clinical judgment as, especially for HFpEF care, many questions remain unanswered. The treating clinician should seek input from relevant experts (eg, pharmacists, cardiologists, HF cardiologists, endocrinologists, nephrologists, palliative care specialists) as needed.
5. This ECDP is based on the best available data. As new discoveries emerge (eg, trials of additional agents and devices), these data will impact the considerations made here. Clinicians should be careful to incorporate relevant information published after this ECDP.
6. Although selected recommendations from this update may be reasonable in the acute inpatient hospital setting, this ECDP is primarily focused on management in the ambulatory setting.

2.2. Definitions

Guideline-directed medical therapy: Treatment options supported for use by clinical practice guidelines. This is distinct from optimal medical therapy, which may include therapies with demonstrated benefit from emerging clinical trials that are not yet reflected in the most recent clinical practice guidelines.

HF: Defined as per the "Universal Definition and Classification of Heart Failure."[20,21] Symptoms, signs, or both of HF caused by structural or functional cardiac abnormalities and at least 1 of: 1) elevated natriuretic peptides; or 2) objective evidence of cardiogenic pulmonary or systemic congestion. An HF event, including hospitalization, is defined by the "2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials."[22]

HFpEF mimics: Clinical diagnosis of HF and left ventricular ejection fraction (LVEF) of ≥50% with a primary noncardiac cause (pulmonary, kidney, liver disease, obesity, frailty) or an underlying cardiac cause (infiltrative cardiomyopathy, hypertrophic cardiomyopathy, valvular disease, pericardial disease, or high-output HF) for which distinct pathophysiology and therapeutic implications are apparent.

New York Heart Association (NYHA) functional classification:

- Class I: No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.
- Class II: Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF.
- Class III: Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF.
- Class IV: Unable to perform any physical activity without symptoms of HF, or symptoms of HF at rest.

2.3. Abbreviations

Abbreviation	Meaning/Phrase
ARB	angiotensin receptor blocker
CAD	coronary artery disease
CKD	chronic kidney disease
CKM	cardiovascular-kidney-metabolic
ECDP	expert consensus decision pathway
FDA	U.S. Food and Drug Administration
GLP-1	glucagon-like peptide-1
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
LV	left ventricular
LVEF	left ventricular ejection fraction
NYHA	New York Heart Association
SGLT2	sodium-glucose cotransporter-2

TABLE 1 Comparison of HFpEF Diagnostic Scoring Systems

	HFA-PEFF Score	H_2FPEF Score	HFpEF-ABA Score
Strengths	■ Strong physiologic basis	■ Derived and validated using invasive exercise hemodynamic assessment ■ Easily calculated point system ■ Uses readily accessible clinical variables ■ Greater accuracy despite fewer input variables	■ Easiest to implement in primary care settings and for population screening ■ No echocardiographic data required
Limitations	■ More complex and involved algorithm ■ Diastolic stress testing and invasive hemodynamic measurements are often not feasible in routine clinical practice ■ Includes natriuretic peptide assessment (less accurate in HFpEF and obesity)	■ May not differentiate between obesity-related symptoms and true HFpEF ■ Many individuals fall into "intermediate (non-diagnostic)" category ■ Diagnostic use depends on pretest probability	■ Requires online calculator to compute probability ■ No established probability thresholds to guide further evaluation
Ideal Use	■ Specialist cardiology practice	■ Inpatient or outpatient setting ■ Primary care ■ General cardiology ■ Specialist cardiology practice	■ Inpatient or outpatient setting ■ Primary care ■ EMR-based population screening

EMR = electronic medical record; HFpEF = heart failure with preserved ejection fraction.

3. DESCRIPTION AND IMPLICATION OF PATHWAY WITH SUMMARY GRAPHIC

The purpose of this document is to update the 2023 ECDP[17] with further data from recent studies and to provide succinct, practical guidance for managing individuals with HFpEF. The format of the 2023 ECDP was thoughtfully revamped, and associated treatment algorithms and tables have been updated to accommodate the evolving evidence. Details regarding changes to the 2023 ECDP included in this updated version are summarized in **Table 1** of the Supplemental Appendix. Of note, Section 8 of the 2023 ECDP, which focuses on Multidisciplinary Considerations in HFpEF,[17] remains relevant and, given the lack of need for revisions, the reader is referred to it for an in-depth discussion of multidisciplinary care not reiterated in this revised version.

Clinicians should: 1) identify individuals with possible HFpEF based on characteristic symptoms and signs; 2) assess for HFpEF noncardiac and cardiac mimics as part of a thorough differential diagnosis; and 3) implement an HFpEF management plan that includes management of comorbidities and nonpharmacologic management as well as optimal medical therapy. The diagnostic assessment and implementation of therapies necessitate multidisciplinary collaboration for optimal care. **Figure 1** provides a summary graphic of the HFpEF evaluation and management pathway.

4. DIAGNOSIS OF HFpEF

4.1. Challenges in the Diagnosis of HFpEF

The "Universal Definition and Classification of HF" requires symptoms, signs, or both of HF caused by structural or functional cardiac abnormalities and at least 1 of these: 1) elevated natriuretic peptides; or 2) objective evidence of cardiogenic pulmonary or systemic congestion.[20,21] Although these criteria are clear, the primary challenge in the diagnosis of HFpEF is that no single test definitively establishes the diagnosis, because the echocardiogram does not provide pathognomonic features and natriuretic peptide levels may be normal, especially in individuals with obesity.[23,24] Thus, a careful differential diagnosis must be performed, HF scoring systems to assess the probability of the diagnosis must be used, and potential mimics must be considered, both noncardiac and cardiac, that may present with symptoms of dyspnea, exercise intolerance, and edema, and signs of congestion and preserved ejection fraction.

4.2. Differential Diagnosis

Although dyspnea and edema are common presenting symptoms of HFpEF, other potential causes of these cardinal symptoms warrant consideration. An approach to the differential diagnosis of dyspnea is shown in **Figure 2A**, organized by cardiac, pulmonary, and other sources. A similar approach can be taken for the differential diagnosis of edema. Once lymphedema has been excluded, the 2 major pathophysiologic sources of edema can be considered: increased hydrostatic pressure and decreased oncotic pressure, as summarized in **Figure 2B**.

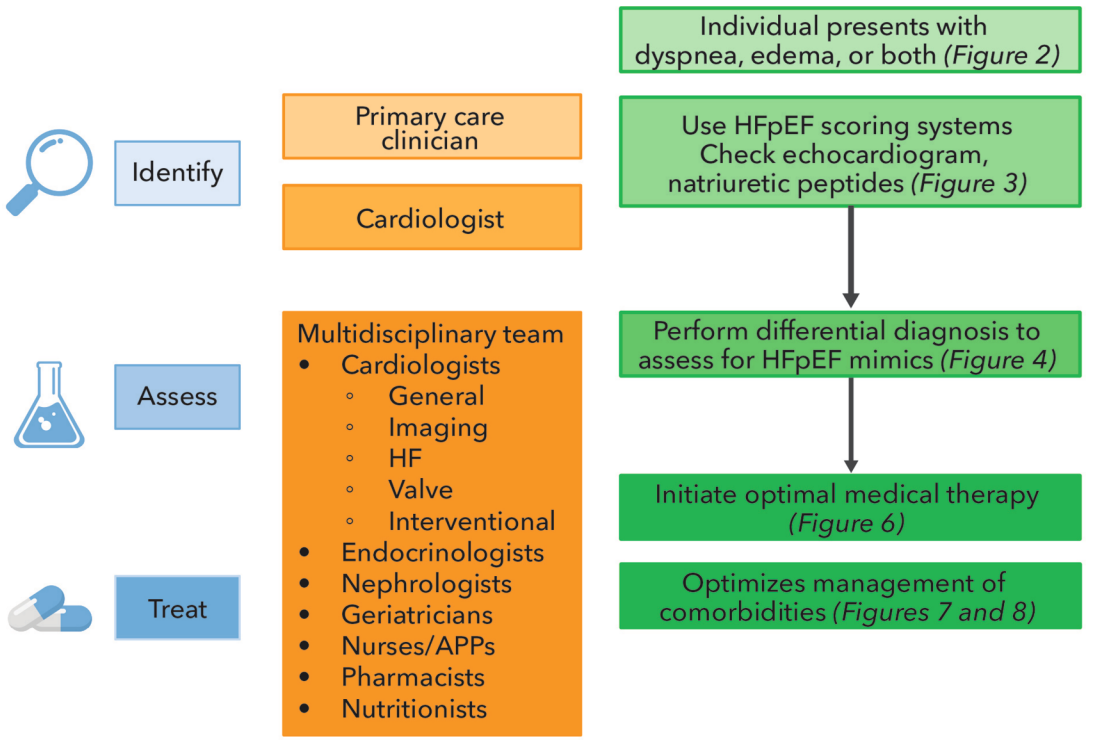
4.3. HF Diagnostic Scores

Given the lack of definitive testing to establish a diagnosis of HFpEF, the use of clinical scoring systems can aid in the diagnostic evaluation.[25-27] Three algorithms—H_2FPEF,[25] HFpEF-ABA,[26] and HFA-PEFF[27]—may be used to determine the likelihood that HFpEF is the underlying cause in an individual with dyspnea or edema.

The H_2FPEF score was derived and validated using a gold-standard reference of invasive exercise hemodynamic measurements and includes 6 readily accessible components (**Figure 3A**).[25] The HFA-PEFF algorithm, in contrast, was developed based on expert consensus and is more complex, involving 4 steps: 1) pretest assessment, 2) echocardiographic and natriuretic peptide score, 3) functional testing, and 4) final etiology (**Figure 3B**).[27]

Of the 2 scores, the H_2FPEF score may be more useful in clinical practice to establish HFpEF as a likely diagnosis, given evidence of greater accuracy despite fewer

FIGURE 1 Summary Graphic for the Evaluation and Management of HFpEF



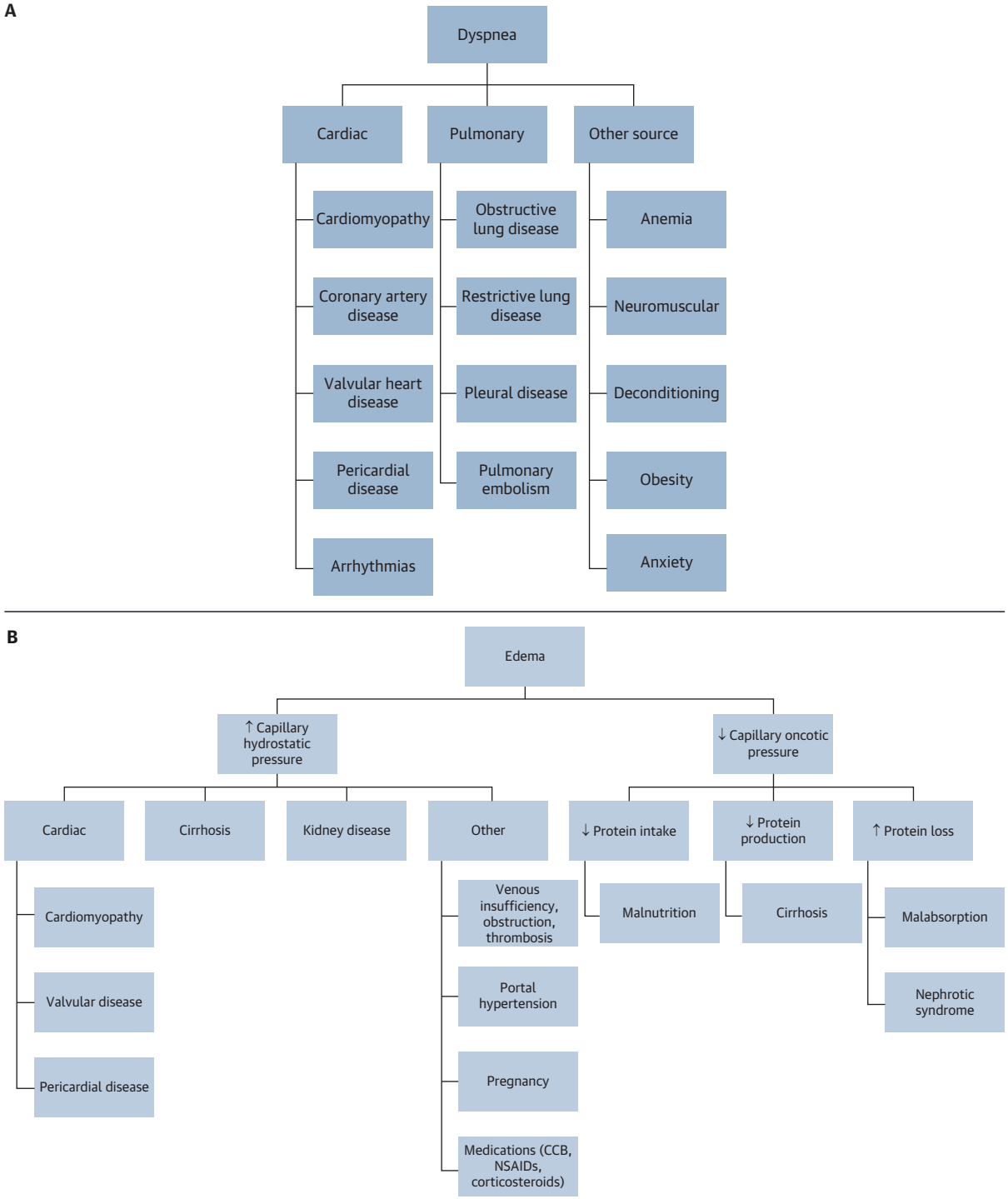
APP = advanced practice professional; HF = heart failure; HFpEF = heart failure with preserved ejection fraction.

input variables.[28] The H_2FPEF score is more sensitive, while the HFA-PEFF score is more specific.[29] An effective strategy is to use the H_2FPEF score as an initial screening tool, followed by the HFA-PEFF algorithm for confirmation; in cases of discordance, further advanced diagnostic testing may be useful. However, a limitation to the HFA-PEFF algorithm is the practicality of Step F1.[27] Diastolic stress testing and invasive hemodynamic measurements are often not feasible in routine clinical practice. Many clinicians, when faced with the diagnostic option of diastolic stress testing or invasive hemodynamic measurements, may instead simply initiate guideline-directed medical therapy for HFpEF (Section 7.1 of the 2023 ECDP)[17] to assess for symptomatic improvement. A therapeutic trial of guideline-directed medical therapy is a reasonable first step instead of more intensive testing to establish an HFpEF diagnosis if the latter is not readily available.

Both H_2FPEF and HFA-PEFF use echocardiographic and laboratory data that may be unavailable at the point of first contact for individuals with dyspnea, particularly in primary care practices. Furthermore, pitfalls exist to the use of natriuretic peptide assessment for the diagnosis of HFpEF; levels are generally lower in individuals with HFpEF compared with those with HFrEF[23] and lower in obesity, Black race, women with increased androgenicity, and individuals with insulin resistance,[23,30-33] and higher in individuals with chronic kidney disease.[34] Individuals with HFpEF may exhibit natriuretic peptide values below the diagnostic threshold for HF, even in the presence of elevated, invasively measured cardiac filling pressures.[23,30,35] Thus, normal natriuretic peptide levels alone are not useful to exclude an HFpEF diagnosis.

To provide a score more useful in primary care settings, the HFpEF-ABA score was derived solely from 3 commonly available clinical variables (ie, age, body mass index, and atrial fibrillation) (**Figure 3C**),[26] informing triage to further assessment of HFpEF with echocardiogram, natriuretic peptides, and cardiology consultation. Nonetheless, use of the HFpEF-ABA score may be limited by the need for further validation and an online calculator to perform the exponential equation for HFpEF probability. In addition, no established probability thresholds have been determined at which further testing should be considered, although thresholds of <25%

FIGURE 2 **Differential Diagnosis of Dyspnea and Edema**



(A) The differential diagnosis of dyspnea. (B) The differential diagnosis of edema. *However, other conditions can also cause these symptoms. Reproduced with permission from Kittleson et al.[17] CCB = dihydropyridine calcium-channel blocker; NSAIDs = nonsteroidal anti-inflammatory drugs.

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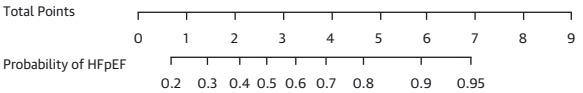
FIGURE 3 HFpEF Diagnostic Scoring Systems

A

H_2FPEF Score

H2	Heavy (BMI >30 kg/m^2) On ≥2 antiHypertensives	2 1
F	Atrial Fibrillation	3
P	Pulmonary hypertension (PASP >35 mm Hg on Doppler echocardiography)	1
E	Elder (age >60 years)	1
F	Filling pressure (E/e' >9 on Doppler echocardiography)	1



≥6 points: highly suggestive of HFpEF

B

HFA-PEFF Score

P Pretest assessment
- Symptoms and/or signs of heart failure
- Comorbidities/risk factors
- Standard echocardiography

E Echo and natriuretic peptide score
- Comprehensive echocardiography
- Natriuretic peptides

F1 Functional testing in case of uncertainty
- Diastolic stress test (exercise echocardiography)
- Invasive hemodynamic measurements

F2 Final etiology
- Special imaging (CMR, CT, PET, scintigraphy)
- Biopsies
- Genetic testing

Functional
Septal e'<7 cm/s OR
Lateral e' <10 cm/s OR
Average E/e' ≥15 OR
TR velocity >2.8 m/s
Average E/e' 9-14 OR
GLS <16%

Morphological
LAVI >34 mL/m^2 OR
LVMI ≥149/122 g/m^2 (M/F) AND
RWT >0.42
LAVI 29-34 OR
LVMI >115/95 g/m^2 (M/F) OR
RWT >0.42 CR
LV wall thickness ≥12 mm

Biomarker (Sinus rhythm)
NT-proBNP >220 pg/mL OR
BNP >80 pg/mL
NT-proBNP 125-220 pg/mL OR
BNP 35-80 pg/mL

Biomarker (Atrial fibrillation)
NT-proBNP >660 pg/mL OR
BNP >240 pg/mL
NT-proBNP 365-660 pg/mL OR
BNP 105-240 pg/mL

≥5 points: HFpEF
Major criteria (2 pts) bolded
Minor criteria (1 pt) non-bolded

C

HFpEF-ABA Score

A Age
B Body mass index
A Atrial fibrillation

Probability of heart failure with preserved EF = Z/(1+Z) × 100 where
- *Z = e^y*
- *y = −7.79 + 0.063 × age + 0.14 × BMI + 2.04 × AF (1 for Yes and 0 for No)*

Low probability → Consider other diagnoses

Intermediate/high probability → Additional testing
- Echocardiography
- Natriuretic peptide assessment
- Cardiology consultation

(A) HFpEF diagnostic scoring systems: H_2FPEF Score. (B) HFpEF diagnostic scoring systems: HFA-PEFF Score. (C) HFpEF diagnostic scoring systems: HFpEF-ABA Score. *(A) The H_2FPEF score includes 6 clinically accessible factors. (B) HFA-PEFF includes a more involved diagnostic algorithm starting with pretest assessment, echocardiographic and natriuretic peptide score, functional testing for an advanced evaluation, and final etiology assessment. (C) HFpEF-ABA includes 3 simple clinical variables input into an online calculator. The equation simplified to 2 decimal points; full equation available at Reddy et al.[26] Probability thresholds have not been established, but low probability may be defined as <25%.[36] Adapted with permission from Kittleson et al.[17]
BMI = body mass index; BNP = B-type natriuretic peptide; CMR = cardiac magnetic resonance; CT = computed tomography; GLS = global longitudinal strain; HFpEF = heart failure with preserved ejection fraction; LAVI = left atrial volume index; LVMI = left ventricular mass index; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PASP = pulmonary artery systolic pressure; PET = positron emission tomography; RWT = relative wall thickness; TR = tricuspid regurgitation.

indicating low probability, 25% to 80% for intermediate, and >80% for high probability have been used.[36]

All 3 scores can aid clinicians in diagnosing HFpEF. However, limitations and discrepancies exist between the scoring systems (**Table 1**),[37,38] and a significant proportion of individuals fall into the "intermediate" (ie, nondiagnostic) categories for which further assessment into HF mimics (Section 4.4) would be important. In addition, a low score in the context of high pretest probability (symptoms and signs of HF) should prompt further diagnostic evaluation.

In clinical practice, the HFpEF-ABA score would function most readily as a screening tool in the primary care setting or in the electronic medical record, with the probability of HFpEF prompting further imaging, natriuretic peptide testing, cardiology referral, or all of these. In cardiology practices where access to echocardiographic data is available, the H_2FPEF score may be easily calculated and potentially more useful than the HFA-PEFF, given evidence of greater accuracy despite fewer input variables.[28]

4.4. HFpEF Mimics

An accurate diagnosis of HFpEF requires careful exclusion of non-HFpEF mimics that can present with overlapping symptoms, hemodynamics, or imaging findings. A systematic evaluation to exclude both noncardiac and cardiac mimics is therefore essential before confirming a diagnosis of HFpEF. Failure to consider additional diagnoses may result in missed opportunities to institute effective specific disease-modifying therapies. Of note, many of the HFpEF mimics are also common HFpEF comorbidities as outlined in Section 5.3, and thus a challenge is to distinguish a primary driver of an individual's presenting symptoms of dyspnea and edema from a comorbid condition. In this section, the focus is on situations where the individual's presentation can be explained by a distinct diagnosis from HFpEF, while Section 5.3 outlines the optimal approach to management of comorbidities commonly associated with HFpEF.

Table 2 summarizes specific mimics, their key clinical findings, and the diagnostic tests to consider, while **Figure 4** outlines a stepwise approach to the diagnosis of HFpEF by excluding first noncardiac and then cardiac mimics. If no noncardiac or cardiac mimic is suggested by the clinical presentation or diagnostic testing, a diagnosis of HFpEF is established, and relevant comorbidities should be identified to inform management strategies.

4.4.1. Noncardiac Mimics

Noncardiac conditions can produce dyspnea, exercise intolerance, edema, or elevated concentration of natriuretic peptides, thereby resembling HFpEF. Important conditions to consider include pulmonary disease, kidney disease, high-output states (particularly anemia and liver disease), obesity, and frailty or deconditioning.

4.4.1.1. Pulmonary Disease

Chronic obstructive pulmonary disease, asthma, interstitial lung disease, and pulmonary hypertension from primary pulmonary etiologies can cause exertional dyspnea and reduced functional capacity.[39] Pulmonary hypertension from lung disease may elevate right-sided pressures, causing right-sided congestion and elevated natriuretic peptide levels without left heart congestion.[39-42]

Pulmonary function testing, high-resolution computed tomography imaging, assessment of gas exchange abnormalities, and cardiopulmonary exercise test help distinguish between a cardiac and pulmonary etiology. Right heart catheterization may be necessary to distinguish precapillary and postcapillary pulmonary hypertension to guide subsequent management.

4.4.1.2. Kidney Disease

Kidney disease can mimic HFpEF through volume overload, peripheral edema, and elevated natriuretic peptides.[43] Distinguishing cardio-kidney physiology from primary kidney disease requires careful evaluation of volume status, echocardiographic assessment of cardiac structure, and review of longitudinal trends in kidney function. In many cases, it is impossible to entirely untangle the cardio-kidney intersection, and treatment of both HF and kidney disease is necessary, as discussed in Section 5.3.4 on chronic kidney disease (CKD).

4.4.1.3. High-Output States

High-output states—including severe liver disease, anemia, hyperthyroidism, arteriovenous fistulas (including those from hemodialysis access), and chronic inflammatory conditions—may produce exertional dyspnea, tachycardia, and fatigue.[44,45] Advanced liver disease, independent of high-output heart failure, can also mimic HFpEF through the development of systemic congestion from cirrhosis and portal hypertension or hypoalbuminemia.

These conditions can lead to elevated cardiac output with secondary chamber dilation. Thorough physical examination, assessment for surgical or traumatic atrioventricular fistulas,[44] along with laboratory evaluation of thyroid function, hemoglobin, liver function, imaging, and inflammatory markers is essential.

4.4.1.4. Obesity

Obesity is another mimic with substantial overlap with HFpEF signs and symptoms.[46] Individuals with obesity may exhibit dyspnea, reduced exercise tolerance, and chronically elevated filling pressures despite normal

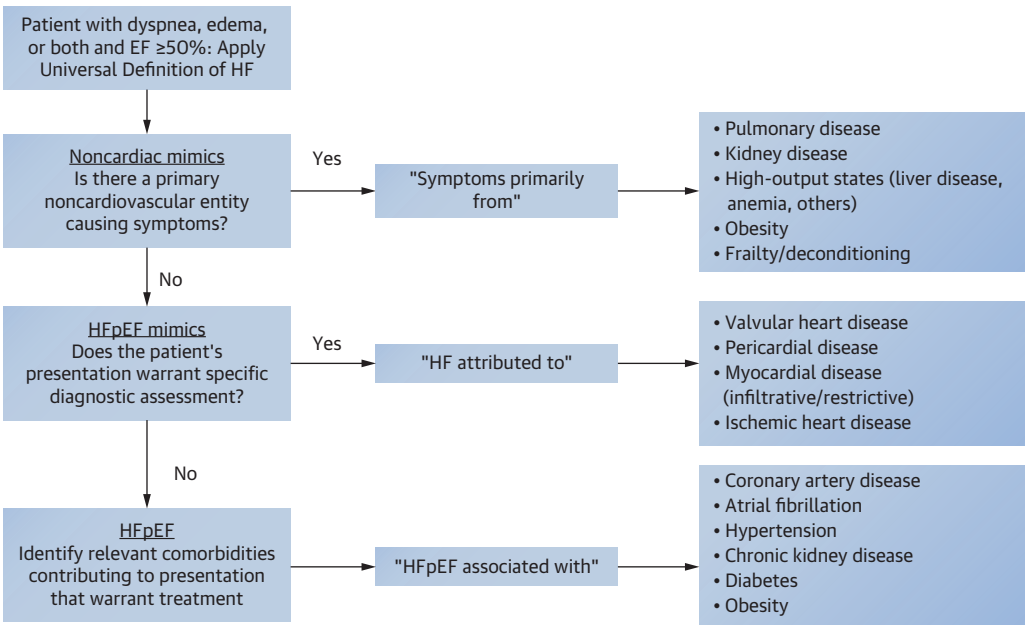
TABLE 2 Mimics of the Diagnosis of HFpEF and Suggested Approaches for Diagnosis

HFpEF Mimic	Clinical Features Suggesting Mimic	Recommended Diagnostic Evaluation
Noncardiac Mimics		
Pulmonary disease[39,42] (chronic obstructive pulmonary disease, asthma, interstitial lung disease, pulmonary hypertension)	■ Chronic cough ■ Wheezing ■ Hypoxemia ■ Reduced DLCO ■ Right heart failure predominance	■ Pulmonary function tests ■ Chest radiography or CT ■ V/Q scan or CT pulmonary angiography when thromboembolic disease suspected ■ Cardiopulmonary exercise testing ■ Right heart catheterization
Kidney disease[43]	■ Volume overload ■ Long-standing CKD ■ Elevated natriuretic peptides unrelated to cardiac dysfunction	■ Kidney function panel ■ Clinical and ultrasound-based volume assessment
High-output states[44,45] ■ Liver disease ■ Anemia ■ Hyperthyroidism ■ Arteriovenous fistula ■ Systemic inflammation	■ Tachycardia ■ Warm extremities ■ Widened pulse pressure ■ Elevated cardiac output	■ CBC ■ TSH ■ Liver function tests and imaging ■ Inflammatory markers ■ Echocardiography ■ Right heart catheterization
Obesity[30,40,41,47]	■ Lower natriuretic peptide levels ■ Preserved cardiac structure ■ Exertional limitation out of proportion to normal imaging	■ Cardiopulmonary exercise testing ■ Right heart catheterization ■ Functional assessment
Frailty or deconditioning[49-52]	■ Weight loss or gain ■ Exhaustion ■ Reduced grip strength ■ Slow walking speed ■ Low physical activity	■ Clinical evaluation ■ Frailty scales ■ Laboratory evaluations including blood chemistries, CBC, TSH ■ Assessment of exercise capacity including cardiopulmonary exercise testing ■ Right heart catheterization
Cardiac Mimics		
Valvular heart disease[53,54,63,64] ■ Aortic stenosis ■ Mitral regurgitation ■ Mitral stenosis	■ Murmurs ■ Symptoms disproportionate to preserved EF	■ Transthoracic echocardiography with Doppler
Pericardial constriction[55,56]	■ Previous cardiac surgery, chest radiation, or pericarditis ■ Kussmaul sign ■ Right-sided congestion	■ Transthoracic echocardiography with Doppler ■ Right and left heart catheterization to demonstrate increased ventricular interdependence and dissociation of intrathoracic and intracardiac pressures
Ischemic heart disease[62]	■ Dyspnea as an anginal equivalent	■ Stress imaging ■ Coronary angiography ■ Coronary functional assessment
Myocardial disease		
■ Cardiac amyloidosis[57]	■ Increased LV wall thickness with discordant voltage on ECG ■ Musculoskeletal issues (carpal tunnel syndrome, lumbar spinal stenosis) ■ Neuropathy (sensory or autonomic)	■ Monoclonal protein screen (serum or urine immunofixation electrophoresis and serum free light chains) ■ Bone-avid radionuclide scintigraphy (interpreted in the context of a negative monoclonal protein screen) ■ Endomyocardial biopsy if monoclonal protein screen is positive ■ *TTR* genetic testing
■ Hypertrophic cardiomyopathy[60]	■ Unexplained LV hypertrophy ■ LV outflow tract obstruction ■ Family history	■ CMR if diagnosis is uncertain based on echocardiogram ■ Genetic testing
■ Cardiac sarcoidosis[59]	■ Extracardiac disease (pulmonary, ocular, dermatologic) ■ High-degree atrioventricular block (especially if age <60 y) ■ Ventricular arrhythmias	■ CMR ■ FDG-PET scan ■ Tissue biopsy (cardiac or extracardiac)
■ Hemochromatosis[58]	■ Family history or history of frequent blood transfusions ■ Diabetes ■ Erectile dysfunction	■ Ferritin and transferrin ■ *HFE* genetic testing ■ CMR with T2* imaging
■ Fabry disease[61]	■ Angiokeratomas ■ Sensory neuropathy ■ Proteinuria ■ X-linked inheritance	■ Serum alpha-galactosidase level (in men) ■ *GLA* genetic testing ■ Biopsy of affected tissue

Adapted with permission from Kittleson et al.[17]

CBC = complete blood count; CT = computed tomography; CMR = cardiac magnetic resonance; DLCO = diffusion capacity of the lungs for carbon monoxide; ECG = electrocardiogram; EF = ejection fraction; FDG-PET = fluorodeoxyglucose-positron emission tomography; *GLA* = galactosidase alpha gene; *HFE* = hereditary hemochromatosis gene; HFpEF = heart failure with preserved ejection fraction; LV = left ventricular; TSH = thyroid-stimulating hormone; V/Q = ventilation/perfusion scan.

FIGURE 4 Stepwise Approach to Assessment of Individuals With Dyspnea, Edema, or Both



Adapted with permission from Kittleson et al.[17] EF = ejection fraction; HF = heart failure; HFpEF = heart failure with preserved ejection fraction.

myocardial structure. Obesity also lowers natriuretic peptide concentrations, potentially masking true HFpEF or creating diagnostic ambiguity.[23,24]

The presence of obesity and deconditioning may lead to dyspnea that is not related to HF. However, a true diagnosis of HFpEF should not be missed in such individuals, given the frequency of masked HF in this population.[47] The mechanism of HF in this context is complicated and multifactorial but includes mechanical restriction, direct effects of visceral adiposity, and deconditioning.[46] Among community-based cohorts, up to 40% of individuals who have obesity may have unrecognized HF on formal testing. In referral populations, including those undergoing invasive testing (where the expected prevalence would be higher), rates of HF among dyspneic individuals who have obesity is even higher, up to 70%, most of which is HFpEF.[30,40,41,46-48]

Objective assessment of volume status, cardiopulmonary exercise testing, and right heart catheterization may be required to accurately diagnose or exclude HF in this context. If HFpEF is confirmed in the context of obesity, incretin-based therapies, exercise, and weight loss can improve outcomes as discussed in detail in Sections 5.1.3 and 5.2.

4.4.1.5. Frailty

Frailty and deconditioning can produce exertional intolerance without intrinsic cardiac dysfunction.[49-52] Besides a full clinical and laboratory evaluation, cardiopulmonary exercise stress testing, with or without invasive hemodynamics assessment, is particularly useful in differentiating peripheral limitations from central cardiac and pulmonary causes.

4.4.2. Cardiac Mimics

Several cardiac conditions may resemble HFpEF but may be a specific form of HF requiring distinct diagnostic and therapeutic approaches. HFpEF should be considered a diagnosis of exclusion after thorough consideration of valvular heart disease, pericardial disease, myocardial disease, and ischemic heart disease.

4.4.2.1. Valvular Heart Disease

Valvular heart disease, particularly aortic stenosis, mitral regurgitation, and mitral stenosis, can produce elevated filling pressures and dyspnea. A detailed discussion of the assessment and management of valvular heart disease is presented in the 2020 valvular heart disease guideline[53] and in more recent expert statements.[54] Accurate diagnosis and treatment of significant valve disease is critical, because management of such lesions often requires surgical or transcatheter treatment for optimal outcomes rather than medical therapy for HFpEF. Comprehensive echocardiography with Doppler assessment is required to identify valvular pathology before attributing symptoms to HFpEF.

4.4.2.2. Pericardial Disease

Pericardial constriction is a classic HFpEF mimic, producing impaired ventricular filling with preserved systolic function, often accompanied by characteristic physical examination findings (eg, Kussmaul sign) and imaging features such as septal bounce or pericardial thickening.[55,56] Heightened awareness of this diagnosis is important in individuals with a history of pericardial effusion, acute pericarditis, or previous chest radiation or cardiac surgery. Cardiac magnetic resonance imaging, computed tomography, and invasive hemodynamics may be required for definitive diagnosis.

4.4.2.3. Myocardial Disease

Infiltrative and restrictive cardiomyopathies, including cardiac amyloidosis, sarcoidosis, and hemochromatosis, frequently present with preserved EF but markedly abnormal diastolic function.[57-59] Clues include increased ventricular wall thickness, low-voltage ECG, discordant strain patterns, and characteristic extracardiac manifestations (eg, carpal tunnel syndrome, spinal stenosis, and sensory peripheral or autonomic neuropathy for transthyretin amyloidosis). High index of suspicion and early identification are essential because of the availability of disease-modifying therapies, particularly for transthyretin and light chain cardiac amyloidosis.[57]

Hypertrophic cardiomyopathy (HCM) may also mimic HFpEF, especially in nonobstructive forms.[60] The nonobstructive form of HCM may be challenging to distinguish from hypertensive heart disease or HFpEF. Distinguishing features of HCM include myocardial hypertrophy out of proportion to the degree of hypertension, asymmetric septal hypertrophy, systolic anterior motion of the mitral valve, and abnormalities in strain pattern.

When evaluating individuals with apparent "HCM," clinicians should be alert to the presence of HCM phenocopies—diagnoses that resemble HCM but have distinctly different pathophysiology.[60] These include the already-mentioned cardiac amyloidosis and rare diagnoses such as storage diseases (eg, Fabry[61] and also Danon, Pompe, or PRKAG2 diseases; mitochondrial myopathies; or RASopathies [eg, Noonan syndrome]). A careful family history and attention to characteristics of extracardiac manifestations may reveal the correct diagnosis.

4.4.2.4. Ischemic Heart Disease

Ischemic heart disease can present with exertional dyspnea and preserved EF, particularly in microvascular angina, ischemia with nonobstructive coronaries, or in individuals with subtle regional left ventricular (LV) dysfunction.[62] This is especially pertinent because of overlapping risk factors. Stress imaging or coronary angiography and functional assessment should be considered for further evaluation. Ischemic heart disease can mimic or be a comorbidity; management is discussed in detail in Section 5.3.1.

4.5. Sex-Specific Considerations

The sex-specific considerations for HFpEF in women versus men are described in **Figure 5**. How the differences in clinical presentation, laboratory tests, and imaging studies, which are described in the next sections, could translate into sex-specific, tailored therapy remains unclear and should be a priority for future HFpEF research.

4.5.1. Risk Factors and Comorbidities

Women have a higher prevalence of HFpEF than HFrEF, although this differs by race; White women have a higher prevalence of HFpEF, whereas Black women have a similar prevalence of HFpEF and HFrEF.[65] Women with HFpEF are often older than men and generally have a similar comorbidity burden.[66] However, a greater attributable risk for HFpEF is observed from traditional risk factors in women versus men, namely hypertension, type 2 diabetes, and obesity.[67]

Visceral adipose tissue is increasingly recognized as a key comorbidity in HFpEF.[9] Women with HFpEF have more subcutaneous adipose tissue and less visceral adipose tissue than men. However, visceral adipose tissue in women is associated with greater adipokine release and linked to heightened inflammation and a more adverse hemodynamic response to exercise.[68] Men have more epicardial coronary artery disease (CAD), whereas women more often manifest coronary microvascular dysfunction.[69]

Unique risk factors for HFpEF in women are their reproductive and hormonal characteristics, including hypertensive disorders of pregnancy, gestational diabetes, infertility, and early onset of menopause.[70]

4.5.2. Clinical Presentation

Compared with men, women with HFpEF tend to have more significant symptoms of dyspnea and worse quality of life.[71] Physical examination is generally similar between women and men with HFpEF; however, diagnostic testing may reveal important sex-based differences. For example, women with HFpEF have lower LV mass and greater concentric LV remodeling than men. With more concentric remodeling, women have smaller LV chamber size and thus typically higher LVEF compared with men.[72] However, except for LV mass index, no recommended sex-specific thresholds for echocardiogram parameters for the diagnosis of HFpEF have been identified.[73]

Physiologically, women have higher levels of natriuretic peptides. In contrast, in women with HFpEF,

FIGURE 5 Sex-Specific Differences in Women: HFpEF Presentation and Diagnosis

Risk Factors	Cardiovascular Structure/Function	Biomarkers	Exercise Physiology /Hemodynamics
Women Greater attributable risk from traditional risk factors - Hypertension - Diabetes mellitus - Obesity Unique sex-specific risk factors - More subcutaneous adiposity - Less visceral adiposity - More microvascular CAD - Heightened inflammation - Hypertensive disorders of pregnancy (including pre-eclampsia) - Gestational diabetes - Infertility - Early menopause	**Women** - Smaller LV cavity size - Lower LV mass - More concentric LV remodeling - More impaired diastolic function - More arterial stiffness - Sex-neutral threshold underestimation of LV dysfunction **Men** - More visceral adipose tissue - More epicardial corornary artery disease	**Women** - Lower natriuretic peptide levels **Men** - Higher high-sensitivity troponin	**Women** - More dyspnea and and worse health status - Lower peak oxygen consumption - Steeper increase in PCWP with exercise **Men** - Worse PA-RV coupling - Worse RV function

Women with HFpEF have distinct risk factors, cardiac structure, biomarkers, and exercise physiology. CAD = coronary artery disease; HFpEF = heart failure with preserved ejection fraction; LV = left ventricular; PA = pulmonary artery; PCWP = pulmonary capillary wedge pressure; RV = right ventricular.

natriuretic peptide levels are lower than in men, particularly in those with central adiposity.[74,75] However, women with HFpEF have significantly lower levels of biomarkers of myocardial injury, such as high-sensitivity troponin I.[76]

Peak oxygen consumption (VO_2) is consistently lower in women with HFpEF than in men (even after accounting for body size and hemoglobin).[77] This is because of reduced oxygen delivery and peripheral oxygen extraction, suggesting that both cardiac and peripheral factors contribute to impaired exercise capacity in women with HFpEF.[78]

Women with HFpEF have greater arterial stiffness than men, which is associated with worse diastolic function, a blunted increase in stroke volume, a steeper increase in pulmonary capillary wedge pressure, and a higher mean pulmonary artery pressure/cardiac output slope during exercise.[79] However, men with HFpEF have worse right ventricular-pulmonary artery coupling compared with women with HFpEF.[80]

5. MANAGEMENT

Management of HFpEF focuses on: 1) optimal medical therapy, which may include SGLT2 inhibitors, MRAs, incretin-based therapies, angiotensin receptor-neprilysin inhibitors, and angiotensin receptor blockers (ARBs); 2) nonpharmacologic management, including the role of

TABLE 3 Key Demographics and Outcomes of Selected Randomized Controlled Trials in Individuals With HFpEF

Variable	DELIVER[11]	EMPEROR-PRESERVED[12]	FINEARTS-HF[13]	TOPCAT[91,*]	PARAGON-HF[102]	CHARM-PRESERVED[104]	STEP-HFpEF[14]	SUMMIT[15]
Size	N = 6263	N = 5988	N = 6001	N = 3445	N = 4822	N = 3023	N = 529	N = 731
Agent	Dapagliflozin	Empagliflozin	Finerenone	Spironolactone	Sacubitril-valsartan	Candesartan	Semaglutide	Tirzepatide
Age (y)	72	72	72	69†	73	67	70†	65
Female (%)	44	45	45	52	52	40	56	53
Median follow-up (y)	2.3	2.2	2.7	3.3	2.9	3.1	1	1
Mean baseline LVEF (%)	54	54	53	56†	58	54	57†	61
Proportion with T2DM (%)	45	49	41	33	43	29	0	48
Diuretic (%)	77	NR	87	82	95	75	81	74
ACEI or ARB (%)	73	81	70	84	86	19‡	80§	80§
ARNI (%)	5	2	9	N/A	N/A	N/A	NR	NR
Beta-blocker (%)	83	86	85	78	80	56	79	69
MRA (%)	43	37	N/A	N/A	26	12	35	35
Primary composite outcome, HR (95% CI)	Worsening HF and CV death 0.82 (0.73-0.92)	Total HHF and CV death 0.79 (0.69-0.90)	Worsening HF and CV death 0.82 (0.71-0.94)	HHF, aborted cardiac arrest, CV death 0.89* (0.77-1.04)	Total HHF and CV death 0.87 (0.75-1.01)	HHF and CV death 0.86 (0.74-1.00)	Change in KCCQ-CSS 7.8 (4.8-10.9) % Change in body weight -10.7 (-11.9 to -9.4)	Worsening HF and CV death 0.62 (0.41-0.95)
HHF, HR (95% CI)	0.77 (0.67-0.89)	0.71 (0.60-0.83)	0.82 (0.71-0.94)	0.83 (0.69-0.99)	0.85 (0.72-1.00)	0.84 (0.70-1.00)	0.08‖ (0.00-0.42)	0.44 (0.22-0.98)
Urgent visit for HF, HR (95% CI)	0.76 (0.55-1.07)	NR	NR	NR	NR	NR	NR	0.41 (0.13-1.16)
CV death, HR (95% CI)	0.88 (0.74-1.05)	0.91 (0.76-1.09)	0.93 (0.78-1.11)	0.90 (0.73-1.12)	0.95 (0.79-1.16)	0.95 (0.76-1.18)	NR	1.58 (0.52-4.83)

Adapted with permission from Kittleson et al.[17]

*A significant reduction in the primary composite outcome was observed in participants enrolled in North America (HR, 0.82 [95% CI, 0.69–0.98]), while no benefit was observed among those enrolled in Russia/Georgia (HR: 1.10 [95% CI: 0.79–1.51]).

†Reported as median.

‡ACE inhibitor use only.

§Combined use of ACEI, ARB, and ARNI reported.

‖Exploratory endpoint.

ACEI = angiotensin converting-enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; CHARM-PRESERVED = Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity; CV = cardiovascular; DELIVER = Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure; EMPEROR-PRESERVED = Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction; FINEARTS-HF = Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients with Heart Failure; HF = heart failure; HHF = hospitalization for heart failure; HR = hazard ratio; KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire - Clinical Summary Score; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid antagonist; N/A = not applicable; NR = not reported; PARAGON-HF = Prospective Comparison of ARNI With ARB Global Outcomes in HF With Preserved Ejection Fraction; STEP-HFpEF = Semaglutide Treatment Effect in People with obesity and Heart Failure with Preserved Ejection Fraction; SUMMIT = Study of Tirzepatide in Participants with Heart Failure With Preserved Ejection Fraction and Obesity; T2DM = type 2 diabetes mellitus; TOPCAT = Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist.

exercise and weight loss and the use of wireless, implantable pulmonary artery monitors; and 3) risk stratification and management of comorbidities, including hypertension, type 2 diabetes, obesity, atrial fibrillation, CAD, CKD, and obstructive sleep apnea.

5.1. Optimal Medical Therapy

Optimal medical therapy can improve symptoms and reduce the risk of HF hospitalizations in individuals with HFpEF with safe and effective implementation in both outpatient and inpatient settings.[81,82] The 2026 AHA/ACC/ADA/ASN Cardiovascular-Kidney-Metabolic Syndrome Guideline offers in-depth guidance on these strategies.[83] Pivotal trials are summarized in **Table 3**. **Table 4** provides recommended starting and target doses. Clinicians should also consider relevant cautions and contraindications when prescribing optimal medical therapy, as outlined in **Table 5**. **Figure 6** outlines an approach to initiation and optimization.

5.1.1. SGLT2 Inhibitors

SGLT2 inhibitors are the cornerstone therapy for HFpEF, supported by randomized controlled trials of dapagliflozin and empagliflozin, which demonstrate that SGLT2 inhibitors significantly reduce the risk of the combined endpoint of hospitalization for HF and cardiovascular death,[11,12] and also improve health status and quality of life.[84,85] Clinical trials with sotagliflozin (an SGLT1 and

TABLE 4 Starting and Target Doses of Optimal Medical Therapy Options for HFpEF

Drug Class	Starting Dose	Target Dose
SGLT2 inhibitors (oral)		
Dapagliflozin	10 mg daily	10 mg daily
Empagliflozin	10 mg daily	10 mg daily
Sotagliflozin*	200 mg daily	400 mg daily
Aldosterone antagonists† (oral)		
Spironolactone	25 mg daily	50 mg daily
Finerenone	10 mg daily (eGFR ≥25 to <60 mL/min/1.73 m^2) 20 mg daily (eGFR ≥60 mL/min/1.73 m^2)	20 mg daily (eGFR ≥25 to <60 mL/min/1.73 m^2) 40 mg daily (eGFR ≥60 mL/min/1.73 m^2)
Incretin-based therapies‡ (subcutaneous)		
Semaglutide	0.25 mg weekly	2.4 mg weekly
Tirzepatide	2.5 mg weekly	15 mg weekly
ARNIs (oral)		
Sacubitril/valsartan	24 mg/26 mg twice daily, respectively	97 mg/103 mg twice daily, respectively
ARBs (oral)		
Candesartan	4–8 mg daily	32 mg daily

Adapted with permission from Kittleson et al.[17]
*Sotagliflozin has demonstrated benefit in only individuals with type 2 diabetes recently hospitalized with HF regardless of ejection fraction.
†Eplerenone has no demonstrated clinical trial benefit in HFpEF but may be used as an alternative to spironolactone of gynecomastia.
‡FDA-approved dose titration schedule for semaglutide for weight loss: increase every 4 wks as tolerated (prescribed once weekly): 0.25 mg, 0.5 mg, 1.0 mg, 1.7 mg, 2.4 mg; and tirzepatide: increase every 4 wks as tolerated (prescribed once weekly): 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg.

ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; eGFR = estimated glomerular filtration rate; FDA = U.S. Food and Drug Administration; HFpEF = heart failure with preserved ejection fraction; SGLT2 = sodium-glucose cotransporter-2.

SGLT2 inhibitor assessed in individuals with type 2 diabetes hospitalized for HF regardless of ejection fraction)[86] and empagliflozin[87] and a meta-analysis of randomized controlled trials that also included dapagliflozin[88] have demonstrated that SGLT2 inhibitors can also be safely initiated in the acute care setting, which could improve long-term medication adherence and persistence with therapy.

5.1.2. Mineralocorticoid Antagonists

Spironolactone is a nonselective, steroidal MRA that improves diastolic function measures in individuals with HfpEF.[89,90] However, evidence supporting improvements in the risk of HF hospitalizations is limited, because the initially published results of the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) trial did not show a significant benefit in the primary outcome that included cardiovascular death and HF hospitalization, although a significant reduction was observed in the secondary endpoint of HF hospitalization.[91] Notably, large regional variations in event rates between those enrolled in North America compared with Russia/Georgia were observed, leading to the suspicion of regional differences in the application of study criteria and trial implementation. Subsequently, a subgroup analysis of TOPCAT found a significant reduction in the primary outcome with spironolactone in participants enrolled in North America, whereas no benefit was observed among those enrolled in Russia/Georgia.[92]

The potential benefit of MRAs in HFpEF observed in TOPCAT was further supported by FINEARTS-HF (Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients With Heart Failure).[13] Finerenone is a nonsteroidal MRA with improved selectivity for the mineralocorticoid receptor, short half-life, minimal hormonal adverse effects, balanced distribution in the heart and kidney, and reduced risk of hyperkalemia.[93] In FINEARTS-HF, finerenone met the primary composite outcome of total worsening HF events and cardiovascular death, primarily driven by a reduction in total worsening HF events. Based on this trial, finerenone was U.S. Food and Drug Administration (FDA)-approved in July 2025 to reduce the risk of cardiovascular death, hospitalization for HF, and urgent HF visits in individuals with HF with LVEF ≥40%.

The SPIRIT-HF (Spironolactone in the Treatment of Heart Failure) trial, presented at the time of this writing in abstract form only, randomized individuals with symptomatic HF and EF of ≥40% to spironolactone or placebo. At 24 months, no difference was observed between groups in the primary endpoint, a composite of HF hospitalization and death from cardiovascular causes, a significantly higher rate of total hospitalizations, hypotension, and hyperkalemia in individuals taking spironolactone was observed. However, a high rate of trial discontinuation was seen due to the COVID-19 pandemic, with just over half of patients in the spironolactone group stopping the study drug, which lowered its ability to conclusively demonstrate differences between the treatment and placebo groups.[94]

Based on this evidence, finerenone should be considered the MRA of choice for individuals with HFpEF. However, if cost or tolerance are prohibitive, spironolactone is a reasonable alternative. Of note, eplerenone has not been studied in HFpEF and is not FDA approved for this indication but is a reasonable alternative for those with intolerance to spironolactone due to gynecomastia.

5.1.3. Incretin-Based Therapies

Incretin-based therapies include agents with effects on glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (formerly known as gastric inhibitory polypeptide). Semaglutide, a GLP-1 receptor

TABLE 5 Contraindications and Cautions for Options for Optimal Medical Therapy in HFpEF

Drug class	Contraindications	Cautions

SGLT2 inhibitor	■ Type 1 diabetes mellitus
	■ Pregnancy
	■ Lactation
	■ Known hypersensitivity
		■ Kidney impairment:
		  ■ For dapagliflozin, eGFR <25 mL/min/1.73 m^2
		  ■ For empagliflozin, eGFR <20 mL/min/1.73 m^2
		■ Pregnancy
		■ Mycotic genital infections
		■ Urinary tract infections
		■ May contribute to volume depletion or hypotension
		■ Ketoacidosis in individuals with poorly controlled diabetes, prolonged fasting, ketogenic diet, excessive alcohol intake, unrecognized insulin deficiency or excessive insulin dose reduction, and dehydration
		■ Acute kidney injury
		■ Necrotizing fasciitis of the perineum (Fournier's gangrene) is rare but can be serious and life-threatening

MRA (spironolactone)	■ Potassium ≥5.0 mmol/L
	■ eGFR <30 mL/min/1.73 m^2 or serum creatinine ≥2.5 mg/dL
	■ Addison disease
	■ Pregnancy
	■ Known hypersensitivity
		■ Worsening kidney function
		■ Concomitant use with drugs and supplements that increase serum potassium, such as:
		  ■ Potassium supplementation
		  ■ ACEI or ARB or ARNI
		  ■ NSAIDs
		  ■ Trimethoprim
		■ Gynecomastia (consider use of eplerenone)
		■ Lactation

Nonsteroidal MRA (finerenone)	■ eGFR <25 mL/min/1.73 m^2
	■ Potassium ≥5.0 mmol/L
	■ Strong or moderate CYP3A4 inhibitors or inducers
	■ Addison disease
	■ Pregnancy
		■ Hyperkalemia: Adjust based on potassium, eGFR, and current dose per prescribing information
		■ Hypotension
		■ Weak CYP3A4 inhibitors or inducers
		■ Concomitant use with drugs and supplements that increase serum potassium, such as:
		  ■ Potassium supplementation
		  ■ ACEI or ARB or ARNI
		  ■ NSAIDs
		  ■ Trimethoprim
		■ Lactation

Incretin-based therapies	■ Personal or family history of thyroid C-cell tumors (including medullary thyroid carcinoma) or in individuals with multiple endocrine neoplasia syndrome type 2 ■ Pregnancy ■ Lactation ■ Known hypersensitivity	■ Severe gastrointestinal adverse reactions with possible subsequent volume depletion ■ Severe gastroparesis ■ Acute gallbladder disease ■ Acute pancreatitis ■ Hypoglycemia with concomitant use of insulin or sulfonylurea ■ Pulmonary aspiration during general anesthesia or deep sedation ■ Hair loss
ARNI	■ Coadministration within 36 h of ACEI use ■ History of any angioedema ■ Pregnancy ■ Lactation ■ Severe (Child-Pugh C) hepatic impairment ■ Known hypersensitivity	Reduce the starting dose to half the usually recommended starting dose if: ■ Not currently taking an ACEI or ARB or taking a low dose of an ACEI or ARB ■ eGFR <30 mL/min/1.73 m^2 ■ Moderate (Child-Pugh B) hepatic impairment ■ Renal artery stenosis ■ Hypotension
ARB	■ Pregnancy/lactation ■ Avoid concomitant use with an ACEI, aliskiren, or ARNI ■ Known hypersensitivity	■ History of any angioedema ■ Hyperkalemia ■ Hypotension ■ Acute kidney injury

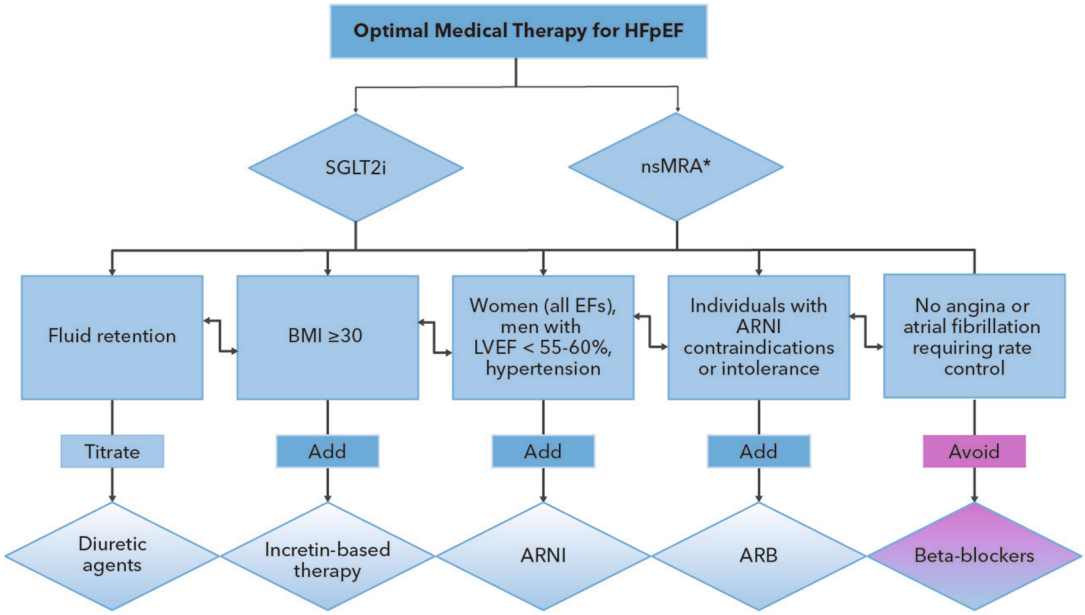
Adapted with permission from Kittleson et al.[17]

ACEI = angiotensin converting-enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor–neprilysin inhibitor; eGFR = estimated glomerular filtration rate; MRA = mineralocorticoid antagonists; NSAIDs = nonsteroidal anti-inflammatory drugs; SGLT2 = sodium-glucose cotransporter-2.

agonist, and tirzepatide, a dual GLP-1 and glucose-dependent insulinotropic polypeptide receptor agonist, were originally FDA approved based on improved outcomes in individuals with type 2 diabetes.[95,96] However, use of semaglutide and tirzepatide has expanded to include: 1) obesity, a major risk factor and prevalent condition in HFpEF; 2) overweight with at least 1 weight-related comorbidity (hypertension, type 2 diabetes or prediabetes, dyslipidemia); 3) obesity with moderate-to-severe obstructive sleep apnea (tirzepatide only); 4) overweight with established cardiovascular disease (semaglutide only); and 5) metabolic-associated steatohepatitis with moderate-to-advanced liver fibrosis (semaglutide only).

Semaglutide and tirzepatide have been evaluated in individuals with symptomatic HFpEF and body mass index of ≥30 kg/m^2 in 3 pivotal trials: the STEP-HFpEF (Semaglutide Treatment Effect in People with obesity and Heart Failure with Preserved Ejection Fraction) program, comprising 2 trials separated by the inclusion of

FIGURE 6 Treatment Algorithm for Optimal Medical Therapy in HFpEF



*A nonsteroidal MRA offers the strongest evidence of benefit, but if cost or tolerance is prohibitive, a steroidal MRA can offer a reasonable alternative. Adapted with permission and reflecting new evidence from Kittleson et al.[17] AF = atrial fibrillation; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; EF = ejection fraction; HFpEF = heart failure with preserved ejection fraction; LVEF = left ventricular ejection fraction; nsMRA = nonsteroidal mineralocorticoid antagonist; NYHA = New York Heart Association; SGLT2i = sodium-glucose cotransporter 2 inhibitor.

individuals with[97] or without[14] type 2 diabetes using semaglutide; and the SUMMIT (Study of Tirzepatide in Participants with Heart Failure With Preserved Ejection Fraction and Obesity) trial using tirzepatide.[15] Oral semaglutide and oral orforglipron are available but not studied in HFpEF.

In the STEP-HFpEF program, semaglutide improved quality of life as measured by Kansas City Cardiomyopathy Questionnaire scores and functional capacity as measured by 6-minute walk distance test.[14,98,99] Both semaglutide and tirzepatide were also associated with substantial weight loss after 1 year (11.6% in SUMMIT and 13.3% in STEP-HFpEF) and greater overall improvement in NYHA functional class.[14,15,97,99]

The SUMMIT trial extended these observations with a coprimary endpoint of time-to-first composite of a worsening HF event or cardiovascular death. Tirzepatide was associated with the primary endpoint, driven by worsening HF events, although the number of events was too small to offer a conclusive assessment of HF benefit. With these caveats, current evidence suggests that, in people with body mass index of ≥30 kg/m^2 and HF with EF ≥45% (semaglutide) or ≥50% (tirzepatide), these agents are associated with safe and effective weight loss and improvements in symptoms and functional capacity.[47] Furthermore, a subsequent post-hoc pooled analysis of semaglutide trials in individuals with HFpEF or HF with mid-range ejection fraction demonstrated a decreased risk of the combined endpoint of cardiovascular death or first worsening HF event, also driven by a reduction in the risk of worsening HF events.[98]

One emerging concern with incretin-based therapies is the development of sarcopenic obesity, a condition characterized by the coexistence of low skeletal muscle mass (sarcopenia) and increased body fat. This poses a significant health risk, particularly in older adults.[100,101] Use of incretin-based therapies should be accompanied by behavioral interventions, including exercise and nutritional support, with the aim of reducing adipose tissue while preserving and ideally increasing muscle mass and function.

5.1.4. Angiotensin Receptor-Neprilysin Inhibitors

The role of the angiotensin receptor-neprilysin inhibitor, sacubitril-valsartan, in individuals with HFpEF was evaluated in the PARAGON-HF (Prospective Comparison

of ARNI With ARB Global Outcomes in HF With Preserved Ejection Fraction) trial.[102] The primary composite endpoint of total hospitalizations for HF and cardiovascular death was numerically lower with sacubitril-valsartan versus valsartan but not statistically significant, nor was the reduction in the secondary endpoint of HF hospitalizations.

Nonetheless, sacubitril-valsartan was associated with modest clinical benefit compared with valsartan in a subset of individuals with an ejection fraction under 57% (below the median for the trial) and women compared with men (perhaps because women with HFpEF exhibit higher EF due to greater concentric remodeling).[102] This benefit was noted in the expanded HF indication from the FDA, which states that the "benefits are most clearly evident in individuals with LVEF below normal."[103] Therefore, sacubitril-valsartan may be a reasonable choice for women or those with LVEF of <57%, particularly if additional blood pressure control is warranted.

5.1.5. Angiotensin Receptor Blockers

ARBs provide a modest benefit in reducing the risk of HF hospitalizations and should be considered when angiotensin receptor-neprilysin inhibitors are contraindicated or unaffordable. The CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity)-Preserved trial demonstrated a reduction in HF hospitalization with candesartan,[104] although this benefit was not substantiated with irbesartan in the I-PRESERVE (Irbesartan in Heart Failure with Preserved Systolic Function) trial.[105] The reason for discordance between these 2 trials is unclear, but study-drug discontinuation was 34% in I-PRESERVE, and the high rate of background use of angiotensin-converting enzyme inhibitors (40%) may have blunted any potential additional benefit from irbesartan. Angiotensin-converting enzyme inhibitors are not considered a suitable alternative due to a lack of benefit with perindopril in the PEP-CHF (Perindopril in Elderly People with Chronic Heart Failure) trial.[106] These observations indicate that ARBs may be a reasonable option for blood pressure management in individuals with HFpEF.

5.1.6. Other Considerations: Diuretics and Beta-Blockers

Loop diuretics should be used judiciously and titrated as needed to alleviate congestion and associated symptoms.[19] Thiazide diuretics[107] and carbonic anhydrase inhibitors[108] can be used as adjunctive diuretics in individuals hospitalized with decompensated HF. Nonetheless, optimal diuretic combination use remains a knowledge gap in HFpEF management.

Importantly, no established benefit of beta-blockers in individuals with HFpEF has been observed.[109] Moreover, beta-blockers may be poorly tolerated, causing exertional intolerance due to chronotropic incompetence.[110-112] Thus, use of beta-blockers should be limited to specific indications, including angina or rate control of AF. The minimal effective dose should be prescribed with a low threshold to reduce or discontinue the beta-blocker if there is evidence of worsening congestion or exertional intolerance.

5.1.7. Approach to Optimal Medical Therapy Initiation and Titration

Based on robust clinical trial evidence, optimal medical therapy for individuals with HFpEF includes an SGLT2 inhibitor and nonsteroidal MRA, unless otherwise contraindicated, to reduce cardiovascular death and HF hospitalization, and improve health status (**Figure 6**). For those individuals with HFpEF and a body mass index ≥30 kg/m^2, incretin-based therapy with semaglutide or tirzepatide may be prescribed to improve health status and exercise function and to potentially reduce worsening HF events. Sacubitril-valsartan offers a reduction in HF hospitalizations in subgroups of women and those with LVEF of <55% to 60%. When sacubitril-valsartan use is not feasible or is contraindicated, an ARB is a reasonable alternative, particularly for use in those with hypertension. Early initiation and titration of these therapies reduce the composite of HF hospitalizations and death.[113]

5.2. Nonpharmacologic Management

5.2.1. Exercise

Exercise is beneficial for individuals with HFpEF, although long-term benefits have not been reliably demonstrated (**Table 6**). Multiple clinical trials have demonstrated that 3 to 4 months of exercise, whether high-intensity interval training, moderate continuous training, aerobic exercise coupled with resistance training, or simply adding 2000 steps daily, is associated with improvement in exercise capacity and quality of life.[114-118] Longer-term studies, up to 12 months, have demonstrated a decrement in these early benefits in some settings[119] and consistency in others.[120]

The lack of consistent evidence of benefit from maintenance exercise in HFpEF may be related to difficulties with adherence. Of note, in a 12-month supervised exercise training trial in individuals with HFpEF, exercise was associated with improved psychological motivation.[121] In turn, effective strategies are available to promote adherence to exercise training, including focusing coaching on barriers to exercise, addressing motivations, recognizing external benefits, and offering advice to others.[122] An ongoing trial seeks to identify whether adherence may be improved by various types of instruction: virtual coaching or in-person coaching compared with usual care.[123]

TABLE 6 Nonpharmacologic Clinical Trials for HFpEF

Study	Sample Size (HFpEF only)	Intervention	Outcome
Exercise, Caloric Restriction, or Both			
Sengupta et al[118]	40	3 mo of increased daily physical activity by 2000 steps from baseline	■ Improvement in left atrial reservoir strain ■ No change in NT-proBNP
Gevaert et al[114]	61	3 mo of moderate continuous or high-intensity interval training	■ Improvements in peak VO_2 and exercise E/e'
Mueller et al[115]	91	3 mo of moderate continuous training (5×/wk) or high-intensity interval training (3×/wk)	■ Peak VO_2 improved with more exercise training frequency and duration/wk ■ Average percent heart rate reserve was negatively associated with peak VO_2 change with moderate training but not high-intensity interval training
Edelmann et al[117]	64	3 mo of endurance/resistance training	■ Peak VO_2 increased by 3.3 mL/kg/min ■ Improved QOL ■ Improvement in E/e' and left atrial volume index
Kitzman et al[116]	63	4 mo of exercise training	■ Peak VO_2 increased by 2 mL/kg/min ■ Improved QOL for short form health survey not Minnesota Living with Heart Failure Questionnaire ■ No change in brachial artery flow-mediated dilation or carotid artery stiffness ■ No change in left ventricular systolic or diastolic function
Mueller et al[119]	176	12 mo of high-intensity interval training, moderate continuous training, or guideline control	■ Improved peak VO_2 at 3 mo for high-intensity interval training and moderate continuous training versus control ■ No difference at 12 mo
Edelman et al[120]	322	12 mo of combined endurance/resistance training	■ No difference in all-cause death/HF hospitalization/change VO_2/diastolic function ■ Secondary exploratory outcomes: increase in mean VO_2 by 1.3 mL/kg/min, improved NYHA functional class
Sadlonova et al[121]	322	12 mo of supervised exercise training	■ Improvements in motivation to exercise: overall, intrinsic (internal satisfaction rather than external outcome), and identified (personal value)
Upadhya et al[127]	16	5 mo of calorie restriction with or without aerobic exercise training	Over a median 28 mo of follow-up from the intervention period: ■ Increase in mean body weight by 5.2 kg due to increased fat mass with no change in lean mass ■ Decrease in peak VO_2 by 2.2 mL/kg/min ■ Decrease in exercise time

Kitzman et al[128]	100	5 mo of caloric restriction, aerobic exercise, or both	■ Increase in peak VO_2 by:
			  ■ Exercise: 1.2 mL/kg/min
			  ■ Diet: 1.3 mL/kg/min
			  ■ Both (additive): 2.5 mL/kg/min
			■ No effect on QOL

Brubaker et al[129]	88	5 mo of (caloric restriction and aerobic exercise) ± resistance training	Addition of resistance training to caloric restriction and aerobic exercise ■ Increase in leg strength and muscle quality ■ No additive increase in peak VO_2 or QOL
Mikhalkova et al[130]	12 (all women)	Gastric bypass	■ Improvement in QOL ■ Improved diastolic relaxation on echocardiogram ■ Decrease in cardiac mass
Device Therapies			
Litwin et al[142] REDUCE LAP-HF I and II	44 in trial 1, 621 in trial 2	Atrial shunt device outcomes at 5 y for trial 1 and 3 y for trial 2	■ No difference in composite cardiovascular death, stroke, HF events, QOL ■ Among trial 2 responders (PVR <1.74 Wood units and no cardiac management device at 3 y): Reduced HF events, better QOL, higher rate of ischemic stroke, lower incidence of worsening kidney function
Stone et al[143] RELIEVE-HF	302	Atrial shunt device	■ No difference in primary effectiveness outcome (hierarchical composite ranking of all-cause death, cardiac transplantation or left ventricular assist device implantation, HF hospitalization, outpatient worsening HF events, and change in QOL from baseline measured by the KCCQ-OSS) expressed a win ratio ■ More cardiovascular events in those with HFpEF with shunt treatment (annualized rate 60.2% vs 35.9%; relative risk, 1.68 [95% CI, 1.29–2.19]; P=0.0001; $P_{interaction}$<0.0001).
Fudim et al[141]	90	Splanchnic nerve ablation	■ No difference in primary safety endpoint at 1 mo ■ No difference in 12-mo HF hospitalizations, exercise function, health status compared with sham placebo

Continued on the next page

TABLE 6 Continued

Study	Sample Size (HFpEF only)	Intervention	Outcome
Adamson et al[133] CHAMPION	119	Implantable pulmonary artery monitor	■ 50% reduction in HF hospitalization with mean follow-up of 17.6 mo
Lindenfeld et al[134] GUIDE-HF	469 (EF >40%), 321 (EF >50%)	Implantable pulmonary artery monitor	■ No reduction in all-cause death, HF hospitalizations, and urgent HF visits. ■ Pre–COVID-19 analysis decreased composite HF hospitalizations/urgent HF visits/death, decreased HF events, decreased HF hospitalizations
MONITOR-HF[135]	358 (97 with EF of ≥40%)	Implantable pulmonary artery monitor	■ Improvement in QOL ■ 44% reduction in HF hospitalization at 12 mo
PROACTIVE-HF[140]	456- single arm	Implantable pulmonary artery monitor	■ 6-mo event rate was 0.15 (95% CI: 0.12–0.20), which was significantly lower than performance goal (0.15 vs 0.43; $P<0.0001$) based on previous trials
Reddy et al[144] RAPID-HF	29	Implantation of pacemaker with atrial rate-responsive pacing	■ No change in QOL ■ No change in peak VO_2 ■ No change in NT-proBNP
Infeld et al[145] myPACE	107	Personalized accelerating pacing using existing pacemaker	■ Improved QOL ■ Improved NT-proBNP ■ Increased physical activity

Adapted with permission from Kittleson et al.[17]

COVID-19 = coronavirus disease 2019; EF = ejection fraction; HF = heart failure; KCCQ-OSS = Kansas City Cardiomyopathy Questionnaire - Overall Summary Score; myPACE = Personalized Pacing: A New Paradigm for Patients With Diastolic Dysfunction or Heart Failure With Preserved Ejection Fraction; NT-proBNP = N-terminal B-type natriuretic peptide; PVR = pulmonary vascular resistance; QOL = quality of life; RAPID-HF = Rate-Adaptive Atrial Pacing in Diastolic Heart Failure; REDUCE LAP-HF I = Reduce Elevated Left Atrial Pressure in Patients With Heart Failure; REDUCE LAP-HF II = Reduce Elevated Left Atrial Pressure in Patients With Heart Failure II; RELIEVE-HF = Reducing Lung Congestion Symptoms in Advanced Heart Failure; VO_2 = oxygen consumption.

Although no evidence exists to date that exercise is associated with a reduction in HF hospitalizations or death,[120] exercise should still be encouraged in individuals with HFpEF because of improvement in important clinical and patient-centered outcomes, including exercise capacity and quality of life. Strategies to promote exercise adherence and motivation are essential, because insurance coverage for cardiac rehabilitation or structured exercise therapy is unavailable in the United States for individuals with HFpEF.[124] This lack of reimbursement for cardiac rehabilitation in HFpEF represents a significant care gap for this vulnerable population. Future strategies should address existing demographic disparities in referral and use of exercise therapy for all forms of HF so that these disparities are not perpetuated in the treatment of HFpEF.[125,126]

5.2.2. Caloric Restriction With or Without Exercise

In obesity-related HFpEF, caloric restriction with or without exercise has resulted in improvement in some clinical outcomes.[127-130] In a small study of women with HFpEF, bariatric surgery improved quality of life, heart mass, and diastolic relaxation.[130] In the short term, 5 months of caloric restriction coupled with aerobic exercise had additive benefits for exercise capacity.[128,129] However, adding resistance training to caloric restriction and aerobic exercise did not improve quality of life or exercise capacity, although leg strength increased.[129]

Unfortunately, the benefits of these interventions do not appear sustained after the intervention is complete; 28 months after a 5-month program of caloric restriction with or without exercise training in individuals with HFpEF, improvements in body weight and exercise capacity diminished, and regained weight was predominantly adipose, resulting in worsened overall body composition compared with baseline.[127] This raises challenges for the sustainability of supervised behavioral interventions and the role of other strategies, including incretin-based therapies, as described in Section 5.1.3.[131]

Efforts to intentionally reduce weight through supervised exercise training, caloric restriction, or both, and psychological motivation strategies, must be distinguished from unintentional weight loss in HFpEF. Unintentional weight loss, usually related to frailty, cardiac cachexia, and worsened comorbidities, have been associated with worse mortality rate in HFpEF.[132]

5.2.3. Device Therapy

5.2.3.1. Implantable Pulmonary Artery Monitors

Implantable pulmonary artery monitors have demonstrated efficacy in reducing HF hospitalizations. The role of an implantable pulmonary artery sensor, CardioMEMS (Abbott) was evaluated in the CHAMPION (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients) trial,[133] GUIDE-HF (Hemodynamic-Guided Management of Heart Failure) trial,[134] and MONITOR-HF (Remote Hemodynamic Monitoring of Pulmonary Artery Pressures in Patients With Chronic Heart Failure) trial.[135]

In the CHAMPION trial, management guided by the CardioMEMS device significantly reduced HF hospitalizations,[136] including in a prespecified subgroup of study participants with LVEF of ≥40%.[133] One concern in the CHAMPION trial was differential contact between study

personnel and individuals in the treatment arm, raising methodologic concerns about the potential for bias to have influenced its results. In the subsequent GUIDE-HF trial, hemodynamic-guided management did not result in a lower composite endpoint rate of death and total HF events compared with the control group in the overall study analysis, although the findings were influenced by the COVID-19 pandemic. In the pre-COVID-19 impact analysis, a nearly 20% reduction was observed in HF hospitalizations or urgent visits in the intervention group. This difference almost disappeared during COVID-19, with a decrease in the control group and virtually no change in the treatment group, resulting in no difference between groups.[137] However, in the MONITOR-HF trial, which enrolled individuals in the Netherlands (28% with ejection fraction of ≥40%), an improvement in quality of life and HF hospitalization was observed,[135] confirmed in meta-analyses including real-world practice studies.[138,139]

An additional pulmonary artery sensor was investigated in PROACTIVE-HF (A Prospective, Multi-Center, Open Label, Single Arm Clinical Trial Evaluating the Safety and Efficacy of the Cordella Pulmonary Artery Sensor System in NYHA Class III Heart Failure Patients).[140] In this single-arm trial, individuals with NYHA functional class III HF symptoms and recent HF hospitalization or elevated natriuretic peptide levels with the implantable hemodynamic monitor had a 6-month event rate of 0.15, which led to approval by the FDA.

Hemodynamic monitoring may be most useful in the subset of individuals with HFpEF who: 1) experience ≥1 hospitalization for HF and continue to experience NYHA functional class III symptoms despite optimal medical therapy; 2) experience significant lability in volume status despite close ambulatory monitoring; 3) have cardiorenal syndrome; or 4) have comorbidities, such as obesity or chronic lung disease, for which differentiation of HF from other causes of dyspnea is difficult. Placement of a remote pulmonary artery pressure monitoring device should be performed in a center capable of regularly monitoring and managing transmitted data.

5.2.3.2. Other Devices

Other device interventions for HFpEF, such as blood volume analysis, cardiac contractility modulation, splanchnic nerve ablation, interatrial shunting devices, and pacemakers, are under evaluation; their benefits remain unclear. Splanchnic nerve ablation, for example, demonstrated no difference in 12-month HF hospitalization, exercise function, or health status.[141]

Similarly, atrial shunt devices have demonstrated no difference in the composite of cardiovascular death, stroke, HF events, or quality of life,[142] with potentially increased risk of cardiovascular events in individuals with HFpEF.[143] This may be due to patient selection, because longer follow-up of atrial shunt device responders (identified in subgroup analyses as those who had an initial reduction in pulmonary vascular resistance) demonstrated reduced HF events, better quality of life, and less worsening of kidney function, although a higher rate of ischemic stroke was observed.[142] Thus, the benefit of these interatrial shunt procedures may lie in better patient selection with attention to short-term hemodynamic benefit as well as atrial and right ventricular function.

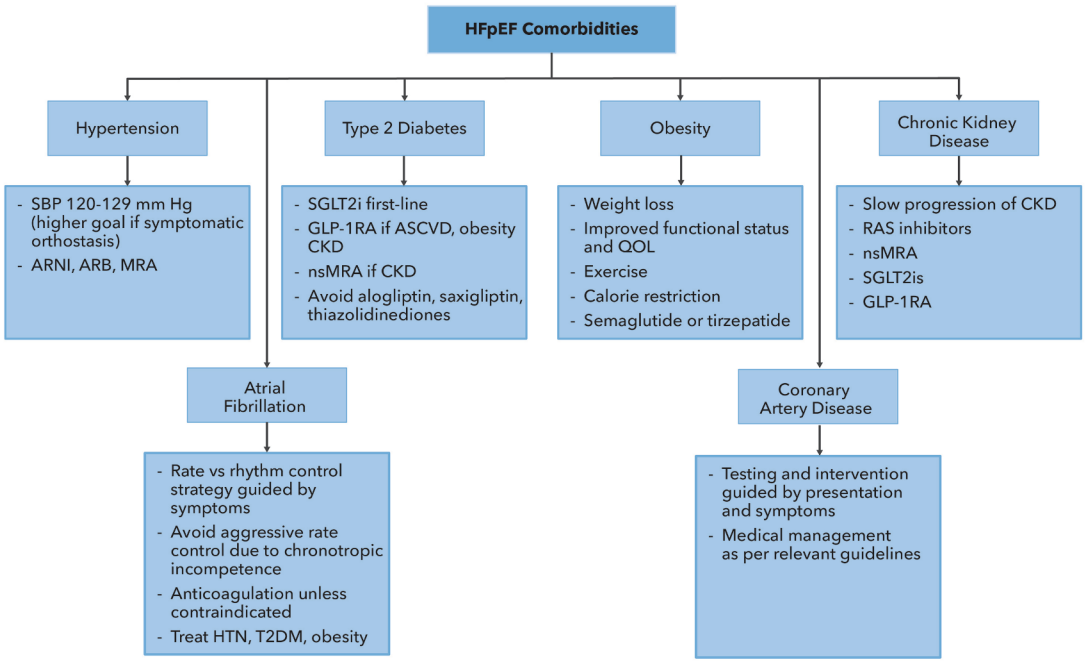
Permanent pacing has not consistently demonstrated benefit in HFpEF, with contrasting results depending on the pacing strategy used. For individuals with HFpEF and chronotropic incompetence, rate-adaptive atrial pacing triggered by exercise increased heart rate during exercise by 14 to 16 bpm, but pacing did not improve peak oxygen consumption or quality of life.[144] Conversely, continuous personalized accelerated pacing at a moderately higher resting heart rate (≈80 bpm) in HFpEF who already had a high proportion of physiologic pacemakers resulted in improvements in quality of life and physical activity.[145] However, future trials may elucidate the role of pacing in addressing chronotropic incompetence in HFpEF.

5.3. Comorbidities

The conceptual framework of HFpEF has evolved to a complex, multisystem syndrome driven by visceral adiposity, inflammatory adipokines,[8] and metabolic dysfunction,[9] with recognition of distinct phenotypic subgroups.[10] Building on this evolving understanding, the unifying concept of cardiovascular-kidney-metabolic (CKM) syndrome was introduced to provide a framework to prioritize comorbidity management.[16] CKM syndrome is characterized by the clustering of insulin resistance, type 2 diabetes, CKD, obesity, and cardiovascular disease, in which dysfunction in 1 organ system amplifies injury in others. This syndrome is particularly relevant to HFpEF given the prevalence of CKM comorbidities and is addressed in detail in the 2026 AHA/ACC/ADA/ASN Cardiovascular-Kidney-Metabolic Syndrome Guideline.[83]

In HFpEF, the cumulative burden and severity of CKM comorbidities are strongly associated with adverse clinical outcomes: a single severely uncontrolled cardiometabolic condition is associated with a 23% increase in all-cause hospitalization risk, whereas the presence of 2 to 3 cardiometabolic conditions confers a 57% increase.[146] Therapies directed at CKM disease processes, including SGLT2 inhibitors, MRAs, and GLP-1 receptor agonists, offer complementary CKM benefits in HFpEF. Management of key comorbidities with an emphasis on CKM-focused therapies are described in the next sections. **Figure 7** summarizes optimal comorbidity

FIGURE 7 Management of Comorbidities Associated With HFpEF



Adapted with permission from Kittleson et al.[17] ARB = angiotensin receptor blocker; ARNI = angiotensin receptor–neprilysin inhibitor; ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; GLP-1RA = glucagon-like peptide-1 receptor agonist; HTN = hypertension; MRA = mineralocorticoid antagonist; nsMRA = nonsteroidal mineralocorticoid antagonist; RAS = renin-angiotensin system; SBP = systolic blood pressure; SGLT2i = sodium-glucose cotransporter 2 inhibitor; T2DM = type 2 diabetes mellitus.

management in HFpEF. **Figure 8** summarizes the overlapping benefits of medications in HF and CKM syndrome.

5.3.1. Coronary Artery Disease

Across contemporary cohorts, >50% of individuals with HFpEF have CAD; when coronary microvascular dysfunction is included, prevalence reaches 91%.[147] Coronary microvascular dysfunction contributes to impaired myocardial perfusion, exercise intolerance, and elevated filling pressures in individuals with HFpEF.[148] CAD in HFpEF is associated with increased death, progressive myocardial remodeling, and transition to HFrEF.[148,149]

In individuals with HFpEF and coexisting CAD, management focuses on guideline-directed secondary prevention and symptom control per the "2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization" and the "2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary Disease."[63,150] Although no prospective trials have evaluated revascularization specifically in HFpEF, observational data suggest that revascularization is associated with preservation of cardiac function and improved survival in individuals with HFpEF and CAD.[149]

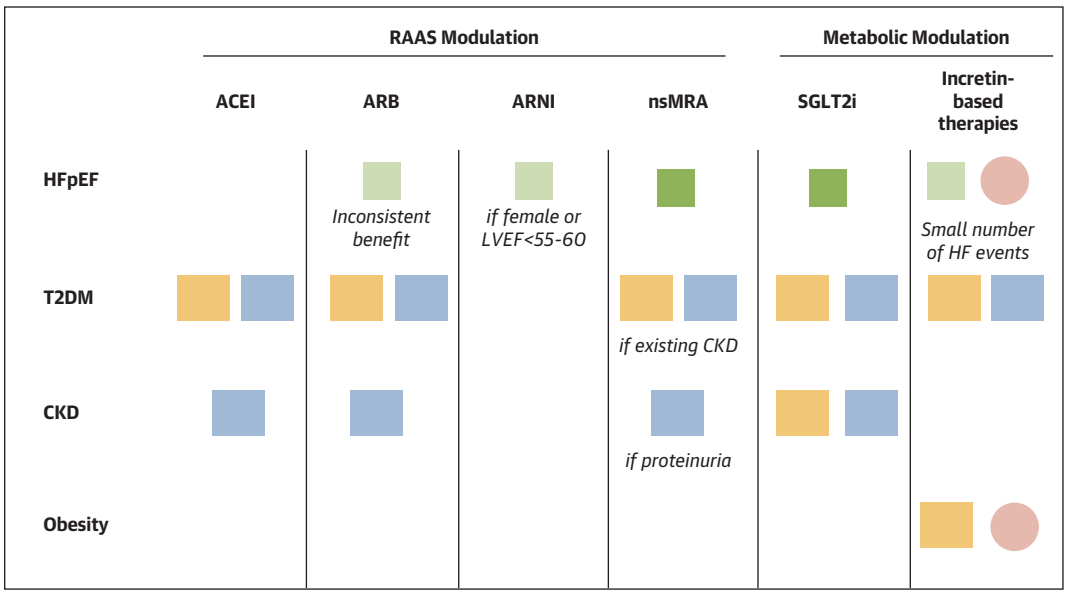
Aggressive secondary prevention, including high-intensity statin therapy, antiplatelet therapy, and optimized blood pressure control, remains central to care.[62] Furthermore, in adults with type 2 diabetes and established atherosclerotic cardiovascular disease, the American Diabetes Association recommends the use of an SGLT2 inhibitor or a GLP-1 receptor antagonist to reduce the risk of major adverse cardiovascular events, regardless of glycemic control,[151,152] with combination therapy providing additive cardiovascular and kidney benefits.[153,154]

5.3.2. Atrial Fibrillation

AF affects up to 41% of individuals with HFpEF.[155,156] Individuals with HFpEF and AF have worse symptoms, more cardiac dysfunction, and increased risk of hospitalizations and death than those in sinus rhythm.[156-159]

AF management, including rate control, rhythm control, and anticoagulation, should follow the "2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation."[160] Rate control remains an important factor for symptom control, although aggressive rate reduction in individuals with HFpEF may impair exercise capacity due to chronotropic incompetence.[161] Registry data, meta-analyses, and secondary

FIGURE 8 **Overlapping Cardiovascular-Kidney-Metabolic Benefit Matrix Across Drug Classes**



See text for supporting clinical trials.

= ↓ HF events
= ↓ CV death + HF events
= weight loss + ↑ QOL
= ↓ MACE
= ↓ CKD progression

ACEI = angiotensin converting-enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; CKD = chronic kidney disease; CV = cardiovascular; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; MACE = major adverse cardiovascular events; nsMRA = nonsteroidal mineralocorticoid antagonist; QOL = quality of life; RAAS = renin-angiotensin aldosterone system; SGLT2i = sodium glucose-cotransporter 2 inhibitor; T2DM = type 2 diabetes mellitus.

randomized trial analyses suggest that rhythm control, particularly catheter ablation, is associated with a lower death rate and fewer cardiovascular and HF events in individuals with HFpEF and AF compared with rate-control strategies[162-166] and can therefore be attempted, particularly if limiting symptoms are attributed to AF. Ongoing randomized trials are expected to clarify the optimal balance between rate and rhythm control in this population.

In addition, management of CKM comorbidities plays a central role in AF risk and progression. With evidence extrapolated from general AF populations, treatment of obesity, type 2 diabetes, and hypertension is associated with a reduction in AF incidence and burden.[167] In particular, both SGLT2 inhibitors[168,169] and GLP-1 receptor antagonists[170] can reduce AF incidence or burden in individuals with HFpEF, further supporting a CKM-targeted approach to AF.

5.3.3. Hypertension

Hypertension is present in up to 90% of individuals with HFpEF[171,172] and represents an important modifiable risk factor. Per the "2025 Multisociety Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults,"[173] individuals with type 2 diabetes, CKD, and HF warrant a target blood pressure below 130/80 mm Hg. In HFpEF, however, optimal systolic blood pressure appears to lie within a narrower range. Pooled data from I-PRESERVE, Americas cohort of TOPCAT, PARAGON-HF, and DELIVER demonstrated that both systolic blood pressure ≥140 mm Hg and systolic blood pressure <120 mm Hg were associated with an increased risk of HF hospitalization or cardiovascular death,[174] a relationship confirmed in other analyses.[175,176] These studies suggest an optimal systolic blood pressure target of 120 to 129 mm Hg for individuals with HFpEF.

The "2025 Multisociety Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults" recommends thiazide-like diuretics, angiotensin-converting enzyme inhibitors or ARBs, and calcium channel blockers as first-line therapy, with angiotensin-converting enzyme inhibitors or ARBs prioritized in individuals with type 2 diabetes or CKD.[173] However, in individuals with HFpEF, ARNIs or ARBs may represent a superior pragmatic antihypertensive option given the potential additional benefit of a decrease in HF hospitalizations.[102,104]

In non-HF populations, evidence suggests that multiple lifestyle interventions, including the DASH (Dietary Approaches to Stop Hypertension) diet, aerobic exercise, resistance training, and limiting excess sodium and alcohol, reduce blood pressure in an additive manner.[177] However, although hypertension clinical practice guidelines recommend potassium-based salt substitutes as part of the DASH diet, the benefit of such agents in individuals with CKM on therapies that increase serum potassium is not established.[178]

5.3.4. Chronic Kidney Disease

CKD, defined as estimated glomerular filtration rate <60 mL/min/1.73 m^2 or albumin-to-creatinine ratio >30 mg/g,[179] is both a major risk factor for the development of HFpEF and a common comorbidity in established HFpEF, affecting up to 60% of individuals.[180] Individuals with HFpEF and CKD share multiple common risk factors and comorbidities, including hypertension, type 2 diabetes, and obesity, and these conditions increase in prevalence with age.[181] These individuals tend to present with greater hypervolemia, high natriuretic peptide concentrations, and worse functional status.[182] Furthermore, the presence of CKD confers a significant increase in death and worsening HF events in individuals with HFpEF.[183,184]

Management of CKD, supported by "KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease"[179] and based on numerous trials, focuses on the use of renin-angiotensin system inhibitors (angiotensin-converting enzyme inhibitors[185,186] or ARBs[187,188]), SGLT2 inhibitors,[189,190] nonsteroidal MRAs,[191,192] and GLP-1 receptor antagonists,[193] all of which demonstrate reduction in the progression of kidney dysfunction, including in individuals with diabetic kidney disease.[194,195] Thus, many pillars of optimal medical therapy in HFpEF not only reduce the risk of HF events but also protect the kidneys.

5.3.5. Diabetes Mellitus

Type 2 diabetes is present in up to half of individuals with HFpEF.[196,197] Individuals with HF and type 2 diabetes experience worse clinical outcomes than those without type 2 diabetes, with an increased risk of death and worse health-related quality of life.[198] Treatment of type 2 diabetes in individuals with HFpEF should be guided by the American Diabetes Association "Standards of Care in Diabetes—2026."[152] A guiding principle is the replacement of agents that offer only glucose control, like sulfonylureas, with those that offer HF-specific benefit.

As noted earlier, SGLT2 inhibitors are foundational therapy for individuals with HFpEF regardless of diabetic status.[11,12] The GLP-1 receptor agonists liraglutide,[199] semaglutide,[95] and dulaglutide[200] also demonstrate benefits in individuals with type 2 diabetes beyond glycemic control, including kidney and cardiovascular protection. However, dipeptidyl peptidase-4 inhibitors (specifically saxagliptin and alogliptin)[201,202] and thiazolidinediones[203-205] should be avoided in individuals with HFpEF due to observed increased risk of HF events.[19]

5.3.6. Obesity

Obesity can be an HFpEF mimic, as described in Section 4.4.1.4, but also a common comorbidity, affecting up to 80% of individuals with HFpEF[206,207] with a graded association between increasing body mass index and HFpEF incidence.[208] Visceral adiposity promotes inflammation and fibrosis, leading to plasma volume expansion, neurohormonal activation, LV remodeling, diastolic dysfunction, and impaired exercise capacity, all of which contribute to the development and progression of HFpEF.[8,30,209] Greater degrees of obesity are associated with higher pulmonary capillary wedge pressures during exercise, more severe symptoms, and reduced exercise capacity.[30]

The ACC published detailed recommendations regarding management of obesity in HF in a 2025 scientific statement.[47] Successful treatment of obesity requires a multidisciplinary approach that includes nutritional support, exercise, incretin-based therapies (Section 5.1.3), and consideration of bariatric surgery.

6. CONCLUSION

This revised ECDP was written to provide timely, practical guidance based on emerging evidence on the diagnosis and management of HFpEF. This document aligns with and operates within the framework of the recommendations published in the "2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure,"[19] but provides a nuanced, updated approach to various aspects of HFpEF care based on emerging evidence. Foremost is the critical need to accurately diagnose these individuals. An accurate diagnosis will allow the institution of evidence- and guideline-based therapies.

As science evolves and further discoveries and developments occur, some of these recommendations may need to be altered to reflect those advances. In the interim, this ECDP addresses contemporary management

of HFpEF. It provides practical tips and structure on clinical decision-making, implementation of the latest advancements in pharmacologic and nonpharmacologic therapy, and management of comorbidities. The specific goal is to identify and implement current best practices for therapy to improve outcomes in HFpEF.

PRESIDENT AND STAFF

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APPENDIX 1. AUTHOR RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (RELEVANT)—MANAGEMENT OF HEART FAILURE WITH PRESERVED EJECTION FRACTION: 2026 ACC EXPERT CONSENSUS DECISION PATHWAY

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Michelle M. Kittleson *(Chair)*	Cedars-Sinai—Professor of Medicine; Director, Education in Heart Failure and Transplantation; Smidt Heart Institute—Director, Heart Failure Research	None	None	None	None	None	None
Gurusher S. Panjrath *(Vice Chair)*	George Washington University Medical Faculty Associates—Director Heart Failure and Mechanical Support Program	■ CVRx*	■ Pfizer*	None	None	■ Guide HF, Abbott Laboratories† ■ CARDIO-TTRansform, IONIS† ■ Franklin & Prokopik, PC*	2022, Heart failure related to eye injury*
Katie Bates	Kittitas Valley Healthcare Cardiology; Mission Cardiology—Cardiology Nurse Practitioner	None	None	None	None	None	None
Khadijah K. Breathett	Indiana University—Executive Director, Krannert Cardiovascular Research Center	None	None	None	None	None	None
Dave L. Dixon	VCU School of Pharmacy—Department Chair and Associate Professor	■ American Pharmacists Association ■ Brigham Women's Hospital (PCORI Grant)	None	None	■ Boehringer Ingelheim Pharmaceuticals* ■ Centers for Disease Control and Prevention*	None	None
James L. Januzzi Jr	Harvard Medical School—Adolph M. Hutter Jr. Professor of Medicine	■ Abbott Laboratories ■ Abiomed ■ AstraZeneca Pharmaceuticals* ■ Eli Lilly and Company ■ Novartis* ■ Novo Nordisk ■ Prevencio* ■ Roche Diagnostics* ■ Siemens	None	None	■ Abbott Laboratories* ■ Janssen Pharmaceuticals* ■ Medtronic ■ AbbVie (DSMB)* ■ Bayer Healthcare Pharmaceuticals (DSMB) ■ CVRx (DSMB)* ■ Takeda Pharmaceuticals North America (DSMB)*	■ Imbria* ■ Jana Care*	None
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ACC = American College of Cardiology; DSMB = Data and Safety Monitoring Board; HF = heart failure; PCORI = Patient-Centered Outcomes Research Institute.

APPENDIX 2. PEER REVIEWER RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (COMPREHENSIVE)—MANAGEMENT OF HEART FAILURE WITH PRESERVED EJECTION FRACTION: 2026 ACC EXPERT CONSENSUS DECISION PATHWAY

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
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Vanessa Blumer	Content Reviewer—ACC Expert	Inova Schar Heart and Vascular—Advanced Heart Failure & Transplant Cardiology	None	None	None	None	■ AstraZeneca Pharmaceuticals†	None
Josephine L. Harrington	Content Reviewer—ACC Expert	Duke School of Medicine—Cardiologist	■ Novo Nordisk‡	None	None	None	■ MOONRAKER program (REDEFINE, CONFIRMATION, FINALITY), CPC Clinical Research*	None
Robert C. Hendel	Official Reviewer—Solution Set Oversight Committee	Tulane University Heart & Vascular Inst—Professor of Medicine and Radiology	None	None	None	None	None	None
Tochi Okwueze	Official Reviewer—ACC Cardiovascular Team Member Section	Ascension Medical Group Illinois—Cardiology, Nurse Practitioner	None	None	None	None	■ Alt-flo, Edwards Lifesciences* ■ CORCINCH-HF, Anorca Heart*	None
Daniel F. Quesada	Official Reviewer—ACC Heart Failure and Transplant Council	San Vicente De Paul Hospital—Chief, Cardiology Department	■ AstraZeneca ■ Servier	None	None	None	None	None
Daniel Nathan Silverman	Official Reviewer—ACC Heart Failure and Transplant Council	Medical University of South Carolina—Assistant Professor of Medicine/Cardiology	■ Novo Nordisk‡	None	None	None	■ CADENCE, Acceleron Pharma Inc.* ■ LEVEL, Tenax Therapeutics* ■ LUX-Dx TRENDS, Boston Scientific Corporation*	None
Barbara S. Wiggins	Official Reviewer—Solution Set Oversight Committee	HeartFlow, Inc—Regional Medical Lead	None	None	None	None	■ ACC Cardiovascular Management Section Leadership Council†	None

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ACC = American College of Cardiology; ATTRIBUTE-CM = Acoramidis (AG10) in Transthyretin Amyloid Cardiomyopathy; CONFIRMATION = Confirming Benefit of Early Combination Therapy; FINALITY = Evaluate Finerenone in HF Patients Intolerant of or Ineligible for Steroidal MRAs; REDEFINE-HF = RandomizEd trial to DEtermine the efficacy and safety of FINErenone on morbidity and mortality among HF patients with LVEF≥40% hospitalized due to an episode of acute decompensated HF.