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EXPERT CONSENSUS DECISION PATHWAY

# 2023 ACC Expert Consensus Decision Pathway on Management of Heart Failure With Preserved Ejection Fraction

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

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## PREFACE

The American College of Cardiology (ACC) has a long history of developing documents (eg, decision pathways, health policy statements, appropriate use criteria) to provide members with guidance on both clinical and nonclinical topics relevant to cardiovascular care. In most circumstances, these documents have been created to complement clinical practice guidelines and to inform clinicians about areas where evidence is new and evolving or where sufficient data is more limited. Despite this, numerous gaps persist, highlighting the need for more streamlined and efficient processes to implement best practices for care.

Central to the ACC's strategic plan is the generation of actionable knowledge—a concept that places emphasis on making clinical information easier to consume, share, integrate, and update. To this end, the ACC has shifted from developing isolated documents to creating integrated "solution sets." These are groups of closely related activities, policies, mobile applications, decision-support tools, and other resources necessary to transform care and/or improve heart health. Solution sets address key questions facing care teams and attempt to provide practical guidance to be applied at the point of care. They use both established and emerging methods to disseminate information for cardiovascular conditions and their related management. The success of solution sets rests firmly on their ability to have a measurable impact on the delivery of care. Because solution sets reflect current evidence and ongoing gaps in care, the associated tools will be refined over time to match changing evidence and member needs.

Expert Consensus Decision Pathways (ECDPs) represent a key component of solution sets. Standard methodology for developing an ECDP is as follows: for a high-value topic that has been selected by the Science and Quality Committee and prioritized by the Solution Set Oversight Committee (SSOC), a group of clinical experts is assembled to develop content that addresses key questions facing our members.[1] This content is used to inform the development of various tools that accelerate real-time use of clinical policy at the point of care. ECDPs are not intended to provide single correct answers to clinical questions; rather, they encourage clinicians to consider a range of important factors as they define treatment plans for their patients. Whenever appropriate, ECDPs seek to provide unified articulation of clinical practice guidelines, appropriate use criteria, and other related ACC clinical policy. In some cases, covered topics will be addressed in subsequent clinical practice guidelines as the evidence base evolves. In other cases, these will serve as standalone policy.

*Nicole M. Bhave, MD, FACC*
*Chair, ACC Solution Set Oversight Committee*

## 1. INTRODUCTION

### 1.1. The Scope of the Problem

Despite advances in therapy, heart failure (HF) continues to be a major cause of morbidity and mortality worldwide with a lifetime risk at age 40 years of approximately 20%.[2] 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.[3,4] HFpEF now accounts for more than 50% of cases of HF,[5] with outcomes comparable to heart failure with reduced ejection fraction (HFrEF).[6] HFpEF is often under-recognized and results in substantial resource utilization.

Historically, treatment options were limited to managing comorbidities; however, revolutionary advances in the past decade regarding the pathophysiology of HFpEF, improved methods of diagnosis, and insights into prognostic predictions now yield novel, effective management strategies. With recent favorable clinical trial results, there is increasing urgency for accurate diagnosis and timely implementation of guideline-directed medical therapy (GDMT). These advances motivate the creation of this ECDP to address pivotal issues pertinent to HFpEF:

1. How to approach a person with shortness of breath
2. How to overcome diagnostic dilemma and identify a need for further testing
3. How to rule out mimics to avoid missed diagnosis
4. How to manage comorbidities and address complexities in care
5. How to initiate and optimize GDMTs
6. When and why to refer to a cardiologist or HF specialist
7. How to improve access to care
8. How to recognize sex-specific differences in diagnosis and care management

### 1.2. Challenges in the Diagnosis of HFpEF

The Universal Definition of HF requires symptoms and/or signs of HF caused by structural/functional cardiac abnormalities *and* at least 1 of the following: 1) elevated natriuretic peptides; or 2) objective evidence of cardiogenic pulmonary or systemic congestion.[7] While these criteria are clear, there are nuances and challenges to be considered in the diagnosis of HFpEF.

The first challenge in the diagnosis of HFpEF is what ejection fraction (EF) threshold constitutes HFpEF. Based on consensus from the U.S. Heart Failure Collaboratory and Academic Research Consortium,[8] as supported by the Universal Definition of HF,[7] HFpEF is defined as a clinical diagnosis of HF with left ventricular ejection fraction (LVEF) ≥50%. Those individuals with EFs between 40% and 50% are noted to have HF with mildly reduced ejection fraction (HFmrEF). Individuals with HFmrEF comprise a diverse group, including those with improving HFrEF or worsening HFpEF. The separation of HFmrEF and HFpEF is useful because it provides a distinct category for those individuals with stable preserved EF and because EF measurement may vary depending on the imaging modality and interpretation method.

Another challenge in the diagnosis of HFpEF is using the correct terminology. HFpEF is not synonymous with

diastolic dysfunction. In fact, the presence of diastolic dysfunction on echocardiogram is neither specific nor sufficient to make the diagnosis of HFpEF and, International Classification of Diseases-Tenth Revision (ICD-10) billing codes notwithstanding, "diastolic heart failure" is not an accurate or appropriate term for the constellation of symptoms in individuals with HFpEF.

Another major diagnostic challenge with HFpEF is that there is no single test that definitively establishes the diagnosis. Thus, it is paramount to consider potential mimics, both noncardiac and cardiac, that may present with signs of congestion and/or symptoms of dyspnea, exercise intolerance, or congestion with preserved EF. These mimics have distinct pathophysiological mechanisms, and failure to consider additional diagnoses may result in missed opportunities to institute effective disease-directed therapies.

### 1.3. Challenges in the Treatment of HFpEF

Even if the diagnosis of HFpEF is confirmed, therapeutic challenges remain. Clinicians must consider the role of comorbidities that contribute to symptoms and prognosis, nonpharmacological options to ameliorate symptoms, and GDMT to improve quality of life, reduce HF as well as non-HF hospitalizations, and improve survival. Implementation of high-quality care requires multidisciplinary collaboration. Given the challenges in diagnosis and advances in therapies, there is a critical opportunity to redefine care of individuals with HFpEF. The purpose of this document is to provide practical and streamlined pathways for diagnosis and management, incorporating the emerging data from clinical trials.

### 1.4. Specific Challenges in the Management of Women With HFpEF

The challenges in the diagnosis and management of HFpEF are even more pertinent in women. Women have higher EFs[9] and more preserved left ventricular (LV) global longitudinal strain[10] compared with men and therefore may be less likely to develop a reduced EF. The prevalence of HFpEF in women is expected to grow substantially; recent projections suggest the incidence of HF in women will rise by more than 30% in the upcoming decades.[11] Women have a lifetime risk for HF of approximately 20% by age 40 years, increasing to nearly 30% by age 55 years.[2]

A careful history of pregnancy is important because both may also be prognostic for HFpEF. A history of preeclampsia is associated with an increased risk for subsequent HFpEF hospitalization,[12] additive to usual risk factors and particularly noteworthy among populations with inadequate access to quality healthcare, such as individuals from under-represented racial and ethnic groups and those with lower socioeconomic status.

Sex-specific differences in HFpEF are discussed further in the later sections on HFpEF diagnosis and management.

## 2. METHODS

The ACC created the Heart House Roundtables, a structured format of interactive discussion among a broad group of stakeholders, to address high-value topics and issues that clinicians and patients face daily, such as the diagnosis and management of HFpEF.[13] The planning committee for the HFpEF roundtable was led by Gurusher S. Panjrath, MD, FACC (Chair), and Kavita Sharma, MD, FACC (Vice Chair). To accommodate the multiple perspectives necessary to synthesize and construct new therapeutic frameworks for individuals with HFpEF, this roundtable was designed to include experts in diverse healthcare disciplines, including physicians, pharmacists, and advanced practice professionals, and patient representatives.

Recognizing the significant impact of trials and approved medications, discussions focused on the real-world challenges faced in working toward the accurate diagnosis and appropriate management of HFpEF for improved outcomes. As a result, the ACC saw an opportunity to provide guidance to bridge a communication gap between cardiovascular and primary care clinicians who jointly manage individuals with HFpEF. To support this effort, a writing committee of multidisciplinary experts was convened in 2022 to develop an ECDP providing guidance on the diagnosis and management of HFpEF. For this update, the writing committee convened in late 2022 via conference call attended only by writing committee members and ACC staff. Differences were resolved by consensus among the group, and no portions of the ECDP required administrative decision overrides. The work of the writing committee was supported only by the ACC and did not have any commercial support. Writing committee members were all unpaid volunteers.

The writing group participants represent broad expertise in the care of the individuals with HFpEF. A review of outstanding questions was facilitated. Subsequent writing assignments were configured according to areas of expertise. E-mail correspondence was used to edit contributed content. Conference calls of the writing committee were confidential and were attended only by committee members and ACC staff.

The ACC and the SSOC recognize the importance of avoiding real or perceived relationships with industry (RWI) or other entities that may affect clinical policy. The ACC maintains a database that tracks all relevant relationships for ACC members and persons who participate in ACC activities, including those involved in the development of ECDPs. ECDPs follow ACC RWI policy in

determining what constitutes a relevant relationship, with additional vetting by the SSOC.

ECDP writing groups must be chaired or cochaired by an individual with no relevant RWI. Although vice chairs and writing group members may have relevant RWI, they must constitute less than 50% of the writing group. Relevant disclosures for the writing group and comprehensive disclosures for external peer reviewers can be found in Appendixes 1 and 2. To ensure complete transparency, a comprehensive list of disclosure information for the writing group, including relationships not pertinent to this document, is available in a Supplemental Appendix. Writing group members are discouraged from acquiring relevant RWI throughout the writing process.

Every ECDP undergoes a formal peer review process consistent with ACC policy and includes a public comment period to obtain further feedback. Following reconciliation of all comments, ECDPs are then vetted and approved for publication by the Clinical Policy Approval Committee.

## 3. ASSUMPTIONS AND DEFINITIONS

### 3.1. General Clinical 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 American Heart Association (AHA)/ACC/Heart Failure Society of American (HFSA) Guideline for the Management of HF.[14]
3. Optimal care decisions should properly reflect the individual's preferences and priorities as well as those of the managing clinician. A shared-decision 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 judgement as, especially for HFpEF care, many questions remain unanswered. The treating clinician should seek input as needed from relevant experts (eg, pharmacists, cardiologists, HF specialists, endocrinologists, nephrologists, palliative care specialists).
5. This ECDP is based on the best data currently available. As new discoveries emerge, (eg, trials of additional agents and devices and including other populations), these data will affect the considerations made here. Clinicians should be careful to incorporate relevant information published after this ECDP.
6. Although implementing relevant portions of these recommendations in the acute inpatient hospital setting may be reasonable, this ECDP is primarily focused on management in the ambulatory setting.

### 3.2. Definitions

*GDMT*: Treatment options supported for use by clinical practice guidelines.

*HF*: defined as per the Universal Definition of Heart Failure[7]: symptoms and/or signs of HF caused by structural/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 criteria outlined by the 2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials.[15]

*HFrEF:* Clinical diagnosis of HF and LVEF ≤40%.[14]

*HFmrEF*: Clinical diagnosis of HF and LVEF 41% to 49%.[14]

HF with improved EF: previous LVEF ≤40% and a follow-up measurement >40%.

*HFpEF*: Clinical diagnosis of HF and LVEF ≥50%[14] not attributable to an underlying cause such as an infiltrative cardiomyopathy, hypertrophic cardiomyopathy, valvular disease, pericardial disease, or high-output HF.

*HFpEF mimics*: Clinical diagnosis of HF and LVEF ≥50% with a primary noncardiac cause (kidney or liver disease) or an underlying cardiac cause (infiltrative cardiomyopathy, hypertrophic cardiomyopathy, valvular disease, pericardial disease, or high-output HF).

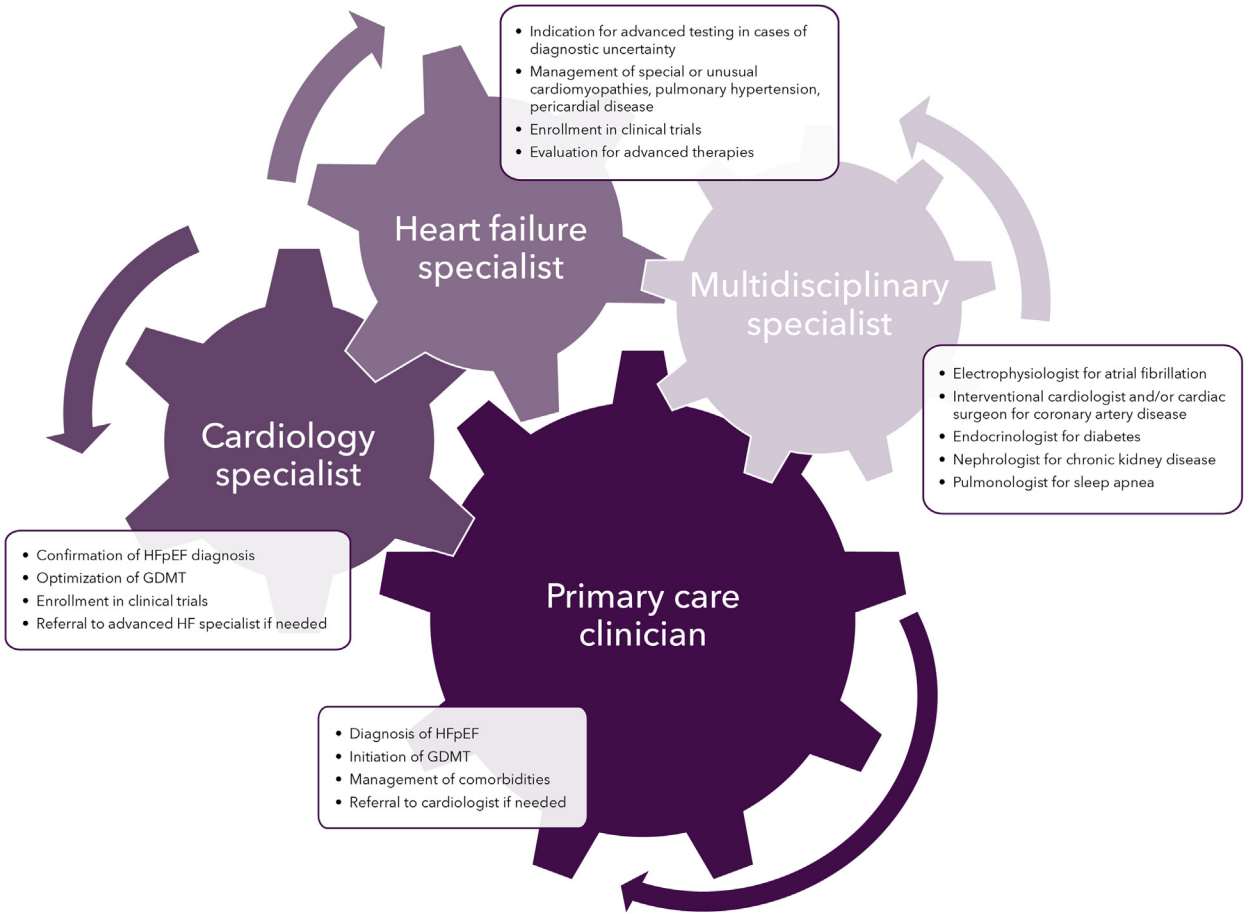
New York Heart Association (NYHA) functional classification:

- 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.

## 4. PATHWAY SUMMARY GRAPHIC

Many individuals present first to their primary care clinicians with symptoms of dyspnea and exercise intolerance and/or signs of congestion. The primary care clinician should be aware of HFpEF in the differential diagnosis of dyspnea, exercise intolerance, and edema; order relevant testing; be able to initiate GDMT; and recognize when a cardiology referral may be useful. The role of the cardiology specialist (cardiologist or cardiology advanced practice professional) is to exclude the presence of an alternative diagnosis to explain the individual's presentation of dyspnea, edema, and preserved EF; optimize GDMT; encourage clinical trials; and identify

**FIGURE 1 Approach to HFpEF**




Abbreviations: GDMT = guideline-directed medical therapy; HF = heart failure; HFpEF = heart failure with preserved ejection fraction.

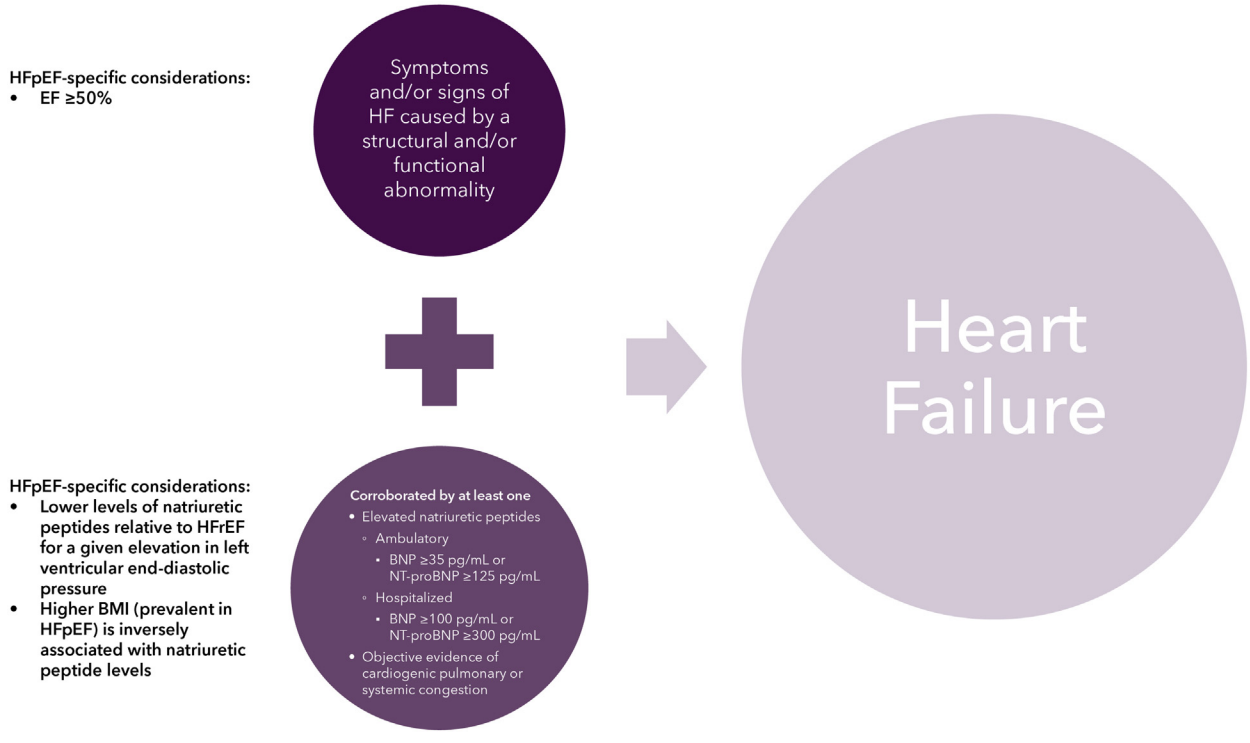
indications for referral to an HF specialist. The role of the HF specialist is to pursue advanced testing in case of diagnostic dilemma; manage special or unusual cardiomyopathies, a particularly important consideration for HFpEF; identify clinical trial eligibility; and assess the need and eligibility for advanced therapies, including heart transplantation. Multidisciplinary specialist collaboration for optimization of comorbidities may include collaboration with electrophysiologists, interventional cardiologists or cardiac surgeons, endocrinologists, nephrologists, and pulmonologists.

## 5. DESCRIPTION, RATIONALE, AND IMPLICATION OF PATHWAY

Clinicians should: 1) perform testing, as guided by the history and physical examination, to exclude cardiac and noncardiac HF mimics and identify comorbidities in individuals with dyspnea and/or edema, and preserved EF; and 2) implement an HFpEF treatment plan with specific attention to the management of comorbidities and the role of nonpharmacological management and GDMT. Because many individuals with HFpEF do not present initially to cardiovascular specialists, multidisciplinary collaboration comprises essential components of the approach to the person with HFpEF (Figure 1):

- **Primary care clinicians** recognize HFpEF as a potential diagnosis in persons with dyspnea, exertional intolerance, and edema; initiate diagnostic testing and appropriate GDMT; and recognize when a cardiology referral is warranted;
- **Cardiology specialists (cardiologists and cardiology advanced practice professionals),** in addition to initiating diagnostic and treatment pathways, may also assess for the presence of alternative diagnoses to explain the presentation of dyspnea, edema, and preserved EF; optimize GDMT; enroll individuals in clinical

**FIGURE 2 The Universal Definition of HF***




*The Universal Definition of HF requires symptoms and/or signs caused by structural/functional cardiac abnormalities *and* at least 1 of: 1) elevated natriuretic peptides; or 2) objective evidence of cardiogenic pulmonary or systemic congestion. In HFpEF, specific additional criteria include EF 50% or greater, and consideration of pitfalls as described in the assessment of natriuretic peptide levels. BMI = body mass index; BNP = B-type natriuretic peptide; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

trials; and identify indications for referral to an HF specialist; and

- **HF specialists**, in addition to confirming the diagnosis and treatment initiation, may pursue more advanced testing in cases of diagnostic uncertainty; manage special or unusual cardiomyopathies; identify clinical trial eligibility; assess the need and eligibility for advanced therapies, including heart transplantation; and determine the prognosis and need for referral to palliative care or hospice.

## 6. DIAGNOSIS OF HFpEF

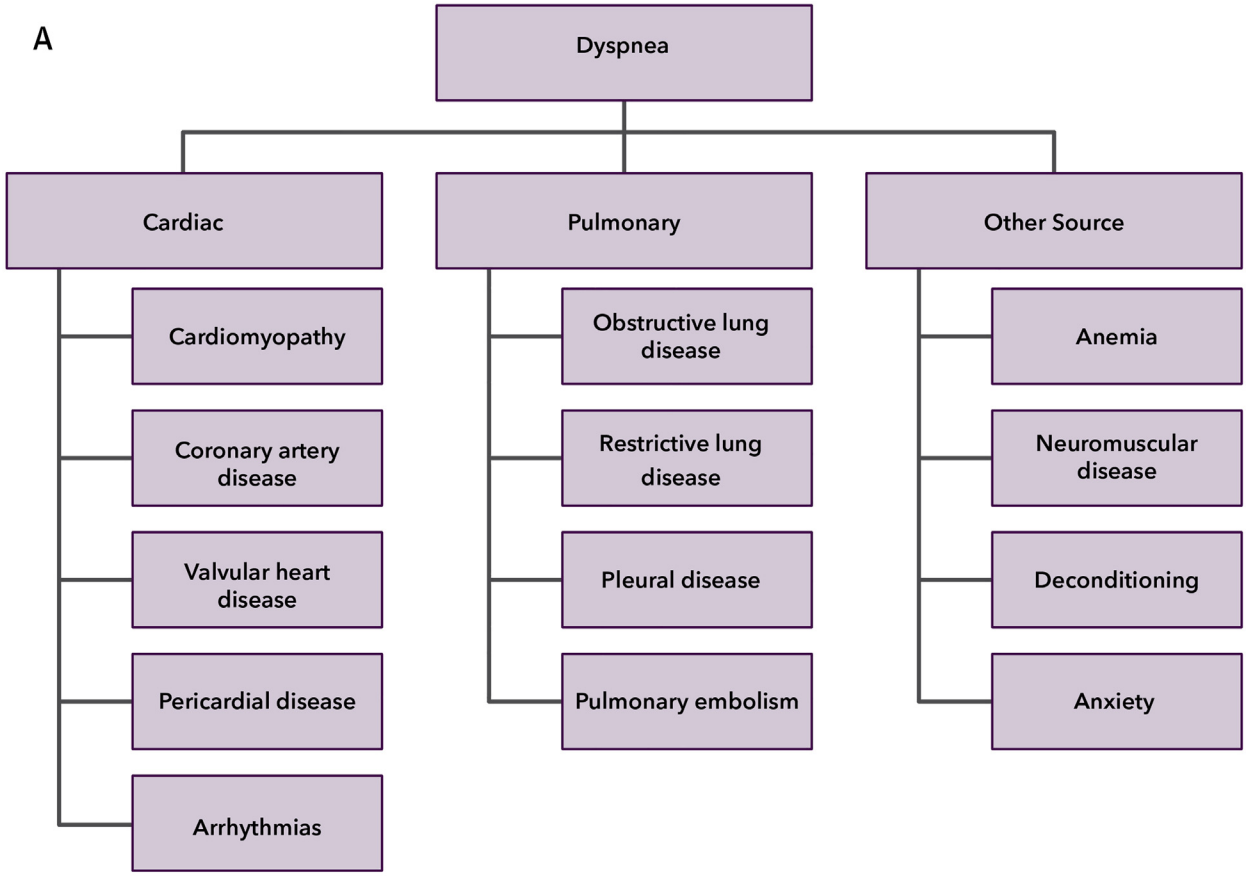
### 6.1. The Universal Definition of HF

The symptoms and signs of HF are well summarized by the Framingham HF Diagnostic Criteria, based on data collected during the Framingham Heart Study.[16] Two or more major criteria or 1 major criterion plus 2 minor criteria are strictly required to make the diagnosis. Although clinicians will rarely resort to classifying patients using these strict criteria, the collection of symptoms and signs included in the Framingham HF Diagnostic Criteria remain useful as a reference. Major criteria include orthopnea, jugular venous distension, hepatojugular reflux, rales, S3 gallop rhythm, acute pulmonary edema, and cardiomegaly. Minor criteria include dyspnea on exertion, nocturnal cough, ankle edema, tachycardia with heart rate over 120 beats per minute, hepatomegaly, and pleural effusion.

The Universal Definition of HF provides a straightforward approach for clinicians to determine if a person's presentation is consistent with HF (**Figure 2** includes HFpEF-specific considerations).[7] The Universal Definition of HF requires symptoms and/or signs of HF, as outlined earlier, caused by structural/functional cardiac abnormalities *and* at least 1 of the following: 1) elevated natriuretic peptides; or 2) objective evidence of cardiogenic pulmonary or systemic congestion.

If a cardiac source for dyspnea and/or edema appears likely based on the history and physical examination, the next steps would include an echocardiogram to assess for structural/functional cardiac abnormalities and

**FIGURE 3 Differential Diagnosis of Dyspnea and Edema***




*However, other conditions can also cause these symptoms. **(A)** The differential diagnosis of dyspnea. **(B)** The differential diagnosis of edema. CCBs = non-dihydropyridine calcium-channel blockers; NSAIDs = nonsteroidal anti-inflammatory drugs.

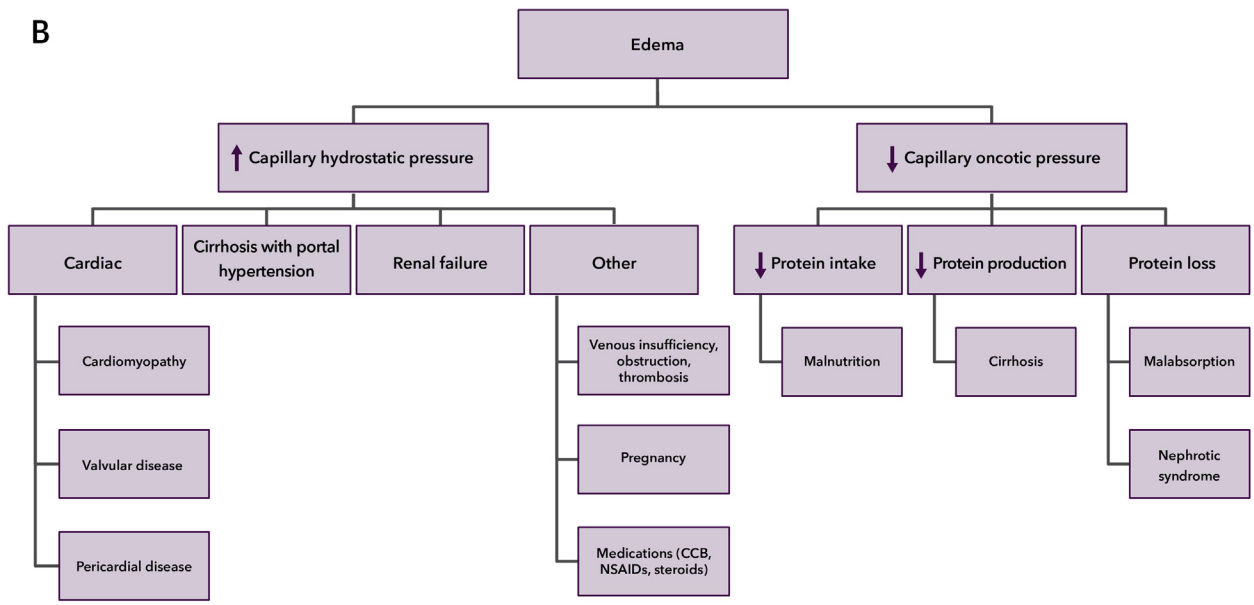
laboratory evaluation, including natriuretic peptides, recognizing that a substantial proportion of individuals with HFpEF have normal natriuretic peptide levels despite unequivocal invasive hemodynamic evidence of HF.[17]

### 6.2. Differential Diagnosis of Dyspnea and Edema

Although dyspnea is a common presenting symptom of HFpEF, it is imperative to consider other causes of dyspnea before assigning the diagnosis. Dyspnea, or shortness of breath, is a frequent cause of emergency visits and hospitalizations across the spectrum of age[18-20] and can pose a diagnostic challenge given the multiple potential sources of symptoms.[21]

An approach to the differential diagnosis of dyspnea is shown in **Figure 3A**, organized by cardiac, pulmonary, and other sources. A similar approach can be taken to the differential diagnosis of edema (**Figure 3B**),[22] although the first step should be to differentiate edema from lymphedema. Lymphedema is defined as the abnormal accumulation of interstitial fluid and fibroadipose tissue resulting from injury, infection, or congenital abnormalities of the lymphatic system. A history suggestive of risk factors such as lymph node dissection is useful, and lymphedema is most commonly unilateral. A useful physical examination finding to distinguish edema from lymphedema is the Stemmer sign. A positive Stemmer sign is characterized by a thickened skin fold at the base of the second toe or second finger. The examiner's inability to lift the skin of the affected limb compared with the contralateral limb is considered to reflect fluid accumulation due to lymphedema. However, obesity may cause a false-positive Stemmer sign.[23,24] Despite being highly sensitive, patients with a negative Stemmer sign and a high clinical suspicion for lymphedema warrant referral for lymphoscintigraphy.

**FIGURE 3 Continued**




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 3B**.

When reviewing the differential diagnosis of dyspnea and edema, it is important to note the multiple potential sources. To determine if a person's dyspnea and/or edema is from HF, the Universal Definition of HF[7] as well as HFpEF diagnostic scoring systems are useful in ascertaining the diagnosis.

### 6.3. HFpEF Diagnostic Scoring Systems

Although the Universal Definition of HF may be useful to guide clinicians, establishing a diagnosis of HFpEF may be more difficult given that the echocardiogram may not demonstrate obvious structural or functional cardiac abnormalities and the natriuretic peptide levels may be normal, especially in individuals with obesity.

Given the lack of testing to definitively establish the diagnosis of HFpEF, the use of clinical scoring systems may be useful to aid in the diagnostic evaluation of suspected HFpEF.[25-28] Both the $H_2$FPEF and HFA-PEFF algorithms use a scoring system to help determine the likelihood that HFpEF is the underlying etiology in a dyspneic person.

The $H_2$FPEF score was derived and validated using a gold-standard reference of invasive exercise hemodynamic measurements and is the more practical system for use by clinicians (**Figure 4A**). The 6 components of the $H_2$FPEF score consist of information that is readily accessible: Heavy (body mass index [BMI] >30 kg/m$^2$), Hypertension (on 2 or more antihypertensive medications), atrial Fibrillation, Pulmonary hypertension (estimated pulmonary artery systolic pressure >35 mm Hg on Doppler echocardiography), Elder (age >60 years), Filling pressures (E/e' >9 on Doppler echocardiography).[27] A score of 6 or more is highly suggestive of HFpEF.

The HFA-PEFF algorithm, in contrast, was developed based on expert consensus and is more involved, including potential hemodynamic assessment (**Figure 4B**).[28] It includes 4 steps: Step 1 is the Pretest assessment to identify individuals who may have HF based on clinical assessment and standard diagnostic tests, including natriuretic peptides, electrocardiograms, and echocardiograms. Step 2 is the Echocardiographic and natriuretic peptide score, with points assigned to echocardiographic parameters and natriuretic peptide levels. Step 3 is Functional testing in cases of uncertainty, including a diastolic stress test with exercise stress echocardiography followed by invasive hemodynamic measurements, if needed. Finally, Step 4 is Final etiology, including testing to exclude other cardiac causes of dyspnea and/or edema such as infiltrative/restrictive cardiomyopathy, valvular disease, or pericardial disease.

The HFA-PEFF algorithm includes natriuretic peptides in its scoring system, and it is important to note the limitations of these thresholds. Natriuretic peptide levels are generally lower in individuals with HFpEF compared with those with HFrEF,[29] making the role of natriuretic peptides challenging, especially in individuals with HFpEF

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**FIGURE 4 HFpEF Diagnostic Scoring Systems***

A

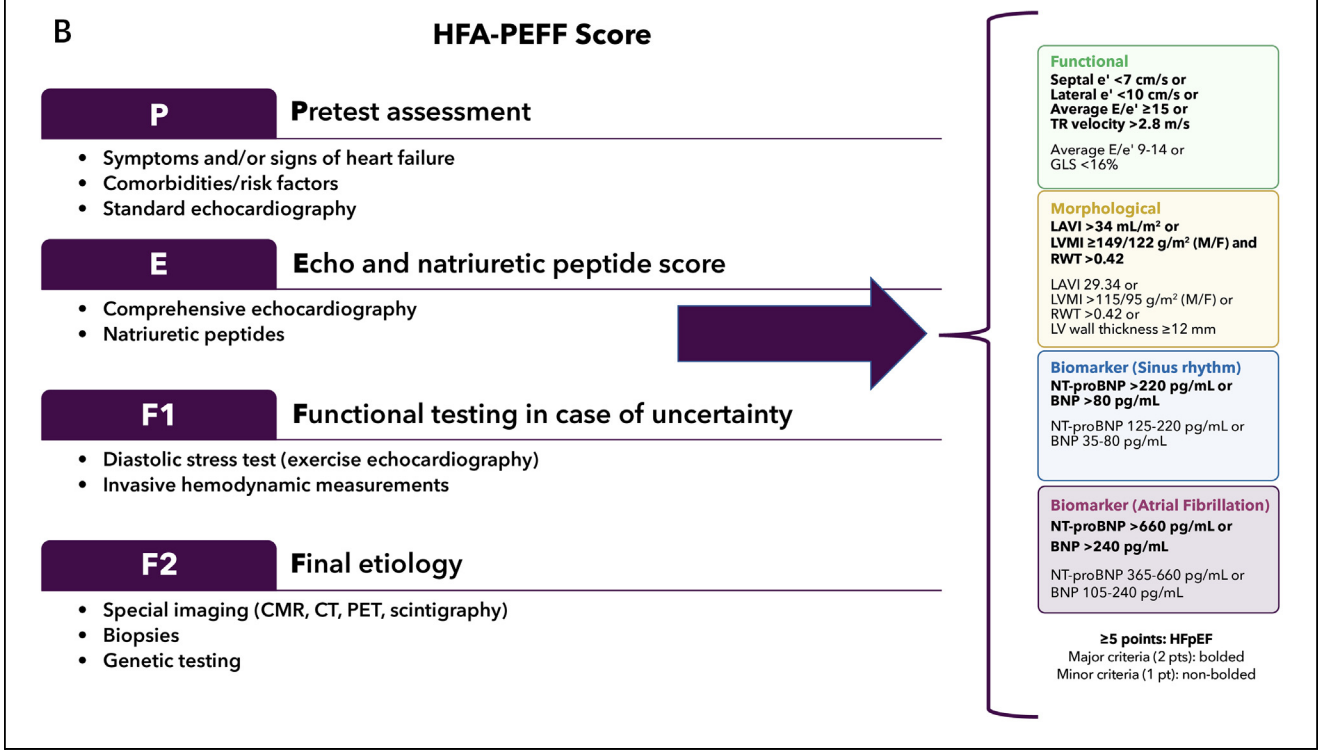
**$H_2$FPEF**

| | | |
|---|---|---|
| $H_2$ | **H**eavy (BMI >30 kg/m²) | 2 |
| | On ≥2 anti**H**ypertensives | 1 |
| F | Atrial **F**ibrilllation | 3 |
| P | **P**ulmonary hypertension (PASP >35 mm Hg on Doppler echocardiography | 1 |
| E | **E**lder (age >60 years) | 1 |
| F | **F**illing pressure (E/e′ >9 on Doppler echocardiography) | 1 |

≥6 points: highly diagnostic of HFpEF

***(A)** The $H_2$FPEF 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. 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.

**FIGURE 4 Continued**




and obesity. Despite worse hemodynamic derangements, individuals with obesity have significantly lower natriuretic peptide concentrations than those without obesity, particularly in HFpEF[17,29,30]; this may result in natriuretic peptide values below the diagnostic threshold for HF, even in the presence of elevated, invasively measured cardiac filling pressures,[17,29,31] although correction for BMI may be performed.[32] However, the $H_2$FPEF score does not include natriuretic peptides in its scoring system, which may also be problematic, because an elevated natriuretic peptide level is one component of the Universal Definition of HF.

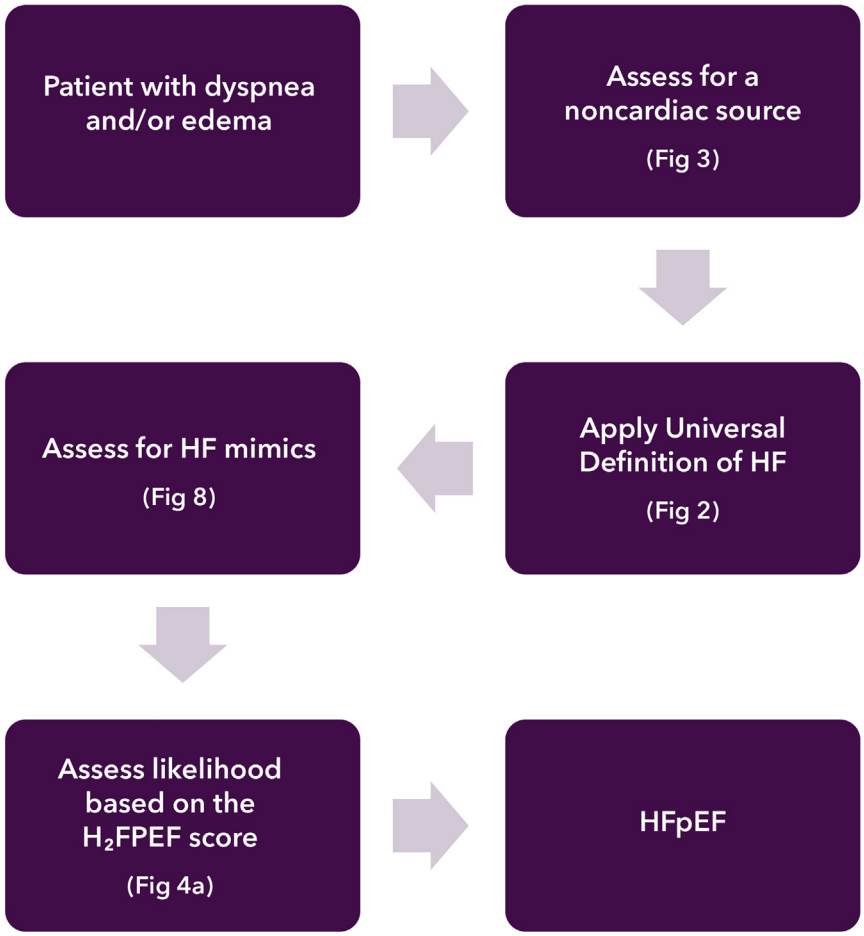
The Heart Failure Association of the European Society of Cardiology has suggested that a 50% reduction in natriuretic peptide cutoff values be used for the diagnosis of HF in individuals with obesity, although this approach has not been validated and is not explicitly incorporated into the HFA-PEFF algorithm.[33] Ultimately, a high suspicion of HFpEF and a low threshold for further evaluation (which may include invasive hemodynamic assessment) is warranted in individuals with dyspnea and obesity before attributing all symptoms to obesity. Indeed, the presence of obesity may result in missed opportunities to identify the presence of HFpEF, and effective treatment of both diagnoses may result in considerable improvement in quality of life and reduced hospitalizations.

Another potential limitation to the HFA-PEFF algorithm is the practicality of Step F1. 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 GDMT for HFpEF (including diuretic therapy and a sodium-glucose cotransporter-2 inhibitor [SGLT2i], outlined in Section 7.1) to assess for symptomatic improvement. A therapeutic trial of GDMT is a reasonable first step instead of more intensive testing to establish a HFpEF diagnosis if the latter is not readily available.

Step F2 of the HFA-PEFF algorithm, however, is invaluable. A focus on excluding an underlying condition for which there may be specific disease-directed therapy to improve outcomes is essential, as discussed in more detail in Section 6.3 on HFpEF mimics.

An aligning commonality in these algorithms is the importance of risk factors and clinical context when considering a diagnosis of HFpEF, explicitly as part of the scoring system in the $H_2$FPEF score and implicitly as part of the pretest assessment in HFA-PEFF. Individuals may be dyspneic, have edema, and meet the Universal Definition of HF with structural/functional cardiac abnormalities and elevated natriuretic peptides or objective

**FIGURE 5 The Diagnostic Approach to HFpEF***




*The diagnostic approach to HFpEF focuses on the evaluating the differential diagnosis of dyspnea and edema, excluding noncardiac causes, establishing diagnostic probability with the $H_2$FPEF score, and excluding cardiac mimics, especially in those with intermediate scores (potentially including referral to a cardiovascular and/or HF specialist) is essential before establishing the likely diagnosis of HFpEF. HF = heart failure; HFpEF = heart failure with preserved ejection fraction.

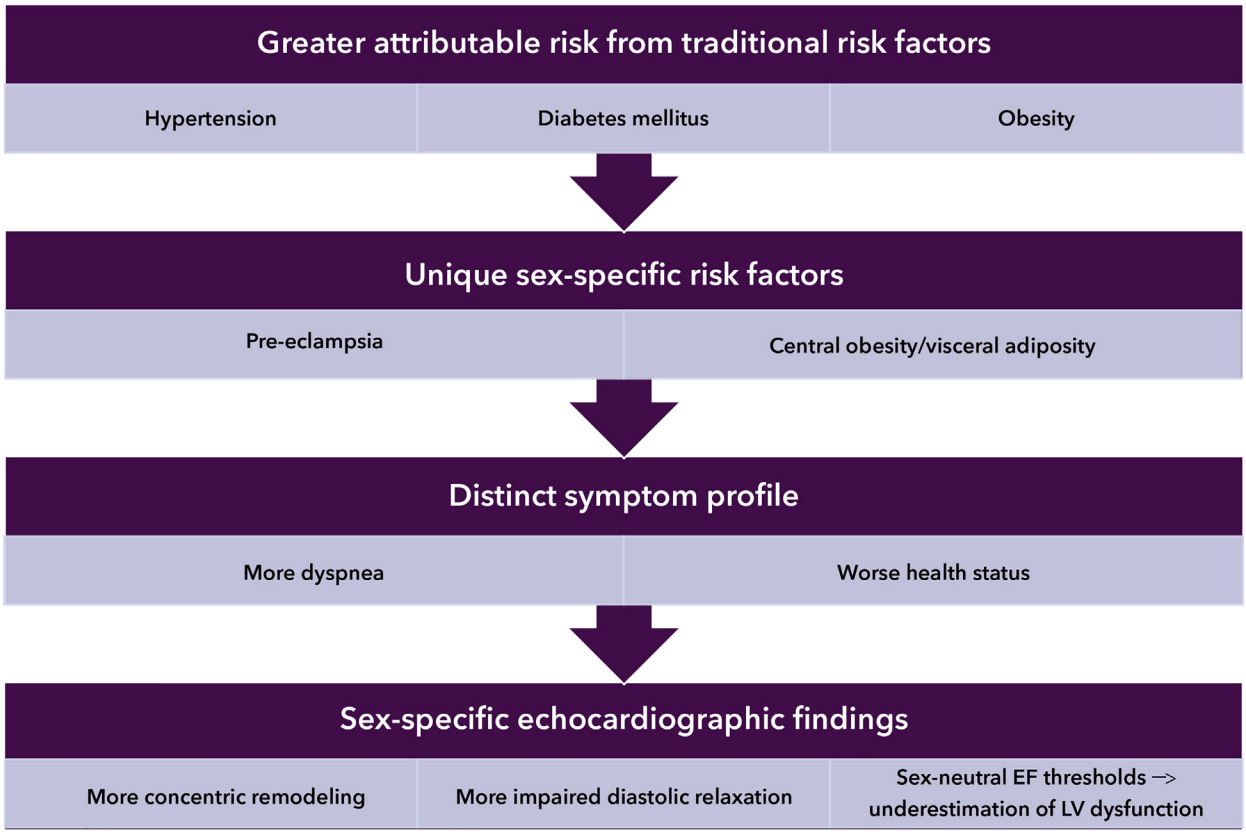
evidence of cardiogenic pulmonary or systemic congestion and still not have HFpEF; noncardiac and cardiac mimics such as kidney disease, liver disease, and infiltrative cardiomyopathy are discussed further in Section 6.2. The pretest probability, however, will increase if the individual has classic demographic and comorbid risk factors, including older age, obesity, DM, hypertension, atrial fibrillation (AF), and CAD.[34-36]

Both the $H_2$FPEF and HFA-PEFF scores can aid clinicians in diagnosing HFpEF. However, there are limitations. There are discrepancies between the HFA-PEFF and $H_2$FPEF scoring systems,[37,38] and a significant proportion of individuals fall into the "intermediate" (ie, nondiagnostic) categories, for which further testing into mimics would be important, as outlined in Section 6.2. In addition, a low $H_2$FPEF score in the context of HF symptoms and signs should not be used to exclude the HFpEF diagnosis, as pretest assessment will probably guide the diagnostic utility of the scoring system. Recognizing this caveat, the $H_2$FPEF score may be more useful in clinical practice to establish HFpEF as a likely diagnosis, given evidence of greater accuracy despite fewer input variables.[39] A diagnostic approach to the person with dyspnea and/or edema is outlined in **Figure 5**.

#### 6.3.1. Sex-Specific Differences in the Diagnosis of HFpEF

Compared with men, women with HFpEF tend to have more significant symptoms of dyspnea and are more likely to have worse health status.[40] Physical examination is generally similar between women and men with

**FIGURE 6 Sex-Specific Differences in Women: HFpEF Presentation and Diagnosis***




*Women with HFpEF have great attributable risk from traditional risk factors, unique risk factors, a distinct symptom profile, and distinct echocardiographic findings. EF = ejection fraction; HFpEF = heart failure with preserved ejection fraction; LV = left ventricular.

HFpEF; however, diagnostic testing may reveal important sex-based differences. For example, on echocardiographic imaging, women with HFpEF are more likely to have more significant concentric LV remodeling accompanied by more impaired LV relaxation and higher diastolic stiffness compared with men with HFpEF.[41] With more concentric remodeling, women tend to have smaller LV chamber size and are thus more prone to demonstrate higher LVEF compared with men.

Given this, the use of sex-neutral thresholds for "normal" may result in underestimation of LV dysfunction in women; an LVEF of 50% to 55% may be abnormal in a woman. In contrast to echocardiography, natriuretic peptides perform relatively similarly for a diagnosis of exclusion of HFpEF in women when compared with men, with similar caveats regarding appropriate cutpoints and the effect of comorbidities.[42] A summary of the sex-specific differences in HFpEF presentation and diagnosis is provided in **Figure 6**.

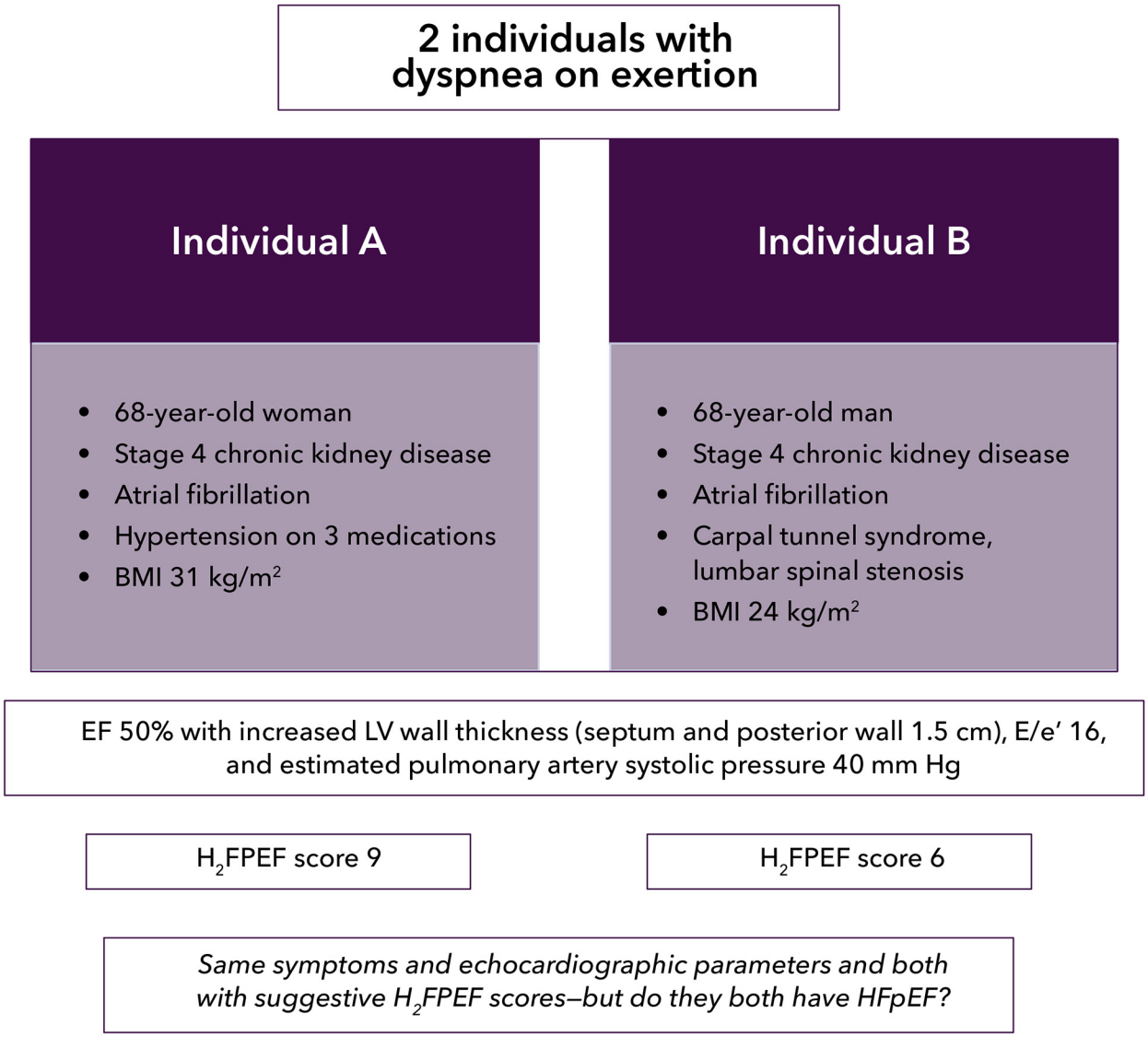
## 6.4. HFpEF Mimics

### 6.4.1. Noncardiac Disease Mimics

As outlined in Section 6.1, some individuals who present with symptoms of dyspnea and/or edema may not have HF. There are noncardiovascular entities that may mimic HF, including kidney failure or nephrotic syndrome, liver failure or cirrhosis, anemia, severe obesity with peripheral edema, lung disease with or without cor pulmonale, primary pulmonary hypertension, and chronic respiratory failure hypoventilation syndrome (**Figure 3**).

Thus, based on the clinical presentation, evaluation of individuals who present with symptoms of dyspnea and/or edema may include urinalysis to assess for proteinuria, abdominal ultrasound to assess for cirrhosis, and pulmonary evaluation with imaging, spirometry, and arterial blood gas. Recognizing that not every individual with shortness of breath or edema has HF is essential. This recognition will guide accurate diagnostic pathways and generate timely specialist referrals with optimal resource

**FIGURE 7 Approach to Individuals With Dyspnea***



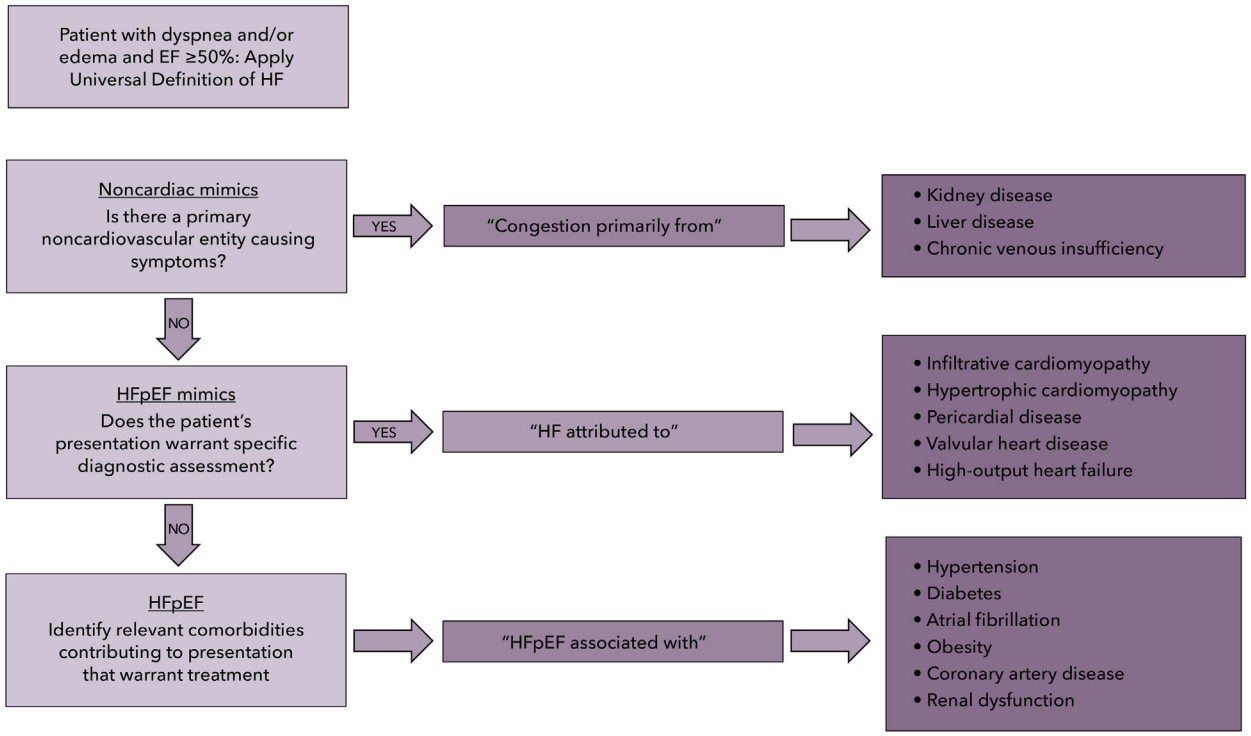

*An example of 2 individuals with the same symptoms and echocardiographic parameters, both with $H_2$FPEF scores suggesting HFpEF. However, the second individual likely has an HFpEF mimic attributable to a specific disease entity and requiring specific disease-directed therapy. BMI = body mass index; EF = ejection fraction; HFpEF = heart failure with preserved ejection fraction; LV = left ventricular.

utilization, resulting in appropriate management strategies.

#### 6.4.2. Cardiac Mimics

Rather than presuming that all individuals with evidence of congestion and preserved EF have HFpEF, such individuals should undergo further diagnostic assessment, as dictated by the clinical presentation, to identify underlying causes for which there are disease-directed therapies. Consider the 2 individuals described in Figure 7. Both have identical symptoms and echocardiogram findings. By the Universal Definition of HF, both have HF and both have $H_2$FPEF scores suggestive of HFpEF. However, the first individual likely has HFpEF with associated comorbidities of hypertension, obesity, AF, and chronic kidney disease (CKD), whereas the second individual has a high likelihood of HFpEF attributed to a specific source, transthyretin cardiac amyloidosis,

**FIGURE 8 Stepwise Approach to Assessment of Individuals With Shortness of Breath and/or Edema**




EF = ejection fraction; HF = heart failure; HFpEF = heart failure with preserved ejection fraction.

warranting further diagnostic evaluation with a monoclonal protein screen and a technetium pyrophosphate scan.[43]

This exercise highlights the importance of the clinical context, namely demographic and comorbid risk factors, in the diagnosis of HFpEF. If a noncardiac mimic is identified, an individual may have "congestion" from noncardiovascular entities such as kidney failure, liver failure, or chronic venous insufficiency. If a primary noncardiovascular entity is not identified, then an individual with evidence of congestion and preserved EF may have "HF attributed to" special or unusual cardiomyopathies such as infiltrative/restrictive cardiomyopathy, hypertrophic cardiomyopathy, valvular heart disease, or pericardial disease; or, if no such condition is suggested by the clinical presentation or diagnostic testing, then a diagnosis of HFpEF is established by exclusion, and the relevant comorbidities should be identified to emphasize management strategies (**Figure 8**).

This exercise is not to imply that every person with HFpEF requires exhaustive testing to exclude special or unusual cardiomyopathies. A history and physical examination along with an echocardiogram may suggest conditions such as right ventricular HF, pulmonary hypertension, and valvular heart disease, or raise suspicion for other myocardial or pericardial diseases, requiring further workup. CMR may support the diagnosis of infiltrative or hypertrophic cardiomyopathy, or pericardial disease. Further workup with invasive hemodynamics, and, in some cases, endomyocardial biopsy or other systemic workup may be needed in selected individuals. A detailed discussion of the diagnostic evaluation for infiltrative cardiomyopathies and high-output HF is beyond the scope of this ECDP,[44] but clinical clues and diagnostic testing are summarized in **Table 1**.

Emphasizing the contribution of noncardiovascular entities as well as HFpEF mimics to the presentation of congestion reinforces the importance of establishing the diagnosis to optimize disease-directed therapies.[45] Even when mimics are excluded and a diagnosis of HFpEF is made, extending the diagnostic label of HFpEF to identify associated comorbidities emphasizes the need to address these contributing comorbidities to improve symptoms and outcomes.

**TABLE 1 Diagnostic Clues and Recommended Testing for HFpEF Mimics**

| HFpEF Mimic | Clinical Clues | Diagnostic Testing |
|---|---|---|
| Cardiac amyloidosis | Increased LV wall thickness<br>Musculoskeletal issues (carpal tunnel syndrome, lumbar spinal stenosis)<br>Neuropathy (sensory or autonomic) | Monoclonal protein screen (serum/urine immunofixation electrophoresis and serum free light chains)<br>Technetium pyrophosphate scan (interpreted in the context of a negative monoclonal protein screen)<br>Endomyocardial biopsy if monoclonal protein screen is positive |
| Hypertrophic cardiomyopathy | Unexplained LV hypertrophy<br>LV outflow tract obstruction<br>Family history | CMR if diagnosis is uncertain based on echocardiogram |
| Cardiac sarcoidosis | Extracardiac disease (pulmonary, ocular, dermatologic)<br>High-degree atrioventricular block (especially if age <60 y)<br>Ventricular arrhythmias | CMR<br>FDG-PET scan<br>Tissue biopsy (cardiac or extracardiac) |
| Hemochromatosis | Family history or history of frequent blood transfusions<br>Diabetes<br>Erectile dysfunction | Ferritin and transferrin<br>*HFE* genetic testing<br>CMR with T2* imaging |
| Fabry disease | Angiokeratomas<br>Sensory neuropathy<br>Proteinuria<br>X-linked inheritance | Serum alpha-galactosidase level (in men)<br>*GLA* genetic testing<br>Biopsy of affected tissue |
| High-output HF | Echocardiogram with 4-chamber enlargement and/or increased LV outflow tract VTI | Investigate and treat underlying cause: anemia, arteriovenous malformations, cirrhosis, fistulas, thiamine deficiency |
| Myocarditis | Antecedent viral infection<br>Elevated troponin in the absence of coronary artery disease<br>Heart block and/or ventricular arrhythmias | CMR<br>Endomyocardial biopsy |
| Pericardial disease | Prior cardiac surgery, chest radiation, or pericarditis<br>Right-sided HF symptoms | CMR<br>Right and left heart catheterization to demonstrate discordance in LV/RV pressure tracings during inspiration |

CMR = cardiac magnetic resonance; FDG-PET = fluorodeoxyglucose-positron emission tomography; HF = heart failure; *HFE* = hereditary hemochromatosis gene; HFpEF = heart failure with preserved ejection fraction; LV = left ventricular; RV = right ventricular; VTI = velocity time integral.

## 7. MANAGEMENT OF HFpEF

Management of HFpEF focuses on: 1) risk stratification and management of comorbidities, including hypertension, DM, obesity, AF, CAD, CKD, and obstructive sleep apnea; 2) nonpharmacological management, including the role of exercise and weight loss and the use of wireless, implantable pulmonary artery monitors; and 3) symptom management and disease-modifying therapy with loop diuretic agents, SGLT2is, mineralocorticoid antagonists (MRAs), angiotensin receptor-neprilysin inhibitors (ARNIs), and angiotensin receptor blockers (ARBs).

### 7.1. Guideline-Directed Medical Therapy for HFpEF

Historically, medical therapy for HFpEF resulted in a discouraging array of negative trials with no demonstrated benefit in HFpEF, including trials of perindopril,[46] irbesartan,[47] beta-blockers,[48,49] nitrates,[50] digoxin,[51] ivabradine,[52] sildenafil,[53] and serelaxin.[54] However, recent clinical trials have demonstrated the benefit of GDMT in individuals with HFpEF, and initiation of key agents is essential to improve symptoms and functional capacity and reduce the morbidity and mortality associated with HF (Table 2).[14] Initiation of GDMT is safe and effective in both acute and chronic-care settings.[55-57] Table 3 provides recommended starting and target doses for GDMT for HFpEF. Clinicians should also consider relevant cautions and contraindications when prescribing GDMT, as outlined in Table 4. Figure 9 outlines the approach to GDMT initiation and titration.

Diuretic agents should be used judiciously as needed to reduce congestion and improve symptoms.[14] Of note, beta-blockers may be used in individuals with HFpEF who have specific indications, including prior myocardial infarction (for up to 3 years),[58] angina, or AF, but exercise tolerance should be monitored due to the potential for chronotropic incompetence.[14]

#### 7.1.1. Sodium-Glucose Cotransporter-2 Inhibitors

Originally developed to improve glucose control in individuals with type 2 diabetes mellitus (T2DM), the SGLT2is have demonstrated significant cardiovascular benefits in individuals with and without T2DM. This is particularly evident in individuals with HF, as SGLT2is significantly reduce the risk of hospitalization for HF and cardiovascular death across all EF subgroups.[59] Therefore, SGLT2i should be initiated in all individuals with HFpEF lacking contraindications.

The DELIVER (Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure)[60] and EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction)[61] trials specifically evaluated

**TABLE 2 Selected Randomized Controlled Trials in Individuals With HFpEF**

| | DELIVER[6] | EMPEROR-PRESERVED[7] | TOPCAT*[16] | PARAGON-HF[19] | CHARM-PRESERVED[24] |
|---|---|---|---|---|---|
| Size | N = 6,263 | N = 5,988 | N = 3,445 | N = 4,822 | N = 3,023 |
| Agent | Dapagliflozin | Empagliflozin | Spironolactone | Sacubitril/valsartan | Candesartan |
| Median age, y | 72 | 72 | 69† | 73 | 67 |
| Female sex | 44% | 45% | 52% | 52% | 40% |
| Median follow-up, y | 2.3 | 2.2 | 3.3 | 2.9 | 3.1 |
| EF entry criteria | >40% | >40% | ≥45% | ≥45% | >40% |
| Mean baseline LVEF | 54% | 54% | 56%† | 58% | 54% |
| Proportion with T2DM | 45% | 49% | 33% | 43% | 29% |
| HF medical therapy | | | | | |
| Diuretic agent | 77% | NR | 82% | 95% | 75% |
| ACE inhibitor or ARB | 73% | 81% | 84% | 86% | 19%‡ |
| ARNI | 5% | 2% | N/A | N/A | N/A |
| Beta-blocker | 83% | 86% | 78% | 80% | 56% |
| MRA | 43% | 37% | N/A | 26% | 12% |
| Primary composite outcome, HR or rate ratio (95% CI) | Worsening HF and CV death: HR: 0.82 (0.73-0.92) | Hospitalization for HF and CV death: HR: 0.79 (0.69-0.90) | Hospitalization for HF, aborted cardiac arrest, CV death: HR: 0.89 (0.77-1.04) | Total hospitalizations for HF and CV death: Rate ratio: 0.87 (0.75-1.01) | Hospitalization for HF and CV death: HR: 0.86 (0.74-1.00) |
| Hospitalization for HF, HR or rate ratio (95% CI) | HR: 0.77 (0.67-0.89) | HR: 0.71 (0.60-0.83) | HR: 0.83 (0.69-0.99) | Rate ratio: 0.85 (0.72-1.00) | HR: 0.84 (0.70-1.00) |
| Urgent visit for HF, HR (95% CI) | 0.76 (0.55-1.07) | NR | NR | NR | NR |
| CV death, HR (95% CI) | 0.88 (0.74-1.05) | 0.91 (0.76-1.09) | 0.90 (0.73-1.12) | 0.95 (0.79-1.16) | 0.95 (0.76-1.18) |

All trials were placebo-controlled, except for PARAGON-HF, which compared sacubitril/valsartan to valsartan.
*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), whereas no benefit was observed in the overall population or among those enrolled in Russia/Georgia (HR: 1.10; 95% CI: 0.79-1.51).
†Reported as median.
‡ACE inhibitor use only.

ACE = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid antagonist; N/A = not applicable; NR = not reported; T2DM = type 2 diabetes mellitus.

the effects of dapagliflozin and empagliflozin, respectively, on clinical outcomes in individuals with HF and LVEF ≥40%. A significant decrease in hospitalization for HF was observed in both trials; a meta-analysis also suggests reduction in cardiovascular death with SGLT2is in individuals with HFmrEF/HFpEF (HR: 0.88; 95% CI: 0.77-1.00).[59] Improvements in health status related to use of SGLT2is were also observed in both trials, with the greatest benefit in those with baseline symptomatic impairment.[62] Additional evidence for improvement in health status and quality of life with SGLT2i use in HFpEF was observed in the PRESERVED-HF (Dapagliflozin in PRESERVED Ejection Fraction Heart Failure) trial.[63]

A meta-analysis of clinical trials evaluating SGLT2i in individuals with HF found a consistent reduction in the composite of hospitalization for HF and cardiovascular death in individuals with HFmrEF and HFpEF (HR: 0.80; 95% CI: 0.73-0.87).[59] The observed benefit was also additive to the use of MRAs and ARNIs.[64] Importantly, the use of empagliflozin was associated with reduced discontinuation of MRAs, possibly due to less risk for hyperkalemia.[65] No unexpected safety events were identified in either the EMPEROR-Preserved or DELIVER trials.

Given that in-hospital initiation of HF GDMT is associated with greater long-term adherence and prescription persistence, it is reassuring to note that the use of SGLT2is appears to be safe and effective when initiated in the context of hospitalization for acutely decompensated HF,

**TABLE 3 Starting and Target Doses of Select GDMTs for HFpEF**

| Drug Class | Starting Dose | Target Dose |
|---|---|---|
| SGLT2is | | |
| Dapagliflozin | 10 mg daily | 10 mg daily |
| Empagliflozin | 10 mg daily | 10 mg daily |
| Aldosterone antagonists | | |
| Spironolactone | 25 mg daily | 50 mg daily |
| ARNIs | | |
| Sacubitril/valsartan | 24 mg/26 mg twice daily | 97 mg/103 mg twice daily |
| ARBs | | |
| Candesartan | 4 mg to 8 mg daily | 32 mg daily |

ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; GDMT = guideline-directed medical therapy; HFpEF = heart failure with preserved ejection fraction; SGLT2 = sodium-glucose cotransporter-2.

**TABLE 4 Contraindications and Cautions for SGLT2i, MRAs, ARNIs, and ARBs**

| Drug Class | Contraindications | Cautions |
|---|---|---|
| SGLT2i | Type 1 diabetes mellitus (limitation to use)<br>Lactation<br>On dialysis<br>Known hypersensitivity | Kidney impairment:<br>For dapagliflozin, eGFR <25 mL/min/1.73 $m^2$<br>For empagliflozin, eGFR <20 mL/min/1.73 $m^2$<br>Pregnancy<br>Increased risk of mycotic genital infections<br>May contribute to volume depletion or hypotension<br>Ketoacidosis (including euglycemic) in individuals with poorly controlled diabetes, dehydration, or fasting<br>Acute kidney injury<br>Necrotizing fasciitis of the perineum (Fournier's gangrene) is rare but can be serious and life-threatening |
| MRA | Potassium ≥5.0 mmol/L<br>Addison disease<br>Pregnancy<br>Known hypersensitivity | Kidney impairment:<br>Avoid if eGFR <30 mL/min/1.73 $m^2$ or serum creatinine ≥2.5 mg/dL<br>Initiate at half dose if eGFR 30 to 50 mL/min/1.73 $m^2$<br>Concomitant use with drugs and supplements that increase serum potassium, such as:<br>Potassium supplementation<br>ACE inhibitors, ARBs, or ARNIs<br>NSAIDs<br>Trimethoprim<br>Gynecomastia (consider use of eplerenone)<br>Lactation |
| ARNI | Coadministration within 36 h of ACE inhibitor use<br>History of any angioedema<br>Pregnancy/lactation<br>Severe (Child-Pugh C) hepatic impairment<br>Known hypersensitivity<br>Use of aliskiren in individuals with diabetes mellitus | Reduce the starting dose to half the usually recommended starting dose if:<br>Not currently taking an ACE inhibitor or ARB or taking a low dose of an ACE inhibitor or ARB<br>Moderate (Child-Pugh B) hepatic impairment<br>Renal artery stenosis<br>Hypotension |
| ARB | Pregnancy/lactation<br>Avoid concomitant use with an ACE inhibitor, aliskiren, or ARNI<br>Known hypersensitivity<br>Renal artery stenosis | History of any angioedema<br>Hyperkalemia<br>Hypotension<br>Acute kidney injury |

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; eGFR = estimated glomerular filtration rate; MRA = mineralocorticoid antagonists; NSAIDs = nonsteroidal anti-inflammatory drugs; SGLT2i = sodium-glucose cotransporter-2 inhibitor.

once clinically stable. The SOLOIST-WHF (Effect of Sotagliflozin on Cardiovascular Events in Participants With Type 2 Diabetes Post Worsening Heart Failure)[57] trial enrolled recently hospitalized individuals with T2DM across the spectrum of LVEF, enrolled before or shortly after discharge, and found that sotagliflozin (an inhibitor of both SGLT1 and SGLT2; not currently Food and Drug Administration [FDA]-approved) resulted in a significantly lower total number of deaths from cardiovascular causes and hospitalizations and urgent visits for HF than placebo, regardless of LVEF (21% of the study population had an LVEF ≥50%). More recently, the EMPULSE (Empagliflozin in Patients Hospitalized With Acute Heart Failure Who Have Been Stabilized) trial[66] evaluated the effect of empagliflozin vs placebo in hospitalized individuals with acutely decompensated HF; approximately 32% had an LVEF >40%. In EMPULSE, treatment with empagliflozin was well-tolerated, led to more rapid and thorough decongestion,[67] and was associated with significant improvement in a secondary composite endpoint including clinical outcome (death, HF events) and health status.[68] The benefit on total HF hospitalizations was similar in patients with EFs of >40% to <50% and 50% to <60%.[69]

### 7.1.2. Mineralocorticoid Antagonists

MRAs significantly improve measures of diastolic function in individuals with HFpEF.[70,71] Spironolactone may reduce the risk of hospitalizations for HF in specific subsets of individuals with HFpEF; however, appropriate monitoring of potassium and kidney function are warranted to reduce the risk of hyperkalemia and worsening kidney function.[71]

The TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) trial[71] enrolled 3,445 individuals with HF and LVEF ≥45% and randomized to spironolactone (15-45 mg daily) or placebo. The initially published results did not show a significant benefit in the primary composite outcome of cardiovascular death, aborted cardiac arrest, or hospitalization for HF (HR: 0.89; 95% CI: 0.77-1.04), although there was a significant reduction in the individual component of hospitalization for HF (HR: 0.83; 95% CI: 0.69-0.99). Large regional variations in event rates between those enrolled in North America compared with Russia/Georgia led to the suspicion of regional differences in the application of study criteria and trial implementation.

A subsequent subgroup analysis of TOPCAT found a significant reduction in the primary composite outcome

with spironolactone in participants enrolled in North America (HR: 0.82; 95% CI: 0.69-0.98), whereas no benefit was observed among those enrolled in Russia/Georgia (HR: 1.10; 95% CI: 0.79-1.51).[72] This observation was further substantiated by evidence demonstrating that levels of canrenone, an active metabolite of spironolactone, were undetectable in a larger proportion of participants from Russia than the United States and Canada (30% vs 3%, respectively; $P < 0.001$), confirming that reported and actual use of spironolactone varied significantly by region.[73] Notably, within the TOPCAT trial, the benefit of spironolactone was most evident in patients within the lower tertile of natriuretic peptide levels, corresponding to a B-type natriuretic peptide <166 pg/mL and an N-terminal pro-B-type natriuretic peptide (NT-proBNP) level <682 pg/mL,[74] among those with an LVEF <60%[75] and in women,[76] where reductions in events were similar across all LVEF strata.

Although MRAs have not been shown to improve quality of life or exercise tolerance in individuals with HFpEF,[70] most individuals with HFpEF will still benefit from MRAs to provide balanced diuresis with sequential nephron blockade, control hypertension, and reduce HF hospitalizations.

#### 7.1.3. Angiotensin Receptor–Neprilysin Inhibitors

Sacubitril inhibits neprilysin, an enzyme that inactivates several important vasoactive peptides that contribute to the pathogenesis and progression of HF, including natriuretic peptides, bradykinin, and substance P. Combination with valsartan is necessary because neprilysin inhibition increases angiotensin levels, which could offset the vasodilatory effect of sacubitril unless also inhibited. Sacubitril/valsartan provides modest additional benefit compared with valsartan in individuals with HFpEF. Although serum creatinine elevations and hyperkalemia occur less frequently with ARNI therapy, hypotension and angioedema, albeit rare, occur more frequently with ARNIs.[77]

The role of an ARNI 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,[19] which enrolled 4,822 study participants with LVEF ≥45%, elevated natriuretic peptides, and evidence of structural heart disease, and randomized them to sacubitril/valsartan (target dose of 97/103 mg twice daily) or valsartan (target dose of 160 mg twice daily). The primary composite endpoint of total hospitalizations for HF and cardiovascular death was numerically lower with sacubitril/valsartan but was not statistically significant (HR: 0.87; 95% CI: 0.75-1.01). Recently hospitalized study participants showed substantially greater reduction in risk from treatment with an ARNI compared with valsartan.[78] Analysis of prespecified subgroups of EF and sex were also performed due to the observed baseline heterogeneity in these groups. A potential benefit was observed in those with LVEF between 45% and 57% (HR: 0.78; 95% CI: 0.64-0.95). There was a greater benefit in women (HR: 0.73; 95% CI: 0.59-0.90) compared with men (HR: 1.03; 95% CI: 0.84-1.25).[79] Based on these data, the FDA granted sacubitril/valsartan an expanded HF indication in February 2021, "to reduce the risk of cardiovascular death and hospitalization for HF in adult patients with chronic HF," and noted that the "benefits are most clearly evident in patients with LVEF below normal."[80]

#### 7.1.4. Angiotensin Receptor Blockers

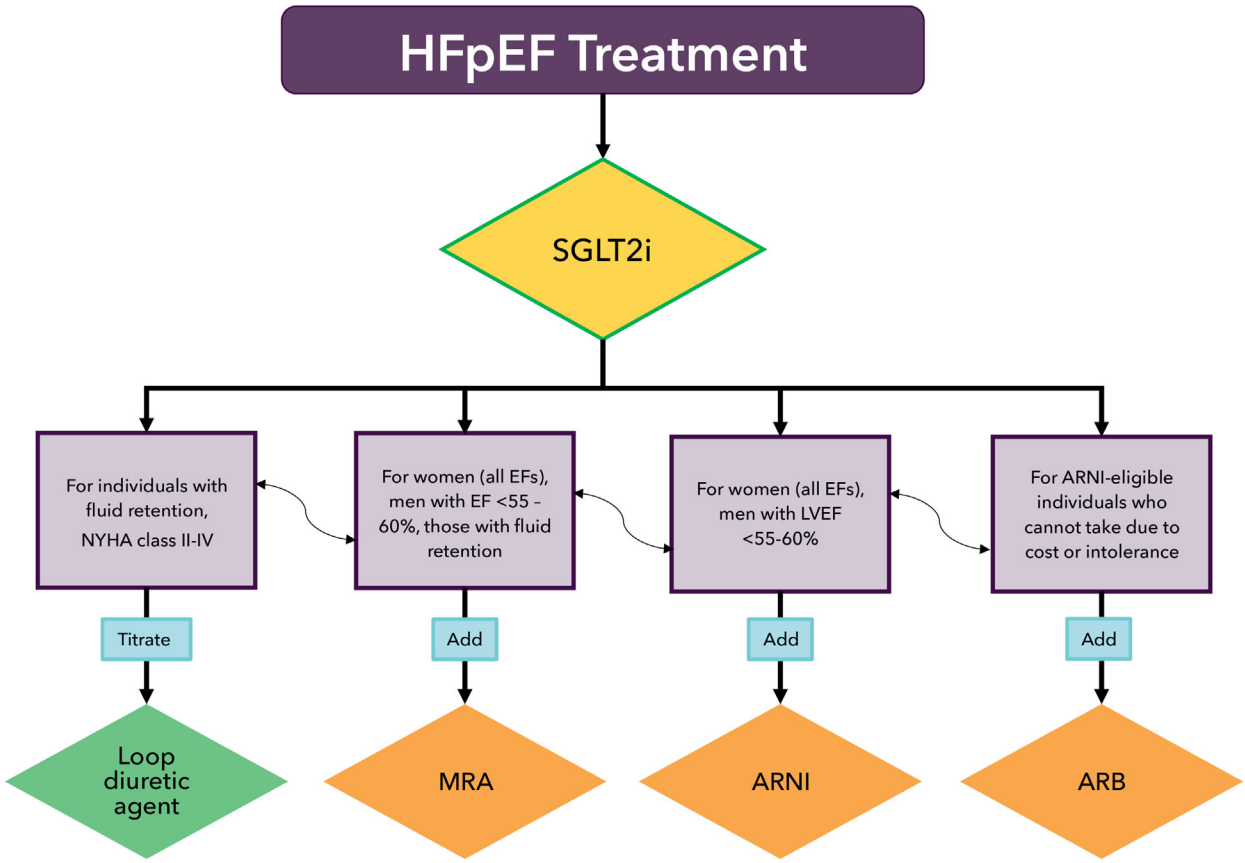
Although an ARNI is likely more effective than an ARB, an ARB may be used when an ARNI is contraindicated (eg, history of angioedema) or lack of affordability impedes access. Angiotensin-converting enzyme (ACE) inhibitors are not considered a reasonable alternative due to lack of benefit with perindopril in the PEP-CHF (Perindopril in Elderly People with Chronic Heart Failure) trial, which enrolled 850 older adults (aged ≥70 years) and LVEF >40%.[46]

The CHARM (Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity)-Preserved trial[81] randomized 3,023 study participants with LVEF ≥40% to candesartan (target dose of 32 mg daily) or placebo, and although the primary composite of hospitalization for HF and cardiovascular death was borderline significant (adjusted HR: 0.86; 95% CI: 0.74-1.00), there was a moderate reduction in the individual component of hospitalizations for HF (adjusted HR: 0.84; 95% CI: 0.70-1.00). The I-PRESERVE (Irbesartan in Heart Failure with Preserved Systolic Function) trial[47] enrolled 4,128 study participants aged ≥60 years with an LVEF ≥45% and randomized them to either irbesartan (target dose of 300 mg daily) or placebo. Irbesartan treatment did not reduce the primary composite outcome of death from any cause or any cardiovascular hospitalization (HR: 0.95; 95% CI: 0.86-1.05), and no benefit was observed with the individual components of the primary outcome or secondary outcomes. 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 ACE inhibitors (40%) may have blunted any potential additional benefit with the addition of irbesartan.

#### 7.1.5. Sex-Specific Differences in HFpEF GDMT

Important differences between response to therapies for HFpEF exist between women and men. Thus, although the use of SGLT2 inhibitors is an expected component of treatment for both sexes, barring contraindication, the use of sacubitril/valsartan[79] as well as spironolactone[76] should be considered across the entire LVEF spectrum

**FIGURE 9 Treatment Algorithm for Guideline-Directed Medical Therapy in HFpEF***




*Green color identifies a Class 1 therapy from clinical practice guidelines,[14] yellow color indicates a Class 2a therapy, and orange color denotes a Class 2b therapy. SGLT2is receive a Class 2a indication in the 2022 AHA/ACC/HFSA HF Guidelines,[14] but the benefit, now confirmed in 2 randomized trials,[60,61] suggests that SGLT2is may receive a stronger class of recommendation in future guidelines, and thus the box is shaded yellow with a green border. 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; MRA = mineralocorticoid antagonist; NYHA = New York Heart Association; SGLT2i = sodium-glucose cotransporter 2 inhibitor.

for women with HFpEF. The reason why women with HFpEF may respond more favorably to these therapies at a relatively higher EF may be because women tend to have smaller LV chamber size and are thus more prone to demonstrate higher LVEFs when compared with men.[82] Although simplistic, this means an LVEF of 50% to 55% in a woman may be abnormally low compared with a man, and identifies potential differential response to therapies with effects on the neurohormonal system.

### 7.1.6. Approach to GDMT Initiation and Titration

Barring contraindication, all individuals with a diagnosis of HFpEF should be treated with an SGLT2i, with the goal of reducing cardiovascular death/HF hospitalization and improving health status. Initiation of an SGLT2i may be considered for either ambulatory individuals with HFpEF or those with acutely decompensated HF. In those with an LVEF <55% to 60%, use of an MRA, ARNI, or ARB (when an ARNI is not feasible based on the strength of evidence and more contemporary evidence of ARNI vs ARB as described earlier) may be considered (**Figure 9**).

ARNIs and MRAs should be titrated to the maximum tolerated dosages based on symptoms, blood pressure, potassium, and creatinine, as confirmed in the STRONG-HF (Safety, Tolerability, and Efficacy of Up-Titration of Guideline-Directed Medical Therapies for Acute Heart Failure) trial.[83] This trial randomized individuals hospitalized with HF, regardless of LVEF, to usual care or high-intensity care, consisting of initiation of GDMT at one-half of the target dosages before hospital discharge with the goal of titration to target dosages over the next 2 weeks, with frequent follow-up visits over the 2 months

**TABLE 5 Nonpharmacological Interventions in HFpEF**

| Study | Sample Size (HFpEF only) | Intervention | Outcome |
|---|---|---|---|
| **WEIGHT LOSS AND/OR EXERCISE TRAINING** | | | |
| Edelmann et al[84] | 64 | 3 months of endurance/resistance training | ■ Peak $V_{O_2}$ increased by 3.3 mL/kg/min<br>■ Improved quality of life<br>■ Improvement in E/e' and left atrial volume index |
| Mueller et al[85] | 176 | 12 weeks of high-intensity interval training and moderate continuous training | ■ Improved peak $V_{O_2}$ at 3 months |
| Kitzman et al[86] | 63 | 16 weeks of exercise training | ■ Peak $V_{O_2}$ increased by 2 mL/kg/min<br>■ Improved quality of life |
| Kitzman et al[87] | 100 | 20 weeks of caloric restriction, aerobic exercise, or both | Increase in peak $V_{O_2}$ by:<br>■ Exercise: 1.2 mL/kg/min<br>■ Diet: 1.3 mL/kg/min<br>■ Both (additive): 2.5 mL/kg/min |
| Brubaker et al[88] | 88 | 20 weeks of (caloric restriction and aerobic exercise) ± resistance training | Addition of resistance training to caloric restriction and aerobic exercise<br>■ increase in leg strength and muscle quality<br>■ no additive increase in peak $V_{O_2}$ or QOL |
| Mikhalkova et al[89] | 12 (all women) | Gastric bypass | ■ Improvement in Minnesota Living with Heart Failure score<br>■ Improved diastolic relaxation on echocardiogram |
| **DEVICE THERAPIES** | | | |
| Adamson et al[90,91] | 119 | Implantable pulmonary artery monitor | 50% reduction in HF hospitalization with mean follow-up of 17.6 months |
| Lindenfeld et al[92] | 795 | Implantable pulmonary artery monitor | No reduction in all-cause mortality, HF hospitalizations, and urgent HF visits. |

HF = heart failure; HFpEF = heart failure with preserved ejection fraction; $V_{O_2}$ = oxygen consumption

following discharge. Study participants in the high-intensity group were more likely to achieve target dosages of GDMT, had greater improvement in health status and larger reduction in natriuretic peptide concentrations, and experienced significant improvement in the composite endpoint of HF readmission or death at 180 days (15% in the high-intensity group vs 23% in the usual-care group). The STRONG-HF trial is key evidence of the importance of GDMT initiation and titration in individuals with HF.

## 7.2. Other Nonpharmacological Management

Other nonpharmacological management of HFpEF includes strategies to target the pathophysiology and contributing comorbidities, such as exercise and weight loss, as well as strategies to guide and titrate pharmacological therapies with pulmonary artery pressure sensor monitoring (**Table 5**).

### 7.2.1. Exercise and Calorie Restriction

Ideally, HFpEF-directed therapy would reduce symptoms of HF, the risk of hospitalization, and mortality. Exercise intolerance is a key symptom of HFpEF; thus, improvement in functional capacity is an important goal. To address this, current clinical practice guidelines recommend optimal management of volume status and treatment of relevant comorbidities[14] (outlined in detail in Section 7.3).

In particular, physical inactivity and obesity are strongly linked with worse health status and poorer prognosis in HFpEF.[93-96] To further support this association, studies have suggested a beneficial effect of weight loss (either due to caloric restriction or bariatric surgery) on incident HF events and exercise tolerance.[97,98] The role of weight loss interventions is discussed in detail in Section 7.3.2. It is essential to adhere to the recommendations of the 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease, including comprehensive lifestyle intervention consisting of a structured program, which includes regular self-monitoring of food intake, physical activity, and weight. Increased physical activity, preferably aerobic physical activity (eg, brisk walking) for ≥150 minutes/week (equal to ≥30 minutes/day on most days of the week), is recommended for initial weight loss.[98a]

Regarding exercise intervention, in a randomized trial of 100 older individuals with obesity and HFpEF, peak oxygen consumption was increased by 1.2 mL/kg/min in individuals randomized to aerobic exercise 3 times per week and/or caloric restriction of 400 kilocalories daily.[87] The addition of resistance training to aerobic exercise and caloric restriction improved leg muscle strength,[88] an important benefit in older individuals with HFpEF. Taken together, these data suggest that exercise may be beneficial in individuals with HFpEF who have obesity, specifically in improving functional status.[99] Although the

benefit of improved exercise capacity has quality-of-life implications and addresses comorbidities in HFpEF, large-scale randomized data are needed to verify and extend their impact on prognosis.

Enrollment in cardiac rehabilitation programs or structured exercise therapy could improve the quality of life and functional capacity of individuals with HFpEF, especially those with prior hospitalization.[100,101] It is unfortunate that insurance coverage for cardiac rehabilitation or structured exercise therapy is not available for individuals with HFpEF in the United States, especially because structured exercise is more effective than passive guidance in improving functional capacity in individuals with HFpEF.[85] Lack of reimbursement for cardiac rehabilitation in those with HFpEF results in a significant gap in care for this vulnerable population.[102,102a]

#### 7.2.2. Pulmonary Artery Pressure Monitoring

As volume management is a key therapeutic strategy in HFpEF,[48] devices have been developed to monitor filling pressures and guide diuretic agent management. The role of one implantable pulmonary artery sensor, CardioMEMS (Abbott, Abbott Mark, Illinois) was evaluated in the CHAMPION (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients) trial. In the CHAMPION trial, care guided by the CardioMEMS device significantly reduced HF hospitalizations,[90] including in a prespecified subgroup of study participants with LVEF ≥40%.[91] Remote hemodynamic monitoring was also associated with a reduction in HF hospitalizations in a postapproval study.[103]

One concern of the CHAMPION-HF trial was that it was nonblinded, with differential contact of study personnel with individuals in the treatment arm, raising methodological concerns about the opportunity for bias to have influenced its results. The subsequent GUIDE-HF (Hemodynamic-GUIDed manage of Heart Failure) trial was blinded and enrolled individuals with symptomatic HF and either a previous hospitalization or elevated natriuretic peptides; 31% had an LVEF of 50% or higher.[92] However, unlike CHAMPION-HF, hemodynamic-guided management of HF in GUIDE-HF did not result in a lower composite endpoint rate of mortality 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, there was a nearly 20% reduction 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.[104]

In the 2022 AHA/ACC/HFSA HF guidelines, PA-sensor monitoring has a Class 2b recommendation for remote PA monitoring.[14] This level of endorsement is based on the differential outcomes of CHAMPION-HF and GUIDE-HF and the methodological concerns of CHAMPION-HF, as outlined earlier.

Nonetheless, because implantable hemodynamic monitoring has been associated with a reduction in HF hospitalizations (a primary goal of HFpEF therapy), this therapy 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 GDMT; 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 the CardioMEMS device should be performed in a center with the ability to regularly monitor remotely transmitted data.

Other device interventions for HFpEF such as blood volume analysis, interatrial shunting devices, splanchnic nerve ablation, or cardiac contractility modulation are under evaluation; their benefits remain ambiguous.[105-107] Such procedures should be considered only within the context of clinical trials.

### 7.3. Management of Comorbidities

As outlined in detail in later discussion, there is a complex interplay between comorbidities, which influences the genesis of HFpEF and outcomes of individuals with HFpEF (**Figure 10**).

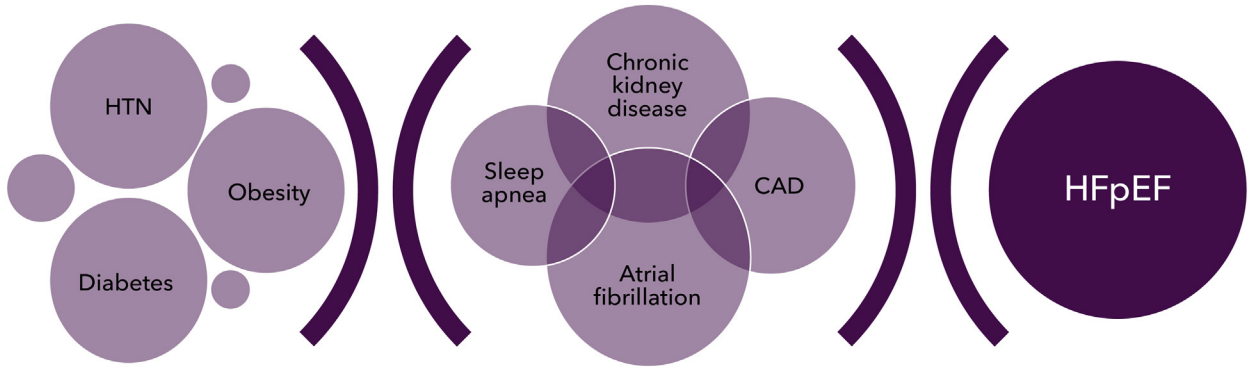
Appropriate management of HFpEF-associated comorbidities is extrapolated from relevant guidelines. A summary of the detailed guidance discussed later is provided in **Figure 11** and **Table 6**.

#### 7.3.1. Hypertension

The role of blood pressure control is well established for the prevention of HF, and for reduction of other cardiovascular events and mortality in individuals without HF.[116-121] Hypertension is the most important identified cause of HFpEF, with a prevalence of 60% to 89% in the HFpEF population.[25,108,122] Furthermore, cardiac structural and functional abnormalities with hypertension, such as LV hypertrophy and diastolic dysfunction, form the substrate for HFpEF most commonly seen in older adults, especially women. Although blood pressure-lowering has not been associated with improved outcomes in trials of individuals with HFpEF,[123-125] uncontrolled blood pressure may precipitate acute HF decompensation, and individuals with HFpEF can have an exaggerated hypertensive response to exercise.[126,127]

The 2017 ACC/AHA guideline for the management of hypertension offers a Class 1 recommendation that adults with HFpEF should have blood pressure medications

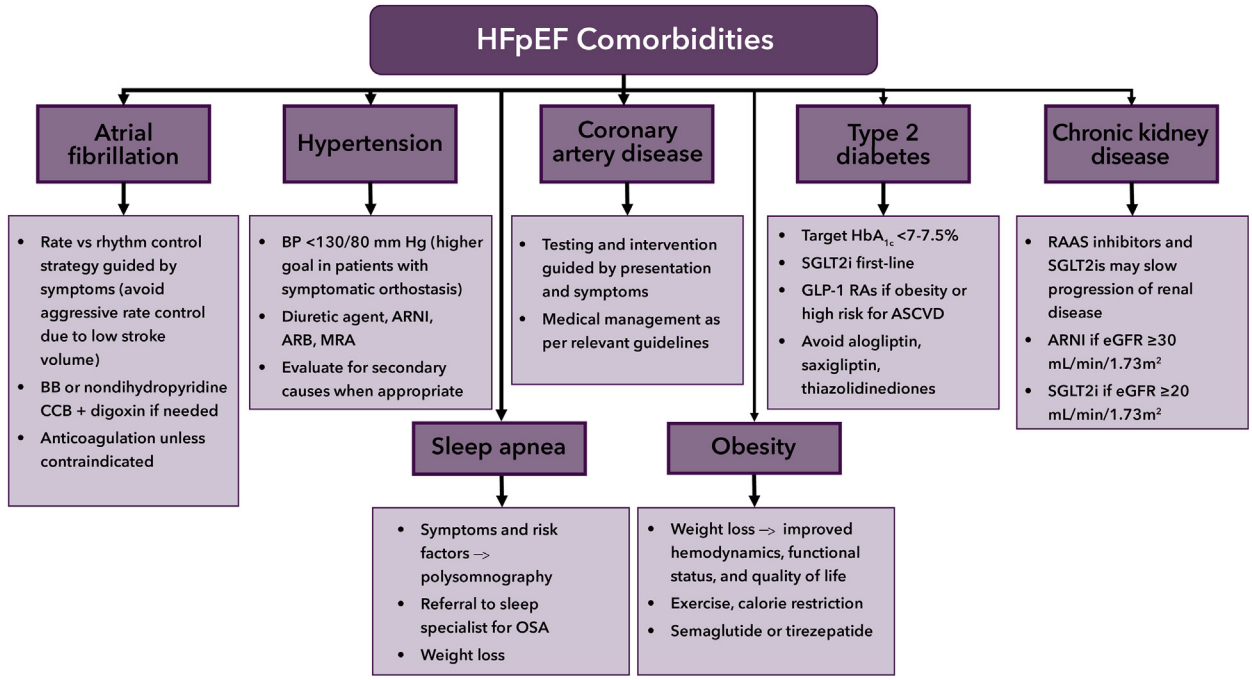
**FIGURE 10 Interplay of HFpEF Comorbidities***




*Hypertension, diabetes mellitus, and obesity can result in coronary artery disease, atrial fibrillation, sleep apnea, and chronic kidney disease. Chronic kidney disease and sleep apnea can, in turn, worsen hypertension. These factors all influence the pathogenesis and outcomes of individuals with HFpEF. CAD = coronary artery disease; HFpEF = heart failure with preserved ejection fraction; HTN = hypertension.

titrated to attain a systolic blood pressure <130 mm Hg.[108] This target blood pressure for HFpEF is extrapolated from benefits noted for the treatment of hypertension in general, because more intensive blood pressure control is associated with a significant reduction in cardiovascular endpoints in individuals at high risk for cardiovascular disease.[108,119,128,129] In SPRINT (Systolic Blood Pressure Intervention Trial), which

**FIGURE 11 Management of Comorbidities Associated With HFpEF**




ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; ASCVD = atherosclerotic cardiovascular disease; BB = beta-blocker; BP = blood pressure; CCB = calcium-channel blocker; CPAP = continuous positive airway pressure; eGFR = estimated glomerular filtration rate; GLP1-RA = glucagon-like peptide-1 receptor agonist; $HbA_{1c}$ = glycosylated hemoglobin; MRA = mineralocorticoid antagonist; OSA = obstructive sleep apnea; RAS = renin-angiotensin system; SGLT2i = sodium-glucose cotransporter 2 inhibitor.

**TABLE 6 Selected Comorbidities in Individuals With HFpEF**

| Comorbidity | Association With HF Outcomes | Clinical Trial Evidence for Modulating Comorbidity | Suggestions/Actions |
|---|---|---|---|
| Hypertension | Inverse for mortality. Strong for HF hospitalization. | Strong for prevention | ■ Treat as per the current ACC/AHA guidelines for the prevention, detection, evaluation, and management of high blood pressure in adults[108]<br>■ Target systolic BP <130 mm Hg, unless evidence for symptomatic orthostasis, labile blood pressure, or observed impact on kidney dysfunction. |
| Obesity | Inverse or U-shaped for mortality | Moderate | ■ Calorie restriction and aerobic exercise to improve functional status and quality of life<br>■ Consideration for treatment for obesity, including drug or bariatric surgical therapy and/or referral to an obesity specialist. |
| Diabetes mellitus | Strong | Medication dependent | ■ Treat according to ACC ECDP on novel therapies for CV risk reduction in patients with T2DM[109] and current ADA standards of medical care in diabetes[110]<br>■ SGLT2is as first-line therapy for T2DM<br>■ GLP1-RAs are an option in individuals with high cardiovascular risk and/or obesity<br>■ Finerenone in diabetic kidney disease<br>■ Metformin is a safe, affordable additional agent<br>■ Avoid thiazolidinediones, saxagliptin, alogliptin<br>■ Collaborative care with endocrinologist |
| Atrial fibrillation/flutter | Strong | Moderate | ■ Treat as per the current AHA/ACC/HRS guideline for the management of patients with AF[111] |
| CAD | Moderate | Weak | ■ Evaluate for CAD if suggestive symptoms and revascularization candidate<br>■ Treat as per the current ACC/AHA/SCAI guideline for coronary artery revascularization,[112] and the ACC/AHA/ASE/CHEST/SAEM/SCCT/SCMR guideline for the evaluation and diagnosis of chest pain[113] |
| Sleep-disordered breathing | Moderate for HF hospitalization | None | ■ Testing for sleep apnea if high suspicion<br>■ Referral to sleep specialist<br>■ Treat OSA for improvement in daytime sleepiness, improved sleep quality, and quality of life<br>■ Treatment of severe nocturnal hypoxemia<br>■ Treat OSA in individuals with drug-resistant hypertension (3 or more drugs) and consider in individuals with AF managed with rhythm control strategies |
| Chronic kidney disease | Strong | Moderate | ■ Treat as per current KDIGO clinical practice guidelines for the evaluation and management of chronic kidney disease,[114] and the KDIGO clinical practice guideline for diabetes management in chronic kidney disease[115]<br>■ Optimize RAAS inhibitors in individuals with proteinuria and with diabetic kidney disease<br>■ SGLT2is<br>■ Collaborative care with nephrology specialist, especially for moderate and severe chronic kidney disease |

ACC = American College of Cardiology; ADA = American Diabetes Association; AF = atrial fibrillation; AHA = American Heart Association; ASE = American Society of Echocardiography; BP = blood pressure; CAD = coronary artery disease; CHEST = American College of Chest Physicians; CV = cardiovascular; ECDP = expert consensus decision pathway; GLP1-RA = glucagon-like peptide 1 receptor agonists; HF = heart failure; HRS = Heart Rhythm Society; OSA = obstructive sleep apnea; RAAS = renin-angiotensin-aldosterone system; SAEM = Society for Academic Emergency Medicine; SCAI = Society for Cardiovascular Angiography and Interventions; SCCT = Society of Cardiovascular Computed Tomography; SCMR = Society for Cardiovascular Magnetic Resonance; SGLT2i = sodium-glucose cotransporter 2 inhibitor; T2DM = type 2 diabetes.

studied participants with hypertension without HF, a more intensive blood pressure intervention targeting a systolic blood pressure <120 mm Hg significantly reduced the incidence of HF, a component of the primary outcome, by 38%.[129,130]

Most individuals with hypertension will require 2 or more antihypertensive agents to control the blood pressure and an investigation of secondary causes of hypertension may be indicated in some individuals with refractory hypertension despite 4 agents, including a diuretic agent. The choice of antihypertensive therapy may be guided by tolerability, cost, comorbidities, and society recommendations. Beta-blockers should generally be avoided given the negative chronotropic effects that may reduce tolerability in HFpEF. Many combination antihypertensive medications are available as affordable generic formulations and may improve adherence in individuals with HFpEF who are at risk for polypharmacy and associated poor outcomes.[131]

For individuals with HFpEF and hypertension, preferred agents would include diuretic agents because they are often required for volume control. Additional agents can be based on the modest benefit in cardiovascular outcomes noted in clinical trials of individuals with HFpEF, including ARNIs, ARBs, and MRAs (as outlined in Section 7.1).[46,71,72,77,81]

### 7.3.2. Obesity

Obesity is one of the strongest risk factors for incident HFpEF, because up to 80% of individuals with HFpEF are either overweight or have obesity.[29,132,133] Multiple pathophysiological links exist between obesity and HFpEF, both through coexisting comorbidities such as DM, CKD, and hypertension, and through independent factors related to obesity itself. Increased adiposity promotes hypertension, insulin resistance, dyslipidemia, sleep apnea, and inflammation, and impairs diastolic, systolic, arterial, skeletal muscle, and exercise tolerance.[133]

Compared with individuals without obesity, those with obesity and HFpEF have an increased plasma volume, concentric LV remodeling, right ventricular dilatation, and right ventricular dysfunction. They also have greater epicardial fat thickness and total epicardial heart volume, resulting in hemodynamic findings consistent with greater pericardial restraint and heightened ventricular interdependence.[30] In individuals with obesity and HFpEF, the magnitude of pulmonary capillary wedge pressure elevation is directly related to the amount of excess body mass.[30] During exercise stress, individuals with obesity and HFpEF demonstrate lower exercise capacity, higher LV and right ventricular filling pressures, and lower pulmonary artery vasodilator reserve.

Increasing severity of obesity is associated with an increased risk for HF hospitalization,[134,135] although the obesity paradox of improved survival in those with elevated BMI has been observed to some extent in HFpEF as in HFrEF.[134,136] In HFpEF, there is a U-shaped relationship between BMI and all-cause mortality, with the lowest event rate at a BMI of 32 to 34 kg/m$^2$. Although the paradox is often ascribed to unintentional weight loss in individuals with advanced HF or concomitant cancer, other factors also likely contribute, including collider bias and lead-time bias.[137] For example, individuals with obesity manifest HF symptoms earlier in the course of the disease process. In addition, those with obesity-related HFpEF develop HF at a younger age, when they are less frail, and may have seemingly better outcomes than older and more frail individuals with similar severity of HF.[138] Finally, the survival benefit of obesity is attenuated or absent in individuals with better cardiorespiratory fitness[139] or when waist or hip circumference is used instead of BMI.[140]

It is important to emphasize that weight loss is beneficial in individuals with obesity.[141] In individuals with obesity without overt HF, substantial weight loss has been associated with significant reductions in heart rate, mean arterial pressure, resting oxygen consumption, pulmonary capillary wedge pressure, and mean pulmonary artery pressure, and in a subset with exercise hemodynamics, there was a reduction in exercise pulmonary artery pressure.[142]

Recently, there has been renewed interest in the use of pharmacological agents to augment weight loss. In the STEP-1 (Semaglutide Treatment Effect in People with Obesity 1) trial, the addition of the GLP-1 receptor agonist semaglutide to lifestyle intervention resulted in a sustained weight loss of over 15 kg over a 68-week period.[143] In the SURMOUNT-1 (Efficacy and Safety of Tirzepatide Once Weekly in Participants Without Type 2 Diabetes Who Have Obesity or Are Overweight With Weight-Related Comorbidities) trial, the use of the novel GLP-1 receptor agonist and glucose-dependent insulinotropic polypeptide tirzepatide demonstrated up to 20% reduction in weight loss sustained over the 72-week trial.[144]

However, there are caveats to these encouraging findings. Semaglutide and tirzepatide have not yet been rigorously evaluated in individuals with HF. This is important, because GLP-1 receptor agonists may result in loss of not only adipose weight but also lean muscle mass. To the extent that sarcopenia is a concern in individuals with HF, the implication of reduced muscle mass in HF requires further information; the ongoing SUMMIT (NCT04847557) and STEP-HFpEF (NCT04788511) randomized controlled trials may provide important insight into the potential benefit and safety of pharmacological weight loss in HFpEF.

To improve symptoms and alleviate shared obesity-associated comorbidities with HFpEF, those with BMIs ≥35 kg/m$^2$ would benefit from referral to a multidisciplinary team of medical, surgical, and nutritional experts in obesity, when available.[145]

#### 7.3.3. Diabetes

Diabetes mellitus (DM) and HF often coexist, and each disease independently increases the risk for the other.[146] The prevalence of DM in individuals with HFpEF varies from 28% to over 40%.[147-149] Individuals with HFpEF and DM tend to be younger than those without DM, with higher BMIs, greater volume overload, worse functional capacity and quality of life, and more hypertension, vascular disease, and CKD.[149] Furthermore, the presence of DM is associated with an increased risk of hospitalization and mortality, reported as a 70% to 100% increased relative risk of cardiovascular death or HF hospitalization and a 48% to 84% increased relative risk of all-cause mortality.[146,149] In addition, CKD and DM both tend to occur together in those with HFpEF, with the presence of both further increasing the risk of adverse cardiovascular outcomes.[150] The treatment principles for DM in individuals with HFpEF are based on the 2023 American Diabetes Association Standards of Medical Care in DM.[130,151-153]

Apart from the risk reduction in microvascular outcomes and a modest reduction in risk of nonfatal myocardial infarction, intensive vs standard glucose control in individuals with established T2DM has not demonstrated additional cardiovascular benefits.[154,155] As recommended by the American Diabetes Association, and as reviewed by the 2019 AHA/HFSA statement on diabetes in HF, the targets of control for T2DM are usually based on the comorbidity burden, polypharmacy, cognitive impairment, hypoglycemic episodes, and overall prognosis. A glycosylated hemoglobin ($HbA_{1c}$) goal of <7% to 7.5% is recommended in individuals with a lower comorbidity burden or lesser severity of HF, with higher targets of $HbA_{1c}$ <8% to 8.5% acceptable in those who are

older with higher comorbidity burden, polypharmacy, risk of hypoglycemia, or advanced HF.[146,156]

Given the recently demonstrated benefit of SGLT2is in improving outcomes in those with HFpEF (including HF hospitalizations and cardiovascular mortality), in addition to improving functional status and quality of life regardless of the presence of T2DM,[59-61,69,157] these agents should be first-line therapy for individuals with HFpEF andT2DM and add-on or alternate therapy in those already on other agents.[151,152] Furthermore, the use of other oral hypoglycemic agents should not obviate initiation of an SGLT2i. Clinicians should consider stopping or adjusting the dose of other hypoglycemic agents in order to accommodate an SGLT2i, given these beneficial effects in HFpEF.

Regardless of the benefits noted with SGLT2is, metformin is recommended as first-line therapy for glycemic control in individuals with T2DM and HF, including HFpEF, with estimated glomerular filtration rates (eGFRs) ≥30 mL/min/1.73 $m^2$. This is based on the demonstrated experience with long-term use; its safety, low cost, and low side effect profile; as well as observational (not clinical trial) data suggesting a 20% relative risk reduction in mortality in individuals with HF, including HFpEF.[158,159]

In cardiovascular outcome trials of glucagon like receptor-1 agonists (GLP-1RAs), which included 10% to 23% of individuals with HF in the study population, these agents demonstrated benefit on atherosclerotic cardiovascular outcomes, with a more modest benefit on HF hospitalizations.[160,161] Given the substantial weight loss observed with the GLP1-RA semaglutide[143] and with the GLP-1RA and gastrointestinal peptide antagonist tirezepatide,[144] these agents are potentially attractive options for individuals with T2DM and obesity. Furthermore, given the benefit of the GLP-1RA class on atherosclerotic cardiovascular disease (ASCVD) risk, these drugs should be considered in individuals with HFpEF with coexisting T2DM and high risk for ASCVD or with pre-existing ASCVD.[109]

*Drugs to be avoided in individuals with DM and HFpEF*: Compared with placebo, the dipeptidyl peptidase-4 (DPP4) inhibitor saxagliptin was associated with an increased risk of HF hospitalization (3.5% vs 2.8%; HR: 1.27; 95% CI: 1.07-1.51), although the effect on the primary composite endpoint of cardiovascular death, myocardial infarction, or ischemic stroke was neutral compared with placebo in a population with established cardiovascular disease or risk factors for cardiovascular disease.[162] A signal for increased HF events was also noted for alogliptin, but not for other DPP4 inhibitors. The FDA contraindicates the use of saxagliptin and alogliptin in individuals with HF.[163] Thiazolidinediones (TZDs) have been associated with an increased incidence of fluid retention, weight gain, and HF events in individuals with or without a previous history of HF, possibly due to increased renal sodium reabsorption rather than direct cardiotoxic effects.[164-167] This risk is further increased when TZDs are combined with insulin therapy; thus, this combination should be avoided.[168] Overall, TZDs are relatively contraindicated in individuals with HFpEF.[14]

#### 7.3.4. Atrial Fibrillation

AF and HF frequently coexist, and both predispose to the development of the other due to shared risk factors and structural cardiac abnormalities.[169-171] The prevalence of AF is higher in individuals with HFpEF compared with HFrEF.[172-174] In the Framingham cohort, compared with HFrEF, prevalent AF was more strongly associated with incident HFpEF and prevalent HF was associated with a 2-fold increase in incident AF.[174] AF is associated with pulmonary hypertension, right HF, and tricuspid regurgitation, all of which can further reduce cardiac output reserve.[175,176] AF is also a common contributing factor to worse functional status and an increased risk of hospitalization and mortality in individuals with HF, and this effect may be greater in those with HFpEF compared with HFrEF.[173,177] Thus, the presence of AF should denote a possible higher-risk HFpEF phenotype that may require more frequent monitoring and management strategies, such as implantable hemodynamic monitoring and/or tricuspid valve repair.

Due to the lack of clinical trial data in persons with HFpEF, the comprehensive care of AF can be extrapolated from the ACC/AHA guidelines for AF.[111] Although overall no significant benefit on cardiovascular outcomes has been noted with a rate vs a pharmacological rhythm control strategy, including in those with HFrEF[178-180] or with a strict vs lenient rate control strategy for care of those without HF,[181] an individualized approach to symptomatic individuals with HFpEF and AF may be needed. For example, in those with continued symptoms after rate control or in those who are not able to achieve adequate rate control, a trial of pharmacological rhythm control to assess symptomatic response with sinus rhythm is reasonable.[182] Dronedarone may be used for pharmacological rhythm control, as it was associated with reduced cardiovascular events in patients with paroxysmal or persistent AF and HF across the spectrum of EF in a post hoc analysis of ATHENA (A Trial With Dronedarone to Prevent Hospitalization or Death in Patients With Atrial Fibrillation).[183]

Interestingly, a subgroup analysis of those with HF enrolled in EAST (Early Treatment for Atrial Fibrillation for Stroke Prevention Trial)[184] suggested benefit of the early, predominantly pharmacological rhythm control strategy compared with rate control in reducing the risk of cardiovascular events.[185] Compared with prior trials of

rate vs rhythm control in HFrEF, the HF subgroup in this trial consisted mostly of HFpEF (56%) and HFmrEF.[178,185] Although the CABANA (Catheter Ablation vs Antiarrhythmic Drug Therapy for Atrial Fibrillation) trial was overall neutral for survival by intention-to-treat analysis, interpretation is complex in the setting of substantial crossover and failure of many study participants to receive the assigned interventions.[118] However, subsequent analyses have suggested greater benefit in the subset with HF, driven primarily by individuals with HFpEF.[186]

Beta-blockers and nondihydropyridine calcium-channel blockers are often considered as first-line agents for heart rate control in those with HFpEF. Aggressive rate control should be avoided, given low stroke volume at rest and poor stroke volume reserve during exertion. However, a smaller, open-label trial, RATE-AF (Rate Control Therapy Evaluation in Permanent Atrial Fibrillation) in elderly individuals with AF and symptoms of HF (the majority with preserved LVEF), compared the use of a beta-blocker, bisoprolol, to digoxin.[187] At 6 months, there was similar rate control in both groups, and the primary endpoint of quality of life was similar between the 2 groups. However, several secondary endpoints, including functional capacity and reduction in NT-proBNP, favored digoxin at 12 months, with higher rates of dizziness, lethargy, and hypotension with beta-blockers.[187] Thus, in specific cases, the use of digoxin may be considered as an add-on strategy if beta-blockers or nondihydropyridine calcium-channel blockers are inadequate or contraindicated in individuals with HFpEF. Anticoagulation is recommended based on the $CHA_2DS_2$-VASc score for the mitigation of thromboembolic risk.[14,111] Nearly all individuals with HFpEF would have an indication for anticoagulation by $CHA_2DS_2$-VASc score given the prevalence of hypertension and older age; anticoagulation should thus be considered in practically all individuals with AF and HFpEF unless contraindicated.

#### 7.3.5. Coronary Artery Disease

Coronary artery disease (CAD) is common in individuals with HFpEF, including epicardial disease in over 50% of individuals and microvascular dysfunction in up to 75%.[188-190] CAD may contribute to symptoms of HF, although the contribution of CAD to the clinical presentation can often be difficult to ascertain. Of note, individuals with HFpEF who are hospitalized with acute pulmonary edema may have significant CAD and be in need revascularization; the presentation of acute pulmonary edema may be a sign of an acute coronary syndrome in these individuals.

There are no prospective trials to determine the impact of revascularization on symptoms or outcomes specifically among individuals with HFpEF, although observational analysis indicates that revascularization may be associated with preservation of cardiac function and improved survival in those with HFpEF and CAD.[191]

However, in individuals with acute coronary syndromes and HFpEF with persistent symptoms of HF or among those with uncontrolled angina despite medical management, following clinical practice guidelines, revascularization might be a viable option. General principles of revascularization and management of elevated cholesterol should be guided by the relevant ACC/AHA guidelines.[112,192]

The COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial enrolled individuals with chronic CAD or peripheral artery disease to rivaroxaban 2.5 mg twice daily plus aspirin 100 mg daily, rivaroxaban 5 mg twice daily alone, or aspirin 100 mg alone and examined events in individuals with and without HF.[193] Of note, in participants with mild to moderate HF vs no HF, combination rivaroxaban and aspirin compared with aspirin alone produced similar relative but larger absolute benefits in the primary composite outcome of cardiovascular death, stroke, or myocardial infarction. However, there was an excess risk of bleeding in individuals receiving aspirin and rivaroxaban, and thus, the role of combination therapy in individuals with CAD and HFpEF is not clear.

Long-acting nitrates are typically prescribed for relief of angina. However, the routine use of nitrates for the treatment of HFpEF itself is not recommended, based on the results of the NEAT-HFpEF (Nitrate's Effect on Activity Tolerance in Heart Failure With Preserved Ejection Fraction) trial.[50] The AHA/ACC/HFSA HF guidelines have specifically recommended against routine use of nitrates to improve exercise capacity in HFpEF with a Class 3 recommendation.[14] Given this, for patients with HFpEF and angina, other antianginal agents may be preferred. Dihydropyridine calcium-channel blockers would be beneficial if there is concomitant need to treat hypertension. Ranolazine may be used if heart rate or blood pressure are limiting.

#### 7.3.6. Sleep Apnea

The prevalence of sleep-disordered breathing is 55% to 80% in those with HFpEF.[194-197] Sleep-disordered breathing adversely affects quality of life, with an increased risk of depression, job-related problems, and motor vehicle accidents.[198] Obstructive sleep apnea (OSA) is the most common form of sleep-disordered breathing observed in HFpEF.[199] Central sleep apnea, in contrast, is more recognized as a marker of HF severity, occurring as a consequence of HF, and is more studied in HFrEF.[200,201]

Symptoms of OSA include daytime sleepiness, morning headaches, memory impairment, irritability or changes in affect, difficulty concentrating, nocturia, decreased libido

and erectile dysfunction, snoring, episodic gasping, choking, or witnessed apneas.[202] Unfortunately, daytime sleepiness, as well as other screening tools used to screen for sleep apnea, correlate poorly with the presence and severity of sleep-disordered breathing in those with cardiac disease, including HF, and have suboptimal sensitivity as a trigger for testing.[202]

Although risk factors for OSA include increased weight[203] and hypertension,[108] there is no definitive benefit of OSA treatment on cardiovascular outcomes.[204] Small studies have suggested improvements in symptoms, diastolic function, arterial stiffness, and even benefit on cardiovascular endpoints in those with HFpEF[205-207]; yet, large clinical trials to date in individuals with HF, of which the majority have enrolled individuals with HFrEF, have not demonstrated improved clinical outcomes with treatment for OSA or central sleep apnea.[207-209] However, in individuals with treatment-resistant hypertension, defined as requiring 3 or more antihypertensive agents, screening for OSA is important, because treatment of OSA may improve blood pressure control.[210] Additionally, an evaluation for OSA should be performed in individuals with AF because treatment with continuous positive airway pressure may reduce the incidence of recurrent AF, although more rigorous clinical trials are required to definitively establish this effect.[211]

Therefore, those with HFpEF and a high suspicion of sleep apnea as well as those with severe obesity, precapillary pulmonary hypertension, resistant systemic hypertension, documented nocturnal hypoxia, or nocturnal bradyarrhythmia may be considered for polysomnography.[14] As oropharyngeal edema alone may cause OSA, diuresis before polysomnography is useful.[212] If abnormal, referral to a sleep specialist is warranted, and a trial of continuous positive airway pressure can be offered to reduce symptoms such as daytime sleepiness and improve sleep quality and quality of life.[14] Weight loss also improves OSA severity,[213] although this strategy has not been tested specifically in individuals with HFpEF. However, treatment of individuals with HFpEF and sleep apnea, in the absence of symptoms or severe hypoxemia during sleep and for the sole purpose of reducing future cardiovascular events, is not justified at this time.[214]

#### 7.3.7. Chronic Kidney Disease

CKD is defined as reduced kidney function for at least 3 months duration, as evidenced by eGFR <60 mL/kg/1.73 $m^2$, albuminuria (albumin to creatinine ratio ≥30 mg/g), or other markers of kidney damage. CKD and HFpEF often coexist, and CKD is a risk factor for incident HFpEF,[215] with a prevalence of ~50% in individuals with HF.[216] Individuals with HFpEF and CKD are usually older, have higher natriuretic peptide concentrations, are more likely to have DM and hypertension, and have worse NYHA functional class.[217] These individuals are predisposed to more fluid overload, diuretic agent resistance, and to a decline in indexes of kidney function with diuresis.[218] Furthermore, CKD is associated with an increased risk of hospitalization and up to a 3-fold increase in mortality in HFpEF, with the magnitude of risk increasing with the severity of kidney disease.[219-222] Concentrations of natriuretic peptides are usually higher in individuals with CKD as compared with those without, making usual cutoffs less specific for the diagnosis of HF.[223,224]

Assessment of CKD can be challenging in patients with HFpEF. Serum creatinine may be falsely reduced due to loss of muscle mass or volume expansion/hemodilution, resulting in a falsely increased eGFR. In this setting, there are other useful markers of CKD, including: 1) the presence of albuminuria[225]; 2) evidence of secondary hyperparathyroidism (low calcium, high phosphorous, increased intact parathyroid hormone, and low 25-hydroxy vitamin D levels)[226]; and 3) increasing creatinine with diuresis as a result of hemoconcentration to identify the true degree of CKD. The management of CKD in those with HFpEF is guided in general by kidney disease guidelines. Collaboration and comanagement by nephrology and cardiology should be considered, with data extrapolated from the large randomized trials in individuals with diabetic kidney disease with increased albuminuria. Agents that reduce the risk of progression to kidney failure in individuals with diabetic kidney disease include ACE inhibitors,[227] ARBs,[228,229] SGLT2is,[230-232] and the nonsteroidal, selective MRA, finerenone.[233,234] These trials have included individuals with eGFRs as low as 30 mL/min/1.73 $m^2$ for ACE inhibitors and ARBs, 25 mL/min/1.73 $m^2$ for finerenone, and 20 mL/min/1.73 $m^2$ for SGLT2is.[231,232]

In individuals specifically with HFpEF, the PARAGON-HF trial demonstrated less decline in renal function with the ARNI compared with the ARB.[235] EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction) also noted less decline in renal function with the SGLT2i empagliflozin vs placebo.[61]

Based on these findings, the use of an SGLT2i (eGFR ≥20 mL/min/1.73 $m^2$) is beneficial in slowing the decline of kidney function in individuals with HFpEF and CKD above and beyond other therapies, such as renin-angiotensin-aldosterone system (RAAS) blockers. When using RAAS blockers and/or SGLT2is, monitoring kidney function and serum potassium is useful 1 to 2 weeks after initiation. However, as a small decrement in eGFR is

expected with the use of both classes of nephroprotective therapies, clinicians should not ascribe such a change to acute kidney injury.

A loop diuretic agent should be maintained at the lowest effective dose in individuals with CKD; evidence-based diuretic agents such as MRAs (with monitoring of serum potassium) and SGLT2is are preferred. Thiazide diuretic agents may be useful in combination with loop diuretic agents for more effective diuresis.[236]

## 8. MULTIDISCIPLINARY CONSIDERATIONS IN HFPEF

### 8.1. Overcoming Barriers to the Delivery of Care

As outlined in detail earlier, the diagnosis and management of HFpEF is challenging. The pathophysiology is not well understood, likely due to multifactorial etiologies, resulting in a more heterogenous population of affected individuals. These combined challenges in diagnosis and estimating prognosis often result in difficulty communicating a diagnosis to individuals and caregivers. It also leads to uncertainty in how to manage older individuals who have more comorbidities, leading to less consistency in GDMT prescription.[237]

Improvements in care delivery require overcoming perception bias; improving access (especially for rural and marginalized populations) to clinicians with adequate knowledge of the disease process, diagnostic testing, and management strategies; understanding of when referral to cardiovascular and HF specialists may be warranted; effective implementation of team-based care; clear communication at transitions in care; and appropriate timing of palliative care.

### 8.2. Cardiovascular Specialist Referral

#### 8.2.1. Indicators for General Cardiology Referral

For individuals with HFpEF cared for by primary care clinicians, referral to a cardiovascular specialist is useful for several reasons. First, the evaluation and management of individuals with suspected or proven HFpEF may be challenging, frequently requiring complex diagnostic evaluation and nuanced decision-making regarding management of risk factors and/or application of GDMT (see Section 7.3). Second, noncardiovascular specialists vary substantially in their skill in diagnosis and management of HFpEF[238]; this may lead to challenges in disease recognition or assessment of its severity, management uncertainty, and inequities in care.[237] Third, data suggest that involvement of specialty care is associated with lower risk for mortality in individuals with HFpEF.[239] Thus, when the diagnosis of HFpEF is suspected or confirmed (see Section 6.1), timely referral to a cardiovascular specialist is an important component of optimal care for many individuals with HFpEF.

For individuals with suspected or proven HFpEF cared for by noncardiovascular specialists, referral should be made for consultation regarding: 1) confirmation of the diagnosis and/or exclusion of other conditions, as outlined in Section 6.2; 2) optimization of risk factors and comorbidities, as outlined in Section 7.3; 3) assessment of prognosis and the potential for advanced HF therapies; and 4) establishment of a framework for ongoing collaboration with primary care clinicians, if needed, regarding management of HF symptoms, comorbid conditions, and prognosis.

Primary care clinicians encounter many individuals with dyspnea, and it may be difficult to identify which individuals require referral to a cardiovascular specialist. A convenient acronym for primary care clinicians for when to consider specialist referral is *CHECK-IN* (**Figure 12**). This includes: 1) poorly controlled comorbidities (such as hypertension, CAD, AF, and kidney dysfunction); 2) concern for the presence of diagnoses that resemble HFpEF but have specialized management (such as hypertrophic cardiomyopathy or cardiac amyloidosis); and 3) worsening prognosis in HFpEF (need for hospitalization, increased diuretic agent requirement, refractory HF symptoms).

Individuals with HFpEF managed in primary care are frequently older, with substantial comorbidities[240] that might reduce their perceived appropriateness for specialty referral. Nonetheless, given the potential to substantially improve the prognosis, even in those of advanced age with multiple comorbidities complicating their HFpEF, specialist referral is advisable in the substantial majority.

Following referral, ongoing evaluation and titration of GDMT to goal may be coordinated between the cardiovascular specialist and primary care clinician. Given their complexity and risk, long-term follow-up of the individual with symptomatic HFpEF should typically involve the cardiovascular specialist working in a team manner.

#### 8.2.2. Indicators for HF Specialist Referral

Because many individuals with HFpEF will not be candidates for advanced HF therapies due to advanced age or substantial comorbidities, referral from cardiovascular specialists to advanced HF specialists might be perceived as less useful. However, referral to an HF specialist can be helpful in cases of diagnostic or therapeutic uncertainty and to identify potential clinical trial candidates. Triggers for referral might include persistent or worsening symptoms, adverse clinical events such as hospitalization, or other features suggesting that the individuals are at high risk for disease progression, hospitalization, or death.

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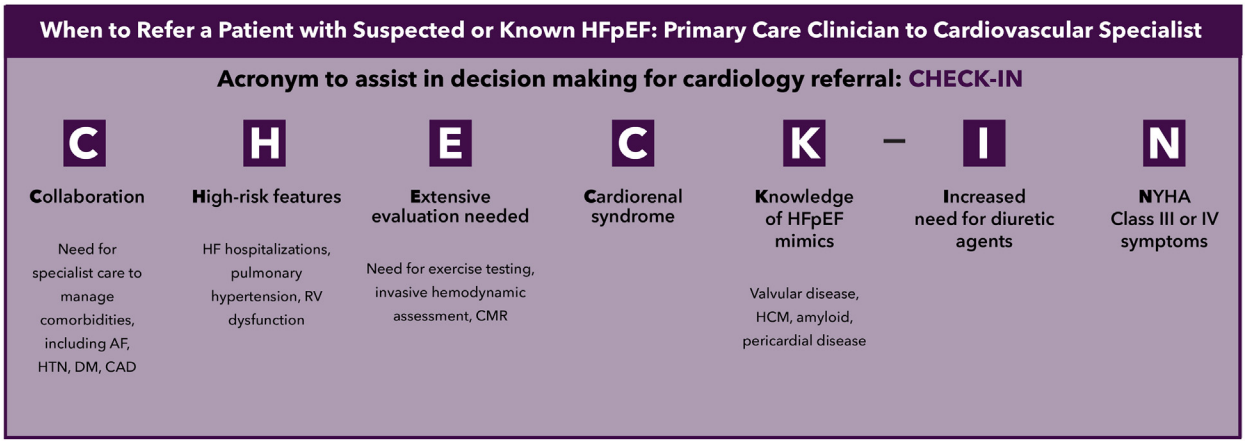
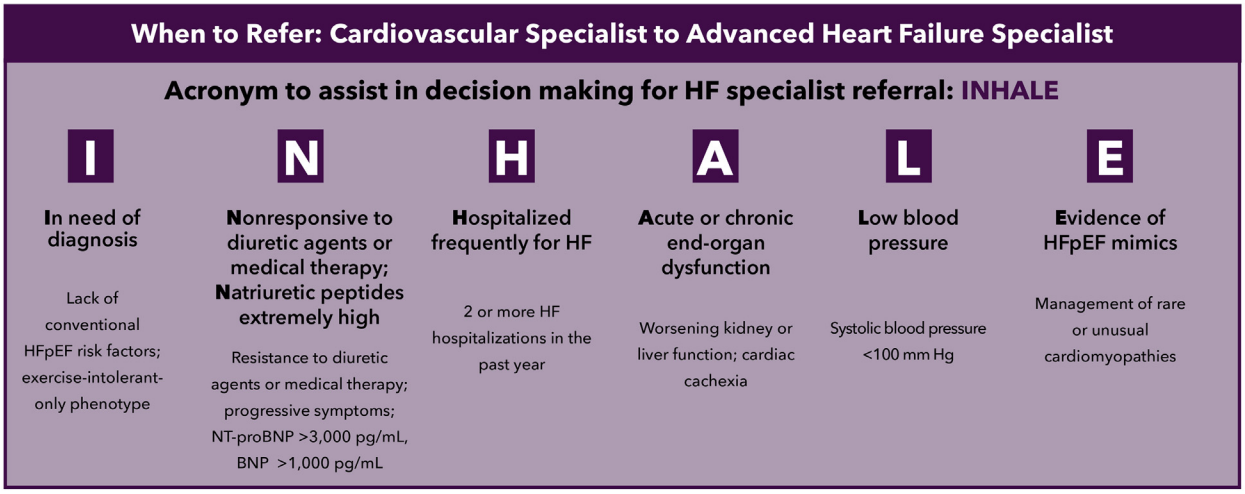
**FIGURE 12 CHECK-IN: When to Refer a Patient With Suspected or Known HFpEF: Primary Care Clinician to Cardiovascular Specialist***




*Most individuals with suspected or proven HFpEF should be considered for referral to a cardiovascular specialist or advanced HF practice. Features to assist in timing of referral are summarized in the acronym *CHECK-IN*, which includes aspects of medical and HF complexity. AF = atrial fibrillation; CAD = coronary artery disease; CMR = cardiac magnetic resonance; DM = diabetes mellitus; HF = heart failure; HCM = hypertrophic cardiomyopathy; HTN = hypertension; NYHA = New York Heart Association; RV = right ventricular.

Referral might also be considered for circumstances of diagnostic uncertainty, such as discerning between restrictive or constrictive heart disease, including identifying the presence of infiltrative or hypertrophic cardiomyopathies. The I*NHALE* mnemonic (adapted from the *I NEED HELP* acronym to identify high-risk features of advanced HFrEF[241] and the *HELP ME NOW* mnemonic for HFpEF[242]) offers general cardiovascular specialists a means to identify individuals with higher-risk HFpEF warranting referral to an HF specialist (Figure 13).

**FIGURE 13 INHALE: Acronym for Advanced HF Specialist Referral***




*Most individuals with suspected or proven HFpEF can be managed by a general cardiovascular specialist. However, there are some situations that suggest a special or unusual cardiomyopathy (such as infiltrative or restrictive cardiomyopathy), pulmonary hypertension, or pericardial disease. Features to assist in identification of individuals with advanced HF not classic for HFpEF are summarized in the acronym "INHALE," which includes markers of advanced HF. BNP = B-type natriuretic peptide; BP = blood pressure; HF = heart failure; HFPEF = heart failure with preserved ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association.

Besides assisting with standards for evaluation and management of general HFpEF, guidance from an HF specialist may prove helpful in cases of therapeutic uncertainty. Examples of this might be in management of pulmonary hypertension, the benefit of procedural interventions for valvular heart disease or CAD, or advice regarding the role of more complex GDMT use. Of note, pulmonary hypertension due to left heart disease (Group 2) commonly occurs in HFpEF, and it is important to recognize the lack of benefit of pulmonary vasodilator therapy in Group 2 pulmonary hypertension. An HF specialist can also assist with access to clinical trials and evaluation (if appropriate) for mechanical circulatory support or transplantation, a rare circumstance in HFpEF. Last, the HF specialist can assist in defining the prognosis and need for a palliative care referral.

### 8.3. Team-Based Approach to Care

As new medications and devices become available for individuals with HFpEF, a team-based approach is needed to optimize care, especially for those with multiple comorbidities associated with HFpEF. Use of multidisciplinary teams to facilitate the implementation of GDMT, address barriers to self-care, reduce readmission for HF, and improve survival in those with Stage C HF is a Class 1 recommendation in the 2022 AHA/ACC/HFSA Guideline for the Management of HF.[14]

Consistent with a team-based approach, multidisciplinary groups of clinicians (eg, primary care, specialists, nurses, advanced practice professionals, pharmacists, dieticians, exercise physiotherapists, and social workers) collaborate to implement evidence-based care that is patient-centered.[243] Team-based programs vary in size and resources. Postgraduate training (eg, for advanced practice professionals) and experience determine team member roles; diversity of backgrounds should be viewed as an asset.[244]

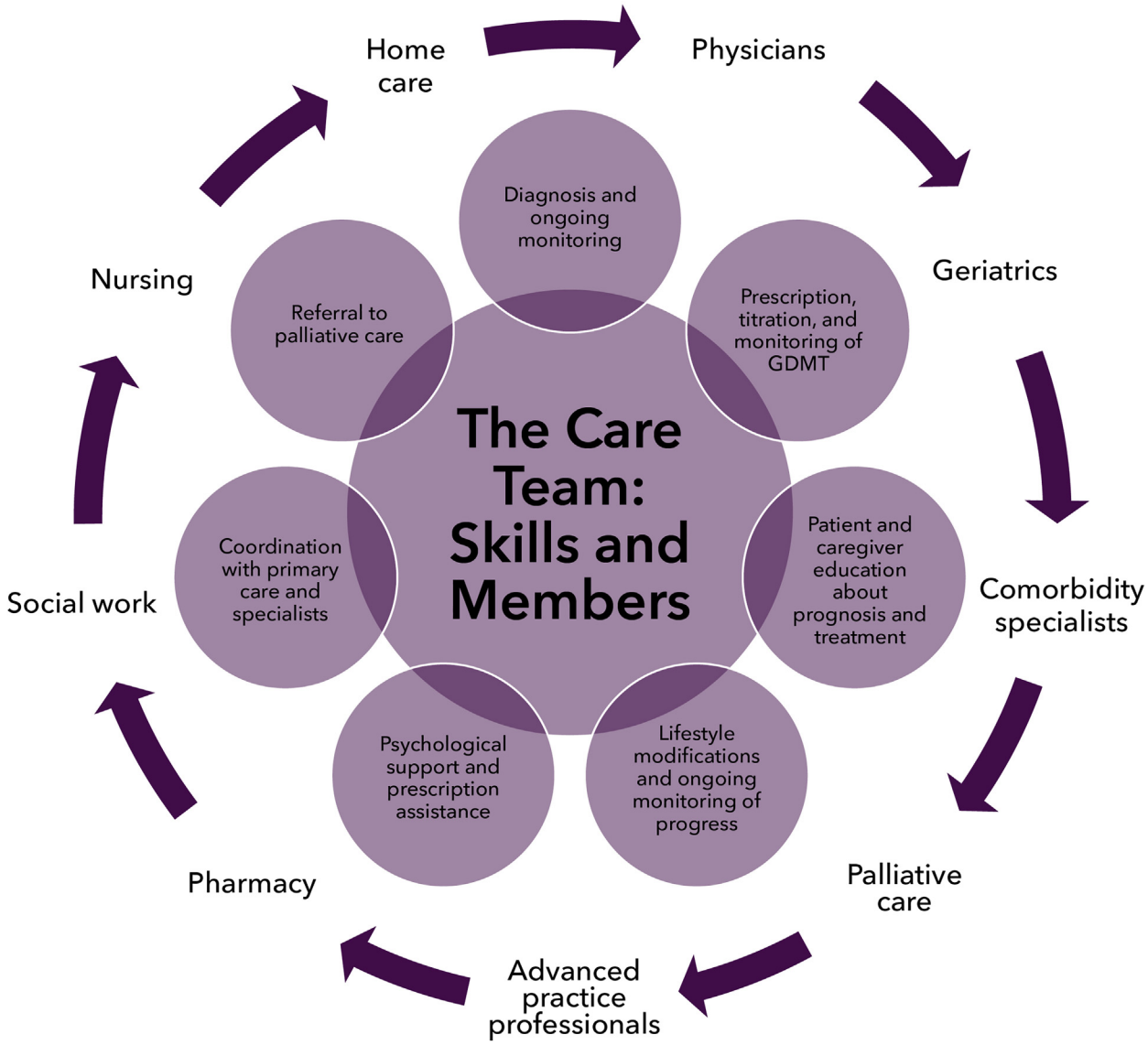
Regardless of the size and composition of the team, a team-based approach requires a clear understanding of each team member's functions and responsibilities, communication across disciplines, and the use of shared decision-making that is culturally appropriate. Requisite skills for the care team include establishing the diagnosis and monitoring for improvement or exacerbations, prescription of medical and lifestyle interventions, educating individuals and their informal caregivers, and coordinating care among team members and other clinicians external to the care team (**Figure 14**). Team-based programs should be systematically developed and include monitoring of effectiveness, with a clear plan for correcting identified deficiencies.[244]

Due to the complexity of underlying pathophysiological mechanisms and associated comorbidities, a team-based approach starts with assessment and treatment of underlying risk factors and comorbidities. Nurses are well positioned to educate individuals and their caregivers about health promotion, self-care (eg, home blood pressure and weight monitoring, reductions in sodium and caloric intake, increase in physical activity, smoking cessation, and medication management), and transitions of care. Advanced practice professionals and clinical pharmacists may focus on medication reconciliation during care transitions, improving medication adherence, and managing complex drug therapy given the high likelihood of polypharmacy.[244]

Dedicated HFpEF programs that use clinical pathways and multidisciplinary teams to coordinate services improve care delivery. Although HF clinics do not usually exclude individuals with HFpEF, specialized HFrEF programs are more common, and individuals with HFpEF mimics such as infiltrative cardiomyopathies may be preferentially referred to HF clinics, leaving a gap in the specialized management of individuals with HFpEF. Given the high population burden of HFpEF, complexities in making the correct diagnosis in many cases, heterogeneity of clinical presentation and underlying pathophysiology, treatment nuances, and the availability of numerous ongoing HFpEF clinical trials, increasing the number of dedicated, multidisciplinary HFpEF clinics within communities and health systems has the potential to greatly improve the care of individuals with HFpEF.[245] Strategies to improve referrals to HFpEF clinics may include systematic screening through low-tech (eg, systematic screening of hospital admissions through quality improvement programs aimed at reducing HF rehospitalization) or high-tech (eg, natural language processing-based queries through the electronic health record) mechanisms.[245]

Once candidates for inclusion in a dedicated HFpEF program are identified, a standardized approach for diagnosis and treatment is essential. However, a "one-size-fits-all" approach that has been relatively effective for those with chronic HFrEF differs from the more personalized approach needed for HFpEF.[246] An alternative approach to a specialized HFpEF program is developing a multidisciplinary "Dyspnea Clinic" where affected individuals receive joint care from cardiologists and pulmonologists.[247] The focus of these types of clinics is on the evaluation and treatment of unexplained dyspnea, often due to HFpEF. Beyond diagnosis, specialists in sleep apnea, weight management, nutrition, and electrophysiology can be involved as needed, with the central focus being to ease the burden of comorbidity management. To achieve this, further refinement may be needed in payment models as well as in supporting alternative modes of delivery of care, such as virtual or electronic health record-based consultations.

**FIGURE 14 The Essential Skills of a Care Team**



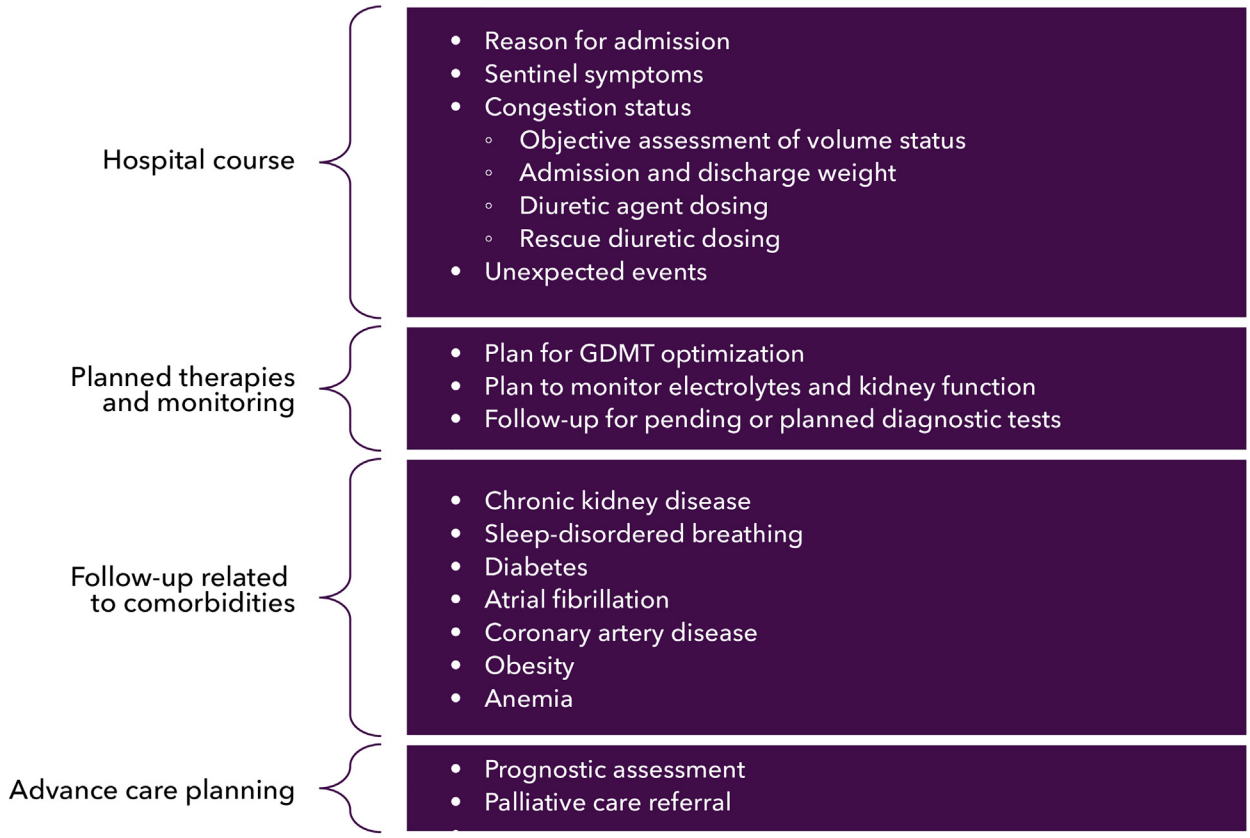

EP = electrophysiology; GDMT = guideline-directed medical therapy; HF = heart failure.

### 8.4. Transitions of Care

Individuals with HFpEF generally have a higher burden of comorbidities. Most admissions with HFpEF are due to noncardiac causes, which may result in uncertainty about who assumes primary responsibility (primary vs specialty care), especially during transitions of care (eg, hospital discharge). This calls for clear communication from clinicians who will assume responsibility for care postdischarge.

The transition from hospital discharge to the ambulatory setting provides clinicians with an opportunity to optimize GDMT and educate individuals and caregivers about specific information related to HFpEF. Because most individuals with HFpEF have complex histories, including multiple comorbidities, it is essential that individuals be well-equipped for self-care. As such, all individuals and caregivers should be given clear written and verbal communication about clinician names, dates, and locations for follow-up appointments postdischarge, with efforts made to confirm adequate health literacy for effective communication. In addition, the discharge

**FIGURE 15 Checklist for Communication to Clinicians Involved in Continuing Care**




Adapted from Hollenberg et al.[56] GDMT = guideline-directed medical therapy.

summary should explicitly note whether additional support is needed to optimize care, including medication availability and support, access to care and medical guidance should symptoms escalate, and psychosocial factors.[56]

Patient-centered transitional care services provided by hospital nurse navigators at the time of discharge have been studied in individuals hospitalized with HF. PACT-HF (Patient-Centered Care Transitions in HF) was a cluster randomized trial of 2,494 adults hospitalized for HF (regardless of EF) across 10 hospitals in Ontario, Canada.[248] The intervention was nurse-led self-care education, a structured hospital discharge summary, a follow-up appointment less than 1 week after discharge with the patient's family physician, and, for high-risk individuals, structured nurse home visits for the first 4 to 6 weeks until follow-up at an HF specialty clinic. There were no differences in readmissions, emergency department visits, or death at 3 months from the intervention. However, patient-reported measures of discharge preparedness, quality of care transition, and health-reported quality of life were improved with the intervention in both women and men.[248,249]

Further support of a team-based approach to transitions in care comes from the STRONG-HF (Safety, Tolerability, and Efficacy of Up-Titration of Guideline-Directed Medical Therapies for Acute Heart Failure) trial.[83] The 8% absolute risk reduction in HF readmission or death at 180 days in this trial was based on frequent postdischarge visits focused on GDMT titration. To make these frequent visits feasible requires collaboration of care team members, from cardiologists to advanced practice professionals to pharmacists, and the use of telehealth visits.

An alternative approach is to develop a more structured checklist to communicate with clinicians involved in continuing care as individuals make the transition from the hospital to the ambulatory setting; one model of items to include is shown in **Figure 15**.

### 8.5. Palliative Care

Due to the multiple comorbidities and challenges with symptom control associated with HFpEF, palliative care

evaluation should be considered to address inadequate control of symptoms despite conventional medical therapy. Palliative care, which has a Class 1 recommendation from the 2022 AHA/ACC/HFSA HF guidelines for individuals with HF, uses a patient- and family-centered focus to optimize health-related quality of life by anticipating, preventing, and treating suffering.[14] Palliative care, synonymous with supportive care, starts with the multidisciplinary team assessing goals of care with individuals and their caregivers, clarifying core values, health outcome goals, and treatment preferences. Optimally, palliative care should begin sooner (eg, at the onset of symptoms) in the disease course than has traditionally been adopted.

In the setting of disease progression, specialty palliative care clinicians may be consulted to address more challenging needs for individuals and their families. Caution should be taken, however, because many individuals incorrectly equate palliative care with hospice care; thus, education is needed to clarify the difference. Regardless, all individuals with HF should have an advance care directive in place (including documented treatment preferences and preference for place of death at the end of life). For individuals with advanced HF with an expected survival of less than 6 months, hospice referral can be useful to improve quality of life.

## 9. DISCUSSION AND IMPLICATIONS OF PATHWAY

This ECDP was written with the goal of providing timely and practical guidance on diagnosis and management of HFpEF. This document is aligned with and operates under the framework of the recommendations published in the recent HF guidelines but provides a nuanced approach to tackle various aspects of care of the individual with HFpEF. Foremost is the critical need to accurately diagnose these individuals. An accurate diagnosis will allow the institution of evidence- and guideline-based therapies. Given that HFpEF is a complex condition with multiple overlapping comorbidities, optimal management will involve a multidisciplinary approach.

Care decisions can be complex and require coordination and careful consideration to provide the most effective recommendations, which may be timely and prevent further delay. These decisions may have a notable impact on morbidity and mortality and might be beneficial to the individuals but also need to be cost-effective. The pathways and algorithms provided need to be carefully structured around the needs of a particular patient. It is key that these recommendations are adopted to provide equitable care with careful consideration of limitations in specific populations highlighted in this document. It is understood that 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 document is the first to specifically address the individual with HFpEF. It provides practical tips and structure on clinical decision-making, management of comorbidities, implementation of the latest advancements in pharmacological and nonpharmacological therapy, and the use of alternative modes of care to provide access and equitable delivery of care. The specific goal is timely identification and implementation of therapy to improve outcomes in HFpEF.

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**KEY WORDS** **ACC Expert Consensus Decision Pathway, cardiomyopathy, dyspnea, edema, guideline-directed medical therapy, heart failure with preserved ejection fraction**

## APPENDIX 1. AUTHOR RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (RELEVANT)—2023 ACC EXPERT CONSENSUS DECISION PATHWAY ON MANAGEMENT OF HEART FAILURE WITH PRESERVED EJECTION FRACTION

| 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 Inc* | None | None | ■ Guide HF, Abbott Laboratories†<br>■ CARDIO-TTRansform, IONIS†<br>■ Franklin & Prokopik, PC* | 2022, Heart failure related to eye injury* |
| Kaushik Amancherla | Vanderbilt University Medical Center—Instructor in Medicine | None | None | None | None | None | None |
| Leslie L. Davis | University of North Carolina at Chapel Hill—Associate Professor | None | None | None | None | None | None |
| Anita Deswal | UT MD Anderson Cancer Center—Professor of Medicine, Chair of Cardiology | None | None | None | None | None | None |
| Dave L. Dixon | VCU School of Pharmacy—Department Chair and Associate Professor | ■ American Pharmacists Association<br>■ Brigham Women's Hospital (PCORI Grant) | None | None | ■ Boehringer Ingelheim Pharmaceuticals, Inc*<br>■ Centers for Disease Control and Prevention* | None | None |
| James L. Januzzi Jr | Harvard Medical School—Hutter Family Professor of Medicine | ■ Abbott Laboratories<br>■ Abiomed<br>■ AstraZeneca Pharmaceuticals*<br>■ Eli Lilly and Company<br>■ Novartis*<br>■ Novo Nordisk Inc<br>■ Prevencio*<br>■ Roche Diagnostics*<br>■ Siemens | None | None | ■ Abbott Laboratories*<br>■ AbbVie, Inc (DSMB)*<br>■ Bayer Healthcare Pharmaceuticals (DSMB)<br>■ CVRx (DSMB)*<br>■ Janssen Pharmaceuticals, Inc*<br>■ Medtronic<br>■ Takeda Pharmaceuticals North America, Inc (DSMB)* | ■ Imbria*<br>■ Jana Care* | None |
| Clyde W. Yancy | Northwestern University, Feinberg School of Medicine—Magerstadt Professor of Medicine; Chief, Division of Cardiology | None | None | None | None | None | None |

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ACC = American College of Cardiology; DSMB = Data Safety Monitoring Board.

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## APPENDIX 2. PEER REVIEWER RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (COMPREHENSIVE)

| Reviewer | Representation | Employment | Consultant | Speakers Bureau | Ownership/ Partnership/ Principal | Personal Research | Institutional, Organizational, or Other Financial Benefit | Expert Witness |
|---|---|---|---|---|---|---|---|---|
| Margaret T. Bowers | Official Reviewer—ACC Cardiovascular Team Section Council | Duke University—Clinical Professor and Nurse Practitioner | None | None | None | None | None | None |
| Biykem Bozkurt | Official Reviewer—Solution Set Oversight Committee (SSOC) | Baylor College of Medicine and DeBakey VA Medical Center—Medical Care Line Executive, Cardiology Chief, Gordon Cain Chair, Professor of Medicine | ■ Amgen Inc.<br>■ Baxter International Inc<br>■ Sanofi Aventis | None | None | ■ Cardurion (DSMB)<br>■ LivaNova USA (DSMB)<br>■ Renovacor (DSMB) | ■ Abbott Laboratories*<br>■ ACC/AHA Task Force for Data Standards†<br>■ ACC/AHA Task Force for Performance Measures†<br>■ Circulation<br>■ Heart Failure Society of America, Past President†<br>■ Janssen Pharmaceuticals, Inc*<br>■ The Journal of the American College of Cardiology*<br>■ Medtronic<br>■ Relypsa<br>■ Vifor Pharma | None |
| Lee R. Goldberg | Content Reviewer—ACC Expert | University of Pennsylvania—Vice Chair of Medicine | ■ Abbott Laboratories<br>■ Respircardia/Zoll*<br>■ Viscardia† | None | None | ■ NIH†<br>■ Respircardia/Zoll† | None | None |
| Carolyn S.P. Lam | Content Reviewer—ACC Expert | National Heart Centre Singapore—Senior Consultant | ■ Alleviant Medical<br>■ Allysta Pharma<br>■ Amgen<br>■ AnaCardio<br>■ Applied Therapeutics<br>■ AstraZeneca Pharmaceuticals*<br>■ Bayer Healthcare Pharmaceuticals*<br>■ Boehringer Ingelheim Pharmaceuticals, Inc*<br>■ Boston Scientific*<br>■ Cytokinetics<br>■ Darma Inc†<br>■ EchoNous Inc*<br>■ Eli Lilly*<br>■ Impulse Dynamics<br>■ Intellia Therapeutics†<br>■ Ionis Pharma<br>■ Janssen Research<br>■ Development*<br>■ Medscape/WebMD*<br>■ Merck<br>■ Co., Inc.<br>■ Novartis*<br>■ Novo Nordisk*<br>■ Prosciento Inc<br>■ Radcliffe<br>■ Recardio<br>■ ReCor Medical<br>■ Roche*<br>■ Sanofi<br>■ Servier<br>■ Siemens Healthcare<br>■ Us2.ai* | None | None | ■ Bayer Healthcare Pharmaceuticals*<br>■ Clinician Scientist Award (National Medical Research Council of Singapore)*<br>■ Roche* | None | None |

*Continued on the next page*

## APPENDIX 2. CONTINUED

| Reviewer | Representation | Employment | Consultant | Speakers Bureau | Ownership/ Partnership/ Principal | Personal Research | Institutional, Organizational, or Other Financial Benefit | Expert Witness |
|---|---|---|---|---|---|---|---|---|
| Ran Lee | Official Reviewer—ACC Heart Failure & Transplant Council | Cleveland Clinic Foundation—Staff Physician | None | None | None | None | None | None |
| Sanjiv Jayendra Shah | Content Reviewer—ACC Expert | Northwestern University Feinberg School of Medicine—Stone Endowed Professor of Medicine | ■ Abbott<br>■ American Board of Internal Medicine<br>■ Amgen<br>■ Aria<br>■ AstraZeneca Pharmaceuticals*<br>■ Axon<br>■ Bayer<br>■ Boehringer Ingelheim Pharmaceuticals, Inc<br>■ Boston Scientific<br>■ Bristol-Myers Squibb Company<br>■ Cardiora<br>■ CVRx<br>■ Cyclerion<br>■ Cytokinetics<br>■ Eisai<br>■ ekoi.ai<br>■ GlaxoSmithKline<br>■ Imara<br>■ Ionis<br>■ Ironwood<br>■ Janssen<br>■ Keyto<br>■ Lilly Medical<br>■ Merck<br>■ MyoKardia<br>■ Novartis*<br>■ Novo Nordisk Inc.<br>■ Pfizer<br>■ Prothena<br>■ Regeneron<br>■ Sanofi<br>■ Shifamed<br>■ Tenax<br>■ United Therapeutics | ■ Pulmonary Hypertension Association | None | ■ Actelion*<br>■ American Heart Association*<br>■ Corvia*<br>■ National Institutes of Health†<br>■ National Institutes of Health* | None | None |
| Michael R. Zile, MD, FACC | Content Reviewer—ACC Expert | Medical University of South Carolina—Professor of Medicine | ■ Abbott<br>■ CVRx*<br>■ Eli Lilly and Company<br>■ Merck<br>■ Novartis* | None | None | ■ Department of VA*<br>■ Medtronic*<br>■ NIH* | None | None |

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*Significant relationship.

†No financial benefit.

ACC = American College of Cardiology; AHA = American Heart Association; DSMB = Data Safety Monitoring Board.

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## APPENDIX 3. ABBREVIATIONS

ACC = American College of Cardiology
ACE = angiotensin-converting enzyme
AF = atrial fibrillation
ARB = angiotensin receptor blocker
ARNI = angiotensin receptor-neprilysin inhibitor
DPP4 = dipeptidyl peptidase-4
ECDP = expert consensus decision pathway
EF = ejection fraction
eGFR = estimated glomerular filtration rate
GDMT = guideline-directed medical therapy
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
NT-proBNP = N-terminal pro-B-type natriuretic peptide
NYHA = New York Heart Association
RAAS = renin-angiotensin-aldosterone system
SGLT2i = sodium-glucose cotransporter-2 inhibitor
T2DM = type 2 diabetes mellitus