2023 HFCT Focused Update of the 2019 HFCT Heart Failure Guidelines Part 2: Diagnosis and Management of HFmrEF and HFpEF

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The Heart Failure Council of Thailand (HFCT) has produced a series of guidelines for heart failure (HF) over the past ten years to provide updated practical recommendation to improve the outcomes and quality of care for individuals with HF in Thailand, with the most recent in 2019. Since that publication, there has been growing knowledge and new evidence published. Therefore, the HFCT recognizes the need to update some sections of the previous guidelines. Part 1 of the Focused Update of the 2019 HFCT Heart Failure Guidelines has been published in 2022, focusing on HF classification and pharmacological treatment for HF with reduced ejection fraction (HFrEF)[1].

In this Part 2, the 2023 HFCT Focused Update of the 2019 HFCT Heart Failure Guidelines looked at the diagnosis and management of HF with mildly reduced ejection fraction (HFmrEF) and HF with preserved ejection fraction (HFpEF). Of note, the other recommendations from the 2019 HFCT Heart Failure Guidelines not mentioned here are considered unchanged.

Recommendations were considered on the basis of the balance of benefits, harm, and costs of the available evidence of each intervention. When the evidence was poor-quality, conflicting, or absent, the writing committee considered the recommendations based on the consensus of experts.

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Section 1. Heart failure with mildly reduced ejection fraction (HFmrEF)

1.1. Prevalence and clinical characteristics of HFmrEF

There is limited data regarding the prevalence of HFmrEF. However, based on the results of the recently published studies and analyses of data from registries of the overall population that embedded HFmrEF within the patients with HF, the prevalence of HFmrEF is 10% to 25%[2]. In the European Society of Cardiology Heart Failure Long-Term registry and the Swedish HF registry, the proportion of patients with HFmrEF was 24% and 21%, respectively[2,3]. Whereas, the prevalence of HFmrEF was slightly lower in Asians[4]. Clinical characteristics of patients with HFmrEF were found to be intermediate between those of HFrEF and HFpEF in some respects[5]. Importantly, HFmrEF is closer to HFrEF than HFpEF with regard to the high prevalence of coronary artery disease (CAD), which is more common in men, younger, and less likely to have atrial fibrillation (AF). Whereas, cardiovascular (CV) mortality is lower in patients with HFmrEF than in patients

with HFrEF. Interestingly, post hoc and subgroup analysis of certain HF studies have suggested that potential benefit of standard therapy for HFrEF may be effective in patients with HFmrEF[5-7].

1.2. Diagnosis of HFmrEF

The diagnosis of HFmrEF is defined as left ventricular ejection fraction (LVEF) between 41% to 49% in combination with the presence of symptoms and/or signs of HF and evidence of increased left ventricular (LV) filling pressure such as elevated levels of plasma natriuretic peptides, defined as B-type natriuretic peptide (BNP) of 35 pg/mL or more or N-terminal pro-B-type natriuretic peptide (NT-proBNP) of 125 pg/mL or more, and invasive and non-invasive hemodynamic measurement (Figure 1).

1.3. Treatment of HFmrEF

Most randomized controlled trials of guideline-directed medical therapy in HFpEF enrolled patients with an LVEF greater than 40% to 45%, which included the HFmrEF category. Moreover, evidence from post hoc and subgroup analysis of randomized controlled trials in HFpEF suggested that some standard therapies for HFrEF might also be effective in patients with HFmrEF. Although, with the limitation of post hoc or subgroup analysis, a strong recommendation cannot be made. As in other categories of HF, diuretic use is recommended to relieve congestion, regardless of LVEF. The recommendation for pharmacological treatment is summarized in Table 1 and Figure 2.

1.3.1. Sodium-glucose co-transporter 2 inhibitor

Two prospective randomized clinical trials, the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR-Preserved)[8] and the Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure (DELIVER)[9] trials, recently demonstrated the benefits of sodium-glucose co-transporter 2 inhibitor (SGLT2i) in patients with symptomatic HF, New York Heart Association (NYHA) class II-IV, with LVEF greater than 40%, and elevated natriuretic peptides. In the EMPEROR-Preserved trial, patients who received empagliflozin had a 21% reduction in primary composite endpoint of CV death or HF hospitalization as well as a significant decrease in the estimated glomerular filtration rate (eGFR) slope decline, over the median follow-up of 26.2 months[8]. In the DELIVER trial, patients who received

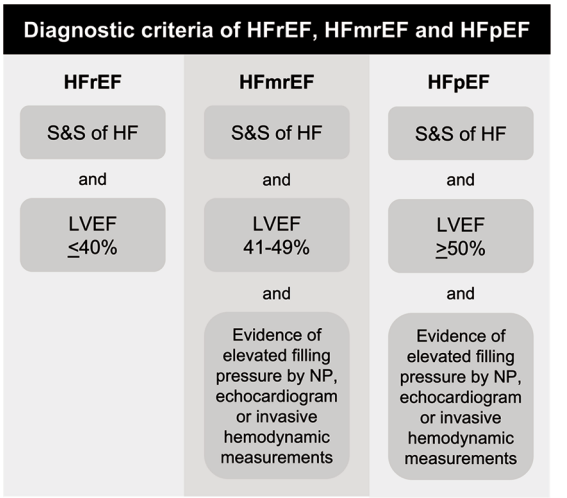

Figure 1. Diagnostic criteria of HFrEF, HFmrEF, and HFpEF.

HF indicates heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; NP, natriuretic peptide; and S&S, symptoms and signs

dapagliflozin had an 18% reduction in the primary composite endpoint of CV death or worsening HF, which was defined as unplanned HF hospitalization or an urgent visit for HF, and a significant decrease in the eGFR slope decline[9]. Both trials showed no benefit of CV mortality reduction. In the subgroup of patients with LVEF of 41% to 49%, both empagliflozin and dapagliflozin reduced the risk of the primary composite endpoint of CV death or hospitalization for HF with the signal of higher benefit in the patients with lower LVEF[8-14].

These data provide the evidence to recommend dapagliflozin and empagliflozin as essential therapy in patients with symptomatic HF with LVEF greater than 40% to reduce the risk of CV death and worsening HF. Dapagliflozin and Empagliflozin are recommended to use in patients with symptomatic HFmrEF to reduce the risk of CV death and hospitalization for HF (Table 1).

1.3.2. Angiotensin-converting enzyme inhibitors

There are no clinical trials of angiotensin-converting enzyme inhibitors (ACEIs) specifically in patients with HFmrEF. In the Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE)[15] study, which enrolled 8,290 patients with stable CAD with LVEF greater than 40% who were receiving standard therapy and 15% of them had LVEF at 40% to 50%, trandolapril failed to show a clinical benefit to reduce a primary outcome of a composite of death from CV causes, non-fatal

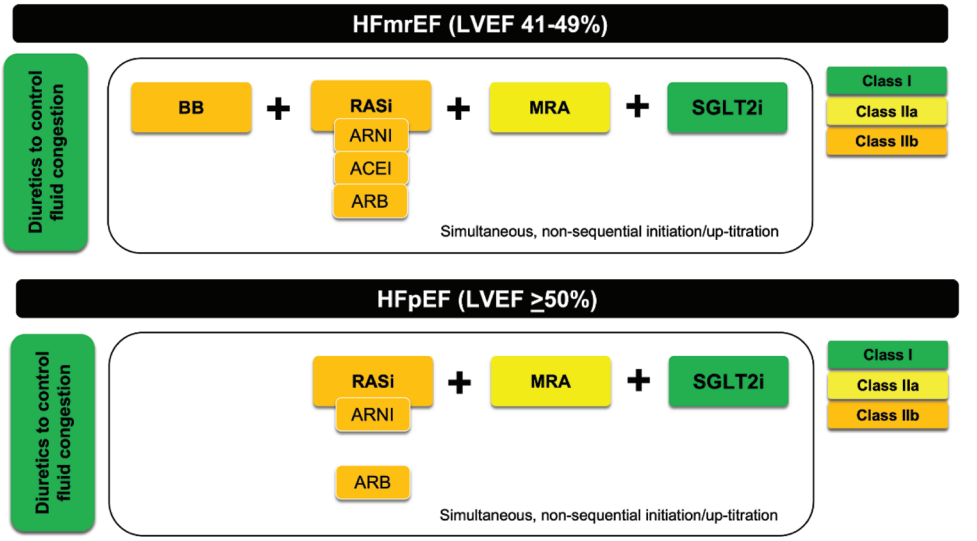

Figure 2. Summary of pharmacologic treatment of HFmrEF and HFpEF.

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitor; BB, beta-blockers; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; MRA, mineralocorticoid receptor antagonist; RASi, renin-angiotensin system inhibitors; SGLT2i, sodium-glucose co-transporter 2 inhibitor

Table 1. Pharmacological treatment for patients with previous or current symptomatic HFmrEF

Recommendations	COR	LOE
Diuretics are recommended in patients with HFmrEF with congestion to relieve heart failure symptoms and prevent worsening heart failure.	I	C
Dapagliflozin or empagliflozin are recommended for HFmrEF to reduce the risk of hospitalization for heart failure and cardiovascular death.	I	A
MRA should be considered for patients with HFmrEF to reduce the risk of hospitalization for heart failure and cardiovascular death.	IIa	C
Sacubitril/valsartan may be considered for patients with HFmrEF to reduce the risk of hospitalization for heart failure and cardiovascular death.	IIb	B
ACEIs or ARBs may be considered for patients with HFmrEF to reduce the risk of hospitalization for heart failure and cardiovascular death.	IIb	B
Beta-blockers may be considered for patients with HFmrEF to reduce the risk of cardiovascular and all-cause mortality, especially in patients with sinus rhythm.	IIb	B

ACEIs=angiotensin-converting enzyme inhibitors; ARBs=angiotensin-receptor blockers; COR=class of recommendation; HFmrEF=heart failure with mildly reduced ejection fraction; LOE=level of evidence; MRA=mineralocorticoid receptor antagonist

myocardial infarction, or coronary revascularization. Patients in the trandolapril group had fewer death or hospitalization from HF[15]. In a post hoc, subgroup analysis of patients with LVEF of 40% to 50%, trandolapril significantly reduced a composite of all-cause death, non-fatal myocardial infarction, and stroke by 21% and all-cause mortality by 15% during the mean follow-up of 4.7 years[16].

These data support that ACEIs may be considered for patients with HFmrEF to reduce the risk of hospitalization for HF and CV death (Table 1).

1.3.3. Angiotensin receptor blockers

There are no clinical trials of angiotensin receptor blockers (ARBs) specifically in patients with HFmrEF. However, a post hoc analysis of the Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM) program, candesartan reduced the risk of a composite of CV death or HF hospitalization for patients with HFrEF and HFmrEF but not in patients with HFpEF[17]. The CHARM-preserved trial has shown no benefit in patients with HF and LVEF greater than 40%. However, when analyzing with a recurrent-event analysis, candesartan significantly reduced the risk of CV death or recurrent HF hospitalization among the entire cohort, including those with HFmrEF[18].

These data support that ARBs may be considered for patients with HFmrEF to reduce the risk of hospitalization for HF and CV death (Table 1).

1.3.4. Beta-blockers

There are no clinical trials of beta-blockers specifically in patients with HFmrEF. However,

a meta-analysis of eleven landmark randomized controlled trials of beta-blockers demonstrated the consistent benefit on a significant reduction in CV and all-cause mortality in patients in sinus rhythm with HFrEF and HFmrEF but not in those with HFpEF[19].

These data support that beta-blockers may be considered for patients with HFmrEF to reduce the risk of CV and all-cause mortality, especially in patients with sinus rhythm (Table 1).

1.3.5. Mineralocorticoid receptor antagonist

There are no clinical trials of mineralocorticoid receptor antagonist (MRA) specifically in patients with HFmrEF. However, in a post hoc analysis of the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) study, which enrolled patients with HF and LVEF of 45% or greater, spironolactone showed more benefit for the primary endpoint of a composite of CV death, HF hospitalization, or resuscitated sudden death in patients at the lower end of the LVEF spectrum[20].

This evidence supports the benefit of MRA in selected patients with HFmrEF. MRA should be considered in symptomatic patients with HFmrEF to reduce the risk of CV death and hospitalization for HF (Table 1).

1.3.6. Angiotensin receptor-neprilysin inhibitor

In the Prospective Comparison of ARNI (angiotensin receptor/neprilysin inhibitor) with ARB Global Outcomes in HF with Preserved Ejection Fraction (PARAGON-HF) study, which enrolled patients with HF and LVEF of 45% and greater, sacubitril/valsartan failed to show superiority compared with valsartan for the primary outcome[21]. A prespecified subgroup analysis showed benefits for those with LVEF of 57% or less. Moreover, a pre-specified pooled analysis of 13,195 patients with HF enrolled the PARADIGM-HF (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) and PARAGON-HF trials demonstrated that the treatment effects of sacubitril/valsartan was superior to renin-angiotensin system (RAS) inhibitors, and varied across the LVEF spectrum with greater benefit in patients with LVEF below normal in reduction of a primary composite outcome of CV death and HF hospitalization, particularly HF hospitalization[22].

These data support that sacubitril/valsartan may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and CV death (Table 1).

Section 2. Heart failure with preserved ejection fraction (HFpEF)

2.1. Prevalence and clinical characteristics of HFpEF

HFpEF accounts for more than half of all patients with clinical HF and its prevalence is still growing[23]. Patients with HFpEF experience limitation of exercise capacity and quality of life, frequent hospitalization, and high mortality, similar to patients with HFrEF[24]. Despite similarly poor outcomes, the lower proportion of CV death is observed in individuals with HFpEF[25]. The prognosis of patients with HFpEF remains poor because of the unmet need for effective management and a challenging diagnosis. Nevertheless, there have been new proposed diagnostic criteria and evidence of emerging treatment showing the benefit in this population.

2.2. Diagnosis of HFpEF

2.2.1. Definition of HFpEF

HFpEF is currently defined by symptoms and signs of HF in patients with LVEF of 50% or more and having supportive evidence of increased LV filling pressure at rest or provocative state such as elevated levels of plasma natriuretic peptides, or invasive and non-invasive hemodynamic measurement (Figure 1). HFpEF is a clinical syndrome with heterogeneity and diversity of pathophysiology, clinical phenotype, and comorbidity. In addition, most patients, particularly with mild severity, have non-specific symptoms and signs, such as breathlessness and exercise intolerance, which is similar to several non-cardiac conditions. One-third of patients with HFpEF have natriuretic peptide levels below the diagnostic threshold[26]. All of these make the diagnosis of HFpEF challenging.

2.2.2. H_2FPEF and HFA-PEFF Scores

There have been two score-based diagnostic algorithms, H_2FPEF and HFA-PEFF (Heart Failure Association Pre-test assessment, Echocardiography & natriuretic peptide, Functional testing, Final etiology), proposed to improve the accuracy of diagnosis (Figure 3). The "H2FPEF" score uses a combination of clinical parameters, including age and common comorbidities, and echocardiographic parameters, including pulmonary artery systolic pressure and mitral inflow E velocity over e' velocity[27]. The "HFA-PEFF" score evaluates the pretest probability based on age and comorbidities and uses both functional and structural parameters of echocardiography and elevation of natriuretic peptide levels to diagnose HFpEF[28]. Patients with higher scores are more likely to be HFpEF, with a

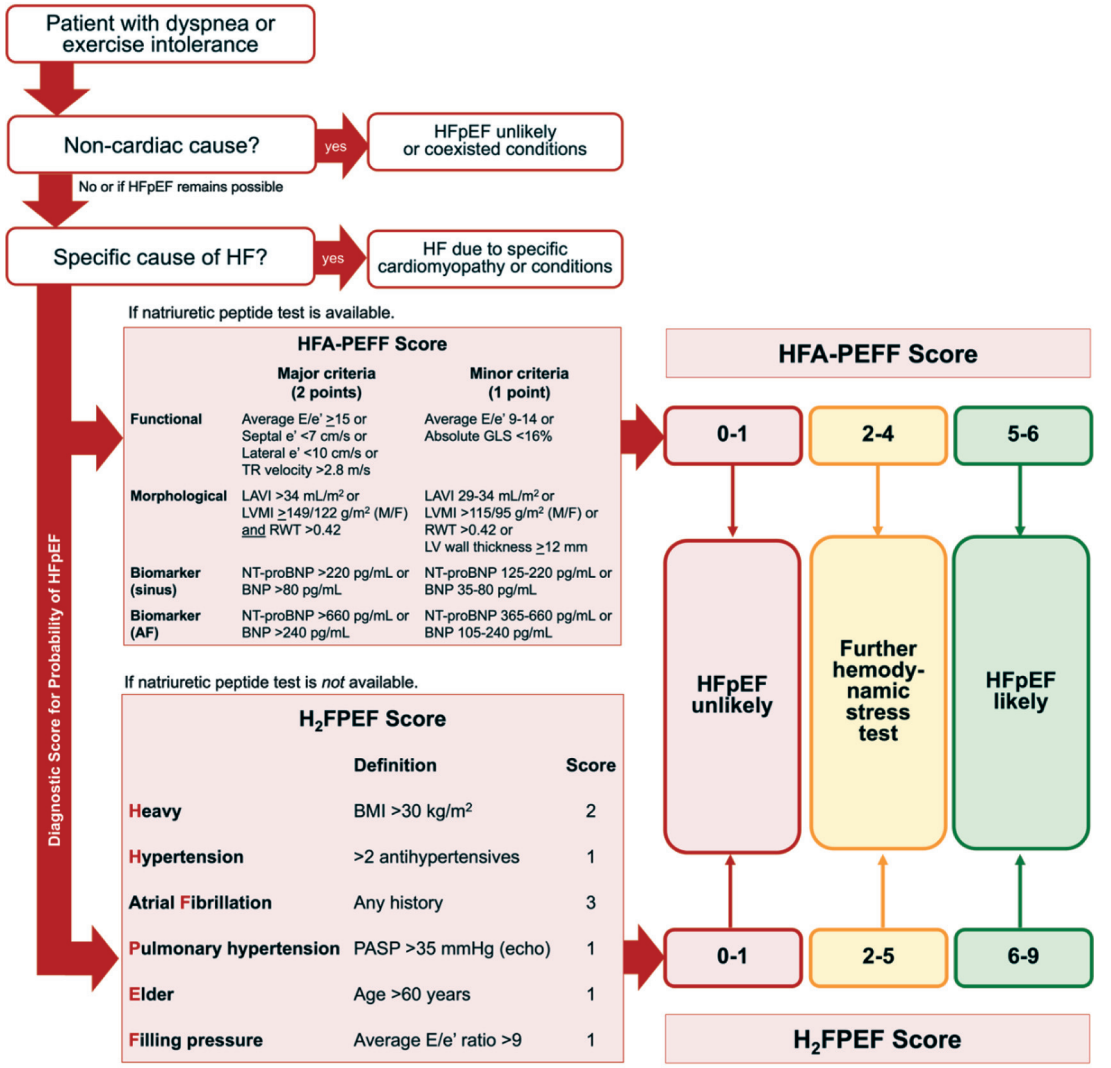

Figure 3. Diagnostic evaluation of HFpEF.

AF indicates atrial fibrillation; BMI, body mass index; BNP, B-type natriuretic peptide; GLS, global longitudinal strain; HFA-PEFF, Heart Failure Association Pre-test assessment, Echocardiography & natriuretic peptide, Functional testing, Final etiology; HFpEF, heart failure with preserved ejection fraction; LAVI, left atrial volume index; LV, left ventricular; LVMI, LV mass index; NT-proBNP, N-terminal pro–B-type natriuretic peptide; PASP, pulmonary artery systolic pressure; RWT, relative wall thickness; and TR, tricupid regurgitation

cut-off level of 6 and 5 or more of the H2FPEF and HFA-PEFF scores, respectively[27,28].

There are limitations of both diagnostic algorithms. Both scoring systems have been validated in trials and cohorts[29-31]. However, their generalizability and diagnostic accuracy have varied, and they have yet to be validated in the Thai population. Patients with the intermediate score also need an additional hemodynamic stress study during exercise, including diastolic stress echocardiography and/or an invasive hemodynamic study. Unfortunately, both diagnostic tests are not available in most institutes in Thailand.

2.2.3. Simplified diagnosis of HFpEF

In the current updated guidelines, the HFCT recommend "the simplified diagnosis criterion of HFpEF" with the combination of symptoms and signs of HF, LVEF of 50% or more, objective evidence of structurally and functionally cardiac abnormalities, and evidence of elevation of LV filling pressure, including echocardiographic findings or elevation of circulating natriuretic peptides (Table 2, Figure 1). The simplified diagnostic criterion is easy to use widely, but there are limitations in its sensitivity and specificity. Some patients with unexplained dyspnea while exertion with likelihood of HFpEF may need

Table 2. Simplified diagnostic criteria of HFpEF

1. Symptoms and signs of heart failure
2. LVEF ≥50%
3. Objective evidence of structurally and/or functionally cardiac abnormalities supporting diastolic dysfunction and elevated LV filling pressure
3.1 Echocardiographic parameters at rest
- LV mass index: ≥95 g/m^2 in female or ≥115 g/m^2 in male
- LA volume index: >34 mL/m^2 in sinus rhythm, >40 mL/m^2 in AF
- Mitral E/average e' ratio >9
- Pulmonary artery systolic pressure >35 mmHg
- Peak TR velocity >2.8 m/s
3.2 Natriuretic peptide levels
- NT-proBNP >125 pg/mL in sinus rhythm or >365 pg/mL in AF
- BNP >35 pg/mL in sinus rhythm or >105 pg/mL in AF

AF=atrial fibrillation; BNP=B-type natriuretic peptide; HFpEF=heart failure with preserved ejection fraction; LA=left atrium; LV=left ventricular; LVEF=left ventricular ejection fraction; NT-proBNP=N-terminal pro-B-type natriuretic peptide; TR=tricuspid regurgitation

additional exercise stress testing, including diastolic stress echocardiography and invasive hemodynamic study during exercise. Physicians should consider referring to the expert centers for a complete diagnostic approach.

2.2.4. HFpEF due to specific cardiomyopathy or conditions

There are potential non-cardiac conditions that may mimic the HFpEF syndrome and need to be excluded, for example, anemia, lung disease, thyroid disorder, obesity, and deconditioning. The common HFpEF-mimic conditions are summarized in Table 3. In patients with supra-normal LVEF, some specific cardiomyopathies such as cardiac amyloidosis and hypertrophic cardiomyopathy, may be considered. Therefore, some selected patients may need further investigation such as cardiac magnetic resonance

Table 3. Specific etiologies of heart failure with LVEF >50%: clinical clues and suggested investigation

Etiology	Clinical clues	Further investigation
Cardiac amyloidosis	• Progressively low blood pressure • Bilateral carpal tunnel syndrome, lumbar spinal stenosis, peripheral neuropathy • Low voltage QRS despite increased LV wall thickness	• Echocardiography with strain imaging • Cardiac MRI with T1 mapping • Nuclear scintigraphy • Serum/urine immunofixation, serum free light chain • Endomyocardial biopsy
Hypertrophic cardiomyopathy	• Family history • High QRS voltage and/or deep T wave inversion in precordial leads by ECG • Unexplained LV hypertrophy, LV outflow tract obstruction	• Echocardiography with strain imaging • Cardiac MRI (if echocardiography is inconclusive)
Cardiac sarcoidosis	• High-grade atrioventricular block in individuals under 60 years of age • Ventricular tachycardia • Extracardiac involvement • Basal interventricular septal thinning or left ventricular aneurysm not caused by coronary artery disease	• Cardiac MRI • FDG-PET scan • Endomyocardial biopsy • Extra-cardiac tissue biopsy
Hemochromatosis	• Family history • History of frequent blood transfusion • Liver disease, diabetes, erectile dysfunction	• Cardiac MRI with T2* imaging • Serum ferritin • HFE genetic testing • Endomyocardial biopsy
Myocarditis	• Flu-like symptoms prior to onset of heart failure • Troponin rising without evidence of acute coronary syndrome • Ventricular arrhythmias, atrioventricular block	• Cardiac MRI • Endomyocardial biopsy
High-output heart failure	• Echocardiographic dilatation of all cardiac chambers, increased LV outflow tract VTI	• Evaluate underlying etiology; e.g., anemia, arteriovenous malformations, cirrhosis, fistulas, thiamine deficiency
Valvular heart disease	• Comprehensive physical examination • Echocardiographic evidence of primary valvular heart disease	• Right/left heart catheterization (if echocardiography is inconclusive) • Cardiac CT for valve calcification in some selected cases
Pulmonary arterial hypertension	• Risk factors of PAH • Echocardiographic evidence of pulmonary hypertension	• Right heart catheterization • Evaluate underlying etiology of PAH
Constrictive pericarditis	• History of cardiac surgery, chest radiation or pericarditis • Right-sided heart failure • Echocardiographic evidence of constrictive pericarditis	• Cardiac CT or MRI • Right/left heart catheterization

CT=computerized tomography; FDG-PET=fluorodeoxyglucose-positron emission tomography; HFE=hereditary hemochromatosis gene; LV=left ventricular; MRI=magnetic resonance imaging; PAH=pulmonary arterial hypertension; VTI=velocity time integral

Table 4. Pharmacological treatment for patients with previous or current symptomatic HFpEF

Recommendations	COR	LOE
Diuretics are recommended in patients with HFpEF with congestion to relieve heart failure symptoms and prevent worsening heart failure.	I	C
Dapagliflozin or empagliflozin are recommended for HFpEF to reduce the risk of hospitalization for heart failure and cardiovascular death.	I	A
MRA should be considered for patients with HFpEF to reduce the risk of hospitalization for heart failure and cardiovascular death, particularly patients with LVEF on the lower end of the spectrum.	IIa	C
Sacubitril/valsartan may be considered for patients with HFpEF to reduce the risk of hospitalization for heart failure and cardiovascular death, particularly patients with LVEF on the lower end of the spectrum.	IIb	B
ARBs may be considered for patients with HFpEF to reduce the risk of hospitalization for heart failure, particularly patients with LVEF on the lower end of the spectrum.	IIb	B

ARBs=angiotensin-receptor blockers; COR=class of recommendation; HFpEF=heart failure with preserved ejection fraction; LOE=level of evidence; LVEF=left ventricular ejection fraction; MRA=mineralocorticoid receptor antagonist

imaging, endomyocardial biopsy, and genetic testing. Referral to the expert centers may be considered.

2.3. Management of HFpEF

After diagnosis of HFpEF is confirmed and alternate diagnosis is excluded, management includes pharmacological and non-pharmacological treatment, and comorbidity management should be initiated.

2.3.1. Pharmacological treatment

Several disease-modifying therapies showing benefits in patients with HFrEF have not demonstrated mortality and morbidity benefits in patients with HFpEF. Fortunately, there has been emerging information supporting the use of medications in patients with HFpEF. Recommendations of pharmacological treatment of HFpEF are shown in Table 4. Guideline-directed medical treatment of HF across the LVEF are summarized in Figure 2.

2.3.1.1. Sodium-glucose co-transporter 2 inhibitor

The EMPEROR-Preserved trial investigated the long-term effects of empagliflozin 10 mg once daily compared to placebo in addition to conventional therapy in patients with symptomatic chronic HF who had a LVEF of more than 40%[8]. All participants were required to have an elevation of serum NT-proBNP and an eGFR of 20 mL/minute/1.73 m² or greater. Therapy with empagliflozin showed a 21% reduction in a primary composite outcome of CV death or hospitalization for HF over the median follow-up period of 26.2 months. The results were consistent in patients with or without diabetes. The primary outcome was driven by a 29% reduction in hospitalization for HF. There was no significant reduction in death from CV cause or any causes. One-third of patients had LVEF between 40% to 50%. The results were consistent across the prespecified subgroups, including LVEF and gender. There was also a significantly slower decline in the eGFR slope in the empagliflozin group.

The DELIVER trial is a randomized controlled trial comparing the effect of dapagliflozin 10 mg once daily versus placebo, in addition to their usual therapy[9]. All patients were required to have LVEF greater than 40%, evidence of structural heart disease, elevation in natriuretic peptides, and eGFR of 25 mL/minute/1.73 m² or higher. Patients with a previous LVEF 40% or less were eligible provided that they had an LVEF greater than 40% at the time of enrollment. Patients could have been enrolled either as outpatients or during hospitalization for HF. Over the median follow-up of 2.3 years, patients who received dapagliflozin had an 18% reduction in a primary composite outcome of CV death or worsening HF. The primary outcome was consistent across all prespecified subgroups, including the presence or absence of diabetes, LVEF, enrollment during or within 30 days of HF or did not occur during or within 30 days of HF hospitalization, and the presence or absence of a previous LVEF of 40% or less that improved to greater than 40% by the time of enrollment. There was no statistically significant reduction in CV death and death from any causes. Dapagliflozin also significantly slowed the rate of decline in eGFR compared with the placebo. The meta-analysis also showed the benefits of SGLT2i for improving the CV outcomes and quality of life in patients with HFpEF[10-14].

These data provide further evidence to recommend dapagliflozin and empagliflozin as essential therapy in patients with symptomatic HF with LVEF of greater than 40% to reduce the risk of CV death and worsening HF. Dapagliflozin and empagliflozin are recommended to use in patients with symptomatic HFpEF to reduce the risk of CV death and hospitalization for HF (Table 4).

2.3.1.2. Angiotensin receptor blockers

Clinical trials with RAS inhibitors (ACEIs and ARBs) have not shown benefit in patients with HFpEF. The CHARM-Preserved trials investigated the effect of candesartan on top of standard of care in participants with symptomatic HF and LVEF greater than 40%[32]. Candesartan did not significantly reduce the primary endpoint of CV death and HF hospitalization. However, patients in the Candesartan group had a lower incidence of HF hospitalization with a borderline statistical significance. A subsequent post-hoc analysis showed the greatest benefit of candesartan in patients in the lowest LVEF spectrum[17].

This evidence supports the benefit of ARBs in selected patients with HFpEF. ARBs may be considered in symptomatic patients with HFpEF to reduce the risk of hospitalization for HF, particularly patients with LVEF on the lower end of the spectrum (Table 4).

2.3.1.3. Angiotensin receptor-neprilysin inhibitor

The PARAGON-HF trial assessed the efficacy of sacubitril/valsartan compared to valsartan, in 4,822 patients with symptomatic HF with LVEF of 45% or more, elevation of natriuretic peptide level, and structural heart abnormalities, including LV hypertrophy or left atrial enlargement by echocardiography[21]. Over the median follow-up of 35 months, there was a trend, although statistically non-significant (p=0.06), to the reduction of the primary composite outcome of total hospitalization of HF and CV death in patients with sacubitril/valsartan group. There was a statistical significance of heterogeneity interaction in pre-specified subgroups. Therapy with sacubitril/valsartan showed a 22% reduction in a primary composite outcome in patients with LVEF at or below the median of 57%[21]. The pre-specified combined analysis of PARADIGM-HF and PARAGON-HF trials showed the therapeutic efficacy of sacubitril/valsartan in patients with LVEF below average, especially in total HF hospitalization[22]. Post-hoc analysis of PARAGON-HF showed a statistically significant reduction in a composite of total worsening HF events, defined by hospitalization for HF and urgent HF visit, and death from CV causes by 14% in the sacubitril/valsartan group[33]. Therapy with sacubitril/valsartan showed better improvement in functional capacity and lowered worsening of renal function[21].

This evidence supports the benefit of sacubitril/valsartan in symptomatic HF with LVEF below normal. Sacubitril/valsartan may be considered in patients with symptomatic HFpEF to reduce the risk of hospitalization for HF, particularly patients with LVEF on the lower end of the spectrum (Table 4).

2.3.1.4. Mineralocorticoid receptor antagonist

The TOPCAT study assessed the efficacy of spironolactone in 3,445 patients with symptomatic HF and LVEF of 45% or greater[34]. Spironolactone did not reduce the primary outcomes of a composite of death from CV causes, aborted cardiac arrest, or hospitalization from HF[34]. However, spironolactone showed a significant reduction of HF hospitalization by 17% over a median follow-up of 3.3 years[34]. Regional variation was observed in a subsequent post-hoc analysis. Participants enrolled in North America has a significant reduction of primary outcomes by 18% in a spironolactone group, whereas there was no benefit among participants enrolled in Russia-Georgia region[35]. Furthermore, a post-hoc analysis of TOPCAT trial showed a greatest benefit of spironolactone in the lower end of LVEF spectrum[20].

This evidence supports the benefit of MRA in selected patients with HFpEF. MRA should be considered in symptomatic patients with HFpEF to reduce the risk of hospitalization for HF, particularly patients with LVEF on the lower end of the spectrum (Table 4).

2.3.2. Non-pharmacological treatment

Physical inactivity and obesity are associated with worse prognosis and quality of life in HFpEF[36,37]. Non-pharmacological interventions have demonstrated benefits in this population. Supervised aerobic exercise training and caloric restriction have demonstrated significant improvement in exercise capacity and quality of life in small randomized clinical trials[38,39]. Enrollment in structured exercise training program may be considered in patient with HFpEF to improve the exercise capacity and quality of life.

2.3.3. Comorbidity management

Comorbidity is common and affects the outcomes and quality of life of patients with HFpEF. Appropriate management of comorbidity is recommended and discussed in detail in the previous 2019 HFCT Guidelines for Heart Failure: Comorbidity in HF[40].

Conclusion

This 2023 HFCT focused update on the 2019 guidelines for management provide the

recommendation for diagnosis and management of HFmrEF and HFpEF as there recently has been emerging evidence supporting the therapeutic options in this population. Significant gaps in evidence and treatment strategies exist and the need for further clinical research remains.

What is already known on this topic?

Since the publication of the 2019 HFCT Heart Failure Guidelines, growing knowledge and new evidence have been published about HFmrEF and HFpEF, leading to the need to update the recommendation.

What does this study add?

In Part 2, the 2023 HFCT Focused Update of the 2019 HFCT Heart Failure Guidelines focused on the diagnosis and management of HFmrEF and HFpEF and provide the new recommendation of SGLT2i, RASi including ARNI and beta blocker for this population.

Conflicts of interest

The authors declare no conflict of interest.

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