2024 Guidelines of the Taiwan Society of Cardiology for the Diagnosis and Treatment of Heart Failure with Preserved Ejection Fraction

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Heart failure with preserved ejection fraction (HFpEF) is a multi-organ systemic syndrome that involves cardiac and extra-cardiac pathophysiological abnormalities. Its growing prevalence causes a major public concern worldwide. HFpEF is usually associated with multiple comorbidities, and non-cardiovascular death is common in patients with HFpEF. In Asia, patients with HFpEF has a younger age, higher prevalence of diabetes and chronic kidney disease than Western countries. A 2-step diagnostic algorithm is recommended in this guideline. In the first step, the diagnosis of HFpEF can be made if patients have symptoms and/or signs of heart failure, left ventricular ejection fraction ≥ 50%, increased natriuretic peptide, and objective evidence of left atrial or left ventricular abnormalities or raised left ventricular filling pressure. If diagnosis is still uncertain, invasive or noninvasive stress test can be performed in the second step. Comorbidities need to be controlled in HFpEF. Weight reduction for obesity and supervised exercise training are recommended for HFpEF. For pharmacological therapy, diuretic is used to relieve congestion and sodium-glucose cotransporter 2 inhibitor, empagliflozin or dapagliflozin, is recommended to improve prognosis of HFpEF. The research on HFpEF is advancing at a rapid pace. It is expected that newer modalities for diagnosis and management of HFpEF could appear in the near future.

Key Words: Guideline • Heart failure with preserved ejection fraction • Taiwan

Abbreviations

ACEI	Angiotensin converting enzyme inhibitor
AF	Atrial fibrillation
AHA GWTG-HF	American Heart Association Get With The Guideline-HF
ARB	Angiotensin receptor blocker
ARNI	Angiotensin receptor-neprilysin inhibitor
ATTR-CM	Transthyretin amyloid cardiomyopathy
BMI	Body mass index
BNP	B-type natriuretic peptide
CAD	Coronary artery disease
CHARM-Preserved	Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity-Preserved
CKD	Chronic kidney disease
COR	Class of recommendation
CT	Computed tomography
CV	Cardiovascular
CXR	Chest X-ray
DKA	Diabetic ketoacidosis
DM	Diabetes mellitus
ECG	Electrocardiography
EF	Ejection fraction
eGFR	Estimated glomerular filtration rate
GLP1RA	Glucagon-like peptide-1 receptor agonists
HCM	Hypertrophic cardiomyopathy
HF	Heart failure
HFmrEF	HF with mildly reduced ejection fraction
HFnEF	HF with normal EF
HFpEF	Heart failure with preserved ejection fraction
HFrEF	HF with reduced ejection fraction
I-Preserve	Irbesartan in Heart Failure with Preserved Ejection Fraction Study
LA	Left atrial
LOE	Level of evidence
LV	Left ventricular
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
MRA	Mineralocorticoid receptor antagonist
MRI	Magnetic resonance imaging
NT-proBNP	N-terminal proB-type natriuretic peptide
PARAGON-HF	Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction
PCV13	13-valent pneumococcal conjugate vaccine
PCWP	Pulmonary capillary wedge pressure
PET	Positron emission tomography
PPV23	23-valent pneumococcal polysaccharide vaccine
RATE-AF	Rate Control Therapy Evaluation in Permanent Atrial Fibrillation
REHAB-HF	Rehabilitation Therapy in Older Acute Heart Failure Patients
RV	Right ventricular
SGLT2	Sodium-glucose cotransporter 2
STRONG-HF	Safety, Tolerability and Efficacy of Up-titration of Guideline-directed Medical Therapies for Acute Heart Failure
TOPCAT	Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist
TR	Tricuspid regurgitation
TTE	Transthoracic echocardiography
US	United States

INTRODUCTION

Heart failure with preserved ejection fraction (HFpEF) is diagnosed as those with symptoms and/or signs of heart failure (HF), left ventricular (LV) ejection fraction (EF) of 50% or greater, elevated natriuretic peptide and cardiac structural change or diastolic dysfunction.[1,2] The growing trend of HFpEF causes public health problem worldwide, including in Asia.[3,4] For many years, how to make a correct diagnosis of HFpEF is still controversial. There is a consensus that the diagnosis of HFpEF needs evidence of elevated cardiac filling pressure and natriuretic peptide with the presence of structural heart disease.[5] Traditionally, management of comorbidities and relief of congestion with diuretics are the main therapies for HFpEF. In recent years, a number of randomized clinical trials demonstrated that some medical therapies could change the natural course of HFpEF and effectively reduce the risk of HF hospitalization. The Taiwan Society of Cardiology published HF Guideline in 2012 and its focus update in 2019.[1,6] Since there have been new scientific evidences regarding the epidemiology, diagnosis and treatment of HFpEF after 2019, the HF committee of Taiwan Society of Cardiology decided to create a new HF guideline specifically for HFpEF.

The guideline writers were invited mainly from the Taiwan Society of Cardiology HF committee which consisted of 15 members nominated by the President of Taiwan Society of Cardiology and endorsed by the Society's board meeting in 2022. Three writer meetings were held on April 16, 2023 in Taipei, June 17, 2023 in Taichung and September 24, 2023 in Kaohsiung. During the meetings, the panel decided the main contents of the HFpEF guideline, including definition, epidemiology, pathophysiology, diagnosis, treatment and future perspective. The writers assigned to one of these sections were responsible for collecting available evidence, reviewing its scientific intensity and making proper recommendations. Consensus about guideline recommendations was achieved by all writers during the meetings. Similar to the recently published guidelines from the Taiwan Society of Cardiology,[7] this guideline adopted class of recommendation (COR) to indicate whether a recommendation is useful or harmful and level of evidence (LOE) to describe the strength of scientific evidence about the recommendations. In COR, Class I recommendations indicate they

are useful and beneficial for the patients. Class IIa recommendations indicate that the evidence favors the recommendations and could be used for the patients. Class IIb recommendations are those may be considered but the scientific strength is less well established. Class III recommendations are the treatment that is unnecessary or harmful. There are three levels for LOE. LOE A recommendations are supported by multiple randomized clinical trials or meta-analyses of randomized clinical trials. LOE B recommendations are from only one randomized clinical trial or non-randomized observational studies. LOE C recommendations are from case series, case reports or consensus of expert opinions.

DEFINITION

HF is a complex clinical syndrome that results from impaired cardiac function, leading to an inability of the heart to meet the body's metabolic demand adequately.[8] Conventionally, HF can be categorized into three main subtypes based on left ventricular ejection fraction (LVEF), a measure of the heart's pumping efficiency. These subtypes are HF with reduced ejection fraction (HFrEF), HF with mildly reduced ejection fraction (HFmrEF), and HFpEF (Table 1).[2,5,9] An expert consensus from the Taiwan Society of Cardiology suggests to reclassify those patients with LVEF $\geq$ 60% as HF with normal EF (HFnEF).[10] HFpEF, previously known as diastolic HF, refers to a clinical syndrome in which patients have signs and symptoms of HF but have a relatively normal EF. The LVEF in HFpEF is typically greater than or equal to 50%.[2,5,9] It is important to note that the definition of HFpEF is not solely based on the EF but includes additional clinical criteria. The EF alone is not sufficient to establish the diagnosis. Additional criteria are necessary to differentiate HFpEF from other causes of dyspnea and to ensure that the clinical syndrome is primarily due to diastolic dysfunction. These criteria include: (1) HF symptoms and/or signs. Patients with HFpEF typically present with exertional dyspnea, fatigue, exercise intolerance, and fluid retention leading to peripheral edema. Elevated jugular venous pressure, pulmonary rales, and peripheral edema often accompany these symptoms. (2) Evidence of structural heart disease. HFpEF is frequently associated with underlying structural heart abnormalities, including LV hypertrophy, increased left atrial (LA) size, and diastolic dysfunction. Echocardiography is commonly used to assess these structural abnormalities and to measure the EF. (3) Evidence of diastolic dysfunction. Diastolic dysfunction refers to abnormalities in the filling of the ventricles during diastole. In HFpEF, impaired relaxation, increased ventricular stiffness, and abnormal filling pressure are commonly observed. These abnormalities can be assessed using Doppler echocardiography which provides information on transmitral flow velocities, pulmonary venous flow, and tissue Doppler imaging. (4) Additional diagnostic tests. In some cases, additional tests may be required to establish the diagnosis of HFpEF and exclude other causes of patients' symptoms. These tests may include cardiopulmonary exercise testing, cardiac catheterization, magnetic resonance imaging (MRI), or nuclear imaging studies.

Recommendation

- HFpEF is defined as the presence of HF symptoms and/or signs with LVEF $\geq$ 50%, structural heart disease and diastolic dysfunction. (COR I, LOE A)

EPIDEMIOLOGY

Prevalence and incidence of HFpEF

In Taiwan, the prevalence of HF may be as high as

Table 1. Definition of heart failure

Type of HF	HFpEF		HFmrEF	HFrEF
LVEF	$\geq$ 50%		41-49%	$\leq$ 40%
	• Symptoms/signs • Evidence of structural and/or functional cardiac abnormalities and LV diastolic dysfunction		• Symptoms/signs	• Symptoms/signs

Natriuretic peptide is usually elevated in HF.
HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LV, left ventricular; LVEF, left ventricular ejection fraction.
* Modified from reference 9.

6%.[11] A recent analysis using HF hospitalization as an adjudicated event showed that the HF prevalence in Taiwan is estimated to be 1.63 to 1.99% from 2020 to 2025.[12] Overall, the projected HF burden in Taiwan will resemble the findings from the United States (US) with an estimated tripled HF prevalence in 2050.[12] Similar to the global trend, the HF incidence is decreasing in Taiwan with an estimated incidence of 2.44 in 2001 to 2.19 per 1000 person-years in 2016.[12,13] However, the age-stratified HF incidence is different with 10-20% decrease in older individuals (≥ 55 years), but approximately 4% increase among younger population (< 44 years).[12,13]

According to the registry data from Western countries, near half of the patients with HF have HFpEF. In patients admitted due to HF between 2005 and 2009 in the American Heart Association Get With The Guideline-HF (AHA GWTG-HF) registry, a prevalence of 46% HFpEF was found.[14] The Olmsted County cohort from the US showed that 52.5% of patients with incident HF were HFpEF.[15] Overall, the prevalence of HFpEF was increasing, but HFrEF prevalence seemed to be stable or declining.[3,16,17] For incidence of HFpEF, the Olmsted County cohort from the US showed that the age- and sex-adjusted incidence of HF declined substantially with a 45% decrease in HFrEF compared with 28% in HFpEF.[15] But more recent data from the Framingham Heart Study and Cardiovascular Health Study, a declining incidence for HFrEF and increasing incidence for HFpEF was oberved.[18] Table 2 shows the prevalence and incidence of HFpEF in different registries or population-based studies.

Recommendation
- There is an increasing prevalence of HFpEF, but the prevalence of HFrEF is stable or declining. (COR I, LOE A)

Table 2. Relative distribution of HFpEF in cross-sectional and longitudinal observational studies

Prevalence of HFpEF	HFrEF	HFmrEF	HFpEF
Study name			
European Society of Cardiology Long-Term Registry	60%	24%	16%
Swedish HF Registry	56%	21%	23%
Multicentre nationwide Italian Network (Spain)	32%	16%	52%
UK-HEART Study	NA	NA	31%[†]
Cardiovascular Health Study	NA	NA	22%*
ADHERE Inpatient Cohort	NA	NA	50%
OPTIMIZE-HF Registry (United States)	49%	17%	24%
Framingham Heart Study (1981-2008)	NA	NA	43%[‡]
Get With The Guidelines-HF (GWTG-HF)	39%	14%	47%
Strong Heart Study (American Indians)	NA	NA	53%*
ADHERE Inpatient Cohort	NA	NA	50%[#]
Global Congestive Heart Failure Registry	54%	21%	24%
Pooled Community Cohorts (Framingham Heart Study, Cardiovascular Health Study, Prevention of Renal and Vascular End-Stage Disease, Multi-Ethnic Study of Atherosclerosis)	NA	NA	48%[‡]
Multicenter Inpatient Cohort (Japan, 2013 to 2014)	36%	21%	43%
Asian-HF Registry	81%	NA	19%
China Hypertension Survey (China, 2012-2015)	40%	23%	37%

Incidence of HFpEF	HFrEF	HFpEF
Study name		
PREVEND Prevention of Renal and Vascular End-Stage Disease (Dutch Community)	66% (< 40%)	34% (≥ 50%)
Olmsted County, Minnesota (2008-2010)	48% (< 50%)	52% (≥ 50%)
Framingham Heart Study/Cardiovascular Health Study (≥ 60 years, 2000-2009)	45% (< 50%)	55% (≥ 50%)
Longitudinal American Community-Based Cohort	52%	48%
Among Canadian Inpatients (Ontario, 1999-2001)	56%	31%
Dutch Community Based Cohort	66%	34%

Abbreviations are the same as the Table 1. NA, not applicable.
LVEF cutoffs: * LVEF ≥ 55%, [†] LVEF ≥ 50%, [‡] LVEF ≥ 45%, [#] LVEF ≥ 40%.

Risk factor, comorbidity and phenotype of HFpEF

Compared with HFrEF, patients with HFpEF tend to be older, predominantly female, and are associated with multiple comorbidities.[16] Older age is strongly associated with HFpEF. On the contrary, the risk factors, such as male sex, previous myocardial infarction (MI), LV hypertrophy, and left bundle branch block, are more commonly associated with HFrEF rather than HFpEF.[19] Lifestyle factor may also play a role as a risk of HFpEF. Previous study showed that individuals with more leisure-time physical activity had a lower risk of HFpEF than those with no leisure-time physical activity; whereas no such association was observed for the risk of HFrEF.[20] Comorbidities are common in patients with HFpEF, including hypertension, diabetes mellitus (DM), chronic kidney disease (CKD), coronary artery disease (CAD), atrial fibrillation (AF), obesity, obstructive sleep apnea, and metabolically associated fatty liver disease.[21-29] Because HFpEF is highly heterogeneous with multiple different comorbidities, several analyses have been performed in clustering patients with HFpEF into different phenotypes. Although there were different methods to classify the patients, several phenotypes of HFpEF are commonly identified, including diabetes and obesity, AF and CKD, young patients with milder HF symptoms and fewer comorbidities, men with AF, and elderly frail women with AF.[30] The findings of diverse phenotypes in patients with HFpEF increase the potential for phenotype-specific treatment in such populations.[31-33] Compared to the findings from Western countries, the comorbidities of HFpEF in Asia demonstrated a younger age, lower prevalence of CAD, AF, and obesity, but a higher prevalence of diabetes and CKD.[34,35] One unique HFpEF phenotype in Asia is patients with lean diabetes.[35] The clinical features of HFpEF in Taiwan were similar to those reported from the Asian studies.[36,37]

Recommendation

- HFpEF patients tend to be older, predominantly female, and are associated with multiple comorbidities. (COR I, LOE A)
- The Asian HFpEF patients tend to be younger and have higher prevalence of diabetes and CKD than Western countries. (COR I, LOE A)

Outcome of HFpEF

Several studies from the US showed that the secular HF hospitalization rates were increasing over time and largely driven by HFpEF events.[38,39] A greater proportion of HFrEF hospitalization was attributed to the male sex, while a greater proportion of HFpEF hospitalization occurred in the female population. Hospitalization for cardiovascular (CV) causes appeared to be higher in individuals with HFrEF. However, non-CV hospitalization was comparable between HFrEF and HFpEF indicating a higher impact of non-CV related comorbidities on HFpEF hospitalization.[40] Albeit the total hospitalization rate among HF patients was similar irrespective of LVEF, the short-term hospitalization rate within 1 year after discharge was still higher in patients with HFrEF than HFpEF.[41,42] Overall, patients with HF have higher 30-day readmission rate after discharge compared with patients admitted with other diagnoses and HF remains the number one cause of hospitalization in the older population.[43]

In Taiwan, the mortality of HF was estimated to be 22.5%, 33.9%, and 42.8% at 1, 2, and 3-year follow-up, respectively. A longer duration study showed the mortality was 62.1%, 69.6%, and 75.5% at 6, 8, and 10-year follow-up.[12,13] Another 16-year analysis in Taiwan revealed an in-hospital mortality rate of 4.12% in patients with newly diagnosed HF and the mortality after discharge was estimated to be 38.5%, 52.2%, 62.1%, 69.6%, and 75.5% at 2, 4, 6, 8, and 10-year follow-up, respectively.[12,44] In general, patients with HFpEF tended to have better overall survival than those with HFrEF.[14,16] In the Asian-HF registry, the crude annual all-cause mortality rate was higher in patients with HFrEF than in those with HFpEF.[45] Importantly, most of the causes of death were CV death among patients with HFrEF.[46] In contrast, non-CV death was more frequent in patients with HFpEF. In Asia, the risk of CV death was slightly higher in patients with HFrEF than in those with HFpEF, whereas non-CV death was more frequent in patients with HFpEF than HFrEF at 1-year follow-up.[45]

Recommendation

- Patients with HFpEF have a better survival than HFrEF and non-CV death is more frequent in patients with HFpEF. (COR I, LOE A)

Cardiomyopathy

HFpEF can be presented in most patients with obstructive hypertrophic cardiomyopathy (HCM) and approximately 10% of patients with nonobstructive HCM.[47]

HCM is an important genetic heart muscle disease, however, its prevalence in the general population has not yet been completely resolved. Most data indicate that the occurrence of HCM is approximately 1 in 500 individuals. However, recent studies suggest that the prevalence of HCM may be more common than previously estimated. A timely diagnosis and treatment are crucial since the development of advanced HF in HCM portends a poor prognosis.[48,49] Infiltrative cardiomyopathy is a heterogeneous group of disease and may present with HFpEF. Among them, transthyretin amyloid cardiomyopathy (ATTR-CM) is an under-recognized cause of HFpEF. In Taiwan, late-onset hereditary ATTR amyloidosis with the A117S mutation and polyneuropathy is often associated with heart involvement. Recent studies have suggested that 10-15% of older adults with HF may have an unrecognized ATTR-CM. The associated carpal tunnel syndrome and lumbar spinal stenosis may raise clinical suspicion and early diagnosis.[50,51] Fabry disease is a X-linked inborn error of glycosphingolipid metabolism due to alpha-galactosidase A deficiency. Newborn screening identified a high frequency of Taiwanese male with Fabry disease (approximately 1 in 1250) with 86% having the IVS4+919G>A mutation.[52] HFpEF is common in infiltrative cardiomyopathy. Irrespective of the etiology, HF is a harbinger of poor outcomes of cardiomyopathy. Disease-modifying therapies are available for cardiac amyloidosis and Fabry disease and carry potential to improve outcomes.

Recommendation

- HFpEF can be presented in most patients with hypertrophic or infiltrative cardiomyopathy. (COR I, LOE A)

PATHOPHYSIOLOGY

The pathophysiology of HFpEF involves multisystem abnormalities with different mechanisms, including cardiac dysfunction (left or right heart), vascular dysfunction, peripheral tissue abnormality, or cardiomyopathy (hypertrophic or infiltrative).

Cardiac dysfunction

LV diastolic dysfunction

Although the pathophysiological mechanisms of HFpEF are multiple and cross-linked, LV diastolic dysfunction forms a major basis of the clinical syndrome of HFpEF.[53-58] However, it does not fully represent the whole pathophysiological abnormalities of HFpEF.[58] Diastolic dysfunction results from decreased LV chamber distensibility and causes increased diastolic pressure at any given LV volume. Patients with HFpEF display an abnormal LV diastolic pressure-volume relationship that is shifted up and to the left indicating an increase in passive chamber stiffness. The primary factors affecting myocardial stiffness include abnormalities in extracellular matrix, cardiomyocytes, matricellular proteins, calcium ion homeostasis, myocardial energy supply, and increased fat content in myocardium and pericardium.[59-62] Patients with HFpEF display prolonged relaxation and inability to hasten relaxation as heart rate increases during exercise.[63,64] Prolonged relaxation usually does not affect LV filling when heart rate is normal at rest, but it significantly increases LV filling pressure during exertion as cycle length shortens in tachycardia. In patients at early stage of HFpEF, LV filling pressure becomes markedly elevated only during exercise; however, at advanced stage of HFpEF, LV filling pressure is elevated even at rest.[65] Increased LV filling pressure during exertion in HFpEF directly correlated with heightened inspiratory drive, symptoms of dyspnea, alterations in gas exchange and pulmonary ventilation, and reduction in aerobic capacity. Elevation in LV filling pressures alters the Starling force across the pulmonary capillaries, pushing water out of the vascular space into the interstitium. Over time, high LV filling pressure may promote vascular remodeling, particularly in pulmonary veins.

LV systolic dysfunction

HFpEF is defined as HF with normal or nearly normal LVEF, but EF is only a rough estimate of LV contractile function. Actually, LV systolic function is relatively impaired in patients with HFpEF compared with the age-matched healthy controls.[66] Impairment in myocardial and chamber-level function is present at rest and becomes more severe during exercise.[66-68] This limits the ability of the heart to increase stroke volume and substantially impairs the cardiac output to meet the need in exercise. In addition, LV systolic reserve deficits compromise diastolic reserve because the ability to enhance contractility plays a key role in determining the restoring force

that enhances early diastolic annular motion or recoil.

Left atrial dysfunction

As the LV diastolic filling pressure elevates intermittently over time in HFpEF, secondary remodeling and dysfunction develop in the LA. Preservation of LA function may be an important adaptation in HFpEF because development of LA dysfunction is associated with worse exercise capacity, more profound pulmonary vascular disease, and increased risk of death.[69] LA remodeling and dysfunction are common features in AF and HFpEF which are frequently coexisting conditions. Both conditions also share several common comorbidities such as hypertension, diabetes and obesity.[17,25,70-72] HFpEF causes AF due to the structural and functional remodeling of the LA, while AF is also associated with LV myocardial fibrosis that contributes to LV diastolic dysfunction and HFpEF.

Coronary microvascular dysfunction

Coronary microvascular dysfunction is a common phenomenon in patients with HFpEF and causes demand-supply mismatch. In the functional aspect, low coronary flow reserve in HFpEF causes impaired myocardial oxygen delivery so that myocardial ischemia and injury occur especially during exercise.[73-75] Myocardial systolic and diastolic reserves both decrease when the severity of coronary microvascular dysfunction increases. In the anatomic aspect, coronary microvascular rarefaction and myocardial fibrosis are noted in an autopsy study of patients with HFpEF.[76] Based on these evidence, coronary microvascular dysfunction seems to be another mechanism that contribute to HFpEF and may be a therapeutic target.

Chronotropic incompetence

Exercise intolerance is partly related to lower peak heart rate achieved in HFpEF patients. Because increasing heart rate is the major contributor of cardiac output during exercise, impairment in heart rate reserve can lead to exertional intolerance. The mechanism of inability to increase heart rate in HFpEF patients is not fully understood. Premature cessation of exercise due to elevated LV filling pressure and beta-blocker use may account for lower maximal heart rate in some patients with HFpEF. Autonomic dysfunction and reduced cardiac beta-receptor response are also observed in some HFpEF patients. However, all these theories only partially explain the chronotropic incompetence in HFpEF.[77,78]

Right ventricular dysfunction

Right ventricular (RV) dysfunction leads to augmented right heart distention and elevated LV filling pressure.[79] Longstanding pulmonary hypertension in HFpEF eventually causes RV dysfunction which is seen in 20%-35% of patients with HFpEF.[80] However, this is not mediated purely by afterload mismatch. RV dysfunction was also independently correlated with male sex and AF which may influence RV function in a load-independent manner. Other potential contributing comorbidities include coronary disease and lung disease.[81,82] The presence of RV dysfunction is associated with increased morbidity and mortality of HFpEF.[83,84]

Vascular dysfunction

Abnormal systemic vascular function

Peripheral vascular function is impaired in HFpEF patients. During exercise, macrovascular stiffness increases and can be reversed by inorganic nitrite.[85,86] It has been reported that the increase of adipocyte free fatty acid binding protein contributes to central arterial stiffness.[87] In the microvascular level, endothelial dysfunction and inflammation lead to impaired flow-mediated and NO-mediated vasodilation.[65,88] Because of systemic vascular dysfunction, the arterial elastance, an estimate of afterload, elevates more than the LV end-systolic elastance, an estimate of LV chamber performance, during exertion and causes ventricular-arterial uncoupling. Abnormal ventricular-arterial coupling develops even at low-level workload.[65,89] Ventricular-arterial uncoupling can be reflected by decreased carotid arterial strain and may serve as a prognostic indicator of HFpEF.[90]

Abnormal pulmonary vascular function

Pulmonary hypertension is defined as mean pulmonary artery pressure > 20 mmHg.[91] Pulmonary hypertension and pulmonary vascular remodeling are present in about 70%-80% of patients with HFpEF.[92] Impaired pulmonary vascular function displays a unique pathophysiology similar to RV dysfunction.[79] In addition, even patients with HFpEF have normal pulmonary vascular resistance at rest, some of them may have inadequate pul-

monary vasodilation in response to exercise.[93] Cardiopulmonary exercise testing may provide some diagnostic clues of abnormal pulmonary hemodynamic response in HFpEF. Using stress echocardiography to non-invasively evaluate mean pulmonary artery pressure – cardiac output relationship, it was found that patients with HFpEF and exercise-induced pulmonary hypertension have worse exercise capacity, lower peak oxygen consumption and depressed RV systolic function.[94] These patients also had higher rates of composite outcomes of all-cause mortality or HF events.[94]

Peripheral tissue abnormality

In addition to CV system, abnormalities in peripheral tissue also contribute to the pathophysiology of HFpEF. The oxygen diffusion and extraction in skeletal muscle are impaired in patients with HFpEF.[69,95,96] Mitochondrial dysfunction, including content and structure abnormalities, in skeletal muscle leads to exercise intolerance as well.[97] The coexistence of obesity and sarcopenia, so called "sarcopenic obesity", is quite often in patients with HFpEF and is associated with adverse clinical outcomes.[98]

Hypertrophic/infiltrative cardiomyopathy

HCM and infiltrative cardiomyopathy are HFpEF mimics which have distinct pathophysiology and clinical outcome. Both of them can present with classic symptoms of HFpEF. Careful history taking, physical examination, and echocardiography are helpful to identify cardiac amyloidosis, cardiac sarcoidosis, hemochromatosis, and Fabry disease. In addition, some gene mutations have been reported to cause cardiomyopathy, such as MYH7 and MYBPC3 gene mutations for HCM, transthyretin gene mutation for cardiac amyloidosis, and GLA gene mutation for Fabry disease.[99] Diagnostic tests for these HFpEF mimics are crucial because there are specific treatments once the diagnosis is made.[100]

In summary, HFpEF is a common form of HF in the elderly, especially in women, and those with multiple comorbidities.[101,102] Table 3 summarizes the pathophysiology of HFpEF that maybe involved in aging, female, and different comorbidities.

Recommendation

- Pathophysiology of HFpEF involves cardiac dysfunction, vascular dysfunction, peripheral tissue abnormality, and cardiomyopathy. (COR I, LOE A)
- Correct diagnosis of hypertrophic or infiltrative cardiomyopathy in patients presenting with HFpEF is important. (COR I, LOE A)

DIAGNOSIS

HF symptoms and signs

To identify symptoms and signs of HF is the beginning step to diagnose HFpEF. The Framingham Diagnostic Criteria describe the major symptoms or signs indicating the presence of HF (Table 4). The criteria are derived from the information gathered during the Framingham Heart Study.[103] A HF diagnosis requires the presence of two major criteria or one major and two minor criteria. The major criteria include orthopnea or paroxysmal nocturnal dyspnea, jugular venous distension, hepatojugular reflux, rales, S3 gallop rhythm, pulmonary edema, and cardiomegaly. The minor criteria include exertional dyspnea, nighttime cough, ankle edema, tachycardia with a heart rate surpassing 120 beats per minute, hepatomegaly, and pleural effusion. Dyspnea or ankle edema are common first presentations of HFpEF. However, it is necessary to make a differential diagnosis and consider other causes before making the diagnosis of HF. For dyspnea, the differential diagnosis includes cardiac diseases other than HF, pulmonary diseases and other causes, such as anemia, neuromuscular disease and anxiety. For edema, renal failure, lymphedema, liver cirrhosis, and drug-related ankle edema (for example, dihydropyridine calcium-channel blockers) should be ruled out.

History and physical examination

Initial assessment of patient with suspected HFpEF includes history and physical examination. An important part of the history and physical evaluation is the scrutiny of clinical congestion which is the manifestation arising from heightened cardiac filling pressures. Addressing congestion is pivotal for adjusting medications and is intertwined with the quality of life and prognosis of HF patients. Various methods exist to evaluate clinical congestion, encompassing the presence of jugular venous distention, orthopnea, bendopnea, a square-wave response to the Valsalva maneuver, and leg edema.[104-106]

Table 3. Pathophysiology of HFpEF involved in aging, female, and different comorbidities

Common comorbidities in HFpEF	Involved pathophysiology
General	
Aging	LV diastolic dysfunction
	LV systolic dysfunction
	Chronotropic incompetence
	Systemic vascular dysfunction
	Peripheral tissue abnormality
Female	LV diastolic dysfunction
	Coronary microvascular dysfunction
	Systemic vascular dysfunction
	Pulmonary vascular dysfunction
Cardiovascular	
Atrial fibrillation	LV diastolic dysfunction
	LA dysfunction
Hypertension	LV diastolic dysfunction
	LV systolic dysfunction
	LA dysfunction
	Coronary microvascular dysfunction
	Systemic vascular dysfunction
Coronary artery disease	LV diastolic dysfunction
	LV systolic dysfunction
	Coronary microvascular dysfunction
Respiratory	
Chronic obstructive pulmonary disease	LV diastolic dysfunction
	RV dysfunction
Sleep apnea syndrome	Pulmonary vascular dysfunction
Metabolic	
Diabetes mellitus	LV diastolic dysfunction
	Coronary microvascular dysfunction
	Chronotropic incompetence
	Systemic vascular dysfunction
	Peripheral tissue abnormality
Obesity	LV diastolic dysfunction
	LV systolic dysfunction
	Coronary microvascular dysfunction
	Systemic vascular dysfunction
	Peripheral tissue abnormality
Nephrogenic	
Chronic kidney disease	LV diastolic dysfunction
	Coronary microvascular dysfunction
	Systemic vascular dysfunction

HFpEF, heart failure with preserved ejection fraction; LA, left atrial; LV, left ventricular; RV, right ventricular.

Table 4. The Framingham diagnostic criteria of heart failure

Major Criteria	Minor criteria
• Acute pulmonary edema	• Ankle edema
• Cardiomegaly	• Dyspnea on exertion
• Hepatojugular reflux	• Hepatomegaly
• Neck vein distention	• Nocturnal cough
• Paroxysmal nocturnal dyspnea or orthopnea	• Pleural effusion
• Pulmonary rales	• Tachycardia (heart rate greater than 120 beats per minute)
• Third heart sound (S3 gallop)	

* Modified from reference 103. Diagnosis of heart failure requires the presence of two major criteria or one major and two minor criteria.

History and physical examination also help to identify the potential causes of clinical deterioration in stable HF, such as myocardial ischemia, pulmonary emboli, or systemic infection. History is important in identification of inherited cardiomyopathies through familial history or other specific conditions such as amyloid heart disease. Body weight should be evaluated because the severity of obesity is another important issue in HFpEF.

Laboratory test

Electrocardiography (ECG) is a routine examination for suspected HFpEF because the data of rhythm, heart rate, QRS morphology/duration provide vital information of the potential underlying causes and prognosis of HFpEF. Chest X-ray (CXR) is another valuable initial diagnostic tool. It enables the evaluation of cardiac size, pulmonary congestion, as well as pleural effusion. Additionally, it has the potential to unveil alternative pulmonary causes of the patient's symptoms.[107] Initial blood examination include a complete blood count, electrolytes, urea nitrogen, creatinine, glucose, fasting lipid profile, and liver function test. Other studies, including iron profile (serum iron, ferritin, transferrin saturation) and thyroid-stimulating hormone level, may be necessary to find coexisting conditions that are contributors or confounders of patients' symptoms.

Recommendations

- A thorough history and physical examination should be performed to search for HF symptoms/signs. (COR I, LOE C)
- Initial evaluation should include 12-lead ECG and CXR. (COR I, LOE C)
- Initial blood examination includes complete blood count, renal function, electrolytes, lipid profile and liver function test. (COR I, LOE C)

HF biomarker

Natriuretic peptide assay, including B-type natriuretic peptide (BNP) or N-terminal proB-type natriuretic peptide (NT-proBNP), is commonly used to confirm the presence and severity of HFpEF. Generally, the levels of BNP and NT-proBNP are comparable, rendering either one is suitable for clinical use.[108,109] When evaluating dyspnea of potentially cardiac origin, measuring BNP and NT-proBNP levels offers important diagnostic insight, par-

ticularly when the cause of dyspnea remains uncertain and physical examination yields inconclusive results. Normal BNP and NT-proBNP levels aid in excluding the diagnosis of HF, however, the natriuretic peptide levels are usually not increased in HF patients with obesity and diminish their diagnostic accuracy.[110,111] Elevated levels of natriuretic peptide possess a strong positive predictive value for HFpEF diagnosis. But it is noteworthy that both BNP and NT-proBNP levels can rise in individuals with a range of noncardiac conditions.[112,113] The normal levels of natriuretic peptide can be considered as a first-line tool to exclude the diagnosis of HF. To avoid overdiagnosis, we suggest NT-proBNP > 300 pg/ mL or BNP > 100 pg/mL as the cut off values to diagnose HF in sinus rhythm and NT-proBNP > 600 pg/mL or BNP > 150 pg/mL for AF. In Taiwan, other biomarkers including galectin-3 and matrix metalloproteinase-2 were reported to be significantly associated with global cardiac fibrosis in HFpEF patients.[114] Connective tissue growth factor was documented to be associated with the presence of HFpEF.[115] Serum CA-125 was also mentioned to serve as a novel biomarker for HFpEF in women.[116]

Recommendations

- NT-proBNP or BNP should be measured in patients with suspected HFpEF. (COR I, LOE A)
- HF should be considered when NT-proBNP > 300 pg/ mL or BNP > 100 pg/mL in sinus rhythm and NT-proBNP > 600 pg/mL or BNP > 150 pg/mL for AF. (COR I, LOE A)

Cardiac imaging

Cardiac imaging plays a pivotal role in the assessment of individuals with suspected HFpEF. Transthoracic echocardiography (TTE) stands as the most valuable initial diagnostic imaging tool. It determines LVEF which is the main criterion to differentiate HFrEF and HFpEF. TTE provides in-depth insights into cardiac structure and function. It identifies abnormalities within the myocardium, heart valves, and pericardium and the information could offer diagnostic value for HFpEF.[117-119] TTE evaluation encompasses RV dimension and function, atrial size, and comprehensive valve analysis, addressing both anatomical and flow-related abnormalities. Diastolic function with estimated LV filling and LA pressures are also covered. Furthermore, indices reflecting myocardial deformation, including global longitudinal strain, have the po-

tential to uncover subclinical LV systolic dysfunction.[120-122]

In addition to TTE, supplementary noninvasive imaging tools can be helpful in evaluating cardiac structure and function. Cardiac MRI offers a precise and consistently replicable evaluation of cardiac volumes, mass, and EF for both LV and RV.[123] Cardiac MRI boasts exceptional anatomical resolution across all aspects of the heart and surrounding structures, without involving ionizing radiation. It is helpful in the diagnosis of HCM, cardiac amyloidosis, cardiac sarcoidosis, and Fabry disease.[51,124-126] ECG-gated cardiac computed tomography (CT) similarly delivers accurate assessments of ventricular size, EF, and abnormalities of wall motion.[127] Radionuclide ventriculography offers highly reproducible LVEF measurements, but exposes patients to ionizing radiation.[128] Positron emission tomography (PET) is a non-invasive imaging technique that provides information on myocardial metabolism, perfusion, inflammation, and fibrosis.[129]

Recommendation

- Transthoracic echocardiography should be performed for cardiac structural and functional evaluation in patients with suspected HFpEF. (COR I, LOE A)
- Other imaging tools, such as CT, MRI, radionuclide study or PET could be considered in patients with suspected HFpEF. (COR I, LOE C)

Diagnostic algorithm of HFpEF

In this guideline, we proposed a 2-step diagnostic algorithm for HFpEF. When patients have HF symptoms and signs fulfilling the criteria of Framingham Diagnostic Criteria and HFpEF is suspected, step-1 work up should be started (Figure 1). NT-proBNP/BNP should be checked. The presence of cardiac structural or functional abnormalities should be evaluated with TTE. The structural abnormalities encompass an enlargement in LA size and/or volume or an increase in LV mass. The functional abnormalities indicate the presence of increased LV filling pressure. In step-1 diagnosis, the patients should fulfill all the following four criteria to make a diagnosis of HFpEF: (1) symptoms and/or signs of HF, (2) LVEF $\geq$ 50%, (3) increased natriuretic peptide (NT-proBNP > 300 pg/mL or BNP > 100 pg/mL in sinus rhythm and NT-proBNP > 600 pg/mL or BNP > 150 pg/mL in AF), (4) objective evidence of LA or LV abnormalities or raised LV filling pressure. The objective evidence of LA or LV abnormali-

ties or raised LV filling pressure include: (1) LV mass index $\geq$ 95 g/m^2 in female and $\geq$ 115 g/m^2 in male, or (2) LA volume index > 29 mL/m^2 in sinus rhythm or > 40 mL/m^2 in AF, or (3) average E/e' > 14, or (4) tricuspid regurgitation (TR) velocity > 2.8 m/s.[1,100,130]

If patients do not fulfill the four criteria of step-1 diagnosis but HFpEF is still highly suspected or in any situation that uncertainty persists after step-1 diagnosis, step-2 diagnosis with stress test could be considered (Figure 1). An exercise stress test combined with echocardiographic evaluation of diastolic parameters should be performed. A diagnosis of HFpEF could be made if an average E/e' $\geq$ 15 or a TR velocity > 3.4 m/s are observed after exercise.[131] If the results of stress echocardiography is still questionable, an invasive hemodynamic measurement during rest and/or exercise could be considered. The invasive hemodynamic measurement serves as the golden criteria for the diagnosis of HEpEF. If a patient has a resting LV end diastolic pressure $\geq$ 16 mmHg or pulmonary capillary wedge pressure (PCWP) $\geq$ 15 mmHg or an exercise PCWP $\geq$ 25 mmHg, a definite diagnosis of HEpEF could be made.[131]

Recommendation

- In step-1 diagnosis, HFpEF can be diagnosed if patients have symptoms and/or signs of HF, LVEF $\geq$ 50%, increased NT-proBNP or BNP, and objective evidence of LA or LV abnormalities or raised LV filling pressure. (COR I, LOE A)
- Step-2 diagnosis using invasive or noninvasive stress test can be performed if HFpEF diagnosis is questionable. (COR I, LOE C)

TREATMENT

The major goals of treatment for patients with HFpEF are to reduce symptoms, improve functional status, and lower the risk of hospitalization for HF. Specific treatment of cardiomyopathy is beyond the scope of this guideline.

Non-pharmacological treatment

Weight reduction

Obesity, especially the central obesity, is associated with a higher incidence of HF and all-cause mortality.[132]

Step-1 Diagnosis

Initial assessment:
- History and physical examination
- ECG
- CXR
- Laboratory test

Yes
(symptoms/signs of HF)

Natriuretic peptide:
- NT-proBNP > 300 pg/mL or BNP > 100 pg/mL in sinus rhythm
- NT-proBNP > 600 pg/mL or BNP > 150 pg/mL in AF

No

Step-2 Diagnosis

Yes

Transthoracic echocardiography:
- LVEF ≥ 50% and
- Objective evidence of structural or functional abnormalities:
  (1) LV mass index ≥ 95 g/m^2 in female and ≥ 115 g/m^2 in male
  or
  (2) LA volume index > 29 mL/m^2 in sinus rhythm or > 40 mL/m^2 in AF
  or
  (3) Average E/e' > 14
  or
  (4) TR velocity > 2.8 m/s

No

HFpEF less likely

Still suspect HFpEF

No

- Stress echocardiography:
  Average E/e' ≥ 15 or TR velocity > 3.4 m/s
  or
- Invasive hemodynamic measurement:
  Resting LVEDP ≥ 16 mmHg or PCWP ≥ 15 mmHg or exercise PCWP ≥ 25 mmHg
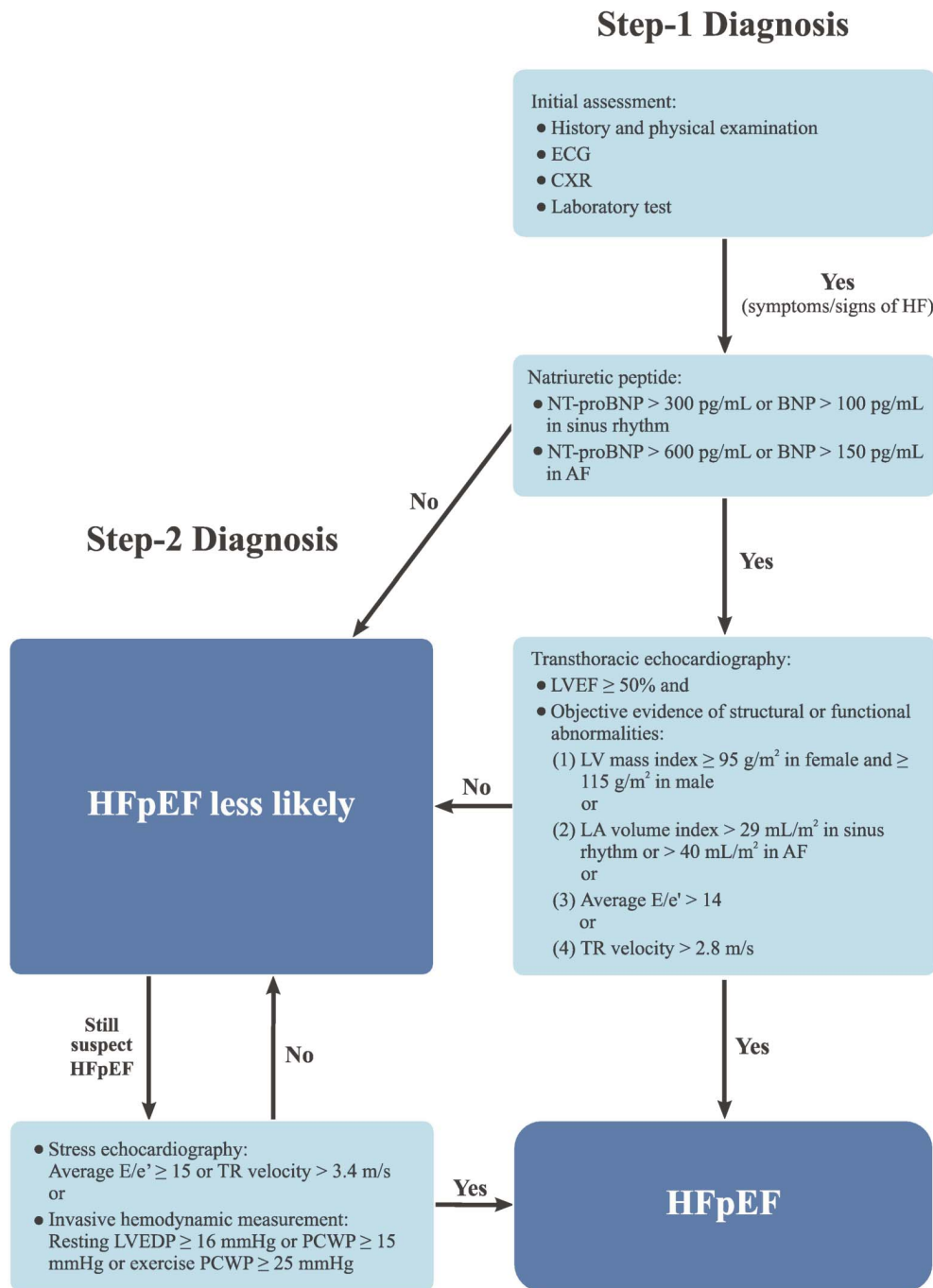
Yes

Yes

HFpEF

Figure 1. *A 2-step diagnostic algorithm of HFpEF. AF, atrial fibrillation; BNP, B-type natriuretic peptide; CXR, chest X-ray; ECG, electrocardiography; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; LVEDP, left ventricular end diastolic pressure; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal proB-type natriuretic peptide; PCWP, pulmonary capillary wedge pressure; TR, tricuspid regurgitation.*

Obesity is recognized as an important phenotype of HFpEF and up to 80% of individuals with HFpEF are either overweight or have obesity.[100,133] Physical inactivity and obesity are also linked with poor prognosis of HFpEF. Low cardiorespiratory fitness has been associated with a higher risk of HF across all categories of body mass index (BMI) and may explain about 50% of HF risk associated with BMI.[134] Implementation of lifestyle modification to increase physical activity and weight reduction are important strategies to lower the risk of HF.

The treatment approach for HFpEF with obesity involves a combination of lifestyle modification, pharmacotherapy, and bariatric surgery. People who achieved ≥ 10% weight loss had a significant 24% risk reduction of nonfatal MI, stroke, hospitalization for HF, or CV death.[135] The goal of lifestyle modification, including dietary change and regular physical activity, is to achieve weight loss while managing the symptoms and underlying causes of HF. Aerobic physical activity with 30-60 minutes of moderate to vigorous intensity in most days of the week is recommended for obese adults who want to achieve body weight loss. Lifestyle intervention with liraglutide have been reported to decrease more visceral adipose tissue compared with lifestyle intervention only.[136] Pharmacotherapy for weight loss (liraglutide or orlistat) can be used for persons with BMI ≥ 30 kg/m^2 or BMI ≥ 27 kg/m^2 with adiposity-related complications, such as type 2 diabetes, nonalcoholic fatty liver disease or gout.[137] In the Semaglutide Treatment Effect in People with obesity and HFpEF (STEP-HFpEF) randomized trial, administration of semaglutide to patients with HFpEF and obesity resulted in significant weight loss, enhancement in exercise capacity, greater decrease in NT-proBNP levels, and reduced occurrence of adjudicated HF events compared to the placebo group.[138] The ongoing SUMMIT (A Study of Tirzepatide in Participants With Heart Failure With Preserved Ejection Fraction and Obesity) trial may provide important insight into the potential benefit and safety of pharmacological weight loss in HFpEF. Bariatric surgery can be considered for people with BMI ≥ 40 kg/m^2 or BMI ≥ 35 kg/m^2 with at least 1 adiposity-related complication to reduce long-term overall mortality. Those with BMI ≥ 35 kg/m^2 should be considered to refer to a multidisciplinary team of medical, surgical, and nutritional experts for obesity treatment.[100]

Recommendation

- Weight reduction is recommended for obese patients with HFpEF. (COR I, LOE B)
- Pharmacotherapy for weight reduction should be considered for obese patients with HFpEF to improve HF symptoms, exercise capacity, and quality of life. (COR I, LOE B)

Exercise training

A significant number of patients with HFpEF have multiple comorbidities which contribute to pathophysiology of HFpEF and hinder exercise capacity.[31,139] Engaging in appropriate physical activity is widely recognized for its numerous beneficial effects on CV system and exercise-based therapy is emerging as a non-pharmacological intervention for HFpEF.[140] Exercise training improves peak oxygen uptake and quality of life but causes no significant changes in LV systolic or diastolic function in patients with HFpEF.[141] The 2022 AHA/ACC/HFSA heart failure guideline suggested a Class I recommendation for exercise training in patients with HF regardless of the LVEF.[2] A meta-analysis of supervised exercise training in stable HFpEF patients indicated that regular aerobic exercise could significantly increase peak oxygen uptake by 14% and increase total exercise time by 21% in the exercise group compared with 1% decrease in the control group.[142] Aerobic exercise also improved the six-minute walk distance by 9% compared with only 3% increase in control subjects.[142] Regarding acute decompensated HF and hospitalized patients, the Rehabilitation Therapy in Older Acute Heart Failure Patients (REHAB-HF) trial showed that early, transitional, tailored rehabilitation improved physical function and quality of life but had no beneficial effect on rehospitalization or death than usual care.[143] Among the individuals in REHAB-HF study, patients with HFpEF might derive greater benefits from early physical rehabilitation for the outcomes of all-cause death, HF rehospitalization, and physical performance than those with HFrEF.[144]

However, there are some controversial issues regarding the exercise-based therapy in HFpEF. First, the evidence is still limited for exercise training to improve clinical outcomes and LV diastolic function of HFpEF. In addition, the setting and modalities of exercise training varied significantly among clinical trials and there is no standard protocol for the exercise-based therapy for HF. Despite the uncertainties, this guideline still recommends exercise training as a non-pharmacological therapy for HFpEF because it is safe and offers substantial improvement in exercise capacity and quality of life for patients with HFpEF. It is crucial to note that these exercise prescriptions should be supervised, individualized, and carefully monitored. A multidisciplinary approach involving collaboration among cardiologists, exercise physiologists, and physical therapists should be considered to optimize the implementation of exercise training and ensure patient safety.

Recommendation

- Supervised exercise training is recommended for patients with HFpEF. (COR I, LOE B)

Vaccination

Pneumonia and respiratory tract infection are important triggers of HF decompensation and cause hospitalization. The risk of pneumonia is high in HF patients especially for HFpEF.[145] The infection events not only increase the in-hospital mortality of HF, but also results in poor long-term prognosis.[146] Influenza and pneumococcal vaccines help to prevent respiratory infections that may probably reduce the risk of exacerbation of HF.

Numerous studies have provided evidence that the influenza vaccine has the potential to decrease CV morbidity and mortality in patients undergoing secondary prevention for CAD, particularly among the elderly population.[147] In Taiwan, elderly MI patients who received influenza vaccination had a lower risk of all-cause mortality and hospitalization for HF.[148] So far, there has been no large-scale randomized clinical trial to evaluate the efficacy of influenza vaccination in HF patients. Retrospective analysis of the Prospective Comparison of ARNI with angiotensin converting enzyme inhibitor (ACEI) to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial demonstrated that HF patients received influenza vaccination had a significant lower risk of all-cause mortality, but the CV death and HF hospitalization did not reach statistical significance.[149] The current European guidelines recommend annual influenza vaccinations for HF patients, especially the elderly.[9]

Previous observational study found that patients diagnosed with pneumococcal pneumonia faced a significant risk of acute CV events, including MI, arrhythmia, and development or worsening of HF.[150] Currently, there are two types of vaccines for prevention of *S. pneumoniae* infection: the 23-valent pneumococcal polysaccharide vaccine (PPV23) and the 13-valent pneumococcal conjugate vaccine (PCV13). The effectiveness of vaccines in preventing invasive pneumococcal infections varies, ranging from approximately 56% to 75%.[7,151] The efficacy for pneumococcal vaccination specifically for HF patients is not well established due to lack of large-scale randomized controlled trials. Based on expert consensus, in adults ≥ 65 years of age who have not previously received a pneumococcal vaccine, the administration of PCV13 followed by PPV23 1 year later is recommended for HF patients.

Recommendation

- Influenza and pneumococcal vaccinations are recommended for patients with HFpEF, especially for the elderly. (COR I, LOE B)

Management of comorbidities

HFpEF is usually associated with multiple comorbidities, such as hypertension, DM, CKD, CAD, or AF. Delivering therapy for underlying comorbidities and treating modifiable HF risk factors are mandatory for HFpEF treatment.

Hypertension and diabetes

Hypertension is the leading cause of HFpEF with a prevalence ranging from 60% to 89% in HFpEF.[17] In line with the Hypertension Guideline of Taiwan Society of Cardiology, the systolic blood pressure target for HFpEF should be less than 130 mmHg.[152] The patient's other comorbidities, such as diabetes, CKD, or CAD, should guide the personalized choice of antihypertensive agents. The preferred agents for hypertension control in HFpEF include diuretics, angiotensin receptor blocker (ARB), and mineralocorticoid receptor antagonist (MRA) because these agents also have some beneficial effects for HFpEF in addition to blood pressure reduction. Since chronotropic incompetence is a potential mechanism contributing to exercise functional limitation in HFpEF, use of beta-blockers in HFpEF may be avoided if there are no other specific indications for beta-blockers.[153] Given the recently demonstrated benefits of sodium-glucose cotransporter 2 (SGLT2) inhibitors in improving outcomes in patients with HFpEF,[154-156] SGLT2 inhibitors should be prescribed as first-line therapy for diabetic patients with HFpEF. However, the use of SGLT2 inhibitors is not recommended if estimated glomerular filtration rate (eGFR) is < 20 mL/min/1.73 m^2. SGLT2 inhibitors should also be avoided in all patients with type 1 diabetes, or in type 2 diabetes with prior diabetic ketoacidosis (DKA) or a condition predisposing to DKA, including pancreatic insufficiency, drug or alcohol addiction, and prolonged fasting. Metformin is also recommended as first-line therapy for glycemic control in diabetic patients with HFpEF. Given

the substantial weight loss effect of the glucagon-like peptide-1 receptor agonists (GLP1RA), these agents should be considered for HFpEF patients with DM and obesity. Due to an increased risk of fluid retention, weight gain, and HF events, thiazolidinediones are relatively contra-indicated in diabetic patients with HFpEF.

Recommendation

- Diuretics, ARB, and MRA are recommended for hypertension in patients with HFpEF. (COR IIa, LOE C)
- SGLT2 inhibitors are recommended for diabetes in patients with HFpEF. (COR I, LOE A)
- GLP1RA should be considered for diabetes and obesity in patients with HFpEF. (COR I, LOE B)

CKD, CAD and AF

Patients with HFpEF and CKD should be treated with evidence-based therapies that reduce the progression of CKD. SGLT2 inhibitors have been shown to improve renal outcome in patients with CKD. Although there is an expected initial decline in eGFR of approximately 4 mL/min/1.73 m^2 when initiation of SGLT2 inhibitors, the rate of eGFR decline is slower compared to patients not on SGLT2 inhibitors after long term follow up.[154-156] Clinical trials also demonstrated significant slow-down of eGFR decline in patients treated with ARB or angiotensin receptor-neprilysin inhibitor (ARNI).[157] CAD is prevalent in HFpEF.[158] To determine the severity of CAD and assess the need for revascularization, CT coronary angiography should be considered in patients with a low to intermediate pretest probability of CAD or those with equivocal non-invasive stress tests. Invasive coronary angiography may be considered in patients with an intermediate to high pretest probability of CAD. Medical therapies of CAD should be given according to the recommendations from the Guidelines of the Taiwan Society of Cardiology on the diagnosis and management of chronic coronary syndrome.[7] Currently, there are no prospective randomized trials to evaluate the effect of revascularization on patients with HFpEF and CAD. For AF, anticoagulant remains the cornerstone therapy for AF and HFpEF to prevent stroke and the indication for anticoagulation is determined by CHA_2DS_2-VASc score. Randomized control trials did not demonstrate an advantage of rhythm control with antiarrhythmic medications over rate control.[159] Ablation of AF may be a better

strategy than antiarrhythmic medications for rhythm control.[160] This guideline recommends that patients with HFpEF and AF should have adequate rate control. Beta-blockers and non-dihydropyridine calcium-channel blockers are the usual first-line agents. A recent clinical trial demonstrated that digoxin may improve functional capacity and reduce more NT-proBNP over bisoprolol in AF patients with HF symptoms.[161]

Recommendation

- SGLT2 inhibitors, ARNI or ARB are recommended for CKD in patients with HFpEF. (COR I, LOE A)
- Beta-blockers, non-dihydropyridine calcium-channel blockers or digoxin are recommended for rate control in patients with HFpEF and AF (COR IIa, LOE B)

Pharmacological treatment

Diuretics

HFpEF patients with volume overload should be treated with diuretics.[48] Loop diuretics should be initiated as the first-line therapy with the type and dose depending on the severity of congestion. For those patients with loop diuretic resistance, sequential nephron blockade can be achieved using thiazide diuretics and/or MRA.

Recommendation

- Diuretics are recommended for HFpEF patients with congestion to relief symptoms. (COR I, LOE C)

SGLT2 inhibitor

Both empagliflozin and dapagliflozin have shown their clear benefits in the management of HFpEF. The Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR-Preserved) trial first demonstrated the advantages of empagliflozin over placebo on the reduction of HF hospitalization or CV death among 5988 patients with HF and LVEF > 40% (hazard ratio: 0.79, 95% confidence interval: 0.69-0.90).[154] In addition, empagliflozin also reduced total HF hospitalization by 27% and delayed the decline of eGFR.[154] The pre-specified analysis clearly showed empagliflozin reduced the risk of HF hospitalization or CV death by 17% in patients with LVEF ≥ 50%. The Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure (DELIVER) trial investigated the ef-

fect of dapagliflozin in 6263 patients with HF and LVEF > 40% and showed similar results.[156] Patients can be enrolled as outpatients or during hospitalization after stabilization for HF. The trial demonstrated a significant 18% reduction in the risk of the primary composite endpoint (CV death or worsening heart failure) with dapagliflozin, primarily due to the reduced HF events, but not CV mortality. The benefit of dapagliflozin were found to be consistent in the subgroup analyzes comparing patients with LVEF ≥ 60% and LVEF < 60% suggesting no attenuation of benefit in patients with higher LVEF.[156] The therapeutic benefit with dapagliflozin was observed consistently, independent of age, BMI, frailty class, presence of AF, or New York Heart Association functional class. The time to first statistically significant reduction of the primary endpoint was only 13 days in DELIVER trial and 18 days in EMPEROR-Preserved study.[154-156] SGLT2 inhibitor, empagliflozin or dapagliflozin, is recommended as a foundation therapy for HFpEF and should be initiated as early as possible.

Recommendation

- SGLT2 inhibitor, empagliflozin or dapagliflozin, is recommended for patients with HFpEF to reduce the risk of worsening HF event or CV death. (COR I, LOE A)

Renin-angiotensin system inhibitor and MRA

Randomized clinical trials of ACEI and ARB, including perindopril in the Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) trial,[162] candesartan in the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity-Preserved (CHARM-Preserved) trial[163] and irbesartan in the Irbesartan in Heart Failure with Preserved Ejection Fraction Study (I-Preserve) trial,[164] failed to achieve a significant reduction in the primary outcome compared with placebo for patients with HFpEF. In the Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction (PARAGON-HF) trial, ARNI did not significantly reduce the risk of HF hospitalization or CV death compared with valsartan (p = 0.059), but the benefit of ARNI over ARB was greater in selected groups of HFpEF patients, such as recently hospitalized patients, women and those with an LVEF at or below the median value of 57%.[165,166] For MRA, although the Treatment of Preserved Cardiac Function Heart Failure With an Aldo-

sterone Antagonist (TOPCAT) trial did not demonstrate mortality benefit or reduction in HF hospitalization in the whole study with LVEF 45% or greater, the benefits of spironolactone was shown at the lower end (up to 55%) of HFpEF.[167] Its subgroup geographic analyses also demonstrated that there was a significant improved prognosis for the 1767 enrolled patients from north and south America.[168] Several upcoming studies (FINEARTS-HF, SPIRRIT, and SPIRIT-HF) are still undergoing to clarify the definite role of MRAs, including finerenone or spironolactone, in HFpEF. An individual patient-level meta-analysis demonstrated the benefits of candesartan, spironolactone, and ARNI extending to the lower end of the LVEF range of HFpEF.[169] Therefore, in selected patients with HFpEF, MRA and ARNI may be considered to decrease HF hospitalizations. An ARB may be considered for patients with HFpEF who are eligible for ARNI but cannot take it due to cost or intolerance. Combination therapy of ARNI, MRA and SGLT2 inhibitor is reasonable and was estimated to reduce CV death and HF hospitalization among HF patients with LVEF between 45% to 65%.[170] An expert consensus from the Taiwan Society of Cardiology suggests a sequencing strategy starting with SGLT2 inhibitor first and combining it with ARNI if systolic blood pressure is ≥ 100 mmHg or MRA if systolic BP is < 100 mmHg for HFpEF treatment.[10]

Recommendation

- ARNI and MRA are recommended for selected groups of patients with HFpEF. (COR IIa, LOE B)
- ARB is recommended as an alternative for HFpEF who cannot tolerate or afford ARNI. (COR IIa, LOE B)
- Combination therapy of SGLT2 inhibitor, ARNI and/or MRA is reasonable in selected group of patients with HFpEF. (COR IIb, LOE C)

Beta-blocker

In the Rate Control Therapy Evaluation in Permanent Atrial Fibrillation (RATE-AF) study that compare digoxin with bisoprolol in AF patients with HF symptoms, the primary outcome of quality of life was comparable between patients treated with bisoprolol and digoxin at 6 months.[161] But beta-blocker caused more adverse effects, such as dizziness, drowsiness, and hypotension than digoxin.[161] Additionally, the improved functional capacity and lower NT-proBNP levels favored di-

goxin group at 12 months. An individual patient-level meta-analysis failed to demonstrate the benefit of beta-blockers over placebo among HFpEF patients.[171] A beta-blocker is not recommended in patients with HFpEF without compelling indications, such as CAD, prior MI or rate control for AF, especially for those with chronotropic incompetence. Figure 2 summarizes the current major non-pharmacological and pharmacological therapies for HFpEF.

Recommendation

- Beta-blocker is not recommended in patients with HFpEF without compelling indications (COR III, LOE C)

Early initiation strategy

Early initiation strategy means starting recommended HF pharmacological therapies as soon as possible, preferably at the clinic visit as the HF is definitely diagnosed or before discharge following HF hospitalization. The Safety, Tolerability and Efficacy of Up-titration of Guideline-directed Medical Therapies for Acute Heart Failure (STRONG-HF) trial, enrolled patients with HFrEF or HFpEF and introduced an intensive care strategy involving early initiation and up-titration of foundation medications for HF. The strategy has been shown to significantly reduce the rates of all-cause death and HF readmission within 180 days after acute decompensated HF hospitalization.[172] In the trial, 15% patients were HFpEF and the clinical benefit of early initiation and up-titration strategy was observed regardless of the baseline LVEF is ≤ 40% vs. > 40%.[173] It is important to note that STRONG-HF focused on triple therapy with renin-angiotensin system inhibitor, beta-blocker and MRA. For patients diagnosed with HFpEF in outpatient clinic or admitted due to acute HFpEF, an early initiation strategy should include the initiation of SGLT2 inhibitor, empagliflozin or dapagliflozin, and/or diuretics to mitigate the
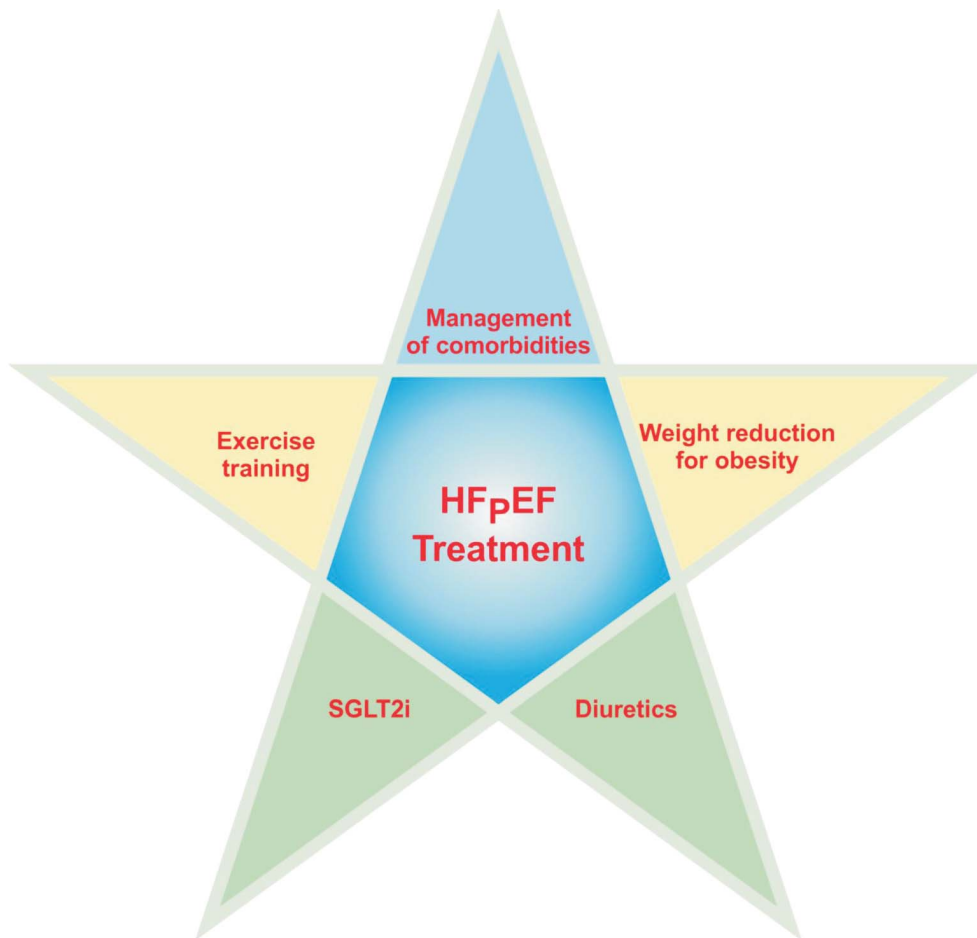

Figure 2. *Current major non-pharmacological and pharmacological therapies for HFpEF. HFpEF, heart failure with preserved ejection fraction; SGLT2i, sodium-glucose cotransporter 2 inhibitor.*

risk of HF readmission or mortality.

Recommendation

- An early initiation and titration strategy of HF foundation therapy before discharge and in the first few weeks following a HF hospitalization is recommended to reduce the risk of HF rehospitalization or death. (COR IIa, LOE B)

FUTURE PERSPECTIVE

HFpEF is an escalating public health concern accounting for more than half of all HF cases and marked by elevated morbidity and mortality.[174] HFpEF often goes unnoticed and leads to extensive utilization of health resource. Treating HFpEF poses formidable challenges involving management of comorbidities, non-pharmacological treatment, and guideline-based medical therapies. In addition to current understanding, gaining more insight into the pathophysiology, including inflammation, vascular dysfunction, fibrosis, and tissue remodeling, is essential for developing novel diagnostic method and treatment of HFpEF.[175] Research is now concentrating on comprehensive phenotyping of HFpEF patients and evaluating targeted treatment in various subtype of HFpEF.[176] Employing machine learning with the help of artificial intelligence system will become a more rapid method to facilitate HFpEF diagnosis and aids in identifying subtypes with more precise intervention.[177,178] Clinical trials with precision medicine approach in various phenotypes of HFpEF have been conducted.[179] Multidisciplinary collaboration is pivotal for administering quality care for HFpEF. Capitalizing on evolving therapies and resolving diagnostic complexities will be a pivotal prospect to redefine HFpEF care. The recommendations in this guideline are proposed based on recent study results. Since the landscape is rapidly evolving, establishing new pathways for diagnosis and management of HFpEF driven by emerging clinical trial data is important in the near future.

DECLARATION OF CONFLICT OF INTEREST

All the authors declare no conflict of interest.

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