REVIEW

Korean J Intern Med 2020;35:514-534
https://doi.org/10.3904/kjim.2020.104

Heart failure with preserved ejection fraction: insights from recent clinical researches

Mi-Na Kim and Seong-Mi Park

Division of Cardiology, Korea University Anam Hospital, Seoul, Korea

Received: March 21, 2020
Accepted: April 23, 2020

Correspondence to
Seong-Mi Park, M.D.
Division of Cardiology, Korea University Anam Hospital, 73 Goryeodae-ro, Seongbuk-gu, Seoul 02841, Korea
Tel: +82-2-920-5445
Fax: +82-2-927-1478
E-mail: smparkmd@korea.ac.kr
https://orcid.org/0000-0002-6710-685X

This paper was contributed by The Korean Society of Heart Failure.

Heart failure (HF) with preserved ejection fraction (HFpEF) accounts for nearly half of the cases of HF and its incidence might be increasing with the aging society. Patients with HFpEF present with significant symptoms, including exercise intolerance, impaired quality of life, and have a poor prognosis as well as frequent hospitalization and increased mortality compared with HF with reduced ejection fraction. The concept of HFpEF is still evolving and may be a virtual complex rather than a real systemic disorder. Thus, beyond solely targeting cardiac abnormalities management strategies need to be extended, such as left ventricular diastolic dysfunction. In this review, we examine new diagnostic algorithms, pathophysiology, current management status, and ongoing trials based on heterogeneous pathophysiology and etiology in HFpEF.

Keywords: Heart failure; Preserved ejection fraction; Therapy

INTRODUCTION

Heart failure with preserved ejection fraction (HFpEF) is the most common form of heart failure (HF) in the elderly, which accounts for about 50% of HF [1]. With the aging of the population and the increasing burden of comorbidities, the prevalence of HFpEF is steadily increasing [2], whereas its prognosis is not improving. The mortality and acute decompensation rate of HFpEF are similar to that of heart failure with reduced ejection fraction (HFrEF) [3]. Moreover, the rehospitalization rate of HFpEF is as high as that of HFrEF [3,4]. Additionally, patients with HFpEF have a similar or poorer quality of life (QOL) than that of patients with HFrEF [5]. Despite the health and economic importance of HFpEF, optimal medical therapy remains unclear. The medical management of HFpEF is challenging because of the diverse phenotypes of HFpEF [5] and there are few therapies that are proven to be effective for HFpEF, regarding the improvement of mortality or HF hospitalization [6]. Here, we summarize the clinical management of HFpEF and review recent clinical trials, and then provide a therapeutic clue for HFpEF.

DIAGNOSIS OF HFpEF

HF is a clinical syndrome that results from a structural or functional impairment of contraction or filling of the heart [7]. Currently, the diagnostic process of HFpEF includes typical symptoms and signs of HF and natriuretic peptides, after that, it is categorized by left ventricular ejection fraction (LVEF) [7-9]. The cut-off LVEF for HFpEF varies between 40%, 45%, and 50%

pISSN 1226-3303
eISSN 2005-6648
http://www.kjim.org

Table 1. Diagnostic of HFpEF [7-9]

	Current guideline of HFpEF		
	2016 KSHF guideline [7]	2016 ESC guideline [8]	2013 AHA guideline [9]
Clinical manifestation	Symptoms and signs of HF	Symptoms and signs of HF	Symptoms and signs of HF
LVEF	≥ 50%	≥ 50%	≥ 50%
Natriuretic peptides	BNP ≥ 35 pg/mL or NT-proBNP ≥ 125 pg/mL	BNP > 35 pg/mL or NT-proBNP > 125 pg/mL	
Imaging	Abnormal LVDD	Relevant structural heart disease (LVH and/or LAE) LVDD -LAVI > 34 mL/m^2 -LVMI ≥ 115/95 g/m^2 (M/W) -E/e' ≥ 13 -Mean e'< 9 cm/sec	Abnormal LVDD

HFpEF, heart failure with preserved ejection fraction; KSHF, Korean Society of Heart Failure; ESC, European Society of Cardiology; AHA, American Heart Association; HF, heart failure; LVEF, left ventricular ejection fraction; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro-B type natriuretic peptide; LVDD, left ventricular diastolic dysfunction; LVH, left ventricular hypertrophy; LAE, left atrial enlargement; LAVI, left atrial volume index; LVMI, left ventricular mass index; M/W, men/women.

Table 2. Diagnostic of H2FpEF [14]

Clinical variable		H2FpEF score [14]	Point
H2	Heavy	BMI > 30 kg/m^2	2
	Hypertension	Antihypertensive medication ≥ 2	1
F	Atrial fibrillation	Paroxysmal or persistent	3
P	Pulmonary hypertension	Doppler echocardiographic estimated PASP > 35 mmHg	1
E	Elder	Age > 60 years	1
F	Filling pressure	Doppler echocardiographic E/e' > 9	1
Sum			0–9

BMI, body mass index; PASP, pulmonary artery systolic pressure.

in clinical trials. In current guidelines [7-9], HFpEF is diagnosed when the patient presents with evidence of increased vascular volume (i.e., elevated natriuretic peptides) or myocardial abnormality to implicate the symptoms and signs of HF with LVEF ≥ 50%. The diagnostic criteria of the current guidelines are summarized in Table 1.

However, the diagnosis of HFpEF remains challenging. The gold standard test for confirming HFpEF is a demonstration of elevated left ventricular filling pressure (LVFP): elevated pulmonary capillary wedge pressure (PCWP) at rest ≥ 15 mmHg or during exercise ≥ 25 mmHg by right catheterization. Although the current guidelines recommend right catheterization in patients with an intermediate pretest probability of HFpEF, the performance of right catheterization is limited in routine clinical practice due to complex technique, cost, and invasiveness. Uncertainty exists in the diagnostic criteria of HFpEF in the current guidelines. The diagnosis of HFpEF depends on the level of natriuretic peptides and echocardiographic data, but the sensitivities of both are quite low [10-12]. In particular, natriuretic peptides might have limited value in evaluating HFpEF [11]. A considerable portion of HFpEF patients with clinical, echocardiographic, and hemodynamic evidence of HF had a normal range of natriuretic peptides [13]. Furthermore, as HFpEF is regarded to have several distinct phenotypes with different pathophysiology, uniform diagnostic criteria of current guidelines could be a major limitation in providing proper treatment of HFpEF.

Table 3. Diagnostic of HFA-PEFF [15]

	HFA-PEFF score [15]			
	Major		Minor	
	Value	Point	Value	Point
Functional	Septal e' < 7 cm/sec or lateral e' < 10 cm/sec or Averaged E/e' ≥ 15 or TR Vmax > 2.8 m/sec (PASP > 35 mmHg)	2	Avergaed E/e' 9–14 or GLS < 16%	1
Morphological	LAVI > 34 mL/m^2 or LVMI ≥ 149/122 g/m^2 (M/W) ± RWT > 0.42	2	LAVI 29–34 mL/m^2 or LVMI ≥ 115/95 m^2 (M/W) or RWT > 0.42 or LV wall thickness ≥ 12 mm	1
Biomarker (SR)	NT-proBNP > 220 pg/mL or BNP > 80 pg/mL	2	NT-proBNP > 660 pg/mL or BNP > 240 pg/mL	1
(AF)	NT-proBNP 125–220 pg/mL or BNP 35–80 pg/mL	2	NT-proBNP 365–660 pg/mL or BNP 105–240 pg/mL	1

≥ 5 points: heart failure with preserved ejection fraction; 2–4 points: exercise stress test or invasive hymodynamic measurement. HFA-PEFF, heart Failure Association-PEFF; TR, tricuspid regurgitation; PASP, pulmonary artery systolic pressure; GLS, global longitudinal strain; LAVI, left atrial volume index; LVMI, left ventricular mass index; M/W, men/women; RWT, regional wall thickness; LV, left ventricular; SR, sinus rhythm; NT-proBNP, N-terminal pro-B type natriuretic peptide; BNP, B type natriuretic peptide; AF, atrial fibrillation.

Therefore, new diagnostic algorithms for HFpEF have been published [14,15]. Reddy et al. [14] reported an H2F-PEF score based on six variables, which were important comorbidities and etiologies of HFpEF (Table 2) and demonstrated that the H2FPEF score was superior to the current algorithm (increase in area under the curve of 0.169; 95% confidence interval [CI], 0.12 to 0.22l; p < 0.0001). A higher H2FPEF score was significantly related to future cardiovascular (CV) or HF-related events [16,17].

The HF association of the European Society of Cardiology reported a new diagnostic algorithm for HFpEF and the Heart Failure Association (HFA)-PEFF diagnostic algorithm in the past year [15]. This algorithm is composed of four steps. First, in step P as a pre-test assessment: medical history, electrocardiogram, laboratory tests including natriuretic peptides, and echocardiography should be performed to exclude other causes of dyspnea in all patients with symptoms and signs of HF. In the next step (step E), the HFA-PEFF score is calculated for each patient (Table 3). If the HFA-PEFF score is ≥ 5, HFpEF is diagnosed and if the score is ≤ 1, HFpEF could be excluded. If the HFA-PEFF score is 2–4, which is the intermediate probability of HFpEF, a functional test is recommended in the third step (step F1). Exercise stress echocardiography and invasive hemodynamic test during exercise are common functional tests for HFpEF. Lastly, the specific etiologies of HFpEF should be evaluated for advanced targeted therapy of HFpEF (step F2). The validation of HFA-PEFF was evaluated in a small cohort, and it is useful to diagnose HFpEF [18].

The H2FPEF score is relatively simple and easy to apply. Contrarily, the HFA-PEFF score is complex and costly, but it is sophisticated and helps in finding the etiology of HFpEF. Moreover, no study has validated both scores in the same study population that could elucidate which score is more accurate in diagnosing HFpEF. The diagnosis of HFpEF is still challenging,

https://doi.org/10.3904/kjim.2020.104

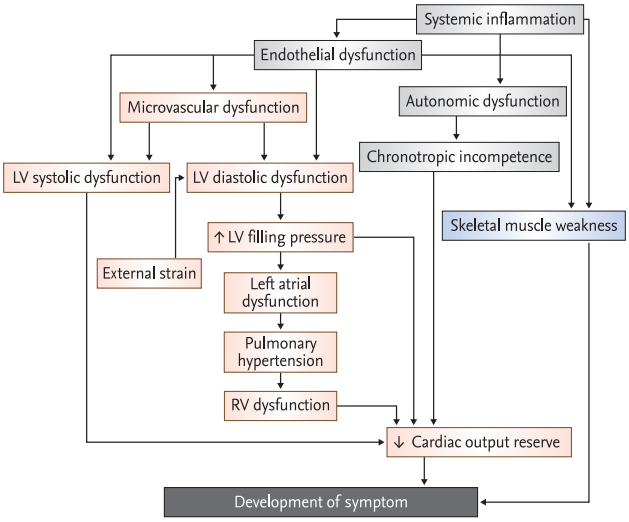

Figure 1. Schematic pathophysiology of heart failure with preserved ejection fraction. LV, left ventricular; RV, right ventricular.

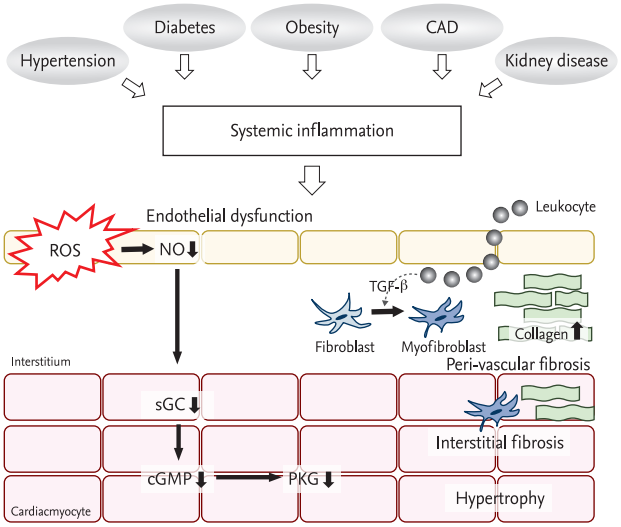

Figure 2. Cellular mechanism of heart failure with preserved ejection fraction. CAD, coronary artery disease; ROS, reactive oxygen species; NO, nitric oxide; TGF-β transforming growth factor-β; sGC, soluble guanylate cyclase; cGMP, cyclic quanosine monophosphate; PKG, protein kinase G.

despite the use of new diagnostic algorithms. Nevertheless, the insights from these new scores are changing the diagnostic paradigm of HFpEF, in which comorbidity, etiology, and phenotype of HFpEF are considered and evaluated in the process of diagnosis.

PATHOPHYSIOLOGY AND ETIOLOGY OF HFpEF

The pathophysiology of HFpEF is intricate and is not yet well understood. Patients with HFpEF are older, predominantly women, and have multiple comorbidities including hypertension, obesity, coronary artery disease (CAD), diabetes, anemia, atrial fibrillation (AF), renal insufficiency, and sleep apnea [13]. These comorbidities affect ventricular and vascular remodeling and are essential for the development of HFpEF (Fig. 1) [19,20]. These comorbidities induce a low-grade systemic inflammation, which induces endothelial dysfunction of systemic and coronary microvasculature [21,22]. The production and bioavailability of nitric oxide (NO) in the endothelium are impaired in HFpEF. Abnormalities in NO-cyclic guanosine monophosphate (cGMP) signaling, including soluble guanylate cyclase (sGC) activity and reduced protein kinase G (PKG) activity in cardiac myocytes, promote myocardial hypertrophy, increased stiffness of the myocardium, and interstitial fibrosis (Fig. 2) [21,23,24]. These result in left ventricular diastolic dysfunction (LVDD) and increased arterial stiffness.

Left ventricular diastolic dysfunction

LVDD is well-known pathophysiology of HFpEF. LVDD is caused by myocardial structural changes, microvascular dysfunction, systematic inflammation, and increased passive chamber stiffness [25]. The increased LVFP, the fundamental and pathologic hemodynamics of HFpEF, predominantly results from LVDD. The passive chamber stiffness is rapidly increased and the prolonged relaxation time is not shortened during exercise and these result in an increase of LVFP in HFpEF [26]. In the earlier stage, LVFP is normal but markedly increases during exercise, while in an advanced stage it increases continuously even at rest [27]. Elevated LVFP leads to elevation of left atrial (LA) pressure (passive LA hypertension) and contributes to an increase in pulmonary capillary hydrostatic pressure and an increase in vascular permeability, resulting in the development of interstitial edema [28]. Increased LVFP is closely related to the development of typical symptoms of HFpEF such as exercise intolerance and exertional dyspnea, symptom severity, and prognosis of HFpEF [29,30].

Left atrial dysfunction

Under the condition of prolonged increased LVFP, secondary structural and functional remodeling of the LA develops. The preservation of LA function might be crucial to the adaptation of HFpEF, which prevents pulmonary congestion and right ventricular (RV) dysfunction [31]. Impaired LA function is related to exacerbation of pulmonary congestion, a change in lung function, and the development and worsening of pulmonary venous hypertension [31-33]. In a recent meta-analysis, it was proven that impaired LA function is valuable for diagnosis as well as for estimating the prognosis of HFpEF [34]. Especially in HFpEF patients with AF, LA structural and functional remodeling is exacerbated, which is a major contributor to disease progression, such as the development of pulmonary hypertension (PH), and RV dysfunction [35].

Pulmonary hypertension and right ventricular dysfunction

The presence of PH in HFpEF patients is associated with poor prognosis [21,36]. PH not only develops from passive LA hypertension but also from increased pulmonary vascular resistance, which is derived from pulmonary vascular disorders such as pulmonary vasoconstriction and pulmonary vascular remodeling [36-38]. A considerable number of HFpEF patients had pulmonary vascular disorders and increased mortality compared to patients with pure passive PH [36]. Regardless of the type of PH, persisting PH eventually induces RV dysfunction. The development of RV dysfunction is associated with a markedly increased risk of mortality [39].

Extrinsic restraint

The extrinsic restraint on the heart by pericardium and epicardial fat could lead to an increase in LVFP. Epicardial fat, as an external restraint, induces an increase in intracavitary pressure [40] that could promote inflammation, fibrosis, and coronary microvascular dysfunction (CMD) [20].

Left ventricular systolic dysfunction

The left ventricular systolic dysfunction evaluated by tissue deformation imaging analysis is present at rest and worsens during exercise in HFpEF [41-43]. Abnormal ventricular-vascular coupling by arterial stiffening is regarded as the cause of subtle left ventricular systolic dysfunction. It results in a significantly impaired proportional increase in stroke volume output in response to exercise, which is one of the major causes of exercise intolerance in HFpEF. The increased left ventricular strain is closely associated with common comorbidities of HFpEF [44], and it has a prognostic value for CV mortality and HF hospitalization in HFpEF [42].

Coronary microvascular dysfunction

A considerable portion of patients presenting with symptoms of ischemia referred for coronary angiography are found to have evidence of ischemia but no significant stenosis of the coronary artery [45]. Most of these patients who have ischemia and no obstructive coronary artery disease (INOCA) have CMD [45]. In epidemiologic studies, INOCA was more prevalent in women and in patients with multiple comorbidities, which are similar to HFpEF [46]. Furthermore, patients with INOCA are likely to have preserved LVEF and a higher incidence of HF hospitalization [47]. Therefore, a link between CMD and HFpEF was strongly suggested [46], and the interaction between LVDD and CMD was clearly associated with an increased risk of HFpEF [48-50]. CMD has become one of the major phenotypes and pathogenic cause of HFpEF.

Chronotropic incompetence

Many patients with HFpEF display impaired cardiac output reserve during exercise, despite normal values at rest [43]. Not only left ventricular systolic dysfunction, as mentioned above, but also chronotropic incompetence results in a reduced cardiac output reserve [43].

Skeletal muscle weakness

Recent studies have identified an important role of the skeletal muscle in HFpEF. In patients with HFpEF, skeletal muscle mass is decreased [51], the composition of skeletal muscle changes with increased fatty infiltration [52] and the capillary density within the muscle is reduced [53]. The oxidative metabolism of skeletal muscle fiber changes to a slow type and a decreased mitochondrial content and abnormal fusion of mitochondria in skeletal muscle are observed [54]. These changes reduce peak O_2 uptake and result in exercise intolerance in patients with HFpEF.

https://doi.org/10.3904/kjim.2020.104

TREATMENT

Currently, there are limited data on disease-modifying agents available for HFpEF, which improve clinical outcomes in randomized controlled trials (RCTs). Therefore, treatment guidelines, focused on optimal volume control using diuretics and proper management of risk factors and comorbidities are required. However, with increasing insight in the pathophysiology of HFpEF, various trials in treatment of HFpEF in accordance with the phenotype, have been published. The important trials of HFpEF treatment are described in Table 4.

TRADITIONAL PHARMACOLOGICAL STRATEGIES OF HF: BLOCKADE OF THE ACTIVATED NEUROHORMONAL SYSTEM

Renin-angiotensin-aldosterone system

Inappropriate activation of the renin-angiotensin-aldosterone system (RAAS) occurs in diseases that are associated with the development and progression of HFpEF, in common with HFrEF [55-58]. RAAS promotes the increase of arterial stiffness and myocardial stiffness and causes LVDD and LVH in HFpEF [55]. Therefore, several randomized clinical trials have been conducted to evaluate the prognostic value of RAAS blockade.

The angiotensin-converting enzyme inhibitor or angiotensin receptor blocker was not efficient for CV mortality and HF hospitalization in three large trials (CHARM-preserved [Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity], PEP-CHF [Perindopril in Elderly people with Chronic Heart Failure], and I-PRESERVED [Irbesartan in Heart Failure With Preserved Ejection Fraction]) [59-61]. They did not improve CV mortality, and only candesartan reduced HF hospitalization slightly [59]. A detailed summary of these trials is described in Table 4.

The Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist Trial (TOPCAT) is a large RCT to investigate the efficacy of aldosterone antagonists in symptomatic patients with HFpEF (LVEF ≥ 45%) [62]. The differences in the primary endpoint between spironolactone and placebo failed to reach a statistical significance; however, HF hospitalization was modestly decreased by spironolactone. Interestingly, in the subgroup analysis, spironolactone reduced primary outcome in patients with elevated natriuretic peptide levels at enrollment [62] in the Americas (hazard ratio [HR], 0.82; 95% CI, 0.69 to 0.98; $p = 0.026$) [63]. In Russia and Georgia, patients were enrolled by clinical judgment rather than having increased natriuretic peptides, and were relatively healthy and had lower compliance with study medication than in the Americas [64]. The result obtained in Russia/Georgia would not reflect a true response to spironolactone. For this reason, re-evaluation of the clinical efficacy of spironolactone in HFpEF is necessary. There is currently an ongoing trial in progress: Spironolactone Initiation Registry Randomized Interventional Trial in Heart Failure with Preserved Ejection Fraction (SPIRRIT, NCT 02901184), and their results are expected.

The angiotensin receptor-neprilysin inhibitor (ARNI) sacubitril-valsartan is a combination of inhibitors of neurohormonal activation and up-regulation of the adaptive natriuretic peptide pathway. In a phase-II study, (PARAMOUNT [65]) sacubitril-valsartan induced a greater decrease in N-terminal pro-B type natriuretic peptide (NT-proBNP), a larger reduction in LA size, and a greater improvement of symptoms than valsartan in patients with HFpEF. Therefore, the outcome trial, Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction (PARAGON-HF) trial [66] was conducted in symptomatic HFpEF patients with increased natriuretic peptides. Despite a numerically lower event rate, the efficacy for HF hospitalization and CV death by sacubitril-valsartan approached but did not achieve a statistical significance (HR, 0.87; 95% CI, 0.75 to 1.01; $p = 0.06$). In *post hoc* analysis [13], the absolute risk reduction of sacubitril-valsartan was greatest in patients who were recently hospitalized within 1 month (approximately 25% to 30% risk reduction) and it gradually decreased with an increased interval from hospitalization. The sacubitril-valsartan might have alleviated the remaining neurohormonal activation after discharge. These data could provide clues for the initiation or switching time to sacubitril-valsartan in patients with HFpEF. The pre-specified analysis of outcomes by gender in the PARAGON-HF trial reported that the beneficial effect of sacubitril-valsartan was greater in women than in men (rate ratio [RR], 0.73, [95% CI, 0.59 to

Table 4. Clinical trials of pharmacological and non-phamacological therapy in HFpEF

Trials, year (no. of patients)	Interventions	Inclusion criteria	Characteristics of study population	Primary endpoint	Trial result
Renin-angiotensin-aldosterone system					
CHARM-preserved 2003 (n = 2,023) [58]	Candesartan	NYHA II–IV HF with prior cardiac hospitalization LVEF ≥ 40%	Mean age: 67 ± 11 years, 40% female 65% hypertension, 28% diabetes Mean LVEF: 54% ± 9.4% Median FU: 36.6 months	CV death or HF hospitalization	No benefit for primary endpoint Reduction of HF hospitalization
PEP-CHF 2006 (n = 850) [59]	Perindopril	Age ≥ 70 years Diastolic heart failure	Mean age: 76 ± 5 years, 55% female 79% hypertension, 20% diabetes Mean LVEF: 64% Median FU: 2.1 years	All cause mortality or HF hospitalization	No benefit for primary endpoint Reduction of HF hospitalization Improvement of symptom and exercise capacity
I-PRESERVED 2008 (n = 4,128) [60]	Irbesartan	Age ≥ 60 years NYHA II–IV LVEF ≥ 45%	Mean age: 72 ± 7 years, 60% female 88% hypertension, 27% diabetes Mean LVEF: 60% ± 9% Mean FU: 49.5 months	Death from any cause or hospitalization for CV cause	No benefit for primary endpoint No improvement of QOL
TOPCAT 2014 (n = 3,445) [63]	Spironolactone	HF with history of HF hospitalization within 12month and elevated BNP within 60 days LVEF ≥ 45%	Median age: 69 years, 52% female 91% hypertension, 32% diabetes Median LVEF: 56% Mean FU: 3.3 years	CV death or cardiac arrest or HF hospitalization	No benefit for primary endpoint Reduction of HF hospitalization
PARAGON-HF 2019 (n = 4,822) [66]	Sacubitril-valsartan	NYHA II–IV LVEF ≥ 45% Elevated NPs	Mean age: 73 ± 8 years, 52% female 96% hypertension, 43% diabetes Mean LVEF: 60% ± 9% Total FU time up to 57 months	HF hospitalization or CV death	No benefit for primary endpoint Reduce primary endpoint in subgroup (patients wuth LVEF below median [≤ 57%] and women)
Beta-blocker					
SENIORS 2009 (n = 752) [80]	Nebivolol	CHF history HF hospitalization within 12month	Mean age: 76 ± 5 years, 51% female 78% hypertension, 24% diabetes Mean LVEF: 49% ± 10% FU: 21 months	All cause mortality or CV hospitalization	No benefit for primary endpoint
J-DHF 2013 (n = 245) [81]	Carvedilol	LVEF ≥ 40%	Mean age: 76 ± 5 years, 55% female 80% hypertension, 33% diabetes Mean LVEF: 63% ± 11% Median FU: 3.2 years	CV death or HF hospi talization	No benefit for primary endpoint Reduce primary endpoints in patients with higher dose
Disease-modifying agents					

https://doi.org/10.3904/kjim.2020.104

Table 4. Continued

Trials, year (no. of patients)	Interventions	Inclusion criteria	Characteristics of study population	Primary endpoint	Trial result
NEAT-HFpEF 2015 (n = 110) [88]	Isosorbide mononitrate (organic nitrate)	LVEF ≥ 50% HF with objective evidence (≥ 1) -HF hospitalization with congestion , increased LVEDP or PCWP, elevated NP, LVDD on ECHO	Mean age: 69 ± 9 years, 49% female 88% hypertension, 43% diabetes Mean LVEF: 62% ± 8% Drug intervention for 6 weeks	Daily activity level	Decreased activity and worsen QOL
INDIE-HFpEF 2018 (n = 105) [94]	Nebulized inorganic nitrate	Age ≥ 40 years LVEF ≥ 50% HF with objective evidence (≥ 1) -HF hospitalization with congestion, increased LVEDP or PCWP, elevated NP, LVDD on ECHO	Mean age: 68 ± 9 years, 68% female 81% hypertension, 38% diabetes Mean LVEF: 61% ± 5% Drug intervention for 4 weeks	Peak O2 consumption	No improvement in exercise capacity
DILATE-1 2014 (n = 21) [95]	Riociguat (sGC stimulator)	HFpEF with PH LVEF ≥ 50% mPAP ≥ 25 mmHg PAWP > 15 mmHg at rest	Mean age: 68 ± 9 years, 68% female 81% hypertension, 44% diabetes Mean LVEF: 62% ± 7%	Peak decrease in mPAP	No significant effect on mPAP
SOCRATES-PRESERVED 2017 (n = 477) [96]	Vericiguat (sGC stimulator)	NYHA II–IV LVEF ≥ 45% Elevated NPs History of HF hospitalization or IV diuretics within 4 weeks	Mean age: 73 ± 10 years, 48% female 49% diabetes Mean LVEF: 57% Drug intervention for 4 weeks	Change of NT-proBNP and LAV	No signigicant change of NT-pro BNP and LAV
RELAX 2016 (n = 216) [98]	Sildenafil	HFpEF with RVD and RV-RA coupling NYHA II–IV LVEF ≥ 50% Evidence of HF (≥ 1) -HF hospitalization, elevated LVFP and LAE	Mean age: 68 ± 9 years, 68% female 81% hypertension, 38% diabetes Mean LVEF: 61% ± 5% Drug intervention for 4 weeks	Peak oxygen uptake	No improvement of RV function, exercise capacity and ventilatory efficiency
Non-pharmacological therapy					
CHAMPION 2011 (n = 119) [101]	Wireless implantable hemodynamic monitoring	HF with NYHA III LVEF ≥ 40%	Mean age: 66 ± 12 years, 40% female 82% hypertension, 58% diabetes Drug intervention for 6 months	HF hospitalization	Reduction of HF hospitalization

https://doi.org/10.3904/kjim.2020.104

Table 4. Continued

Trials, year (no. of patients)	Interventions	Inclusion criteria	Characteristics of study population	Primary endpoint	Trial result
REDUCE LAP-HF 2016 (n = 66) [103]	Interatrial shunt device	Age ≥ 40 years LVEF ≥ 40% Exercise PCWP ≥ 25 mmHg, PCWP-RAP gradient ≥ 5 mmHg	Mean age: 69 ± 8 years, 65% female 81% hypertension, 33% diabetes Drug intervention for 6 months	Successful device implantation Reduction of PCWP	Safe Reduction of LAP during exercise during exercise
REDUCE LAP-HF I 2018 (n = 94) [104]	Interatrial shunt device	NYHA III, IV LVEF ≥ 40% Exercise PCWP ≥ 25 mmHg, PCWP-RAP gradient ≥ 5 mmHg	Mean age: 70 ± 9 years, 50% female 82% hypertension, 55% diabetes Drug intervention for 1 months	Exercise PCWP	Reduction of PCWP during exercise
Manage of comorbidities					
Ex-DHF 2011 (n = 64) [115]	Endurance/ resistance training	Age ≥ 45 years NYHA II–III LVEF ≥ 50% CV risk factor (overweight, diabetes, hypertension, hyperlipidemia, smoking)	Mean age: 65 ± 7 years, 56% female 86% hypertension, 14% diabetes Drug intervention for 3 months	Peak VO_2	Improvement of exercise capacity and QOL
SECRET-1 2016 (n = 200) [117]	Caloric restriction Aerobic exercise training	HF with obesity Age ≥ 60 years BMI ≥ 30 LVEF ≥ 50%	Mean age: 61 ± 5 years, 56% female 95% hypertension, 35% diabetes Intervention for 3 months	Peak VO_2 Disease-specific QOL	Increased of peak oxygen uptake both caloric restriction and aerobic exercise training with addictive value

HFpEF, heart failure with preserved ejection fraction; CHARM, Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity; NYHA, New York Heart Association; HF, heart failure; LVEF, left ventricular ejection fraction; FU, follow-up; CV, cardiovascular; PEP-CHF, Perindopril in Elderly people with Chronic Heart Failure; I-PRESERVED, Irbesartan in Heart Failure With Preserved Ejection Fraction; QOL, quality of life; TOPCAT, Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist Trial; BNP, brain natriuretic peptide; PARAGON-HF, Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction; NP, natriuretic peptide; SENIORS, Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure; CHF, congestive heart failure; J-DHF, Japanese Diastolic Heart Failure Study; NEAT-HFpEF, Nitrate's Effect on Activity Tolerance in Heart Failure with Preserved Ejection Fraction; LVEDP, left ventricular end diastolic pressure; PCWP, pulmonary capillary wedge pressure; LVDD, left ventricular diastolic dysfunction; ECHO, echocardiography; INDIE-HFpEF, Inorganic Nitrite Delivery to Improve Exercise Capacity in HFpEF; DILATE-1, Acute Hemodynamic Effects of Riociguat in Patients with Pulmonary Hypertension Associated with Diastolic HF; sGC, soluble guanylate cyclase; PH, pulmonary hypertension; mPAP, mean pulmonary artery pressure; PAWP, pulmonary arterial wedge pressure; SOCRATES-PRESERVED, Soluble guanylate Cyclase stimulatoR in heArT failurE patients with PRESERVED EF; NT-proBNP, N-terminal pro-B-type natriuretic peptide; LAV, left atrial volume; RELAX, phosphodiesterase-5 inhibition to improve clinical status and exercise capacity in diastolic heart failure; RVD, right ventricular dysfunction; RV-RA, right ventricular-right atrial; LVFP, left ventricular filling pressure; LAE, left atrial enlargement; CHAMPION, CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients; REDUCE LAP-HF, Reduce Elevated Left Atrial Pressure in Patients with Heart Failure; RAP, right atrial pressure; Ex-DHF, enhancement of physical activity in elderly patients with diastolic heart failure; VO_2, oxygen uptake; SECRET-1, Study of the Effect of Caloric Restriction and Exercise Training in patients with heart failure and a normal ejection fraction-1; BMI, body mass index.

https://doi.org/10.3904/kjim.2020.104

0.90] in women vs. RR, 1.03, [95% CI, 0.84 to 1.25] in men, *p* interaction = 0.017) [67]. The possible reasons were further myocardial remodeling even in the same LVEF, more prominent age-related arterial stiffening in female patients with HFpEF, and differences in the signaling of natriuretic peptide [67]. Recently, Solomon et al. [68] reported the results of a pooled analysis of combined data from the Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) [69] and PARAGON-HF [66] trials. The overall treatment benefit was at LVEF ≤ 42.5% and was maximized at lower ejection fraction. The sacubitril-valsartan was valuable in women with LVEF ≤ 60%, contrarily the threshold of LVEF at which efficacy of sacubitril-valsartan was highest was 45% to 50% in men. Therefore, it could be presumed that sacubitril-valsartan is effective for all patients with middle-ranged ejection fraction (HFmrEF). This result was consistent with the clinical characteristics of HFrEF and HFmrEF, which were similar and different from those of HFpEF [70].

There should be a careful application of RAAS blockade to patients with HFpEF because the phenotypes of patients in the real world are different from the inclusion criteria of trials. As the LVEF cutoff of trials varied, a considerable portion of registered patients to these trials might belong to HFmrEF. Neurohormonal activation is less prominent in HFpEF, rather than in HFmrEF or HFrEF. Furthermore, a large proportion of trial patients had already taken RAAS blocker (20% to 86% of the study population) and beta-blocker (55% to 80% of the study population) at enrollment [71], because of their comorbidities including CAD and arrhythmia and their neurohormonal system might be stabilized. Thus, it might leave a little room for the additional benefit from another RAAS inhibitor. Therefore, the messages of clinical trials should be interpreted and accepted judiciously.

Beta-adrenergic signaling

Beta-blockers are the cornerstone of the management of HFrEF [8] because of a significant improvement in mortality and morbidity [72]. Sympathetic activation induces an increment of HR and leads to a shortening of the left ventricular diastolic filling time. Therefore, slowing HR and reversal of sympathetic overactivation could provide a benefit in HFpEF. A lower heart rate at discharge was closely related to a survival benefit in patients with HFpEF [73]. Several observational studies reported a modest benefit of beta-blockers for survival in HFpEF [74-76]. However, in pre-specified sub-analysis of the Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure (SENIORS) [77] the effect of beta-blockers nebivolol was similar between patients with HFrEF (LVEF ≤ 35%) and patients with HFpEF (LVEF > 35%), although the efficacy of nebivolol to reduce mortality was not statistically significant in both the patient groups. In the Japanese Diastolic Heart Failure Study (J-DHF) [78], an RCT to evaluate the effect of carvedilol in HFpEF (LVEF > 40%), it did not decrease CV death and HF hospitalization. Even in several meta-analyses, the efficacy of beta-blockers for mortality as well as HF hospitalization, in HFpEF is still controversial [79-81]. Recently, a pre-specified TOPCAT trial reported that the use of beta-blockers was related to an increase in HF hospitalization and was not associated with CV mortality in HFpEF [82]. The explained mechanism of ineffectiveness, even harm, was due to an increase in central blood pressure (BP) and myocardial wall stress due to increment of left ventricular volume and pressure by prolonged diastolic filling time [83,84]. However, recently reported Korean registry data showed that the use of beta-blockers reduced all-cause mortality in patients with HFpEF (LVEF ≥ 40%) and acute exacerbation of HF [85]. This benefit existed in patients with global longitudinal strain (GLS) < 14%, but not in patients with GLS ≥ 14% [86]. The conflicting results regarding the efficacy of beta-blockers are still unknown. This is due to the difference in the definition of HFpEF, especially LVEF cut-off value, heart rate at enrollment, and their changes after medication and pre-existing comorbidities, such as AF and CAD [87]. Despite these, beta-blockers might be beneficial to patients with HFpEF, especially in patients with myocardial remodeling with reduced GLS.

DISEASE-MODIFYING PHARMACOLOGICAL STRATEGIES

As mentioned above, the deregulation of the NO-sGC-cGMP-PKG pathway is a potentially key mechanism of

HFpEF. Therefore, therapeutic approaches have been tried to use medications that act on this pathway, including nitrates, phosphodiesterase-5 inhibitors, and sCG stimulators. Several trials have evaluated the role of these agents in the pathogenesis and treatment of HFpEF, with limited success.

Organic and inorganic nitrates

In altered endothelium-cardiomyocyte signaling by inflammation, NO is absent in cardiomyocytes. Therefore, organic NO supplementation was supposed to be helpful for HFpEF due to the restoration of myocardial NO content as well as alleviation of increased arterial load [5]. In the Nitrate's Effect on Activity Tolerance in Heart Failure with Preserved Ejection Fraction (NEAT-HFpEF) trial [88], organic nitrate isosorbide mononitrate did not improve QOL and NT-proBNP, even if the daily activity level was reduced and HF symptoms worsened in the isosorbide mononitrate group. The possible causes were excessive hypotension and decreased cardiac output due to preload reduction [89], the rapid development of tolerance, and endothelial dysfunction by organic nitrates [90]. In contrast, inorganic nitrate (NO_3) has a different NO metabolism: the nitrate-nitrite pathway. The nitrate-nitrite pathway could be an important route to restore NO in HFpEF, especially in the presence of hypoxia and acidosis such as skeletal muscle during exercise [91]. In small trials, the delivery of inorganic nitration via NO_3^--rich beetroot juice improved the exercise capacity of HFpEF patients [92,93]. The administration of sodium nitrite via infusion or inhalation improved cardiac output reserve, ventricular filling pressure, and pulmonary artery pressure during exercise in HFpEF. However, Inorganic Nitrite Delivery to Improve Exercise Capacity in HFpEF (INDIE-HFpEF) trial [94] showed that inhaled inorganic nitrite for 4 weeks failed to improve exercise capacity and QOL. The nitrite inhalation with its short-acting nature could be the cause of this result, as other administrations of inorganic nitrite, which provide a persistent and higher level of NO, achieved positive results. It is necessary to confirm the effectiveness of NO_3 in larger and long-term trials.

sGC stimulators

The sGC stimulators (riociguat and vericiguat) enhance cGMP production by acting on the NO receptor of sGC and activating sGC to generate cGMP. In Acute Hemodynamic Effects of Riociguat in Patients with Pulmonary Hypertension Associated with Diastolic HF (DILATE-1) [95] and Soluble guanylate Cyclase stimulatoR in heArT failurE patients with PRESERVED EF (SOCRATES-PRESERVED) [96] trials, sGC stimulators showed limited improvement in hemodynamic and echocardiographic parameters.

Sildenafil

Despite the possible positive effect of sildenafil in HFrEF [97], two separate studies for evaluating the efficacy of sildenafil in HFpEF with PH or RV dysfunction failed to show improvement in exercise capacity and QOL, and sildenafil was associated with impairment of renal function and increment of neurohormone level [98,99].

Other PKG-stimulating drugs, sacubitril

PKG is an intrinsic suppressor of ventricular hypertrophy and interstitial fibrosis [5]; therefore, stimulation of PKG is a potential therapy in HFpEF. cGMP is mandatory to stimulate PKG. As mentioned above, cGMP is synthesized by sGC via the NO-sGC-cGMP-PKG pathway and is generated by receptor guanyl cyclase linked to natriuretic peptide receptors. Therefore, the sacubitril, a neprilysin inhibitor, stimulates PKG by elevating the level of natriuretic peptides. The efficacy of ARNI in HFpEF is described above.

NON-PHARMACOLOGICAL THERAPY

Devices targeted to high LVFP

Pressure monitoring

As mentioned above, increased LVFP is a hallmark of the pathophysiology of HFpEF. PCWP is a hemodynamic parameter that reflects LA pressure and LVFP. A therapeutic strategy of hemodynamic monitoring accompanied by early therapeutic intervention might improve the clinical outcome of HFpEF patients. The CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients (CHAMPION) trial demonstrated that active reduction of LVFP guided by an assessment of

https://doi.org/10.3904/kjim.2020.104

central hemodynamics in HF patients regardless of LVEF significantly decreased HF hospitalization [100]. This finding persisted in additional analysis in HFpEF patients (LVEF ≥ 50%) [101] and real-word data [102].

Interatrial septal shunt

The other device targeted to high LVFP is an interatrial septal shunt to reduce LA pressure. In the Reduce Elevated Left Atrial Pressure in Patients with Heart Failure (REDUCE LAP-HF) study, an interatrial shunt was efficient in decreasing LAP and improving functional capacity [103] and these efficacies were confirmed in a long-term study with the improvement of hemodynamic data during exercise without significant complication [104,105]. The interatrial shunt might be helpful in the management of HFpEF, especially high LA filling pressure due to LA dysfunction, even though further studies to evaluate the long-term improvement are required.

Pacing

Chronotropic incompetence contributes to impaired cardiac output reserve, as described above. The restored normal heart rate response during exercise by pacemaker might be beneficial to HFpEF with chronotropic incompetence. The Rate-Adaptive Atrial Pacing In Diastolic Heart Failure (RAPID-HF) trial is ongoing to evaluate the impact of rate-adaptive atrial pacing on exercise capacity (NCT 02145351).

PREVENTIVE STRATEGIES FOR HFPEF: MANAGEMENT OF COMORBIDITIES

Hypertension

Hypertension is the most common comorbidity of HFpEF patients. In many previous RCTs of antihypertensive medication, optimal treatment of hypertension reduced the incidence of HF [106]. In HFpEF, the additional benefit of lowering BP is uncertain. As mentioned above, there was discordance between BP lowering and clinical outcome in large trials with neurohormonal inhibitors in HFpEF, even though neurohormonal inhibition had a favorable effect on ventricular hypertrophy, interstitial fibrosis, and myocardial stiffness [5]. Nevertheless, a recent meta-analysis showed that BP lowering was closely related to the reduction in HF hospitalization rather than all-cause mortality in HFpEF patients [107]. Furthermore, optimal BP control is important to prevent other major CV outcomes, including stroke and CAD, even in HFpEF patients.

Sodium-glucose cotransporter-2 inhibitors

The diabetes is prevalent in 20% to 40% of HFpEF patients [21]. Three RCTs on sodium-glucose cotransporter-2 (SGLT2) inhibitors in type 2 diabetes with high CV risk or established CV disease demonstrated a valuable effect of SGLT2 inhibitors [108]. McMurray et al. [109] reported that dapagliflozin significantly reduced worsening HF or CV death in HFrEF patients. The benefit of dapagliflozin on HF was similar between the patients with and without diabetes. The potential mechanism of the beneficial effect of SGLT2 inhibitors is not only to decrease intravascular volume via osmotic diuresis and natriuresis but also to reduce neurohormonal activation [110]. SGLT2 inhibitors increase metabolic efficiency and myocardial energy supply [110]. Furthermore, SGLT2 inhibitors induce a decrease in oxidative stress and fibrosis, an increase of endothelial function, and vascular compliance, which may be favorable in HFpEF [110,111]. The diastolic parameter was improved by the administration of SGLT2 inhibitors in patients with type 2 diabetes patients [112,113]. The RCTs for the efficacy of SGLT2 inhibitor in HFpEF (EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction [EMPEROR-Preserved; NCT 03057951], Effect of EMpaglifozin on ExeRcise ability and heart failure symptoms, In patients with chronic heArt faiLure with preserved ejection fraction [EMPERIAL-preserved; NCT 03448406], Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure [DELIVER; NCT 03619213], dapagliflozin in PRESERVED Ejection Fraction Heart Failure [PRESERVED-HF; NCT 03030235]) are ongoing and we look forward to the results of these studies shortly.

Lifestyle modification

Lifestyle modifications, including exercise, weight reduction, and dietary composition, are beneficial in preventing and treating HF [114]. However, the potential benefit of lifestyle modification has not been fully

Table 5. Ongoing trials in HFpEF

Name ClinicalTrials.gov identifier	Intervention	Inclusion criteria	Primary endpoint	Estimated completion
SPIRRIT-HFPEF NCT 02901184	Spironolactone	Age ≥ 50 years LVEF ≥ 40% in last 12 months Stable HF defined by symptoms ans signs NT-proBNP > 300 ng/L in SR or > 750 ng/L in AF	Time to CV death or first HF hospitalization.	6/2,022
PARAGLIDE-HF NCT 03988634	Sacubitril/ valsartan	Age ≥ 40 years LVEF ≥ 40% Elevated NT-proBNP Currently hospitalized for or within 30 days following discharge of an acute decompensated HFpEF admission	Proportional change in NT-proBNP at weeks 4 and 8	9/2,021
PRISTINE-HF NCT 04128891	Sacubitril/ valsartan	Age ≥ 40 years LVEF ≥ 45% NYHA II–III Structural heart disease: LAE, LVH Elevated NT-proBNP	Improvement in microvascular function and ischaemia, as assessed by OS-CMR	2/2,024
KNO3CK OUT HFPEF NCT 02840799	Potassium nitrate (KNO_3) Potassium chloride (KCl)	Age 18–90 years LVEF ≥ 50% NYHA II–III Elevated filling pressure on echocardiography	Peak VO_2	12/2,020
CAPACITY-HFpEF NCT 03254485	IW-1973 (sGC stimulator)	Age ≥ 45 years LVEF ≥ 40% Peak VO_2 < 80% of age-and sex-adjusted normal value Medical history of HF At least 2 of comorbidities (diabetes, hypertension, BMI > 30 kg/m^2, age ≥ 70 years)	Treatment-emergent adverse event Peak VO_2 at week 12	Complete
SATELLITE NCT 03756285	AZD4831 (myeloperoxidase inhibitor)	Age 45–85 years LVEF ≥ 40% NYHA II–IV Elevated NT-proBNP One of the following: - HF hospitalization within 12 months - Structural heart disease on echocardiography - PCWP at rest > 15 or > 25 mmHg at exercise - E/e' ratio ≥ 13 at rest	Change of myeloperoxidase activity	10/2,020

https://doi.org/10.3904/kjim.2020.104

https://doi.org/10.3904/kjim.2020.104

Table 5. Continued

Name ClinicalTrials.gov identifier	Intervention	Inclusion criteria	Primary endpoint	Estimated completion
NCT 03611153	Oral myeloperoxidase inhibitor	Age ≥ 30 years LVEF ≥ 50% NYHA II–III Evated filling pressures at rest (PCWP ≥ 15) or with exercise (PCWP ≥ 25)	Exercise PCWP	1/2,021
DELIVER NCT 03619213	Dapaglifqlozin	Age ≥ 40 years NYHA II–IV LVEF > 40% and evidence of structural heart disease	Time to the first occurrence of any of the components of this composite: (1) CV death; (2) hospitalisation for HF; (3) urgent HF visit	6/2,021
DETERMINE-preserved NCT 03877224	Dapagliflozin	Age ≥ 40 years NYHA II–IV LVEF > 40% and evidence of structural heart disease Elevated NT-proBNP	Change of 6MWD at week 16 Exercise capacity HF symptom relieve	7/2,020
EMPEROR-Preserved NCT 03057951	Empagliflozin	Age ≥ 18 years NYHA II–IV LVEF > 40% and evidence of structural heart disease Elevated NT-proBNP	Time to first event of adjudicated CV death or adjudicated HF hospitalization	11/2,020
FAIR-HFpEF NCT 03074591	Ferric carboxymaltose (IV iron)	Age ≥ 18 years NYHA II–III LVEF > 45% One of the following - Elevated NT-proBNP or previous hospitalization Evidence of LVDD ID (Hb 9–14 g/dL) with ferritin < 100 ng/mL or ferritin 100–299 with transferrin saturation < 20%	Exercise capacity-change of 6MWT at week 52	7/2,021
INABLE-Training NCT 02713126	Exercise training Oral sodium nitrite	Age ≥ 40 years NYHA II–IV LVEF ≥ 50% One of the following: - Previous HF hospitalization with radiographic evidence - Catheterization documented elevated filling pressures - Elevated natruretic peptide - Echo evidence of LVDD/elevated filling pressures	Change of peak VO_2 at week12	12/2,020
RAPID-HF NCT 02145351	Rate-adaptive atrial pacing	Age ≥ 18 years NYHA II–III LVEF > 40% Baseline sinus rhythm Documented chronotropic incompetence	Change of peak VO_2 at week 4	5/2,021

Table 5. Continued

Name ClinicalTrials.gov identifier	Intervention	Inclusion criteria	Primary endpoint	Estimated completion
CCM-HFpEF NCT 03240237	Cardiac contractility modulation	Age 40–80 years LVEF ≥ 50% NYHA II–III Elevated NTproBNP Has the following: - LAVI ≥ 34 mL/m^2 or LVH > 12mm and either - E/e' ≥ 13 OR or septal e' < 7 cm/sec (or lateral e' < 10 cm/sec)	Mean change from baseline to 24 weeks in Kansas City Cardiomyopathy questionnaire	12/2,023
NCT 00327649	Low level transcutaneous vagus nerve stimulation	HFpEF, defined as signs and symptoms of heart failure Plus 2 of the following 4 comorbidities - Age ≥ 65years, diabetes, hypertension, obesity	Diastolic dysfunction	8/2,020
NCT 02499601	CORolla™ TAA device	Age ≥ 18 years NYHA III, IV LVEF > 50% PCWP > 15 mmHg by RHC Echocardiographic criteria: - LVEDVI < 97 mL/m^2, E/e' > 12, LAVI > 29 mL/m^2	Number of participants with all-cause mortality and serious adverse events	9/2,020

HFpEF, heart failure with preserved ejection fraction; SPIRRIT-HFPEF, Spironolactone Initiation Registry Randomized Interventional Trial in Heart Failure with Preserved Ejection Fraction ; LVEF, left ventricular ejection fraction; HF, heart failure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SR, sinus rhythm; AF, atrial fibrillation; CV, cardiovascular; PARAGLIDE-HF, A Multicenter, Randomized, Double-blind, Double-dummy, Parallel Group, Active Controlled Study to Evaluate the Effect of Sacubitril/Valsartan (LCZ696) Versus Valsartan on Changes in NT-proBNP and Outcomes, Safety, and Tolerability in HFpEF Patients With Acute Decompensated Heart Failure (ADHF) Who Have Been Stabilized During Hospitalization and Initiated In-hospital or Within 30 Days Post-discharge; PRISTINE-HF, PRospectIve Study of Sacubitril/ValsarTan on MyocardIal OxygenatioN and Fibrosis in PatiEnts With Heart Failure and Preserved Ejection Fraction; NYHA, New York Heart Association; LAE, left atrial enlargement; LVH, left ventricular hypertrophy; OS-CMR, oxygenation sensitive cardiac magnetic resoance; KNO3CK OUT HFPEF, Effect of KNO3 Compared to KCl on Oxygen UpTake in Heart Failure With Preserved Ejection Fraction; VO_2, oxygen uptake; CAPACITY-HFpEF, A Multicenter, Randomized, Double-blind, Placebo-controlled, Phase 2 Study Evaluating the Safety and Efficacy of Different Doses of IW-1973 Over 12 Weeks in Patients With Heart Failure With Preserved Ejection Fraction; sGC, soluble guanylate cyclase; BMI, body mass index; SATELLITE, Safety and Tolerability Study of AZD4831 in Patients With Heart Failure; PCWP, pulmonary capillary wedge pressure; DELIVER, Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure; DETERMINE-preserved, Dapagliflozin Effect on Exercise Capacity Using a 6-minute Walk Test in Patients With Heart Failure With Preserved Ejection Fraction; 6MWD, 6-minute walk distane; EMPEROR-Preserved, EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction; FAIR-HFpEF, Effect of IV Iron in Patients With Heart Failure With Preserved Ejection Fraction; IV, intravenous; LVDD, left ventricular diastolic dysfunction; Hb, hemoglobin; 6MWT, 6-minute walk teast; INABLE-traing, Inorganic Nitrite to Amplify the Benefits and Tolerability of Exercise Training in Heart Failure With Preserved Ejection Fraction; RAPID-HF, Rate-Adaptive Atrial Pacing In Diastolic Heart Failure; CCM-HFpEF, Cardiac Contractility Modulation Therapy in Subjects With Heart Failure With Preserved Ejection Fraction; RHC, right heart catheterization; LAVI, left atrial volume index; LVEDVI, left ventricular end-diastolic volume index.

https://doi.org/10.3904/kjim.2020.104

elucidated in RCT or cohort studies. Nevertheless, the efficacy of exercise was reported in several studies that included endurance and resistance training, improved exercise capacity, and QOL in HFpEF [115,116]. About half of HFpEF patients have obesity, and an increase in body adiposity triggers systemic inflammation and impairment of cardiac, vascular, and skeletal muscle function [5]. Kitzman et al. [117] demonstrated that caloric reduction during 20 weeks significantly improved peak O_2 consumption, symptoms, and QOL in older and obese patients. The additive benefit was derived by a combination of caloric restriction and exercise. Lifestyle modification might be important for the management of HFpEF as well as a cardiometabolic syndrome, representative comorbidity of HFpEF. Further investigation to prove the beneficial effect of lifestyle modification in HFpEF is required.

CONCLUSIONS

HFpEF is the most common form of HF with an increase in the elderly population, and its prognosis has not yet improved. The trials of medications have been neutral or less effective in terms of their primary outcomes. The possible explanations for this result are incomplete understanding of the pathophysiology, heterogeneity of the study populations, lack of universal diagnostic criteria of HFpEF, unconnected pathophysiological mechanisms related to treatment, and suboptimal designs for statistical power of the trials. Currently, the concept of HFpEF is evolving; HFpEF is a multifaceted syndrome. The pathophysiology of HFpEF is multifactorial, with several mechanisms and comorbidities involved, and different from that of HFrEF. HFpEF results from a complex interaction of heart, vasculature, and peripheries: LVDD, systolic functional reserve, autonomic imbalance, and macro- and microvasculature response to increased oxygen demand. Substantial heterogeneity exists in these interactions and dominance in each patient with HFpEF. Therefore, the definition of HFpEF by LVEF is bound to be limited. Recently, new diagnostic strategies have been proposed that appear promising; however, further validation is required. Treatment of HFpEF needs to be approached differently according to various phenotypes of HFpEF, and several treatment trials are on the way as per different therapeutic approaches (summarized in Table 5). In our daily clinical practice, we need to understand the nature of the diversity of HFpEF and approach each patient with HFpEF individually.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Kitzman DW, Gardin JM, Gottdiener JS, et al. Importance of heart failure with preserved systolic function in patients > or = 65 years of age. CHS Research Group. Cardiovascular Health Study. Am J Cardiol 2001;87:413-419.
2. Heidenreich PA, Albert NM, Allen LA, et al. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. Circ Heart Fail 2013;6:606-619.
3. Chamberlain AM, Dunlay SM, Gerber Y, et al. Burden and timing of hospitalizations in heart failure: a community study. Mayo Clin Proc 2017;92:184-192.
4. Fonarow GC, Stough WG, Abraham WT, et al. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. J Am Coll Cardiol 2007;50:768-777.
5. Shah SJ, Kitzman DW, Borlaug BA, et al. Phenotype-specific treatment of heart failure with preserved ejection fraction: a multiorgan roadmap. Circulation 2016;134:73-90.
6. Upadhya B, Kitzman DW. Heart failure with preserved ejection fraction: new approaches to diagnosis and management. Clin Cardiol 2020;43:145-155.
7. Kim MS, Lee JH, Kim EJ, et al. Korean guidelines for diagnosis and management of chronic heart failure. Korean Circ J 2017;47:555-643.
8. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2016;18:891-975.

9. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;62:e147-e239.
10. Michaud M, Maurin V, Simon M, Chauvel C, Bogino E, Abergel E. Patients with high left ventricular filling pressure may be missed applying 2016 echo guidelines: a pilot study. Int J Cardiovasc Imaging 2019;35:2157-2166.
11. Richards AM. N-terminal B-type natriuretic peptide in heart failure. Heart Fail Clin 2018;14:27-39.
12. Abergel E, Lafitte S, Mansencal N. Evaluation of left ventricular filling pressure: Updated recommendations lack new evidence and have severe interpretation issues. Arch Cardiovasc Dis 2018;111:707-711.
13. Vaduganathan M, Claggett BL, Desai AS, et al. Prior heart failure hospitalization, clinical outcomes, and response to sacubitril/valsartan compared with valsartan in HFpEF. J Am Coll Cardiol 2020;75:245-254.
14. Reddy YNV, Carter RE, Obokata M, Redfield MM, Borlaug BA. A simple, evidence-based approach to help guide diagnosis of heart failure with preserved ejection fraction. Circulation 2018;138:861-870.
15. Pieske B, Tschope C, de Boer RA, et al. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). Eur Heart J 2019;40:3297-3317.
16. Segar MW, Patel KV, Berry JD, Grodin JL, Pandey A. Generalizability and implications of the H₂FPEF score in a cohort of patients with heart failure with preserved ejection fraction. Circulation 2019;139:1851-1853.
17. Sueta D, Yamamoto E, Nishihara T, et al. H2FPEF score as a prognostic value in HFpEF patients. Am J Hypertens 2019;32:1082-1090.
18. Barandiaran Aizpurua A, Sanders-van Wijk S, Brunner-La Rocca HP, et al. Validation of the HFA-PEFF score for the diagnosis of heart failure with preserved ejection fraction. Eur J Heart Fail 2020;22:413-421.
19. Mohammed SF, Borlaug BA, Roger VL, et al. Comorbidity and ventricular and vascular structure and function in heart failure with preserved ejection fraction: a community-based study. Circ Heart Fail 2012;5:710-719.
20. Zakeri R, Cowie MR. Heart failure with preserved ejection fraction: controversies, challenges and future directions. Heart 2018;104:377-384.
21. Pfeffer MA, Shah AM, Borlaug BA. Heart failure with preserved ejection fraction in perspective. Circ Res 2019;124:1598-1617.
22. Gevaert AB, Boen JRA, Segers VF, Van Craenenbroeck EM. Heart failure with preserved ejection fraction: a review of cardiac and noncardiac pathophysiology. Front Physiol 2019;10:638.
23. Franssen C, Chen S, Unger A, et al. Myocardial microvascular inflammatory endothelial activation in heart failure with preserved ejection fraction. JACC Heart Fail 2016;4:312-324.
24. Zile MR, Baicu CF, Ikonomidis JS, et al. Myocardial stiffness in patients with heart failure and a preserved ejection fraction: contributions of collagen and titin. Circulation 2015;131:1247-1259.
25. Westermann D, Kasner M, Steendijk P, et al. Role of left ventricular stiffness in heart failure with normal ejection fraction. Circulation 2008;117:2051-2060.
26. Borlaug BA, Jaber WA, Ommen SR, Lam CS, Redfield MM, Nishimura RA. Diastolic relaxation and compliance reserve during dynamic exercise in heart failure with preserved ejection fraction. Heart 2011;97:964-969.
27. Borlaug BA, Kane GC, Melenovsky V, Olson TP. Abnormal right ventricular-pulmonary artery coupling with exercise in heart failure with preserved ejection fraction. Eur Heart J 2016;37:3293-3302.
28. Melenovsky V, Andersen MJ, Andress K, Reddy YN, Borlaug BA. Lung congestion in chronic heart failure: haemodynamic, clinical, and prognostic implications. Eur J Heart Fail 2015;17:1161-1671.
29. Obokata M, Olson TP, Reddy YNV, Melenovsky V, Kane GC, Borlaug BA. Haemodynamics, dyspnoea, and pulmonary reserve in heart failure with preserved ejection fraction. Eur Heart J 2018;39:2810-2821.
30. Dorfs S, Zeh W, Hochholzer W, et al. Pulmonary capillary wedge pressure during exercise and long-term mortality in patients with suspected heart failure with preserved ejection fraction. Eur Heart J 2014;35:3103-3112.
31. Melenovsky V, Hwang SJ, Redfield MM, Zakeri R, Lin G, Borlaug BA. Left atrial remodeling and function in advanced heart failure with preserved or reduced ejection fraction. Circ Heart Fail 2015;8:295-303.
32. Reddy YNV, Obokata M, Wiley B, et al. The haemodynamic basis of lung congestion during exercise in heart failure with preserved ejection fraction. Eur Heart J

https://doi.org/10.3904/kjim.2020.104

2019;40:3721-3730.
33. Telles F, Nanayakkara S, Evans S, et al. Impaired left atrial strain predicts abnormal exercise haemodynamics in heart failure with preserved ejection fraction. Eur J Heart Fail 2019;21:495-505.
34. Khan MS, Memon MM, Murad MH, et al. Left atrial function in heart failure with preserved ejection fraction: a systematic review and meta-analysis. Eur J Heart Fail 2020;22:472-485.
35. Patel RB, Shah SJ. Therapeutic targeting of left atrial myopathy in atrial fibrillation and heart failure with preserved ejection fraction. JAMA Cardiol 2020 Mar 4 [Epub]. https://doi.org/10.1001/jamacardio.2020.0136.
36. Vanderpool RR, Saul M, Nouraie M, Gladwin MT, Simon MA. Association between hemodynamic markers of pulmonary hypertension and outcomes in heart failure with preserved ejection fraction. JAMA Cardiol 2018;3:298-306.
37. Andersen MJ, Hwang SJ, Kane GC, et al. Enhanced pulmonary vasodilator reserve and abnormal right ventricular: pulmonary artery coupling in heart failure with preserved ejection fraction. Circ Heart Fail 2015;8:542-550.
38. Gorter TM, Obokata M, Reddy YNV, Melenovsky V, Borlaug BA. Exercise unmasks distinct pathophysiologic features in heart failure with preserved ejection fraction and pulmonary vascular disease. Eur Heart J 2018;39:2825-2835.
39. Obokata M, Reddy YNV, Melenovsky V, Pislaru S, Borlaug BA. Deterioration in right ventricular structure and function over time in patients with heart failure and preserved ejection fraction. Eur Heart J 2019;40:689-697.
40. Obokata M, Reddy YNV, Pislaru SV, Melenovsky V, Borlaug BA. Evidence supporting the existence of a distinct obese phenotype of heart failure with preserved ejection fraction. Circulation 2017;136:6-19.
41. Tan YT, Wenzelburger F, Lee E, et al. The pathophysiology of heart failure with normal ejection fraction: exercise echocardiography reveals complex abnormalities of both systolic and diastolic ventricular function involving torsion, untwist, and longitudinal motion. J Am Coll Cardiol 2009;54:36-46.
42. Shah AM, Claggett B, Sweitzer NK, et al. Prognostic importance of impaired systolic function in heart failure with preserved ejection fraction and the impact of spironolactone. Circulation 2015;132:402-414.
43. Abudiab MM, Redfield MM, Melenovsky V, et al. Cardiac output response to exercise in relation to metabolic demand in heart failure with preserved ejection fraction. Eur J Heart Fail 2013;15:776-785.
44. Potter E, Marwick TH. Assessment of left ventricular function by echocardiography: the case for routinely adding global longitudinal strain to ejection fraction. JACC Cardiovasc Imaging 2018;11:260-274.
45. Herscovici R, Sedlak T, Wei J, Pepine CJ, Handberg E, Bairey Merz CN. Ischemia and no obstructive coronary artery disease (INOCA): what is the risk? J Am Heart Assoc 2018;7:e008868.
46. Elgendy IY, Pepine CJ. Heart failure with preserved ejection fraction: is ischemia due to coronary microvascular dysfunction a mechanistic factor? Am J Med 2019;132:692-697.
47. Murthy VL, Naya M, Taqueti VR, et al. Effects of sex on coronary microvascular dysfunction and cardiac outcomes. Circulation 2014;129:2518-2527.
48. Taqueti VR, Solomon SD, Shah AM, et al. Coronary microvascular dysfunction and future risk of heart failure with preserved ejection fraction. Eur Heart J 2018;39:840-849.
49. Shah SJ, Lam CSP, Svedlund S, et al. Prevalence and correlates of coronary microvascular dysfunction in heart failure with preserved ejection fraction: PROMIS-HFpEF. Eur Heart J 2018;39:3439-3450.
50. Park SM, Wei J, Cook-Wiens G, et al. Left ventricular concentric remodelling and functional impairment in women with ischaemia with no obstructive coronary artery disease and intermediate coronary flow reserve: a report from the WISE-CVD study. Eur Heart J Cardiovasc Imaging 2019;20:875-882.
51. Haykowsky MJ, Brubaker PH, Morgan TM, Kritchevsky S, Eggebeen J, Kitzman DW. Impaired aerobic capacity and physical functional performance in older heart failure patients with preserved ejection fraction: role of lean body mass. J Gerontol A Biol Sci Med Sci 2013;68:968-975.
52. Heinonen I, Bucci M, Kemppainen J, et al. Regulation of subcutaneous adipose tissue blood flow during exercise in humans. J Appl Physiol (1985) 2012;112:1059-1063.
53. Kitzman DW, Nicklas B, Kraus WE, et al. Skeletal muscle abnormalities and exercise intolerance in older patients with heart failure and preserved ejection fraction. Am J Physiol Heart Circ Physiol 2014;306:H1364-H1370.
54. Molina AJ, Bharadwaj MS, Van Horn C, et al. Skeletal muscle mitochondrial content, oxidative capacity, and Mfn2 expression are reduced in older patients with heart failure and preserved ejection fraction and are related to

exercise intolerance. JACC Heart Fail 2016;4:636-645.
55. Jia G, Aroor AR, Hill MA, Sowers JR. Role of renin-angiotensin-aldosterone system activation in promoting cardiovascular fibrosis and stiffness. Hypertension 2018;72:537-548.
56. Pugliese NR, Masi S, Taddei S. The renin-angiotensin-aldosterone system: a crossroad from arterial hypertension to heart failure. Heart Fail Rev 2020;25:31-42.
57. Cabandugama PK, Gardner MJ, Sowers JR. The renin angiotensin aldosterone system in obesity and hypertension: roles in the cardiorenal metabolic syndrome. Med Clin North Am 2017;101:129-137.
58. Seccia TM, Caroccia B, Muiesan ML, Rossi GP. Atrial fibrillation and arterial hypertension: a common duet with dangerous consequences where the renin angiotensin-aldosterone system plays an important role. Int J Cardiol 2016;206:71-76.
59. Yusuf S, Pfeffer MA, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet 2003;362:777-781.
60. Cleland JG, Tendera M, Adamus J, et al. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. Eur Heart J 2006;27:2338-2345.
61. Massie BM, Carson PE, McMurray JJ, et al. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med 2008;359:2456-2467.
62. Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med 2014;370:1383-1392.
63. Pfeffer MA, Claggett B, Assmann SF, et al. Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial. Circulation 2015;131:34-42.
64. de Denus S, O'Meara E, Desai AS, et al. Spironolactone metabolites in TOPCAT: new insights into regional variation. N Engl J Med 2017;376:1690-1692.
65. Solomon SD, Zile M, Pieske B, et al. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. Lancet 2012;380:1387-1395.
66. Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. N Engl J Med 2019;381:1609-1620.
67. McMurray JJV, Jackson AM, Lam CSP, et al. Effects of sacubitril-valsartan versus valsartan in women compared with men with heart failure and preserved ejection fraction: insights from PARAGON-HF. Circulation 2020;141:338-351.
68. Solomon SD, Vaduganathan M, Claggett BL, et al. Sacubitril/valsartan across the spectrum of ejection fraction in heart failure. Circulation 2020;141:352-361.
69. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371:993-1004.
70. Koh AS, Tay WT, Teng THK, et al. A comprehensive population-based characterization of heart failure with mid-range ejection fraction. Eur J Heart Fail 2017;19:1624-1634.
71. Kuno T, Ueyama H, Fujisaki T, Briasouli A, Takagi H, Briasoulis A. Meta-analysis evaluating the effects of renin-angiotensin-aldosterone system blockade on outcomes of heart failure with preserved ejection fraction. Am J Cardiol 2020;125:1187-1193.
72. Chatterjee S, Biondi-Zoccai G, Abbate A, et al. Benefits of β blockers in patients with heart failure and reduced ejection fraction: network meta-analysis. Version 2. BMJ 2013;346:f55.
73. Lam PH, Dooley DJ, Deedwania P, et al. Heart rate and outcomes in hospitalized patients with heart failure with preserved ejection fraction. J Am Coll Cardiol 2017;70:1861-1871.
74. Shah R, Wang Y, Foody JM. Effect of statins, angiotensin-converting enzyme inhibitors, and beta blockers on survival in patients >or=65 years of age with heart failure and preserved left ventricular systolic function. Am J Cardiol 2008;101:217-222.
75. Gomez-Soto FM, Romero SP, Bernal JA, et al. Mortality and morbidity of newly diagnosed heart failure with preserved systolic function treated with β-blockers: a propensity-adjusted case-control populational study. Int J Cardiol 2011;146:51-55.
76. Yanagihara K, Kinugasa Y, Sugihara S, et al. Discharge use of carvedilol is associated with higher survival in Japanese elderly patients with heart failure regardless of left ventricular ejection fraction. J Cardiovasc Pharmacol 2013;62:485-490.
77. van Veldhuisen DJ, Cohen-Solal A, Bohm M, et al. Beta-blockade with nebivolol in elderly heart failure patients with impaired and preserved left ventricular ejection fraction: data from SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospital-

https://doi.org/10.3904/kjim.2020.104

ization in Seniors With Heart Failure). J Am Coll Cardiol 2009;53:2150-2158.
78. Yamamoto K, Origasa H, Hori M; J-DHF Investigators. Effects of carvedilol on heart failure with preserved ejection fraction: the Japanese Diastolic Heart Failure Study (J-DHF). Eur J Heart Fail 2013;15:110-118.
79. Bavishi C, Chatterjee S, Ather S, Patel D, Messerli FH. Beta-blockers in heart failure with preserved ejection fraction: a meta-analysis. Heart Fail Rev 2015;20:193-201.
80. Martin N, Manoharan K, Thomas J, Davies C, Lumbers RT. Beta-blockers and inhibitors of the renin-angiotensin aldosterone system for chronic heart failure with preserved ejection fraction. Cochrane Database Syst Rev 2018;6:CD012721.
81. Liu F, Chen Y, Feng X, Teng Z, Yuan Y, Bin J. Effects of beta-blockers on heart failure with preserved ejection fraction: a meta-analysis. PLoS One 2014;9:e90555.
82. Silverman DN, Plante TB, Infeld M, et al. Association of β-blocker use with heart failure hospitalizations and cardiovascular disease mortality among patients with heart failure with a preserved ejection fraction: a secondary analysis of the TOPCAT trial. JAMA Netw Open 2019;2:e1916598.
83. Williams B, Lacy PS, Thom SM, et al. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. Circulation 2006;113:1213-1225.
84. Meyer M, LeWinter MM. Heart rate and heart failure with preserved ejection fraction: time to slow β-blocker use? Circ Heart Fail 2019;12:e006213.
85. Kim SH, Yun SC, Park JJ, et al. Beta-blockers in patients with heart failure with preserved ejection fraction: results from the Korea Acute Heart Failure (KorAHF) registry. Korean Circ J 2019;49:238-248.
86. Park JJ, Choi HM, Hwang IC, Park JB, Park JH, Cho GY. Myocardial strain for identification of β-blocker responders in heart failure with preserved ejection fraction. J Am Soc Echocardiogr 2019;32:1462-1469.
87. Cho JY. Beta-blockers in heart failure with preserved ejection fraction: could their use be vindicated as an acceptable option in the future treatment guideline? Korean Circ J 2019;49:249-251.
88. Redfield MM, Anstrom KJ, Levine JA, et al. Isosorbide mononitrate in heart failure with preserved ejection fraction. N Engl J Med 2015;373:2314-2324.
89. Schwartzenberg S, Redfield MM, From AM, Sorajja P, Nishimura RA, Borlaug BA. Effects of vasodilation in heart failure with preserved or reduced ejection fraction implications of distinct pathophysiologies on response to therapy. J Am Coll Cardiol 2012;59:442-451.
90. Upadhya B, Haykowsky MJ, Kitzman DW. Therapy for heart failure with preserved ejection fraction: current status, unique challenges, and future directions. Heart Fail Rev 2018;23:609-629.
91. Chirinos JA, Zamani P. The nitrate-nitrite-NO pathway and its implications for heart failure and preserved ejection fraction. Curr Heart Fail Rep 2016;13:47-59.
92. Eggebeen J, Kim-Shapiro DB, Haykowsky M, et al. One week of daily dosing with beetroot juice improves submaximal endurance and blood pressure in older patients with heart failure and preserved ejection fraction. JACC Heart Fail 2016;4:428-437.
93. Shaltout HA, Eggebeen J, Marsh AP, et al. Effects of supervised exercise and dietary nitrate in older adults with controlled hypertension and/or heart failure with preserved ejection fraction. Nitric Oxide 2017;69:78-90.
94. Borlaug BA, Anstrom KJ, Lewis GD, et al. Effect of inorganic nitrite vs placebo on exercise capacity among patients with heart failure with preserved ejection fraction: the INDIE-HFpEF randomized clinical trial. JAMA 2018;320:1764-1773.
95. Bonderman D, Pretsch I, Steringer-Mascherbauer R, et al. Acute hemodynamic effects of riociguat in patients with pulmonary hypertension associated with diastolic heart failure (DILATE-1): a randomized, double-blind, placebo-controlled, single-dose study. Chest 2014;146:1274-1285.
96. Pieske B, Maggioni AP, Lam CSP, et al. Vericiguat in patients with worsening chronic heart failure and preserved ejection fraction: results of the SOluble guanylate Cyclase stimulatoR in heart failurE patientS with PRESERVED EF (SOCRATES-PRESERVED) study. Eur Heart J 2017;38:1119-1127.
97. Zhuang XD, Long M, Li F, Hu X, Liao XX, Du ZM. PDE5 inhibitor sildenafil in the treatment of heart failure: a meta-analysis of randomized controlled trials. Int J Cardiol 2014;172:581-587.
98. Hussain I, Mohammed SF, Forfia PR, et al. Impaired right ventricular-pulmonary arterial coupling and effect of sildenafil in heart failure with preserved ejection fraction: an ancillary analysis from the phosphodiesterase-5 inhibition to improve clinical status and exercise capacity

in diastolic heart failure (RELAX) trial. Circ Heart Fail 2016;9:e002729.
99. Liu LC, Hummel YM, van der Meer P, et al. Effects of sildenafil on cardiac structure and function, cardiopulmonary exercise testing and health-related quality of life measures in heart failure patients with preserved ejection fraction and pulmonary hypertension. Eur J Heart Fail 2017;19:116-125.
100. Abraham WT, Adamson PB, Bourge RC, et al. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. Lancet 2011;377:658-666.
101. Adamson PB, Abraham WT, Bourge RC, et al. Wireless pulmonary artery pressure monitoring guides management to reduce decompensation in heart failure with preserved ejection fraction. Circ Heart Fail 2014;7:935-944.
102. Desai AS, Bhimaraj A, Bharmi R, et al. Ambulatory hemodynamic monitoring reduces heart failure hospitalizations in "real-world" clinical practice. J Am Coll Cardiol 2017;69:2357-2365.
103. Hasenfub G, Hayward C, Burkhoff D, et al. A transcatheter intracardiac shunt device for heart failure with preserved ejection fraction (REDUCE LAP-HF): a multicentre, open-label, single-arm, phase 1 trial. Lancet 2016;387:1298-1304.
104. Feldman T, Mauri L, Kahwash R, et al. Transcatheter interatrial shunt device for the treatment of heart failure with preserved ejection fraction (REDUCE LAP-HF I [Reduce Elevated Left Atrial Pressure in Patients With Heart Failure]): a phase 2, randomized, sham-controlled trial. Circulation 2018;137:364-375.
105. Shah SJ, Feldman T, Ricciardi MJ, et al. One-year safety and clinical outcomes of a transcatheter interatrial shunt device for the treatment of heart failure with preserved ejection fraction in the Reduce Elevated Left Atrial Pressure in Patients With Heart Failure (REDUCE LAP-HF I) trial: a randomized clinical trial. JAMA Cardiol 2018;3:968-977.
106. Kjeldsen SE, von Lueder TG, Smiseth OA, et al. Medical therapies for heart failure with preserved ejection fraction. Hypertension 2020;75:23-32.
107. Kawano H, Fujiwara A, Kai H, et al. Effects of blood pressure lowering in patients with heart failure with preserved ejection fraction: a systematic review and meta-analysis. Hypertens Res 2019;42:504-513.
108. Stewart Coats AJ. Common co-morbidities in heart failure: diabetes, functional mitral regurgitation and sleep apnoea. Int J Heart Fail 2019;1:25-41.
109. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med 2019;381:1995-2008.
110. Lan NSR, Fegan PG, Yeap BB, Dwivedi G. The effects of sodium-glucose cotransporter 2 inhibitors on left ventricular function: current evidence and future directions. ESC Heart Fail 2019;6:927-935.
111. Kato ET, Kimura T. Sodium-glucose co-transporters-2 inhibitors and heart failure: state of the art review and future potentials. Int J Heart Fail.2020;2:12-22.
112. Soga F, Tanaka H, Tatsumi K, et al. Impact of dapagliflozin on left ventricular diastolic function of patients with type 2 diabetic mellitus with chronic heart failure. Cardiovasc Diabetol 2018;17:132.
113. Pabel S, Wagner S, Bollenberg H, et al. Empagliflozin directly improves diastolic function in human heart failure. Eur J Heart Fail 2018;20:1690-1700.
114. Aggarwal M, Bozkurt B, Panjrath G, et al. Lifestyle modifications for preventing and treating heart failure. J Am Coll Cardiol 2018;72:2391-2405.
115. Edelmann F, Gelbrich G, Dungen HD, et al. Exercise training improves exercise capacity and diastolic function in patients with heart failure with preserved ejection fraction: results of the Ex-DHF (Exercise training in Diastolic Heart Failure) pilot study. J Am Coll Cardiol 2011;58:1780-1791.
116. Kitzman DW, Brubaker PH, Herrington DM, et al. Effect of endurance exercise training on endothelial function and arterial stiffness in older patients with heart failure and preserved ejection fraction: a randomized, controlled, single-blind trial. J Am Coll Cardiol 2013;62:584-592.
117. Kitzman DW, Brubaker P, Morgan T, et al. Effect of caloric restriction or aerobic exercise training on peak oxygen consumption and quality of life in obese older patients with heart failure with preserved ejection fraction: a randomized clinical trial. JAMA 2016;315:36-46.

https://doi.org/10.3904/kjim.2020.104