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Heart failure with preserved ejection fraction update: A review of clinical trials and new therapeutic considerations

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Abstract

Between 2013 and 2016 there were approximately 6.2 million adults in the United States living with heart failure; nearly half had an ejection fraction that was preserved. Despite the high prevalence of heart failure with preserved ejection fraction (HFpEF), our understanding of this disease is limited and it still carries significant morbidity and mortality worldwide. At present, physicians are burdened by the inconclusive benefits of currently available treatment options. Recently the scientific community has seen an influx of new pathophysiology studies and outcome trials that have reshaped our understanding of HFpEF as a complex, multi-systemic disease. Pharmacological trials involving beta-blockers, angiotensin II receptor antagonists, aldosterone antagonists, and angiotensin-neprilysin inhibitors have demonstrated encouraging results, but have yet to reach the significance of advancements made in the treatment of heart failure with reduced ejection fraction. This review aims to summarize landmark clinical trials that have influenced current treatment guidelines, and reports on emerging evidence supporting/refuting new treatment modalities including pharmacotherapy, lifestyle modification and device therapy. (Cardiol J 2022; 29, 4: 670–679)

Key words: heart failure, heart failure with preserved ejection fraction, HFpEF, diastolic heart failure, clinical trials

Introduction

Approximately half of patients with heart failure (HF) have a left ventricular ejection fraction (LVEF) that is preserved [1, 2]. HF with preserved ejection fraction (HFpEF) is a clinical syndrome affecting millions of people worldwide, whose pathophysiology is still poorly understood. Diagnosis relies on a combination of symptomatology, echocardiographic evidence, exclusion of noncardiac causes of dyspnea, and in some cases invasive hemodynamic measurements. According to the latest guidelines, there is inconclusive evidence for the benefit of any pharmacotherapy in reducing morbidity, mortality or HF hospitalizations in these patients [3, 4]. This review provides an update on HFpEF, addressing the epidemiology, pathophysiology, diagnosis and current management strategies

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based on a review of clinical trials and provides therapeutic rationale for new treatment options.

Definition

HFpEF is a clinical syndrome in which patients have signs and symptoms of HF, a normal LVEF (≥ 50%), elevated natriuretic peptide levels, and evidence of diastolic dysfunction or relevant structural heart disease. Diastolic dysfunction is characterized by structural changes such as an increase in left ventricular (LV) wall thickness and/or left atrial (LA) size which result in abnormal LV filing and elevated LV filling pressure (LVFP) [1, 3, 5]. The stratification of patients according to LVEF is important because patients within their respective dichotomy often share similar underlying etiologies and co-morbidities, which has implications on selection of therapy and prognosis [2].

Epidemiology

The American Heart Association (AHA) estimated that between 2013 and 2016 there were approximately 6.2 million adults in the United States living with HF [6]. Nearly half had a preserved ejection fraction (EF) [1, 2]. Recent data suggests the age-specific incidence of HF may be decreasing, however longitudinal studies from Mayo Clinic using the Olmsted County Cohort, the Framingham Heart Study, and the Cardiovascular Health Study, have all shown a proportional increase in the prevalence of HFpEF over the past two decades [7–9]. It is well documented that the risk of HFpEF increases with age and is related to conditions such as hypertension, obesity, and coronary artery disease (CAD). Multimorbidity is ubiquitous in HFpEF with approximately half of patients having five or more major comorbidities. Conceivably, HFpEF patients experience a higher proportion of non-cardiovascular (CV) deaths, albeit the majority of deaths are CV in etiology. Unlike heart failure with reduced ejection fraction (HFrEF) where there is a predilection for the male gender, the prevalence of HFpEF is equal among men and women [3, 9].

Pathophysiology

Although HFpEF is common, the pathophysiology remains largely unknown. Coronary microvascular dysfunction is an important factor in disease development, however recent data has also pointed towards extracardiac pathologies [1, 10]. Obesity and diabetes mellitus, which often coexist, cause intramyocardial inflammation that results in epicardial fat expansion and LV fibrosis that may play an essential role in the pathophysiology of HFpEF [1, 10].

One demonstrable hemodynamic abnormality that characterizes HFpEF patients is increased LVFP due to diastolic dysfunction, defined as the inability to fill the LV to an adequate end-diastolic volume at acceptably low pressures [1, 11, 12]. In mild cases of HFpEF, LVFP is only elevated during exertion [1, 11, 13]. Ventricular diastolic function can be conceptualized as the sum of early active LV relaxation and late passive 'stiffness', related to myocardial structural tension [11, 14]. HFpEF patients have prolonged active LV relaxation that is more apparent with exertion [1, 11, 15, 16]. They also lose LV suction, a phenomenon caused by intraventricular pressure gradients determined by the speed of relaxation, velocity of mitral annular longitudinal motion, LV "untwisting", and end-systolic volume (ESV) achieved during the preceding contraction cycle. Loss of LV suction means that LA hypertension becomes necessary to drive LV filling [1, 11, 17]. Ventricular diastolic stiffness also serves as an important factor driving elevated LVFP. Previously, it was thought to be determined by collagen quantity and qualities of extracellular matrix, however recent data theorizes that myocytes are responsible for increased stiffness via phosphorylation of the sarcomeric protein titin [11, 18].

Reduced systolic function is also implicated in HFpEF pathophysiology [1, 11]. Despite preserved LVEF, studies have identified subtle abnormalities in systolic function, made evident by tissue Doppler and strain-based imaging [11, 17]. Systolic dysfunction promotes LA hypertension by reducing early LV suction due to elevated ESV while also directly leading to reduced anterograde flow. Chronically elevated LVFP correlates with secondary LA dysfunction and remodeling [1, 11]. When LA dysfunction occurs, HFpEF patients lose the barrier between the LV and pulmonary circulation leading to pulmonary hypertension and right HF [1, 11, 19]. Additionally, one third of the HFpEF patients develop right ventricular dysfunction that confers an increased risk for adverse outcomes via systemic venous congestion causing intestinal edema, congestive hepatopathy and cardiorenal syndrome [11, 20].

Autopsy studies in HFpEF patients have shown reduced coronary microvascular density and the degree of reduction correlates with the magnitude of myocardial fibrosis [1, 13]. Vascular

abnormalities are common [21], such as the inability of peripheral vessels to dilate appropriately, leading to greater afterload and increased ESV. This, in part, is caused by endothelial dysfunction and decreased nitric oxide levels [1, 11]. HFpEF patients also exhibit changes in skeletal muscle, manifesting as sarcopenia and decreased oxygen utilization [1, 21]. Other rarely considered causes of HFpEF are infiltrative cardiomyopathies, such as amyloidosis. The disease pathophysiology is distinct from what is discussed above. While generally thought to be rare, the prevalence of wild-type transthyretin cardiac amyloidosis is estimated to be 13% to 19% among HFpEF patients [1].

Diagnosis

Since there is no single test or biomarker that identifies HFpEF, diagnosis continues to be a challenge. In addition to clinical suspicion, three important criteria are essential. Patients must present with one or more symptoms of HF (i.e., dyspnea, orthopnea, edema). Next, using Doppler echocardiography or invasive hemodynamic testing, a quantitative assessment of preserved LVEF and elevated LVFP is required. Finally, all other etiologies that can explain the clinical symptoms of HF such as obesity, pulmonary disease, cardiomyopathy, pericardial or valvular heart disease must be excluded [5]. Once the aforementioned criteria are met, the H2FPEF or HFA-PEFF scores can be calculated to further discriminate HFpEF from other noncardiac causes of unexplained dyspnea [22, 23].

The H2FPEF score [22] uses 6 clinical and echocardiographic features that predict HF: body mass index > 30 kg/m^2, use of two or more antihypertensives, presence of atrial fibrillation, age > 60, Doppler echocardiographic estimated pulmonary artery systolic pressure > 35 mmHg and E/e' ratio > 9. Each variable is assigned a point value totaling a maximum of 9 points. A score < 2 predicts low likelihood of HFpEF, while a score > 6 predicts high likelihood. Calculation of the HFA-PEFF score [23] is the second step in an advanced algorithm which involves pretest assessment, diagnostic work-up, functional testing and etiologic investigation. The score comprises functional and morphologic parameters evaluated by echocardiography or cardiac magnetic resonance imaging, in addition to different threshold serum natriuretic peptide levels. The sum of points across all three domains is calculated (2 points for major criteria, 1 point for minor criteria), with a maximum of 2 points for each domain. Scores from 0 to 6 predict the probability of HFpEF with a score ≥ 5 considered diagnostic and ≤ 1 excluding the diagnosis. Intermediate scores of 2–4 require evaluation with exercise stress echocardiography or invasive hemodynamic measurements [23]. The applicability and prognostic value of these scoring systems has been validated such that they can help identify patients who may benefit from certain pharmacotherapies as well as predict the risk of HF hospitalization or death [24–27].

Trials

Beta-blockers

The SENIORS trial [28] investigated the use of nebivolol, a beta-1-selective blocker, in elderly patients (≥ 70 years) with HF, looking at a primary composite outcome of all-cause mortality and CV hospitalization. One third of the 2128 participants had LVEF > 35%. After a median follow-up of 21 months, the primary endpoint was seen in 31.1% and 35.3% of patients receiving nebivolol or placebo, respectively (hazard ratio [HR] 0.86; 95% confidence interval [CI]: 0.74–0.99; p = 0.039). Although the trial did not assess exercise capacity, it concluded that nebivolol was well tolerated and effective in reducing morbidity and mortality in elderly patients across a spectrum of measured LVEF [28]. The ELANDD trial [29] explored the effects of nebivolol, particularly nitric oxide-mediated vasodilation, on exercise capacity in HFpEF patients. The multicenter randomized controlled trial (RCT) recruited 116 participants and assigned them to either 6-month treatment with nebivolol or placebo. No improvement in the primary endpoint, change in 6-minute walk test (6MWT) distance, was seen between groups (from 420 ± 143 to 428 ± 141 m with nebivolol vs. from 412 ± 123 to 446 ± 119 m with placebo; p = 0.004 for interaction). A significant correlation was seen between the change in peak exercise heart rate and peak oxygen consumption ($\dot{V}O_2$) (r = 0.391; p = 0.003). Overall treatment with nebivolol resulted in an unfavorable outcome on exercise capacity, likely owing to negative chronotropic effects [29]. J-DHF [30], a prospective randomized, open, blinded-endpoint study, assessed the efficacy of carvedilol vs. placebo in HFpEF patients, looking at a composite outcome of CV death and CV hospitalization. Participants receiving carvedilol were further subdivided into standard-dose (> 7.5 mg/day) and low-dose (≤ 7.5 mg/day) groups. After a median follow-up of 3.2 years, the primary outcome occurred in 24.2% and 27.2% of patients

in the carvedilol and placebo groups, respectively (HR 0.902; 95% CI: 0.546–1.488; p = 0.6854). In the standard-dose group, the composite primary endpoint was significantly reduced compared to placebo (HR 0.539; 95% CI: 0.303–0.959; p = 0.0356), whereas in the low-dose group the same endpoint was comparable to placebo. The study was underpowered and failed to show prognostic benefit after treatment with carvedilol. However, administration of standard-dose carvedilol was associated with a reduction in CV death or CV hospitalization which may incite further study [30].

Angiotensin-converting-enzyme inhibitors/angiotensin receptor blockers

The CHARM-Preserved trial [31], a multicenter study across 26 European countries, studied the efficacy of candesartan, looking at a primary composite outcome of CV death and HF hospitalization. 3023 HFpEF participants were randomized 1:1 to receive candesartan (target dose 32 mg once daily) or placebo. After a median follow-up of 36.6 months, the primary endpoint was seen in 22% and 24% of patients in the candesartan and placebo groups respectively (HR 0.86; 95% CI: 0.74–1.00; p = 0.051). Although no clear benefit was seen, there was a modest reduction in HF hospitalization rate (HR 0.84; 95% CI: 0.70–1.00; p = 0.051), prompting a class IIb recommendation by the American College of Cardiology/American Heart Association (ACC/AHA) for treatment of HFpEF with angiotensin receptor blockers (ARBs) [4, 31]. PEP-CHF [32], a double-blinded, multicenter RCT, looked at the effects of perindopril in patients aged ≥ 70 years with diastolic dysfunction confirmed by Doppler echocardiography. 850 participants were divided into two treatment groups, perindopril (4 mg once daily) or placebo, and monitored for a mean follow-up of 26.2 months. No significant reduction in the primary endpoint, a composite of all-cause mortality and HF hospitalization, was observed (HR 0.92; 95% CI: 0.70–1.21; p = 0.55). The study was insufficiently powered resulting from many patients leaving early to start open-label angiotensin-converting-enzyme inhibitors [32]. In the I-PRESERVE trial, Massie et al. [33] assessed the efficacy of irbesartan in HFpEF patients, looking at a composite endpoint of all-cause mortality or CV hospitalization. 4128 participants from 25 countries across 5 continents were randomly assigned 1:1 to receive irbesartan (300 mg once daily) or placebo. After a mean follow-up of 49.5 months, the primary endpoint occurred in 36% and 37% of patients in the respective treatment groups (HR 0.95; 95% CI: 0.86–1.05; p = 0.35). The trial failed to replicate the therapeutic benefits of ARB therapy seen in the CHARM-Preserved Trial [33].

Mineralocorticoid receptor antagonists

TOPCAT [34], an international RCT, investigated treatment of HFpEF with mineralocorticoid receptor antagonists (MRAs). The trial enrolled 3445 patients aged ≥ 50 years with LVEF ≥ 45%, and HF hospitalization within 12 months or elevated natriuretic peptide levels within 60 days of randomization. It consisted of 1767 participants from the United States, Canada, Brazil, Argentina, grouped as the Americas, and 1678 participants from Russia/Georgia. Patients were treated with spironolactone (15–45 mg once daily) or placebo during mean follow-up of 3.3 years, and the primary outcome was a composite of CV death, aborted cardiac arrest or HF hospitalization. Secondary outcomes included all-cause mortality or hospitalization, hyperkalemia (> 5.5 mmol/L), hypokalemia (< 3.5 mmol/L), serum creatinine level > 2 times baseline and above the upper limit of normal, and serum creatinine 3.0 mg/dL or greater [34]. Dose adjustments of spironolactone were limited by elevations in serum creatinine and potassium, therefore one-third of participants discontinued therapy but continued study participation. The overall incidence of the primary composite outcome was not reduced by treatment; events occurred in 18.6% and 20.4% of patients in the spironolactone and placebo groups, respectively (p = 0.14). Importantly, there was a lower incidence of HF hospitalization in the spironolactone group when compared to placebo (206 [12.0%] vs. 245 [14.2%]; HR 0.83; 95% CI: 0.69–0.99; p = 0.04) [34]. A post hoc analysis identified significant regional variations, almost a 4-fold difference, in clinical outcomes of patients from Russia/Georgia compared to the Americas [34, 35]. Demographic characteristics revealed that trial results may have been confounded by enrollment of two distinctly different populations. Patients from Russia/Georgia were younger, had less atrial fibrillation, diabetes mellitus, and chronic kidney disease, but were more likely to have had prior myocardial infarction or HF hospitalization. Differences also included lower baseline LVEF and creatinine but higher diastolic blood pressure. When comparing outcome measures, patients from the Americas experienced hyperkalemia and doubling of creatinine more frequently with spironolactone but had fewer hypokalemic events. Rates of the primary composite outcome were also significantly reduced by spironolactone therapy in patients from the Americas but were

unaffected in patients from Russia/Georgia [35]. It was concluded that spironolactone therapy may improve prognosis by lowering rates of CV death and HF hospitalization, with an incremental added risk of hyperkalemia and renal impairment [35, 36].

Nitrates

The first trial to examine nitrate therapy for HFpEF was NEAT-HFpEF [37], a multicenter crossover study that tested the effects of extended-release isosorbide mononitrate (ISMN) vs. placebo on daily activity. 110 participants were randomly assigned to either a 6-week dose-escalation regimen of ISMN (30 mg to 60 mg to 120 mg once daily) or placebo, followed by crossover to the opposite group for 6 weeks. The primary endpoint was daily activity level measured by patient-worn accelerometers, specifically average daily accelerometer units during the 120-mg phase of ISMN. Secondary endpoints included hours of activity per day during the maximum dose phase, daily accelerometer units during all three phases, quality of life (QOL) scores, 6MWT distance, and natriuretic peptide levels. Subgroup analysis revealed that in the group receiving the maximum dose of ISMN, there was a significant decrease in hours of activity per day compared to placebo (−0.30 hours; [−0.55 to −0.05]; p = 0.02). During all dose phases, activity in the ISMN group was lower than in the placebo groups and the decline was dose-dependent (−439 accelerometer units; [−792 to −86]; p = 0.02). There were no significant between-group differences in the secondary outcome measures, but the results were numerically unfavorable to nitrates. Overall treatment with ISMN did not improve submaximal exercise capacity, QOL scores, or natriuretic peptide levels [37–39]. In fact, nitrate therapy may be detrimental in HFpEF patients due to an increased risk for CV events [38, 40]. NEAT-HFpEF may have been limited by its dose-escalation strategy because HFpEF patients are hypersensitive to rapid changes in hemodynamics [38]. INDIE-HFpEF [41], a follow-up trial with similar design, also failed to show any benefits of inorganic nitrates on exercise capacity. There was no improvement in peak oxygen consumption, daily activity levels, health status, functional class (New York Heart Association [NYHA]), cardiac filling pressures or natriuretic peptide levels in HFpEF patients treated with nebulized nitrate therapy for 4 weeks.

Angiotensin-neprilysin inhibition

PARAGON-HF [42], was a prospective comparison of angiotensin-neprilysin inhibition vs. ARB therapy in patients with NYHA class II–IV HF, LVEF ≥ 45%, elevated natriuretic peptide levels, and structural heart disease. It hoped to replicate the results of its predecessor, PARADIGM-HF, which demonstrated significant benefits of sacubitril/valsartan compared to submaximal doses of enalapril in HFrEF patients [43]. Solomon et al. [42] organized a double-blinded, active-comparator trial, in which 4822 HFpEF participants from 848 centers in 43 countries, were randomized 1:1 to receive sacubitril/valsartan (target dose 97 mg of sacubitril with 103 mg of valsartan twice daily) or valsartan (target dose 160 mg twice daily). The primary endpoint was a reduction in incidence of HF hospitalization or death. After a median follow-up of 35 months there were 894 primary events in 526 patients receiving sacubitril/valsartan and 1009 events in 557 patients receiving valsartan (HR 0.87; 95% CI: 0.75–1.01; p = 0.06). Concerning the primary composite outcome, sacubitril/valsartan therapy did not result in a statistically significant benefit, however, among 12 prespecified subgroups, there was possible benefit for women and patients with lower EF (45–57%) [42, 44]. Despite using a framework for interpretation of treatment heterogeneity in subgroups, and evaluation of key considerations such as biological plausibility, age-related arterial stiffening, and incidence of risk factors predisposing to HF exacerbations, the mechanistic basis for sex-related benefits remains unclear [44].

SGLT-2 inhibition

The efficacy of sodium-glucose co-transporter 2 (SGLT-2) inhibitors in patients with HFrEF with and without diabetes has been well established in DAPA-HF and EMPEROR-Reduced trials [45, 46]. Dapagliflozin and empagliflozin showed lower rates of hospitalization and mortality benefit in patients with HFrEF [45, 46]. PRESERVED-HF was designed to study whether dapagliflozin improves symptoms, physical limitations and exercise capacity in patients with HFpEF irrespective of diabetes status [47]. 324 patients with an LVEF ≥ 45% were randomized 1:1 to receive dapagliflozin or placebo. The primary endpoint was improvement of Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CS) a self-administered instrument that quantifies HF-related symptoms, physical function, QOL and social life, higher scores reflecting better health status [47]. Dapagliflozin led to an improvement in KCCQ-CS at 12 weeks by 5.8 points (95% CI 2.3–9.2; p = 0.001) [47]. The EMPEROR-Preserved trial built on its predecessor EMPEROR-Reduced. EMPEROR-Preserved

was a multicenter, double-blind, randomized clinical trial that randomized 5988 patients with an LVEF > 40% 1:1 to receive either empagliflozin or placebo, in addition to usual therapy [48]. The primary endpoint was a composite outcome of CV death or hospitalization for HF and occurred in 13.8% of patients in the empagliflozin group and in 17.1% of patients in the placebo group (HR 0.79; 95% CI: 0.69–0.90; p < 0.001), number needed to treat 31 (95% CI: 20–69) [48]. The benefit was mainly driven by reduced HF hospitalizations with a secondary outcome of reduced CV death not reaching statistical significance [48]. The authors did not provide subgroup analyses to separate patients with HFmrEF and HFpEF. PRESERVED-HF and EMPEROR-Preserved demonstrated that the beneficial effects of SGLT-2 inhibitors also apply to patients with HFpEF, however, the outcomes are more modest in comparison to those with HFrEF. Most recently sotagliflozin has had promising results in patients with HF evaluated in two large randomized clinical trials, SCORED and SOLOIST--WHF. The SCORED trial was a multicenter, double blinded, randomized clinical trial comparing sotagliflozin to placebo in patients with diabetes and chronic kidney disease. The primary endpoints were total number of deaths due to CV causes, hospitalizations for HF and urgent visits for HF. After a follow up period of 16 months, the total primary end-point events were 5.6 and 7.5 per 100 patient-years in the sotalgliflozin and placebo groups, respectively (HR 0.74; 95% CI: 0.6–0.88; p < 0.001) [49]. The SOLOIST-WHF was a multicenter, double blinded, randomized clinical trial that compared sotafliflozin to placebo in patients with type 2 diabetes mellitus and HF. The primary end-points were total number of deaths due to CV causes, hospitalizations for HF and urgent visits for HF. After a follow up period of 9 months, the rate of primary end-point events in the sotagliflozin and placebo groups were 51.0 vs. 76.3, respectively (HR 0.67; 95% CI: 0.52–0.85; p < 0.0010 [50]. Bhatt et al. [50] performed a pooled analysis of both SCORED and SOLOIST--WHF trials stratified by EF with primary end--points of total number of deaths from CV causes and hospitalization. They noted that for patients with HFpEF (EF > 50%) there was a 30% reduction in total number of deaths due to CV causes, hospitalizations and urgent visits for HF [51].

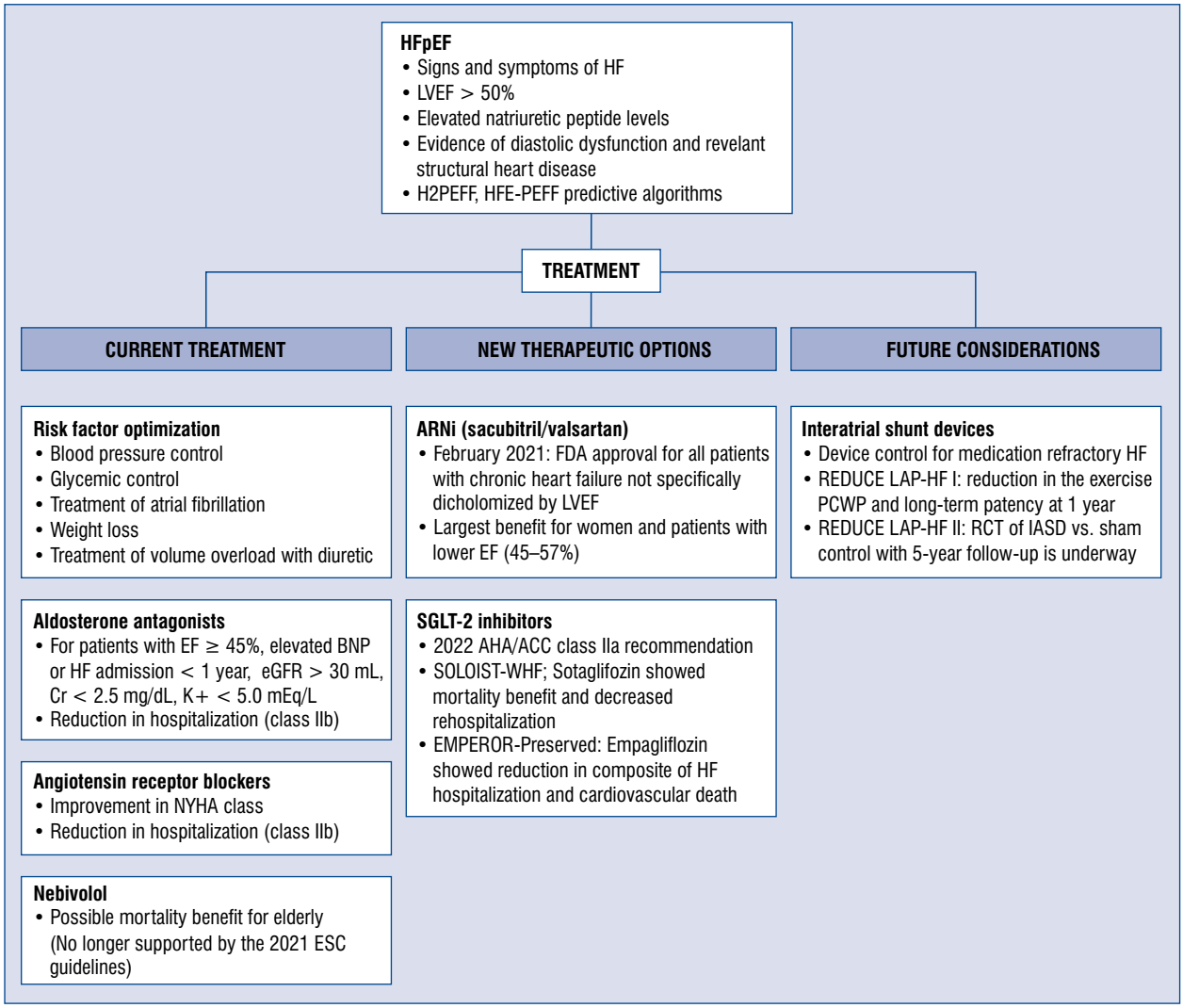
Guideline recommendations

Guidelines on the management of HFpEF from the ACC/AHA (2022) [4] and European Society of Cardiology (ESC) (2021) [3], suggest there is inconclusive evidence that treatment with any pharmacotherapy reduces morbidity, mortality or HF related hospitalizations. The consensus is a focus on management of underlying comorbidities which contribute to the development of HF and prevention of symptom progression. Both societies agree on the importance of controlling blood pressure, maintaining healthy body weight, managing volume overload with diuretics, optimizing glycemic control, and treating atrial fibrillation [3, 4]. For symptomatic treatment, only diuretics have shown convincing benefit. Improvement in NYHA class has only otherwise been seen with candesartan [31] The ACC/AHA advocates a class IIa recommendation for use of SGLT-2 inhibitors as well as management of atrial fibrillation and a class IIb recommendation for treatment of select patients with ARBs, angiotensin receptor blocker neprilylisn inhibitor and MRAs to reduce HF hospitalization (Central illustration) [4, 31, 34]. Treatment with candesartan reduced HF hospitalizations in the CHARM-Preserved trial, but it is unclear whether the objective benefits of ARB therapy are class specific or limited to candesartan. Based on findings from the TOPCAT trial, treatment with MRAs can be effective in patients with EF ≥ 45%, elevated natriuretic peptide levels or HF admission within the last year, estimated glomerular filtration rate > 30 mL/min, creatinine < 2.5 mg/dL, and potassium < 5.0 mEq/L [4, 34, 35]. As opposed to the 2016 guidelines, the ESC no longer names candesartan, spironolactone, digoxin and nebivolol as effective therapeutic options for reducing HF hospitalization [3, 28, 49]. The 2021 update to the ESC HF guidelines takes an aggressive approach and only supports the use of diuretics for symptomatic relief in congested patients with HFpEF [3]. Based on results from the NEAT-HFpEF and RELAX trials, the ACC/AHA refutes any benefit of using nitrates or phosphodiesterase inhibitors for improvement of activity level or QOL [4, 37, 50]. Regarding patients with diabetes, the ESC recommends using SGLT-2 inhibitors to prevent HF hospitalizations [3, 51].

New considerations

Expanded indications for sacubitril/valsartan

Subgroup analysis of the PARAGON-HF trial demonstrated a heterogeneous treatment effect of sacubitril/valsartan, with statistically significant benefits seen in women and patients with lower EF [42, 44]. A subsequent pooled meta-analysis that



Central illustration. Overview of current guideline directed management, new therapeutic options and future considerations for the treatment of heart failure with preserved ejection fraction (HFpEF); ACC — American College of Cardiology; AHA — American Heart Association; ARNi — angiotensin receptor blocker neprilylisn inhibitor; BNP — B-type natriuretic peptide; Cr — creatinine; EF — ejection fraction; eGFR — estimated glomerular filtration rate; ESC — European Society of Cardiology; FDA — Food and Drug Administration; HF — heart failure; IASD — interatrial shunt device; K+ — potassium; LVEF — left ventricular ejection fraction; NYHA — New York Heart Association; PCWP — pulmonary capillary wedge pressure; RCT — randomized control trial; SGLT-2 — sodium-glucose co-transporter 2.

combined the PARAGON-HF and PARADIGM-HF trials, identified a graded benefit of angiotensin-neprilysin inhibition depending on measured EF. Patients with lower EF benefited most from therapy, however benefits also extended to patients with mildly reduced EF. In women, therapeutic effects of sacubitril/valsartan extended to a higher LVEF range [44, 52, 53]. In February 2021, in light of the aforementioned observations, the Food and Drug Administration approved an expansion of the indications for ENTRESTO® (sacubitril/valsartan) to all patients with chronic HF not specifically dichotomized by LVEF (Central illustration) [54, 55]. Millions of HFpEF patients previously deemed ineligible were now qualified to receive treatment. This recommendation should be considered carefully because it is based on a subgroup analysis that involves a trial that did not reach its primary endpoint. At present, there are no plans to study sacubitril/valsartan vs. an active comparator in a cohort of patients believed to benefit most from therapy.

Optimal exercise training regimen

Mueller et al. [56] questioned whether different modes of exercise had different effects on change in $\dot{V}O_2$. They conducted a prospective, multicenter RCT, assigning HFpEF patients to one of three treatment groups: high-intensity interval training, moderate continuous training, and guideline-based physical activity. Patients were followed for 12 months and the primary endpoint was change in peak $\dot{V}O_2$ after 3 months, with the minimal clinically important difference set at 2.5 mL/kg/min. The study failed to meet significance, delineating no benefit of alternative training regimens. After 12 months, no statistically or clinically significant changes in metrics of cardiorespiratory fitness, diastolic function, QOL scores, or natriuretic peptide levels were observed [56, 57].

Device therapy

Mechanical reduction of LA pressure is an important therapeutic target in HFpEF. It is achieved by transcatheter implantation of an interatrial shunt device (IASD) and monitored by invasive hemodynamic measurement of workload corrected exercise pulmonary capillary wedge pressure (PCWP) [58]. REDUCE LAP-HF [58], an open-label, single-arm study of IASDs in 64 adult patients with chronic symptomatic HF and LVEF > 40%, provided evidence of clinical efficacy and safety at 6 and 12 months [59]. A subsequent parallel-group, sham-controlled RCT (REDUCE-LAP HF I) [60] corroborated these findings showing reductions in exercise PCWP and long-term patency of devices at 12 months. Due to the small sample size of 44 patients, the trial was underpowered to detect clinically significant differences in HF hospitalization rates, functional capacity, QOL scores, or 6MWT distance [61]. A pooled analysis of these two trials concluded that implantation of IASDs improves pulmonary vascular function at rest and during exercise without compromising systemic perfusion [62]. REDUCE LAP-HF II [63], a comprehensive trial enrolling 608 patients randomized 1:1 to IASD vs. sham control, with plans for 5-year follow-up, is underway and will provide further insight about the potential of device therapy for medication refractory HFpEF (Central illustration).

Conclusions

Our understanding of the pathophysiology and management of HFpEF is limited. Epidemiologic studies have demonstrated a high prevalence of HFpEF [1, 2] and this provides a unique opportunity to affect the lives of many. Several ongoing studies are in search of therapeutic modalities that will improve prognosis and QOL. Recent expansion of the indications for sacubitril/valsartan to all patients with chronic HF [54, 55], has made this therapeutic modality available to a larger population. Promising results from trials involving the use of SGLT-2 inhibitors in patients with HFpEF have earned this drug class a class IIa recommendation in 2022 ACA/AHA guidelines for possible reduction in HF hospitalizations and CV mortality [4]. At present SGLT-2 inhibitors are the only medications with a class IIa recommendation making them the mainstay of HFpEF management [4]. Current trial involving IASDs [63] is also showing early promise. Future studies with intelligent subgroup design and specific phenotyping, could provide answers that explain the enigmatic pathophysiology of HFpEF and uncover treatment strategies which offer patients hope and empower clinicians.

Conflict of interest: None declared

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