Review Article

Essential Therapy for Heart Failure with Preserved Ejection Fraction in 2022

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Abstract

Heart failure with preserved ejection fraction (HFpEF) is a syndrome in which there is clinical evidence of heart failure (HF), left ventricle ejection fraction (LVEF) ≥50%, and evidence of diastolic dysfunction and/or structural cardiac changes. The pathophysiology of HF with preserved LVEF is related to the primary morbidities responsible for cardiac and vascular aggression via a chronic proinflammatory state involving the endothelium. Currently, the foundation of management of HFpEF rests on 5 pillars: control of circulatory congestion, management of primary morbidities or etiologies, use of medications with proven clinical benefit, identification and management of secondary etiologies, and cardiopulmonary rehabilitation. Essential therapy for HFpEF is founded on precise diagnosis, definition of etiology, estimation of severity, and use of medications with cardiovascular action of proven efficacy.

Introduction

Heart failure with preserved ejection fraction (HFpEF) is a complex and heterogeneous clinical syndrome, in which affected populations have a diverse range of phenotypes, frequently associated with multiple comorbidities, and which, in summary, can be diagnosed in the presence of clinical evidence of heart failure (HF), left ventricle ejection fraction (LVEF) ≥50%, and evidence of diastolic dysfunction and/or structural cardiac changes.[1,2] In the vast majority of cases, effective interventions are targeted on the basis of the combination of phenotypes and morbidities present, since there are not yet any treatments that reduce adverse clinical outcomes as effectively as those available for HF with reduced LVEF.[2] The primary explanation for this phenomenon lies in the type of cardiovascular aggression involved, which in HFpEF is caused by the primary morbidities that are responsible for cardiac and, most importantly, vascular aggression, namely: diabetes, hypertension, obesity, chronic kidney disease, chronic obstructive pulmonary disease (COPD), and anemia/iron deficiency. These diseases impose a chronic proinflammatory state that affects the endothelium, reducing nitric oxide bioavailability. This effect is associated with reduced protein kinase G activity in cardiomyocytes with consequent reduction of muscle elasticity, stimulating hypertrophy of these cells. In parallel, vascular cell adhesion molecules and E-selectin provoke interstitial migration of monocytes which are converted into fibroblasts and deposit collagen in the interstitial space, worsening the myocardium's diastolic properties.[3] The result of this process is an absence of myocyte necrosis and, therefore, no, or minimal, systolic dysfunction (figure 1). In this scenario, stimulation of the sympathetic nervous system and renin-angiotensin-aldosterone is much less important than in heart failure with reduced ejection fraction (HFrEF), which partially explains the reduced efficacy of medications that modulate these systems in studies undertaken in populations with HFpEF.

Keywords

Heart Failure; Stroke Volume; Functional Residual Capacity.

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Essential therapy

Management of HFpEF is based on: 1- control of circulatory congestion with diuretics; 2- management of the primary morbidities or etiologies of the syndrome; 3- specific medications that have recently demonstrated clinical benefits; 4- identification and management of secondary etiologies, such as myocardiopathies, which can even provoke advanced states of HF;[4] and 5- cardiopulmonary rehabilitation.

Control of circulatory congestion

Conventional studies comparing diuretics with placebo in congested patients with HFpEF are ruled out by bioethical considerations, for obvious reasons, but occult and variable congestion is common among these patients and other models of investigation provide evidence that is useful for designing management strategies. The Hong Kong study[5] tested quality of life, functional capacity, and cardiac function indices in a population of 150 participants with New York Heart Association (NYHA) class II-IV HF and LVEF>45% before and after treatment with diuretics (furosemide or thiazide) in isolation or associated with angiotensin converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARB) in a model without comparison with placebo. After 12 months of follow-up, use of the diuretic in isolation reduced the symptoms of

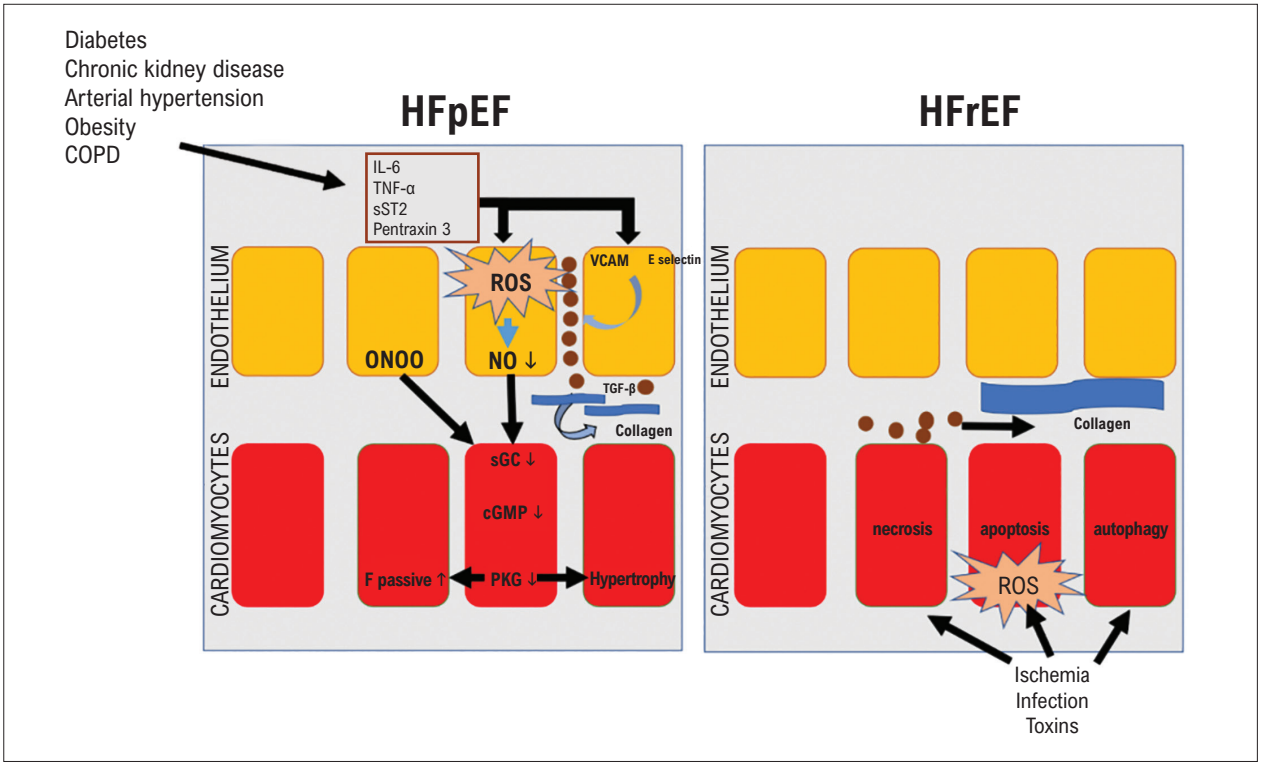

Figure 1 – *Pathophysiology of heart failure according to left ventricle ejection fraction. cGMP: cyclic guanosine monophosphate; COPD: chronic obstructive pulmonary disease; Fpassive: resting tension; IL-6: interleukin 6; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; NO: nitric oxide; ONOO: peroxynitrite; PKG: protein kinase G; sCG: soluble guanylate cyclase; sST2: soluble ST2; TNF: tumor necrosis factor; VCAM: vascular cell adhesion molecule; ROS: oxidative stress; TGF-β: transforming growth factor β. Adapted from Paulus et al.*[3]

HF and improved quality of life (QoL). The association with ACEi or ARB did not result in any additional clinical benefit.

Also focused on the variable pattern of hypervolemia in HFpEF, CardioMEMS is sensor that can be implanted in the pulmonary artery to monitor pulmonary artery blood pressure, offering a potential guide for diuretic therapy. Analysis of data from the CHAMPION study with 119 patients with HFpEF (LVEF ≥40%, ≈50.6%) revealed a 46% reduction in HF-related hospitalizations in 6 months when compared with a traditionally-managed group, with no impact on mortality. Recently, the randomized study GUIDE-HF[7] tested management of HF patients guided by pulmonary artery pressure. The outcomes mortality or HF events (hospital admissions or unplanned emergency visits because of HF) over 12 months were no different in the intervention group. However analysis of the pre-COVID-19 pandemic results demonstrated reductions in primary outcomes, primarily driven by the low rate of hospital admissions (28% reduction in relative risk, p = 0.007). Around 30% of the patients in the study had HFpEF and the reduction in primary outcomes remained consistent even when patients with EF ≥ 50% were analyzed, making the findings consistent with those of the CHAMPION trial.[6] Among other results, these findings provide the foundation for the class I recommendation with evidence level B for diuretic therapy for HFpEF associated with clinical congestion that is contained in the recently published 2021 Updated Brazilian Heart Failure Guidelines.[4]

Management of comorbidities

Control of obesity, hypertension, diabetes, myocardial ischemia, arrhythmia, and peripheral arterial disease has the potential actions of reducing pathophysiologic feedback and improving quality of life and functional capacity. The Brazilian Guidelines for Chronic and Acute HF, from 2018,[8] rate management of morbidities as recommendation class I and evidence level C.

Medications for reduction of robust HF outcomes

There is a discrepancy between the LVEF cutoff point that medical societies use for diagnosis of HFpEF (≥50%) and those used in the designs of randomized clinical trials (RCT) that test the efficacy of drugs for this syndrome. The majority of RCTs allocate participants with LVEF exceeding 40 or 45%, i.e., they are grouped together with an HF population with mildly reduced ejection fraction (HFmrEF), which constitutes a challenge for interpretation and potential extrapolation of the results. Regardless, the drugs for which RCTs had the most appropriate designs were sodium-glucose cotransporter 2 inhibitors (SGLT2i); sacubitril/valsartan; sprinolactone; and, to a lesser extent, angiotensin II receptor blockers (Figure 2) (Table 1).

Sodium-glucose cotransporter 2 inhibitors (SGLT2i)

This drug class has multiple and systemic effects that address several crucial points in the pathophysiology of HFpEF, with

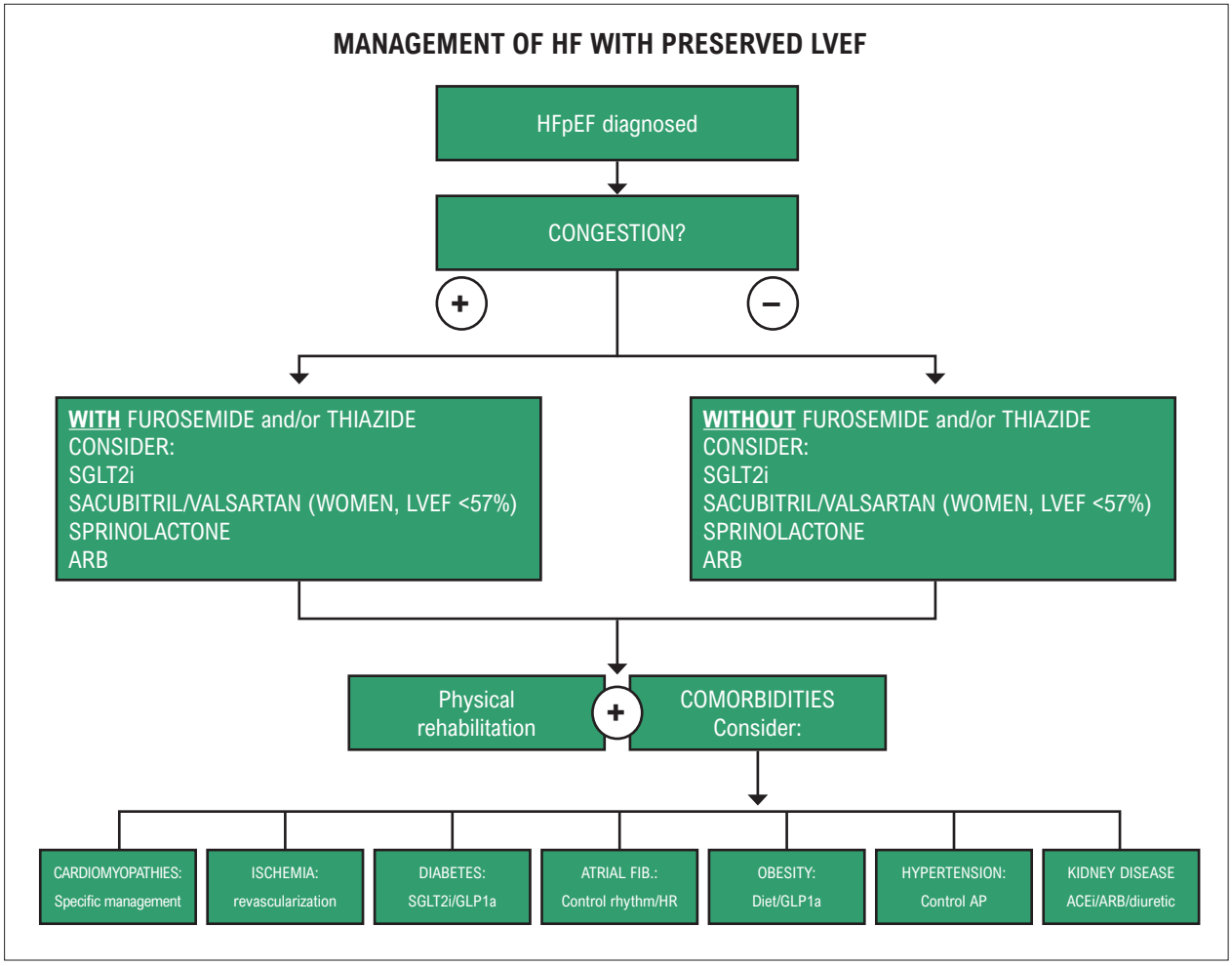

Figure 2 – *Flow diagram of management of HFpEF. ARB: angiotensin II receptor blockers; SGLT2i: sodium-glucose cotransporter 2 inhibitors; Sac-Valsartan: sacubitril-valsartan; LP1a: glucagon-like peptide 1 agonists; Atrial Fib.: atrial fibrillation; AP: atrial pressure; ACEi: angiotensin converting enzyme inhibitors.*

the following potential mechanisms: improved arterial blood pressure; increased natriuresis; improved cellular energy in cardiomyocytes; prevention of inflammation; reduced body weight; improved glucose control; prevention of myocardial remodeling; prevention of ischemia/reperfusion cellular injury; inhibition of the sympathetic nervous system; inhibition of Na+/H+ channels; reduction of hyperuricemia; reduction of epicardial fat; increased serum erythropoietin levels; reduced oxidative stress; improved vascular function; and preserved glomerular function, among others.[9]

Of investigations testing SGLT2i for populations with HFpEF, the SOLOIST-WHF RCT[10] was designed to determine the efficacy of sotagliflozin, an $SGLT_1$ and $SGLT_2$ inhibitor to test the benefit of the drug for the composite outcome primary cardiovascular mortality and/or hospital admissions/urgent visits for HF. Only patients with type 2 diabetes, a diagnosis of HFrEF or HFpEF, and either a recent admission for HF or a need for IV diuretics for exacerbated HF were enrolled. The group allocated to receive the drug exhibited a significant reduction in the primary outcome, both in patients with reduced LVEF and in those with preserved EF (RR=0.67 (95% CI, 0.52–0.85, p<0.001). These results were important and, even though the drug was tested in a specific population of diabetics with recent decompensated HF and follow-up was interrupted prematurely, the effect size of the intervention was striking and statistically significant.

The PRESERVED HF[11] study was a small RCT that tested the efficacy of 10mg of dapagliflozin for 12 weeks for improving quality of life and the functional capacity of the participants with New York Heart Association (NYHA) functional class II, III, and IV HF and LVEF≥45%. The results demonstrated that dapagliflozin improved the Kansas City Cardiomyopathy Questionnaire – Clinical Score (KCCQ-CS) by 5.8 points (95%CI 2.3-9.2, p = 0.001), which was the predefined primary outcome measure. Dapagliflozin also improved performance on the 6-minute walk test (mean effect size was 20.1 meters [95%CI 5.6-34.7, p = 0.007]). It is important to consider that this improvement in KCCQ-CS score was of a higher magnitude than other drugs previously tested for QoL in HF had achieved.

Table 1 – Primary outcomes in phase III randomized clinical trials with cardiovascular outcomes in patients with HFPEF

Study/ Year of publication	Drug	Patients (n)	LVEF (%)	Outcome	Treatment effect, RR (95%CI)
ACEI/ARB					
CHARM- Preserved (2003)	Candesartan vs. Placebo	3023	> 40	Primary: composite of CV mortality or hospital admissions for HF	No difference in primary outcome or all causes mortality
MRA					
TOPCAT (2014)	Sprinolactone vs. Placebo	3445	≥ 45	Primary: composite of CV mortality or hospital admissions for HF	Women: 0.89 (0.71-1.12) Men: 0.89 (0.73-1.09)
TOPCAT- Americas (2014)	Sprinolactone vs. Placebo	1767	≥ 45	Primary: composite of CV mortality or hospital admissions for HF	Women: 0.81 (0.63-1.05) Men: 0.85 (0.67-1.08)
ARNI					
PARAGON (2019)	Sacubitril Valsartan vs. Valsartan	4882	≥ 45	Primary: composite of CV mortality and total hospital admissions for HF	Women: 0.73 (0.59-0.90) Men: 1.03 (0.84-1.25)
SGLT2i					
EMPEROR-PRESERVED (2021)	Empaglifozin vs. Placebo	5988	> 40	Primary: composite of CV mortality and first hospital admissions for HF	Women: 0.75 (0.61-0.92) Men: 0.81 (0.69-0.96)
SOLOIST- WHF (2021)	Sotaglifozin vs. Placebo	1222	All	Primary: composite of CV mortality, hospital admissions for HF, and urgent consultations for HF	Women: 0.80 (0.51-1.25) Men: 0.62 (0.47-0.82)

ARNI: Angiotensin receptor-neprilysin inhibitor; ARB: Angiotensin receptor blocker; CV: Cardiovascular; EMPEROR-Preserved,: Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction; LVEF: Left ventricle ejection fraction; RR: relative risk; HF: heart failure; HFPEF: Heart failure with preserved ejection fraction; ACEI: angiotensin-converting enzyme inhibitor; MRA: mineralocorticoid receptor antagonist; PARAGON: Prospective Comparison of ARNI With ARB on Global Outcomes in HFpEF; SGLT2i: sodium-glucose cotransporter 2 inhibitor; SOLOIST-WHF: Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure; TOPCAT: Treatment of Preserved Cardiac Function HF With an Aldosterone Antagonist.

Empagliflozin is one of the drugs in the class that has been most investigated to date and it was tested at a dosage of 10mg per day against placebo in the EMPEROR Preserved RCT.[12] The study randomized 5988 participants with signs and symptoms of HF, with a HFmrEF + HFpEF profile (LVEF>40%) and elevated serum natriuretic peptides levels. The composite primary outcome was cardiovascular mortality (CV) and/or hospital admissions for HF and secondary outcomes were hospital admissions for HF and progression of decline in glomerular filtration rate (GFR) over the course of the study follow-up period. The population was balanced in terms of sex (55% male), predominantly Caucasian (76%), hypertense (90%), and 49% diabetic. The study's main finding was a 21% reduction in the relative risk of the composite primary outcome (RR=0.79 [95%CI 0.69–0.90], p < 0.001). There was a 29% reduction in the secondary outcome of hospital admissions for HF (RR=0.71 [95%CI: 0.60–0.83], p < 0.001) and the mean progressive decline in GFR was lower in the empagliflozin group (−1.25ml/min/1.73m^2 x -2.62 ml/min/1.73m^2, p < 0.001). The pre-specified analysis of primary outcome results by LVEF strata detected larger effect sizes from the drug in lower LVEF strata, but did not technically demonstrate a difference in interaction between groups that was significant from a statistical point of view (LVEF<50% RR=0.71 [95%CI 0.57–0.88], LVEF≥50%-<60%, RR= 0.80 [95%CI 0.64–0.99], LVEF≥60% RR=0.87 [95%CI 0.69–1.10], P for the interaction was NS). With regard to safety, a higher rate of genital and urinary tract infection and more episodes of uncomplicated hypotension were observed in the empagliflozin group. Publication of this study was a watershed moment for knowledge about HFpEF, since it was the first to demonstrate the efficacy of a drug for reduction of the classic primary outcomes of HF in patients with > 40% LVEF and, although additional data are awaited from ongoing investigations with other SGLT2i, these results have disruptive potential with regard to management of the syndrome.

Sacubitril-valsartan

The sacubitril-valsartan molecule is an inhibitor of both angiotensin and neprilysin that encompasses molecular portions of the neprilysin (neutral endopeptidase) inhibiting pro-drug AHU377 and the ARB valsartan in a single complex. AHU377 is metabolized by enzymatic cleavage into LBQ657, the active neprilysin inhibitor. Neprilysin degrades biologically active natriuretic peptides, including atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), and C-type natriuretic peptide, but not

the biologically inert NT-proBNP, which is not a substrate for this enzyme. By increasing active natriuretic peptide, neprilysin inhibition increases generation of myocardial cyclic guanosine 3',5'-monophosphate, which improves myocardial relaxation and reduces hypertrophy. Natriuretic peptides also stimulate diuresis, natriuresis, and vasodilation and may have an additional anti-fibrotic effect and anti-sympathetic effects. However, neprilysin also contributes to degradation of angiotensin, which is the reason for the complex's double action, inhibiting this enzyme and blocking angiotensin activity or generation.[13] The functions performed by this molecule therefore act to partially antagonize the pathophysiologic components of HFpEF mentioned above, provoking natriuresis, vasodilation, and improved myocardial relaxation. In the mechanistic HFmrEF model, blocking angiotensin II provokes vasodilation, reduces stimulation of the sympathetic system, and has anti myocardial fibrosis potential.

The PARAGON-HF study[10] allocated 4822 participants aged ≥50 years, with NYHA HF functional class from II to IV, LVEF≥45%, elevated natriuretic peptide levels, and structural cardiac disease to take either sacubitril-valsartan (target dose of 97 mg of sacubitril with 103 mg of valsartan twice a day) or valsartan (target dose of 160 mg twice a day). The primary outcome was the classic endpoint for HF studies: a composite of hospitalizations for HF and CV mortality. Secondary outcomes were: change in NYHA class; deterioration of renal function, and changes on the Kansas City cardiomyopathy questionnaire (KCCQ) for symptoms and physical limitations. Exclusion criteria were history of LVEF <40%; myocardial infarction, myocardial revascularization surgery, or any event within the 6 months prior to screening; acute decompensated HF requiring treatment; need for treatment with two or more of the following: ACEI, ARB, or renin inhibitor; systolic blood pressure (SBP) <110 mmHg or SBP>180 mmHg at screening; serum potassium >5.2 mmol/L at screening or >5.4 mmol/L at the end of each run-in period; GFR<30 mL/min/1.73m^2 at screening or at the end of each run-in period, GFR <25 mL/min/1.73m^2 or >35% reduction in GFR compared to GFR at screening.

The study design employed the run-in screening model, by which all patients were given valsartan for the first time at half of the target dose, followed by sacubitril-valsartan at half of the target dose in order to only enroll participants who did not have any unacceptable side effects in either run-in phase. Subgroups of the total population were prespecified for the final analysis. The results did not demonstrate statistical significance for reduction of the primary outcome when the entire population of the trial was analyzed (RR: 0.87; 95%CI 0.75 - 1.01, p = 0.06). With regard to the secondary outcomes, NYHA class improved in 15.0% of the patients in the sacubitril-valsartan group and in 12.6% of those in the valsartan group (RR: 1.45; 95%CI, 1.13-1.86); renal function worsened in 1.4% and 2.7%, respectively (RR: 0.50; 95%CI, 0.33 to 0.77). In terms of safety, statistically significant adverse effects were: episodes of systolic pressure < 90 mmHg (2.7% x 1.4%, p<0.001) and angioedema ([0.6 x 0.2] p=0.02). With regard to the 12 prespecified subsets, the sacubitril-valsartan arm had significant benefits for reduction of the primary outcome in participants with LVEF≤ median (57%) (RR:0.78 [95%CI 0.64−0.95]) and females (RR:0.73 [95%CI 0.59-0.90]). On the basis that the benefit of sacubitril-valsartan for patients with LVEF equal to or less than the median is biologically plausible, since several post-hoc analyses of RCTs[14,15] had already shown that drugs classically prescribed for HFrEF, such as sprinolactone and candesartan, had efficacy in patients with HF and LVEF of 40 to 55%, populations that have discrete impairment of systolic function and share mechanisms with populations with preserved LVEF, who are at greater risk of hospital admissions for heart failure, the regulatory agencies ANVISA (National Agency for Sanitary Vigilance [Agência Nacional de Vigilância Sanitária]) in Brazil and FDA (Food and Drug Administration) in the United States approved sacubitril-valsartan for use in patients with HF and LVEF below normal.

Mineralocorticoid receptor antagonists

The largest and most important study to test mineralocorticoid receptor antagonists (MRA) was the *TOPCAT* trial.[16] This RCT randomized 3445 participants with symptoms and signs of HF and LVEF ≥45%, with endogenous creatinine clearance rate >30ml/Kg and serum potassium <5mEq/l, to test sprinolactone vs. placebo. One relevant feature of the study design was the additional eligibility criterion of either a hospital admission for HF or elevation of BNP≥100pg/mL/ Nt pro-BNP≥ 360pg/mL. The overall result of the trial was negative for the primary outcome (RR 0.89 [95%CI 0.77–1.04], p= 0.14), but the rate of hospital admissions for HF was 17% lower in the sprinolactone group (RR 0.83 [95%CI 0.69–0.99], p= 0.04). A post-hoc analysis[17] analyzing the efficacy of the drug among participants allocated from the Americas, who had a more congested profile (with eligibility criterion predominantly on the basis of elevated natriuretic peptides) and who also had more events along the time line of the investigation, found an 18% reduction in the primary outcome in the intervention group (RR:0.82 [95%CI 0.69–0.98] p=0.026), contextualizing the potentially better performance of the drug in more hypervolemic patients. The data described above support the current class IIa recommendation in the Brazilian HF Guidelines, since 2018,[8] for sprinolactone for patients with HFpEF, with the main objective of reducing rates of hospital admissions for HF.

Angiotensin II receptor blockers

Angiotensin II receptor blockers are an option for treatment of HFpEF primarily in scenarios in which hypertension is combined with congestion. The best RCT evidence for this drug class is from the CHARM-Preserved study.[18] This trial enrolled 3025 participants with signs and symptoms of HF, NYHA functional class II to IV, and LVEF>40%, but without a need for an objective element of congestion, such as serum natriuretic peptides levels. Candesartan was tested with a target dose of 32mg per day vs. placebo. Approximately 60% of the final sample comprised patients with NYHA class II and around 65% had hypertension. The primary outcome of CV mortality and/or hospital admissions for HF was not different

between the groups (RR: 0.89 [95%CI 0.77-1.03], p=0.118). The secondary outcome of number of individuals with at least one hospital admission for HF was lower in the candesartan group than in the placebo group (230 vs. 279; p=0.017) and the total number of admissions for HF followed the same pattern (402 x 566, p=0.014). In summary, this study provides the only evidence of positive results for ARB in patients with HFmrEF + HFpEF (LVEF>40%). Since 2018, the Brazilian HF Guidelines[8] have given it a IIb recommendation for reduction of hospital admissions in patients with ICFE.

Medications without proven efficacy in clinical trials

RCTs that tested beta blockers; calcium blockers; cardiac glycosides; phosphodiesterase-5 inhibitors; ivabradine; vericiguat; and isosorbide were unable to prove benefit in terms of the outcomes CV mortality or hospital admissions for HF in populations with HFpEF. Currently, they are considered reasonable pharmacological options if prescribed for specific morbidities that cause or are associated with HF.[19]

Management of advanced HFpEF

An advanced heart failure consensus[20] was recently published by the Heart Failure Association (HFA) and European Society of Cardiology (ESC) recognizing that not only patients with HFREF have advanced HF, widening the perspective on treatment and severity of HFPEF, providing that patients meet the criteria for disease severity. In this context, early recognition and referral of these patients is of fundamental importance, since more in-depth assessments and more advanced treatments, such as implantable devices, ventricular assist devices, and heart transplantation can be offered to this patient population in selected cases.

Hypervolemia appears to be the central pathophysiologic mechanism in patients with HFPEF without secondary causes and treatment of the symptoms of HFPEF prioritizes use of diuretics,[21] which has already been covered in this article. Management of congestion in patients with advanced HFPEF can be challenging in certain situations because of the diversity of pathophysiologic mechanisms and comorbidities involved. In patients with uncontrolled arterial hypertension, concomitant vasodilation with blood volume adjustment should be performed with caution, primarily in patients with decompensated HFPEF, since sodium nitroprusside can trigger a more accentuated response in arterial blood pressure drop and systolic volume depression.[22] In hypervolemia cases that are refractory to drug treatment, ultrafiltration should be considered as a useful resource.

Pulmonary hypertension (PH) is a prevalent condition in HFPEF, associated with disease severity and chronicity and worse prognosis.[23] Presence of PH can vary considerably between different phenotypes and may be influenced by the different stages of HFPEF severity, denoting the importance of invasive hemodynamic assessment in this population. We can classify PH according to increase in mean pulmonary artery pressure ≥ 20mmHg, which can be classified a pre-capillary PH, post-capillary PH, or combined PH.[24] This categorization is important, since patients with HFPEF with combined PH may benefit from treatment with pulmonary vasodilators.[25] Assessments of the contractile function of the right ventricle and of the PH of patients with advanced HF are of fundamental importance. Assessment with direct cardiac catheterization at rest and during exercise, when indicated, yields more trustworthy parameters of right ventricular function and PH. Even in advanced HF, we may see normal right ventricular function at rest, but then abnormal under exercise if the dilatation capacity of the pulmonary vasculature is lost in response to the increase in volume. Under normal conditions, the right ventricle is less resistant to changes in afterload and this mechanism is exacerbated in individuals with HFpEF.[26,27] Use of inotropics in decompensated HFPEF is still a gray area, with only small studies in patients with associated PH, and should be reserved for selected cases.[28] Use of levosimendan in these patients is being tested in an ongoing randomized study, the HELP RCT (NCT 03541603), which should provide further explanations.

Treatments targeting PH with the aim of reducing right ventricle afterload have so far yielded disappointing results. In a small, randomized, double-blind study with 44 patients, sildenafil was associated with improvement in pulmonary pressure, right ventricular function, left ventricular relaxation, and pulmonary hydrostatic balance.[29] Although the drug exhibited good tolerability, later randomized studies did not report the same findings, with positive results only reported by one observational study with no control group, which observed improvements in NYHA HF, TC6M, and NT-proBNP levels at 3 and 12 months in patients with combined PH.[30] Ongoing studies in this population, such as DYNAMIC (NCT02744339) which is investigating riociguat, SERENADE (NCT03153111), testing macitentan, and the VITALITY-HFpEF RCT (NCT03547583), which will assess vericiguat, will provide more answers. Long-stay ventricular assist devices (VAD) are part of the therapeutic arsenal for treatment of patients with advanced HF in patients with HFrEF, demonstrating improved morbidity and mortality statistics.[31] However, there are few studies reporting data on VADs implanted in patients with HFPEF, in the majority of cases in patients with hypertrophic and restrictive cardiomyopathy.[32-35] This is because of the peculiar and pathophysiologic characteristic of these patients, the majority of whom have increased myocardial rigidity, altered complacency and, in some situations, small left ventricular dimensions. These characteristics may favor complications linked to VAD, such as obstructions of cannulae, suction events, inadequate pump flow, and pump thrombosis.[33,36] An additional myectomy at the time that the VAD is implanted may be a viable option, as has been performed in some cases of hypertrophic cardiomyopathy.[33]

A small proportion of patients with HFPEF meet the criteria for heart transplantation, although published data are scant. In this population, hypertrophic and restrictive cardiomyopathies and selected cases of right ventricular dysfunction stand out. For individuals with severely symptomatic hypertrophic cardiomyopathy (NYHA III-IV HF) with EF ≥ 50% (without obstruction of the LV outlet) and with impaired cardiopulmonary exercise testing results, with peak VO_2 ≤ 14 ml/mun/Kg or ≤ 50% of predicted, unfavorable hemodynamic profile, or acute hemodynamic deterioration, consideration of heart transplantation appears to be beneficial,

with favorable post-transplant outcomes. In restrictive cardiomyopathies, after ruling out constrictive pericarditis, it is mandatory to conduct etiological assessment for adequate treatment of the underlying condition (amyloidosis, Anderson-Fabry, sarcoidosis, etc.) and assessment of involvement of other organs (amyloidosis, hemochromatosis) and it may even be necessary to plan post-transplant treatment, with a need for double transplant in some situations.[37]

Advanced treatments such as long-stay circulatory support and heart transplantation are applicable and more consolidated for HFPEF of secondary etiology, such as hypertrophic and restrictive cardiomyopathies. This is why it always essential to identify the etiology.

Cardiopulmonary rehabilitation in HFpEF

In this group, exercise intolerance may be because of remodeling and ventricular rigidity, causing impairment of the Frank-Starling mechanism, which, associated with chronotropic deficit, are determinants of failure to raise cardiac output, thereby reducing maximum oxygen uptake. Garcia et al,[38] observed the dynamics of patients with HFPEF vs. controls and identified lower oxygen consumption (VO_2) and reduced capacity to reduce heart rate after effort and this was associated with atrial remodeling and elevation of the estimated diastolic pressure of the LV. As a result, rehabilitation focused on aerobic activity has been tested with these patients. In a recent systematic review, Pandey, et al.,[39] demonstrated that patients with HFpEF who enrolled on a cardiac rehabilitation program improved their cardiorespiratory fitness (2ml/kg/min), quality of life (by seven points), and diastolic function after 12 weeks of intervention. Although there is no evidence of CV mortality reductions with exercise in this population, Kavanagh, et al.[40] have demonstrated that for each 1ml/kg/min unit increase in oxygen consumption, cardiovascular mortality drops by 10%.

Alternative rehabilitation methods such as training of inspiratory musculature are already in use. Menezes MG, et al.[41] demonstrated that one acute session of high intensity inspiratory muscles training (80% of the maximum inspiratory effort) improved late arterial rigidity (60 min after the assessment) and diastolic function indices. Supplementing this from a practical point of view, Palau et al.[42] allocated a sample of 26 patients with HFPEF to a program of 12 weeks' inspiratory muscle training at 30% of maximum inspiratory effort or usual treatment, observing a significant improvement in maximum inspiratory pressure ($p < 0.001$), peak VO_2 ($p < 0.001$), oxygen consumption during exercise at the anaerobic threshold ($p = 0.001$), ventilatory efficiency ($p = 0.007$), metabolic equivalents ($p < 0.001$), and the 6-minute walk test ($p < 0.001$), in comparison to the control group.

Prospects for management of HFpEF

The future of treatment of HFpEF lies in studies with designs that are more compatible with the real population, possibly with higher LVEF cutoff points, and respecting phenotypical characteristics, and in investing in molecules with activity on fibrosis, inflammation, improvement of mitochondrial function, anti-remodeling, optimizers of endothelial function, and in devices to regulate circulatory overload.

Conclusions

Essential therapy for HFpEF is intimately related to precise diagnosis, definition of etiology, and estimation of severity, and use of medications with cardiovascular action of proven efficacy. After this first step, treatment of morbidities, rational use of diuretic therapy, and physical training for stable patients is the foundation of management. Finally, use of drugs with cardiovascular activity of proven efficacy can benefit clinical outcomes, when well-chosen.

Author Contributions

Conception and design of the research: Danzmann LC, Brum JCJ, Braun P; Acquisition of data: Danzmann LC, Brum JCJ, Kunst L, Braun P; Analysis and interpretation of the data, Statistical analysis and Critical revision of the manuscript for intellectual contente: Danzmann LC; Obtaining financing: Danzmann LC, Brum JCJ; Writing of the manuscript: Danzmann LC, Brum JCJ, Kunst L, Garcia EL.

Potential Conflict of Interest

Dr. Luiz Cláudio Danzmann - speaker: Novartis, Astra Zeneca, Boehringer e Lilly.

Dra. Joana Carolina Junqueira de Brum - speaker: Novartis.

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Study Association

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Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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