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Review Article

Heart failure with preserved ejection fraction diagnosis and treatment: An updated review of the evidence☆

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ABSTRACT

Over the last several decades, clinicians and clinical scientists have had growing interest in heart failure (HF) diagnosis and treatment. While HF with reduced ejection fraction (EF) is a well-known clinical entity with several therapeutic strategies proven to be successful, HF with preserved ejection fraction is a more heterogenous syndrome with a prevalence that has increased in the last two decades, without effective therapeutic strategies. Great strides have been made in the detection of predisposing risk factors and pathological mechanisms; however, pharmacological therapies have shown to be ineffective in reducing cardiovascular mortality in the HF with preserved EF (HFpEF) population, opening the way to the necessity of developing new precision medicine based approaches. On the other hand, novel therapies and device interventions still require refinements with the ultimate goal of offering new clinically treatments for the HFpEF population. The aim of the present review is to provide insights into the HFpEF pathophysiology, diagnostic pathways and the latest updates on treatment strategies and their potential future application in routine clinical practice.

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☆ Statement of conflict of interest: see page XX.

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Introduction

Heart failure (HF) with preserved ejection fraction (EF; HFpEF) is a clinical entity characterized by symptoms of HF despite a "preserved" (i.e. 50%) left ventricular (LV) ejection fraction (LVEF) with evidence of cardiac dysfunction as a primary cause of symptoms (eg, abnormal LV filling and elevated filling pressures). Currently, HFpEF affects approximately 4.9% of the general population aged ≥60 years and accounts for approximately half of total HF hospitalizations.[1] Initial retrospective and observational studies including mostly hospitalized patients classified on LVEF alone, the rates of hospitalization and death in patients with HFpEF were similar to those of patients diagnosed with HF with reduced EF (HFrEF).[2] In prospective and randomized studies in which the diagnosis of HFpEF was made using stricter criteria and other causes of HF (eg, valvular heart diseases, restrictive/infiltrative cardiomyopathies, pericardial diseases) were excluded, however, the cardiovascular (CV) mortality observed was lower in HFpEF compared to those with HFrEF.[3,4]

To date, several randomized controlled trials have failed to identify effective pharmacological therapies on clinical outcomes in HFpEF, perhaps due to the unfavorable one-size-fits-all approach for its management[5]. The scientific community of clinicians and clinical scientists has a growing interest in understanding the underlying pathophysiological mechanisms and phenotypic heterogeneity of HFpEF, with hopes to develop new therapeutic strategies.[6] The aim of the present review is to provide an overview on HFpEF pathophysiology and diagnostic pathways, with a focus on the latest developments of treatment strategies and their potential future applications in routine clinical practice.

Abbreviations and acronyms

6MWD	6-minute walking distance
ACEi	angiotensin-converting enzyme inhibitors
AF	Atrial fibrillation
ARBs	angiotensin II receptor blockers
ARNI	angiotensin receptor-neprilysin inhibitors
BBs	Beta-blockers
BNP	brain natriuretic peptide
CCM	Cardiac Contraction Modulation
CI	chronotropic incompetence
CV	cardiovascular
ESC	European Society of Cardiology
GLS	global longitudinal systolic strain
HF	Heart failure
HFA	Heart Failure Association
HFpEF	Heart failure with preserved EF
HFrEF	Heart failure with reduced ejection fraction
LVEF	left ventricular ejection fraction
MRAs	mineralocorticoid receptor antagonists
NT-proBNP	N-terminal-pro hormone BNP
PDE-5a	Phosphodiesterases-5a
QoL	Quality of life
sGC	soluble guanylate cyclase
SGLT-2	sodium–glucose cotransporter 2

HFpEF pathophysiology

HFrEF is characterized by the presence of definitive cardiac abnormalities central to which is depressed LV systolic function, while HFpEF has traditionally been diagnosed as a clinical syndrome of HF in the setting of normal EF.[7] Diastolic dysfunction has emerged as fundamental to the HFpEF syndrome and there is compelling evidence for failure of the Frank-Starling mechanism, defined as the ability to translate an increase in LV filling pressure to an increase in cardiac output or only doing so with an inappropriately elevated filling pressures.[8] The main determinants of diastolic dysfunction are impaired LV relaxation (impaired lusitropy) and/or increase of LV stiffness (reduced compliance),[9] that often co-exist and result in increased LV end-diastolic pressure and impaired ventricular filling, as shown by changes in LV pressure volume loop.[10] However, in recent years there has been a paradigm shift from HFpEF as "diastolic HF" to a more complex multiorgan syndrome caused by an interplay of multiple significant abnormalities, that often co-exist, such as LV systolic dysfunction (reduced LV long-axis systolic function), right ventricular systolic dysfunction and pulmonary hypertension, chronotropic incompetence (CI)/autonomic dysfunction, atrial dysfunction (reduced left atrial [LA] reservoir and contractile function), systemic vascular dysfunction, pericardial restraint, abnormal cardiorenal interaction and abnormalities in the periphery (skeletal muscle dysfunction)[8,11,12] (Fig. 1). Many of these abnormalities are not apparent at rest but are noted only under physiological stressors (reduced reserve capacity).[13,14] These impairments in cardiac, pulmonary, vascular, and peripheral reserve can be caused by common risk factors for HFpEF, such as ageing, adiposity, hypertension, and systemic metabolic disorders.[8] A unifying hypothesis is that the systemic multimorbidity driven pro-inflammatory milieu may promote diffuse microvascular endothelial inflammation leading to microvascular rarefaction and cardiac and extracardiac fibrosis that synergistically

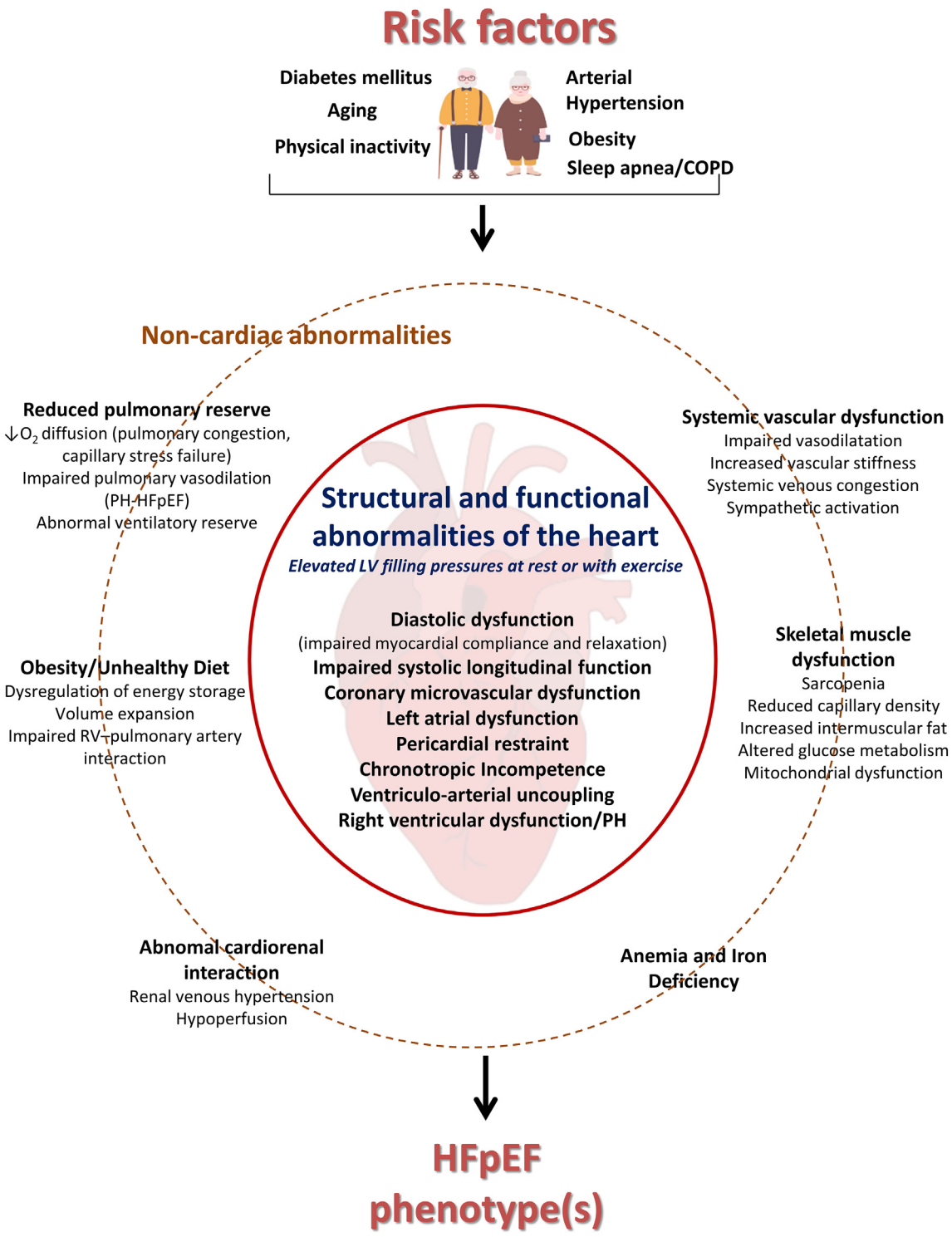

Fig. 1. Diagnostic work-up for HFpEF diagnosis. The algorithm resumes a stepwise multimodality approach to diagnose HFpEF, integrating the two scoring systems that have been developed for this purpose, the H_2FPEF score and HFA-PEFF score. *Abbreviations:* AF: Atrial fibrillation; CAD: Coronary artery disease; CMR: Cardiac magnetic resonance; CT: Computed tomography; EF: Ejection fraction; GLS: Global longitudinal strain; HF: Heart failure; HFA: Heart failure association; LAVI: Left atrial volume index; LV: left ventricular; LVEDP: Left ventricular end diastolic pressure; LVH: left ventricular hypertrophy; LVMI: Left ventricular mass index; NT-proBNP: N-terminal pro b-type natriuretic peptide; PASP: Pulmonary artery systolic pressure; PCWP: Pulmonary capillary wedge pressure; PET: Positron emission tomography; RWT: Relative wall thickness; SR: Sinus rhythm; TR: Tricuspid regurgitation.

contribute to HFpEF development and progression.[15,16] Of note, patients presenting with HF, LVEF≥50%, symptoms secondary to an identifiable cause of diastolic dysfunction and exercise intolerance should not be considered as HFpEF, but should be referred to as "HFpEF mimics" or "secondary" HFpEF (e.g. due to valvular, myocardium or pericardial diseases) (Table 1).[3,5] Classification of these secondary HFpEF phenotypes is highly relevant to determine the most appropriate treatment, which can, in fact, markedly improve symptomatology. Moreover, the prognostic outlook significantly differs depending to the causal pathologies, which may treatable (i.e., valvular heart disease, pericardial

Table 1
Secondary causes of HFpEF or HFpEF mimics.

Restrictive cardiomyopathy
• With increased LV wall thickness: infiltrative cardiomyopathies (i.e. amyloidosis, glycogen storage diseases)
• With preserved LV wall thickness: endomyocardial fibrosis, radiation cardiomyopathy, hemochromatosis, idiopathic
Valvular heart disease (moderate to-severe)
Constrictive pericarditis
High-output HF (ie. severe anemia, thyrotoxicosis)
Others: ischemic cardiomyopathy/myocarditis with large areas of regional wall motion abnormalities and preserved global EF (≥50%)

disease) or untreatable (i.e., restrictive cardiomyopathy following radiotherapy).

HFpEF definition and diagnostic algorithm

According to the latest European Society of Cardiology (ESC) guidelines, HFpEF diagnosis requires the presence of compatible signs and symptoms, a 'preserved' EF (defined as LVEF ≥50%), elevated levels of natriuretic peptides (brain natriuretic peptide [BNP] > 35 pg/mL and/or N-terminal-pro hormone BNP [NT-proBNP] > 125 pg/mL) and objective evidence of cardiac functional and structural alterations consistent with HF.[17] Moreover, stress testing or invasive measures of elevated LV filling pressures may be needed in cases of uncertainty.[17–19]

Over the last several years, additional diagnostic criteria have been proposed using an integrated diagnostic approach.[20] In 2018 Reddy et al. proposed a novel score system (H_2FPEF score) able to discriminate between HFpEF and non-cardiac causes of dyspnea. The H_2FPEF score (ranging from 0 to 9) is calculated from universally available criteria and includes six clinical and echocardiographic variables (Obesity [body mass index, BMI] > 30 kg/m2), 2 points; atrial fibrillation (AF), 3 points; age > 60 years, 1 point; treatment with 2 or more antihypertensive drugs, 1 point; E/e' ratio > 9, 3 points; and pulmonary artery systolic pressure > 35 mmHg, 1 point.[20] A major advantage of the H_2FPEF score is that the probability that HFpEF is the cause of symptoms can be estimated accurately, which helps to guide further evaluation. A low composite score (0–1) corresponds to a pretest probability of <20%, making the HFpEF diagnosis unlikely and suggesting non-cardiac causes for the symptoms. Conversely, a high score (6–9) is associated with a probability of HFpEF exceeding 90%, strongly suggesting HFpEF diagnosis. Patients with an intermediate score (2–5) fall between these extremes and require further evaluation to reach a definitive diagnosis (Fig. 2).[20] Some of the criteria in the H2FPEF score such as older age and obesity are not specific to HFpEF and are commonly seen in cohorts without disease.[21] As such, based upon current data, the score should only be applied clinically in the way it was first studied: to patients presenting with unexplained dyspnea.

Recently, the Heart Failure Association (HFA) of the ESC elaborated a new consensus document with the most updated information about pathophysiology and diagnostic options developing the 'HFA–PEFF diagnostic algorithm'.[22] This novel algorithm is based on a stepwise approach including four phases (Fig. 2). Step 1 (P=Pre-test assessment) is performed in the ambulatory setting and includes an assessment for HF symptoms and signs, clinical features compatible with the HFpEF phenotype, diagnostic laboratory tests (including NT-proBNP values) and electrocardiogram. In the absence of overt non-cardiac causes of breathlessness, HFpEF can be suspected if there is a normal LVEF (>50%), no significant heart valve disease or cardiac ischemia, and at least one typical risk factor. Elevated natriuretic peptides support the diagnosis, but normal levels do not exclude HFpEF, as the increase of NT-proBNP is usually less relevant in HFpEF compared to HFrEF[23] due to a high prevalence of obesity, which is associated with greater clearance and lower synthesis of natriuretic peptides, and the possibility of elevated LV filling pressures that only manifests during exercise testing (especially in the earlier stage of the syndrome).[24] Once the first assessment following step 1 is completed, it is possible to proceed with Step 2 (E: Echocardiography and Natriuretic Peptide Score). In this phase the involvement of a specialist in CV disease or HF is crucial as a comprehensive and detailed echocardiography is required. In order to increase specificity, a higher cut-off value of NPs is recommended as a major criterion and are also stratified for the presence of sinus rhythm or AF. However, as aforementioned, normal natriuretic peptides levels do not definitely exclude HFpEF diagnosis and in the context of clinical suspicion it requires further investigations (ie. hemodynamic exercise testing).[19]

According to the values obtained using echocardiographic functional, morphological, and biomarker domains, major (2 points) and minor (1 point) criteria were defined in order to obtain a comprehensive scoring system. Each domain can contribute maximally 2 points. A score ≥ 5 points implies definite HFpEF diagnosis; ≤1 point makes the diagnosis of HFpEF unlikely. An intermediate score (2–4 points) implies diagnostic uncertainty, in which case Step 3 (F1: Functional testing) is recommended with echocardiographic or invasive hemodynamic exercise stress tests. The latter is currently considered the "gold standard" for HFpEF diagnosis, both for the high accuracy of this test and for the early diagnosis ensured. In fact, in a recent study of 267 individuals with normal filling pressures at rest, 45% of patients had elevated filling pressures only during invasive hemodynamic exercise testing.[20] Step 4 (F2: Final aetiology) is ultimately recommended to establish a possible specific, "secondary" cause of HFpEF or alternative explanations.[22] The new HFA consensus document further highlights the importance of a differentiation between "primary" and "secondary/masquerade" forms of HFpEF (Table 1).

Pharmacological and non-pharmacological treatments of HFpEF

To date, no treatment has been shown to reduce clinical events including CV and all-cause mortality in HFpEF. For such reason, guidelines merely recommend diuretics for fluid removal and symptoms relief (eg, edema),[25] and management of associated comorbidities (eg, hypertension, obesity, chronic obstructive pulmonary disease).[17] Beta-blockers (BBs), angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), mineralocorticoid receptor antagonists (MRAs) and angiotensin receptor-neprilysin inhibitors (ARNI) have all failed to reduce their prespecified primary endpoints in their respective CV outcomes trials, although some have shown potential improvements in their secondary outcomes, as described below. The current lack of beneficial therapeutic options on clinical outcomes is likely related to complexity of HFpEF pathophysiology; multiple factors may variably contribute to the development and progression of HFpEF and new pathophysiologic pathways are currently being studied as potential therapeutic targets. Furthermore, interventional devices and novel techniques have been developed with promising results. Table 2 summarizes the major pharmacological and non-pharmacological clinical trials in HFpEF. Table 3 summarizes the effect of the more well investigated pharmacological and non-pharmacological interventions on cardiovascular mortality, HF hospitalization, HF symptoms and exercise capacity in HFpEF.

Pharmacological treatments

Beta-blockers

Treatment with BBs has consistently been shown to reduce death and hospitalizations in patients with HFrEF (EF <35%), but this has not been shown in the HFpEF population.[17] In the SENIORS trial (Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure), which investigated the role of nebivolol, a beta-1-selective antagonist with vasodilator properties in elderly patients with HF of whom approximately one-third had an EF >35%,[26] nebivolol showed benefit on the composite outcome of death or CV hospitalization that seemed to be similar between HF patients with

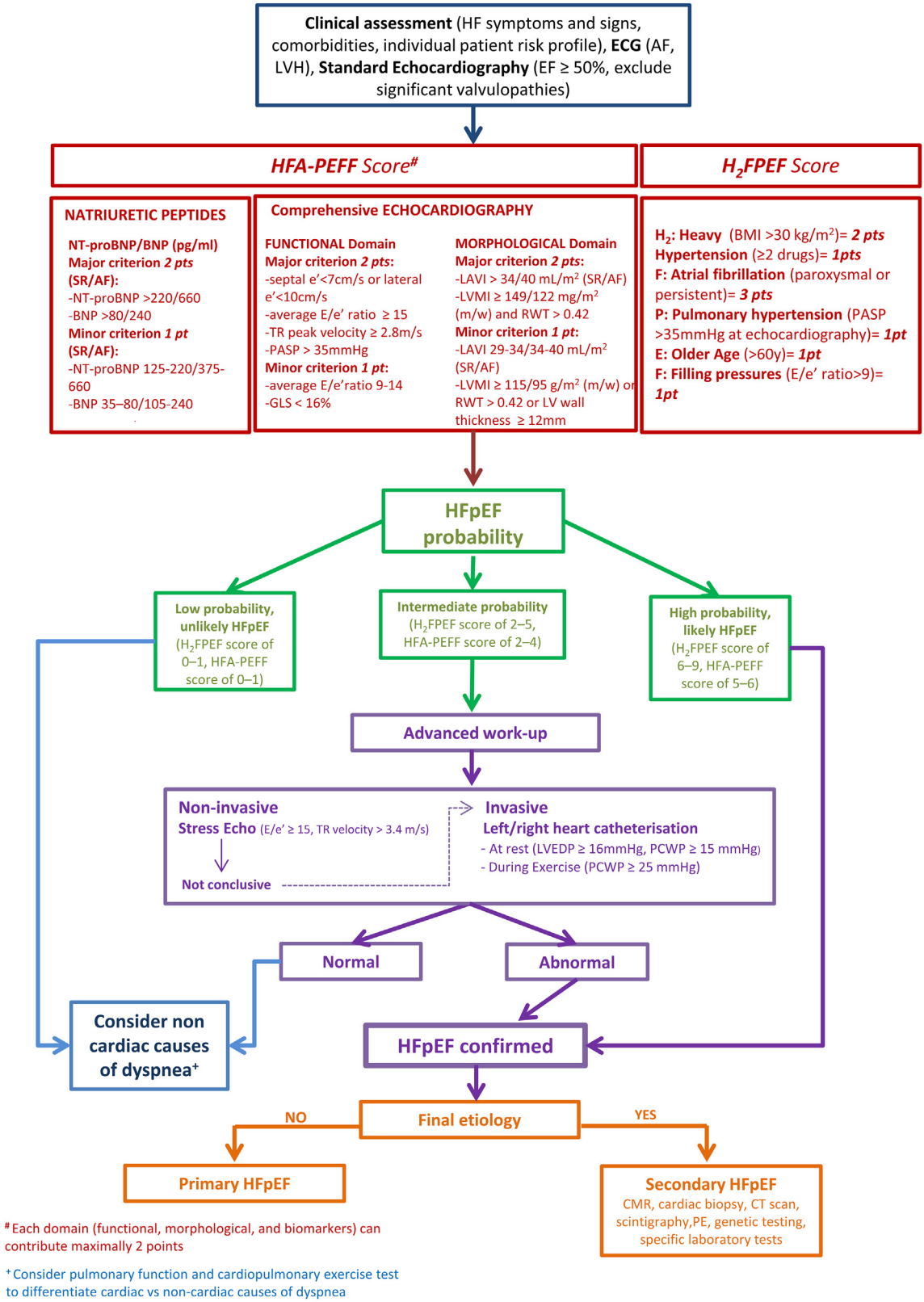

Fig. 2. Pathophysiology of HFpEF. While diastolic dysfunction plays a central role in determining symptoms and clinical outcomes in HFpEF, it is now being recognized that HFpEF is a more multifaced syndrome in which the interwoven contributions of multimorbidities result in pulmonary hypertension, autonomic dysfunction, systemic vascular dysfunction, pericardial restraint, cardiorenal perturbations and skeletal muscle dysfunction. These mechanisms meaningfully contribute to determine symptoms and prognosis. *Abbreviations:* COPD: Chronic obstructive pulmonary disease; PH: Pulnonary hypertension; RV: right ventricle.

impaired and with preserved EF. Of note, all-cause mortality was not reduced. The effects of nebivolol in HFpEF population (LVEF >45%) were investigated in The Effect of Long-term Administration of Nebivolol on clinical symptoms, exercise capacity and left ventricular function in patients with Diastolic Dysfunction (ELANDD) study, in which nebivolol treatment resulted in no improvement in 6-min walk distance

Table 2
Pharmacological and non-pharmacological treatments of HFpEF. HFpEF: heart failure with preserved ejection fraction.

Class of drug/intervention	trial	Methods	Patients (n)	Major inclusion criteria	Mean follow-up (months)	Primary endpoints	Ref
A) Pharmacological treatments							
Beta-blockers	SENIORS	Nebivolol vs placebo	2128	Age > 70, history of HF (35% with HFmrEF and HFpEF)	21	Reduction in composite of all-cause mortality or HF hospitalization (P = 0.04)	26
	ELANDD	Nebivolol vs placebo	116	LVEF ≥45%, NYHA II-III, echocardiographic evidence of diastolic dysfunction	6	No difference in 6MWD and QoL	27
	J-DHF	Carvedilol vs placebo	245	LVEF ≥40%, age ≥ 20, signs/symptoms of HF	38	No difference in primary of CV death and HF hospitalization (P = 0.7). Significant reduction of secondary of all cause death and CV hospitalization in standard (>7.5 mg daily) vs low dose (≤7.5 mg daily) (P = 0.03)	28
ACEi/ARB	PEP-CHF	Perindopril vs placebo	850	LV wall motion index >1.4 (corresponding LVEF >40%), age >70, symptomatic HF, echocardiographic diastolic dysfunction.	25	No difference in combined all-cause mortality or CV hospitalization (P = 0.35).	31
	I-PRESERVE	Irbesartan vs placebo	4128	LVEF ≥45%, age ≥ 60, NYHA III–IV, NYHA II with HF hospitalization in recent 6 months	50	No difference in combined all-cause mortality or HF hospitalization (P = 0.54).	32
	CHARM-Preserved	Candesartan vs placebo	3023	LVEF >40%, NYHA II–IV, history of hospitalization for HF.	37	Trend towards a reduction in combined CV mortality or HF hospitalization (adjusted P = 0.051)	30
MRA	Aldo-DHF	Spironolactone vs placebo	422	LVEF ≥50%, age ≥ 50, NYHA II-III, echocardiographic evidence of diastolic dysfunction	12	Improvement in E/e' ratio as marker of diastolic function (P < 0.001) but no difference in the other primary endpoints of exercise capacity.	35
	TOPCAT	Spironolactone vs placebo	3445	LVEF ≥45%, age ≥50, ≥1 HF sign, ≥1 HF symptom, HF hospitalization within recent 12 months, elevated natriuretic peptides.	40	No difference in combined CV death, aborted cardiac arrest, or HF hospitalization (P = 0.14). However geographic differences noted.	36
	SPIRRIT (NCT02901184)	Spironolactone vs placebo	3200 est	LVEF≥40%, symptoms/signs of HF, elevated NTproBNP	24	Combined of CV death or time to HF hospitalization	
ARNI	PARAGON-HF	Sacubitril/Valsartan vs Valsartan	4822	LVEF≥45%, NYHA II-IV, elevated natriuretic peptides and structural heart disease	35	No difference in combined of CV death and hospitalization for HF (P = 0.06). Reduction in 2 prespecified subgroups of females and LVEF.	39
	PARAGLIDE-HF (NCT03988634)	Sacubitril/Valsartan vs Valsartan	800 est	LVEF≥40%, age ≥40, recent hospitalization for HF (within 30 days), elevated NTproBNP	2	Change in NTproBNP as primary endpoint. CV death, HF hospitalization of HF urgent visit as secondary endpoints.	
Digoxin	DIG-PEF	Digoxin vs placebo	988	HF with LVEF >45%, sinus rhythm.	37	No difference in combined HF mortality or HF hospitalization (P = 0.14)	45
Ivabradine	EDIFY	Ivabradine vs placebo	179	LVEF≥45%, NYHA II-III, sinus rhythm≥70 bpm, NTproBNP≥220 pg/mL (BNP ≥ 80 pg/mL)	8	No difference in the 3 co-primary endpoints: E/e' (P = 0.14), 6MWD (P = 0.88) and NTproBNP (P = 0.88)	47
Nitrates	NEAT-HFPEF	Isosorbide mononitrate vs placebo	110	LVEF≥50%, age ≥50, evidence of HF, elevated natriuretic peptides or echocardiographic evidence of diastolic dysfunction	3	No increase but rather decrease in daily activity level measured in accelerometer units in patients receiving Isosorbide mononitrate (P = 0.02)	49
	INDIE-HFPEF	Inhaled nebulized inorganic nitrite vs placebo	105	LVEF≥50%, age ≥40, evidence of HF and chronic diuretic treatment	3	No difference in peak VO2 (P = 0.27)	50
PDE-5a inhibitors and sGC activators	RELAX	Sildenafil vs placebo	216	LVEF≥50%, NYHA II-IV, objective evidence of HF	6	No difference in peak VO2 (P = 0.90)	52
	Sildenafil on invasive Hemodynamics and exercise capacity in HFpEF and pulmonary hypertension	Sildenafil vs placebo	52	HFpEF (LVEF≥45%) causing pulmonary hypertension (mean pulmonary artery pressure > 25 mmHg; pulmonary artery wedge pressure > 15 mmHg),	3	No difference in primary of change in pulmonary artery pressure (P = 0.14)	53
	SOCRATES-PRESERVED	Vericiguat vs placebo	477	LVEF≥45%, age ≥ 18, NYHA II-IV, elevated natriuretic peptides	3	No changes in NTproBNP (P = 0.20) and LAV (P = 0.82)	54
	VITALITY-HFPEF (NCT03547583)	Vericiguat vs placebo	788 est	LVEF≥45%, age ≥ 45, HF decompensation within 6 months, elevated natriuretic peptides, echocardiographic structural changes	6	Completed, waiting for results (KCCQ score change).	
Iloprost	ILO-HOPE (NCT03620526)	Iloprost vs placebo	34 est	LVEF ≥45%, HF signs/symptoms, elevated natriuretic peptides, echocardiographic	NA	PCWP changes after exercise	

(continued on next page)

Table 2 (*continued*)

Class of drug/intervention	trial	Methods	Patients (n)	Major inclusion criteria	Mean follow-up (months)	Primary endpoints	Ref
				structural/functional abnormalities			
A1-agonists	PANACHE	Neladenoson bialanate vs placebo	305	LVEF≥45%, NYHA II-IV, elevated NTproBNP	5	No difference in 6MWD (P = 0.52)	60
SGLT2-inhibitors	DELIVER (NCT03619213)	Dapaglifozin vs placebo	6100 est	LVEF≥40%, age > 40, NYHA II-IV and evidence of structural heart disease	33	Composite of CV death, HF hospitalization or urgent HF visit	
	EMPEROR-PRESERVED (NCT03057951)	Empaglifozin vs placebo	5750 est	LVEF≥40%, age ≥ 18, NYHA II-IV and elevated natriuretic peptides	38	Composite of CV death and HF hospitalization.	
	EMPERIAL-preserved (NCT03448406)	Empaglifozin vs placebo	315	LVEF≥40%, age ≥ 18, NYHA II-IV, evidence of HF and elevated natriuretic peptides	3	Completed. No difference in 6MWD (preliminary results).	
Anti-inflammatory drugs	D-HART	Anakinra vs placebo	12	LVEF≥50%, age ≥ 18, NYHA II-III, echocardiographic evidence of diastolic dysfunction and elevated CRP	1	Significant improvement in peak VO2 (+1.2 mL/kg/min, P = 0.009) and reduction in plasma CRP levels (−74% P = 0.006)	78
	D-HART 2	Anakinra vs placebo	31	LVEF≥50%, age ≥ 18, NYHA II-III, echocardiographic evidence of diastolic dysfunction and elevated CRP	2	No difference in peak VO2 (P = 0.89) and VE/VCO2 slope (P = 0.40)	77
Anti-fibrotic drugs	PIROUETTE (NCT02932566)	Pirfenidone vs placebo	129 est	LVEF≥45%, sign/symptoms of HF, elevated natriuretic peptides and myocardial fibrosis at CMR	13	Change in myocardial ECM volume.	
Iron supplementation	FAIR-HFpEF (NCT03074591)	Ferric Carboxymaltose vs placebo	200 est	LVEF≥45%, age ≥ NYHA II-III, evidence of diastolic dysfunction, ferritin<100 ng/mL	13	Change in 6MWD.	
B) Non-pharmacological treatments							
Lifestyle interventions	SECRET	Exercise, diet, exercise+diet vs control	100	LVEF≥50%, age ≥ 60, sign/symptoms of HF and BMI ≥ 30 kg/m2	1	Increase in peak VO2 (P < 0.0001), but no difference in co-primary outcome of QoL assessed with MLHF score (P = 0.70)	103
	Training HF trial	IMT, FES, or IMT + FES vs usual care	61	LVEF≥50%, NYHA II-III	24	Improvement in peak VO2 at 12 (omnibus value P < 0.001) and 24 weeks (omnibus value P < 0.001)	104
	UFA-Preserved	UFA rich diet	9	Symptomatic HFpEF, obesity, reduced cardiorespiratory fitness	3	Increase in patient reported consumption of UFA and in plasma UFA biomarkers	102
	UFA-Preserved2 (NCT03966755)	UFA rich vs general diet	30 est	LVEF ≥50%, age ≥ 18, NYHA II-III, BMI ≥ 30 kg/m2	8	Change in 24-h dietary recall and in biomarkers of dietary compliance	
Interatrial shunts	REDUCE LAP-HF I	IASD vs sham procedure	44	LVEF≥45%, NYHA III or IV, exercise PCWP≥25 mmHg		Reduction in PCWP	107
	REDUCE LAP-HF II (NCT03088033)	IASD vs sham procedure	608 est	LVEF >40%, age > 40, chronic symptomatic HF, elevated PCWP	12	Composite of CV death, first non-fatal ischemic stroke, HF hospitalization and KCCQ score.	
LV expanders	Corolla (NCT02499601)	Corolla TAA device	10 est	LVEF ≥50%, NYHA III-IV and echocardiographic structural abnormalities	6	All-cause mortality and serious adverse events	
Left atrial pacing	LEAD (NCT01618981)	Left atrial pacing active vs inactive	NA	LVEF ≥50%, NYHA III-IV, atrial dyssynchrony	NA	Completed, waiting for results.	
Rate adaptive pacing	RAPID-HF (NCT02145351)	Rate adaptive pacing active vs inactive	30 est	LVEF ≥40%, NYHA II-III, chronotropic incompetence	1	VO_2 at ventilatory anaerobic threshold as measure of exercise capacity	
	PREFECTUS (NCT03338374)	Biventricular pacing versus rate adaptive pacing	10 est	LVEF ≥50%, NYHA II-IV, chronotropic incompetence	6	Diastolic and systolic reserve indexes	
CCM	CCM-HFpEF (NCT03240237)	CCM	60 est	LVEF ≥50%, HF signs/symptoms, elevated natriuretic peptides, echocardiographic diastolic abnormalities.	6	KCCQ change.	
Pericardiotomy	The effects of pericardiotomy on diastolic reserve in humans	Pericardiotomy	19	Subjects undergoing clinically indicated cardiac surgery	NA	Reduction in rise of PCWP induced with volume load	114
	Minimally invasive pericardiotomy as a new treatment for HF (NCT03923673)	Pericardiotomy	4 est	LVEF ≥50%, age ≥ 30, NYHA III-IV, activity limitation primarily by HF	6	Composite of MACCE and LV filling pressure during loading	

Abbreviations: HFmrEF: Heart Failure with moderately reduced Ejection Fraction; HFpEF: Heart Failure with preserved Ejection Fraction, 6MWD: 6 Minute Waking Distance; QoL: Quality of Life; ACEi: Angiotensin-Converting Enzyme Inhibitor; ARB: Angiotensin Receptor Blocker; LV:Left Ventricular; LVEF: Left Ventricular Ejection Fraction; CV: Cardiovascular; MRA: Mineralcorticoid Receptor Antagonist; ARNI: Angiotensin Receptor Neprilysin Inhibitor;NYHA: New York Heart Association; VO2: Oxygen consumption; PDE-5a: Phosphodiesterase-5a; sGC: soluble Guanylate Cyclase; LAV: Left Atrial Volume; KCCQ: Kansas City Cardiomyopathy Questionnaire; VAS: Visual Analog Scale; sBP: systolic Blood Pressure; CRP: C-Reactive Protein; VE/VCO2 slope: minute ventilation-carbon dioxide production slope; LVEDP; Left Ventricular End Diastolic Pressure; CPET: Cardiopulmonary Exercise Testing; BMI: Body Mass Index; MLHF: Minnesota Living with Heart Failure; UFA: Unsatured Fatty Acids; PCWP: Pulmonary Capillary Wedge Pressure; SGLT2_ Sodium-Glucose Transport protein 2; CMR: Cardiac Magnetic Resonance; ECM: Extra-Cellular Matrix; IASD: InterAtrial Shunt Device; CCM: Cardiac Contractility modulation; MACCE: Major Adverse Cardiovascular and Cerebral Events; NA: Not Available, est.: estimated.

Table 3
Effect of HFpEF interventions on cardiovascular mortality, HF hospitalization, HF symptoms and exercise capacity.

Treatment	Cardiovascular death	HF Hospitalization	Exercise capacity (VO_2/6MWD)	HF symptoms (QoL questionnaires/NYHA class)
Diuretics	=	- (in volume overload states)	+ (in volume overload states)	− (in volume overload states)
Beta-blockers	=	=	=	=
ACEi/ARBs	=	=/−	=/−	=/−
MRA	=	=/−	=/+	=/−
ARNI	=	=/−	?	-
Digoxin	=	=	?	?
Ivabradine	?	?	=	?
Nitrates	?	?	−	=
PDE-5a inhibitors/and sGC activators	=	=	=	=/−
A_1-Agonists	?	?	=	?
SGLT2 inhibitors	?	?	=	?
Lifestyle interventions	?	?	+	−

Abbreviations: HF: Heart Failure; VO_2: Oxygen Consumption; 6MWD: 6 Minute Walking Distance; QoL: Quality of Life; NYHA: New York Heart Association ACEi: Angiotensin-Converting Enzyme inhibitor; ARB: Angiotensin Receptor Blockers; MRA: Mineralcorticoid Receptor Antagonist; ARNI: Angiotensin Receptor Neprilysin Inhibitor; PDE-5a Phosphodiesterase-5a; QoL; quality of life; SGLT2: Sodium-Glucose Transport protein 2; sGC: soluble guanylate cyclase; VO2: oxygen consumption. +: More; - : Less; ?_: no data yet.

(6MWD), peak oxygen consumption (VO_2), New York Heart Association (NYHA) classification or Minnesota Living with HF questionnaire, versus placebo.[26,27] Later, in The Japanese Diastolic Heart Failure Study (J-DHF) study enrolling HFpEF patients (LVEF >40%), the primary composite outcome (cardiovascular or all-cause death and unplanned hospitalization for any cardiovascular causes) was not reduced with carvedilol compared to placebo.[28] In conclusion, an individual patient-level meta-analysis of 11 randomized controlled trials of BBs in patients with HF found no evidence of benefit in the small subgroup of patients in sinus rhythm with LVEF ≥50%.[29]

ACEIs/ARBs

CV pharmacotherapy targeting maladaptive overactivation of the renin-angiotensin-aldosterone system (RAAS) is the cornerstone of therapy in HFrEF. However, three randomized controlled trials conducted in HFpEF, the Candesartan in Patients With Chronic Heart Failure and Preserved Left-Ventricular Ejection Fraction (CHARM preserved),[30] the Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF)[31] and Irbesartan in Heart Failure with Preserved Ejection Fraction Study (I-PRESERVE),[32] all failed to improve the primary outcomes in HFpEF cohorts.

The CHARM-Preserved randomized 3023 HF patients with New York Heart Association (NYHA) class II–IV HF, a prior cardiac hospitalization, and an LVEF >40% (by site report) to candesartan versus placebo. At a median follow-up of 36.6 months the primary end point of composite of CV death or HF hospitalization occurred in 22% and 24% in the candesartan and placebo arms respectively (hazard ratio [HR], 0.89; 95% confidence interval [CI]: 0.77–1.03; P =0.12), which was due to a significant reduction in hospitalization for HF with candesartan (adjusted HR 0.84; 95% CI: 0.70–1.00; P = 0.047).

The PEP-CHF trial randomized 850 patients with HF aged ≥70 years with an LVEF >40% and echocardiographic findings of diastolic

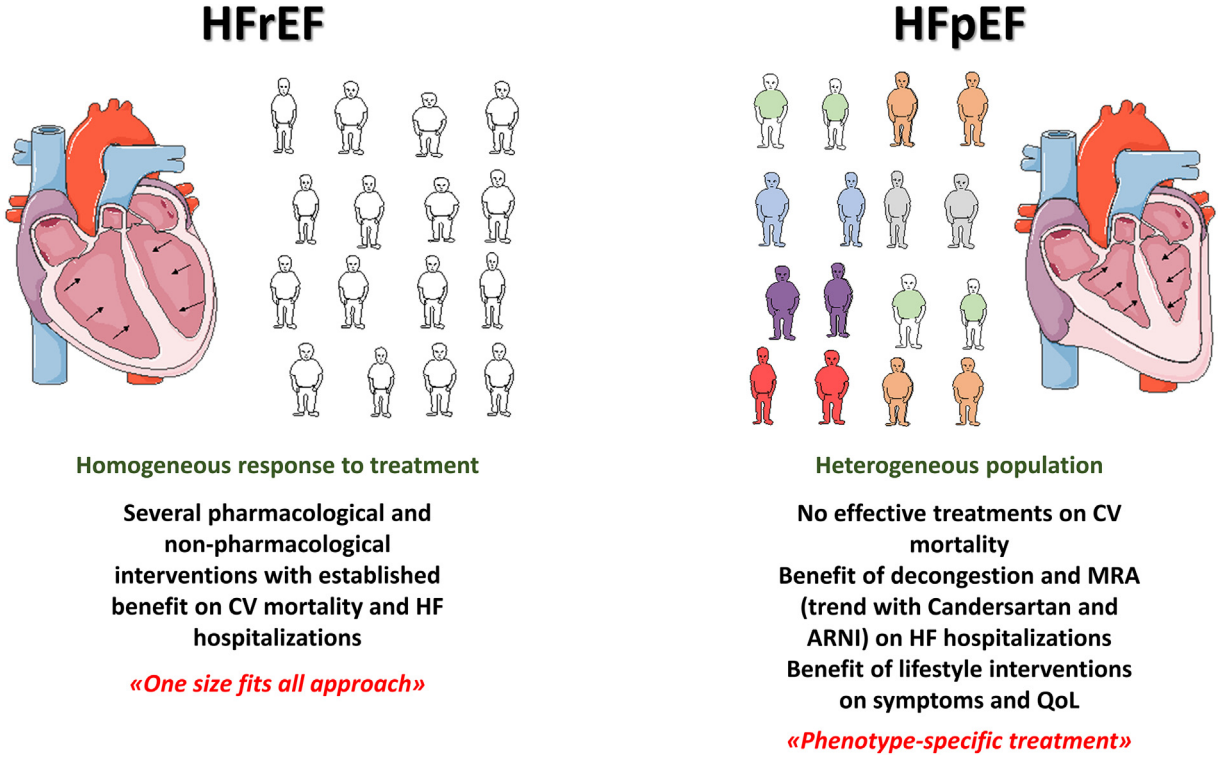

Fig. 3. HFpEF versus HFrEF. In contrast with patients suffering from HFrEF, HFpEF population is widely heterogeneous and at present no effective treatments have consistently reduced CV mortality. *Abbreviations:* HFrEF: heart failure with preserved ejection fraction; CV: Cardiovascular; ARBs: Angiotensin receptor blockers; MRA: Mineralcorticoid receptor antagonist, ARNI: Angiotensin receptor neprilysin inhibitor; HF: Heart failure; QoL: Quality of life.

dysfunction to perindopril versus placebo. At a mean follow-up of 26.2 months, perindopril failed to reduce the composite primary end point of all-cause mortality and HF hospitalization (HR, 0.92; CI:0.70–1.21; P = 0.55 compared to placebo) and nor was the secondary end point of HF hospitalization (HR, 0.86; CI: 0.61–1.20; P = 0.38). The patients treated with perindopril also had significant improvements in functional NYHA class and 6MWD. However, the trial was prematurely stopped and resulted underpowered due to lower than expected enrolment and event rate as well as a high proportion of discontinued treatment in the perindopril group.

The I-PRESERVE trial randomized 4128 persons aged ≥60 years, with NYHA class II–IV HF and an LVEF ≥45% to irbesartan versus placebo. Irbesartan was not associated with improvements in the primary (all-cause mortality or CV hospitalization) or any prespecified secondary end points.[32]

In conclusion, even if there could be a pathophysiological rationale for RAAS targeting with ACEi/ARBs in HFpEF, clinical results are mostly neutral with a weak signal for candersartan in reducing HF hospitalizations.[30]

MRAs

MRAs, such as spironolactone and eplerenone, are proven to be effective in reducing overall mortality and hospitalizations for HFrEF.[33,34] In the ALDO-DHF, improved measures of diastolic function but did not affect maximal exercise capacity, patient symptoms, or quality of life (QoL) in patients in HFpEF.[35] In the TOPCAT trial (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist), 3445 patients with HF and LVEF≥45% were randomized to receive Spironolactone or placebo.[36] There was no difference at a mean follow-up of 3.3 years in the primary outcome of death from CV causes, aborted cardiac arrest, or hospitalizations for HF between the groups (HR, 0.89, CI: 0.77–1.04; P = 0.14), although a reduction in the secondary end point of HF hospitalizations favoring spironolactone was observed (HR, 0.83; IC: 0.69–0.99; P = 0.04). A significant interaction for the prespecified endpoint was found between patients enrolled in the Americas compared to those from Russia or Georgia, in which the number of clinical events was extremely low. In the Americas, but not in Russia or Georgia, spironolactone was associated with reductions in the primary outcome (HR, 0.82; CI: 069–0.98; P = 0.03) and its components.[36]

Additional studies are needed and the SPIRRIT (Spironolactone Initiation Registry Randomized Interventional Trial in Heart Failure With Preserved Ejection Fraction, NCT02901184) study that will test the hypothesis that spironolactone plus standard of care compared to standard of care alone reduces the composite endpoints of CV mortality and HF hospitalization, hopefully providing resolution to the degree of therapeutic efficacy.

The STRUCTURE study (SpironolacTone in myocardial dysfunction with reduced ExeRcisE capacity), showed improvement in exercise capacity after 6 months of spironolactone treatment in patients with HFpEF NYHA class II-III and increased E/e' response on exertion (E/e' > 13, 37). The positive effect on exercise capacity (measured using cardiopulmonary exercise testing parameters) appeared related to an improvement in E/e' ratio during exercise. The inclusion of patients with exertional E/e' > 13 reflecting elevated filling pressure and exclusion of subjects with atrial arrhythmias and ischemic heart disease, might have helped to select a subpopulation of patients more responsive to MRA.[37]

ARNI

Sacubitril/Valsartan, which combines the neprilysin inhibitor sacubitril and the angiotensin receptor blocker valsartan, simultaneously inhibits the RAAS and augments the endogenous vasoactive peptide system. The PARAGON-HF trial (Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction) was designed following the positive results of this drug in improving prognosis in the HFrEF patients in the PARADIGM-HF study (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure)[38,39] and in lowering natriuretic peptide levels (NT-proBNP) in HFpEF patients in the PARAMOUNT trial (Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fracTion).[40] In the PARAGON-HF trial, a total of 4822 patients with signs and symptoms of HF and LVEF≥45% were randomly assigned to sacubitril/valsartan or valsartan alone.[39] The primary composite endpoint of total (first and recurrent) HF hospitalizations and CV death was reduced by a relative risk of 13%, narrowly missing statistical significance (Rate Ratio [RR] 95% CI: 0.75–1.1; p = 0.06). In the exploratory analysis of the individual components of the primary composite endpoint, there was a modest, although nonsignificant, lower rate of hospitalization for HF with sacubitril/valsartan than valsartan (RR 0.85; 95% CI: 0.72–1.00).

In a prespecified subgroup analyses, there were significant interactions for the primary endpoint in the subpopulation with EF below the median of 57%, with a 22% relative risk reduction (RR 0.78; 95% CI 0.64–0.95), and in women, that experienced a 28% relative risk reduction (RR 0.73; 95% CI 0.59–0.90).[41,42] Moreover, in a recent post-hoc analysis of PARAGON-HF trial, sacubitril/valsartan showed an efficacy gradient in relative risk reduction in primary events from patients enrolled within 30 days from a previous hospitalization to patients never hospitalized, thus demonstrating that sacubitril/valsartan beneficial effects could be amplified when initiated in the high-risk time window[43,44]. In this regard, the PARAGLIDE-HF study (Safety and Tolerability of Inhospital Initiation of LCZ696 Compared to Valsartan in HFpEF Patients With Acute Decompensated Heart Failure [ADHF] Who Have Been Stabilized During Hospitalization; NCT03988634) will evaluate the effects of sacubitril/valsartan on changes in natriuretic peptides at 4–8 weeks in HFpEF patients who have been stabilized during hospitalization for acute decompensated HF and initiated sacubitril-valsartan in-hospital or within 30 days post-discharge.

Digoxin

Digoxin is the oldest and one of the least expensive drugs for the management of HF, with a residual role in the management of HFrEF and AF to slow rapid ventricular rate.[17] The Ancillary DIG trial (Ancillary Digitalis Investigation Group) assessed the effect of Digoxin in ambulatory patients in sinus rhythm, with HF and LVEF>45%, compared to placebo. However it failed to show any significant effect on the primary composite endpoint of HF hospitalization or HF mortality.[45]

Ivabradine

The selective sinus node inhibitor ivabradine demonstrated improvements in CV outcomes in HFrEF patients with an LVEF ≤35%, in a sinus heart rate of ≥70 beats per minute who were treated with a BB.[46] The EDIFY (prEserveD left ventricular ejectIon fraction chronic heart Failure with ivabradine studY) randomized placebo-controlled trial tested whether heart rate reduction with Ivabradine could improve diastolic function and exercise capacity and reduce NT-proBNP concentration in patients with HFpEF, but after 8 months of treatment no evidence of improvement was found in any of the three coprimary endpoints.[47]

Nitrates

The comorbidity-driven systemic low-grade proinflammatory state in HFpEF causes endothelial dysfunction with diminished production of Nitric Oxide (NO), which in turn, can result in insufficient stimulation of soluble Guanylate Cyclase (sGC), ultimately leading to a deficiency in cyclic guanosine monophosphate (cGMP) and its dependent protein kinase G (PKG) signaling.[48] The cGMP pathway plays a pivotal role in regulating normal CV function and it is reduced in patients with HF, including those with HFpEF.[48] Initial attempts were made to restore intracellular cGMP signaling directly via nitrate and nitrite administration in the NEAT-HFpEF trial (Nitrate's Effect on Activity Tolerance in Heart

Failure with Preserved Ejection Fraction), using isosorbide mononitrate[49] and in the INDIE-HFpEF trial (Inorganic Nitrite Delivery to Improve Exercise Capacity in Heart Failure With Preserved Ejection Fraction), using inhaled inorganic nitrite,[50] respectively. Both studies failed to improve exercise capacity, with the former also demonstrating a tendency to reduce the total physical activity level objectively measured using an accelerometer. Trials testing oral formulations of inorganic nitrate/nitrite in HFpEF are currently underway (ClinicalTrials.gov: NCT02713126, NCT02840799, and NCT02918552). Reasons behind these negative results may be related to the limits of NO substitution with nitrates (eg, tolerance, pseudo-tolerance, paradoxical endothelial dysfunction), or problems with the inhaled nitrite delivery device.[50]

Phosphodiesterases-5 inhibitors

The Phosphodiesterases-5a (PDE-5a) isoform is known from preclinical studies to metabolize the NO and natriuretic peptide systems' second messenger cGMP.[51] The PDE-5 inhibitor sildenafil in a single-center, randomized, placebo-controlled trial of 44 patients with HFpEF (LVEF ≥50%) and pulmonary hypertension (pulmonary artery systolic pressure > 40 mmHg) was shown to improve hemodynamics at 6 and 12 months as well as QoL measures. The initial improvements reported with sildenafil were not confirmed in the larger multicenter RELAX trial (Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure with Preserved Ejection Fraction) in HFpEF patients with and without pulmonary hypertension.[47,52] These conflicting data had suggested that sildenafil may be effective in selected HFpEF patients with associated pulmonary hypertension. However, a later small trial with sildenafil failed to improve hemodynamic (pulmonary artery wedge pressure, cardiac output) or clinical parameters (peak VO_2) on HFpEF patients with predominantly isolated post-capillary pulmonary hypertension.[53] One possible explanation is that the uncoupling of endothelial NO synthase lies on an inadequate production of endogenous cGMP rather than excessive breakdown by PDE-5. This has led to new therapeutic strategies capable of modulating sGC using direct sGC stimulators that do not require biotransformation and can increase cGMP production in a NO-independent manner.

Soluble guanylate cyclase (sGC) activators

In the phase II dose-finding SOCRATES-PRESERVED study (SOluble guanylate Cyclase stimulatoR in heArT failurE patientS with PRESERVED ejection fraction) [54] vericiguat, an oral soluble sGC activator, did not change the prespecified primary end points of NT-proBNP or LA volume over a 12-week treatment period; however, an exploratory post-hoc analyses showed clinically significant improvements in patient-relevant domains of the Kansas City Cardiomyopathy Questionnaire (KCCQ). These findings led to the design of the recently completed VITALITY-HFpEF randomized placebo-controlled trial (Evaluate the Efficacy and Safety of the Oral sGC Stimulator Vericiguat to Improve Physical Functioning in Daily Living Activities of Patients With Heart Failure and Preserved Ejection Fraction, NCT03547583) to test the hypothesis that Vericiguat improves physical functioning in patients with HFpEF. The results of the trial are yet to be presented.

Iloprost

Iloprost, a synthetic prostacyclin analogue, dilates systemic and pulmonary arterial vasculature, suppresses vascular smooth muscle proliferation, and alters pulmonary vascular resistance when used long-term.[55] The ILO-HOPE (Inhaled Iloprost and Exercise Hemodynamics and Ventricular Performance in Heart Failure with Preserved Ejection Fraction, NCT03620526) is a double-blind, randomized, placebo-controlled trial in which subjects with HFpEF undergo invasive cardiac catheterization with simultaneous expired gas analysis at rest and during exercise, before and 15 min after treatment with either inhaled iloprost or matching placebo. While waiting for the results of this trial, the authors investigated the echocardiographic impact of inhaled iloprost on myocardial performance during exercise in a subgroup of patients already enrolled in the ILO-HOPE.[56] This study demonstrated that nebulized iloprost administered before exercise favorably improved LV systolic function measured by global longitudinal systolic strain (GLS) as well as LV diastolic filling load in terms of E/Strain Rate during isovolumic relaxation and pulmonary pressure estimated through tricuspid regurgitation pressure gradient.[56]

Adenosine A_1-agonists

Neladenoson bialanate is a partial adenosine A_1 receptor agonist that has been shown in preclinical models to improve mitochondrial function, enhance sarco/endoplasmic reticulum 2a activity and optimize energy substrate utilization without the adverse effects of full A_1 receptor agonists or A_1 receptor antagonists.[57] Partial adenosine A_1-receptor agonists can improve mitochondrial function in both skeletal muscle and myocardium, a significant contributor to exercise intolerance in individuals with HFpEF.[58] The two phase 2b trials PANTHEON (A Trial to Study Neladenoson Bialanate Over 20 Weeks in Patients With Chronic Heart Failure With Reduced Ejection Fraction) and PANACHE (Partial AdeNosine A1 receptor agonist in patients with Chronic Heart failure and preserved Ejection fraction) conducted to investigate the potential benefit of this drug in humans with HFrEF and HFpEF respectively[58] failed to improve clinical outcomes in HFrEF[59] and exercise capacity in HFpEF.[60]

SGLT2-inhibitors

Large clinical trials involving patients with type 2 diabetes mellitus have shown that sodium–glucose cotransporter 2 (SGLT2) inhibitors (dapaglifozin, empaglifozin and canaglifozin) reduce hospitalizations for HF with also a reduced all-cause mortality and cardiovascular death with empagliflozin and trends towards similar reductions with canagliflozin.[61–63] Post-hoc analysis of these trials also suggested greater benefit in reducing HF events in HFrEF population[64,65]. These beneficial effects were observed early after randomization, suggesting that the possible mechanisms of action may be different from those usually postulated to explain the CV benefits of glucose-lowering therapies.[66,67] They promote osmotic diuresis and natriuresis and related favorable hemodynamic consequences on myocardial and renal function, but without activating the RAAS.[68]SGLT-2 inhibitors also interact with the sodium-hydrogen exchanger that in the kidneys may help overcome the typical diuretic resistance observed in HF. In the myocardium, this ion pump is involved in processes such as hypertrophy, fibrosis, remodeling and systolic dysfunction.[69] In addition, other metabolic effects related to myocardial energetics and endothelial function have been proposed.[70]

The DAPA-HF trial (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) prospectively evaluated the safety and efficacy of the SGLT2 inhibitor dapagliflozin compared to placebo in patients with established HFrEF. Dapagliflozin reduced the risk of worsening HF or death from CV causes, even in patients without type 2 diabetes mellitus. Dapagliflozin also improved QoL of HF measured by the KCCQ,[71] two trials are currently evaluating dapagliflozin in HFpEF: the DELIVER (Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure, NCT03619213) and EMPEROR-PRESERVED (EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction, NCT03057951) studies will respectively test whether Dapaglifozin and Empaglifozin are able to reduce CV death or HF events in these individuals, irrespective of diabetes. On the other hand, preliminary results from the EMPERIAL-reduced (ExeRcise Ability and Heart Failure Symptoms, In Patients With Chronic HeArt FaiLure With Reduced Ejection Fraction (HFrEF) [NCT03448419]) and the EMPERIAL-preserved (ExeRcise Ability and Heart Failure Symptoms, In Patients With Chronic HeArt FaiLure With Preserved Ejection Fraction (HFpEF) [NCT03448406]) showed no improvements in exercise ability measured by the 6MWD in both HFrEF and HFpEF patient populations after 12 weeks of Empaglifozin administration.[72] Another trial (Dapagliflozin in PRESERVED Ejection Fraction Heart Failure; PRESERVED-HF

[NCT03030235]) is evaluating the effects of dapagliflozin on quality of life as well as 6MWD.

Anti-inflammatory drugs

Interleukin-1 (IL-1) is a cytokine with a prominent role in fever and systemic inflammation.[73] Early investigations demonstrated that IL-1 has systolic cardiodepressant properties, induces CI[74] and impairs diastolic function, through modulation of sarcoplasmic reticulum phospholamban and calcium-ATPase.[75,76] Recently, in the D-HART2 trial (Diastolic Heart Failure Anakinra Response Trial 2), anakinra, a recombinant IL-1 receptor antagonist, for 12 weeks, was shown to reduce the systemic inflammatory response, as shown by reduced C-reactive protein (CRP) levels but, failed to improve aerobic exercise capacity or ventilatory efficiency in patients with HFpEF.[77] These data are in contrast with the previous favorable outcomes of the pilot study D-HART (Diastolic Heart Failure Anakinra Response Trial)[78] and may be explained, at least in part, by the limited power of the study and the presence of non-cardiac factors (i.e., obesity) that severely limited exercise capacity and blunted the potential beneficial effects of anakinra.[77] Of note, despite the lack of improvement in aerobic capacity and ventilatory efficiency, anakinra was associated with favorable trends in the reduction in NT-proBNP levels, changes in exercise time and improvements in QoL measures. Whether IL-1 blockade with anakinra or other agents similarly targeting IL-1 pathway will be clinically valuable in the treatment of patients with HFpEF requires further and larger clinical studies.

Anti-fibrotic drugs

Similarities between idiopathic pulmonary fibrosis (IPF), in which repetitive lung injury can promote the over-production of fibrotic mediators and an excessive extra-cellular matric deposition, and HFpEF, in which comorbidities cause a systemic pro-inflammatory state followed by microvascular endothelium dysfunction and collagen deposition, has led to hypothesize a beneficial effect of anti-fibrotic drugs used in IPF on cardiac outcomes.[79] Pirfenidone and nintedanib have been tested in two large phase III trials in IPF, the ASCEND (Efficacy and Safety of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis) and INPULSIS (Safety and Efficacy of BIBF 1120 at High Dose in Idiopathic Pulmonary Fibrosis patients), respectively, both demonstrating slowing of disease progression, with a generally acceptable side-effect profile[80,81]: the former acts through inhibition of TGF-β-stimulated collagen synthesis,[82] the latter is an antagonist of vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF) and platelet derived growth factor (PDGF) receptors.[83] Pirfenidone is currently being tested in the PIROUETTE phase 2 study enrolling HFpEF patients (PIRfenidOne in patients with heart failUre and preserved lEfT venTricular Ejection fraction, NCT02932566).

Iron supplementation

Iron deficiency is a common comorbidity affecting approximately 50% of both HFrEF and HFpEF patients, irrespective of the presence of anemia,[84] and it is associated with worse exercise capacity and functional outcomes with inconsistent results in terms of improved hospitalization or mortality.[85] Given that oral absorption is limited and many patients may experience gastrointestinal intolerance, intravenous iron supplementation is being currently evaluated in the FAIR-HFpEF trial (Effect of IV Iron in Patients with Heart Failure with Preserved Ejection Fraction, NCT03074591) to find if there is a beneficial effect regarding exercise capacity as assessed with 6MWD test.

Non-pharmacological treatments

Nonpharmacological therapeutics remain, to date, the most effective therapeutics in this population, at least with regards to exercise capacity and QoL. Long-term clinical effects are, however, largely unknown.

Lifestyle interventions

Low fitness level, physical inactivity and obesity are strongly associated with risk of developing HF over time and with structural cardiac abnormalities (i.e. LV stiffness) more typical of the HFpEF phenotype.[12,86–89] Of note, the risk of HF associated with physical inactivity is consistent across all BMI categories, suggesting additive effects of obesity and physical inactivity.[90]

The prognostic role of physical activity levels remains in patients with established HFpEF. In a secondary analysis of the ALDO-DHF (Aldosterone Receptor Blockade in Diastolic Heart Failure) trial the investigators observed that whereas the amount of overall physical activity was associated with 6MWD and QoL, only higher amounts of intense physical activity were significantly associated with higher levels of peak oxygen consumption (VO_2).[91]

In most clinical trials in HFpEF, overweight and obesity are present in >80% of patients and significantly contribute to exercise intolerance. Importantly, increased BMI has been recently proposed to be a much stronger predictor for HFpEF compared to HFrEF.[88,92,93] Despite obesity being a major risk factor for HFpEF, in patients with established HF, obese patients have a short-term and medium-term improved prognosis compared with the leaner counterparts. This phenomenon is known as 'obesity paradox' and may be, at least in part, due to the inaccuracy of the BMI in characterizing the severity of obesity.[94–96]

The strong association between low fitness, physical inactivity, obesity and risk of HFpEF propose a central role for lifestyle interventions aimed at improving exercise capacity first, and possibly improving clinical outcomes.[97] Supervised exercise training has been shown to improve exercise capacity and QoL in patients with HFpEF, but this was not associated with any major changes in LV diastolic or systolic function, thus suggesting extra-cardiac mechanisms responsible for this benefit (e.g. improved O_2 muscle extraction and/or utilization).[98] Intentional weight loss has been shown to have significant favorable impact in patients with HFpEF,[99] and has been shown to also improve hemodynamics in patients without frank HF.[100]

Of note, recent data also suggest that improvements in quality of diet, such as increased consumption of foods rich in unsaturated fatty acids, independent of caloric intake, may also improve exercise capacity in HFpEF.[101,102] The combined approach of exercise training and intentional weight loss was evaluated by Kitzman et al. in a randomized controlled trial that highlighted an additive beneficial effect of combination therapy on exercise capacity obtaining a 17.5% improvement in peak VO2 (joint effect, 2.5 mL/kg/min) versus <10% improvement in peak VO2 with exercise training and diet used alone (respectively 1.2 mL/kg body mass/min and 1.3 mL/kg body mass/min).[103]

More recently, the Training HF trial (Inspiratory Muscle Training and Functional Electrical Stimulation for Treatment of Heart Failure With Preserved Ejection Fraction) demonstrated that rehabilitation strategies such as inspiratory muscle training and functional electrical stimulation were effective in improving exercise capacity (measured as peak VO_2) and QoL (assessed through the Minnesota Living with Heart Failure Questionnaire) in HFpEF subjects. No sizable changes were found for the echocardiographic indices of diastolic impairment tested as secondary endpoints.[104]

An understanding of the mechanisms underlying the protective effect of physical activity and weight loss are still incomplete but would allow the design of more precisely targeted physical activity programs, dietary approaches or drugs that promote weight loss or reproduce the effects of exercise training. In conclusion, a healthy diet and an active lifestyle intervention in the form of increased physical activity and/or exercise training should be encouraged as the background-therapy of almost every patient with HFpEF, especially given their positive extra-cardiac beneficial impact, ultimately resulting in improved exercise capacity.

Interventional and device therapies

Acknowledging that we are currently unable to target the numerous biological altered pathways in HFpEF with effective pharmacologic

treatments, several interventional alternatives and devices discussed below have been explored to counteract the resulting mechanical (mal)adaptations in HFpEF.

Inter-atrial shunts. Interatrial shunts reduce the elevated LA pressure through creation of an iatrogenic inter-atrial passage. Currently, promising devices designed for this purpose and whose safety has been validated in preliminary studies are the V-Wave®[105] and the IASD® (InterAtrial Shunt Device).[106] In the REDUCE LAP-HF I (Reduce Elevated Left Atrial Pressure in Patients with Heart Failure I) sham controlled trial 44 patients with EF ≥40% were randomized to the IASD® and control group; those who received the device had a significantly greater reduction of pulmonary capillary wedge pressure during exercise after 1 month.[107] The increase in pulmonary blood flow and O_2 content following septostomy is associated with improvements in pulmonary vascular function in patients with HFpEF, particularly improvements in pulmonary artery compliance[108]. The ongoing RCT REDUCE LAP-HF II (Reduce Elevated Left Atrial Pressure in Patients with Heart Failure II, NCT03088033) will address the effects of the IASD® device on the composite primary endpoint of CV mortality, ischemic stroke, HF hospital admissions and change in baseline KCCQ at 12 months.

LV expanders. The LV device CORolla® aims to improve LV diastolic function, LV filling and LA pressure through a direct internal self-expansion. An ongoing trial (CORolla® TAA for Heart Failure with Preserved Ejection Fraction and Diastolic Dysfunction, NCT02499601) enrolling 10 patients will try to demonstrate the safety and feasibility of the CORolla® device during 12 months follow-up in patients with HFpEF and NYHA class III/IV.

Left atrial pacing. Recent echocardiographic studies suggest that HFpEF patients present with an increased intra-atrial dyssynchrony and reduced LA diastolic and systolic function compared with normal patients,[109] supporting the so-called "atrial hypothesis". In a pilot study by Laurent et al. a lead was inserted in the coronary sinus for active LA pacing in six patients with HFpEF NYHA III/IV and evidence of atrial dyssynchrony, under optimal medical treatment. After 3 months of pacing, there was a significant improvement in 6MWD and in echocardiographic parameters (longer mitral A wave and smaller E/A and E/e' ratio).[110] Inactivation of pacing for 1 week led to a significant reduction in the 6MWD, with an on/off response. These novel beneficial effects await confirmation in the randomized, controlled, crossover 'LEAD' study (LEft Atrial Pacing in Diastolic Heart Failure, NCT01618981).

Rate adaptive pacing. CI plays a key role in limiting exercise reserve in HFpEF patients and therefore targeting the chronotropic response may provide benefit in this population[12,111] and 2 actively recruiting clinical trials are currently testing this idea. RAPID-HF (Rate-Adaptive Atrial Pacing In Diastolic Heart Failure, NCT02145351) aims to determine whether rate adaptive atrial pacing using a dual-chamber pacemaker in HFpEF subjects with established CI can improve VO_2 at ventilatory anaerobic threshold as a measure of exercise capacity. In the PREFECTUS study (Cardiac Resynchronisation Therapy Versus Rate-responsive Pacing in Heart Failure With Preserved Ejection Fraction, NCT03338374), 10 patients with HFpEF and CI will undergo implantation of a biventricular pacemaker: the device will be initially programmed to normal dual-chamber rate adaptive pacing for 12 weeks and then cardiac resynchronization therapy (CRT) function will be added for another 12 weeks. At each stage diastolic and systolic echocardiographic parameters will be measured to detect changes from baseline and possible incremental benefit of CRT on the background of rate adaptive pacing.

Furthermore, Cardiac Contraction Modulation (CCM) is a pacemaker-like therapy, consisting of an implantable pulse generator with a rechargeable battery that delivers CCM signals, and an atrial and 2 ventricular pacing leads that applies nonexcitatory electrical signals to the right ventricular septum during the absolute refractory period. The prospective, multicenter, single arm, open-label 24-week exploratory study CCM-HFpEF (CCM in Heart Failure with Preserved Ejection Fraction, NCT03240237) is currently evaluating this device therapy in subjects with EF ≥50%, with KCCQ change from baseline as primary endpoint.

Pericardiectomy. A component of the increase in filling pressure in HFpEF may not be related to alterations in ventricular diastolic properties but rather mediated by external pericardial restraining effects due to the contact pressure exerted by the pericardium and right heart.[112]

There is evidence from animal models with hemodynamic features of HFpEF that pericardiectomy or just minimally-invasive resection of the anterior pericardium substantially mitigates the elevation in LV filling pressures with volume loading.[113] In a human pilot study, Borlaug et al. demonstrated that surgical pericardiotomy substantially attenuates the increase in LV filling pressures that develops during volume loading in humans with risk factors for HFpEF and no pericardial disease,[114] and this strategy is currently being tested in patients with clinical HFpEF (NCT03923673). Further studies are warranted to determine if this method is safe and produces benefits sustained over time.

Phenotyping treatment for HFpEF

Therapeutic futility in HFpEF may be, at least in part, explained by the phenotypic diversity within the HFpEF population (Fig. 3). The potential benefit of some interventions could have been diluted in an "unselected" HFpEF population or offset by conjunctive non-effective strategies. In the last years, many attempts in phenotyping HFpEF have been made by stratifying HFpEF patients on the basis of associated comorbidities (e.g. obesity, diabetes, coronary artery disease, AF, arterial hypertension),[115] by combing comorbidities with the principal clinical presentation (e.g. lung congestion, right heart failure/pulmonary hypertension, AF, skeletal muscle weakness),[115] however with some obvious and inevitable overlaps. Recently, new sophisticated machine-learning techniques from independent dataset have been used to identify complex phenotypes using multi-dimensional data based on aggregate features, relationships and interactions, where individuals sharing similar characteristics are intersected in varied combinations to identify groups with similar clinical profile and adverse cardiovascular outcome.[116–118] However, machine learning-based approaches by using the same technology led to different results and, without incorporating underlying clinically based a-priori assumptions, the collection of features without known physiologic basis may not be clinically useful for developing future therapeutic approaches. Whatever this approach may be useful to design future trials to tailor personalized therapies in specific HFpEF phenotypes requires, therefore, further investigation.

Controversies and future directions

To date, pharmacological therapies have shown to be ineffective in reducing CV mortality in HFpEF patients, as well as exercise capacity. On the other hand, nonpharmacologic strategies such as exercise training, caloric restriction-induced weight loss and improvement in quality of diet may offer new prospective treatment and hopes for HFpEF.

Far from being only a primitive heart disease, HFpEF has to be considered a heterogenous systemic condition involving the heart with different comorbidity profiles; this accounts at least in part for the failure of recent "one size fits all" attempts and points towards the necessity of developing precision medicine based approaches that will target specific HFpEF phenotypes in future clinical trials and consequently in therapeutic strategies.[6]

Furthermore, HFpEF is associated with an impaired QoL, disabling symptoms and a high risk of hospitalization, but with a lower rate of CV death than HFrEF.[4] Due to the relatively high incidence of non-CV death, it remains to be determined whether interventions will reduce

CV mortality in this cohort of patients, or whether the focus should be more aimed at improving symptoms and QoL and reduce HF hospitalizations.

Conclusions

In conclusion, although HFpEF pathophysiological mechanisms are becoming clearer over the years, there is still no effective treatment. Numerous trials are underway for future successful therapies; in the meantime, we should not forget the importance of preventive strategies and to aggressively address associated comorbidities. To finish with the words of Samuel Beckett: "*Ever tried. Ever failed. No matter. Try again. Fail again. Fail better.*"

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Statement of conflict of interest

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