

Clinical update

New strategies for heart failure with preserved ejection fraction: the importance of targeted therapies for heart failure phenotypes

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The management of heart failure with reduced ejection fraction (HF-REF) has improved significantly over the last two decades. In contrast, little or no progress has been made in identifying evidence-based, effective treatments for heart failure with preserved ejection fraction (HF-PEF). Despite the high prevalence, mortality, and cost of HF-PEF, large phase III international clinical trials investigating interventions to improve outcomes in HF-PEF have yielded disappointing results. Therefore, treatment of HF-PEF remains largely empiric, and almost no acknowledged standards exist. There is no single explanation for the negative results of past HF-PEF trials. Potential contributors include an incomplete understanding of HF-PEF pathophysiology, the heterogeneity of the patient population, inadequate diagnostic criteria, recruitment of patients without true heart failure or at early stages of the syndrome, poor matching of therapeutic mechanisms and primary pathophysiological processes, suboptimal study designs, or inadequate statistical power. Many novel agents are in various stages of research and development for potential use in patients with HF-PEF. To maximize the likelihood of identifying effective therapeutics for HF-PEF, lessons learned from the past decade of research should be applied to the design, conduct, and interpretation of future trials. This paper represents a synthesis of a workshop held in Bergamo, Italy, and it examines new and emerging therapies in the context of specific, targeted HF-PEF phenotypes where positive clinical benefit may be detected in clinical trials. Specific considerations related to patient and endpoint selection for future clinical trials design are also discussed.

Keywords

Heart failure, Diastolic • Clinical trial • Diabetes mellitus • Exercise tolerance • Phenotype • Preserved ejection fraction

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Introduction

Heart failure with preserved ejection fraction (HF-PEF) is a complex syndrome characterized by heart failure (HF) signs and symptoms and a normal or near-normal left ventricular ejection fraction (LVEF). More specific diagnostic criteria have evolved over time and include signs/symptoms of HF, objective evidence of diastolic dysfunction, disturbed left ventricular (LV) filling, structural heart disease, and elevated brain natriuretic peptides (Table 1).^{1–3} However, multiple cardiac abnormalities are often present apart from diastolic LV dysfunction, including subtle alterations of systolic function,⁴ impaired atrial function,⁵ chronotropic incompetence, or haemodynamic alterations, such as elevated pre-load volumes.⁶

Extracardiac abnormalities and comorbidities, such as hypertension, atrial fibrillation, diabetes, renal or pulmonary disease, anaemia, obesity, and deconditioning, may contribute to the HF-PEF syndrome. Low-grade inflammation with endothelial dysfunction, increased reactive oxygen species production, impaired nitric oxide (NO) bioavailability, and the resulting adverse effects on cardiac structure and function are considered a mechanistic link between frequently encountered comorbidities and the evolution and progression of HF-PEF.⁷ The complex pathophysiology of the syndrome is also reflected by ongoing discussion on its terminology. Heart failure with a normal ejection fraction (HFNEF) is preferred over HF-PEF by many authors.¹

Prevention of HF-PEF through treatment of risk factors (e.g. hypertension) is effective,⁸ but once HF-PEF is present, specific treatments are lacking. Drug classes that improve outcomes in heart failure with reduced ejection fraction (HF-REF) have not been similarly beneficial in HF-PEF.^{9–11} There is no single explanation for the negative results of past HF-PEF trials. Potential contributors include an incomplete understanding of HF-PEF pathophysiology, inadequate diagnostic criteria, recruitment of patients without true HF or at early stages of the syndrome, poor matching of therapeutic mechanisms and primary pathophysiological processes, suboptimal study designs, inadequate statistical power, or patient heterogeneity; the latter is possibly the most relevant.¹²

Since novel strategies need to be investigated for the treatment of HF-PEF, this manuscript advocates better phenotyping of patients to target therapies, reviews emerging therapies, and examines the cumulative experience from previous trials to suggest approaches for the design and conduct of future HF-PEF trials.

Heterogeneity of patients with heart failure and preserved ejection fraction: targeting patient subgroups

Heart failure with preserved ejection fraction is difficult to define as illustrated by the various classifications proposed by experts (Table 1) and by disparate inclusion criteria of clinical trials (Table 2); these factors contribute to HF-PEF patient heterogeneity so far recruited into trials and registries. Even for the key diagnostic criterion, LVEF, consensus has not been reached on the optimal cut-off that defines HF-PEF, and different cut-offs have been used across classifications and trials. Debate continues as to whether HF-REF and HF-PEF

Table 1 Diagnostic criteria for heart failure with preserved ejection fraction

	European Study Group on Diastolic Heart Failure ¹	Framingham ²	ESC Guidelines ³
Symptoms or signs	Lung crepitations, pulmonary oedema, ankle swelling, hepatomegaly, dyspnoea on exertion, and fatigue. Distinguish between effort related or nocturnal dyspnoea. Objective evidence of reduced exercise performance includes reduced peak oxygen consumption (<25 mL/kg/min) or 6 minute walking test distance <300 m	Clinical signs and symptoms, supportive laboratory test (e.g. chest X-ray), and a typical clinical response to treatment with diuretics, with or without documentation of elevated LV filling pressure (at rest, on exercise, or in response to a volume load) or a low cardiac index	Symptoms (e.g. breathlessness, ankle swelling, and fatigue) and signs (e.g. elevated jugular venous pressure, pulmonary crackles, and displaced apex beat) typical of HF
LV systolic function	Normal or mildly reduced LV systolic function LVEF >50% and LVEDVI <97 mL/m ²	LVEF ≥ 50% within 72 h of HF	Normal or only mildly reduced LVEF and LV not dilated
Diastolic dysfunction	Evidence of abnormal LV relaxation, filling, diastolic distensibility and diastolic stiffness using invasive haemodynamic measurements, tissue Doppler, or biomarkers (see McMurray et al. ³ for specific values)	Assessment of diastolic function is not needed for probable diagnosis	Relevant structural heart disease (LV hypertrophy/LA enlargement) and/or diastolic dysfunction

Table 2 Heterogeneity in heart failure with preserved ejection fraction in recent registries or trials

	ADHERE ¹³	OPTIMIZE ¹⁴	Swedish HF Registry ¹⁵	DIG ¹⁶	PEP-CHF ¹⁰	CHARM-Preserved ¹¹	I-Preserve ^{9,17}	Aldo-DHF ¹⁸	PARAMOUNT ¹⁹	RELAX ²⁰	TOPCAT ⁷²	IN-HF Registry ²¹
Definition	LVEF ≥ 40%	LVEF > 50%	Clinician judged HF with LVEF ≥ 40%	LVEF > 45%	At least three of nine clinical criteria and two of four echo criteria as specified in the protocol (roughly equivalent to LVEF between 40 and 50%)	LVEF > 40, NYHA class II–IV for a least 4 weeks, and a history of cardiac hospitalization	LVEF ≥ 45%, hospitalized for HF during previous 6 months and have current NYHA class II–IV symptoms with corroborative evidence (if no previous hospitalization then only NYHA class III–IV allowed)	LVEF ≥ 50, echo evidence of ≥ grade 1 diastolic dysfunction Objective evidence of exercise intolerance (spiroergometry)	LVEF ≥ 45%, documented history of HF with signs or symptoms. NT-proBNP > 400 pg/mL, on diuretics	LVEF ≥ 50%, NYHA class II–IV, objective evidence of HF, peak VO ₂ ≤ 60% of normal (adjusted for age and sex) with respiratory exchange ratio (RER) ≥ 1.0 and NT-proBNP ≥ 400 pg/mL or if NT-proBNP < 400 pg/mL then mean PCWVP > 20 mmHg rest (or > 25 mmHg with exercise)	≥ 50 years of age, have HF signs and symptoms, LVEF ≥ 45% within 6 months prior to randomization, systolic blood pressure, 140 mmHg (or ≤ 160 mmHg and on ≥ 3 antihypertensive medications), serum potassium < 5 mmol/L, and either a hospitalization within 1 year before randomization with HF management being a major component (not adjudicated) or BNP ≥ 100 pg/mL or NT-proBNP ≥ 360 pg/mL within 60 days before randomization. Specific criteria for diastolic dysfunction are not required	LVEF ≥ 50%
n	26 322	10 072	16 216	988	850	3,023	4,128	422	301	216	3445	377
Age, mean (SD)	73.9 ± 13.2	75.6 ± 13.1	74 ± 11	67	75	67	72	67 ± 8	71	69	68.7	75 ± 11
Women (%)	62	68	46	41	57 placebo, 54 perindopril	40	60	52	57 LCZ696, 56 valsartan	48	51.6	60
LVEF %, mean (SD)	NR	61.8 ± 7	LVEF 40–49%: 49% LVEF ≥ 50%: 51%	55	64 placebo, 65 perindopril	54	60 placebo, 59 irbesartan	67 ± 8	58	60 (median)	56 (median) 51–61 (IQR)	58.3 ± 6.9
BMI, mean, kg/m ²	NR	Median weight 78 kg	NR	NR	27.6	29	29.7	28.9 ± 3.6	30	32.9 (median)	31 (median)	29.0 ± 6.5
NT-proBNP, median (IQR), pg/mL	NR	BNP 601.5 (320, 1190)	1840 (780–4148)	NR	453 (206–1045) placebo; 335 (160–1014) perindopril	NR	320 (131–946) placebo; 360 (139–987) irbesartan	158 (83–299)	828 (460–1341) LCZ696; 939 (582–1490) valsartan	700 (283–1553)	887	NR
Hypertension, %	77	77	52	58 placebo, 62 digoxin	79	88	92	95 LCZ696, 92 valsartan	85	91 spironolactone, 91.9 placebo	70.3	
Ischaemic Heart Disease, %	50	32	44	56	26	65	History of MI: 23 placebo, 24 irbesartan	40	History of MI: 21 LCZ696, 20 valsartan	39	57.4 spironolactone, 60.1 placebo	NR
Atrial fibrillation, %	21	32	52	0	22 placebo, 19 perindopril	29	29	40 LCZ696, 45 valsartan	51	35.5 spironolactone, 35.1 placebo	52.5	
Diabetes, %	45	16 (insulin) 25 (non-insulin)	24	30 placebo, 27 digoxin	20 placebo, 21 perindopril	28	27 placebo, 28 irbesartan	17	41 LCZ696, 35 valsartan	43	32.8 spironolactone, 32.2 placebo	39
Pulmonary hypertension, %	NR	NR	NR	NR	NR	NR	NR	NR, chronic obstructive pulmonary disease 3%	NR	NR, chronic obstructive pulmonary disease 19	NR	NR
Renal impairment, %	26	Median SCr 1.5 mg/dL	Mean CrCl: 67 ± 34 mL/min	52 placebo, 48 digoxin	NR	NR	30 placebo, 31 irbesartan	Mean eGFR 79 ± 19 mL/min/1.73 m ²	Mean eGFR 67 LCZ696, 64 valsartan (mL/min per 1.73 m ²) eGFR < 60: 38% LCZ696, 45% valsartan	Median GFR 57	Median eGFR 65.3 mL/min/1.73 m ²	25.2

Continued

Table 2 Continued

	ADHERE ¹³	OPTIMIZE ¹⁴	Swedish HF Registry ¹⁵	DIG ¹⁶	PEP-CHF ¹⁰	CHARM-Preserved ¹¹	I-Preserve ^{9,17}	Aldo-DHF ¹⁸	PARAMOUNT ¹⁹	RELAX ²⁰	TOPCAT ⁷²	IN-HF Registry ²¹
Anaemia, %	NR	Median Hb 11.8 g/dL	Mean Hb 13.1 g/dL	NR	NR	NR	13 placebo, 12 irbesartan	Mean Hb 13.8 ± 1.2 g/dL	NR	35	Median Hb 13.2 g/dL	48.7 (Hb <12 g/dL)
Clinical outcomes	In-hospital mortality: 2.8%	In-hospital mortality: 2.9%	Propensity score-matched all-cause mortality (for renin-angiotensin system antagonist yes vs. no)	Mean 37 months: 23% all-cause mortality	1 year: Death or hospitalization 65% vs. 46%	36.6 months: CV death or HF hosp: 22% vs. 24%	49.5 months: all-cause death or CV hosp: 36–37%	Placebo vs. spironolactone (mean f/u 11.6 months)	Not powered to assessed clinical outcomes, but select serious adverse events include:	Death at 24 weeks, (placebo vs. sildenafil): 0 vs. 3%, P = 0.25	Primary composite of CV death, aborted cardiac arrest, or HF hospitalization spironolactone 18.6% vs. placebo 20.4%, HR 0.89, 95% CI 0.77–1.04, P = 0.14	30-day mortality 4.5%, 90 day mortality 9.6%, 1 year mortality 19.6%
		Post-discharge (60–90 days): 9.2%	HR 0.91 (95% CI: 0.85–0.98), P = 0.008					Death 0 vs. 1	Death: 1% LCZ696, 1% valsartan	Hospitalization for CV or renal cause: 13% vs. 13%, P = 0.89		
								Hospitalization 24% vs. 28%	Heart failure: 3% LCZ696, 4% valsartan			
								CV hosp: 7 vs. 10% Non-CV hosp: 18 vs. 22%				
Hospitalization for HF											Spironolactone 12% vs. placebo 14.2%, HR 0.83, 95% CI 0.69–0.99, P = 0.04	
Study Limitations	Observational study, non-randomized study	Observational, non-randomized study	Non-randomized study	Patients defined only by LVEF >45%, assessed by various methods	High crossover rate	Trend towards benefit on hospital admissions, but not CV mortality, but confidence intervals wide. Longer treatment and/or follow-up might be needed	High rate (34%) study drug discontinuation; high rate of concomitant ACE-inhibitor use (39–40%) and spironolactone use (28–29%)	Patients were generally stable with mild-to-moderate symptoms,	Phase 2, short-term treatment and follow-up, and change in BNP as the primary outcome measure	Results raise hypothesis that significant pulmonary arterial hypertension or right ventricular failure might be needed to show a treatment effect with this intervention; these characteristics were not highly prevalent in RELAX; possibly inadequate dosing or duration of therapy; greater number of sildenafil patients could not perform exercise testing which may have biased results	Marked regional variation in event rates. Primary composite endpoint significantly reduced in patients from America. Significant interaction of treatment effect with recruitment strategy.	Observational, non-randomized study

represent distinct disease entities, or similar processes along one disease continuum.^{22–25} In fact, recent data suggest that LVEF may decline over time even in patients with HF-PEF.²⁶ This issue becomes even more apparent when patients within the ‘grey zone’ of LVEF (i.e. 40–50%) are considered. To avoid mixing overt systolic dysfunction and HF-PEF, a higher threshold (LVEF \geq 50%) should be used for future clinical trials. Others have argued that the syndrome referred to as HF-PEF represents either normal ageing, or vascular and renal dysfunction.^{23,27}

Irrespective of specific diagnostic criteria and cut-offs, HF-PEF is a syndromal disease where multiple cardiac and vascular abnormalities, cardiovascular risk factors, and overlapping extracardiac comorbidities may be present in various combinations (Figure 1).

In many disciplines of medicine, targeted therapy is the key to success. For example, breast cancer or haematological disorders use phenotyping strategies that include genetic testing, novel biomarkers, or histology for matching specific therapies to patient subgroups. Matching treatment strategies to a specific patient’s phenotype in HF-PEF is a promising approach that warrants testing in clinical trials and may increase the likelihood of demonstrating clinical benefit (Figure 2). Targeting specific phenotypes instead of following the ‘one-size-fits-all’ approach becomes increasingly important in light of several failed, non-targeted, large-scale HF-PEF trials.

Targeting the diastolic dysfunction phenotype

Diastolic dysfunction is a dominant feature in many HF-PEF patients, and many factors contribute to diastolic dysfunction, including both vascular and myocardial stiffening. Generalized stiffening that occurs throughout the cardiovascular system due to ageing or comorbidities interferes with the forces that are normally

developed during systole that produce ventricular suction, and thus, reduces early diastolic filling. Left ventricular diastolic dysfunction may be related to extracellular matrix changes, changes in intrinsic myocyte stiffness, microvascular dysfunction, and metabolic abnormalities.

Modulation of myocyte passive diastolic stiffness

Alterations within myocytes increase their intrinsic diastolic stiffness. Titin is a giant cytoskeletal structural protein expressed in sarcomeres that functions as a molecular ‘spring’, storing energy during contraction and releasing this energy during relaxation. Stiffer titin increases diastolic myocyte stiffness. The expression of titin isoforms differs between patients with HF-REF and HF-PEF, with a lower ratio of the compliant (N2BA) isoform to the stiff (N2B) isoform in patients with HF-PEF.²⁸ Phosphorylation of the N2B isoform by protein kinase A or protein kinase G (PKG) decreases cardiomyocyte resting stiffness.^{28–33} Protein kinase G is activated by cyclic guanosine monophosphate (cGMP); therapies that increase cGMP may decrease myocardial diastolic stiffness in HF-PEF. This observation provides a compelling rationale to pharmacologically modulate this pathway in HF-PEF patients (Figure 3).³⁴ Cyclic guanosine monophosphate levels can be increased by preventing breakdown (PDE5 inhibitors) or stimulating their production (cGMP stimulators). In fact, orally active soluble guanylate cyclase (sGC) stimulators (e.g. riociguat) have been developed, and both approaches are under clinical testing (Table 3).

Phosphodiesterase-5 inhibition

Cyclic guanosine monophosphate is catabolized by phosphodiesterases, and phosphodiesterase-5 (PDE5) inhibitors prevent the hydrolysis of cGMP, thereby indirectly raising cGMP levels. It has been hypothesized that PDE5 inhibitors may improve diastolic function

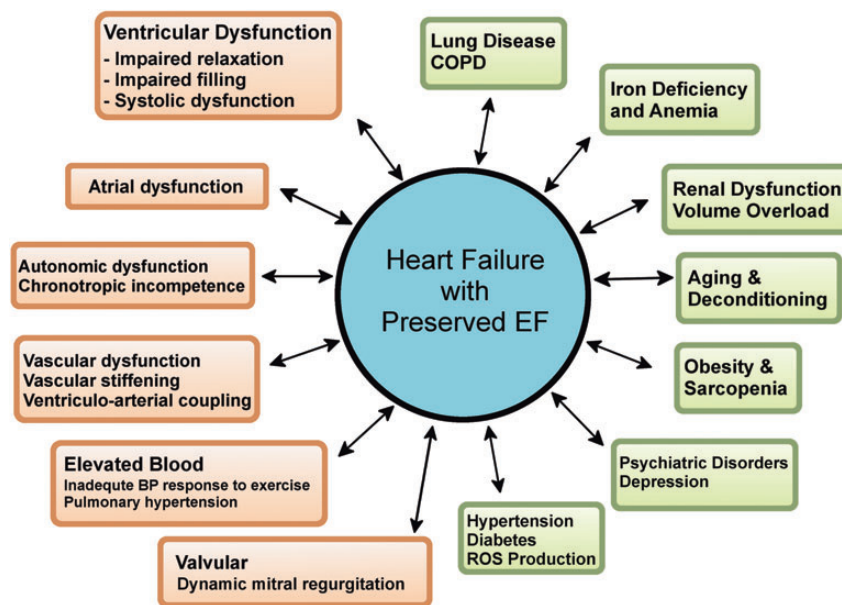
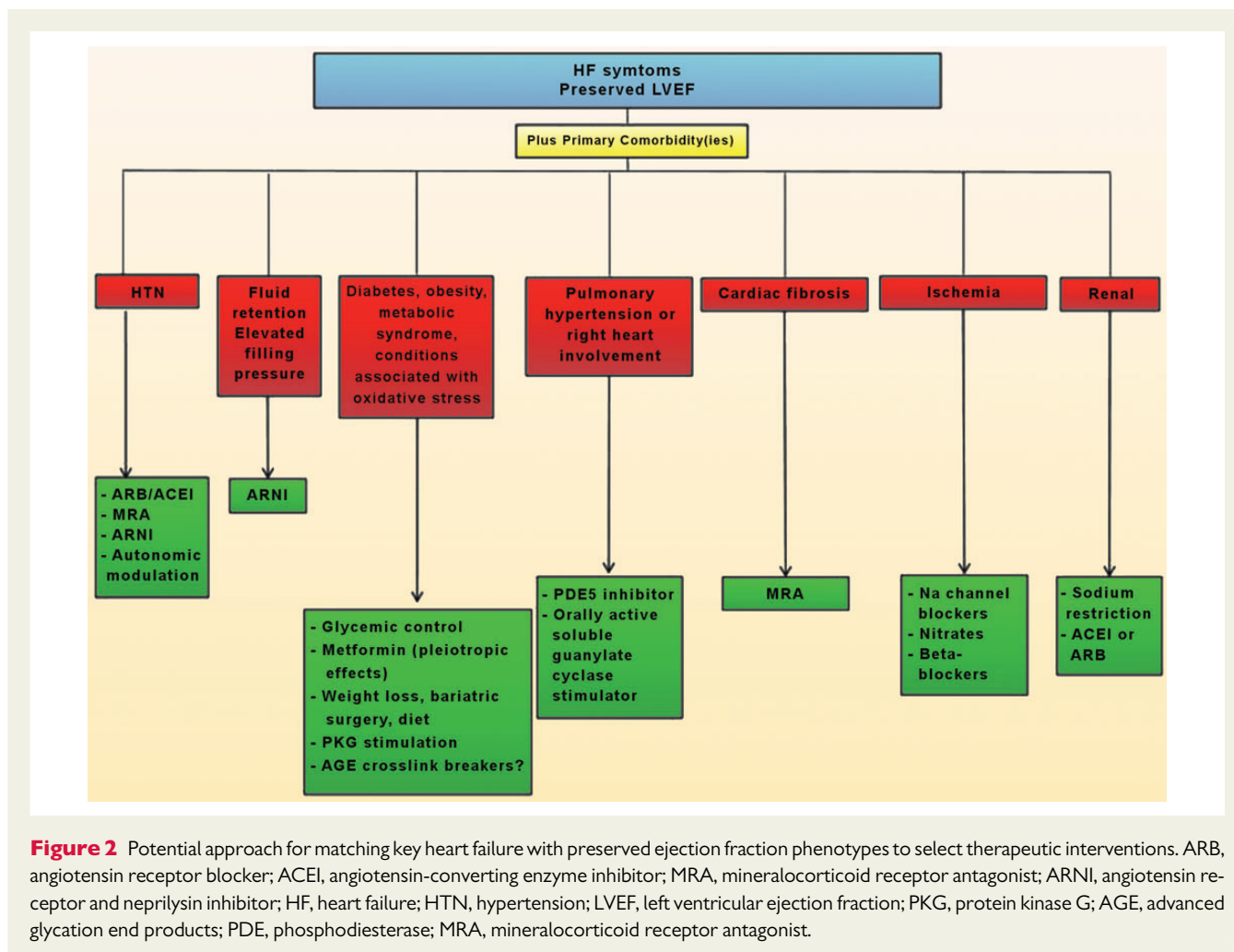


Figure 1 Heterogeneity of the heart failure with preserved ejection fraction syndrome. BP, blood pressure; COPD, chronic obstructive pulmonary disease; EF, ejection fraction.



through PKG-mediated regulation of titin stiffness.^{28,31,35} Sildenafil reduced LV wall thickness, LV mass index (LVMI), deceleration time, isovolumic relaxation time, and the E/e' ratio compared with placebo in a study of 44 patients with pulmonary hypertension, recent new onset dyspnoea, and LVEF $\geq 50\%$.³⁶

The PDE5 inhibition to Improve Clinical Status and Exercise Capacity in Diastolic Heart Failure (RELAX) study enrolled 216 patients with New York Heart Association (NYHA) class II–IV HF and LVEF $\geq 50\%$.^{20,37} Patients were randomized to matching placebo or sildenafil 20 mg three times daily for 12 weeks followed by 60 mg three times daily for 12 weeks. The primary endpoint was the change in peak VO_2 .^{20,37} Median baseline values of peak VO_2 and 6-minute walk distance were 11.7 mL/kg/min and 308 m, respectively. The patients had evidence of chronically elevated LV filling pressures at baseline (median E/e' 16, left atrial volume index 44 mL/m², and pulmonary artery systolic pressure 41 mmHg). After 24 weeks, no significant differences between the sildenafil and placebo group were observed in the median change in peak VO_2 , 6-minute walk distance, or the mean clinical rank score.²⁰ The reasons for the contradicting results of PDE5 inhibition in HF-PEF are not fully understood, but may include differences in patient populations and recruitment of patients with phenotypes not amenable to PDE5 inhibitor therapy. In addition, preventing breakdown in a situation where cGMP

levels are intrinsically low due to insufficient generation may result in little effectiveness in this hypothetical subset of patients.

Although PDE5 inhibition was not effective in RELAX, increasing cGMP levels might be of value in treating other features of HF-PEF. In line with reduced production of cGMP, possibly related to impaired NO-dependent guanylate cyclase stimulation, orally active sGC stimulators have been developed. The ongoing phase II dose-finding study SOCRATES will test the effects of a new once-daily sGC stimulator in 478 prospectively randomized HF-PEF patients (NCT01951638). The RELAX experience adds more evidence to the hypothesis that specific phenotyping and identification of a primary pathophysiology that can be pharmacologically targeted might be key to finding successful treatments for HF-PEF.

Late sodium current inhibition

Increased cytosolic calcium (Ca^{2+}) during diastole is another potential mechanism of HF-PEF pathophysiology. In the setting of ischaemia or HF, increases in late sodium (Na^+) currents occur during the myocyte depolarization process. This increase in Na^+ influx leads to elevated intracellular Na^+ , thereby resulting in excess Ca^{2+} during diastole via $\text{Na}^+/\text{Ca}^{2+}$ exchanger, with attendant impaired relaxation.^{38–41}

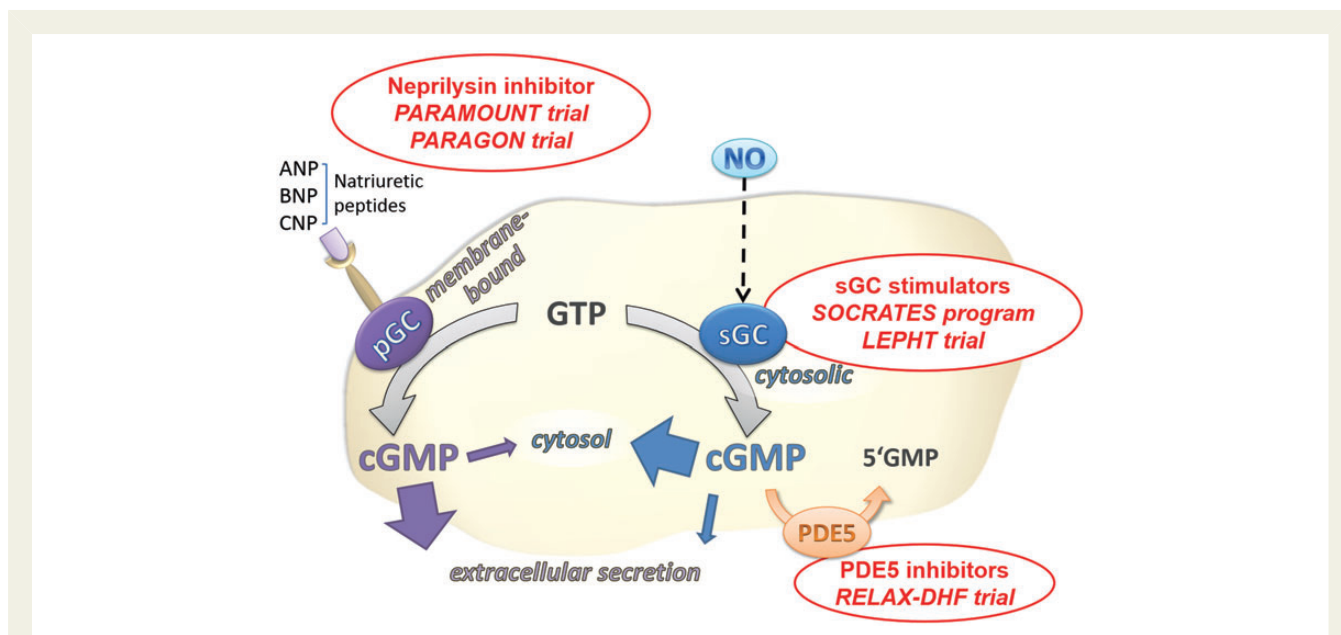


Figure 3 Role of the nitric oxide–cyclic guanosine monophosphate–protein kinase G pathway in the cardiomyocyte. Cardiomyocyte signalling pathways involved in regulating cardiac titin stiffness. ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; CNP, c-type natriuretic peptide; NO, nitric oxide; PDE5, phosphodiesterase-5; pGC, particulate guanylyl cyclase; sGC, soluble guanylyl cyclase. Adapted with permission from the *Journal of Molecular and Cellular Cardiology* 2009;46:490–498.

Ranolazine inhibits the increased late Na^+ current, a mechanism that may minimize intramyocyte Na^+ accumulation and the resultant Ca^{2+} overload. Reduced diastolic tension was observed in failing human heart ventricular tissue after exposure to ranolazine.⁴¹ Ranolazine improved diastolic function in non-infarcted ischaemic myocardium,⁴² in isolated myocardium from failing human hearts,⁴¹ and in chronic stable angina.⁴³ It is hypothesized that ranolazine may have similar effects in HF-PEF, a condition associated with substantial alterations of the microcirculation even in the absence of coronary artery stenosis.

The Ranolazine for the Treatment of Diastolic Heart Failure (RALI-DHF) study was a proof-of-concept trial that evaluated the effect of ranolazine vs. placebo on haemodynamics, measures of diastolic dysfunction, and biomarkers in 20 patients with HF-PEF and diastolic dysfunction.⁴⁴ After 30 min of infusion, significant decreases from baseline were observed in LV end-diastolic pressure (LVEDP) and pulmonary capillary wedge pressure (PCWP) in the ranolazine group, but not in the placebo group.⁴⁵ Although invasively determined relaxation parameters and the non-invasive E/e' ratio were unaltered, these limited data justify additional studies of ranolazine in HF-PEF (Table 3).

Targeting fibrosis as a phenotype

Left ventricular fibrosis occurs early in the evolution to HF-PEF and represents a worthy therapeutic target in the syndrome. Fibrosis comprises both the heart and vascular system and impacts on both diastolic and systolic function. Fibrosis will lead to myocardial stiffening, impede both suction and filling, and the loss of early diastolic suction may have major deleterious effects on impaired exercise capacity in HF-PEF.⁴⁶ Fibrosis is mediated by alterations in the amount and composition of collagen within the extracellular matrix.^{47–49}

Collagen synthesis is enhanced in the setting of increased load or activation of the renin–angiotensin–aldosterone system (RAAS).^{47,48} Down-regulation of enzymes that degrade collagen occurs in patients with HF-PEF.^{47,49–52} It is important to note that elevated myocardial collagen is present in many, but not all patients,⁵³ clinical tools to identify it are only evolving in practice settings, and the reliability of serum markers to reflect cardiac processes is uncertain. Nevertheless, recent research has suggested galectin-3 as an emerging biomarker with potential utility in identifying patient subgroups that may specifically respond to anti-fibrotic therapy.⁵⁴

Mineralocorticoid receptor antagonists

Aldosterone mediates vascular and cardiac remodelling. It binds to the mineralocorticoid receptor (MR), stimulates cardiac fibroblasts, and increases collagen synthesis and deposition. These events lead to myocardial fibrosis and increased LV stiffness.^{55–61} Inflammation and oxidative stress are also involved in aldosterone-mediated fibrosis.⁶² Aldosterone stimulates the expression of several profibrotic molecules [e.g. transforming growth factor-1 (TGF-1), plasminogen activator inhibitor-1 (PAI-1), and endothelin-1] that contribute to the pathogenesis of fibrosis.⁶² Animal studies showed that MR antagonists (MRA) prevent collagen synthesis and remodelling.^{63–67} Small studies in HF-PEF patients showed improvement in diastolic dysfunction parameters after treatment with an MRA.^{68,69}

The Aldo-DHF study was a randomized, double-blind, placebo-controlled trial of spironolactone 25 mg/day or placebo in 422 patients with chronic NYHA class II or III HF, LVEF $\geq 50\%$, and grade ≥ 1 diastolic dysfunction.^{18,70} The co-primary endpoint E/e' was reduced in the spironolactone group, whereas it increased from baseline in the placebo group. The difference between groups

Table 3 Select planned or ongoing studies in heart failure with preserved ejection fraction

Trial acronym	Target/intervention	n, Phase	Patient characteristics	Key end-points
FAIR-HFPEF ^a (not yet recruiting)	Iron deficiency: ferric carboxymaltose (i.v. iron)	n = 260, phase II, 24 weeks	NYHA II–III, LVEF > 45, on diuretic, HF hosp < 12 mo OR $E/e' > 13$ OR LAVI > 28 OR NBNP/BNP > 300/100pg/mL	Change in 6-minute walk distance
Mito-HFPEF ^b (not yet recruiting)	Energy deficit: bendavia (mitochondrial enhancer)	n = 42, phase I, acute i.v.	LVEF \geq 45%; $E/e' > 14$ OR $E/e' > 9-14$ and NBNP > 220 pg/mL; exercise-induced increase in E/e' of ≥ 5	E/e' during exercise, dose finding, safety
EDIFY ^c (EUDRA CT 2012 002742-20)	Heart rate: ivabradine (sinus node inhibition)	n = 400, phase II, 8 months	SR, HR > 70, NYHA II–III, LVEF \geq 45%, $E/e' > 13$ OR $e' < 10/8$ OR LAVI > 34, NBNP/BNP \geq 220/80 pg/mL	Co-primary: E/e , NTproBNP, 6-minute walk
Ex-DHF ^d (ISRCTN86879094)	Deconditioning: endurance/resistance training	n = 320, phase I, 12 months	$pVO_2 < 25$, EF ≥ 50 $E/e' > 15$ OR $E/e' > 8 < 15$ and NBNP > 220 pg/mL or Afib	Clinical composite score (Packer score)
OPTIM-EX ^e (NCT02078947)	Deconditioning: high-intensity interval training	n = 180, phase I, 3 months	EF > 50%, NYHA II/III, $E/e' > 15$ OR $E/e' > 8-15$ and NBNP/BNP > 220/80 pg/mL	Peak VO_2 , E/e' , LAVI, NT-pro-BNP
SOCRATES-Preserved ^f (NCT01951638)	cGMP deficiency: vericiguat (soluble guanylate cyclase stimulation)	n = 470, phase I, 12 weeks	WCHF/i.v. diuretics, EF ≥ 45 ; NBNP/BNP > 300/100 (600/200 in Afib); LAVI ≥ 28	Co-primary: NT-pro-BNP and LAV
PARAGON-HF ^g (NCT01920711)	cGMP deficiency: LCZ696 (neprilysin inhibition)	n = 4300, phase III, up to 57 months	EF $\geq 45\%$, NYHA II–IV, LA enl. or LV hypertrophy; HF hosp. < 9 mo. or elevated NBNP	Composite: CV death and total (recurrent) HF hospitalizations

^aEffect of IV iron (ferric carboxymaltose, FCM) on exercise tolerance, symptoms, and quality of life in patients with heart failure and preserved LV ejection fraction (HFpEF) and iron deficiency with and without anaemia.

^bAn Exploratory Proof of Concept Clinical Pharmacology Study of the Effects of a Single 4 Hour Intravenous Infusion of Bendavia™ (MTP-131) in patients hospitalized patients with heart failure and preserved left ventricular ejection fraction.

^cEffect of ivabradine vs. placebo on cardiac function, exercise capacity, and neuroendocrine activation in patients with chronic heart failure with preserved left ventricular ejection fraction.

^dExercise training in diastolic heart failure, a prospective, randomized, controlled study to determine the effects of exercise training in patients with heart failure and preserved ejection fraction.

^eOptimizing exercise training in prevention and treatment of diastolic heart failure.

^fPhase IIb safety and efficacy study of four dose regimens of BAY1021189 in patients with heart failure and preserved ejection fraction suffering from worsening chronic heart failure.

^gEfficacy and safety of LCZ696 compared with valsartan on morbidity and mortality in heart failure patients with preserved ejection fraction.

LAVI, left atrial volume index (mL/m^2); NBNP, NT-pro-BNP; SR, sinus rhythm; HR, heart rate; Afib, atrial fibrillation; WCHF, worsening chronic heart failure; LA enl., left atrial enlargement.

was statistically significant (-1.5 , 95% CI: -2 to -0.9 , $P < 0.001$). The co-primary endpoint peak VO_2 was not affected by spironolactone. Left ventricular ejection fraction increased, and LV end-diastolic dimension (LVEDD), LVMI, and NT-proBNP significantly decreased from baseline in the spironolactone group, suggesting reverse functional and structural remodelling.¹⁸

The findings from pre-clinical studies and intermediate size clinical trials of MRAs in HF-PEF support the hypothesis that MRAs may improve outcomes in HF-PEF. The NIH-funded phase III Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial tested this hypothesis (Table 2).^{71,72} The TOPCAT trial found that, compared to placebo, spironolactone did not reduce the composite of cardiovascular death, aborted cardiac arrest, or heart failure hospitalization in patients with symptomatic heart failure and a LVEF 45% or greater, although the individual component of heart failure hospitalization was reduced by spironolactone. However, there was a significant interaction between treatment effect and patient recruitment strategy (natriuretic peptides vs. hospitalisation with HF management being a major component), highlighting the importance of patient selection criteria and recruitment of patients with true heart failure and preserved EF for future trials. Novel, non-steroidal, MRAs with greater selectivity than spironolactone and stronger MR binding affinity than eplerenone are currently under clinical development. In the recently presented phase II dose-finding study ARTS [MinerAlocorticoid Receptor Antagonist Tolerability Study (ARTS; NCT01345656)] in HF-REF patients with impaired renal function, BAY 94–8862 had beneficial effects on the cardiovascular system comparable with spironolactone with less renal and electrolyte side-effects.⁷³ New anti-fibrotic therapies with less side-effects may represent an important step towards better management of suitable subgroups of HF-PEF patients.

Other renin–angiotensin–aldosterone system inhibitors

Several studies have evaluated the role of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) for the treatment of HF-PEF, including PEP-CHF,¹⁰ CHARM-preserved,¹¹ or I-Preserve.^{9,17} (Table 2). Improvement in clinical outcomes was not detected among patients randomized to the ACE-inhibitor or ARB in these trials, but the studies were limited by high crossover rates and, in part, insufficient power. Renin–angiotensin–aldosterone system blockers are indicated in the HF-PEF syndrome to control risk factors such as blood pressure and to prevent progression of end-organ damage such as renal dysfunction. In this context, RAAS inhibitors are clearly recommended in major guidelines as baseline therapy for patients with HF-PEF. The recent ACC/AHA 2013 HF guidelines recommend ACE-inhibitors, ARBs, or beta-blockers in hypertensive patients with HF-PEF with the goal of controlling blood pressure (class IIa recommendation, level of evidence C),⁷⁴ but data on beneficial outcome effects beyond risk factor control are inadequate to support recommendations for the use of these agents specifically for the treatment of HF-PEF.

Targeting fluid retention as a phenotype

Elevated filling pressures are the primary haemodynamic abnormality in HF-PEF patients.⁴⁹ Volume overload or congestion may be present, but visible evidence of fluid retention is absent in many patients. Some patients have normal haemodynamics at rest, but

elevated filling pressures with exercise, leading to reduced early diastolic filling and producing HF symptoms.⁷⁵ Elevated atrial pressures may also lead to atrial remodelling, fibrosis, and the development of atrial fibrillation. Atrial fibrillation is common in patients with HF-PEF, and it is associated with worse outcomes. Therapies that chronically reduce atrial pressures and prevent atrial remodelling and fibrosis might reduce the risk of developing atrial fibrillation. Left atrial dysfunction is also common in these patients, and the decline in atrial function in the setting of poor diastolic filling may be a significant contributor to symptoms during exercise. Diuretic therapy is generally recommended, but diuretics are often insufficient to control symptoms, have not been shown to improve outcomes, and are associated with undesirable side-effects, such as neuroendocrine activation. Therefore, new therapies for modulating fluid homeostasis and renal function are under investigation.

Natriuretic peptide axis

Natriuretic peptides [BNP and atrial natriuretic peptide (ANP)] have antiproliferative and natriuretic properties. Nephilysin (NEP) is the primary enzyme that degrades natriuretic peptides. The novel angiotensin receptor and NEP inhibitor (ARNI) LCZ696 combines angiotensin type 1 (valsartan) and NEP receptor (AHU377) antagonism,⁷⁶ thereby increasing the bioavailability of natriuretic and vasodilator peptides.⁷⁷ The phase II Prospective Comparison of ARNI with ARB on Examination of Heart Failure with Preserved Ejection Fraction (PARMOUNT) trial randomized 301 patients with LVEF $\geq 45\%$, HF signs and symptoms, and elevated NT-proBNP plasma levels to LCZ696 50 mg twice daily (titrated to 200 mg twice daily) or valsartan 40 mg twice daily (titrated to 160 mg twice daily) for 12 weeks.¹⁹ The primary endpoint was change in NT-proBNP from baseline to 12 weeks. Over three-fourths of the patients had LVEF $\geq 50\%$. The ratio of change in NT-proBNP for LCZ696 vs. valsartan was 0.77 (95% CI: 0.64–0.92, $P = 0.005$) at 12 weeks. Left atrial volumes and dimensions were significantly reduced after 36 weeks in the LCZ696 group.¹⁹ These data suggest that LCZ696 may reduce LA volumes and wall stress. An outcomes trial, PARAGON-HF, is being planned to assess the effects of LCZ696 on clinical endpoints.

Targeting the pulmonary hypertension phenotype

Pulmonary hypertension is a haemodynamic consequence of HF-PEF with a reported prevalence of 53–83% in epidemiological cohorts; the prevalence in patients enrolled in clinical trials may be lower.^{78–80} Pulmonary hypertension is associated with higher mortality in patients with HF-PEF,⁷⁹ leading to the hypothesis that it is an active pathophysiological factor in HF-PEF progression, rather than solely secondary to left heart dysfunction. In fact, both pre-capillary (related to pulmonary arteriolar remodelling, intimal fibrosis, or reactive increases in pulmonary arterial tone)⁷⁹ and post-capillary (pulmonary venous hypertension) components contribute to pulmonary hypertension in HF-PEF.⁷⁹ Therefore, the pulmonary vascular bed, including endothelial dysfunction, may represent a novel therapeutic target in HF-PEF.⁸¹

Phosphodiesterase-5 inhibition

Inhibition of PDE5 leads to accumulation of intracellular cGMP- and NO-induced pulmonary vasodilation in patients with pulmonary arterial hypertension.⁸² Phosphodiesterase-5 inhibitors demonstrated

Table 4 Considerations for future clinical trials

Category	Consideration
Eligibility criteria	<p>Inclusion criteria should reflect pathophysiologically distinct patient populations, for example</p> <ul style="list-style-type: none"> Require echocardiographic evidence of diastolic dysfunction for therapies expected to impact cardiac structure or function Require reduced $\text{VO}_{2\text{max}}$ or moderate limitation in 6 minute walk distance for therapies expected to improve exercise tolerance or patient-reported outcomes Use biomarker criteria to identify high-risk patients, or patients with evidence of a pathophysiological process (e.g. galectin-3 and cardiac fibrosis) Use the diagnostic potential of an (echo) stress test Require a higher LVEF threshold (e.g. $\text{LVEF} \geq 50\%$) to avoid the confounding effects of HF-REF
Investigational intervention (device or drug)	<p>Primary pathophysiological target should be defined</p> <p>The investigational intervention should be selected to specifically target the primary pathophysiology</p>
Sample size	<p>Targeted therapy may</p> <ul style="list-style-type: none"> Result in a greater treatment effect, or Reduce 'noise' of no effect, or Result in less variation on the treatment effect <p>These factors may decrease the required sample size, but little experience has accumulated regarding event rate or anticipated treatment effects in pathophysiologically distinct subgroups</p> <p>Phase II proof-of-concept studies will inform assumptions needed to determine sample size</p> <p>Proof-of-concept studies to identify the pathophysiological target other than clinical endpoints (e.g. resolving the thrombus in acute myocardial infarction)</p> <p>Adaptive designs that prospectively plan interim analyses with the purpose of determining whether aspects of study design require modification (e.g. sample size)¹⁶⁸ may also be considered</p>
Endpoint selection	<p>Consider cardiovascular-specific endpoints as primary (e.g. cardiovascular mortality)</p> <p>Consider repeat (HF) hospitalizations</p> <p>Consider all-cause endpoints for safety</p> <p>Symptom relief, quality of life, and other patient-reported outcomes should be a key primary or secondary endpoint in HF-PEF trials</p> <p>Improvement in measures of exercise capacity</p> <p>Consider changes in biomarkers with known information on severity of disease and outcome</p>

antiproliferative effects in the pulmonary vasculature.⁸³ Guazzi et al.³⁷ randomized 44 patients with HF-PEF, $\text{LVEF} \geq 50\%$, sinus rhythm, and $\text{PASP} > 40$ mmHg (estimated by echocardiography) to placebo or sildenafil 50 mg three times daily for 12 months. At 6 and 12 months, patients randomized to sildenafil had significantly lower right atrial pressure, pulmonary artery pressures, wedge pressure, transpulmonary gradient, pulmonary vascular resistance and elastance, and increased quality of life scores, compared with the placebo group. Pulmonary function also improved in the sildenafil group compared with placebo, and sildenafil induced structural and functional reverse remodelling.³⁷ These findings support the hypothesis that treating pulmonary hypertension may be effective in patients with this phenotype. However, PDE5 inhibition was not effective in the RELAX study,²⁰ (see above) but patients with the pulmonary hypertension phenotype were not specifically targeted. Small randomized clinical trials with sildenafil are ongoing in patients with HFPEF and evidence of pulmonary hypertension (clinicaltrials.gov NCT01726049). Further analysis of the RELAX data and evidence from ongoing studies in patients with pulmonary hypertension will determine the potential utility of PDE5 inhibitors in HFPEF patients with this specific phenotype.

Orally active soluble guanylate cyclase stimulators

Other agents are also being tested in HF-PEF patients with the pulmonary hypertension phenotype. Riociguat is an oral sGC stimulator

that was evaluated in the Acute Hemodynamic Effects of Riociguat in Patients with Pulmonary Hypertension Associated with Diastolic Heart Failure (DILATE-1) study of patients with pulmonary hypertension associated with LV diastolic dysfunction (clinicaltrials.gov NCT01172756). Preliminary results were presented in the abstract form at ESC 2013 and demonstrated improved haemodynamics with riociguat.⁸⁴

Targeting diabetes and obesity as a phenotype

Diabetes

Diabetes mellitus is a major risk factor for diastolic dysfunction and the development of HF-PEF. Diabetes directly affects myocardial structure and function⁸⁵ through a variety of mechanisms⁸⁶ independent from other cardiovascular risk factors. Lipotoxicity, lipopoptosis, free fatty acid oxidation, advanced glycation end products (AGE), oxidative stress, impaired NO bioavailability, mitochondrial dysfunction, and myocardial fibrosis have all been implicated.^{86–90} Other signalling pathways are the subject of ongoing research.^{91,92}

Diastolic dysfunction has been detected in patients classified as pre-diabetes⁹³ and in up to 74% of asymptomatic, normotensive patients with type 2 diabetes mellitus.^{94–98} The risk of hospitalizations or death related to HF increased with increasing HbA_{1c} in a large registry of patients with diabetes and no documented HF

($n = 74,993$).⁹⁹ In the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) study, diabetes was an independent predictor of cardiovascular death or cardiovascular hospitalization in patients with either HF-PEF or HF-REF.¹⁰⁰

Targeting the diabetes phenotype may be one treatment strategy for HF-PEF, but the optimal treatment approach has not been determined. Tight glycaemic control (insulin vs. metformin plus repaglinide) did not reverse mild diastolic dysfunction in patients with type 2 diabetes, but this study was small with short-term follow-up.¹⁰¹ In another small study, improved glycaemic control over 5 years did not improve subclinical dysfunction in patients who remained hypertensive and overweight.¹⁰²

Some oral hypoglycaemic agents (e.g. metformin) may have pleiotropic effects that extend beyond their ability to reduce HbA_{1c} or improve insulin sensitivity [e.g. 5' adenosine monophosphate (AMP)-activated protein kinase activation, attenuation of TNF- α expression, increased myocardial vascular endothelial growth factor (VEGF) signalling, and/or stimulation of NO production].¹⁰³ Metformin was associated with a lower risk of all-cause mortality in a propensity score-matched analysis of 6185 patients with HF (45% of patients with LVEF $\geq 40\%$) and diabetes (HR: 0.76, 95% CI: 0.63–0.92, $P < 0.01$).¹⁰⁴ Novel drugs that break glucose crosslinks (alagebrium chloride) promoted regression of LV hypertrophy and improved diastolic function and quality of life in HF-PEF patients,¹⁰⁵ but data from larger controlled trials are lacking. Prospective, randomized trials are warranted to assess the safety and efficacy of treatments targeting the diabetes phenotype in HF-PEF (Table 3).

Obesity and metabolic syndrome

Obesity, atherogenic dyslipidaemia, hypertension, insulin resistance, glucose intolerance, and inflammation are components of the metabolic syndrome.¹⁰⁶ Obesity may lead to HF-PEF through several hypothesized mechanisms including inflammation of adipose tissue, endocrine effects of adiposity,¹⁰⁷ or increased loading conditions.

Subclinical diastolic dysfunction was detected in 48 obese, otherwise healthy women compared with 25 normal weight women.¹⁰⁸ In a study of 109 overweight or obese subjects, increasing body mass index (BMI) was associated with a reduced mitral annular velocity, myocardial early diastolic velocity, and elevated filling pressure. Insulin levels were inversely associated with measures of diastolic function, but on multivariate analysis, BMI remained a significant predictor after adjustment for age, mean arterial pressure, LVMI, and insulin level.¹⁰⁹

Left ventricular mass index, LVEDD, and left atrial volume were higher in obese subjects compared with lean controls in a study of 612 adolescents who were either (i) obese and had type 2 diabetes; (ii) obese without type 2 diabetes; or (iii) non-obese without type 2 diabetes. An average E/e' ratio was significantly different across the three groups, with the highest value in the obese diabetic group.¹¹⁰ These data show that obesity contributes to diastolic dysfunction and suggest that type 2 diabetes mellitus may confer additional risk. A recent *post hoc* analysis of I-Preserve demonstrated that obesity was common in HF-PEF patients and was associated with a U-shaped relationship for outcome. The greatest rate of adverse outcomes was confined to the lowest and highest BMI categories.¹¹¹ A recent study demonstrated improvement in some echocardiographic measures of

diastolic function after weight loss among obese patients with atrial fibrillation.¹¹²

Targeting anaemia or iron deficiency as a phenotype

Anaemia

Anaemia is a known prognostic factor in patients with HF-REF,^{113–116} but its role in patients with HF-PEF is less well established. Potential contributors to anaemia in HF-PEF include renal impairment, cytokine activation, volume overload (dilutional anaemia), malabsorption, malnutrition, or bone marrow suppression.^{117–123} An analysis from the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure (SENIORS) revealed that the prevalence of anaemia was similar in patients with HF-REF and HF-PEF (including mildly reduced LVEF $> 35\%$).¹²⁴ Patients with anaemia had a higher risk of all-cause mortality or cardiovascular hospitalization during the follow-up, regardless of ejection fraction.¹²⁴ In the 3C-HF score, a haemoglobin level < 11 g/dL was a non-cardiac independent predictor of 1-year mortality among patients with HF-PEF (LVEF $\geq 50\%$).¹²⁵ However, in a recent small trial, epoetin alfa increased haemoglobin, but it did not change end-diastolic volume, stroke volume, or 6-minute walk distance compared with placebo in a prospective, randomized, single-blind 24-week study in 56 patients with HF-PEF and mild anaemia.¹²⁶

Functional iron deficiency

Functional iron deficiency (FID) is an independent risk factor for poor outcome in advanced HF-REF, but its role in HF with HF-PEF remains unclear.^{127,128} In an initial small study, FID was present in almost 50% of HF-PEF patients, but it did not correlate with diastolic function parameters or exercise capacity.¹²⁹ More research is needed into the therapeutic options of FID and anaemia in HF-PEF.

Targeting deconditioning and the periphery as a phenotype

Peripheral muscle exercise training

Vascular stiffness increases and diastolic function declines with age, as a consequence of ageing, a culmination of risk factors, or both.^{130,131} These processes may lead to inadequate LV filling during exercise, resulting in symptoms of HF. Decreased LV compliance has been demonstrated in healthy, but untrained elderly subjects, but trained elderly had diastolic pressure volume relations similar to young sedentary subjects.¹³² In a recent analysis from the Framingham data set, the level of physical activity at a study entry was associated with the risk for long-term incident HF-PEF, and even moderate physical activity prevented HF-PEF.¹³³

The multicentre Exercise Training in Diastolic Heart Failure Pilot study (Ex-DHF-P) randomized patients with NYHA class II–III symptoms, LVEF $\geq 50\%$, echocardiographic evidence of diastolic dysfunction (grade ≥ 1), sinus rhythm, and ≥ 1 additional cardiovascular risk factor to 32 sessions of combined endurance/resistance exercise training ($n = 46$) or usual care ($n = 21$).¹³⁴ Peak VO_2 after 3 months (the primary endpoint) increased in the training group, resulting in a between-group difference of 3.3 mL/min/kg ($P < 0.001$). Several measures of diastolic function and quality of life also improved at 3 months.¹³⁴

A systematic review of five exercise training studies (228 patients) in patients with HF-PEF or diastolic HF with follow-up ranging from 12 to 24 weeks showed an overall between-group difference in peak VO_2 of 2.9 mL/kg/min (95% CI: 2.36–3.56) in favour of exercise training.¹³⁵ Overall improvements in Minnesota Living With Heart Failure total scores were also noted for exercise training compared with control.¹³⁵

Additional studies are needed to confirm the safety of exercise training, determine the effect on clinical outcomes, define the optimal exercise modalities (intensity, frequency, duration, and type of exercise), address adherence issues, and establish cost-effectiveness. The ongoing phase II Ex-DHF study (ISRCTN 86879094, www.controlled-trials.com) will further evaluate the role of exercise training in this population (Table 3).

Developing concepts in pathophysiology and treatment of heart failure with preserved ejection fraction

Renal function and fluid homeostasis

The cardiorenal interactions potentially contributing to HF-PEF are complex and include volume overload (due to inadequate renal handling of salt or fluid), renal hypertension, or oxidative stress and inflammatory processes.¹³⁶ The Cardiovascular Health Study showed that development of HF-PEF was associated with mild renal dysfunction, and subtle chronic volume overload was proposed to underlie structural and functional cardiac remodelling.¹³⁷ In patients hospitalized for HF-PEF, an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m² on admission independently predicted total and cardiovascular mortality over 7 years of follow-up.¹³⁸ Heart failure with preserved ejection fraction was observed in 21% of patients undergoing peritoneal dialysis in a university teaching dialysis centre, and it was associated with an increased risk of fatal or non-fatal cardiovascular events in this population.¹³⁹

Animal models suggest that high dietary sodium intake in the setting of abnormal renal sodium handling may be a stimulus for the development and progression of HF-PEF through increased oxidative stress, perivascular inflammation, and increased 'local' renal and cardiac angiotensin II and aldosterone (despite suppression of circulating levels).^{140,141} The demographics and comorbidities found in human salt-sensitive hypertension are nearly identical to those of HF-PEF. Salt-sensitive subjects develop cardiovascular structural and functional abnormalities associated with HF-PEF,^{142–147} leading to the hypothesis that high sodium intake contributes to HF-PEF pathophysiology.

Observational evidence suggests that dietary sodium restriction may reduce morbid events in patients with HF-PEF. In a propensity score, adjusted multivariable analysis of 1700 patients discharged from a HF hospitalization ($n = 724$ with HF-PEF), documentation that a sodium-restricted diet was associated with a lower risk of 30-day death or rehospitalization (OR: 0.43, 95% CI: 0.24–0.79, $P = 0.007$).¹⁴³ The Dietary Approaches to Stop Hypertension in Diastolic Heart Failure (DASH-DHF) pilot study showed that a sodium-restricted DASH diet significantly reduced clinic and 24-h

ambulatory blood pressure; while improving diastolic function and ventricular-arterial coupling.^{148,149} The DASH-DHF 2 study (Table 3) will provide mechanistic data needed to determine whether large, randomized clinical trials of dietary modification in patients with HF-PEF are warranted.

Electrical and mechanical dyssynchrony

Both systolic and diastolic mechanical dyssynchrony have been reported in patients with HF-PEF.¹⁵⁰ In one study of 138 patients, the prevalence of inter- and intraventricular dyssynchrony was comparable for patients with HF-PEF and HF-REF, if the QRS duration was ≥ 120 ms (42 vs. 55%).¹⁵¹ In other small studies of HF-PEF, the prevalence of electrical and/or mechanical dyssynchrony varies between 10 and 60%; its association with clinical outcomes is uncertain.¹⁵² In an analysis of 25 171 patients from the Swedish Heart Failure Registry, a QRS ≥ 120 ms was an independent predictor of mortality even after adjustment for LVEF.¹⁵³ In patients with left bundle branch block, there is usually marked shortening of the LV diastolic filling time due to prolongation of isovolumic contraction and relaxation.^{154,155} The Karolinska–Rennes (KaRen) study is an ongoing prospective, multicentre, observational study designed to evaluate the prevalence and prognostic importance of electrical and mechanical dyssynchrony in patients with HF-PEF.¹⁵⁶ Even in the absence of electrical dyssynchrony, exercise-induced torsional dyssynchrony has been reported in patients with HF-PEF, but validation of the techniques used to detect torsional dyssynchrony and determination of threshold values is needed.¹⁵⁷ The potential effect of cardiac resynchronization therapy on electrical, mechanical, and torsional dyssynchrony in HF-PEF patients remains to be determined. Recently, the concept of atrial dyssynchrony and left atrial pacing as a potential therapeutic approach was introduced.¹⁵⁸ This concept clearly needs further research before more definite answers can be given.

The timing of ventricular–arterial coupling may also be important in HF-PEF patients. Lower amplitude of mid-systolic wave reflections predicted better clinical outcomes in a substudy of the ASCOT trial.¹⁵⁹ Women demonstrate less efficient ventricular–arterial coupling than men (higher wall stress development for any given LV geometry, arterial properties, and flow output),¹⁶⁰ which may be a factor in HF-PEF development. Modulation of the timing and amplitude of wave reflections merits further pathophysiological investigation.

Autonomic modulation and chronotropic incompetence

Autonomic dysfunction is a potential pathophysiological factor in HF-PEF, contributing to exertional dyspnoea and fatigue.^{161–164} Modulation of autonomic function is being investigated as a strategy for treating patients with HF-PEF, for example, by baroreceptor activation, vagal nerve stimulation, and renal artery denervation.¹⁶⁵ Importantly, a significant subgroup of HF-PEF patients suffers from chronotropic incompetence.^{162–164} Chronotropic incompetence can be readily detected by an exercise stress test, and it largely impairs cardiac output in patients with a small stiff ventricle. Without a clear indication, beta-blockers (often prescribed for arterial hypertension) should be avoided. Rate-responsive pacing may be

an option in selected patients, but data from clinical trials in HF-PEF are lacking.

Heart rate as a therapeutic target

Elevated heart rate is a risk factor for cardiovascular events, both in the general population, and in patients with HF-REF. In a diabetes mouse model of HF-PEF, selective heart rate reduction by I_f inhibition improved vascular stiffness, LV contractility, and diastolic function.¹⁶⁶ Short-term treatment with the I_f channel inhibitor ivabradine increased exercise capacity, with a contribution from improved LV filling pressure response to exercise, in a small, placebo-controlled trial.¹⁶⁷ Therefore, I_f inhibition might be a therapeutic concept for HF-PEF. Currently, a phase II trial with ivabradine in HF-PEF has started.

Considerations for future clinical trials

As new clinical trials are planned, it is important to apply the lessons learned from previous studies.^{9–11} Clinical trials to date have not produced therapies that improve clinical outcomes, but the knowledge gained can guide the development of future studies (Table 4).

Patient selection

Heart failure with preserved ejection fraction is a heterogeneous syndrome, and a 'one-size-fits-all' approach may not be effective. This concept is the critical element that has 'doomed' many past clinical trials. Heart failure with preserved ejection fraction encompasses a broad patient population, reflecting many comorbidities and pathophysiological processes.¹⁶⁹ Comorbidities influence ventricular-vascular properties and outcomes in HF-PEF, but fundamental disease-specific changes in cardiovascular structure and function underlie this disorder,¹⁷⁰ supporting the search for mechanistically targeted therapies in this disease. It is unlikely that patients with different phenotypes will respond uniformly to a single drug or device. Future clinical trials should identify pathophysiologically distinct groups and target the key pathophysiological mechanism with a specific therapeutic strategy (Figures 1 and 2). It may be appropriate to enrol patients at an earlier stage of the natural history of HF-PEF, for example, before myocardial interstitial fibrosis becomes prominent and possibly irreversible. Although this targeted approach may result in a smaller pool of eligible patients for a specific trial or in clinical practice, the probability of observing a significant and meaningful benefit may be greater. It is important to note that results generated from trials with specific patient subpopulations will not be broadly generalizable but will only apply to patients similar to those enrolled in such trials.

Importantly, elderly, deconditioned patients without true HF need to be excluded from targeted HF trials in HF-PEF. Hence, confirming the HF diagnosis is key in patient selection. Some trials have enrolled patients with only mild elevations in NT-proBNP, which may have contributed to the neutral findings of prospective, randomized trials to date (Table 2). On the other hand, in the observational Swedish study, the positive result was likely in part related to higher levels of NT-proBNP (Table 2).¹⁵

Also, trials have used different LVEF thresholds to define HF-PEF. Requiring a higher LVEF threshold (e.g. $LVEF \geq 50\%$) should be considered in future HF-PEF trials to avoid the confounding effects of HF-REF. However, in addition to HF-PEF ($LVEF \geq 50\%$), a substantial number of patients are in a 'grey zone' of global LV function with an LVEF between 40 and 50%. Similar to HF-PEF, almost no guideline-recommended proven HF therapies exist for this substantial subgroup of patients, since few studies have enrolled these patients. Renin–angiotensin–aldosterone system antagonist therapies might be particularly beneficial in this group, and further investigation in the subgroup of patients with LVEF 40–50% is urgently needed.

Some trials require evidence of diastolic dysfunction, whereas others do not. The ideal balance between sensitivity and specificity of the HF-PEF diagnosis is hard to achieve, particularly since HF-PEF is a disease of the elderly in whom age-associated comorbidities are common with multiple reasons for breathlessness. The definition of HF-PEF used in future trials may largely depend on the therapeutic intervention being studied. It may be necessary to require evidence of diastolic dysfunction for therapies expected to impact cardiac structure and function. Evidence of exercise intolerance or a greater symptomatic burden may be necessary for therapies expected to improve peak VO_2 , submaximal exercise capacity, or patient-reported outcomes. Experts have not reached consensus on the optimal methods to define HF-PEF patients for clinical trials, although most agree that assessments at rest are not sufficient. In the future, objective evidence of exercise intolerance (e.g. low or reduced $VO_{2\max}$, or limited distance on the 6 min walk) will become important for a firm diagnosis. The diastolic stress test (echocardiography during exercise) is being validated, and HF-PEF patients with a history of recent HF hospitalization are a subgroup at particular high risk for future adverse cardiovascular events. Emerging biomarkers are on the horizon, such as galectin-3, that are not only elevated but may also point to a specific pathology for the disease, thereby allowing patient selection for targeted therapies. Additional work is needed to refine principles of patient selection for clinical trials. Future trials should strive to phenotype patients into relevant pre-specified categories so that adequately powered subgroups of responders and non-responders can be identified. Such subgroup data, although insufficient to guide clinical practice, could help generate specific hypotheses for prospective testing.

Endpoint selection

Although combined all-cause mortality and HF hospitalization is a widely accepted primary endpoint for HF-REF trials, it may be sub-optimal for phase III HF-PEF trials. Large community-based cohort data suggest that HF-PEF is associated with high mortality similar to HF-REF.^{171,172} However, a recent meta-analysis using individual data from 41 972 patients contributing 10 774 deaths showed that patients with HF-PEF ($LVEF \geq 50\%$) had a lower risk of total mortality (HR: 0.68, 95% CI: 0.64–0.71) and cardiovascular mortality (HR: 0.55, 95% CI: 0.49–0.61) than patients with HF-REF.¹⁷³ When the analysis was performed by LVEF subgroups, an increased risk of either total or cardiovascular mortality was only observed when the LVEF was $<40\%$ (when compared with $LVEF \geq 60\%$).¹⁷³ Similar findings were reported in an analysis of the CHARM programme.¹⁷⁴

Another complicating factor is that non-cardiovascular death accounts for a greater proportion of deaths in HF-PEF than in

HF-REF.¹⁷⁴ Thus, all-cause mortality or hospitalization may be insensitive to detect disease-specific therapeutic effects. Clinical trialists are often tempted to add components to composite endpoints to increase event rates and achieve adequate study power with small sample sizes. However, statistical noise is introduced, rather than power, when endpoints are used that a therapeutic agent is unlikely to influence (e.g. all-cause mortality includes non-cardiovascular death, which most cardiovascular drugs do not impact). Consideration should be given to assessing all-cause mortality as a safety endpoint and choosing cardiovascular-specific endpoints to assess drug efficacy. Heart failure is a chronic disease characterized by frequent exacerbations necessitating hospitalization. Traditional time-to-first-event endpoints do not reflect the full burden of disease. Efforts to develop methods that robustly evaluate recurrent events are ongoing.¹⁷⁵ The Food and Drug Administration has now accepted study designs in HF-PEF that use recurrent HF hospitalizations as a component of the primary endpoint.

A cardinal feature of HF-PEF is reduced exercise tolerance, which reflects symptoms as well as quality of life. Many patients with HF-PEF are elderly and often frail, and for them, the therapy that quickly improves symptoms or exercise capacity may be more important than an uncertain possibility of a brief prolongation of survival. Symptom relief is, therefore, an important target of therapy, but it is a subjective endpoint and difficult to evaluate. The 6-minute walk test is a simple stress test that can be used in clinical trials. In addition, several instruments have evolved to assess the impact of disease and the effect of treatment on health-related quality of life and other patient-reported outcomes.

It may also be important in future clinical trials to avoid relying on simple, single surrogate echocardiographic endpoints. Particular indices can be selected that reflect the expected mechanism of action of a drug. Recent studies have used E/e' as a correlate of the mean LV filling pressure, but the utility of this variable in HF-PEF has been seriously questioned.^{176,177} Alternative indices include the propagation velocity of mitral inflow (an excellent correlate of early diastolic LV suction),¹⁷⁸ and the difference in duration between antegrade flow into the LV and retrograde flow into the pulmonary veins during atrial contraction (an indicator of LV end-diastolic pressure in patients with HF-REF and HF-PEF).¹⁷⁹ Left atrial volume is increasingly recognized as an integrated parameter for elevated LV filling pressures and the duration of the disease (similar to HbA1c in diabetes), and it is currently used as an inclusion criterion and as a secondary endpoint in several Phase II HF-PEF trials. Finally, HF is pathophysiologically defined as impaired pump function, and the non-invasive estimation of filling pressures and stroke volume (e.g. by 3D echocardiography) during rest and stress may improve diagnostic accuracy and assessment of an eventual treatment effect.

Conclusion

Significant progress has been made in understanding HF-PEF pathophysiology, recognizing the importance of disease heterogeneity, and identifying novel therapies that may reduce symptoms and improve clinical outcomes. Designing therapies to match specific patient phenotypes may prove to be a more effective approach than the traditional model of applying a given treatment uniformly to all patients, which has not been successful in clinical HF-PEF

trials to date. Adaptations to current clinical trial methodology may be needed to accommodate this paradigm shift. The forthcoming results of several clinical trials are eagerly awaited, and they will provide direction for future research and guide the clinical management of these patients.

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