

Facts and numbers on epidemiology and pharmacological treatment of heart failure with preserved ejection fraction

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Abstract

Heart failure with preserved ejection fraction (HFpEF) is a major and growing public health problem. Epidemiologic studies demonstrated that heart failure (HF) can be clinically diagnosed in patients with normal or preserved left ventricular ejection fraction. These patients are therefore termed as having HFpEF. In the past, this was often called diastolic HF. Because of the permanent increase of the prevalence of HFpEF during the past decades, HFpEF now accounts for more than 50% of the total HF population. There are uncertainties and debates regarding the definition, diagnosis, and pathophysiology with the consequence that all outcome trials performed so far used criteria for inclusion and exclusion that were not consistent. These trials also failed to document improved prognosis. Recent smaller proof-of-concept or Phase II clinical trials investigating different pathophysiological approaches with substances such as the neprilysin inhibitor–angiotensin receptor blocker— combination (LCZ 696), ranolazine, or ivabradine were successful to improve biomarkers, haemodynamics, or functional capacity. Future trials will need to document whether also prognosis can be improved.

Keywords Treatment; diastolic; heart failure with preserved ejection fraction

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Introduction

Heart failure with preserved ejection fraction (HFpEF) is a major and growing public health problem. Epidemiologic studies demonstrated that heart failure (HF) can be clinically diagnosed in patients with normal or preserved left ventricular ejection fraction (LVEF).¹ These patients are therefore termed as having HFpEF. Because of the permanent increase of the prevalence of HFpEF during the past decades, HFpEF now accounts for more than 50% of the total HF population.^{2,3} In contrast to heart failure with reduced ejection fraction (HFrEF), outcomes in HFpEF remained unchanged over the last years.^{2,3} In a recent meta-analysis, the mortality rate in HFpEF was 121 [95% confidence interval (CI): 117 to 126] deaths per 1000 patient-years, which is underscoring the need for effective therapies in this highly relevant condition.⁴ However, there are uncertainties regarding the definition, diagnosis, and pathophysiology with the consequence that all outcome trials performed so far failed to improve prognosis in this condition.⁵

Recent smaller proof-of-concept or Phase II trials investigating different pathophysiological approaches with substances such as the neprilysin inhibitor–ARB— combination, ranolazine, and ivabradine were successful to improve biomarkers, hemodynamics, or functional capacity.

Pharmacological Treatment of heart failure with preserved ejection fraction

Current HF guidelines of the ESC acknowledge the complete lack of evidence in the prognostic management of HFpEF.¹ Only the use of diuretic agents to relieve breathlessness and oedema is recommended. Furthermore, supported by expert opinion, a focused management of important underlying or concomitant conditions such as hypertension, myocardial ischemia, and to control heart rate and to preserve sinus rhythm can be recommended. The following therapeutic

concepts were investigated in proof-of-concept, larger parallel group, or outcome studies.

Beta-blockers and calcium-channel blockers

The role of beta-blockers remains to be investigated more comprehensively. Nebivolol was investigated in $n=2128$ elderly patients with a history of HF or known LVEF $\leq 35\%$ in the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure (SENIORS).⁶ There was a 14% reduction in the primary composite outcome [all-cause mortality or cardiovascular (CV) admission]. A similar benefit was observed in patients with 'preserved' LVEF (LVEF $> 35\%$). However, the cut-off of LVEF was 35%, wherefore no extrapolation of the results to patients with really preserved LVEF can be drawn from this analysis. In the Effects of Long-term Administration of Nebivolol on the clinical symptoms, exercise capacity, and left ventricular function of patients with Diastolic Dysfunction trial, a randomized, double-blind, multicenter, parallel group, placebo-controlled trial designed to investigate the effects of Nebivolol in patients with HFpEF. Nebivolol did not positively affect signs and symptoms in HFpEF.⁷ In contrast, a direct correlation between the decrease in peak heart rate and the decrease in peak oxygen consumption in the Nebivolol group could be observed. Although data regarding the calcium-channel blocker verapamil from a very small study suggested improvements of signs and symptoms of HF as well as of exercise capacity in these patients, no sufficient evidence for the benefit of beta-blockers or verapamil in HFpEF is available.⁸

Ivabradine

In a recent trial, $n=61$ patients with HFpEF and increased heart rate were randomized to ivabradine 5 mg b.i.d. or placebo.⁹ The follow-up was for 7 days. Exercise capacity was significantly improved by ivabradine when compared with

placebo. The ongoing PrEServeD left ventricular ejection fraction chronic heart Failure with ivabradine study (EDIFY) study (effect of ivabradine vs. placebo on cardiac function, exercise capacity, and neuroendocrine activation in patients with chronic HF with preserved LVEF; EUDRA CT no. 2012 002742-20) will prospectively enrol $n=400$ patients with HFpEF and will more comprehensively investigate the effect of ivabradine on diastolic function, exercise capacity, and on N-terminal pro brain natriuretic peptide (NT-proBNP) plasma levels after 8 months follow-up.

Digitalis

In the Digitalis Interaction Group trial, $n=988$ patients (LVEF $> 45\%$) were randomized to digoxin or placebo. After 37 months follow-up, no differences were observed in all-cause, HF, or CV mortality, as well as in the composite outcome of HF death or hospitalization.¹⁰

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers

The Perindopril for Elderly People with Chronic Heart Failure trial prospectively included $n=850$ elderly patients with HF, preserved LVEF (LVEF $> 40\%$), and echocardiographic evidence of diastolic dysfunction.¹¹ After the mean follow-up of 26.2 months, no significant reduction in all-cause mortality or HF hospitalization (primary composite endpoint) was observed in the perindopril group (Table 1). The Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity trial prospectively included $n=3023$ patients with HF and preserved LVEF (LVEF $\geq 40\%$).¹² They were randomized to receive candesartan or placebo. As shown in Table 1, there was no significant benefit on CV mortality (primary outcome). In contrast, a significant reduction in HF hospitalizations in the candesartan group was observed. The Irbesartan in HF with Preserved Systolic Function trial prospectively enrolled $n=4128$ elderly HF patients with

Table 1. Outcome trials in heart failure with preserved ejection fraction

	PEP-CHF ¹¹	CHARM—preserved ¹²	I-PRESERVE ¹³	TOPCAT ¹⁶
Patients, $n=$	850	3.023	4.128	3.445
Study drug	Perindopril	Candesartan	Irbesartan	Spironolactone
Mean follow-up (years)	2.1	3.0	4.1	3.3
Primary endpoint	All-cause death/HF hospitalization	CV death/HF hospitalization	All-cause death/CV hospitalization	CV death/aborted cardiac arrest/HF hospitalization
Hazard ratio	0.92 (0.70–1.21)	0.89 (0.77–1.03)	0.95 (0.86–1.05)	0.89 (0.77–1.04)
P-value	0.54	0.12	0.35	0.14

PEP-CHF, Perindopril for Elderly People with Chronic Heart Failure; CHARM, Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity; I-PRESERVE, Irbesartan in HF with Preserved Systolic Function; TOPCAT, Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist Trial; HF, heart failure; CV, cardiovascular.

preserved LVEF (LVEF $\geq 45\%$).¹³ They were randomized to receive irbesartan or placebo. Again, no significant reduction in the primary composite outcome (death from any cause or hospitalization for a cardiovascular cause—heart failure, myocardial infarction, unstable angina, arrhythmia, or stroke) or in major secondary outcome measures could be observed (Table 1).

Neprilysin inhibitors combined with angiotensin receptor blockers

LCZ 696 is an angiotensin receptor neprilysin inhibitor that combines an inhibitory effect of neprilysin together with an angiotensin receptor blocker. In the Prospective Comparison of Arni With ARB on Management of Heart Failure with Preserved Ejection Fraction Trial, LCZ 696 was compared with valsartan in $n=301$ patients with HFpEF patients.¹⁴ The follow-up period was 36 weeks. The primary endpoint was the change of NT-proBNP (24 weeks). LCZ 696 significantly lowered the plasma level of NT-proBNP compared with valsartan. Interestingly, the effect on NT-proBNP was not reproducible after the total follow-up period of 36 weeks. The Efficacy and Safety of LCZ 696 Compared with Valsartan, on Morbidity and Mortality in Heart Failure Patients with Preserved Ejection Fraction trial is ongoing and will investigate whether LCZ 696 is of prognostic relevance in this condition (ClinicalTrials.gov identifier: NCT01920711).

Mineralocorticoid receptor antagonists

Smaller studies suggested that mineralocorticoid receptor antagonists such as spironolactone and eplerenone might positively affect cardiac function in patients with HFpEF. In the Aldosterone receptor Blockade in Diastolic Heart Failure trial, $n=422$ patients with HFpEF (LVEF $\geq 50\%$) were randomized to receive spironolactone 25 mg/day or placebo.¹⁵ The follow-up period was 12 months. Diastolic function assessed by the left ventricular filling index E/e' ratio on Doppler echocardiography was significantly improved by spironolactone, along with reduction in LV mass and NT-proBNP. No change was observed in maximal exercise capacity (co-primary endpoint), patient signs and symptoms, or quality of life.

In the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist trial, randomized $n=3445$ patients with symptomatic heart failure and a preserved LVEF (LVEF $\geq 45\%$) to receive spironolactone or placebo.¹⁶ The mean follow-up was 3.3 years. The primary outcome was a composite of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of HF. The primary outcome occurred in $n=320$ of $n=1722$ patients in the spironolactone group (18.6%) and 351 of 1723 patients in the placebo group (20.4%) (Hazard ratio, 0.89; 95% CI, 0.77 to

1.04; $P=0.14$). Only hospitalization for HF had a significantly lower incidence in the spironolactone group than in the placebo group [206 patients (12.0%) vs. 245 patients (14.2%); hazard ratio, 0.83; 95% CI, 0.69 to 0.99, $P=0.04$]. Neither total deaths nor hospitalizations for any reason were significantly reduced by spironolactone (Table 1).

Phosphodiesterase-5 inhibitors

A small clinical trial demonstrated that sildenafil improved LV diastolic function, lowered LV hypertrophy, and reduced pulmonary pressures after 12 months in HFpEF patients and pulmonary hypertension.¹⁷ These effects could not be confirmed by the RELAX trial including $n=216$ elderly patients with HFpEF.¹⁸ After the follow-up period of 24 weeks, no effects of sildenafil on exercise capacity (primary endpoint: change in peak VO₂), on clinical status, quality of life, LV remodelling, or diastolic function were noted.

Soluble guanylate cyclase stimulators

The Phase IIa Acute Haemodynamic Effects of Riociguat in Patients with Pulmonary Hypertension Associated with Diastolic Heart Failure study investigated the hemodynamic effects, safety, and pharmacokinetics of different dosages of riociguat in patients with HFpEF and pulmonary hypertension.¹⁹ There was no significant change in the primary endpoint (peak change in mean pulmonary artery pressure (mPAP) from baseline to 6 h) due to riociguat compared with placebo. In the Soluble Guanylate Cyclase stimulator Heart Failure Studies—preserved trial, the new oral soluble guanylate cyclase stimulator (BAY1021189) will be further investigated in hospitalized patients with HFpEF (clinicaltrials.gov identifier: NCT01951638).

Ranolazine (selective inhibitor of the late sodium (I_{Na+}) current)

The RALI DHF trial was a small trial that included $n=20$ patients with HFpEF.²⁰ After i.v. administration, some hemodynamic improvements were noted. However, after further 2 week oral treatment, no effects on echocardiographic parameters, NT-proBNP, or exercise performance could be detected.

New concepts

Whether other treatment approaches such as the use of statins, advanced glycation end-products cross-link breakers, calcium-cycling modulators, the replacement or blockade of specific micro-RNAs, or an i.v. iron therapy are beneficial in

HFpEF needs to be investigated in adequate powered randomized controlled trial (RCTs).

There is an ongoing discussion regarding the disappointing results of all outcome trials. First of all, the definition of patients with HFpEF was considered as problematic because signs and symptoms of HF in patients with preserved or normal LVEF are unspecific and are heavily influenced by other conditions than HF. Furthermore, there is no real consensus on the definition (HF guidelines and clinical trials) of preserved or normal LVEF (40%, 45%, or 50%). Finally, there is no consensus on the verification of a cardiac abnormality such as an invasive or non-invasive confirmation of the presence of LV diastolic function (E/e' ratio, left atrial enlargement, LV hypertrophy, or increased natriuretic peptide plasma levels) to validate the diagnosis of HFpEF. Also, trial-related problems need to be considered. Most of the

outcome trials suffered from a substantially prolonged recruitment period resulting in higher drop-out rates and unplanned cross-over. Also, the chosen primary endpoints need to be questioned because a large number of patients with preserved LVEF die from non-cardiovascular causes. Recurrent HF hospitalizations are of relevance for patients with HF and should be therefore considered as an interesting component of primary composite endpoints in future studies.¹⁶

In summary, the treatment of HFpEF remains challenging. Some progress has been made in the understanding of the pathophysiology of HFpEF also leading to improvements regarding the definition of this clinical syndrome. There are several novel pharmacological approaches that were promising in proof-of-concept or Phase II trials. However, they need to be investigated in larger, well-designed RCTs.

References

- McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Kober L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Ronnevik PK, Rutten FH, Schwitzer J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A. ESC Committee for Practice Guidelines. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2012; **33**: 1787–1847.
- Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med* 2006; **355**: 251–259.
- Bhatia RS, Tu JV, Lee DS, Austin PC, Fang J, Haouzi A, Gong Y, Liu PP. Outcome of heart failure with preserved ejection in a population-based study. *N Engl J Med* 2006; **355**: 260–269.
- Meta-analysis Global Group in Chronic Heart Failure (MAGGIC). The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis. *Eur Heart J* 2012; **33**: 1750–1757.
- Cleland JG, Pellicori P. Defining diastolic heart failure and identifying effective therapies. *JAMA*. 2013 Feb 27; **309**(8): 825–6.
- Flather MD, Shibata MC, Coats AJ, Van Veldhuisen DJ, Parkhomenko A, Borbola J, Cohen-Solal A, Dumitrascu D, Ferrari R, Lechat P, Soler-Soler J, Tavazzi L, Spinarova L, Toman J, Böhm M, Anker SD, Thompson SG, Poole-Wilson PA. SENIORS Investigators. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). *Eur Heart J* 2005; **26**: 215–225.
- Conraads VM, Metra M, Kamp O, De Keulenaer GW, Pieske B, Zamorano J, Vardas PE, Böhm M, Dei Cas L. Effects of the long-term administration of nebivolol on the clinical symptoms, exercise capacity, and left ventricular function of patients with diastolic dysfunction: results of the ELANDD study. *Eur J Heart Fail* 2012; **14**: 219–225.
- Setaro JF, Zaret BL, Schulman DS, Black HR, Soufer R. Usefulness of verapamil for congestive heart failure associated with abnormal left ventricular diastolic filling and normal left ventricular systolic performance. *Am J Cardiol* 1990; **66**: 981–986.
- Kosmala W, Holland DJ, Rojek A, Wright L, Przewlocka-Kosmala M, Marwick TH. Effect of If-channel inhibition on hemodynamic status and exercise tolerance in heart failure with preserved ejection fraction: a randomized trial. *J Am Coll Cardiol* 2013; **62**: 1330–1338.
- Ahmed A, Rich MW, Fleg JL, Zile MR, Young JB, Kitzman DW, Love TE, Aronow WS, Adams KF Jr, Gheorghade M. Effects of digoxin on morbidity and mortality in diastolic heart failure: the ancillary Digitalis Investigation Group trial. *Circulation* 2006; **114**: 397–403.
- Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. *Eur Heart J* 2006; **27**: 2338–2345.
- Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, Olofsson B, Ostergren J. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved trial. *Lancet* 2003; **362**: 777–781.
- Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, Anderson S, Donovan M, Iverson E, Staiger C, Ptaszynska A. Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med* 2008; **359**: 2456–2467.
- Solomon SD, Zile M, Pieske B, Voors A, Shah A, Kraigher-Krainer E, Shi V, Bransford T, Takeuchi M, Gong J, Lefkowitz M, Packer M, McMurray JJ. Prospective comparison of ARNI with ARB on management of heart failure with preserved ejection fraction (PARAMOUNT) investigators. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. *Lancet* 2012; **380**: 1387–1395.
- Edelmann F, Wachter R, Schmidt AG, Kraigher-Krainer E, Colantonio C, Kamke W, Duvinage A, Stahrenberg R, Durstewitz K, Löffler M, Düngen HD, Tschöpe C, Herrmann-Lingen C, Halle M, Hasenfuss G, Gelbrich G, Pieske B. Aldo-DHF investigators. Effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection fraction: the Aldo-DHF randomized controlled trial. *JAMA* 2013; **309**: 781–791.
- Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, Harty B, Heitner JF, Kenwood CT, Lewis EF, O'Meara E, Probstfield JL, Shaburishvili T, Shah SJ, Solomon SD, Sweitzer NK, Yang S, McKinnlay SM. TOPCAT investigators. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med*. 2014 Apr 10; **370**(15): 1383–92.

17. Guazzi M, Vicenzi M, Arena R, Guazzi MD. Pulmonary hypertension in heart failure with preserved ejection fraction: a target of phosphodiesterase-5 inhibition in a 1-year study. *Circulation* 2011; **124**: 164–174.
18. Redfield M, Chen HH, Borlaug BA, Semigran MJ, Lee KL, Lewis G, LeWinter MM, Rouleau JL, Bull DA, Mann DL, Deswal A, Stevenson LW, Givertz MM, Ofili EO, O'Connor CM, Felker GM, Goldsmith SR, Bart BA, McNulty SE, Ibarra JC, Lin G, Oh JK, Pater MR, Kim RJ, Tracy RP, Velasquez EJ, Anstrom KJ, Hernandez AF, Mascette AM, Braunwald E. RELAX trial. Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: a randomized clinical trial. *JAMA* 2013; **309**: 1268–1277.
19. Bondermann D, Pretsch I, Steringer-Mascherbauer R, Rosenkranz S, Tufaro C, Frey R, Ochan M, Kilama S, Unger S, Roessig L, Lang IM. Acute hemodynamic effects of rilociguat in patients with pulmonary hypertension associated with diastolic heart failure (DILATE-1): a randomized double-blind, placebo-controlled, single-dose study. *Eur Heart J*, Abstract 3321 ESC Amsterdam 2013. doi:10.1093/eurheartj/ehi115 (10 January 2005).
20. Maier LS, Layug B, Karwatowska E. Ranolazine for the treatment of diastolic heart failure in patients with preserved ejection fraction: the RALI-DHF proof-of-concept study. *J Am Coll Cardiol Heart Failure* 2013; **1**: 115–122.