ESC European Society of Cardiology

European Journal of Heart Failure (2023) **25**, 925–928
doi:10.1002/ejhf.2976

July 2023 at a glance: heart failure with preserved ejection fraction and comorbidities

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Heart failure with preserved ejection fraction

Heart failure (HF) with preserved ejection fraction (HFpEF) is a heterogeneous syndrome.[1–3] A scientific statement from the Heart Failure Association (HFA) described most common HFpEF phenotypes, related comorbidities and treatment options for each phenotype.[4]

Exercise testing has a key role in the diagnosis and prognostic assessment of HFpEF.[1,5,6] In a study by Alogna *et al.*,[7] 398 patients with HFpEF undergoing comprehensive echocardiography and invasive cardiopulmonary exercise testing were categorized low versus preserved biventricular cardiac power output (BCPO) reserve (< vs ≥ median of 1.57 W). Lower BCPO was associated with more advanced HFpEF, increased systemic and pulmonary vascular resistance, reduced exercise capacity and increased adverse events.

Atrial fibrillation (AF) is common among patients with HFpEF. Filippatos *et al.*[8] performed a secondary analysis of the EMPEROR-Preserved trial to assess efficacy of empagliflozin in patients with and without AF. Empagliflozin successfully reduced the risk of serious HF events and slowed the decline of renal function, irrespective of AF.

Quality of life is impaired also in patients with HFpEF.[9,10] Pooling data from DAPA-HF and DELIVER trials, Bhatt *et al.*[11] analysed the benefits of dapagliflozin on health status, measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ), across the full spectrum of left ventricular ejection fraction (LVEF). A total of 11 007 participants were included and KCCQ was evaluated at 4 and 8 months. Dapagliflozin improved all key domains of health status irrespective of LVEF.

Some studies showed a U-shaped relationship between LVEF and outcome, with patients with supranormal ejection fraction (HFsnEF, LVEF >65%) having a higher risk of events.[12–14] Among 11 573 patients hospitalized for HF and enrolled in the nationwide Japanese registry, 16.8% were classified as HFsnEF, 28.3% as HF with normal ejection fraction (HFnEF), 17.5% as HF with mildly reduced ejection fraction (HFmrEF) and 37.4% as HF with reduced ejection fraction (HFrEF). Patients with HFsnEF were older, more likely to be women, had lower natriuretic peptide values, and had smaller left ventricles than those with HFnEF. Patients with HFsnEF, compared to those with HFnEF, had a similar risk of the primary composite endpoint of cardiovascular (CV) death or HF readmission but with a lower adjusted hazard ratio (HR) for HF readmission.[15]

Medical therapy

Sodium–glucose cotransporter 2 (SGLT2) inhibitors improve prognosis and quality of life across the entire LVEF spectrum.[1,16–18] Talha *et al.*[19] studied their potential impact on health care resources and showed that a global and optimal implementation of SGLT2 inhibitors can prevent or postpone approximately 7–8 million worsening HF events and CV deaths over 3 years.

Vericiguat significantly reduced the primary composite outcome of HF hospitalization or CV death in a high-risk HFrEF population with a recent episode of worsening HF.[20] Pieske *et al.*[21] evaluated the effects of vericiguat, compared with placebo, in a subset of 419 patients from the VICTORIA trial with available echocardiography at baseline and 8 months. A significant and similar improvement in left ventricular structure and function from baseline was observed in both the study groups with no difference between them.

Comorbidities

Valvular heart disease

Acute HF is a life-threatening condition with several precipitating factors.[1,22–25] Valvular heart disease (VHD) is frequently associated with acute HF. On one hand, a new significant valvular lesion can be the cause of acute decompensation, on the other hand, acute HF may worsen an already compromised haemodynamic status caused by a chronic valve disease. A scientific statement of the HFA, the Association for Acute CardioVascular Care and the European Association of Percutaneous Cardiovascular Interventions provides insights into the epidemiology and treatment options in patients with VHD and acute HF.[26]

Among 15 216 patients with HF enrolled in the ESC-HFA EORP HF Long-Term Registry including both chronic and acute HF (62.5% with HFrEF; 14.0% with HFmrEF; 23.5% with HFpEF), 706 (4.6%), 648 (4.3%) and 234 (1.5%) had moderate to severe aortic regurgitation, aortic stenosis and mixed aortic valve disease, respectively.

Aortic stenosis and mixed aortic valve disease were more common among patients with HFpEF and were independently associated with an increased risk of in-hospital mortality and 12-month CV death and HF hospitalization, regardless of ejection fraction categories.[27]

A further analysis from the same registry investigated prevalence, clinical characteristics, and outcomes of patients with or without isolated or combined mitral regurgitation (MR) and tricuspid regurgitation (TR). Among 11 298 outpatients enrolled, 7541 (67%) had no MR/TR, 1931 (17%) had isolated MR, 616 (5.5%) isolated TR and 1210 (11%) combined MR/TR. Compared to HFrEF, HFpEF was associated with a lower risk of isolated MR and combined MR/TR, but a two-fold increased risk of isolated TR. Isolated TR was associated with the highest event rates.[28]

Renal function and iron deficiency

Sakaniwa *et al.*[29] examined the longitudinal trajectories of urinary albumin excretion (UAE) and serum creatinine and their association with new-onset HF and all-cause mortality during a follow-up of 11 years in 6881 subjects from the Prevention of Renal and Vascular End-stage Diseases (PREVEND) study. Participants with persistently high UAE had a higher risk of new-onset HF or all-cause mortality.

Iron deficiency is common among patients with HF and is associated with poor outcomes and quality of life.[30–32] Despite several trials showing an improvement in symptoms with intravenous ferric carboxymaltose, it remains uncertain whether intravenous iron replacement may reduce HF hospitalizations and CV mortality.[1,31,33] In a Bayesian meta-analysis pooling data from randomized controlled trials performed to date, treatment of iron deficiency with intravenous iron was associated with a significant reduction in recurrent HF hospitalizations and CV mortality.[34]

Coronary artery disease and pulmonary hypertension

The role of coronary revascularization remains uncertain also in patients with HFrEF and chronic coronary disease.[1] Iaconelli *et al.*[35] conducted a systematic review and meta-analysis of randomized clinical trials including 2842 patients with HF and coronary artery disease, receiving guideline-recommended medical therapy (GRMT). Compared to medical therapy alone, coronary revascularization was associated with a lower risk of all-cause mortality (HR 0.88, 95% confidence interval [CI] 0.79–0.99; $p = 0.0278$) and CV mortality but not the composite of hospitalization for HF or all-cause mortality. Of note, several randomized controlled trials were not blinded, and this might have biased the results. Thus, further evidence is needed.

A double-blind, randomized, placebo-controlled, multicentre superiority trial investigated the impact of the phosphodiesterase-5-inhibitor tadalafil on right ventricular systolic function in 100 adults with congenital heart disease and systemic right ventricles. Tadalafil 20 mg once daily versus placebo was administered for 3 years and the primary endpoint was the change in right ventricular end-systolic volume. No changes were observed in either group nor significant differences between treatment groups.[36]

Post-heart failure hospitalization care

A scientific statement by the HFA summarized recent findings that have implications for clinical management both in the pre-discharge and the early post-discharge phase after a hospitalization for acute HF. First, the early detection and effective treatment of residual or recurrent congestion may reduce the risk or rehospitalization. Second, the initiation and up-titration of GRMT is crucial in order to improve both the short- and long-term clinical course.[37]

Implementation of GRMT for HFrEF remains limited.[38] Schrage *et al.*[39] investigated the association of HF hospitalizations with the initiation/discontinuation of GRMT and consequent outcomes. Among 6893 patients with LVEF <50% who experienced an HF hospitalization from the Swedish HF Registry, hospitalization usually leads to an implementation of GRMT, although it remains sub-optimal. Early initiation of GRMT was associated with a better survival.

In a secondary analysis of the STRONG-HF trial, the high-intensity care (HIC) strategy was safe and significantly reduced all-cause mortality and HF readmission at 180 days compared to usual care without a significant interaction of age and sex.[40,41] However, older patients had smaller benefits in terms of quality of life.[40]

The detection of B-lines through lung ultrasound (LUS) is of utmost importance for the diagnosis of congested acute HF. A secondary analysis of the BLUSHED-AHF trial, designed to investigate the effect of LUS-guided therapy in patients with acute HF, tested the use of artificial intelligence/machine learning (AI/ML)-based automated guidance systems in order to detect lung congestion. The algorithm correlated with expert-level-B-lines detection.[42]

Chatur *et al.* examined the effects of dapagliflozin versus placebo on estimated glomerular filtration rate slope (acute and chronic), 1-month change in systolic blood pressure, and the occurrence of serious hypovolaemic or renal adverse events in patients enrolled in the DELIVER trial with and without HF hospitalization within 30 days of randomization.[43,44] Dapagliflozin showed protective effects, with a minimal impact on blood pressure and without increase in renal or hypovolaemic serious adverse events.[45] Similar results were previously found with empagliflozin.[46,47]

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